Environment International 143 (2020) 105974

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review article

Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis

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ARTICLE INFO

Handling editor: Adrian Covaci

Keywords:
Meta-analysis
Air pollution
Systematic review
Health effects

ABSTRACT

As new scientific evidence on health effects of air pollution is generated, air quality guidelines need to be periodically updated. The objective of this review is to support the derivation of updated guidelines by the World Health Organization (WHO) by performing a systematic review of evidence of associations between long-term exposure to particulate matter with diameter under 2.5 μm ($PM_{2.5}$) and particulate matter with diameter under 10 μm (PM_{10}), in relation to all-cause and cause-specific mortality. As there is especially uncertainty about the relationship at the low and high end of the exposure range, the review needed to provide an indication of the shape of the concentration–response function (CRF).

We systematically searched MEDLINE and EMBASE from database inception to 9 October 2018. Articles were checked for eligibility by two reviewers. We included cohort and case-control studies on outdoor air pollution in human populations using individual level data. In addition to natural-cause mortality, we evaluated mortality from circulatory diseases (ischemic heart disease (IHD) and cerebrovascular disease (stroke) also specifically), respiratory diseases (Chronic Obstructive Pulmonary Disease (COPD) and acute lower respiratory infection (ALRI) also specifically) and lung cancer. A random-effect meta-analysis was performed when at least three studies were available for a specific exposure-outcome pair. Risk of bias was assessed for all included articles using a specifically developed tool coordinated by WHO. Additional analyses were performed to assess consistency across geographic region, explain heterogeneity and explore the shape of the CRF. An adapted GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment of the body of evidence was made using a specifically developed tool coordinated by WHO.

A large number (N = 107) of predominantly cohort studies (N = 104) were included after screening more than 3000 abstracts. Studies were conducted globally with the majority of studies from North America (N = 62) and Europe (N = 25). More studies used $PM_{2.5}$ (N = 71) as the exposure metric than PM_{10} (N = 42). $PM_{2.5}$ was significantly associated with all causes of death evaluated. The combined Risk Ratio (RR) for $PM_{2.5}$ and natural-cause mortality was 1.08 (95%CI 1.06, 1.09) per 10 $\mu g/m^3$. Meta analyses of studies conducted at the low mean $PM_{2.5}$ levels (< 25, 20, 15, 12, 10 $\mu g/m^3$) yielded RRs that were similar or higher compared to the overall RR, consistent with the finding of generally linear or supra-linear CRFs in individual studies. Pooled RRs were almost identical for studies conducted in North America, Europe and Western Pacific region. PM_{10} was significantly associated with natural-cause and most but not all causes of death. Application of the risk of bias tool showed that few studies were at a high risk of bias in any domain. Application of the adapted GRADE tool resulted in an assessment of "high certainty of evidence" for $PM_{2.5}$ with all assessed endpoints except for respiratory mortality (moderate). The evidence was rated as less certain for PM_{10} and cause-specific mortality ("moderate" for circulatory, IHD, COPD and "low" for stroke mortality.

Compared to the previous global WHO evaluation, the evidence base has increased substantially. However, studies conducted in low- and middle- income countries (LMICs) are still limited. There is clear evidence that both $PM_{2.5}$ and PM_{10} were associated with increased mortality from all causes, cardiovascular disease, respiratory disease and lung cancer. Associations remained below the current WHO guideline exposure level of 10 $\mu g/m^3$ for $PM_{2.5}$.

Systematic review registration number (PROSPERO ID): CRD42018082577.

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https://doi.org/10.1016/j.envint.2020.105974
Received 27 February 2020; Received in revised form 19 June 2020; Accepted 24 June 2020
Available online 20 July 2020

1. Introduction

Air pollution is a major environmental hazard to human health and a leading cause of mortality and morbidity worldwide (WHO, 2006; USEPA, 2019). Particulate matter (PM), which comprises multiple components and size fractions, is an important health relevant outdoor air pollutant regulated in many countries. Most earlier routine air quality monitoring systems measured particulate matter with diameter under 10 μm (PM_{10}), whereas more recent networks have added particulate matter with diameter under 2.5 μm ($PM_{2.5}$) measurements. PM_{10} includes both fine particles ($PM_{2.5}$) and coarse ($PM_{10\text{-}2.5}$) particles. $PM_{2.5}$ originates primarily from combustion sources, while $PM_{10\text{-}2.5}$ is composed largely of crustal material, sea salt and biological material (WHO, 2006). The proportion of particles in these two size ranges varies substantially depending on local geography, meteorology and specific PM sources such as construction work, unpaved roads or nearby deserts, all contributing to large amounts of coarse particles. Health effects of fine and coarse particles may differ because of different chemical composition and different penetration into the respiratory tract. In the 2019 Integrated Science Assessment (ISA) by the US Environmental Protection Agency (EPA), the association between $PM_{2.5}$ and natural mortality was rated as "causal" while the association between $PM_{10\text{-}2.5}$ and natural-cause mortality was rated as "suggestive" (U.S. EPA, 2019). Causal or likely causal relationship between long-term exposure to fine PM and all-cause, cardiovascular, respiratory and lung cancer mortality have also been reported by the International Agency for Research on Cancer (IARC, 2013) and Health Canada (HC, 2013). The Global Burden of Disease (GBD) study estimated that ambient $PM_{2.5}$ was the fifth-ranking mortality risk factor in 2015, with 4.2 million deaths caused by exposure to $PM_{2.5}$ (Cohen et al., 2017; WHO, 2018).

The World Health Organization (WHO) has published several volumes of Air Quality Guidelines (AQGs) to provide guidance to the public, especially to policy and other decision makers, on the health risks of air pollution. The latest version was published in 2006 with an annual average guideline exposure level of 10 $\mu g/m^3$ for $PM_{2.5}$ and 20 $\mu g/m^3$ for PM_{10} (WHO, 2006). The guideline exposure levels represent the lower end of the range over which significant effects on survival were observed in the 2006 evaluation of the evidence. Guideline values are designed to advise national policy makers to what levels air pollution should be reduced to protect public health. The guideline was developed based on evaluation of a small number of cohort studies predominantly conducted in North America. Particularly, the American Cancer Society (ACS) study was important to derive the guideline. Concerns were raised regarding applying the guideline to other areas in the world where PM sources and population characteristics are different. A large number of new cohort studies has been published since 2006, including several large studies based on administrative databases (Hoek et al., 2013). A number of studies conducted in areas with PM levels below the current WHO guidelines (Cakmak et al., 2016; Dehbi et al., 2017; Gan et al., 2013; Pinault et al., 2016) suggested that health effects may occur at low pollution levels. This has increased the interest in the shape of the concentration–response function (CRF), including detection of a potential threshold in the CRF.

As new evidence is generated, the WHO air quality guidelines need to be periodically updated. The overall objective of the update of WHO Global AQGs is to develop public health recommendations for ambient air quality. To support the update of the guidelines, we performed a systematic review of evidence of associations between long-term exposure to PM and mortality. The most important goal of the systematic review was to provide quantitative information about the magnitude of risks, not to contribute to the debate about a potential causal relationship. The specific question formulated in terms of Population, Exposure, Comparator, Outcome, Study Design (PECOS) was: "In any population, including subgroups of susceptible individuals (P), what is the increase in risk of all-cause and cause-specific mortality (O) per 10 unit increase (C) in $\mu g/m^3$ of long-term exposure (in the order of months to years) to ambient concentrations of $PM_{2.5}$ and PM_{10} (E), observed in cohort and case-control studies (S)? In these studies, is an increased risk observed at low levels, specifically below the current WHO guideline?" In particular, we used meta-analysis to quantitatively pool risk estimates across studies, and qualitatively summarized the concentration–response gradient evaluated in individual studies. The current review was based on a previous review which evaluated the epidemiological evidence for cardiovascular and respiratory mortality effects of long-term exposure to fine particulate matter (Hoek et al., 2013).

2. Methods

The study protocol was developed from a draft generic text provided by WHO to all systematic review teams. The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO, registered ID: CRD42018082577).

2.1. Eligibility criteria and search strategy

We applied the following eligibility (inclusion and exclusion) criteria structured by PECOS items:

2.1.1. Population

Studies reporting general human population exposed to $PM_{2.5}$ and PM_{10} via inhalation through ambient air predominantly were included. Studies reporting on exposures of populations in the workplace exclusively were excluded. There were no restrictions on ages, geographical areas, occupations of population.

2.1.2. Exposure

Studies reporting long-term exposure (in the order of months to years) to ambient air $PM_{2.5}$ and PM_{10} expressed in a concentration unit ($\mu g/m^3$) were included. Studies that have translated other particle metrics such as total suspended particles (TSP) into PM_{10} or $PM_{2.5}$ using local and time specific conversion factors were also included. Studies reporting exposure to $PM_{2.5}$ and PM_{10} as a result of occupational exposure (measured in the workplace) or indoor exposure exclusively were excluded.

2.1.3. Comparator

In air pollution epidemiology, the association between a continuous exposure and the risk of death is evaluated. The risk of death is thus compared for subjects with relatively high and relatively low concentrations in each study. The comparator in each individual study was exposure to relatively low levels of $PM_{2.5}$ and PM_{10} in the same population (cohort studies) or in a control population (case-control studies).

2.1.4. Outcome

Health outcomes were selected by the Guideline Development Group (GDG) based on evidence on causality according to the latest determination (causal or likely causal) from the US Environmental Protection Agency (EPA), the International Agency for Research on Cancer (IARC), Health Canada (HC) or other integrated science assessments available. Additional most severe health outcomes with suggestive causality were also included based on other considerations such as contribution to burden of disease (prevalence of disease, disability weight, etc), policy implications and expected increase in exposure to a pollutant in the future.

Health outcomes selected in relation to long-term exposure to $PM_{2.5}$ and PM_{10} included (the 10th revision of the International Classification of Diseases (ICD-10) codes, version 2016 in brackets): all-cause mortality (A00 – Z99) and cause-specific mortality including circulatory diseases (I00 – I99), ischemic heart diseases (IHD, I20 – I25),

cerebrovascular diseases (stroke, I60 – I69), respiratory diseases (J00-J99), chronic obstructive pulmonary diseases (COPD, J40 – J44, J47), acute lower respiratory infection (ALRI, J12 – J18, J20 – J22) and lung cancer mortality (C30 – C39). Natural-cause mortality or non-accidental mortality (A00 – R99) is mortality from all-causes except external causes such as accidents, suicide and homicide. We considered natural-cause mortality equivalent to all-cause mortality as natural-cause mortality accounts for the majority of all-cause mortality and there is no clear evidence that air pollution is associated with accidental mortality. Equivalent definitions using ICD-9 or other versions of ICD-10 were included.

2.1.5. Study

Human epidemiological studies using prospective and retrospective cohort study designs, case-control and nested case-control study designs were included. Published journal articles in any language (abstract in English language) were included. If suitable articles were identified published in languages not known by the authors, further assistance was sought after.

Studies without individual level data (i.e. ecological studies with aggregated outcome, exposure and covariates data), studies where no original data were analyzed, methodological studies, non-human studies (in vivo, in vitro, other) and conference abstracts were excluded. Relevant reviews and systematic reviews were not included in the current systematic review but used to scan for references.

Ecological studies were excluded because they are not sufficiently informative for risks at the individual level. Studies analyzing exposure in categories were included in the review, but not in the *meta*-analysis, because of the uncertainty of transformations. Conference abstracts were excluded as they were expected to not contain sufficient information to perform data extraction and risk of bias assessment.

Studies matching the PECOS questions were searched systematically in the database MEDLINE using PubMed and the database EMBASE through EMBASE.com between database inception and 9 October 2018. Literature search strategies using free text and MeSH terms/ Emtree terms, considering exposure, health outcomes and study design, are presented in Appendix 1.

2.2. Study selection and data collection

We (GH and JC) independently screened references by titles and abstracts for potential relevance. We further assessed the full-text of the articles resulting from abstract screening independently for compliance with eligibility criteria in section 2.1. The specific reasons for excluding articles at this stage were recorded (Appendix 2). Any disagreement on inclusion was resolved by discussion.

We conducted data extraction in duplicate. When the data extraction did not agree, we went back to the original paper. We did not document the rate of agreement. We drafted a data extraction form in Excel and piloted the form with a few example studies by the two authors independently. We adapted the form based on these comparisons. The form was then reviewed by WHO with a few adaptations before being used in the current study (Appendix 3). The following characteristics of the included articles were extracted: citation details, study name, study design, study location; characteristics of the study population; follow up period(s); details on exposure; details on outcome assessment; details of confounders adjusted for; data to calculate the effect estimates and their confidence intervals; methods and results of assessment of the shape of the exposure response function; conflicts of interest. For a specific pollutant-outcome pair, most articles reported effect estimates from more than one single-pollutant models with increasing adjustment for potential confounders. When multiple estimates were reported, we extracted estimates from 1) the crude model (only adjusted for age and sex), 2) the most adjusted model, and 3) the authors favored model (usually shown in abstract). Additionally, we extracted estimates from two pollutant models with NO_2, O_3 or coarse particles as the second pollutant.

2.3. Risk of bias (RoB) assessment

A domain-based RoB assessment tool (WHO, 2020), developed by a group of experts convened by WHO, was used to assess all articles included in the *meta*-analyses. RoB assessments were conducted at outcome level; therefore, if a primary study reported on two relevant outcomes RoB was evaluated twice. There were six domains in the RoB assessment tool: confounding, selection bias, exposure assessment, outcome measurement, missing data, and selective reporting. Each domain contained several subdomains. Specifically, we examined the extent to which potential confounders were adjusted for, whether the methods for measuring and controlling for the potential confounders were valid; whether there was a selection of participants into the study that related to exposure or outcome; whether the methods used for exposure assessment were valid; whether the outcome measurement methods were valid; whether missing data were related to exposure or outcome; and whether all results were reported. In evaluating each article, we assigned a 'low', 'moderate' or 'high' RoB for each subdomain. To come to an overall assessment for a domain, the following approach was applied: if any of the subdomains had a rating of high risk of bias, the entire domain was rated as high risk of bias; if all the subdomains had a rating of low risk of bias, the entire domain was rated as low risk of bias; when at least one subdomain had a rating of moderate risk of bias and none of the other subdomains was at high risk of bias, the entire domain was rated as moderate risk of bias. No overall risk of bias was determined across domains for a single article, because we were uncomfortable with assigning equal weight to the different domains.

To judge the RoB per study, the tool contained specific guidelines, for example on what should be considered critical and potential confounders for the different outcomes (WHO, 2020). Critical confounders (age, sex, individual- or area-level socioeconomic status, body mass index/smoking) and additional potential confounders (year of enrolment, ethnicity, diet, physical activity, marital status) were identified prior to the evaluation. An article can only be classified as low risk of bias if all critical and additional potential confounders were adjusted for; if not all critical potential confounders were adjusted for, the article was classified as high RoB; otherwise, a moderate RoB was assigned. For other subdomains, criteria were also specified, though not always as straightforward as the list of confounders (WHO, 2020).

RoB assessment was conducted independently by one reviewer (JC) and checked for accuracy by a second reviewer (GH). A 10% selection of articles were assessed by a WHO methods expert (RM) for cross-checking. Reviewer assessments and rationales were recorded in an Excel file (Appendix 4).

2.4. Meta-analysis

In case three or more studies were identified for the same pollutant and health outcome, a *meta*-analysis was performed. Because of the expected differences in both populations and pollution, we *a priori* decided to pool estimates by a random-effect *meta*-analysis (DerSimonian-Laird estimator). We used Risk Ratios (RRs) as the effect measure of associations between health outcomes and per 10 $\mu g/m^3$ increase in particulate air pollution. Hazard Ratios (HRs) were considered equivalent to RRs. If RR estimates were reported for increments other than per 10 $\mu g/m^3$ (e.g. per IQR increase), we converted the estimates to RR per 10 $\mu g/m^3$. We calculated slope (Beta) and standard error (SE) per 1 $\mu g/m^3$, multiplied by 10 and then exponentiated.

We used the standard equations below.

$$Beta = LN(RRo)/increment$$

$$SE = (LN(RRo\_high) - LN(RRo\_low))/(2 \times 1.96 \times increment)$$

$$RRc = EXP(Beta \times 10)$$

$$RRc\_low = EXP(Beta \times 10 - 1.96 \times SE \times 10)$$

$$RRc\_high = EXP(Beta \times 10 + 1.96 \times SE \times 10)$$

RRo is the effect estimate originally reported in the paper with its low (RRo_low) and high (RRo_high) end of the confidence interval (CI); RRc is the estimate we converted to.

In the main *meta*-analysis we did not include studies conducted in patient groups because the patient population is very different from the general population, and the main interest for WHO of the review is to develop a quantitative summary estimate that applies to the general population, although this was not explicitly stated. In sensitivity analysis, we tested the combined effect estimates after including patient populations.

We only included in the *meta*-analysis the most recent published article when estimates for the same study population were reported in several articles, unless it has a smaller population or a different focus.

In *meta*-analysis, we used one estimate for a specific pollutant-health outcome from a single article. If an article reported two or more estimates for subgroups of the study population separately (e.g. male and female, age groups, regions) only, we combined the estimates by a fixed-effect *meta*-analysis. If an article reported more than one estimates from multiple single-pollutant models with increasing adjustment for potential confounders, we included the estimate from the authors favored model (usually shown in abstract). The authors favored model was always from adjusted models, but not necessarily the most adjusted model, for example in the case of testing for sensitivity to adding in variables that could both be a confounder and on the causal pathway from air pollution towards mortality, such as hypertension for cardiovascular mortality.

Statistical heterogeneity of effect estimates between studies were assessed using tau-squared, presented in the form of an 80% prediction interval around the mean effect in a random-effects *meta*-analysis (Borenstein et al., 2017). In addition, the Chi^2 test (Cochran's Q) with a significance level < 0.1 and the I^2 value, where I^2 values of 25%, 50% and 75% are taken as of low, moderate and high degree of heterogeneity, respectively (Woodward, 2013).

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

2.5. Additional analyses

In an attempt to explain heterogeneity, we further performed subgroup analysis for $PM_{2.5}$ and natural-cause mortality in pre-specified subgroups: geographical location (WHO Regions (African Region, Region of Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region)); sex (men, women, men + women); age groups (average age ≤ 65 years old or > 65 years old); level of mean $PM_{2.5}$ concentrations (< 10 μg/m^3, 10–25 μg/m^3, > 25 μg/m^3). A meta regression was conducted by including all subgroup factors as covariates.

For each *meta*-analysis, a funnel plot was made to detect any evidence of publication bias. Egger's test was also applied.

We assessed the shape of the CRF by *meta*-analysing studies with mean $PM_{2.5}$ concentrations below certain cut-off values (10, 12, 15, 20, 25 μg/m^3) for $PM_{2.5}$ and natural-cause mortality. We further reviewed assessments within individual studies to assess the shape of the CRF, e.g. spline analyses, subset analyses, quartile/ quintile analyses or information from the discussion sections (Appendix 5).

For $PM_{2.5}$ and natural-cause mortality, further sensitivity analyses were conducted: (1) Effect estimates from two pollutant models adjusting for coarse particles, O_3 or NO_2; (2) Excluding studies at high risk of bias; (3) Excluding studies without individual level lifestyle confounders, specifically the large cohort studies based upon administrative databases; (4) Including studies in patient populations or infants.

2.6. Evaluation of certainty of evidence

A GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework, adapted by a group of experts convened by WHO, was used to assess the overall certainty of evidence across studies for each exposure-outcome pair. A common guidance document for all assessors was prepared to assist the rating, which is added in Appendix 6a. Briefly, we started the rating process at moderate certainty evidence because of the risk of unmeasured confounding in observational studies. Then, we downgraded or upgraded the certainty of evidence based on five and four GRADE domains respectively. Reasons for downgrading included 1. Limitations in studies; 2. Indirectness; 3. Inconsistency; 4. Imprecision; 5. Publication bias. Reasons for upgrading include 1. Large magnitude of effect size; 2. All plausible confounding decreases observed RR; 3. Concentration-response gradient. The assessments for the GRADE domains were mostly based on results of the Risk of Bias assessment, heterogeneity, sensitivity and publication bias analyses, which were previously described in the methods section.

Reasons for downgrade

Limitations in studies: the certainty of evidence was downgraded with one or two levels if serious or very serious risk of bias was present in studies that had a considerable weight in the *meta*-analysis. If high risk of bias studies differ in effect size from low/moderate risk of bias studies, consideration should be given to exclude high risk of bias studies from the *meta*-analysis.

Indirectness: the certainty of evidence was downgraded if the studies did not answer the PECOS question of the systematic review.

Inconsistency: the certainty of evidence was downgraded if severe heterogeneity was detected, for example, if there were studies in the body of evidence that show a harmful effect and also studies that show a preventive effect. Some heterogeneity is expected given differences in study location, type of population, level and composition of PM and methodological differences between studies. We assessed whether the 80% prediction interval of the *meta*-analytic risk estimate included unity and was more than twice the width of confidence interval. We further assessed whether heterogeneity could be explained by study-level factors and whether there was a sizable number of studies with HRs below 1. The latter criterium was assessed because a mere difference in magnitude of positive effect estimates between studies is of less concern than a mix of positive and negative associations.

Imprecision: the certainty of evidence was downgraded if the number of person-years of follow-up was less than 940 000 person-years.

Publication bias: the certainty of evidence was downgraded if publication bias was detected by visual inspection of the funnel plot in combination with the Egger's test. Careful consideration of heterogeneity as a cause for non-symmetric funnel plots and significant Egger tests was applied.

Reasons for upgrade:

Large effect size: the certainty of evidence had to be upgraded if the pooled effect size was large or very large. Calculation of a single E-value was proposed to evaluate how strong the relationship between an unmeasured confounder and both exposure and mortality needs to be to explain away the RRs we observed. We lacked the information to apply this procedure in our review. We had insufficient information to judge the strength of the relationships between exposure and confounders in the body of evidence. Furthermore, the relationship between a confounder and mortality is typically much stronger than between a confounder and air pollution exposure, so the use of a single E-value in our review is difficult to interpret. The certainty of evidence was therefore not upgraded based on this domain, consistent with RRs being typically low in well-executed air pollution epidemiological studies.

Confounding domain: the certainty of evidence was upgraded if all plausible confounding shifted the relative risk towards the null.

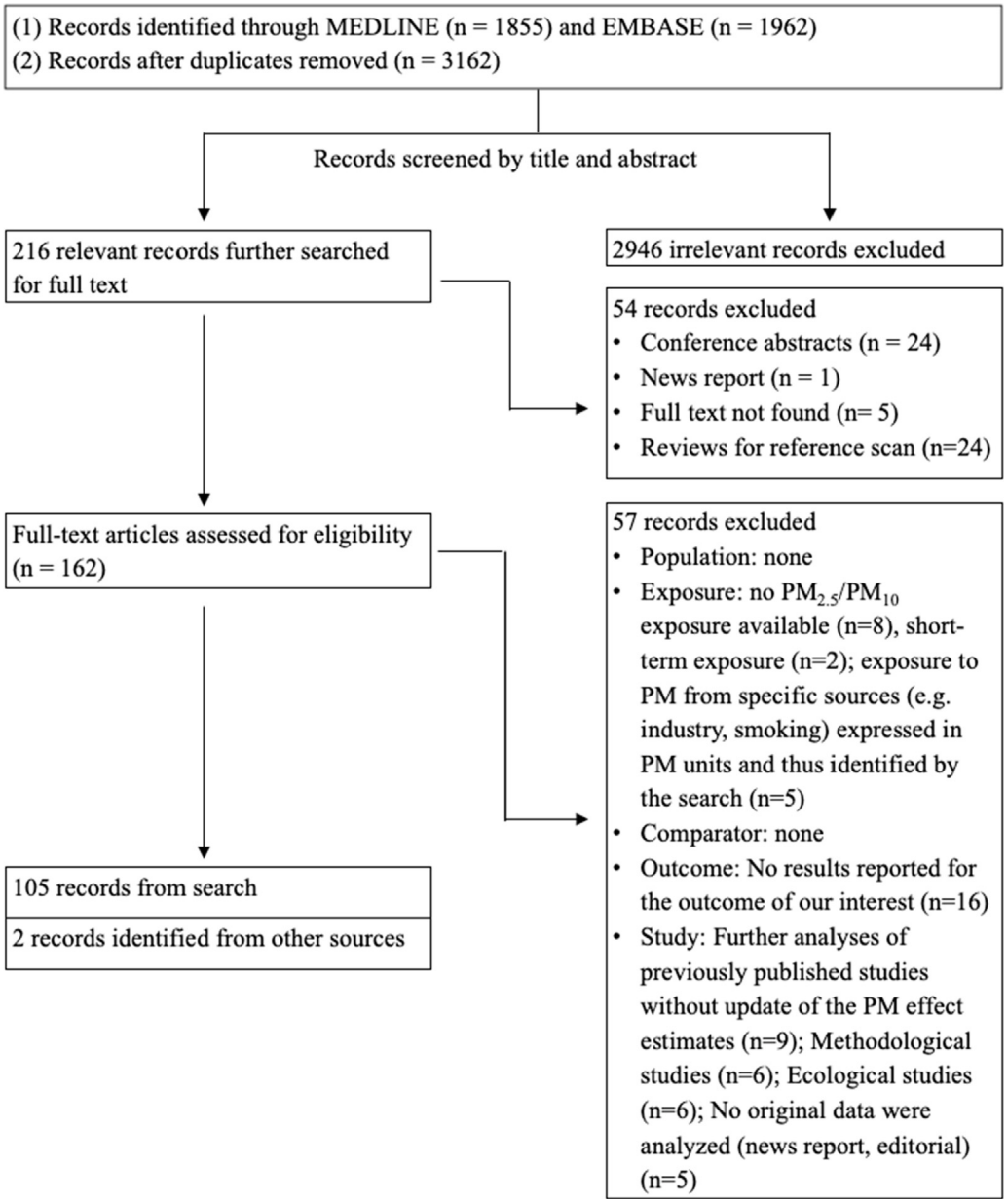

Fig. 1. Flowchart of assessment of eligible studies.

Concentration-response gradient domain: the certainty of evidence was upgraded if there was a concentration–response relationship between exposure and adverse mortality outcomes, either linearly or non-linearly."

3. Results

3.1. Article selection and description

After screening 3162 abstracts, we identified 216 records with potential relevance for the systematic review (Fig. 1). We further excluded 54 records including 24 conference abstracts, 1 news report, 5 items with no full-text and 24 reviews. Reviews were not included in the study but used for references screening and thus not excluded with search terms. Titles of the reviews were recorded in Appendix 2.1. We considered the 5 items with no full-text very unlikely to be relevant for this systematic review and did not put more efforts obtaining the full texts (documented in Appendix 2.2). Of 162 articles which remained for full-text assessment based on the eligibility criteria, we excluded 57 records with rationales documented in Appendix 2.2. We categorized excluded studies by PECOS items in the flowchart (Fig. 1). With 2 additional records identified from scanning references of the identified reviews, we included 107 articles for further data extraction (Appendix 2.3). The descriptive information of the included articles is shown in Table 1. More detailed information is available in the data extraction file (Appendix 3).

There is a large number of studies now that have evaluated mortality effects of long-term exposure to $PM_{2.5}$ or PM_{10}. The vast majority uses the cohort study design, with only three articles use a case-control study design (two in patient population and one in infants). Studies have been conducted in a wide range of countries, though the majority has been conducted in North America (N = 62) and Europe (N = 25). There is an increasing number of studies from Asia (N = 19), but currently no studies from Africa, Central and South America. Widely different populations have been studied, including general population samples, elderly, specific occupational groups (nurses, agricultural workers). Studies further differ in their follow-up period, with the start of follow-up ranging from the 1970 to 2003 across studies. Several very

Table 1
Summary of articles included in the systematic review.

ID	Author and Year	Study Population	Exposure	Mean/ median exposure ($\mu g/m^3$)	Outcome[a]	Study[b]	Study Period	Study Location	Study Size	Confounders adjusted for					
										age, sex	individual SES	individual smoking	other individual lifestyle	area-level SES	indirect adjustment for smoking
1	Abbey et al., 1999	Non-smoking, non-Hispanic white Seventh-day Adventists, age 27–95	PM_{10}	51.24	A; R; LC	AHSMOG	1977–1992	California, U.S.	2,278 males; 4,060 females	y	y	y	y	n	n
2	Badaloni et al., 2017	general population age 30 +	$PM_{2.5}$ PM_{10}	19.6 36.6	A; C	Rome longitudinal study	2001–2010	Rome, Italy	1,249,108	y	y	n	n	y	y
3	Beelen et al., 2009	general population age 55–69	$PM_{2.5}$		C	NLCS	1987–1996	the Netherlands	120,852	y	n	y	n	y	n
4	Beelen et al., 2008	general population age 55–69	$PM_{2.5}$	28.3	A; C; R; LC	NLCS-AIR	1987–1996	the Netherlands	120,852	y	n	y	n	y	n
5	Beelen et al., 2014a	population in 22 cohorts from 13 countries across Europe	$PM_{2.5}$/ PM_{10}		A	ESCAPE	1990 s-2008	Europe	367,251	y	y	y	y	y	n
6	Beelen et al., 2014b	population in 22 cohorts from 13 countries across Europe	$PM_{2.5}$/ PM_{10}		C	ESCAPE	1990 s-2008	Europe	367,383	y	y	y	y	y	n
7	Bentayeb et al., 2015	employees of the French national electricity and gas company	PM_{10} $PM_{2.5}$	25 17	A; C; R	Gazel	1989–2013	France	20,327	y	y	y	y	y	n
8	Bowe et al., 2018	US veterans with no previous history of diabetes	$PM_{2.5}$	11.8	A	U.S. veterans	2003–2012	U.S.	1,729,108	y	n	y	y	y	n
9	Brunekreef et al., 2009	general population age 55–69	$PM_{2.5}$	28.3	A; C; R; LC	NLCS-AIR	1987–1996	the Netherlands	120,227	y	n	y	n	y	n
10	Cakmak et al., 2018	non-immigrants aged 25–90 years	$PM_{2.5}$		A; C; R; LC	1991 CanCHEC	1991–2011	Canada	2,291,250	y	y	n	n	n	y
11	Cakmak et al., 2016	general population ≥ 25 years of age at baseline	$PM_{2.5}$	8.9	A; C	1991 CanCHEC	1991–2006	Canada	2,521,525	y	y	n	n	n	n
12	Carey et al., 2013	general population age 40–89	PM_{10} $PM_{2.5}$	19.7 12.9	A; C; R; LC	English national cohort	2002–2007	England	835,607	y	n	y	y	y	n
13	Cesaroni et al., 2013	general population age 30 +	$PM_{2.5}$	43.6	A; C; R; LC	Rome longitudinal study	2001–2010	Rome, Italy	1,265,058	y	y	n	n	y	n
14	Chen et al., 2005	Non-smoking, non-Hispanic white SDAs, age > =25, lived within an airshed	PM_{10} $PM_{2.5}$	52.6 29	C	AHSMOG	1977–1998	3 metropolitan areas in California, U.S.	3,239	y	y	y	y	n	n
15	H. Chen et al., 2016	AMI patients age ≥ 35	$PM_{2.5}$	10.7	A; C	EFFECT study	1999–2011	Ontario, Canada	8,873	y	y	y	y	y	n
16	X. Chen et al., 2016	general population age > =23 at baseline	PM_{10}	144.34	A; LC	Northern China	1998–2009	4 cities in Northern China	39,054	y	y	y	y	n	n
17	Chen et al., 2017	general population age > =23 at baseline	PM_{10}	144.3	R	Northern China	1999–2009	4 cities in Northern China	39,054	y	y	y	y	n	n

(*continued on next page*)

Table 1 (*continued*)

ID	Author and Year	Study Population	Exposure	Mean/ median exposure ($\mu g/m^3$)	Outcome[a]	Study[b]	Study Period	Study Location	Study Size	Confounders adjusted for					
										age, sex	individual SES	individual smoking	other individual lifestyle	area-level SES	indirect adjustment for smoking
18	Crouse et al., 2012	general population ≥ 25 years of age at baseline, immigrants	$PM_{2.5}$	8.7	A; C	1991 CanCHEC	1991–2001	Canada	2,145,400	y	y	n	n	y	n
19	Crouse et al., 2015	general population ≥ 25 years of age at baseline	$PM_{2.5}$	8.9	A; C; R; LC	1991 CanCHEC	1991–2006	Canada	2,521,525	y	y	n	n	y	y
20	Dehbi et al., 2017	NSHD: singleton births occurring in March 1946; SABRE: tri-ethnic population age 40–69 in 1989	PM_{10} $PM_{2.5}$	16.7 9.9	C	NSHD, SABRE	1989–2015	England	7,529	y	y	y	n	y	n
21	Di et al., 2017	general population covered by Medicare age > =65	$PM_{2.5}$	11	A	Medicare	2000–2012	continental USA	60,925,443	y	y	n	n	y	y
22	Dimakopoulou et al., 2014	Participants from 11 European cohorts	$PM_{2.5}$/ PM_{10}		R	ESCAPE	1985–2008	Europe	307,553	y	y	y	y	y	n
23	Dockery et al., 1993	white subjects age 25–74 at enrolment	$PM_{2.5}$/ inhalable particles		A; LC	Harvard Six Cities	1974–1989	Six US cities	8,111	y	y	y	y	n	n
24	Dong et al., 2012	general population age > =25 at baseline	PM_{10}	154	R	Shenyang	1998–2009	Shenyang, China	9,941	y	y	y	y	n	n
25	Eckel et al., 2016	lung cancer patients	PM_{10} $PM_{2.5}$	31.8 13.7	A; LC	lung cancer patients	1988–2009	California, USA	320,940 160,707	y	n	n	n	y	n
26	Eftim et al., 2008	general population age > =65	$PM_{2.5}$	13.6	A	Med-ACS	2000–2002	110 counties in USA	7,333,040	y	n	n	n	y	y
		general population age > =65	$PM_{2.5}$	14.1	A	Med-SCS	2000–2002	6 counties in USA	341,099						
27	Enstrom, 2005	43–99 yr (mean 65.7) old adults	$PM_{2.5}$	23.4	A	CA CPS I	1973–2002	11 counties in California, U.S.	35,783	y	y	y	y	n	n
28	Enstrom, 2017	general population age > =30 living in households with at least one person age > =45	$PM_{2.5}$	21.16	A	ACS-CPS II	1982–1988	U.S. 85 counties	292,277	y	y	y	n	n	n
29	Fischer et al., 2015	general population age > =30	PM_{10}	29	A; C; R; LC	DUELS	2004–2011	the Netherlands	7,218,363	y	y	n	n	y	y
30	Gan et al., 2011	general population age 45–86	$PM_{2.5}$	4.08	C	Canadian	1994–2002	Vancouver, Canada	466,727	y	n	n	n	y	n
31	Gan et al., 2013	general population age 45–85	$PM_{2.5}$	4.1	R	Canadian	1994–2002	Vancouver, Canada	467,994	y	n	n	n	y	n
32	Gehring et al., 2006	women age 50–59	PM_{10}	43.7	A	German	1985–2003	North Rhine-Westphalia, Germany	4,752	n	y	y	y	n	n
33	Gerber et al., 2014	MI patients aged ≤ 65	$PM_{2.5}$	24	A; C	Israel Study of First Acute Myocardial Infarction	1992–2011	Israel	1,120	y	y	y	y	y	n
34	Hales et al., 2012	general population, age 30–74	PM_{10}	8.3	A; C; R; LC	New Zealand Census-Mortality Study	1996–1999	New Zealand	1,364,454	y	y	y	n	y	n

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Table 1 (*continued*)

ID	Author and Year	Study Population	Exposure	Mean/ median exposure ($\mu g/m^3$)	Outcome[a]	Study[b]	Study Period	Study Location	Study Size	Confounders adjusted for					
										age, sex	individual SES	individual smoking	other individual lifestyle	area-level SES	indirect adjustment for smoking
35	Hansell et al., 2016	general population at all ages	PM_{10}	20.7	A; C; R; LC	ONS longitudinal study	1971–2009	England and Wales	367,658	y	y	n	n	y	y
36	Hart et al., 2011	men in U.S. trucking industry, average age 42	PM_{10} $PM_{2.5}$	26.8 14.1	A; C; R; LC	trucking companies	1985–2000	continental US	53,814	y	n	n	n	n	n
37	Hart et al., 2015	married female nurses, age 54–79 in 2000	$PM_{2.5}$	12	A	NHS	2000–2006	U.S.	108,767	y	y	y	y	y	n
38	Hartiala et al., 2016	patients undergoing elective diagnostic coronary angiography or elective cardiac computed tomographic angiography	$PM_{2.5}$	14.6	A	Cleveland Clinic GeneBank study	2001–2010	Ohio, USA	5,854	y	y	y	n	n	n
39	Heinrich et al., 2013	women age 50–59	PM_{10}		A; R; LC	German	1985–2008	North Rhine-Westphalia, Germany	4,752	y	y	y	n	n	n
40	Huss et al., 2010	general population age > 30	PM_{10}		C; LC	Swiss National Cohort	2000–2005	Switzerland	~4.6 million	y	y	n	n	y	n
41	Jerrett et al., 2005	general population age > =30 living in households with at least one person age > =45	$PM_{2.5}$		A; C; LC	ACS-CPS II	1982–2000	Los Angeles, USA	22,905	y	y	y	y	y	n
42	Jerrett et al., 2009	general population age > =30 living in households with at least one person age > =45	$PM_{2.5}$		A; C; R	ACS-CPS II	1982–2000	U.S. 86 metropolitan areas	448,850	y	y	y	y	y	n
43	Jerrett et al., 2013	general population age > =30 living in households with at least one person age > =45	$PM_{2.5}$	14.09	A; C; R; LC	ACS-CPS II	1982–2000	California, USA	73,711	y	y	y	y	y	n
44	Katanoda et al., 2011	general population age > =40	$PM_{2.5}$/ SPM		R; LC	Three-prefecture Cohort Study	1983–1995	3 prefectures in Japan	63,520	y	y	y	y	n	n
45	H. Kim et al., 2017	general population without previous CVD, age > =18	$PM_{2.5}$	25.03	A; C	NHIS-NSC	2007–2013	Seoul, Korea	136,094	y	y	n	y	n	n
46	O.J. Kim et al., 2017	general population, employees, age 20–65	PM_{10}	56	A; C; R	NHIS-NSC	2002–2013	South Korea	275,337	y	y	y	y	y	n
47	Kioumourtzoglou et al., 2015	old adults age > =65	$PM_{2.5}$	12.8	A	Medicare	2000–2010	U.S.	19,274,534	y	n	n	n	y	y
48	Koton et al., 2013	MI patients aged ≤ 65	$PM_{2.5}$	23.9	A; C	Israel Study of First Acute Myocardial Infarction	1992–2011	Israel	1,120	y	y	y	y	y	n
49	Krewski et al., 2009	general population age > =30	$PM_{2.5}$	21.2	A; C; LC	ACS-CPS II	1982–2004	58 MSAs, U.S.	351,338	y	y	y	y	y	n
		general population age > =30	$PM_{2.5}$	14.02			1982–2004	116 MSAs, U.S.	499,968	y	y	y	y	y	n
		general population age > =30	$PM_{2.5}$	14.3			1982–2000	New York, U.S.	44,056						
		general population age > =30	$PM_{2.5}$				1982–2000	Los Angeles, U.S.	22,905						

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Table 1 (*continued*)

ID	Author and Year	Study Population	Exposure	Mean/ median exposure ($\mu g/m^3$)	Outcome[a]	Study[b]	Study Period	Study Location	Study Size	Confounders adjusted for					
										age, sex	individual SES	individual smoking	other individual lifestyle	area-level SES	indirect adjustment for smoking
50	Laden et al., 2006	white subjects age 25–74 at enrolment	$PM_{2.5}$		A; C; R; LC	Harvard Six Cities	1974–1998	six cities in U.S.	8,096	y	y	y	y	n	n
51	Lepeule et al., 2012	white subjects age 25–74 at enrolment	$PM_{2.5}$	15.9	A; C; R; LC	Harvard Six Cities	1974–2009	six cities in U.S.	8,096	y	y	y	y	n	n
52	Lipfert et al., 2006	male U.S. military veterans diagnosed as hypertension	$PM_{2.5}$ PM_{10}	14.34 30.6	A	U.S. veterans	1976–2001	U.S.	~70,000	y	n	y	y	y	n
53	Lipsett et al., 2011	female public school professionals	PM_{10} $PM_{2.5}$	29.21 15.64	A; C; R; LC	California Teachers Study	1995–2005	California, U.S.	101,784 73,489	y	n	y	y	y	n
54	Loop et al., 2018	> 45 yr blacks and whites free from CHD	$PM_{2.5}$	13.6	C	REGARDS	2003–2012	8 Southeastern U.S. states	17,126	y	y	y	y	n	n
55	Maheswaran et al., 2010	South London Stroke Register	PM_{10}	25	A	patients	1995–2006	London	3,320	y	y	y	y	y	n
56	Mcdonnell et al., 2000	male, non-smoking, white, non-Hispanic, age > = 27 in 1977, lived within an airshed	PM_{10} $PM_{2.5}$	59.2 31.9	A; R; LC	AHSMOG	1977–1992	California, U.S.	1,266	y	y	y	y	n	n
57	Miller et al., 2007	postmenopausal women without previous CVD, age 50–79	$PM_{2.5}$	13.5	C	WHI	1994–2003	36 U.S. metropolitan areas	65,893	y	y	y	y	n	n
58	Næss et al., 2007a	inhabitants in Oslo, aged 51–90 years in 1992	PM_{10} $PM_{2.5}$	19 15	A; C; R; LC	Oslo Admin	1992–1998	Oslo, Norway	143,842	y	y	n	n	n	n
59	Næss et al., 2007b	inhabitants in Oslo, aged 50–74 in 1992	$PM_{2.5}$	14.2	C; R; LC	Oslo Admin	1992–1998	Oslo, Norway	105,359	y	y	n	n	n	n
60	Nishiwaki et al., 2013	residents aged 40–59, without a history of lung cancer, myocardial infarction, angina pectoris, or stroke	PM_7		C; LC	JPHC	1990–2008	9 public health centers, Japan	78,057	y	n	y	y	n	n
61	Ostro et al., 2011	current and former female teachers and administrators, age > 30 at baseline	$PM_{2.5}$	17.5	A; C; R	California Teachers Study	2002–2007	California, U.S.	44,847	y	y	y	y	y	n
62	Ostro et al., 2015	current and former female teachers and administrators, age < 30 in 1995	$PM_{2.5}$	17.9	A; C; R	California Teachers Study	2001–2007	California, U.S.	101,884	y	y	y	y	n	n
63	Parker et al., 2018	adults > =25	$PM_{2.5}$	11.8	A; C	NHIS	1997–2011	US	657,238	y	y	n	n	y	n
64	Peng et al., 2017	tuberculosis (TB) patients	$PM_{2.5}$	53.53	A; R	patients	2003–2013	Shanghai, China	4,444	y	y	y	n	n	n
65	Pinault et al., 2016	non-institutional Canadian population aged 25–90	$PM_{2.5}$	6.32	A; C; R; LC	CCHS-Mortality Cohort	2000–2011	Canada	299,500	y	y	y	y	y	n
66	Pinault et al., 2017	non-immigrants, non-institutionalized aged 25–90 years	$PM_{2.5}$	7.37	A; C; R; LC	2001 CanCHEC	2001–2011	Canada	2,448,500	y	y	n	n	y	n
67	Pope et al., 1995	general population age > =30	$PM_{2.5}$	18.2	A; LC	ACS-CPS II	1982–1989	U.S. 50 MSAs	295,223	y	y	y	y	n	n
68	Pope et al., 2002	general population age > =30	$PM_{2.5}$	21.1	A; LC	ACS-CPS II	1982–1998	U.S.	~359,000	y	y	y	y	n	n

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ID	Author and Year	Study Population	Exposure	Mean/ median exposure ($\mu g/m^3$)	Outcome[a]	Study[b]	Study Period	Study Location	Study Size	Confounders adjusted for					
										age, sex	individual SES	individual smoking	other individual lifestyle	area-level SES	indirect adjustment for smoking
69	Pope et al., 2004	general population age > =30	$PM_{2.5}$	17.1	C; R	ACS-CPS II	1982–1998	U.S.	~319,000	y	y	y	y	n	n
70	Pope et al., 2015	general population age > =30	$PM_{2.5}$	12.6	A; C	ACS-CPS II	1982–2004	U.S.	669,046	y	y	y	y	y	n
71	Puett et al., 2008	female registered nurses, age 30–55 at baseline, without cancer before 1992	PM_{10}	21.6	A; C	NHS	1992–2002	13 states in U.S.	66,250	y	n	y	y	y	n
72	Puett et al., 2010	female registered nurses, age 30–55 at baseline, without cancer before 1992	$PM_{2.5}$	13.9	A; C	NHS	1992–2002	U.S.	66,250	y	n	y	y	y	n
73	Puett et al., 2011	male professionals, age 40–75, without MI	$PM_{2.5}$ PM_{10}	17.8 27.9	A; C	Health Professionals Followup Study	1986–2003	U.S.	17,545	y	n	y	y	n	n
74	Pun et al., 2017	Medicare beneficiaries age 65–120	$PM_{2.5}$	12.29	A; C; R; LC	Medicare	2000–2008	continental USA	18,937,461	n	n	n	n	y	n
75	Ritz et al., 2006	infant death during first year of life	PM_{10}		A	infant	1989–2000	Southern California, USA	4,855 cases; 51,947 controls	y	y (maternal)	n	n	n	n
76	Rosenlund et al., 2009	cases: MI patients age 15–79; controls: using registers stratified on sex, age	PM_{10}	2.2	C	Stockholm Heart Epidemiology Program [SHEEP]	1985–1996	Stockholm, Sweden	43,275 cases; 511,065 controls	y	y	n	n	n	n
77	Rosenlund et al., 2006	cases: first-time MI patients age 45–70; controls: using registers stratified on sex, age	PM_{10}	2.4	C	Stockholm Heart Epidemiology Program [SHEEP]	1992–1994	Stockholm, Sweden	1,397 cases; 1,870 controls	y	y	y	y	n	n
78	Ruttens et al., 2016	lung transplantation patients	PM_{10}		A	lung transplantation patients	1987–2013	13 major lung transplant centers from 10 European countries	3,556 for macrolide-free group; 2,151 for macrolide group	y	n	n	n	n	n
79	Schwartz et al., 2008	white subjects age 25–74 at enrolment	$PM_{2.5}$	17.5	A	Harvard Six Cities	1974–1998	six cities in U.S.	8,096	y	y	y	y	n	n
80	Sese et al., 2018	Idiopathic pulmonary fibrosis patients	PM_{10} $PM_{2.5}$	19.46 26.23	A	COFI	2007–2014	France	192	n	n	y	n	n	n
81	Shi et al., 2016	Medicare cohort age > =65	$PM_{2.5}$	8.12	A	Medicare	2003–2008	New England, U.S.	10,938,852 person-years	n	n	n	y	y	y
82	Son et al., 2011	Infants with 37–44 weeks of gestation	PM_{10} $PM_{2.5}$	61 30.6	A; R	infant	2004–2007	Seoul, South Korea	352,405 for normal birth weight; 7,054 for low birth weight	y	y (maternal)	n	n	n	n
83	Spencer-Hwang et al., 2011	non-smoking kidney transplant patients	PM_{10}	25.3	A; C	kidney transplant patients	1997–2003	US	32,239	y	y	n	y	n	n
84	Thurston et al., 2016a	general population age 50–71	$PM_{2.5}$	12.2	A; C; R	NIH-AARP	2000–2009	six US states and Atlanta and Detroit	517,041	y	y	y	y	y	n

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ID	Author and Year	Study Population	Exposure	Mean/ median exposure ($\mu g/m^3$)	Outcome[a]	Study[b]	Study Period	Study Location	Study Size	Confounders adjusted for					
										age, sex	individual SES	individual smoking	other individual lifestyle	area-level SES	indirect adjustment for smoking
85	Thurston et al., 2016b	general population age > =30	$PM_{2.5}$	15	C	ACS-CPS II	1982–2004	100 metropolitan areas in USA	445,860	y	y	y	y	y	n
86	Tonne and Wilkinson, 2013	patients with Acute coronary syndrome	$PM_{2.5}$	11 in England, 9.1 in Wales	A	MINAP	2004–2010	England and Wales	154,204	y	n	y	n	y	n
			PM_{10}	17 in England, 14.6 in Wales											
87	Tonne et al., 2016	MI patients aged ≤ 65	PM_{10}	23.2	A	MINAP	2003–2010	London	18,138	y	n	y	n	y	n
			$PM_{2.5}$	14.6											
88	Tseng et al., 2015	civil service employees and teachers	$PM_{2.5}$		A; C	civil servants cohort	1989–2008	Greater Taipei, Taiwan	43,227	y	y	y	y	n	n
89	Turner et al., 2011	general population age > =30, never-smokers	$PM_{2.5}$	17.6	R; LC	ACS-CPS II	1982–2008	U.S.	120,917	y	y	y	y	n	n
90	Turner et al., 2016	general population age > =30	$PM_{2.5}$	12.6	A; C; R; LC	ACS-CPS II	1982–2004	U.S., esp. Ioawa and North Carolina	669,046	y	y	y	y	y	n
91	Ueda et al., 2012	general population age > =30 without history of CHD or stroke	PM_7	33.1–36.6 (40-60th)	A; C	NIPPON	1980–2004	Japan	7,250	y	n	y	y	n	n
92	Vedal et al., 2013	postmenopausal women, Ages 50–79, without a history of CVD	$PM_{2.5}$	12.9	C	WHI-OS	1994–2005	46 cities in the continental U.S. and Hawaii	73,094	y	y	y	y	n	n
93	Villeneuve et al., 2002	Caucasian subjects age 25–74 at enrolment	$PM_{2.5}$		A	Harvard Six Cities	1974–1991	six cities in U.S.	8,111	y	y	y	y	n	n
94	Villeneuve et al., 2015	healthy and free of cancer women age 40–59	$PM_{2.5}$	9.1	A; C; R; LC	CNBSS	1980–2005	Canada	89,835	y	y	y	y	y	n
95	Wang et al., 2017	Medicare beneficiaries ages > =65	$PM_{2.5}$	10.7	A	Medicare	2000–2013	7 Southeastern states, U.S.	~13.1 million	y	n	n	n	y	n
96	Weichenthal et al., 2014	commercial pesticide applicators, farmers, and their families	$PM_{2.5}$	9.52	A; C; LC	AHS	1993–2009	Iowa and North Carolina, U.S.	83,378	y	y	y	y	n	n
97	Weichenthal et al., 2016	non-immigrants aged 25–90 years	$PM_{2.5}$	9.81	A; C; R; LC	1991 CanCHEC	1991–2009	Canada	193,300	y	y	n	n	n	y
98	Weichenthal et al., 2017	non-immigrants aged 25–90 years	$PM_{2.5}$	7.37	A; C; R	2001 CanCHEC	2001–2011	Canada	2,448,500	y	y	n	n	y	n
99	Wong et al., 2015	age ≥ 65	$PM_{2.5}$	35.3	A; C; R	HongKong elderly	1998–2011	Hong Kong	66,820	y	y	y	y	y	n
100	Yang et al., 2018	age ≥ 65	$PM_{2.5}$	42.2	A; C; R	HongKong elderly	1998–2011	Hong Kong	66,820	y	y	y	y	y	n
101	Yin et al., 2017	men age > =40	$PM_{2.5}$	43.7	A; C; R; LC	Chinese men	1990–2006	45 districts in China	189,793	y	y	y	y	y	n
102	Zanobetti and Schwartz, 2007	Medicare data, MI patients age > =65	PM_{10}	28.8	A	MI patients	1985–1999	21 U.S. cities	196,000	y	n	n	n	y	n
103	Zanobetti et al., 2008	Medicare data, COPD patients age > =65	PM_{10}	29.4	A	COPD cohort	1985–1999	34 U.S. cities	1,039	y	n	n	n	y	n

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Table 1 (*continued*)

ID	Author and Year	Study Population	Exposure	Mean/ median exposure ($\mu g/m^3$)	Outcome[a]	Study[b]	Study Period	Study Location	Study Size	Confounders adjusted for						
										age, sex	individual SES	individual smoking	other individual lifestyle	area-level SES	indirect adjustment for smoking
104	Zeger et al., 2008	persons in the U.S. Medicare system, age ≥ 65	$PM_{2.5}$	14	A	Medicare	2000–2005	eastern U.S.	~12.5 million	n	n	n	n	y	y
			$PM_{2.5}$	10.7				central U.S.	~3.7 million						
			$PM_{2.5}$	13.1				western U.S.	~3.1 million						
105	Zhang et al., 2014	general population age > =23 at baseline	PM_{10}	144	A; C	Northern China	1998–2009	4 cities in Northern China	39,054	y	y	y	y	n	n
106	Zhang et al., 2011	general population age > =25 at baseline	PM_{10}	154	A; C	Shenyang	1998–2009	Shenyang, China	9,941	y	y	y	y	n	n
107	Zhou et al., 2014	men age > =40	PM_{10}	104	A; C; R; LC	Chinese men	1990–2006	45 districts in China	71,431	y	y	y	y	n	n

[a] A = All-cause mortality/ natural-cause mortality; C = Cardiovascular mortality including subgroup of cardiovascular mortality (mortality from ischemic heart diseases, cerebrovascular diseases/ stroke); R = Respiratory mortality including subgroup of respiratory mortality (mortality from chronic obstructive pulmonary diseases, acute lower respiratory infection); LC = Lung Cancer mortality

[b] All cohort studies except study ID 75, 76 and 77 (these three are case-control studies)

large studies based upon administrative databases with more than a million subjects have been reported. Studies further differ in the detail of information available on potential confounders. Exposure assessment has evolved from assigning of city-average concentrations in the earlier studies to more individualized exposure assessment in later studies, using land use regression, dispersion modelling or interpolation.

3.2. Meta analyses

3.2.1. Main analyses

In addition to the forest plots showing articles included in the *meta*-analyses (Figs. 2 – 5, Figure A7.1 – A7.11), we also presented all articles relevant for a specific exposure-outcome pair in a separate plot (Figure A7.12 – A7.26). The second set of plots (plot with all articles) were used to document our selection of a specific article in case of multiple articles from the same study population. Three studies that performed methodologically incorrect analyses were excluded from meta analyses as these results are biased (H. Kim et al., 2017; Pun et al., 2017; Zhang et al., 2014). Two of these studies assigned mean exposure over the follow-up on an individual basis, with subjects who did not die receiving the average of the full follow-up period (H. Kim et al., 2017; Zhang et al., 2014). Ostro et al. (2011) showed that assigning follow-up averages exposure to each individual while there was a downward trend in long-term ambient air pollution, resulted in severe overestimates of the air pollution risks. In Pun et al. (2017), HRs were biased upwards because of incorrect incorporation of exposure in analysis model: results affected by downward trend in exposure contrast in longer exposure window. The effect estimates extracted from these three studies were documented in the second set of plots (plot with all articles).

For $PM_{2.5}$ and natural-cause mortality, the all-articles plot illustrates that several cohorts (e.g. ACS, CanCHEC) have been studied multiple times (Figure A7.12). The large majority of articles report a positive association between $PM_{2.5}$ and natural-cause mortality. The overall summary estimate of the 25 studies is 1.08 (95% CI 1.06, 1.09). No single study has a large weight (Fig. 3). Similar patterns were observed for other pollutant-outcome combinations. For PM_{10} and ALRI mortality, no *meta*-analysis was performed as only two studies were identified (Figure A7.24).

The pooled effect estimates for all exposure-outcome pairs are shown in Table 2. $PM_{2.5}$ was significantly associated with natural-cause mortality and all evaluated causes of death separately. HRs for all evaluated specific causes were moderately large than for natural-cause mortality. PM_{10} was significantly associated with natural-cause, ischemic heart disease, respiratory and lung cancer mortality. For PM_{10}, effect estimates for the respiratory but not the cardiovascular outcomes were larger than for natural-cause mortality. For all outcomes, the number of studies included in *meta*-analysis for PM_{10} is less than that for $PM_{2.5}$, thus might lead to less precise pooled effect estimates.

For most exposure-outcome pairs, there is a large degree of heterogeneity across studies as evidenced by the high I^2 and the larger 80% prediction interval compared to the 95% random effects interval. High heterogeneity is to be expected, given differences in study location, population characteristics, level and composition of PM and methodological differences between the studies (Table 1).

3.2.2. Analyses of the shape of concentration–response function (CRF)

Four studies assessed natural-cause mortality effects for participants exposed to $PM_{2.5}$ concentrations below certain exposure levels (Figure A7.27). The positive associations remained below 10 $\mu g/m^3$ in Medicare (1.09 (95%CI 1.01, 1.19)) and below 5 $\mu g/m^3$ in CanCHEC (1.27 (95%CI 1.09,1.49)). More assessments of the shape of the CRF by individual studies are documented in Appendix 5. These studies typically used non-parametric splines. The majority of studies which analyzed the CRF had no evidence of a threshold and showed linear or supra-linear functions.

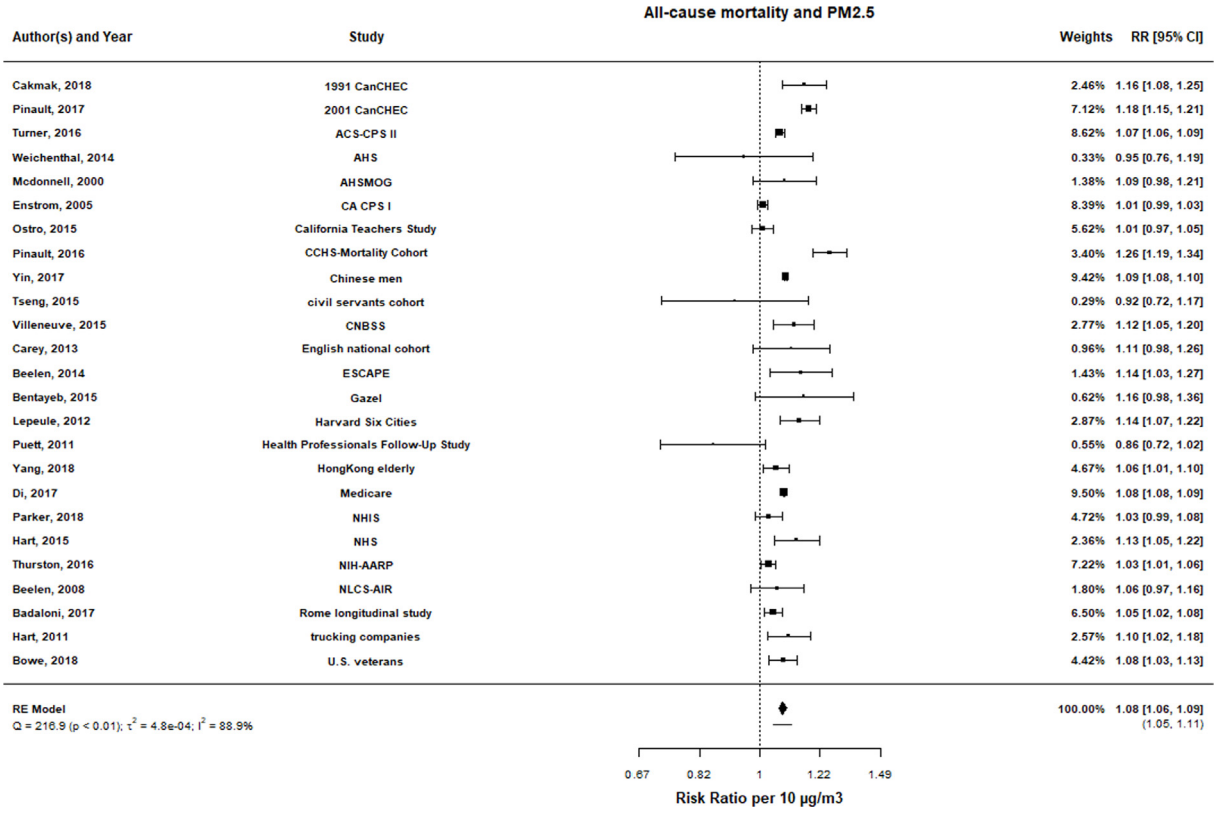

Fig. 2. Forest plot of $PM_{2.5}$ and natural-cause mortality.

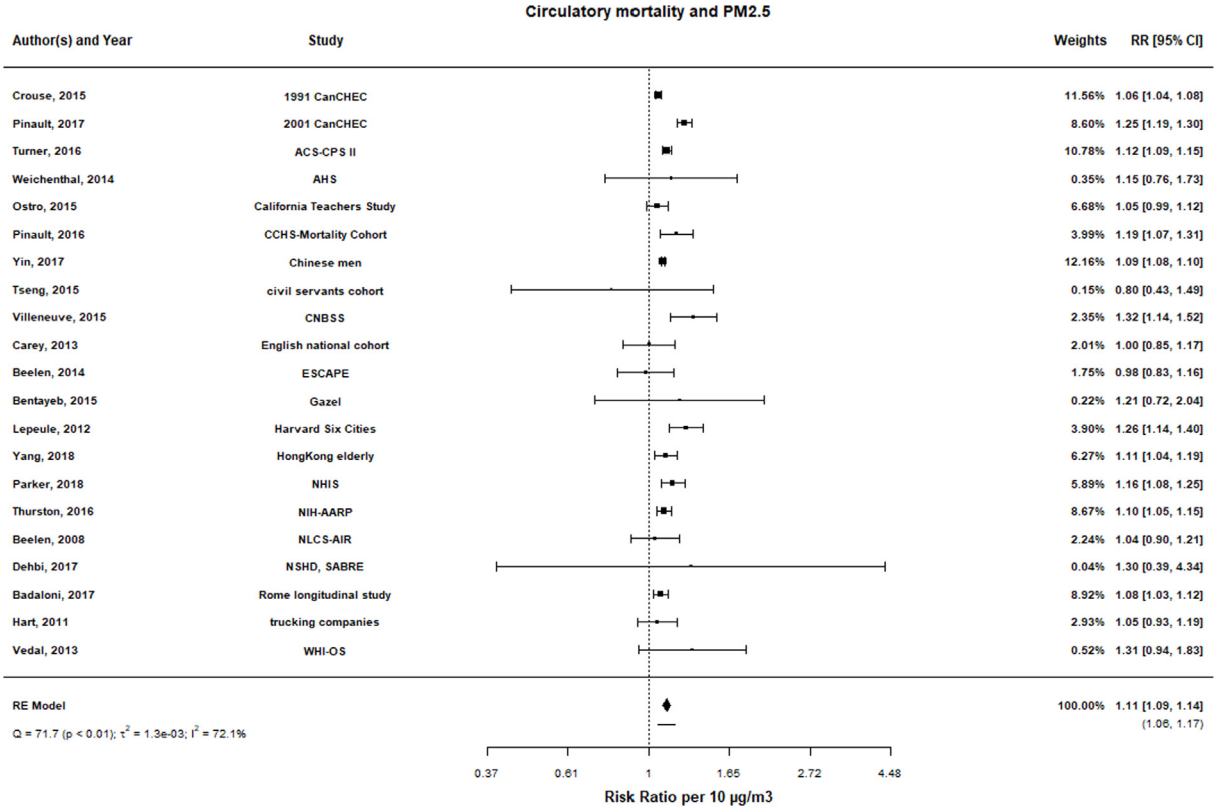

Fig. 3. Forest plot of $PM_{2.5}$ and circulatory mortality.

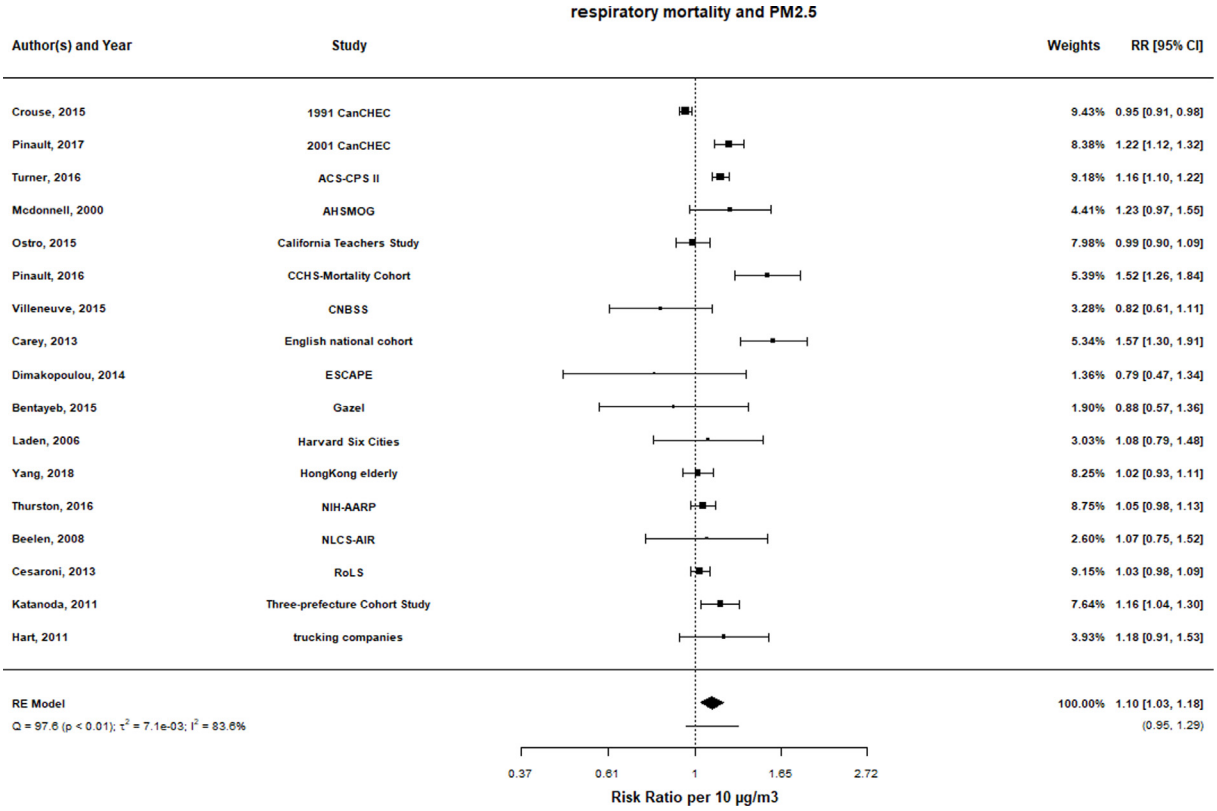

Fig. 4. Forest plot of $PM_{2.5}$ and non-malignant respiratory mortality.

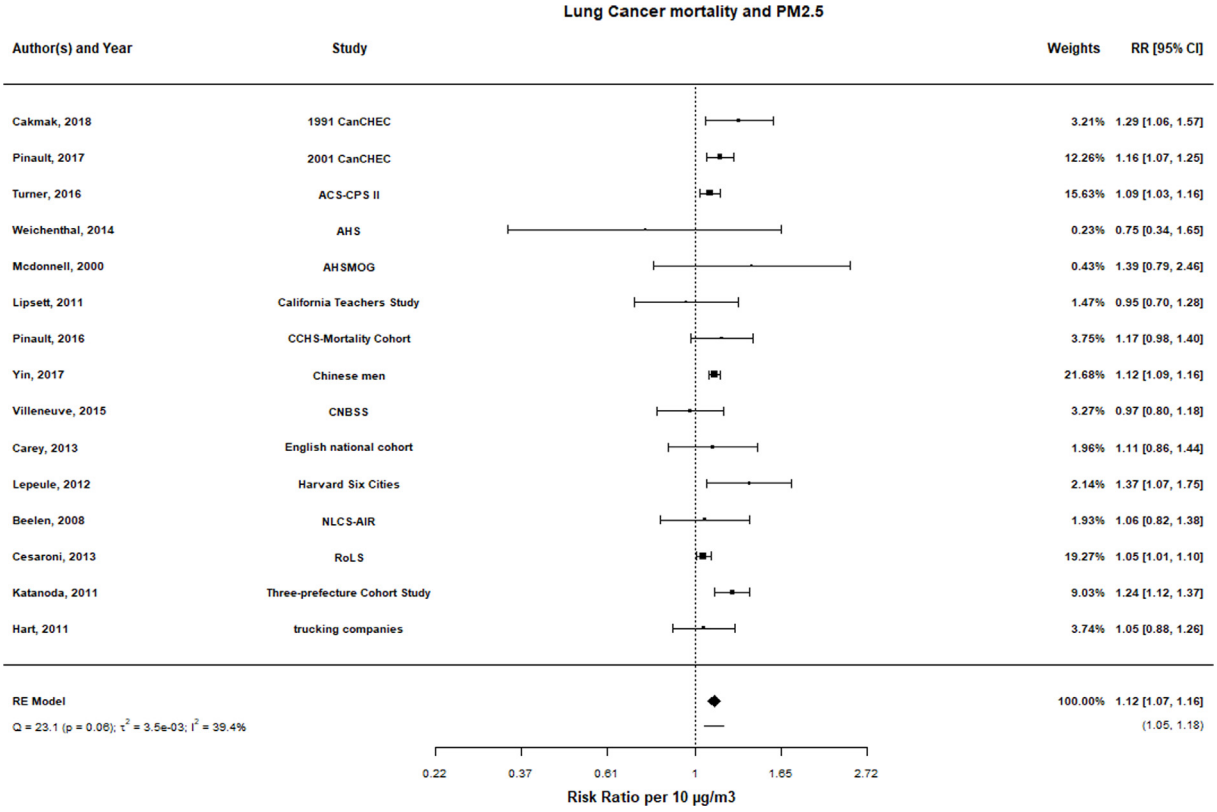

Fig. 5. Forest plot of $PM_{2.5}$ and lung cancer mortality.

Table 2
Pooled effect estimates for all pollutant-outcome combinations.

	$PM_{2.5}$				PM_{10}			
	N	pooled RR per 10 μg/m^3	I^2 (%)	Prediction interval	N	pooled RR per 10 μg/m^3	I^2 (%)	Prediction interval
Natural-cause	25	1.08 (1.06, 1.09)	88.9	(1.05, 1.11)	17	1.04 (1.03, 1.06)	94.0	(1.00, 1.09)
Circulatory	21	1.11 (1.09, 1.14)	72.1	(1.06, 1.17)	15	1.04 (0.99, 1.10)	98.5	(0.92, 1.19)
IHD	22	1.16 (1.10, 1.21)	77.5	(1.04, 1.29)	13	1.06 (1.01, 1.10)	73.4	(0.98, 1.14)
Stroke	16	1.11 (1.04, 1.18)	84.7	(0.98, 1.25)	9	1.01 (0.83, 1.21)	99.0	(0.67, 1.51)
Respiratory	17	1.10 (1.03, 1.18)	83.6	(0.95, 1.29)	13	1.12 (1.06, 1.19)	86.8	(0.99, 1.27)
COPD	11	1.11 (1.05, 1.17)	49.6	(1.02, 1.21)	5	1.19 (0.95, 1.49)	85.4	(0.78, 1.82)
ALRI	4	1.16 (1.01, 1.34)	83.0	(0.88, 1.54)	2	–	–	–
Lung cancer	15	1.12 (1.07, 1.16)	39.4	(1.05, 1.18)	13	1.08 (1.04, 1.13)	92.4	(0.99, 1.18)

N = number of studies

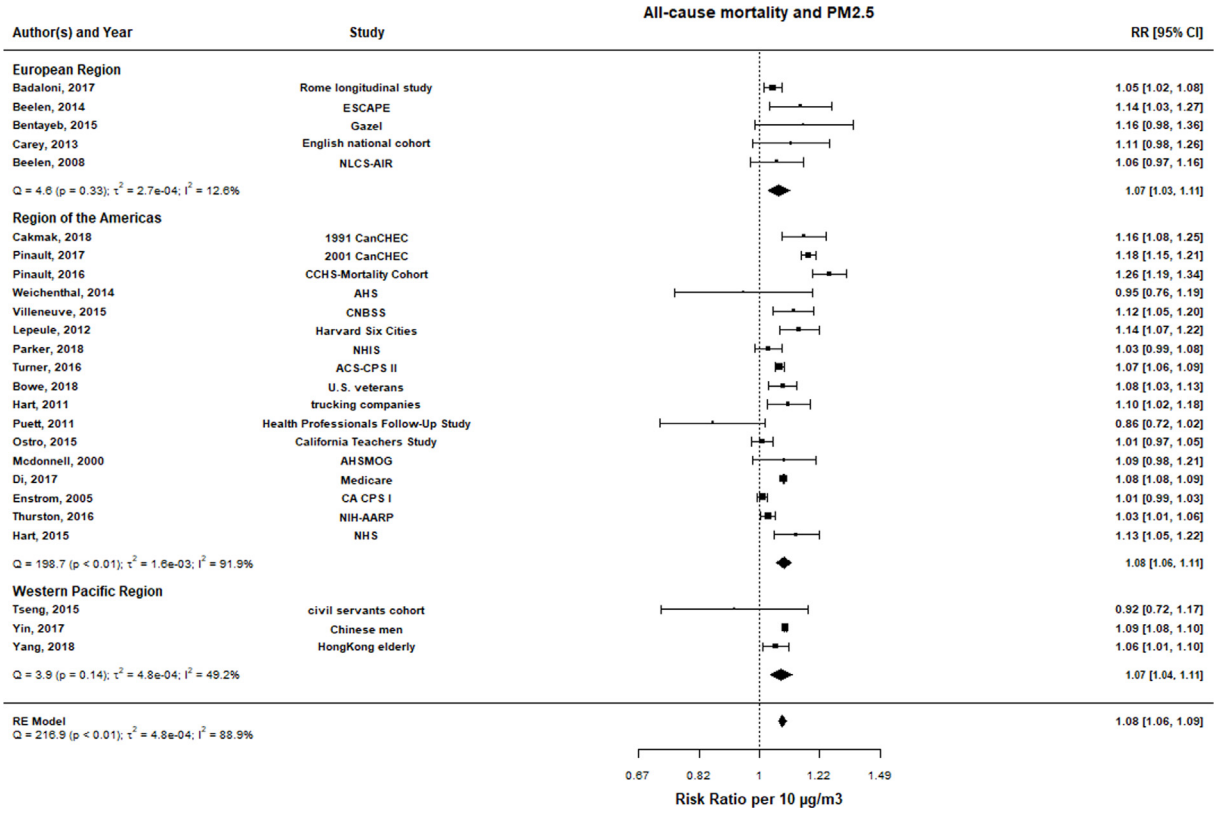

Fig. 6. Meta-analysis of $PM_{2.5}$ and natural-cause mortality: by geographical regions.

We further combined effect estimates for studies with mean $PM_{2.5}$ concentrations below certain cut-off exposure levels (Figure A7.28 – A7.32). The combined effect estimate is 1.17 (95% CI 1.12, 1.23) for the five studies with a mean concentration below 10 μg/m^3. The limitation of this approach is that subjects exposed to pollution concentration higher than the cut-off exposure levels in the cohorts were also included.

3.2.3. Subgroup analyses

Virtually the same effect estimates were found for European Region, Region of the Americas and Western Pacific Region (Fig. 6). Heterogeneity especially remained within the large group of North American studies. Virtually no difference in effect estimates was found between studies in men, women or combined (Figure A7.34). Studies performed in predominantly elderly showed somewhat smaller RRs but the confidence intervals overlapped (Figure A7.35). RRs tended to be larger in the studies with a mean $PM_{2.5}$ concentration below 10 μg/m^3 (Figure A7.36). No single factor can explain the source of high heterogeneity between studies. Meta-regression did not explain the source of high heterogeneity between studies (residual heterogeneity (I^2) = 86.53%), probably because little effect-modifier information is available on study-level factors.

3.2.4. Additional analyses

Two-pollutant models adjusting for NO_2 were specified by five studies and documented overall much lower RRs for $PM_{2.5}$ compared to the single pollutant estimates in studies that specified two pollutant models (Figure A7.37 and A7.38: 1.07 (95% CI 1.05, 1.08) in single pollutant models versus 1.02 (95% CI 1.00, 1.04) in two-pollutant models). Two pollutant models can be difficult to interpret when the correlation between pollutants is high or exposure for pollutants is assessed with different methods or at a different spatial resolution. RRs remained stable after adjusting for coarse particles or O_3: 1.14 (95% CI 1.05, 1.24) based upon three studies and 1.08 (95% CI 1.04, 1.11) based upon seven studies respectively.

The combined effect estimate remained the same (1.08 (95%CI 1.06, 1.09)) after we excluded one study that was at high risk of bias in any domain for $PM_{2.5}$ and natural-cause mortality combination. The

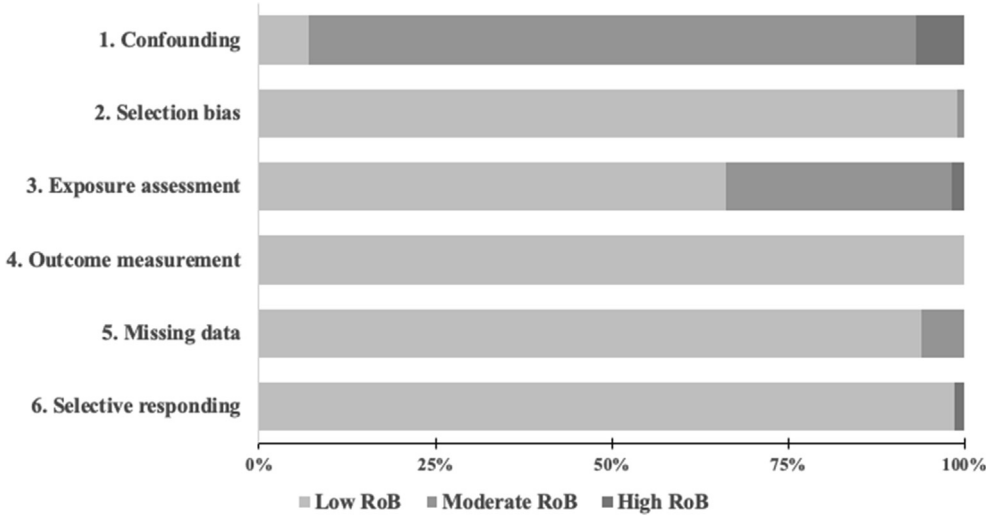

Fig. 7. Summary of all RoB assessments (total number of assessments across all exposure-outcome pairs = 216).

combined estimate slightly increased with a slightly wider confidence interval (1.09 (95%CI 1.06, 1.11)) after we further excluded studies that score moderate on an item that all other studies score low (Figure A7.39). The combined effect estimate remained stable as these two studies had little weight on the *meta*-analysis.

Exclusion of the large administrative cohorts, which have limited information on individual lifestyle factors resulted in an identical effect for $PM_{2.5}$ and natural-cause mortality, but with a slightly wider confidence interval: 1.08 (95% CI 1.05, 1.10) (Figure A7.40).

Inclusion of studies conducted in the very diverse patient populations resulted in a modest increase in effect estimates and a further increase in heterogeneity for $PM_{2.5}$ and natural-cause mortality (Figure A7.41: 1.11 (95% CI 1.07, 1.14)). With the exception of a study in lung cancer patients, these typically smaller studies had less precise effect estimates than the general population studies. Including one small study reported effect estimate for $PM_{2.5}$ and natural-cause mortality in infants with low precision did not change the overall effect estimate (Figure A7.42).

3.3. Risk of bias (RoB) assessment

Fig. 7 shows a summary of RoB assessments for all studies included in the *meta*-analyses. The individual RoB assessments are presented in Appendix 4b. Most but not all of the cohort studies had similar evaluations because of the similar study design they used – following the classical cohort studies conducted in the USA, specifically the Six city study (Dockery et al., 1993) and the American Cancer Society study (Pope et al., 2002).

Confounding Most of the studies were rated as 'moderate risk' in this domain. The most critical subdomain was "Were all confounders considered adjusted for in the analysis?". Individual-level smoking and BMI were usually not available in large administrative cohorts, and were indirectly adjusted for in some studies using an ancillary dataset (Badaloni et al., 2017; Crouse et al., 2015; Di et al., 2017; Fischer et al., 2015). Some studies were rated as 'moderate risk' because one or two of the confounders in the list of other/ additional potential confounders were not adjusted for. Studies that adjusted for a large number of individual- and area-level risk factors, such as the ACS study typically did not adjust for at least one of this list and we therefore rated the study as moderate risk of bias (Turner et al., 2016). This characterization is questionable however and some studies such as the ACS study would qualify as low risk of bias. Since the ACS study has adjusted for BMI and a large number of SES variables, it is highly likely that this will also adjust for effects of lack of physical activity. Similar examples apply to a large number of cohort studies, e.g. (Beelen et al., 2014a; Carey et al., 2013; Thurston et al., 2016a; Turner et al., 2016): 'low risk' might be more reasonable given the large number of covariates adjusted for.

Selection bias We found few studies where selection was related to exposure. Therefore, most of the studies were rated as 'low risk'.

Exposure assessment The exposure assessment methods varied across the studies. We considered most of the exposure assessment methods appropriate when they had documented validity such as good agreement between model predictions and measurements. Change in spatial exposure contrasts is not a potential risk for studies assigning time-varying exposures. In cohort studies where exposures were assigned to the participants for the same period, several reported the stability of spatial contrast. For studies that did not report stability of the contrasts, we made an assessment based on previous studies in the same study area and time period. We generally assessed spatial exposure contrasts did not change much in well-developed areas in North America and Europe. In strongly developing areas such as Asia, spatial exposure contrasts might have changed in the past decade(s). If the change of spatial exposure contrasts was not accounted for, we rated as 'moderate' or 'high' risk of bias.

Outcome measurement Most of the studies used a mortality registry to link health outcomes of the participants. Some earlier studies used interviews to confirm the vital status of participants. Deaths were classified according to the International Classification of Diseases (ICD) in most of the studies using the underlying cause of death. The same outcome measurement methods were applied for all subjects within a particular study, irrespective of the level of exposure, therefore all studies were rated as 'low risk'. We note that misclassification of cause of death may have contributed to additional noise in the data.

Missing data Studies measuring outcome by linkage to mortality registries were unlikely to have frequent missing outcome data. Most of the studies excluded subjects if they had missing exposure data. No studies used imputation of exposure. Percent of missing data of exposure was typically low. Therefore, most but not all of the studies were rated as 'low risk'.

Selective reporting Studies typically reported all risk estimates for the outcomes and pollutants identified in the Methods section therefore were rated as 'low risk'. One study (McDonnell et al., 2000) selectively reported effects for males only because effects for females were weak or inverse, thus was rated as "high risk".

3.4. Assessment of the certainty of evidence

Table 3 lists the application of the adapted GRADE tool to the body

Table 3
Detailed assessment of certainty of evidence for each exposure-outcome pair ('+' implies increase in confidence).

	reasons for downgrading									reasons for upgrading				overall	Final certainty assessment
	A1	rationale	A2	rationale	A3	rationale	A4	rationale	A5	rationale	B1	rationale	B2	rationale	B3	rationale		
$PM_{2.5}$ and natural-cause	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM_{10} and natural-cause	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
$PM_{2.5}$ and circulatory	0	little influence on the overall effect	0	no evidence of indirectness	0	prediction interval does not include unity	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	+1	High
PM_{10} and circulatory	0	little influence on the overall effect	0	no evidence of indirectness	−1	prediction interval includes unity and larger than twice the CI	0	sample size large enough to assess RR with sufficient precision	0	no evidence of publication bias	0	insufficient basis for upgrading	0	confounders would shift the RR in both directions	+1	evidence of increase in risk with increasing exposure	0	Moderate

A1 = limitations in studies (risk of bias); A2 = indirectness; A3 = inconsistency; A4 = imprecision; A5 = publication bias.
B1 = large RR; B2 = all confounding decreases observed RR; B3 = concentration–response gradient.

of evidence for $PM_{2.5}$ and PM_{10} related to natural-cause and circulatory mortality. The complete evaluations are documented in Appendix 6b. The starting point was at moderate certainty of evidence reflecting the risk of unmeasured confounding in observational studies. We concluded an upgrade of the evidence with one level for all assessed endpoints associated with $PM_{2.5}$ except respiratory mortality, and for natural-cause, respiratory and lung cancer mortality associated with PM_{10}, resulting in a 'high certainty of evidence'. A downgrade with one level was concluded for PM_{10} and stroke mortality, resulting in a 'low certainty of evidence'. A 'moderate certainty of evidence' was assessed for the remainder of the exposure-endpoint combinations. Most of the rationales for the assessments in the various GRADE domains are documented in the previous sections. Briefly:

A1 Limitations in studies (risk of bias) No downgrading was applied as few studies were identified as 'high risk of bias' and exclusion of these studies had little impact on the overall effect estimate (section 3.2). This decision is supported by the stability of risk estimates excluding the large administrative cohorts with no direct information on individual lifestyle (section 3.2).

A2 Indirectness No downgrading was applied as all studies answered the PECOS (Population, Exposure, Comparator, Outcome and Study) question directly as shown in Table 1.

A3 Inconsistency We downgraded the certainty of the evidence for PM_{10} and circulatory mortality, PM_{10} and stroke mortality, and $PM_{2.5}$ and respiratory mortality because the 80% prediction interval included unity; the width of the prediction interval was more than twice the width of confidence interval and there was a sizable number of studies with HRs below 1. Heterogeneity was partly explained by the level of pollution and differences in population: higher HRs for studies with lower mean $PM_{2.5}$ concentrations, somewhat lower HRs in elderly and higher HRs in patient populations.

A4 Imprecision No downgrading was applied as the included cohort studies followed a large population for several years, resulting in large number of person-years (Table 1). Several single studies included much > 940 000 person-years. All exposure outcome pairs (except PM_{10} and ALRI, 2 studies) fulfilled the criterium by a wide margin. The small width of the confidence interval around the summary HR further supports that no downgrade is needed.

A5 publication bias

No downgrading was applied as no evidence of publication bias was found in funnel plots and Egger's tests. Upon visual inspection, no funnel plots showed that small studies with RRs below 1 were missing, indicating no evidence for publication bias (Figure A7.33). Egger's test has good performance for continuous outcomes but is less sensitive for the binary outcomes reported in the current review, especially for the outcomes with a small number of studies. The funnel plot is not sensitive with small number of studies for some outcome pollution pairs either. Cohort studies require a large effort often of different institutes and hence investigators generally try to get studies published irrespective of the results of the study. This qualitative interpretation cannot be investigated directly, because no registries of planned studies exist. We further do not imply that publication bias is absent in easier to conduct air pollution epidemiology studies. Most Funnel plots show a pattern with studies outside the area defined by uncertainty. This mostly reflects the large degree of heterogeneity across studies (Lau et al., 2006; Sterne et al., 2011). Egger's test is sometimes significant (e.g. natural-cause mortality and PM_{10}, IHD and PM_{10}), more reflecting heterogeneity than publication bias.

B1 Large RR No upgrading was applied as RRs are typically low in air pollution epidemiological studies. We did not apply the procedure based on a single E-value (section 2.6).

B2 All confounding decreases observed RR No upgrading as confounding may decrease or increase observed RRs depending on the direction of the association between exposure and confounder in individual studies.

B3 Concentration-response gradient Upgrading was applied for most

combinations. We considered upgrading for a specific combination when there was at least one study reported evidence of a concentration–response gradient (Appendix 5).

4. Discussion

4.1. Summary of evidence

4.1.1. Quantitative effect estimates in meta-analysis

In meta analyses, $PM_{2.5}$ was associated with significantly increased risks of all causes of mortality evaluated. PM_{10} was associated with significantly increased risks of natural-cause and most but not all cause-specific mortality. The evidence base has increased substantially compared to the previous global WHO evaluation published in 2006 (WHO, 2006).

For natural-cause mortality, the combined effect estimate across 25 studies was 1.08 (95%CI:1.06, 1.09) per 10 μg/m^3 increase in $PM_{2.5}$, which is slightly higher than the combined estimate of 1.06 (95% CI:1.04, 1.08) across 11 studies reported in a 2013 review used extensively by the European Environment Agency for European health impact assessment (Hoek et al., 2013). The previous estimate was based on studies predominantly conducted in North America with two studies from Europe (Beelen et al., 2008; Cesaroni et al., 2013). The evidence was strengthened by including new evidence generated in Asia (Tseng et al., 2015; Yang et al., 2018; Yin et al., 2017), North America (Bowe et al., 2018; Pinault et al., 2017), Europe (Beelen et al., 2014b; Carey et al., 2013), and longer follow-up (Cakmak et al., 2018; Di et al., 2017). For PM_{10}, the combined estimate increased from 1.035 (95%CI:1.004, 1.066) reported in the Hoek, 2013 review to 1.04 (95%CI:1.03, 1.06) in the current review. The previous review was based on only 6 cohort studies while the updated combined estimate was based on 17 cohort studies.

The combined effect estimate was larger for cardiovascular (particularly ischemic heart disease) than for natural-cause mortality associated with exposure to $PM_{2.5}$. This pattern is consistent with findings in the previous reviews (Chen et al., 2008; Hoek et al., 2013; Liu et al., 2018). One potential source of heterogeneity for effects on IHD is misclassification of the underlying cause of death as Heart Failure rather than IHD. Both WHO and GBD consider heart failure as a "junk category" and re-assign most to IHD (WHO, 2006; Cohen et al., 2017). For stroke mortality, a significant increased risk was found to be associated with $PM_{2.5}$ but not with PM_{10}. A previous review derived the same conclusion but in addition, reported a significant increased risk for stroke incidence associated with both $PM_{2.5}$ and PM_{10} (Scheers et al., 2015).

In the Hoek et al. (2013) review no significant association was found for $PM_{2.5}$ and non-malignant respiratory mortality across six studies (Hoek et al., 2013). An increased risk of non-malignant respiratory mortality associated with both $PM_{2.5}$ and PM_{10} in this review was found by including more recent findings. This increases the coherence with the time-series studies which have consistently shown short-term associations between PM and respiratory mortality (Brunekreef and Holgate, 2002; WHO, 2006; Pope and Dockery, 2006). Studies investigating long-term exposure and acute lower respiratory infection (ALRI) are still scarce.

Association between lung cancer and PM has been widely investigated as lung cancer is one of the most common cancers and has a poor prognosis. In this review we found significantly increased risk in lung cancer mortality associated with both $PM_{2.5}$ and PM_{10}. This pattern is consistent with several previous reviews (Chen et al., 2008; Cui et al., 2015; Yang et al., 2016). The effect estimates were slightly higher than that reported in (Cui et al., 2015): 1.09 (95%CI 1.06, 1.11) for 10 μg/m^3 increase in $PM_{2.5}$ and 1.05 (95%CI 1.03, 1.07) for PM_{10}. In the review resulting from the IARC evaluation of carcinogenicity of outdoor air pollution, the estimates were 1.09 (95% CI 1.04, 1.14) and 1.08 (95% CI 1.00, 1.17) associated with 10 μg/m^3 increase in $PM_{2.5}$ and PM_{10} respectively (Hamra et al., 2014). IARC has designated outdoor air pollution and particulate air pollution specifically as a Group 1 human carcinogen (IARC, 2013). Studies investigating lung cancer incidence were not included in the current review.

In general, associations with $PM_{2.5}$ were more consistent than with PM_{10}, particularly for cardiovascular outcomes. PM_{10} is made up of fine ($PM_{2.5}$) and coarse particles. The less consistent association for PM_{10} may reflect the smaller number of studies compared to $PM_{2.5}$ and the lower risk of long-term exposure to coarse particles (Adar et al., 2014; Hoek et al., 2013). We note that we cannot compare the presented effect estimates for $PM_{2.5}$ and PM_{10} as the applied increment of 10 μg/m^3 represents a larger contrast for $PM_{2.5}$ than for PM_{10}.

4.1.2. Heterogeneity of effect estimates

In all meta analyses we observed a moderate to high degree of heterogeneity. This is to be expected given the wide diversity of studies conducted. Heterogeneity is likely due to a combination of differences in methodology, concentration and composition of PM, population, geographical location and time period. We primarily interpret this diversity of populations and methods as support for an association, as it decreases the likelihood that residual confounding explains the associations observed between PM and mortality. Documenting heterogeneity is important for health impact assessment of PM in different countries across the globe.

The exposure assessment methods varied across the studies, from assigned exposure to the nearest monitoring station, to land use regression or dispersion models. Exposures were assigned on very different spatial scales, ranging from residential address to US county. In the risk of bias assessment, we considered all exposure assessment methods appropriate if they had documented validity. However, differences of exposure assessment methodology may affect effect size estimation (Vodonos et al., 2018). For example, in studies characterizing exposure by an area-level value (Nishiwaki et al., 2013; Zhang et al., 2011), only a small number of exposure values were assigned to the population, resulting in difficulties to interpret associations.

The body of evidence includes several very large cohorts of several million subjects based upon administrative registry data, which is new compared to the REVIHAAP assessment (WHO, 2013). These large studies have strong statistical power but often lack individual lifestyle information. Importantly, we found identical RR with wider CI after excluding these studies without individual lifestyle factors. The wider CI is to be expected as the number of subjects in the *meta*-analysis decreased substantially and lowered the statistical power. Confounding may affect RR estimates for $PM_{2.5}$ and PM_{10} in both directions. While risk factors such as smoking, high BMI or low SES affect mortality in the same (adverse) direction, the correlations between these factors and air pollution exposure actually vary across studies. In the Rome cohort study and the Canadian studies (Badaloni et al., 2017; Cakmak et al., 2018), lifestyle tends to be more favorable among the higher exposed subjects living in metropolitan areas, potentially leading to underestimation of air pollution RRs in case of insufficient confounder control. In other studies such as the ESCAPE study (Beelen et al., 2014a), adjustment for confounding reduced air pollution effect estimates. For the entire body of evidence it is therefore not likely that important confounding has occurred.

The body of evidence was based on studies conducted globally, though the majority of studies was from Europe and North America. Differences in geographical location lead to differences in population, concentration and composition of PM. Previous studies have suggested some population groups are more susceptible (Di et al., 2017) and some components are more harmful than others (Vedal et al., 2013). An important observation of our study is that the combined effect estimates were similar across the three WHO regions (Region of the Americas, European Region and Western Pacific Region) where studies have been conducted. This comparison has become possible because of the increase of studies in different regions and addressed concerns about the

applicability of results from in the past primarily North-American studies to assess health risks in Europe and other regions.

4.1.3. Concentration-Response function (CRF) at low pollution levels

As the levels of ambient air pollution have declined significantly over the last few decades in North America, Europe, and in other developed regions, it is important to examine whether associations with adverse health effects continue to be observed at low levels. Two recently published studies indicated that health effects occur well below 12 μg/m^3 (the US-EPA NAAQS exposure level) (Brauer et al., 2019; Dominici et al., 2019). In our review, a *meta*-analysis of studies investigating natural-cause mortality conducted at mean annual average $PM_{2.5}$ levels below 25 μg/m^3 (the EU limit exposure level) yielded a significantly positive RR, very similar to the overall RR estimate from all studies. An analysis of studies conducted at mean annual average $PM_{2.5}$ levels below 10 μg/m^3 (the current WHO guideline exposure level) yielded an even higher RR, coherent with an increasing number of studies showing linear or supra-linear concentration response relationships (Pinault et al., 2016, 2017; Cesaroni et al., 2013; Crouse et al., 2015; Di et al., 2017; Hart et al., 2015; Pope et al., 2002). Monotonically rising concentration response relationships were also reported in individual studies for mortality from other diseases related to long-term exposure to $PM_{2.5}$, including CVD, IHD, stroke, Respiratory disease, COPD and lung cancer (Cesaroni et al., 2013; H. Chen et al., 2016; Crouse et al., 2012; Lepeule et al., 2012; Pinault et al., 2017; Thurston et al., 2016a; Weichenthal et al., 2014). Nonlinear CRFs were sometimes reported with usually wide CIs at both the higher and lower ends of the concentration distribution (Crouse et al., 2012; Gan et al., 2013; Villeneuve et al., 2015). Burnett et al. (2018) has recently reported on an analysis of a large number of cohorts included in the current review and showed a near-linear ensemble curve for natural-cause mortality and $PM_{2.5}$. The study involved analysis using a standardized code allowing non-linear functions applied by local analysts and subsequent combination of the curves. The study also showed near-linear ensemble CRFs for lower respiratory infection, stroke, COPD, lung cancer and IHD associated with long-term exposure to $PM_{2.5}$. While most studies suggested there is little evidence of a threshold for $PM_{2.5}$ and mortality from all causes and specific causes (Di et al., 2017; Lepeule et al., 2012; Pinault et al., 2016; Schwartz et al., 2008), a threshold of 11 μg/m^3 for $PM_{2.5}$ and nonaccidental mortality was reported in (Villeneuve et al., 2015). Studies that evaluated the shape of the CRF for PM_{10} are more limited (Fischer et al., 2015).

4.1.4. Certainty of evidence

We applied an adapted GRADE method to assess certainty in the epidemiological body of evidence. In general, $PM_{2.5}$ was more consistently associated with mortality than PM_{10}, particularly for cardiovascular outcomes. PM_{10} is made up of fine ($PM_{2.5}$) and coarse particles. The less consistent association for PM_{10} may reflect the smaller number of studies compared to $PM_{2.5}$ and the lower risk of long-term exposure to coarse particles (Adar et al., 2014; Hoek et al., 2013).

The assignment of high certainty of evidence to most long-term $PM_{2.5}$ exposure and mortality associations agrees well with recent assessments made by the USEPA using a different methodology (U.S. EPA, 2019). In the 2019 Integrated Science Assessment (ISA), the association between $PM_{2.5}$ and natural mortality was rated as “causal” based on assessment of different scientific disciplines beyond the epidemiological air pollution mortality studies. For long-term PM_{10} exposure and mortality associations, the assessments are generally stronger than the ISA assessments for coarse particles. The 2019 PM ISA evaluated evidence from studies of $PM_{10\text{-}2.5}$ and natural-cause mortality as “suggestive”. The assessment for coarse PM is not directly comparable to PM_{10}, as PM_{10} is the sum of $PM_{2.5}$ and coarse PM. We also rated the evidence for specific causes of death lower for PM_{10} than for $PM_{2.5}$. The high certainty assessment for lung cancer mortality agrees well with the assessment in 2013 by IARC, which designated outdoor air pollution and particulate air pollution specifically as a Group 1 human carcinogen (IARC, 2013).

The biological plausibility of associations between mortality and PM have been identified previously (U.S. EPA, 2019). Inhalation of PM may result in injury, oxidative stress, and inflammation in the respiratory tract and lead to systemic inflammation and oxidative stress. Persistent or intermittent exposure to PM over months to years may lead to cumulative or chronic effects including mortality from respiratory, cardiovascular disease, lung cancer or possibly other diseases.

Application of the adapted GRADE approach was challenging in some domains. Limitations in studies were assessed based on results of the risk of bias assessments. Risk of Bias application is more complex than following a simple checklist and requires careful interpretations to make a proper judgment. The criteria for the confounding domain were clear, but probably a more refined list of confounders would have distinguished studies better. The missing data and exposure contrast subdomains required careful examination as data were not always reported in the epidemiological paper, but occasionally in a companion paper. Change in exposure contrast during follow-up also required additional information to be inspected. Consideration of heterogeneity was complex, as distinguishing differences in magnitude of effect size and differences in direction of effect across studies was needed. Publication bias was difficult to assess as the tools are somewhat problematic for non-continuous outcomes, for a small number of studies and settings with heterogeneity. The imprecision criterium was based upon comparison with a set number of person-years determined with a power calculation. Probably, the evaluation of the *meta*-analytical confidence interval would have been more direct. We did not apply the upgrade procedure for large RR, based upon the suggested evaluation of an E-value. None of these challenges likely has materially affected the overall certainty of evidence assessment.

4.2. New studies published after last search

A number of studies has been published after the date of our final search (October 2018), which is more than a year ago. Table A7.1 lists the new studies including RR estimates. Some of the new evidence is from an update of the included cohorts with longer follow-up or with more advanced methodology, including the National Health Interview Survey cohort (Pope et al., 2018, 2019b) and the National Institutes of Health-AARP Diet and Health Study (Hayes et al., 2019). These new studies are unlikely to change our estimates as the same populations were already included. Some new studies were conducted in the included cohorts with a different focus (Lim et al., 2019; Sun et al., 2019), which would not fulfil the criteria to replace the estimates used in the meta analyses.

Two recently published reports funded by the Health Effect Institute (HEI) suggested health effects of air pollution exist at low levels, even below the current annual U.S. national ambient air quality standard for $PM_{2.5}$ of 12 μg/m^3 (Brauer et al., 2019; Dominici et al., 2019). This is coherent with findings from a number of studies included in the current review. These two reports were conducted in the Medicare cohort and four Canadian cohorts (three CanCHEC and CCHS). Estimates in the Medicare report were identical as previously reported in (Di et al., 2017), which was included in our review. Estimates in the Canadian report were published separately in Christidis et al. (2019) and Pappin et al. (2019). Three of the four Canadian cohorts were included in our review with a shorter follow-up, with exception of the 1996 CanCHEC.

The Dutch Environmental Longitudinal Study (DUELS) and the Korean National Health Insurance Service-based National Sample Cohort were included in the current review with effect estimates reported only for PM_{10} (Fischer et al., 2015; O.J. Kim et al., 2017). In the recent articles derived from these cohorts, health effect estimates associated with $PM_{2.5}$ were reported (Fischer et al., 2020; Kim et al., 2019). However, the Korean cohort only reported $PM_{2.5}$ estimates in a two-pollutant model adjusted for O_3. Evidence was also generated from

new cohorts including the Chinese Longitudinal Healthy Longevity Survey (CLHLS) (Li et al., 2018), the Danish Diet, Cancer and Health cohort (Hvidtfeldt et al., 2019) and the '45 and up study' cohort (Hanigan et al., 2019). Most of these studies have reported positive associations between $PM_{2.5}$ and mortality. Importantly, sensitivity analysis including this new evidence did not change our combined estimates. The summary RR for $PM_{2.5}$ and natural mortality was 1.08 (95%CI 1.07, 1.10) after including 5 new studies (Figure A7.43). The body of evidence is already based on a large number of well conducted studies without a large weight from a single study, therefore including new evidence is unlikely to change the combined effect estimate materially.

4.3. Strengths and limitations

A strength of our study is the efforts made throughout the design and the conduct of the systematic review to ensure its validity, including the incorporation of risk of bias assessment. Another strength is the large number of studies included in our systematic review, with the diversity of populations. This decreases the likelihood that residual confounding explains the associations observed between PM and mortality.

This systematic review has a number of limitations. First, we acknowledge that our search strategy had limitations. The use of "NOT" operators in our search strategy and inclusion of study design might lead to missing relevant evidence. However, we also scanned references of identified reviews to identify papers that were potentially missed by our search strategy. Compared to a very recent review article (Pope et al., 2019a), our systematic search only missed two studies published in the search period – one from a cohort we already included in our review (Wong et al., 2016), one from a patient group (Goss et al., 2004). We therefore think that the risk of missing key papers was small. Second, we found that relatively few studies were performed in low- and middle-income countries (LMICs) which typically experience higher air pollution levels than observed in the countries where the majority of cohort studies have been performed (Burns et al., 2019). Therefore, uncertainty about the shape of the CRF remains especially for the high end of the concentration distribution. To support health impact assessment in LMICs and global burden of disease assessment, new studies in LMICs are needed. Third, the review focused on $PM_{2.5}$ and PM_{10} without assessing particle composition. As most included studies have been conducted in areas with combustion as the main source of (primary and secondary) particles, it is not clear whether the risk estimates can be applied in settings where other sources are dominant such as desert dust (Kotsyfakis et al., 2019; Naidja et al., 2018). More research investigating which components/sources are most responsible for health effects is needed. Fourth, in a *meta*-analysis of published studies, we had limited possibilities to assess the shape of the CRF.

4.4. Implications

Results of this and other systematic reviews commissioned by WHO are currently being used in developing new air quality guidelines by WHO. Our results suggest that $PM_{2.5}$ is associated with increased risk for mortality, even below the current WHO guideline exposure level of 10 $\mu g/m^3$. If a threshold is present, it is at very low levels. These results suggest an update of the current guideline needs to be considered by WHO. An update of the PM_{10} guideline needs to be considered as well.

The large heterogeneity of effect estimates across studies suggests that health impact assessment in specific locations may have fairly large uncertainty. The full body of evidence should be used with caution in regions where no or few studies have been conducted such as the African Region, South-East Asia Region, and Eastern Mediterranean Region. Particularly in areas where dust contributes significantly to overall $PM_{2.5}$ levels, our combined RRs may not apply. Also, as the summary RR estimates were derived assuming a linear relationship, application of this relationship in e.g. burden of disease assessments may be problematic when evaluating settings with very high concentrations such as in polluted regions of Asia (Pant et al., 2016).

5. Conclusions

The evidence base has increased substantially compared to the previous global WHO evaluation, however studies conducted in low- and middle-income countries (LMICs) are still scarce. There is clear evidence that both $PM_{2.5}$ and PM_{10} are associated with increased mortality from all causes, cardiovascular disease, respiratory disease and lung cancer. The combined HRs for natural-cause mortality are 1.08 (95%CI:1.06, 1.09) per 10 $\mu g/m^3$ increase in $PM_{2.5}$, and 1.04 (95%CI:1.03, 1.06) per 10 $\mu g/m^3$ increase in PM_{10}. The associations with $PM_{2.5}$ remained below the current WHO annual average guideline exposure level of 10 $\mu g/m^3$.

Declaration of Competing Interest

None.

Acknowledgements

This systematic review has been funded by the World Health Organization Regional Office for Europe, supported by the European Commission (DG Environment), Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (Germany), Federal Ministry of Health (Germany), Government of the Republic of Korea, Federal Office for the Environment (Switzerland) and United States Environmental Protection Agency, and delivered as part of the evidence base that informs the ongoing development of WHO global air quality guidelines. All rights in the work, including ownership of the original work and copyright thereof, are vested in WHO. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or the stated policy of the World Health Organization. We thank Jos Verbeek, Rebecca Morgan (methodologists), Román Pérez-Velasco, Hanna Yang, Dorota Jarosinska (WHO Secretariat), the rest of the Systematic Review Team and the Guideline Development Group for their contributions to the conduct of the systematic review.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105974.

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