Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Long-Term $PM_{2.5}$ Exposure and Risks of Ischemic Heart Disease and Stroke Events: Review and Meta-Analysis

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BACKGROUND: Fine particulate matter <2.5 μm in diameter ($PM_{2.5}$) has known effects on cardiovascular morbidity and mortality. However, no study has quantified and compared the risks of incident myocardial infarction, incident stroke, ischemic heart disease (IHD) mortality, and cerebrovascular mortality in relation to long-term $PM_{2.5}$ exposure.

METHODS AND RESULTS: We sought to quantitatively summarize studies of long-term $PM_{2.5}$ exposure and risk of IHD and stroke events by conducting a review and meta-analysis of studies published by December 31, 2019. The main outcomes were myocardial infarction, stroke, IHD mortality, and cerebrovascular mortality. Random effects meta-analyses were used to estimate the combined risk of each outcome among studies. We reviewed 69 studies and included 42 studies in the meta-analyses. In meta-analyses, we found that a 10-μg/m^3 increase in long-term $PM_{2.5}$ exposure was associated with an increased risk of 23% for IHD mortality (95% CI, 15%–31%), 24% for cerebrovascular mortality (95% CI, 13%–36%), 13% for incident stroke (95% CI, 11%–15%), and 8% for incident myocardial infarction (95% CI, –1% to 18%). There were an insufficient number of studies of recurrent stroke and recurrent myocardial infarction to conduct meta-analyses.

CONCLUSIONS: Long-term $PM_{2.5}$ exposure is associated with increased risks of IHD mortality, cerebrovascular mortality, and incident stroke. The relationship with incident myocardial infarction is suggestive of increased risk but not conclusive. More research is needed to understand the relationship with recurrent events.

Key Words: air pollution ■ cardiovascular ■ long-term ■ mortality ■ particulate matter

There is substantial evidence that exposure to fine particulate matter <2.5 μm in diameter ($PM_{2.5}$) increases the risk of cardiovascular events and death, as concluded by the American Heart Association (AHA) scientific statement on particulate matter air pollution and cardiovascular disease in 2010.[1] Moreover, that report also concluded that long-term exposures (eg, ≥1 year) posed an even greater risk to cardiovascular mortality than short-term exposures (eg, a few days).[1] While a number of different cardiovascular disease (CVD) event end points have been studied in relation to long-term $PM_{2.5}$ exposure, there are few quantitative summaries available that synthesize and compare the magnitudes of these effects.

Early studies of long-term $PM_{2.5}$ exposure examined all-cause mortality, lung cancer mortality, and cardiopulmonary mortality.[2] Subsequent studies of mortality end points have focused on cardiovascular mortality specifically[3–5] and subtypes such as ischemic heart disease (IHD) mortality[6] and stroke mortality.[7] While many studies have focused exclusively on mortality end points, some studies have examined incident cardiovascular events[8–10] or recurrent events among populations with preexisting CVD.[11,12] However, many studies of long-term $PM_{2.5}$ exposure and cardiovascular end points have published null or inconsistent findings,[8,13–19] which is a key reason to conduct a review and meta-analysis.

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.016890

For Sources of Funding and Disclosures, see page 18.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Evidence among 69 studies shows a clear relationship between long-term particulate air pollution exposure and increased risk of cardiovascular events.
- The largest risks were found for ischemic heart disease mortality and cerebrovascular mortality.
- The association with incident myocardial infarction was suggestive of increased risk but not conclusive.

What Are the Clinical Implications?

- Particulate air pollution exposure is a modifiable risk factor for cardiovascular events and should be considered along with other lifestyle and behavioral risk factors.
- Populations at high risk for cardiovascular disease may be recommended to change behaviors to reduce personal exposure to particulate air pollution.

Nonstandard Abbreviations and Acronyms

AHA	American Heart Association
IHD	ischemic heart disease
$PM_{2.5}$	fine particulate matter <2.5 μm in diameter
REGARDS	Reasons for Geographic and Racial Differences in Stroke

Many studies have been published in the past decade, making a recent review important for understanding the current evidence. Furthermore, early studies of long-term $PM_{2.5}$ exposure focused more on the United States and Europe,[13,20–24] whereas in the past decade more studies have been published in other regions including China, Taiwan, Korea, Israel, Canada, and Australia.[7,12,14,19,25–41] There may also be differences in how cardiovascular end points are defined, such as using self-reported outcomes, medical records, death certificate data, or different combinations of *International Classification of Diseases* (*ICD*) codes. While previous reviews have synthesized the overall evidence of $PM_{2.5}$ and reviewed plausible mechanisms,[1,42,43] there is no recent quantitative meta-analysis that compares the risks of IHD mortality, cerebrovascular mortality, incident stroke, and incident myocardial infarction in relation to long-term $PM_{2.5}$ exposure. Without this quantitative summary and comparison between CVD event types, it is difficult to determine which of these particular cardiovascular events have the greatest risk in relation to long-term $PM_{2.5}$ exposure. Furthermore, this information will help guide future studies needed to address research gaps.

We sought to quantitatively summarize the studies of long-term $PM_{2.5}$ exposure and risk of IHD and stroke events, including incident acute myocardial infarction (AMI), recurrent AMI, IHD mortality, incident stroke, recurrent stroke, and cerebrovascular mortality via meta-analyses. This quantitative summary yields insight into which cardiovascular end points have the strongest associations in relation to long-term $PM_{2.5}$ exposure. Secondary objectives were to determine the consistency of the definitions used for the event end points and to identify gaps in the current knowledge.

METHODS

The authors declare that all supporting data are available within the article and its supplementary files.

Search Process

To identify publications of long-term ambient $PM_{2.5}$ exposure and IHD and stroke events, SEA conducted a search of the National Library of Medicine's MEDLINE database through December 31, 2019, using PubMed.[44] Search terms included "air pollution," "particulate matter," "cohort," "long-term," "annual," "cardiovascular," "CVD," and "mortality." X.L. independently reviewed the reference lists of several previous review articles[1,45,46] and identified relevant publications. Our inclusion criteria required articles to be peer-reviewed, original, and empirical articles published in English.

Ischemic Heart Disease and Stroke Events

We restricted our review to studies of incident AMI, recurrent AMI, IHD mortality, incident stroke, recurrent stroke, and cerebrovascular mortality. In a supplementary analysis, we also provided an updated meta-analysis of overall cardiovascular mortality. This review does not include more general mortality end points such as all-cause mortality, natural-cause mortality, cardiometabolic mortality (combining cardiovascular and diabetes mellitus mortality), or cardiopulmonary mortality (combining cardiovascular and lung disease mortality).

Statistical Analysis

We conducted a meta-analysis for all outcomes that were analyzed in at least 4 studies. For sensitivity analyses examining subgroups of the main outcomes, we only required 3 studies to conduct meta-analyses. When multiple studies examined the same outcome

using the same cohort, we included only 1 study per cohort. We selected the largest study with the most years of follow-up and the most recent air pollution estimates that reported the association for the main effect of long-term average $PM_{2.5}$ exposure (ie, not an interaction effect, effect modification, or an association of $PM_{2.5}$ components). All study effect estimates were converted to represent a change of 10 μg/m^3. We quantified heterogeneity by the I^2 statistic[47] and random effects meta-analysis was used to account for heterogeneity.[48] We assessed outliers and publication bias using funnel plots. We also used the Newcastle-Ottawa Scale for cohort studies to assess the risk of bias for individual studies.[49] For studies that were extreme outliers, we computed the meta-analysis twice, where the primary meta-analysis excluded the extreme outlier study and the secondary meta-analysis included the extreme outlier in order to understand the sensitivity of the results on the extreme outlier study.

RESULTS

Articles Identified

Article identification is summarized using the PRISMA flow diagram (Figure S1). The MEDLINE database search using PubMed resulted in 2138 potentially relevant publications. X.L. independently identified 29 relevant publications from reference lists of previously published review articles.[1,45,46] After record screening, 165 full-text articles were assessed for eligibility. Our final list included 69 studies that examined the relationship between long-term $PM_{2.5}$ exposure and incident AMI, recurrent AMI, IHD mortality, incident stroke, recurrent stroke, and/or cerebrovascular mortality among 37 unique cohorts or consortia. These cohorts or consortia represented different international populations: United States (14 cohorts), Europe (9 cohorts and 1 consortia of cohorts), Asia (6 cohorts), Canada (6 cohorts), and Australia (1 cohort). The year of publication of the identified articles is illustrated in Figure S2. Notably, 62 of these 69 studies (90%) have been published in the past decade, after the 2010 AHA scientific statement on $PM_{2.5}$ exposure and CVD risk.

Cardiovascular Event End Points

Our first objective was to determine which of the cardiovascular event end points have been studied the most. We found that IHD mortality was the most frequently studied cardiovascular end point (45 studies), followed by cerebrovascular mortality (27 studies), stroke (23 studies; includes incident and recurrent events), and AMI (20 studies; includes incident and recurrent events).

Study Characteristics

The Table presents characteristics of the 69 studies[4,8,10–36,38–40,50–80] examining the association between long-term $PM_{2.5}$ exposure and CVD events. All studies appropriately controlled for basic demographics such as age and sex, and most studies accounted for race and calendar time such as year of study enrollment. Nearly all studies controlled for socioeconomic status (SES) and many studies also included marital status. Education and income were the most common SES variables used and were measured on individual or neighborhood levels depending on data availability in studies. Numerous studies controlled for variables related to health and lifestyle, including body mass index, smoking, alcohol consumption, diet, and relevant comorbidities such as diabetes mellitus, hypertension, and hyperlipidemia. Additionally, some studies controlled for personal or family history of risk factors and diseases (history of myocardial infarction, stroke, or coronary heart disease), medication use (blood pressure medication, statins, or aspirin), or revascularization procedures (percutaneous coronary intervention or coronary artery bypass grafting).

IHD Mortality

IHD mortality was the most studied outcome, analyzed in 45 studies among 24 cohorts.* Nearly all studies (37 of 45) defined IHD deaths by the same set of *ICD* codes (*ICD, Ninth Revision* [*ICD-9*]: 410–414; *ICD, Tenth Revision* [*ICD-10*]: I20–I25) with data on death obtained from a national database of death records (Table). Some studies obtained data on deaths from medical records, proxy reports, and/or church records often with death certificate review by a certified nosologist or physician adjudicator. One study described these IHD deaths as "coronary heart disease deaths," defined by the same set of *ICD* codes.[39] Two studies used a slightly broader definition of IHD mortality: 1 study added deaths caused by "CVD unspecified" (*ICD-9*: 429.2) and 1 study added deaths caused by "certain sequelae of myocardial infarction not elsewhere classified" (*ICD-9*: 429.7).[14,19] Last, 3 studies used narrower definitions, with 1 study[56] excluding causes of death from "angina pectoris" and "other forms of chronic ischemic heart disease" (*ICD-9*: 413–414, *ICD-10*: I23–I25), 1 study[6] defining IHD deaths using a code only for "chronic ischemic heart disease" (*ICD-10*: I25), and another study[60] only defining death from myocardial infarction (*ICD-10*: I21–I22).

Funnel plots indicated no extreme outlier studies and no evidence of publication bias for IHD mortality (Figure S3). Figure 1 illustrates the meta-analysis of

*References 4, 6, 7, 13–24, 26–30, 34, 35, 37, 39–41, 51, 53, 56, 58–60, 63–65, 67–70, 72–74, 76, 79, 80

Table. Characteristics of 69 Studies Examining the Association Between Long-Term $PM_{2.5}$ Exposure and CVD Events

First Author and Year	Cohort	Total Participants	Study Region	Follow-Up Period	Covariates Adjusted for	Outcome Event (no. of Cases)	*ICD-9* and *ICD-10* Codes	Source of Outcome Data
Atkinson 2013[8]	CPRD	836 557	England	2003–2007	Age, sex, comorbidities,* BMI, smoking, SES†	Incident AMI (n=13 956), incident stroke (n=13 012)	AMI: *ICD-10*: I21-I23 Stroke: *ICD-10*: I61, I63	Incident: national database and medical records
Badaloni 2017[53]	RoLS	1.2 million	Italy	2001–2010	Age, sex, calendar time, marital status, SES,† other covariates‡	IHD mortality (n=22 234)	IHD: *ICD-9*: 410–414	Mortality: national database
Bai 2019[25]	ONPHEC	5.1 million	Canada	2001–2015	Age, sex, education, income, SES,† other covariates‡	Incident AMI (n=197 628)	AMI: *ICD:9*: 410; *ICD-10*: I21	Incident: national database and medical records
Beelen 2014[16]	ESCAPE	367 383	Europe	Varies by cohort 1985–2004	Age, sex, calendar time, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=4992), cerebrovascular mortality (n=2484)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25 Cerebrovascular: *ICD-9*: 430–438; *ICD-10*: I60–I69	Mortality: national database
Cakmak 2016[26]	CanCHEC	2.4 million	Canada	1991–2006	Age, sex, race, marital status, SES†	IHD mortality (n=57 310), cerebrovascular mortality (n=17 565)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25 Cerebrovascular: *ICD-9*: 430–438; *ICD-10:* I60–I69	Mortality: national database
Cakmak 2018[27]	CanCHEC	2.3 million	Canada	1991–2011	Age, sex, race, marital status, SES†	IHD mortality (n=NL)	IHD: *ICD-9:* 410–414; *ICD-10:* I20–I25	Mortality: national database
Carey 2013[15]	CPRD	835 607	England	2003–2007	Age, sex, BMI, smoking, SES†	IHD mortality (n=8168), cerebrovascular mortality (n=5458)	IHD*: ICD-10*: I20–I25 Cerebrovascular: *ICD-10*: I61, I63	Mortality: national database
Carey 2016[50]	CPRD	211 016	England	2005–2011	Age, sex, BMI, smoking, SES†	Incident AMI (n=2582), incident stroke (n=3716)	AMI: *ICD-10*: I21–I23 Stroke: *ICD-10*: I61, I63	Incident: medical records
Cesaroni 2013[51]	RoLS	1.3 million	Italy	2001–2010	Age, sex, marital status, SES,† other covariates‡	IHD mortality (n=22 562), cerebrovascular mortality (n=13 576)	IHD: *ICD-9*: 410–414 Cerebrovascular: *ICD-9*: 430–438	Mortality: national database
Cesaroni 2014[54]	ESCAPE	100 166	Europe	1997–2007	Age, sex, calendar time, smoking, marital status, SES†	Incident AMI (n=5157)	AMI: *ICD-9*: 410, 411; *ICD-10*: I21, I23, I20.0, I24	Incident: national database and medical records
Chen 2005[13]	AHSMOG	3239	United States	1977–1998	Age, sex, calendar time, BMI, smoking, diet,§ SES†	IHD mortality (n=250)	IHD: *ICD-9*: 410–414	Mortality: national database and other sources‖
Chen 2016[28]	EFFECT	8873	Canada	1999–2011	Age, sex, family history,¶ comorbidities,* smoking, CVD history,¶ revascularization, medications, marital status, SES,† other covariates‡	IHD mortality (n=1650)	IHD: *ICD-9*: 410–414	Mortality: national database
Chi 2016[52]	WHI study	51 754	United States	1993–2005	Age, race, comorbidities,* BMI, smoking, SES†	Incident AMI (n=NL), incident stroke (n=NL)	NL	Incident: national database, medical records, and other sources‖
Crichton 2016[55]	SLSR	357 308	England	2005–2012	Age, sex, SES†	Incident stroke (n=1800)	NL	Incident: medical records

(*Continued*)

Table. Continued

First Author and Year	Cohort	Total Participants	Study Region	Follow-Up Period	Covariates Adjusted for	Outcome Event (no. of Cases)	*ICD-9* and *ICD-10* Codes	Source of Outcome Data
Crouse 2012[29]	CanCHEC	2.1 million	Canada	1991–2001	Age, sex, race, marital status, SES,† other covariates‡	IHD mortality (n=43 400), cerebrovascular mortality (n=13 300)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25 Cerebrovascular: *ICD-9*: 430–434, 436–438; *ICD-10*: I60–I69	Mortality: national database
Crouse 2015[30]	CanCHEC	2.5 million	Canada	1991–2006	Age, sex, race, marital status, SES†	IHD mortality (n=63 050), cerebrovascular mortality (n=19 725)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25 Cerebrovascular: *ICD-9*: 430–438; *ICD-10*: I60–I69	Mortality: national database
Danesh Yazdi 2019[61]	Medicare beneficiaries	11.1 million	United States	2000–2012	Age, sex, race, calendar time, SES,† other covariates‡	Incident AMI (n=570 668), incident stroke (n=991 077)	Stroke: *ICD-9*: 430–438 AMI: *ICD-9*: 410	Incident: national database and medical records
Dirgawati 2019[31]	HIMS	10 126	Australia	1996–2012	Age, comorbidities,* BMI, smoking, SES†	Cerebrovascular mortality (n=325); incident stroke (n=1453)	Cerebrovascular: *ICD-9*: 430–431, 433, 434.x1, 435–436; *ICD-10*: I60–I61, I63–I64, I66, I69 Stroke: *ICD-9*: 430–431, 433. x1, 434. x1, 436; *ICD-10*: I60–I61, I63–I64	Mortality: national database Incident: medical records
Gan 2011[19]	Residents in Vancouver	452 735	Canada	1999–2002	Age, sex, comorbidities*, SES†	IHD mortality (n=3104)	IHD: *ICD-9*: 410–414, 429.2; *ICD-10*: I20–I25	Mortality: national database
Gandini 2018[62]	ILS	74 989	Italy	1999–2008	Age, sex, BMI, smoking, physical activity, marital status, SES,† other covariates‡	Incident AMI (n=NL), incident stroke (n=1505)	AMI: *ICD-9*: 410 Stroke: NL	Incident: national database and medical records
Hart 2011[18]	Trucking industry men	53 814	United States	1985–2000	Age, race, calendar time, other covariates‡	IHD mortality (n=1109)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25	Mortality: national database
Hart 2015[56]	Nurses' Health Study	114 537	United States	1989–2006	Age, race, calendar time, family history,¶ comorbidities,* BMI, smoking, marital status, SES,† other covariates‡	Incident IHD (n=3878), incident stroke (n=3295)	AMI: *ICD-9*: 410–412; *ICD-10*: I21–I22 Stroke: NL	Mortality: national database and other sources‖ Incident: medical records and other sources§
Hartiala 2016[57]	Cleveland Clinic GeneBank study	6575	United States	2001–2010	Age, sex, smoking, SES†	Nonfatal AMI (n=5854), nonfatal stroke (n=5875)	NL	Incident: medical records and other sources‖
Hayes 2020[59]	NIH-AARP	565 477	United States	1995–2011	Age, sex, race, BMI, smoking, alcohol, marital status, SES,† other covariates‡	IHD mortality (n=23 328), cerebrovascular mortality (n=5894)	IHD: *ICD-10:* I20–I25 Cerebrovascular: *ICD-10:* I60–I69	Mortality: national database
Heritier 2019[60]	SNC	4.4 million	Switzerland	2000–2008	Age, sex, race, marital status, SES†	AMI mortality (n=19 261)	AMI: *ICD-10*: I21–I22	Mortality: national database

(*Continued*)

Table. Continued

First Author and Year	Cohort	Total Participants	Study Region	Follow-Up Period	Covariates Adjusted for	Outcome Event (no. of Cases)	*ICD-9* and *ICD-10* Codes	Source of Outcome Data
Hoffmann 2015[58]	RECALL (part of ESCAPE)	4433	Germany	2000–2012	Age, sex, calendar time, BMI, smoking, alcohol, physical activity, marital status, SES†	IHD mortality (n=135); incident stroke (n=71)	IHD: *ICD-10*: I20–I25 Stroke: *ICD-10*: I61, I63	Mortality: national database and other sources‖
Huang 2019[32]	China-PAR	117 575	China	2000–2015	Age, sex, comorbidities,* BMI, smoking, alcohol, physical activity, SES,† other covariates‡	Incident stroke (n=3540)	Incident stroke: *ICD-10:* I60–I69	Incident: other sources‖
Jerrett 2005[20]	American Cancer Society CPS-II	22 905	United States	1982–2000	Age, sex, race, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=1462)	IHD: *ICD-9*: 410–414	Mortality: national database after 1989 and other sources‖ before 1989
Jerrett 2013[63]	American Cancer Society CPS-II	73 711	United States	1982–2000	Age, sex, race, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=4540), cerebrovascular mortality (n=3068)	NL	Mortality: national database after 1989 and other sources‖ before 1989
Jerrett 2017[64]	American Cancer Society CPS-II	668 629	United States	1982–2004	Age, sex, race, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=45 624)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25	Mortality: national database after 1989 and other sources‖ before 1989
Kim 2017[33]	NHIS-NSC	136 094	Korea	2007–2013	Age, sex, comorbidities,* BMI, SES,† other covariates‡	Incident AMI (n=354), incident stroke (n=934)	AMI: *ICD-10*: I21–I23 Stroke: *ICD-10*: I60–I63	Incident: national database and medical records
Koton 2013[12]	Israel Study of First Acute Myocardial Infarction	1120	Israel	1992–2011	Age, sex, comorbidities,* BMI, smoking, physical activity, CVD history,¶ revascularization, SES,† other covariates‡	Recurrent AMI (n=341), stroke hospitalizations (n=160)	NL	Recurrent and hospitalizations: medical records and other sources‖
Lim 2019[69]	NIH-AARP	548 845	United States	1995–2011	Age, sex, race, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=22 329), cerebrovascular mortality (n=5592)	IHD: *ICD-9:* 410–414; *ICD-10:* I20–I25 Cerebrovascular: *ICD-9*: 430–438; *ICD-10:* I60–I69	Mortality: national database
Lipsett 2011[65]	CTS	73 489	United States	1999–2005	Age, race, family history,¶ BMI, smoking, alcohol, diet,§ physical activity, medications,# marital status, SES,† other covariates‡	IHD mortality (n=773), cerebrovascular mortality (n=382); incident AMI (n=722), incident stroke (n=969)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25 Cerebrovascular: *ICD-9*: 430–438; *ICD-10:* I60–I69 AMI*: ICD-9*: 410; *ICD-10*: I21 Stroke*: ICD-9*: 431–434, 436; *ICD-10*: I61–I64	Mortality: national database Incident: national database, medical records, or other sources‖
Ljungman 2019[71]	Swedish cohorts (includes the Primary Prevention Study (PPS) and the Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (GOT-MONICA))	114 758	Sweden	1990–2011	Age, sex, calendar time, smoking, alcohol, physical activity, marital status, SES†	Incident AMI (n=5166), incident stroke (n=3119)	AMI: *ICD-9*: 410–414; *ICD-10*: I20–25 Stroke: *ICD-9*: 431–436; *ICD-10*: I61–I65	Incident: national database and medical records

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Table. Continued

First Author and Year	Cohort	Total Participants	Study Region	Follow-Up Period	Covariates Adjusted for	Outcome Event (no. of Cases)	*ICD-9* and *ICD-10* Codes	Source of Outcome Data
Loop 2018[70]	REGARDS	17 126	United States	2003–2012	Age, sex, race, calendar time, comorbidities,* BMI, smoking, alcohol, physical activity, medications,# SES,† other covariates‡	IHD mortality (n=215); nonfatal AMI (n=413)	NL	Mortality: national database and other sources‖ Incident: medical records and other sources‖
Madrigano 2013[66]	Worcester Heart Attack Study	4467	United States	1995–2003	Age, sex, SES,† other covariates‡	Incident AMI (n=4467)	NL	Incident: medical records
Miller 2007[21]	WHI study	65 893	United States	1994–2003	Age, race, comorbidities,* BMI, smoking, SES,† other covariates‡	IHD mortality (n=139), cerebrovascular mortality (n=122); incident AMI (n=584), incident stroke (n=554)	IHD: NL Cerebrovascular: NL AMI: *ICD-9*: 410 Stroke: *ICD-9*: 430–434, 436.0	Mortality: national database and other sources‖ Incident: national database and other sources‖
Ostro 2010[67]	CTS	44 847	United States	2002–2007	Age, race, family history,¶ BMI, smoking, alcohol, diet,§ physical activity, medications,# marital status, SES,† other covariates‡	IHD mortality (n=474)	IHD: *ICD-10*: I20–I25	Mortality: national database
Ostro 2015[68]	CTS	101 884	United States	2001–2007	Age, race, family history,¶ BMI, smoking, alcohol, diet,§ physical activity, medications,# marital status, other covariates‡	IHD mortality (n=1085)	IHD: *ICD-10*: I20–I25	Mortality: national database
Parker 2018[74]	NHIS	657 238	United States	1997–2011	Age, sex, race, calendar time, marital status, SES,† other covariates‡	IHD mortality (n=NL), cerebrovascular mortality (n=NL)	IHD: NL Cerebrovascular: *ICD-10*: I60–I69	Mortality: national database
Pinault 2016[34]	CCHS	299 500	Canada	2000–2011	Age, sex, race, BMI, smoking, alcohol, diet,§ marital status, SES†	IHD mortality (n=4700), cerebrovascular mortality (n=1500)	IHD*: ICD-10:* I20–I25 Cerebrovascular: *ICD-10*: I60–I69	Mortality: national database
Pinault 2017[35]	CanCHEC	2.4 million	Canada	2001–2011	Age, sex, race, marital status, SES,† other covariates‡	IHD mortality (n=40 400), cerebrovascular mortality (n=13 300)	IHD: *ICD-10*: I20–I25 Cerebrovascular: *ICD-10*: I60–I69	Mortality: national database
Pope 2004[22]	American Cancer Society CPS-II	500 000	United States	1982–1998	Age, sex, race, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=26 663), cerebrovascular mortality (n=7650)	IHD: *ICD-9*: 410–414	Mortality: national database after 1989 and other sources‖ before 1989
Pope 2009[23]	American Cancer Society CPS-II	500 000	United States	1982–1988	Age, sex, race, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=NL)	IHD: *ICD-9*: 410–414	Mortality: national database after 1989 and other sources‖ before 1989
Pope 2011[73]	American Cancer Society CPS-II	794 784	United States	1982–1988	Age, sex, race, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=11 607)	IHD: *ICD-9*: 410–414	Mortality: national database after 1989 and other sources‖ before 1989

(*Continued*)

Table. Continued

First Author and Year	Cohort	Total Participants	Study Region	Follow-Up Period	Covariates Adjusted for	Outcome Event (no. of Cases)	*ICD-9* and *ICD-10* Codes	Source of Outcome Data
Pope 2015[72]	American Cancer Society CPS-II	669 046	United States	1982–2004	Age, sex, race, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=45 644), cerebrovascular mortality (n=17 085)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25	Mortality: national database after 1989 and other sources‖ before 1989
Pope 2019[75]	NHIS	635 539	United States	1986–2015	Age, sex, race, calendar time, BMI, smoking, marital status, SES,† other covariates‡	Cerebrovascular mortality (n=6297)	Cerebrovascular: *ICD-10*: I60–I69	Mortality: national database
Puett 2009[24]	Nurses' Health Study	66 250	United States	1992–2002	Age, calendar time, family history,¶ comorbidities,* BMI, smoking, physical activity, SES,† other covariates‡	IHD mortality (n=379), nonfatal AMI (n=854)	NL	Mortality: national database and other sources‖ Incident: medical records and other sources‖
Puett 2011[17]	HPFS	17 545	United States	1989–2003	Age, calendar time, family history,¶ comorbidities,* BMI, smoking, alcohol, diet,§ physical activity, other covariates‡	IHD mortality (n=746); nonfatal stroke (n=300), nonfatal AMI (n=646)	NL	Mortality: national database and other sources‖ Incident: medical records and other sources‖
Pun 2017[76]	Medicare beneficiaries	18.9 million	United States	2000–2008	Age, sex, race, calendar time, SES,† other covariates‡	IHD mortality (n=890 806), cerebrovascular mortality (293 786)	IHD: *ICD-10*: I20–I25 Cerebrovascular: *ICD-10*: I60–I69	Mortality: national database
Qiu 2017[36]	Elderly Health Centre of the Department of Health	61 447	China	1998–2012	Age, sex, BMI, smoking, alcohol, physical activity, medications,# SES,† other covariates‡	Incident stroke (n=6733)	Stroke: *ICD-9:* 430–436	Incident: medical records
Shin 2014[78]	CanCHEC	2.1 million	Canada	1991–2001	Age, sex, race, marital status, SES,† other covariates‡	IHD mortality (n=NL)	NL	Mortality: national database
Shin 2019[38]	ONPHEC	5.1 million	Canada	2001–2015	Age, sex, SES,† other covariates‡	Incident stroke (n=122 545)	Incident stroke: *ICD-9*: 430–431, 434, 436; *ICD-10*: I60–I61, I63.x (excluding I63.6), I64	Incident: national database and medical records
Stafoggia 2014[10]	ESCAPE	99 446	Europe	1992–2010	Age, sex, calendar time, smoking, marital status, SES†	Incident stroke (n=3086)	NL	Incident: national database, medical records, other sources‖
Stockfelt 2017[77]	PPS Sweden	5850	Sweden	1990–2011	Age, calendar time, smoking, physical activity, marital status, SES†	Incident stroke (n=1139)	Stroke: *ICD-9*: 431–436; *ICD-10*: I61–I65	Incident: national database and medical records

(*Continued*)

Table. Continued

First Author and Year	Cohort	Total Participants	Study Region	Follow-Up Period	Covariates Adjusted for	Outcome Event (no. of Cases)	*ICD-9* and *ICD-10* Codes	Source of Outcome Data
Stockfelt 2017[77]	GOT-MONICA	4500	Sweden	1990–2011	Age, sex, calendar time, smoking, physical activity, marital status, SES†	Incident stroke (n=252)	Stroke: *ICD-9*: 431–436; *ICD-10*: I61–I65	Incident: national database and medical records
Thurston 2016[4]	American Cancer Society CPS-II	445 860	United States	1982–2004	Age, sex, race, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=34 408)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25	Mortality: national database after 1989 and other sources‖ before 1989
Tonne 2016[11]	MINAP	18 138	London	2003–2010	Age, sex, calendar time, CVD history,¶ revascularization, SES,† other covariates‡	Recurrent AMI (n=390)	NL	Recurrent: national database and medical records
Tseng 2015[14]	Civil servants	43 227	Taiwan	1992–2008	Age, sex, BMI, smoking, alcohol, marital status, SES†	IHD mortality (n=139), cerebrovascular mortality (n=141)	IHD: *ICD-9*: 410–414, 429.2, 429.7; *ICD-10*: I20–I25 Cerebrovascular: *ICD-9*: 430–438; *ICD-10*: I60–I69	Mortality: national database
Turner 2016[80]	American Cancer Society CPS-II	669 046	United States	1982–2004	Age, sex, race, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=45 644), cerebrovascular mortality (n=17 085)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25 Cerebrovascular: *ICD-9*: 430–438; *ICD-10*: I60–I69	Mortality: national database after 1989 and other sources‖ before 1989
Turner 2017[79]	American Cancer Society CPS-II	429 406	United States	1982–2004	Age, sex, race, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=13 478), cerebrovascular mortality (n=5582)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25 Cerebrovascular: *ICD-9*: 430–438; *ICD-10*: I60–I69	Mortality: national database after 1989 and other sources‖ before 1989
Villeneuve 2015[39]	CNBSS	89 248	Canada	1980–2005	Age, calendar time, BMI, smoking, marital status, SES†	IHD mortality (n=903), cerebrovascular mortality (n=434)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25 Cerebrovascular: *ICD-9*: 430–438; *ICD-10*: I60–I69	Mortality: national database
Weichenthal 2014[6]	AHS	83 378	United States	1993–2009	Age, sex, calendar time, BMI, smoking, alcohol, diet,§ marital status, SES,† other covariates‡	IHD mortality (n=213), cerebrovascular mortality (n=242)	IHD: *ICD-10*: I25 Cerebrovascular: *ICD-10*: I60–I69	Mortality: national database
Weichenthal 2016[40]	CanCHEC	193 300	Canada	1991–2009	Age, sex, race, marital status, SES†	IHD mortality (n=8600)	IHD: *ICD-9*: 410–414; *ICD-10*: I20–I25	Mortality: national database
Wolf 2015[9]	ESCAPE	100 166	Europe	1992–2007	Age, sex, calendar time, smoking, marital status, SES†	Incident AMI (n=5157)	AMI: *ICD-9*: 410–411; *ICD-10*: I20.0, I21, I23–I24	Incident: national database and medical records
Wong 2015[41]	Elderly Health Centre of the Department of Health	66 820	China	1998–2011	Age, sex, BMI, smoking, physical activity, SES,† other covariates‡	IHD mortality (n=1810), cerebrovascular mortality (n=1621)	IHD: *ICD-10*: I20–I25 Cerebrovascular: *ICD-10:* I60–I69	Mortality: national database

(*Continued*)

Table. Continued

First Author and Year	Cohort	Total Participants	Study Region	Follow-Up Period	Covariates Adjusted for	Outcome Event (no. of Cases)	*ICD-9* and *ICD-10* Codes	Source of Outcome Data
Yin 2017[7]	Chinese men	189 793	China	1990–2006	Age, BMI, smoking, alcohol, diet,[§] marital status, SES,[†] other covariates[‡]	IHD mortality (n=3752), cerebrovascular mortality (n=11 301)	IHD: *ICD-9*: 410–414 Cerebrovascular: *ICD-9*: 431–438	Mortality: national database
Yitshak-Sade 2018[81]	Medicare beneficiaries	2.0 million	United States	2001–2011	Age, sex, race, calendar time, SES,[†] other covariates[‡]	Ischemic stroke hospitalizations (n=211 235)	Ischemic stroke: *ICD-9*: 432–435	Hospitalizations: medical records

AHS indicates Agricultural Health Study; AHSMOG, Adventist Health Study on the Health Effects of Smog; American Cancer Society CPS-II, Cancer Prevention Study-II; AMI, acute myocardial infarction; BMI, body mass index; CanCHEC, Canadian Census Health and Environment Cohort; CCHS, Canadian Community Health Survey; China-PAR, Prediction for Atherosclerotic Cardiovascular DiseaseRisk in China; CNBSS, Canadian National Breast Screening Study; CPRD, Clinical Practice Research Datalink; CTS, California Teachers Study; EFFECT, Enhanced Feedback For Effective Cardiac Treatment; ESCAPE, European Study of Cohorts for Air Pollution Effects; GOT-MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases; HIMS, Health in Men Study; HPFS, Health Professionals Follow-up Study; *ICD-9*, *International Classification of Diseases, Ninth Revision*; *ICD-10*, *International Classification of Diseases, Tenth Revision*; IHD, ischemic heart disease; ILS, Italian Longitudinal Study; MINAP, Myocardial Ischaemia National Audit Project; NHIS, National Health Interview Survey; NHIS-NSC, National Health Insurance Service–National Sample Cohort; NIH-AARP, National Institutes of Health—AARP Diet and Health Study; NL, not listed; ONPHEC, Ontario Population Health and Environment Cohort; $PM_{2.5}$, fine particulate matter <2.5 μm in diameter; PPS, Primary Prevention Study; RECALL, Heinz Nixdorf Recall Study; REGARDS, Reasons for Geographic and Racial Differences in Stroke; RoLS, Rome Longitudinal Study; SLSR, South London Stroke Register; SNC, Swiss National Cohort; and WHI, Women's Health Initiative.

*Comorbidities may include diabetes mellitus, hyperlipidemia, hypertension, chronic obstructive pulmonary disease, chronic renal failure, end-stage renal disease, or cancer.

†Socioeconomic status (SES) may include education, income, occupation/employment, Medicaid eligibility, or other indicators. These variables were measured on individual or neighborhood levels depending on data availability in studies.

‡Other covariates may include menopausal status/hormone replacement therapy use, cardiac risk scores/disease severity indices, blood measures (blood glucose, cholesterol, hemoglobin), blood pressure, thrombolysis, acute pulmonary edema, Killip class, asthma, admitting hospital/in-hospital care, second-hand smoke exposure, occupational/industrial exposure, household exposure, survey design, or other neighborhood factors such as population size, urban/rural area, airshed location, residential location/Census region, place of birth, percent of race/ethnicity or age group, county-level smoking, distance to supermarket/recreation area, or season of year/temperature.

§Diet may include intake of vegetables, fruit/citrus, grains/fiber, fat, and calories.

‖Other mortality outcome sources: interviews or reports from physicians, relatives, postal authorities, or other witnesses (often with death certificate, medical record, or autopsy confirmation or adjudication by an end point committee or physician); or church records with nosologist review. Other incident outcome sources: self-reported questionnaires, personal interviews, next-of-kin/proxy reports, or postal authorities (often death certificate or medical record confirmation or adjudication by an end point committee or physician).

¶Family history may include history of myocardial infarction, stroke, or coronary heart disease; cardiovascular disease (CVD) history may include previous myocardial infarction (or subtype, eg, ST-segment–elevation myocardial infarction), previous stroke, or chronic coronary heart disease.

#Medications may include blood pressure medication, statins, or aspirin.

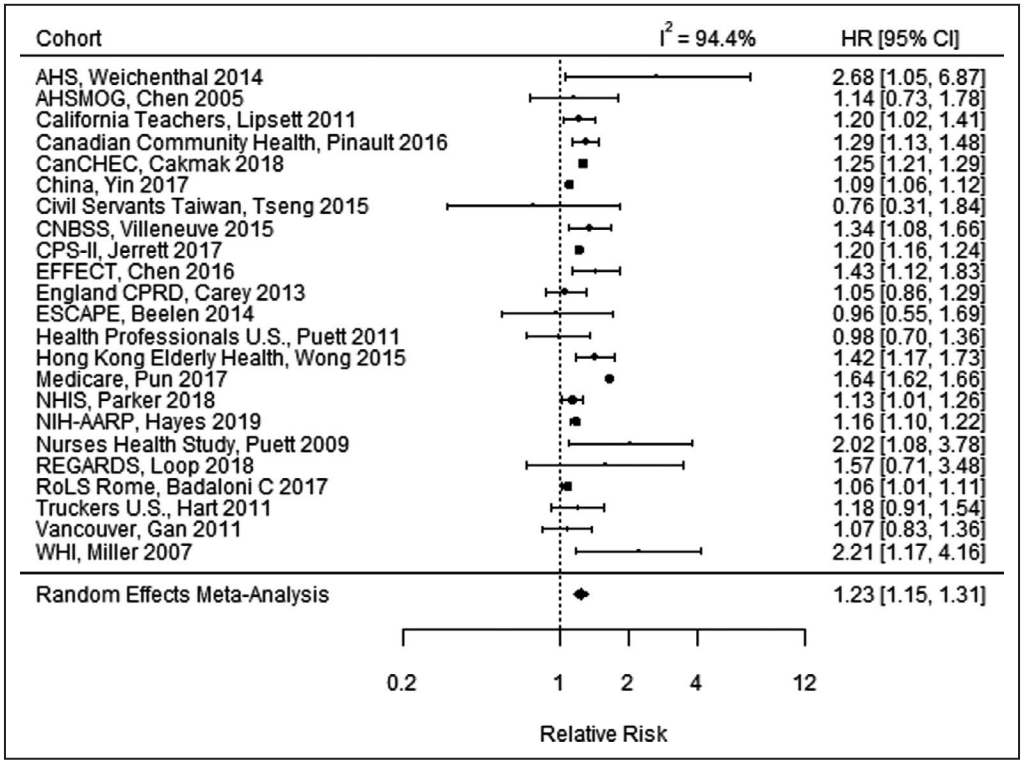

Figure 1. Meta-analysis of the relative risk of ischemic heart disease mortality per 10-μg/m^3 increase in long-term fine particulate matter <2.5 μm in diameter exposure, combining the effects of 23 studies.[11]

AHS indicates Agricultural Health Study; AHSMOG, Adventist Health Study on the Health Effects of Smog; CanCHEC, Canadian Census Health and Environment Cohort; CNBSS, Canadian National Breast Screening Study; CPRD, Clinical Practice Research Datalink; CPS-II, American Cancer Society Cancer Prevention Study-II; EFFECT, Enhanced Feedback For Effective Cardiac Treatment; ESCAPE, European Study of Cohorts for Air Pollution Effects; HR, hazard ratio; NHIS, National Health Interview Survey; NIH-AARP, National Institutes of Health—AARP Diet and Health Study; REGARDS, Reasons for Geographic and Racial Differences in Stroke; RoLS, Rome Longitudinal Study; and WHI, Women's Health Initiative.

the relative risk (RR) of IHD mortality associated with long-term $PM_{2.5}$ exposure, combining effects of 23 studies.† Fifteen of the 23 studies reported a statistically significant increased risk in IHD mortality, while 8 studies reported a CI that included the null. The combined estimate of the RR of IHD mortality among studies was 1.23 (95% CI, 1.15–1.31) per 10-μg/m^3 increase in long-term $PM_{2.5}$. There was substantial heterogeneity among studies (I^2=94.4%).

Incident Myocardial Infarction

We identified 17 studies‡ of long-term $PM_{2.5}$ exposure and incident AMI events in study populations of adults without a previous AMI. Most studies included incident events that may be fatal or nonfatal, while 4 studies[17,24,57,70] focused specifically on incident nonfatal AMI events. Of the 17 studies of AMI, five[21,25,61,62,65] restricted the definition of AMI to codes explicitly for AMI (*ICD-9*: 410; *ICD-10*: I21). Two studies[8,50] used a broader definition of AMI that also included diagnoses for "subsequent ST-segment–elevation myocardial infarction and non–ST-segment–elevation myocardial infarction" and "certain current complications following ST-segment–elevation myocardial infarction and non–ST-segment–elevation myocardial infarction" (*ICD-10*: I22–I23), and 2 additional studies further broadened the definition of AMI by adding diagnoses of "unstable angina and other acute and subacute ischemic heart diseases" (*ICD-9*: 410; *ICD-10*: I20.0, I24).[9,54] Two studies did not examine AMI directly but instead examined the broader end point of incident IHD.[56,71] In most of these studies, *ICD* codes were obtained from a combination of hospitalization records, medical records, and a national database of death records. Six studies used self-report or proxy report to define AMI with confirmation by medical records and did not list specific *ICD* codes used to define the outcome (Table).

†References 6, 7, 13–19, 21, 24, 27, 28, 34, 39, 41, 53, 59, 64, 65, 70, 74, 76.

‡References 8, 9, 17, 21, 24, 25, 33, 50, 52, 54, 56, 57, 62, 65, 66, 70, 71.

Figure 2 illustrates the results of the meta-analysis pooling results among 11 studies[4] for incident AMI. Four of the 11 studies reported a statistically significant increased risk of incident AMI, while 6 studies reported a CI that included the null, and 1 study (REGARDS [Reasons for Geographic and Racial Differences in Stroke] trial, 2018) reported a decreased risk. The combined RR of incident AMI in the meta-analysis was 1.08 (95% CI, 0.99–1.18) per 10-μg/m^3 increase in long-term $PM_{2.5}$. Funnel plots indicated no evidence of publication bias but did identify 1 extreme outlier study (Kim et al, 2017)[33], which was excluded from the primary meta-analysis (Figure S3). The REGARDS trial, which reported a decreased risk of AMI, did not appear to be an outlier. The extreme outlier study of patients in Seoul, Korea, reported an RR of 21.65 (95% CI, 5.49–85.36) per 10-μg/m^3 increase in long-term $PM_{2.5}$.[33] In a sensitivity analysis, we recomputed the meta-analysis with the outlier study included, which resulted in a combined RR of 1.09 (95% CI, 0.99–1.20). Thus, the meta-analysis results were not sensitive to the inclusion or exclusion of this extreme outlier study.

Recurrent Myocardial Infarction

Two studies[11,12] looked at recurrent AMI events in a population of adults with previous AMI. Koton et al[12] reported an RR of 1.7 (95% CI, 0.9–2.9) per 10-μg/m^3 increase in long-term $PM_{2.5}$ exposure. Tonne et al[11] measured risk for a combined outcome of recurrent AMI events with all-cause mortality and found an RR of 1.94 (95% CI, 0.51–6.98) per 10-μg/m^3 increase in exhaust $PM_{2.5}$ and 2.68 (95% CI, 0.72–13.01) for nonexhaust $PM_{2.5}$. Another study examined hospital admissions for AMI, yet patient history of a previous AMI was unknown so hospitalizations included both incident and recurrent events.[61] Since there were only 2 studies of recurrent AMI events, we did not conduct a meta-analysis for the association of long-term $PM_{2.5}$ exposure and recurrent AMI.

Cerebrovascular Mortality

The relationship between long-term $PM_{2.5}$ exposure and cerebrovascular mortality was analyzed in 27 studies among 17 cohorts.[5] Most studies (19 of 27) defined cerebrovascular deaths by the same set of *ICD* codes (*ICD-9*: 430–438; *ICD-10*: I60–I69) obtained from a national database of death records. Some studies obtained data on death from medical records, proxy reports, and/or postal officials with death certificate review by physician adjudicators. One study looked only at fatal strokes (*ICD-9*: 430–431, 433.x1, 434.x1, 436; *ICD-10*: I60–I61, I63–I64).[31] For consistency between *ICD-9* and *ICD-10* codes, 1 study explicitly excluded "transient cerebral ischemia" from the list of *ICD-9* codes (*ICD-9*: 435), which in *ICD-10* is now listed as G45, within diseases of the nervous system.[29] Other definitions of cerebrovascular mortality were similar but excluded some

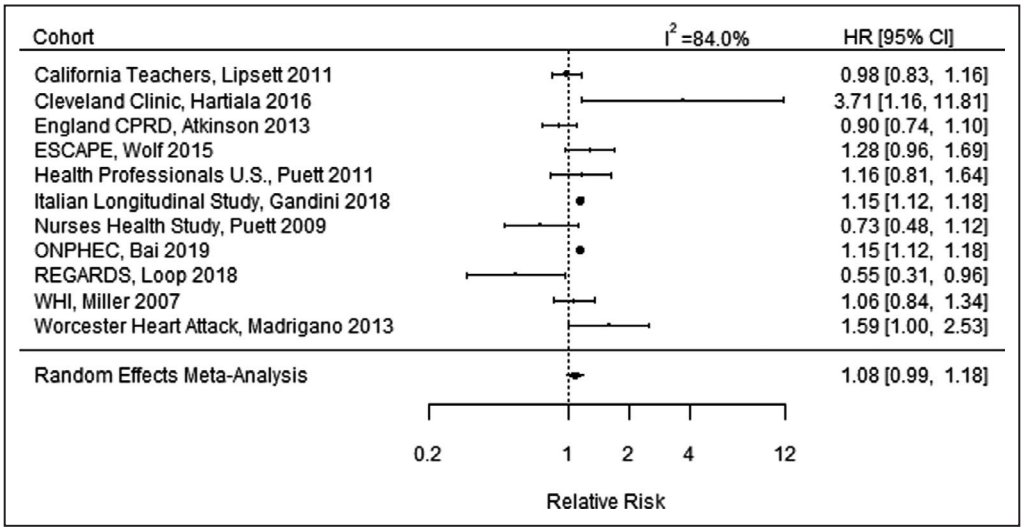

Figure 2. Meta-analysis of the relative risk of incident acute myocardial infarction per 10-μg/m^3 increase in long-term fine particulate matter <2.5 μm in diameter exposure, combining the effects of 11 studies.[12]

CPRD indicates Clinical Practice Research Datalink; ESCAPE, European Study of Cohorts for Air Pollution Effects; HR, hazard ratio; ONPHEC, Ontario Population Health and Environment Cohort; REGARDS, Reasons for Geographic and Racial Differences in Stroke; and WHI, Women's Health Initiative.

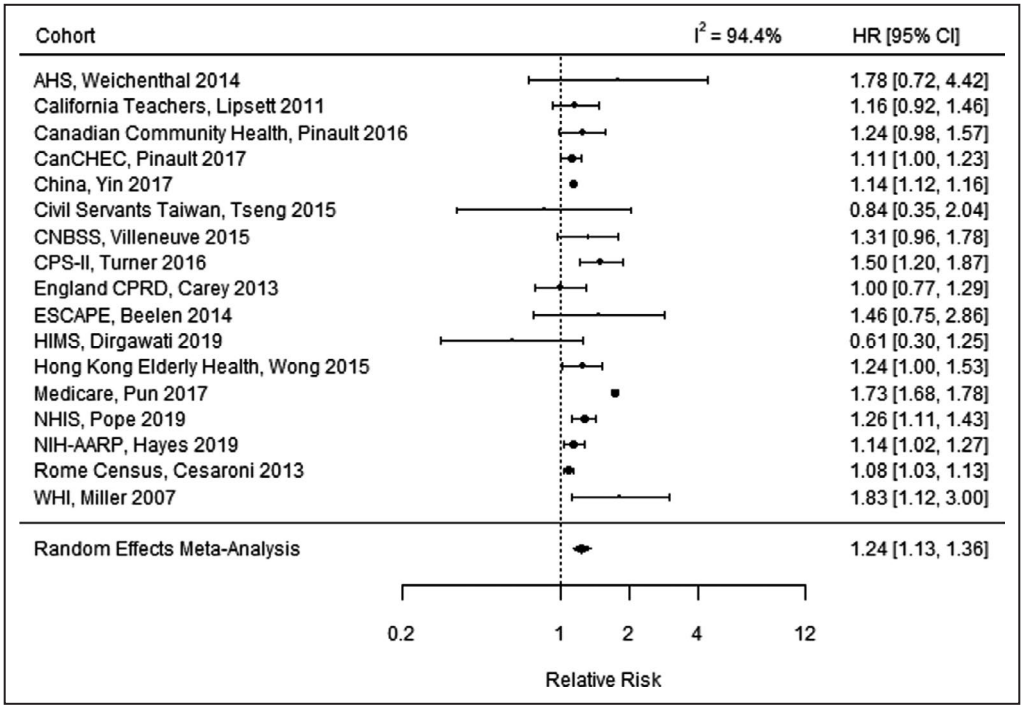

Figure 3. Meta-analysis of the relative risk of cerebrovascular mortality per 10-μg/m^3 increase in long-term fine particulate matter <2.5 μm in diameter exposure, combining the effects of 17 studies.[13]

AHS indicates Agricultural Health Study; CanCHEC, Canadian Census Health and Environment Cohort; CNBSS, Canadian National Breast Screening Study; CPRD, Clinical Practice Research Datalink; CPS-II, American Cancer Society Cancer Prevention Study-II; ESCAPE, European Study of Cohorts for Air Pollution Effects; HR, hazard ratio; HIMS, Health in Men Study; NHIS, National Health Interview Survey; NIH-AARP, National Institutes of Health—AARP Diet and Health Study; and WHI, Women's Health Initiative.

causes of death such as death from "subarachnoid hemorrhage" (*ICD-9*: 430, *ICD-10*: I60). The narrowest definition of cerebrovascular mortality, used in 1 study, included only "nontraumatic intracerebral hemorrhage" (*ICD-10*: I61) and "cerebral infarction" (*ICD-10*: I63).[15] Two studies did not list specific *ICD* codes used to define the outcome (Table). No studies of cerebrovascular mortality examined ischemic stroke mortality separately from hemorrhagic stroke mortality.

Figure 3 illustrates the results of the meta-analysis for cerebrovascular mortality, combining results among 17 studies.[#] Funnel plots indicated no extreme outlier studies and no evidence of publication bias for cerebrovascular mortality (Figure S3). Nine of the 17 studies reported a statistically significant increased risk in cerebrovascular mortality, while 8 studies reported a CI that included the null. The combined RR of cerebrovascular mortality was 1.24 (95% CI, 1.13–1.36) per 10-μg/m^3 increase in long-term $PM_{2.5}$. There was substantial heterogeneity among studies (I^2=94.4%).

Incident Stroke

We identified 20 studies of long-term $PM_{2.5}$ exposure and incident stroke with study populations restricted to patients without a previous stroke.[‖] Of these 20 studies, 3 studies[8,50,58] defined stroke events narrowly, only including "nontraumatic intracerebral hemorrhage" (*ICD-10*: I61) and "cerebral infarction" (*ICD-10*: I63) (Table). Two studies broadened this definition to also include other cerebrovascular disease diagnoses such as "other and unspecified nontraumatic intracranial hemorrhage" (*ICD-10*: I62)[65] or "nontraumatic subarachnoid hemorrhage" (*ICD-10*: I60).[38] Multiple studies used a wider definition, with 1 study using codes *ICD-10* I60–I69,[32] another study[36] using codes *ICD-9* 430–436, and 4 studies using slightly varied versions of the latter definition: 1 study[21] excluded "transient cerebral ischemia" (*ICD-9*: 435), 1 study[31] excluded "other and unspecified intracranial hemorrhage" (*ICD-9*: 432), and 2 studies[71,77] excluded "subarachnoid hemorrhage" (*ICD-9*: 430). In total, 4 studies included transient cerebral ischemia attack events (*ICD-9*: 435; *ICD-10*: G45) in their definition of stroke[31,71,77] and no studies

[#]References 6, 7, 14–16, 21, 31, 34, 35, 39, 41, 51, 59, 65, 75, 76, 80.

[‖]References 8, 10, 17, 21, 31–33, 36, 38, 50, 52, 55–58, 62, 65, 71, 77.

examined transient cerebral ischemia attack events as a separate outcome. Two studies only included nonfatal incident strokes.[17,57] *ICD* codes were obtained from a combination of hospitalization records, medical records, and a national database of death records. Eight studies used self-report or proxy report to define stroke events with confirmation by medical records, and 4 of those studies did not list specific *ICD* codes used to define the outcome.

Figure 4 illustrates the meta-analysis for incident stroke, combining effects among 14 studies.[8] The RR of an incident stroke in the random effects meta-analysis was 1.13 (95% CI, 1.11–1.15) per 10-μg/m^3 increase in long-term $PM_{2.5}$. Funnel plots indicated no evidence of publication bias but did identify 1 extreme outlier study, which was excluded from the primary meta-analysis (Figure S3). The outlier study of patients in Seoul, Korea, reported an RR of 21.65 (95% CI, 5.49–85.36) per 10-μg/m^3 increase in long-term $PM_{2.5}$.[33] As a sensitivity analysis, we recomputed the meta-analysis with the outlier study included, which resulted in an RR of 1.28 (95% CI, 0.92–1.78), a substantial change. Thus, the meta-analysis results were sensitive to the inclusion or exclusion of this extreme outlier study, where inclusion of this outlier study caused both the combined effect estimate and width of the CI to increase substantially. This increase in variability was also reflected in the heterogeneity estimate, where I^2 increased from 0% to 99.4% when the extreme outlier study was included.

Six studies of incident stroke further analyzed ischemic and hemorrhagic strokes separately.[17,32,33,36,38,55] Therefore, we conducted separate meta-analyses of incident ischemic stroke and incident hemorrhagic stroke. Our meta-analyses included 5 studies; the extreme outlier study from the overall incident stroke meta-analysis above was excluded. The RR of an incident ischemic stroke in the random effects meta-analysis was 1.18 (95% CI, 1.14–1.22), with low heterogeneity among studies (I^2=11.8%). The RR of an incident hemorrhagic stroke in the random effects meta-analysis was 1.10 (95% CI, 1.05–1.16), with no heterogeneity among studies (I^2=0.0%). The excluded outlier study[33] reported an RR of 41.08 (95% CI, 14.88–117.02) for ischemic stroke and 7.30 (95% CI, 1.63–33.33) for hemorrhagic stroke per 10-μg/m^3 increase in long-term $PM_{2.5}$.

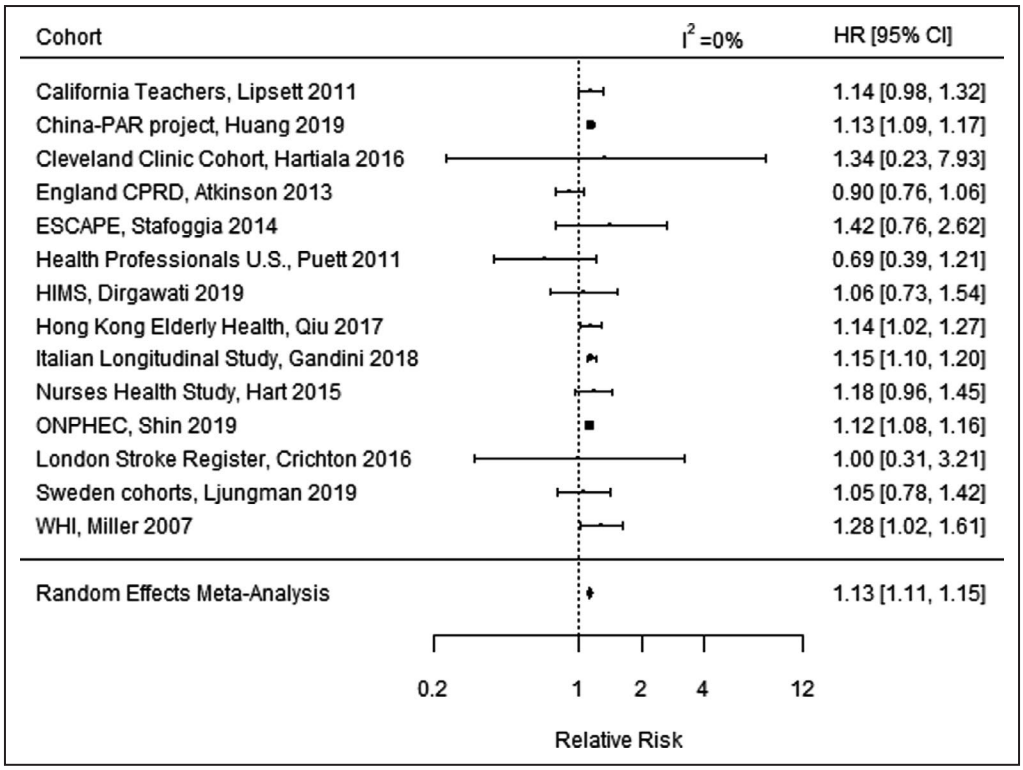

Figure 4. Meta-analysis of the relative risk of incident stroke per 10-μg/m^3 increase in long-term fine particulate matter <2.5 μm in diameter exposure, combining effects of 14 studies.[11]
China-PAR indicates Prediction for Atherosclerotic Cardiovascular Disease Risk in China; CPRD, Clinical Practice Research Datalink; ESCAPE, European Study of Cohorts for Air Pollution Effects; HR, hazard ratio; HIMS, Health in Men Study; ONPHEC, Ontario Population Health and Environment Cohort; and WHI, Women's Health Initiative.

Recurrent Stroke

No studies examined recurrent stroke directly, although several studies included recurrent strokes. For example, 3 studies[12,61,81] examined stroke hospitalizations where patient history of a previous stroke was unknown; therefore, these hospitalizations could include both incident and recurrent events. One of these studies[12] examined stroke hospitalizations among a cohort of patients with a previous AMI and found an RR of 1.1 (95% CI, 0.5–2.5) per 10-μg/m^3 increase in long-term $PM_{2.5}$. The other 2 studies were among Medicare beneficiaries: 1 study[61] reported an RR of 1.36 (95% CI, 1.34–1.36) per 10-μg/m^3 increase in long-term $PM_{2.5}$, and the other study[81] specifically examined ischemic stroke hospitalizations and reported an RR of 1.04 (95% CI, 0.97–1.11). Since these stroke hospitalizations could be incident or recurrent, we did not include these 3 studies in the meta-analysis for the association of long-term $PM_{2.5}$ exposure and incident stroke, and we were unable to conduct a meta-analysis of recurrent stroke because of an insufficient number of studies.

Cardiovascular Mortality

In a supplementary analysis, we also provide an updated meta-analysis of overall cardiovascular mortality by combining the effects of 28 studies.†† We found an RR of 1.14 (95% CI, 1.08–1.21) per 10-μg/m^3 increase in long-term $PM_{2.5}$. Details are provided in Figure S4.

Heterogeneity Among Studies

We found high heterogeneity in the estimated associations among studies for 3 of the study outcomes (I^2=94.4% for IHD mortality, 94.4% for cerebrovascular mortality, 84.0% for incident AMI), and no heterogeneity (I^2=0%) for incident stroke. There are many factors that may have contributed to heterogeneity among studies, including differences in the age, sex, race, and SES of study participants; adjustment of covariates; follow-up period; country and region of exposure; and variability in the *ICD* codes used to define each outcome as described above and in the Table. Newcastle-Ottawa Scale rankings and details are also provided in Table S1. Overall, studies rated from 7 to 9, which demonstrates that studies used in our meta-analyses generally had low risk of bias according to the scale. More attention should be placed on the finer differences between studies such as sample size, covariates adjusted for, *ICD* codes used, and sources of outcome data provided in the Table. We analyzed which studies contributed most to the heterogeneity of each meta-analysis. For IHD mortality and cerebrovascular mortality, Pun[76] performed a study of 18.9 million Medicare beneficiaries, which was most influential; when this study was removed, I^2 changed from 94.4% to 73.0% for IHD mortality and from 94.4% to 42.1% for cerebrovascular mortality. Pun reported an RR of 1.64 (95% CI, 1.62–1.66) for IHD mortality and 1.73 (95% CI, 1.68–1.78) for cerebrovascular mortality per 10-μg/m^3 increase in long-term $PM_{2.5}$, with a narrow CI because of the large size of the study. This study included Medicare beneficiaries among the United States who were 65 years and older, used zip code–level rather than address-level $PM_{2.5}$ exposure, and adjusted for age, sex, race, calendar time, and county-level variables for smoking, diabetes mellitus, body mass index, alcohol consumption, asthma, and median income because of lack of data on personal health characteristics. These factors likely contributed to the heterogeneity of results found in this study.

For the incident AMI meta-analysis, Atkinson et al[8] was most influential; when this study was removed, the I^2 changed from 84.0% to 0%, and the combined effect estimate changed from an RR of 1.08 (95% CI, 0.99–1.18) to an RR of 1.15 (95% CI, 1.13–1.17) per 10-μg/m^3 increase in long-term $PM_{2.5}$. Atkinson and colleagues included 836 557 patients aged 40 to 89 years in England; adjusted for all key covariates including age, sex, smoking, body mass index, diabetes mellitus, hypertension, and SES; had a short follow-up period of 5 years (2003 through 2007); used a mean annual $PM_{2.5}$ exposure of 12.9 μg/m^3 and a small interquartile range of 1.9 μg/m^3; and did not include any model performance statistics for $PM_{2.5}$ exposures. The study also reported a large change in the effect estimate caused by control for SES (hazard ratio [HR] of 1.12 [95% CI, 0.92–1.36] without SES and 0.90 [95% CI, 0.74–1.10] with SES) per 10-μg/m^3 increase in long-term $PM_{2.5}$. These factors likely contributed to the heterogeneity of results found in this study.

We also considered differences in effects by world region by conducting separate meta-analyses for IHD mortality and cerebrovascular mortality by world region: North America, Europe, and Asia. Meta-analysis results are reported per 10-μg/m^3 increase in long-term $PM_{2.5}$ exposure. For IHD mortality, we found the highest risk in North America (combined HR, 1.27; 95% CI, 1.18–1.38 [I^2=93.2%]; 17 studies), moderately increased risk in Asia (combined HR, 1.18; 95% CI, 0.93–1.50 [I^2=73.0%]; 3 studies), and the smallest increases in risk in Europe (combined HR, 1.06; 95% CI, 1.01–1.11 [I^2=0%]; 3 studies). For cerebrovascular mortality, we also found the highest risk in North America (combined HR, 1.32; 95% CI, 1.17–1.49 [I^2=85.1%]; 10 studies), moderately

††References 3, 5–7, 12, 14–18, 21, 28, 34, 35, 39, 41, 53, 59, 64, 65, 75, 76, 82–87.

increased risk in Asia (combined HR, 1.14; 95% CI, 1.12–1.16 [I^2=0%]; 3 studies), and the smallest increases in risk in Europe (combined HR, 1.08; 95% CI, 1.03–1.13 [I^2=0%]; 3 studies).

DISCUSSION

This study reviewed 69 published articles examining the effect of long-term $PM_{2.5}$ exposure on risks of IHD and stroke events. We found that IHD mortality and cerebrovascular mortality were the most frequently studied end points and that these end points had the greatest increases in risk. In meta-analyses, we found that a 10-μg/m^3 increase in long-term average $PM_{2.5}$ exposure was associated with a 23% increased risk of IHD mortality and a 24% increased risk of cerebrovascular mortality. We found that these 2 mortality outcomes were the most frequently studied cardiovascular end points, and that the definitions (primarily *ICD* codes) used to define these mortality end points have generally been consistent, although not identical among every study. Our meta-analyses found more modest associations between long-term $PM_{2.5}$ exposure and increased risk of incident stroke and incident AMI: 13% and 8% increased risk per 10-μg/m^3 increase in long-term average $PM_{2.5}$ exposure, respectively. These outcomes have not been studied as extensively as the mortality outcomes. Furthermore, we were unable to conduct any meta-analyses for recurrent AMI and stroke events because of an insufficient number of studies, indicating that more research is needed. Further research on recurrent events is crucial for assessing whether current $PM_{2.5}$ regulatory standards are protective of populations with a history of cardiovascular events.

While there have been a number of qualitative reviews of long-term cardiovascular effects of $PM_{2.5}$, including the AHA statements,[46,88] the Environmental Protection Agency integrated science assessment,[89] and other journal review articles,[42,43] there have been relatively few meta-analyses. To our knowledge, this is the first meta-analysis that quantifies and compares the effect of long-term $PM_{2.5}$ on the risks of both incident AMI and IHD mortality. Notably, we found a substantial difference in these risks, with a 23% increased risk of IHD mortality and an 8% increased risk of incident AMI per 10-μg/m^3 increase in long-term average $PM_{2.5}$ exposure.

There is only 1 previous meta-analysis of the effect of long-term $PM_{2.5}$ on the risks of nonfatal stroke[78] and 1 of incident stroke and stroke mortality.[90] Noticeably, Yuan et al[90] included only 6 studies in the meta-analysis for stroke mortality, overlooking 9 studies[‡‡] that we identified and were published by December 2018 (the cutoff for inclusion in their meta-analysis); thus, our meta-analysis is not only more up-to-date, including 3 more studies published in 2019,[31,59,75] but also much more fully representative of the published literature by including many more relevant studies. Comparing results per 10-μg/m^3 increase in long-term average $PM_{2.5}$ exposure, our finding of a 13% increased risk of incident stroke is smaller than the 23% increase in risk (95% CI, 10%–37%) reported by Yuan et al in 2019[90] and larger than the 6% increase in risk of nonfatal stroke (95% CI, 0%–13%) reported by Shin et al in 2014.[78] Notably, the stronger association in Yuan et al was largely driven by 2 studies that we excluded because they did not study incident stroke: To and colleagues[91] studied the prevalence of a previous stroke diagnosis and Lin et al[92] published a cross-sectional association between average $PM_{2.5}$ and self-reported stroke in the past year. Additionally, the meta-analysis pooled risk ratios for long-term $PM_{2.5}$ exposure reported by Shin et al were only among 4 studies.

Our supplementary analysis of overall cardiovascular mortality demonstrated a 14% increase in risk of cardiovascular mortality per 10-μg/m^3 increase in long-term $PM_{2.5}$. This is consistent with the AHA 2010 statement that "a 10-μg/m^3 increase in long-term average $PM_{2.5}$ exposure is associated with an ≈10% increase in all-cause mortality and a similar or greater increase in the risk of cardiovascular death,"[88] and is slightly larger than the 2013 meta-analysis that found a 11% increase in risk of cardiovascular mortality per 10-μg/m^3 increase in long-term $PM_{2.5}$.[45]

Mechanisms

Mechanisms have been reviewed in detail in previous review articles.[1,42,43] Briefly, oxidative stress and inflammation are key mechanisms by which $PM_{2.5}$ acts to increase risk of CVDs. Numerous in vitro studies have demonstrated that exposure to particulate air pollution activates pathways that generate reactive oxygen species in both cultured cells and in pulmonary and vascular tissue.[93–101] Activation of reactive oxygen species–dependent pathways can affect vascular inflammation, atherosclerosis, basal vasomotor balance, coagulation and thrombosis, and platelet activation.[102] Inflammatory cytokines are activated in response to air pollution exposures, with evidence of increased pulmonary inflammation and increased levels of circulating proinflammatory mediators.[103–107] Similarly, epidemiologic studies have demonstrated the relationship of particulate air pollution with inflammatory markers, as well as with atherosclerosis.[108,109] Studies in mice have also demonstrated inhibited vascular repair after $PM_{2.5}$ exposure via depletion of circulating endothelial progenitor cells and functional

[‡‡]References 6, 7, 14, 15, 34, 35, 39, 51, 76.

impairment that prevents endothelial progenitor cell–mediated vascular recovery.[110] Furthermore, increasing the antioxidant capacity of the lung prevented this dysfunction, supporting the role of oxidative stress in $PM_{2.5}$-induced cardiovascular injury.[110] Another mechanism that may underly the cardiovascular responses to air pollution is altered autonomic nervous system balance.[111] Experimental studies have found that air pollution exposure is associated with rapid changes in autonomic nervous system balance, marked by sympathetic nervous system activation and parasympathetic withdrawal.[111,112] The mechanism of changes in autonomic nervous system balance is also supported by epidemiologic evidence demonstrating associations between air pollution exposure and changes in heart rate variability.[113–115] Notably, many epidemiologic studies have focused on older populations, and it has been hypothesized that the elderly are more susceptible to air pollution effects.[88] However, several epidemiologic and experimental studies have reported that $PM_{2.5}$ is associated with blood pressure,[111] vasodilatation,[116] heart rate variability,[117,118] and ischemic stroke[119] among younger adults (aged 18–55 years).

We observed a noticeable difference in the risk of IHD mortality (23% increased risk) compared with the risk of incident AMI events (8% increased risk). These differences in risk may be related to differences in IHD and AMI survival. IHD morality is the leading cause of death worldwide,[120] and most IHD deaths occur before hospitalization and before a person is able to seek medical attention.[121] Furthermore, adults who are younger or who have no history of IHD are more likely to have an IHD death that occurs before hospitalization, although they have much less risk of IHD death overall.[121] In contrast, the AMI fatality rate among older adults who have been hospitalized has decreased substantially over the past several decades, and is now estimated to be ≈7%.[122] In addition, the increased risk observed for IHD mortality could be driven in part by an increased risk of IHD mortality among patients with a previous AMI event; however, little research has been performed examining that at-risk population.

Notably, the differences in the strength of association in IHD mortality and incident AMI were sometimes observed within the same cohort study. For example, the REGARDS trial reported a statistically significant decreased risk of AMI (HR, 0.55; 95% CI, 0.31–0.96) and a strong but not statistically significant increased association with IHD mortality for the same cohort (HR, 1.57; 95% CI, 0.71–3.48).[70] Funnel plots in Figure S3 indicated that this study did not appear to be an outlier for incident AMI when compared with the expected distribution of effect estimates and standard errors. There is no obvious reason for the decreased HR in the REGARDS trial. The REGARDS cohort was younger and more racially and geographically diverse than many previous studies; however, the authors found no evidence that results differed by race, sex, or rural versus urban regions. The study did not account for changes in residential address during follow-up, and instead assumed that patients remained at their baseline address for the duration of the study, which is a common study limitation.

In analyses of incident stroke types, we found that long-term $PM_{2.5}$ exposure may have a stronger association with risk of incident ischemic stroke (HR, 1.18; 95% CI, 1.14–1.22) than hemorrhagic stroke (HR, 1.10; 95% CI, 1.05–1.16). Ischemic strokes are the most common stroke subtype, while hemorrhagic strokes account for only 10% to 15% of all strokes. Ischemic and hemorrhagic strokes have different causes. Ischemic strokes occur when blood flow to the brain is blocked by a blood clot, whereas hemorrhagic strokes occur when a weak blood vessel bursts and bleeds into the brain. AMI is most often caused by decreased blood flow to a portion of the heart, typically caused by a blood clot in the epicardial artery that supplies the heart muscle.[123] Thus, ischemic strokes and AMI share a common pathway, where thrombosis is the most common underlying mechanism of AMI and ischemic stroke. There are also some differences in risk factors for ischemic and hemorrhagic strokes, where hypertension is the strongest risk factor for hemorrhagic stroke[124] and older age, cigarette smoking, hypercholesterolemia, and family history of stroke are more predictive of ischemic versus hemorrhagic stroke.[125]

Gaps in Current Knowledge

Our final objective in this study was to identify gaps in the current knowledge of the relationship between long-term exposures to $PM_{2.5}$ and risk of cardiovascular morbidity and mortality. Mortality outcomes have been the most studied, and the meta-analyses of these mortality outcomes showed clear, strong effects in relation to long-term exposures to $PM_{2.5}$. More studies of nonmortality outcomes are needed to clarify other effects, such as incident AMI events and recurrent AMI and stroke events.

Few studies have examined the effects of long-term exposures to $PM_{2.5}$ among patients with a history of CVD and measured their risk of recurrent cardiovascular events. The World Health Organization has reported that patients with a previous myocardial infarction or stroke are the groups at highest risk for further coronary and cerebral events.[126] Specifically, the annual death rate of patients who experienced an AMI is estimated to be 6 times that of same-aged individuals without coronary heart disease.[126]

Survivors of stroke have an increased risk of a subsequent stroke of 7% per year compared with those with no previous stroke.[126] Given the growing burden of CVD globally, compounded by increased survival rates among cardiac patients as a result of healthcare improvements, more research is needed to understand the health effects of long-term air pollution exposure among these high-risk groups.

This review article focuses on $PM_{2.5}$ mass, the total exposure to $PM_{2.5}$, which is the exposure measure most commonly studied and the measure that is currently regulated.[89,127,128] Notably, $PM_{2.5}$ is composed of numerous elements, including organic carbon, black carbon, sulfate particles, metal oxides (aluminum, silicone, potassium, calcium, titanium, iron, and zinc), and sea salt (sodium and chorline).[129] Sources that contribute to $PM_{2.5}$ exposure include regional pollution, motor vehicles, sea salt, crustal/road dust, oil combustion, and wood burning.[129] $PM_{2.5}$ composition varies regionally; eg, rural areas have higher levels of crustal materials (silicone and aluminum) driven by agricultural activities and unpaved roads, urban areas have higher levels of secondary aerosol (nitrate, sulfate, and ammonium) and combustion (organic and black carbon), and industrialized areas have higher levels of trace metals (iron, palladium, and zinc).[130] Recent research has also shown differences in cardiovascular health effects related to different $PM_{2.5}$ components. For example, some $PM_{2.5}$ metals have been associated with increased levels of inflammatory blood markers[131] and an increased risk of coronary events.[9] Given this emerging research, differences in $PM_{2.5}$ components may also contribute to differences in findings among studies, and future research is needed to better understand the role of $PM_{2.5}$ components in cardiovascular health risk.

Last, more research on long-term exposure to $PM_{2.5}$ and cardiovascular health effects is needed in Asian and Middle-Eastern countries, where ambient air pollution exposure is higher compared with the rest of the world[132] and where a large proportion of the world's population lives, such as in China and India. Populations in East Asian countries have shown higher risks of stroke mortality and lower risks of IHD mortality compared with Western countries,[133] which emphasizes the importance of studying these diverse populations who may have different underlying health risks compared with more frequently studied populations in Europe and North America. Some researchers have also suggested that air pollution effects may be greater in Asian countries.[134] However, our meta-analysis by world region found the highest risks in North America, moderately increased risks in Asia, and the smallest increased risks in Europe. Notably, there were only 3 studies included from Asia, therefore more research is needed to verify and better understand these potential differences.

CONCLUSIONS

Our study builds on previous work that has established the causal link between $PM_{2.5}$ exposure and CVDs. Using meta-analyses, we provide quantitative evidence of the strength of associations with specific CVD event end points. We found a clear relationship between long-term $PM_{2.5}$ exposure and increased risk of cardiovascular events, with larger effects for IHD mortality and cerebrovascular mortality than incident stroke and incident AMI. The relationship with incident AMI was suggestive of a positive association but not conclusive. More research is needed to better quantify the relationships for incident AMI and for recurrent stroke and recurrent AMI events.

ARTICLE INFORMATION

Received April 2, 2020; accepted October 21, 2020.

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Acknowledgments

Stacey E. Alexeeff, Xi Liu, and Noelle S. Liao had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Sources of Funding

This study was funded by National Institute of Environmental Health Services grant R01 ES029557 Particulate Air Pollution, Cardiovascular Events, and Susceptibility Factors (PACES).

Disclosures

None.

Supplementary Material

Figures S1–S4
Table S1
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Supplemental Material

Figure S1. Article Identification flow chart following the PRISMA guidelines.[137]

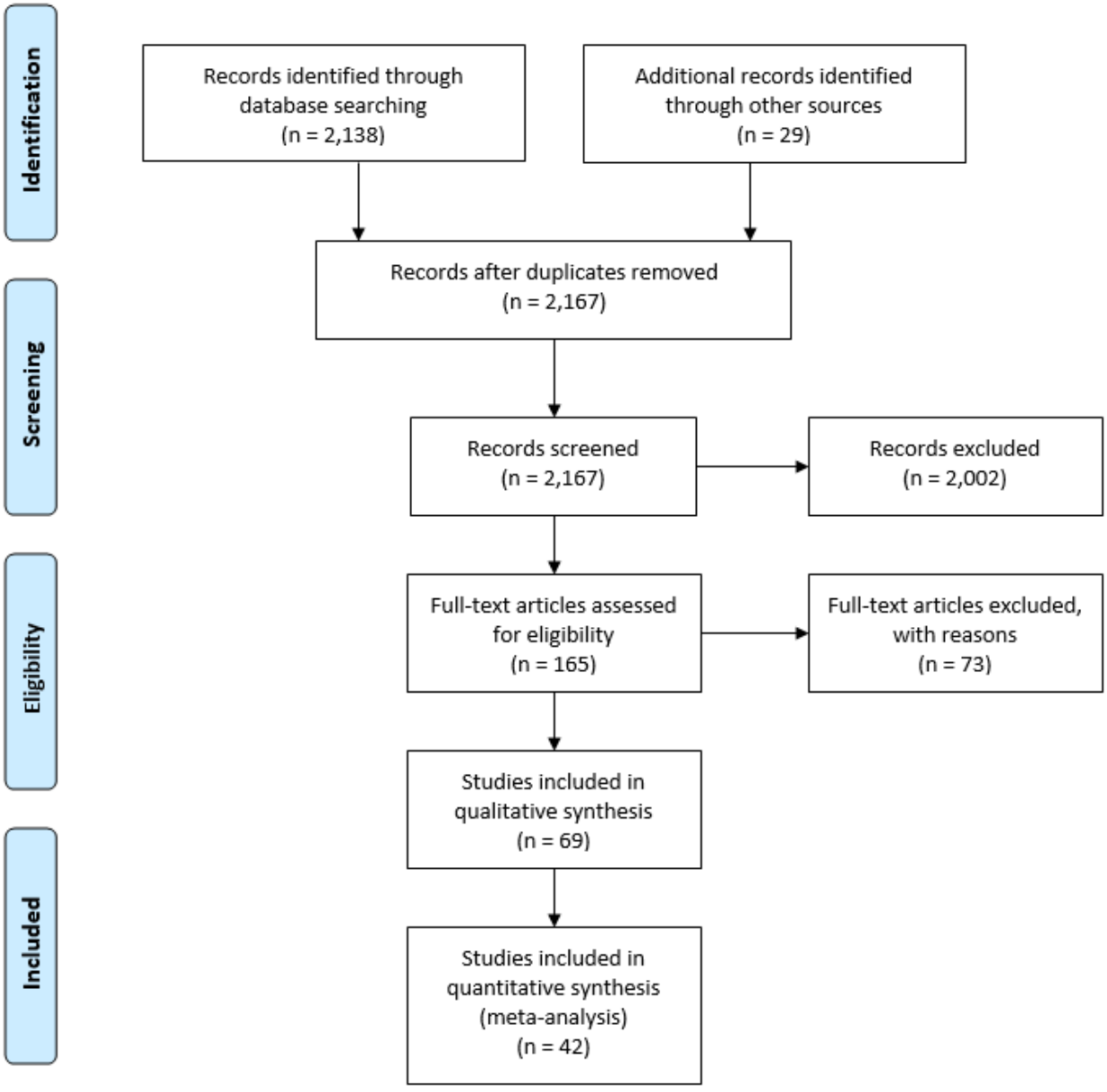

Figure S2. Number of publications by year reporting the association of long-term $PM_{2.5}$ exposure and CVD events.

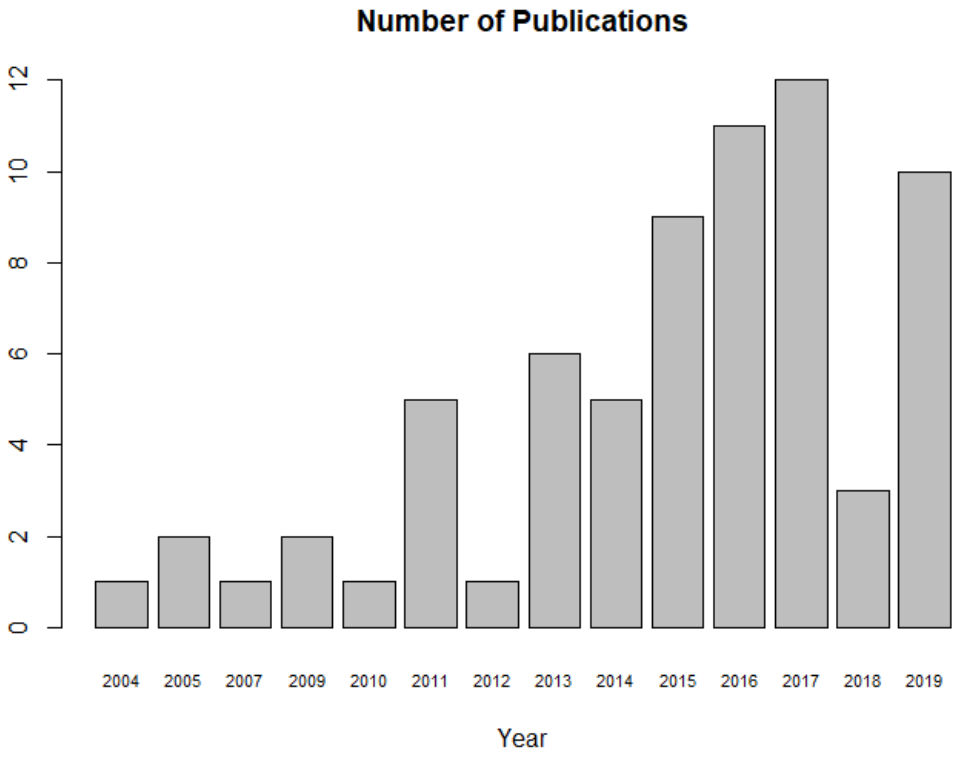

Figure S3. Funnel plots indicating extreme outlier studies in meta-analyses.

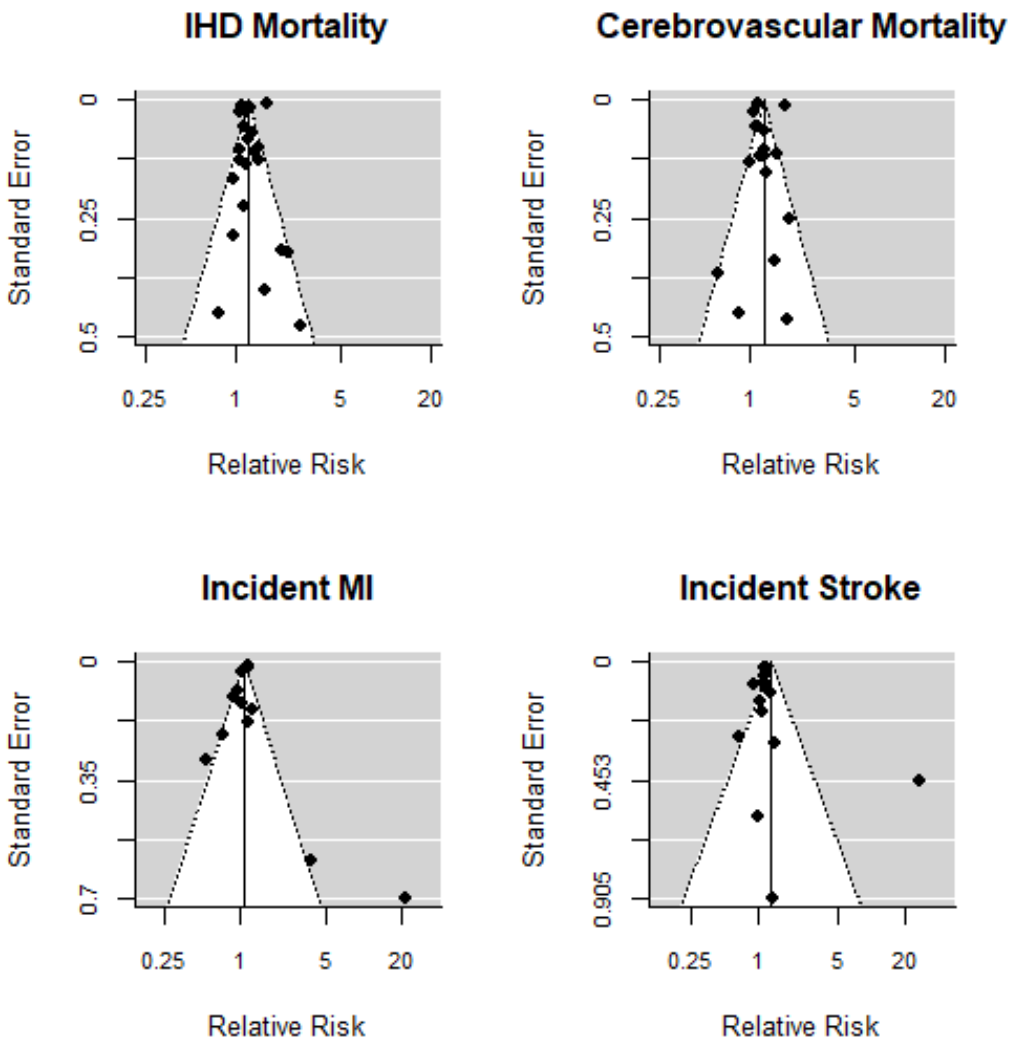

Figure S4. Meta-analysis of the relative risk of cardiovascular mortality per 10 µg/m^3 increase in long-term $PM_{2.5}$ exposure, combining effects of 28 studies.

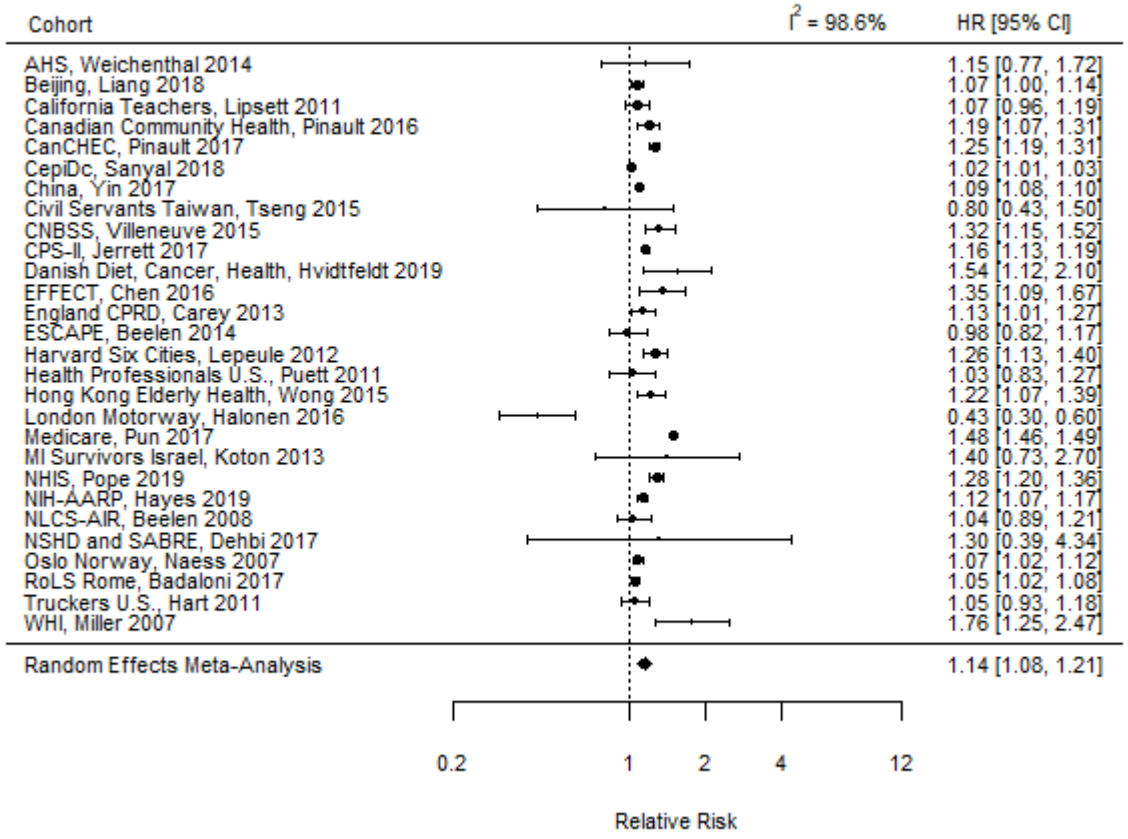

Figure S4 shows the results of our meta-analysis for long-term $PM_{2.5}$ exposure and CVD mortality, combining associations of 28 studies. We found that the combined relative risk of CVD mortality was 1.14 (95% CI 1.08 to 1.21) per 10 µg/m^3 increase in long-term $PM_{2.5}$ exposure. The meta-analysis excluded one extreme outlier study of residents of Seoul, Korea that reported a relative risk of 21.65 (95% CI: 2.95 to 158.88) per 10 µg/m^3 increase in long-term $PM_{2.5}$ exposure (Kim et al. 2017). As a sensitivity analysis, we recomputed the meta-analysis with this outlier study included, which resulted in a combined relative risk of 1.14 (95% CI 1.08 to 1.22). Thus, results of the meta-analysis were not sensitive to the inclusion or exclusion of this extreme outlier study.

Table S1. Newcastle-Ottawa Scale[*] for assessing the quality of nonrandomized studies.

Study, Cohort	Selection[†]	Comparability	Outcome	Total Stars
Atkinson 2013, England CPRD	***	**	***	8
Badaloni 2017, RoLS Rome	***	**	***	8
Bai 2019, ONPHEC	****	**	***	9
Beelen 2014, ESCAPE	***	**	***	8
Cakmak 2018, CanCHEC	***	**	***	8
Carey 2013, England CPRD	***	**	***	8
Cesaroni 2013, RoLS Rome	***	**	***	8
Chen 2005, AHSMOG	***	**	***	8
Chen 2016, EFFECT	**	**	***	7
Crichton 2016, London Stroke Register	****	**	***	9
Dirgawati 2019, HIMS	***	**	***	8
Gan 2011, Vancouver	****	**	***	9
Gandini 2018, Italian Longitudinal Study	****	**	***	9
Hart 2011, Truckers U.S.	**	**	***	7
Hart 2015, Nurses Health Study	***	**	***	8
Hartiala 2016, Cleveland Clinic	***	**	***	8
Hayes 2019, NIH-AARP	**	**	***	7
Huang 2019, China-PAR project	****	**	***	9
Jerrett 2017, CPS-II	**	**	***	7
Lipsett 2011, California Teachers	***	**	***	8
Ljungman 2019, Sweden cohorts	****	**	***	9

Loop 2018, REGARDS	****	**	***	9
Miller 2007, WHI	***	**	***	8
Parker 2018, NHIS	***	**	***	8
Pinault 2016, Canadian Community Health	***	**	***	8
Pinault 2017, CanCHEC	***	**	***	8
Pope 2019, NHIS	***	**	***	8
Puett 2009, Nurses Health Study	***	**	***	8
Puett 2011, Health Professionals U.S.	***	**	***	8
Pun 2017, Medicare	***	**	***	8
Qiu 2017, Hong Kong Elderly Health	***	**	***	8
Shin 2019, ONPHEC	****	**	***	9
Stafoggia 2014, ESCAPE	****	**	***	9
Tseng 2015, Civil Servants Taiwan	**	**	***	7
Turner 2016, CPS-II	**	**	***	7
Villeneuve 2015, CNBSS	**	**	***	7
Weichenthal 2014, AHS	**	**	***	7
Wolf 2015, ESCAPE	****	**	***	9
Wong 2015, Hong Kong Elderly Health	**	**	***	7
Yin 2017, China	**	**	***	7

Table S1 displays the Newcastle-Ottawa Scale for cohort studies. Selection included 4 possible stars (1. Representativeness of the exposed cohort, 2. Selection of the non-exposed cohort, 3. Ascertainment of exposure, and 4. Demonstration that outcome of interest was not present at start of study). Rankings for selection biases varied across studies, with differences mostly driven by representativeness of the exposed cohort (selected groups were not given a star) and demonstration that the outcome of interest was not present at the start of the study (incident events). Comparability included two possible stars for the degree of comparability of cohorts on the basis of the design or analysis. All studies received two stars for comparability as they appropriately controlled for important covariates (specific details are provided in Table 1).

Outcome included three possible stars (1. Assessment of outcome, 2. Length of follow-up, 3. Adequacy of follow up). Regarding the outcome section, all studies received a star for assessment of outcome (reference to secure records and/or use of ICD codes), long enough follow-up time, and adequacy of follow-up.

* The scale includes three categories (Selection, Comparability, and Outcome), each with numbered items ranking the possibility for bias. Stars were given to each numbered item according to study design and quality, with a maximum of 9 stars per study. One study (Madrigano et al. 2013) used a case-control study design and therefore was not compared to the other cohort studies using NOS.

† We gave every study a star for selection of non-exposed cohort ("drawn from the same community as the exposed cohort") and a star for ascertainment of exposure ("secure record"). For these air pollution studies, there are no "unexposed" subjects but instead "less exposed" subjects drawn from the same cohort. All studies also used sufficient sources of air pollution data.