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The concentration-response between long-term $PM_{2.5}$ exposure and mortality; A meta-regression approach

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ABSTRACT

Background: Long-term exposure to ambient fine particulate matter (≤ 2.5 μg/m^3 in aerodynamic diameter; $PM_{2.5}$) is significantly associated with increased risk of premature mortality. Our goal was to provide an updated meta-analysis of all-cause and cause-specific mortality associated with exposure to $PM_{2.5}$ and to better estimate the risk of death as a function of air pollution levels.

Methods: We systematically searched all published cohort studies examining the association between long term exposure to $PM_{2.5}$ and mortality. We applied multivariate linear random effects meta-analysis with random effects for cohort, and study within cohort. Meta-regression techniques were used to test whether study population or analytic characteristics modify the $PM_{2.5}$ mortality association and to estimate the shape of the concentration-response curve.

Results: A total of 53 studies that provided 135 estimates of the quantitative association between the risk of mortality and exposure to $PM_{2.5}$ were included in the meta-analysis. There were 39 studies from North America, 8 from Europe, and 6 from Asia. Since 2015, 17 studies of long-term air pollution exposure have been published, covering, wider geographic areas with a wider range of mean exposures (e.g. < 12 or > 20 μg/m^3). A penalized spline showed the slope decreased at higher concentrations but appeared to level off. We found that the inverse transform of average $PM_{2.5}$ well approximated that spline and provided a parametric estimate that fit better than a linear or logarithmic term for average $PM_{2.5}$. In addition, we found that studies using space time exposure models or fixed monitors at Zip-code scale (as compared to land use regression method), or additionally controlling for area level socio-economic status, or with mean exposure less than 10 μg/m^3 were associated with higher mortality effect estimates.

Conclusions: This meta-analysis provides strong evidence for the adverse effect of $PM_{2.5}$ on mortality, that studies with poorer exposure have lower effect size estimates, that more control for SES increases effect size estimates, and that significant effects are seen below 10 μg/m^3. The concentration -response function produced here can be further applied in the global health risk assessment of air particulate matter.

1. Introduction

Long-term exposure to ambient fine particulate matter (≤ 2.5 μg/m^3 in aerodynamic diameter; $PM_{2.5}$) is significantly associated with increased risk of premature mortality. Epidemiological cohort studies, conducted largely in United States (the Harvard Six cities (HSC) cohort (Lepeule et al., 2012; Dockery et al., 1993), the American Cancer Society (ACS) cohort (Turner et al., 2016; Pope et al., 2002), the US Medicare Cohort (Di et al., 2017; Zeger et al., 2008), the Women's Health Initiative cohort (Miller et al., 2007), the Nurses' Health Study (NHS) cohort (Hart et al., 2015; Puett et al., 2009) and Europe (Beelen et al., 2014a, 2014b), reported this association at low to moderate annual ambient average concentrations (from approximately 5 to 30 μg/m^3). Recently evidence from Asia, where the levels of $PM_{2.5}$ exceed the World Health Organization (WHO) annual limit (10 μg/m^3) (World Health Organization, 2005) also showed an association between long-term $PM_{2.5}$ exposure and all-cause, lung cancer and cardiovascular mortality (Tseng et al., 2015; Katanoda et al., 2011; Ueda et al., 2012; Wong et al., 2016).

Given quantitative evidence of long-term exposure to $PM_{2.5}$ impact on mortality, researchers have conducted systematic reviews (Hoek et al., 2013; Chen et al., 2015; Hamra et al., 2014; Pelucchi et al., 2009) that integrate existing information and provide concentration-response for health impact assessments. In this meta-analysis, we extend those reviews in several ways. First, we incorporate additional studies; (Di et al., 2017; Crouse et al., 2015; Ostro et al., 2015; Pinault et al., 2017;

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Wang et al., 2017; Shi et al., 2016; Weichenthal et al., 2014; Pinault et al., 2016; Weichenthal et al., 2016; Villeneuve et al., 2015; Hao et al., 2015; Hart et al., 2015; Dehbi et al., 2017; Dimakopoulou et al., 2014; Yin et al., 2017; Wong et al., 2015) that have been published since 2015. Importantly, some of those studies provide vital evidence of the shape of the association at both the low end of the exposure distribution and at the high end. Specifically, 14 studies were conducted on cohorts with mean exposure less than 10 $\mu g/m^3$, and 8 were conducted on cohorts with mean exposure above 20 $\mu g/m^3$. Second, earlier reviews primarily examined studies of all-cause mortality, excluding ones that only looked at mortality at age above 65, or at cardiovascular deaths. Some reviews have examined those outcomes separately. However, 70–80% (Kochanek et al., 2016) of all deaths in the developed world occurs at ages above 65, so it is unreasonable to assume that studies of deaths of people above age 65 are not informative about the risk of deaths at all-ages and vice versa. Moreover, in 2012, WHO estimated that about 80% of outdoor air pollution-related premature deaths were due to ischemic heart disease and strokes (World Health Organization, 2016), suggesting again, that studies reporting associations with cardiovascular deaths are informative about the risk of all-cause deaths, and vice versa. The Global Burden of Disease (GBD) compare tool estimates that worldwide 58% of early deaths due to particulate air pollution are cardiovascular deaths and 19% are from chronic respiratory disease. Since most of the cohort studies examining the impact of air pollution on mortality were performed in developed countries, the proportions of deaths due to air pollution exposure that are cardiovascular was even higher in the studies contributing to the meta-regression. Thus, combined analyses with studies using all types of mortality as outcome should have an advantage for estimating effect sizes for all of these outcomes, particularly in estimating the shape of the concentration-response, where additional studies at concentrations that were less represented in outcome specific meta-analyses can be very useful.

Further, estimates of pollution-related excess mortality depend on biases due to exposure error, which may differ from study to study by exposure assessment method. The most common exposure assessment methods in epidemiological studies include; hybrid space time model (which use combinations of satellite remote sensing, meteorology and land use as predictors) (Kloog et al., 2014; Di et al., 2016), chemical transport models (which use bottom up physics and chemistry models, weather data and emissions data to simulate the atmospheric formation and transport of particles) (Geng et al., 2015), land use regression models (which use land use and meteorology as predictors) (Hoek et al., 2008) and fixed monitors data. The first three sets of models are calibrated at monitoring sites. The exposure-response may also differ by particle composition or population characteristics.

Previous quantitative summaries of effect size estimates of $PM_{2.5}$ and mortality have been meta-analyses, which estimate a common effect size across studies. Meta-regressions, in contrast, have independent variables that predict differences in effect size estimates (the dependent variable in the meta-regression) across studies based on study characteristics, which can include the average concentration in the study, or the other potential effect modifiers described above. This analysis applies such an approach to investigate whether heterogeneity between the studies may be explained by differences in characteristics of the studies (e.g. exposure assessment method) or study populations characteristics (age, gender and socio-economic status) or exposure level. This next step in integrative methodology can help us better understand concentration-response, and which study-level factors drive the measures of effect.

In this manuscript, we provide an updated meta-analysis, specifically using meta-regression to assess the dependence of the effect size on mean $PM_{2.5}$ concentration, on exposure assessment method, on cause of death, on source of particles and on population characteristics.

2. Methods

2.1. Literature search

We systematically searched all published cohort studies that examined the association between long term exposure to $PM_{2.5}$ and mortality. This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). We identified studies through a search in Pubmed (Medline Ovid), Embase, EBSCO, Web of Science and Global Health on CAB databases (last accessed on April 20, 2017). The following keywords were used: 'mortality ', 'air pollution', 'particulate matter', 'PM2.5'. Hand searching of selected journals and checking of bibliographies in relevant published reviews or articles were also performed to supplement the electronic searches. The complete search strategy used for the databases is shown in Table 1 in supplemental material.

2.2. Inclusion and exclusion criteria

Studies were included in the current meta-analysis based on the following criteria; (1) studies of long-term association of outdoor $PM_{2.5}$ with mortality, including all-cause-all-age, respiratory, cardiovascular, cardiopulmonary or lung cancer mortality; and all-cause, age 65 + (2) information on study period, locations and population was explicit (3) effect estimates such as beta coefficient (β) with standard error (SE) or relative risk (RR) with 95% confidence interval have been provided. The description of the method for assigning exposure also had to be present. Experimental studies, case reports, studies on short-term associations between $PM_{2.5}$ and mortality, publications with no or incomplete results and studies provided data on only specific subpopulations were excluded. Articles not written in English were not considered for inclusion. For each study, the data were independently extracted by two investigators (AV and YA), and if their evaluations differed, the discrepancy was resolved by discussion and adjudicated by a third investigator (JS). Based on the above criteria, the selected mortality outcomes associated with particle exposure used in this analysis were as follows; all-cause mortality, elderly all-cause mortality, cardiovascular mortality, elderly cardiovascular mortality, lung cancer mortality, cardiopulmonary mortality, and respiratory mortality. Studies were included regardless of significance of results.

2.3. Statistical analysis

For the selected studies, the title, authors, region, publication year, study period and specific mortality risk estimates were extracted and entered into a Microsoft Excel database (Version2010 Microsoft, Redmond, WA, USA). All risk estimates were expressed as beta coefficient and their standard errors (SE). Variables that might modify the effects of $PM_{2.5}$ on mortality such as percent of study population that was female, age distribution, mean $PM_{2.5}$ concentration, percent of smoking and different exposure assessment methods were collected.

2.4. Meta-analysis

To estimate the overall mortality effect size, we applied multivariate linear random effects meta-analysis and meta-regression models. Some of the large cohorts (Medicare, Harvard Six Cities, ESCAPE, ACS etc.,) were represented by more than one study. This could be because different studies examined different outcomes, used different exposure methods, or had different follow-up periods. Rather than only use the latest study, we used all of them, because that can help inform our understanding of what is associated with differences in coefficients. To address the correlation among multiple analyses of the same cohort, we incorporated random nested random effects of study within cohort. We ran these analyses using the function 'rma.mv' within the {metafor}

package (Viechtbauer, 2010) under the R platform (version 3.1.3; R Core Team 2015) (CORE TEAM, 2015).

The model assumes:

$$\beta_{ijk} = b_0 + f(averagePM_{2.5}) + c_k I_k + b_1 Elderly + b_2 Female + \boldsymbol{\gamma modifiers} + u_i + v_{ij}$$

where β_{ij} is the coefficient extracted from study j in cohort i, I_k are indicator variables for categories of death (CVD, lung cancer, etc) c_k *are the coefficients capturing the difference in effect size estimate for* $PM_{2.5}$ *between each category and the reference category (all cause),* elderly is a variable indicating whether the coefficient was extracted from an elderly population study, and female is an indicator variable for a coefficient extracted from a study comprising only females. Modifiers is the matrix of covariates (e.g. percent smoking, exposure assessment), and γ is the vector of coefficients for those modifiers. Each coefficient entered the analysis once. We used a random effects meta-analysis with a two-level random intercept where u_i was a random intercept for cohort i, and v_{ij} was a random intercept for study j within cohort i. That is, we assumed that even conditional on the modifiers, there were some unexplained differences in effect sizes across studies, with a variance component that needed to be estimated. That variance in the effect size was assumed to be across cohorts, and if more than one study was found from a cohort, across studies nested within the underlying cohort. The variance across outcomes is captured by the fixed effect indicators I_k.

We defined $averagePM_{2.5}$ as the mean $PM_{2.5}$ in each study from each cohort and used it as an effect modifier to examine how the shape of the concentration-response curve changed with mean exposure level. To choose the most appropriate form of f ($averagePM_{2.5}$) we first fit our meta-regression as a generalized additive mixed model, using the the '*mgcv*' package with a penalized spline for $averagePM_{2.5}$ using our baseline model, which controlled for outcome (e.g. whether the study was restricted to all age cardiovascular deaths, all cause deaths over 65, etc). This took advantage of meta-analyses being a form of a mixed model. Since nonparametric concentration-response curves make it more difficult to use the results to estimate the number of premature deaths given the range of the air pollution concentrations and the baseline mortality rates in each region, we fit a parametric dose-response curve that is very similar to the non-parametric one, but with the advantage that we can provide a single parameter, which, with transformation of the $PM_{2.5}$ values, allows estimation of the slope at any concentration in the range that we examined. We considered a linear, a logarithmic transform, an inverse transform, and an inverse square root transform and chose the best fitting one, defined by AIC. We then compared that graphically with the penalized spline model.

2.5. Meta-regression

WE considered other factors that may modify the $PM_{2.5}$ mortality association. These were; study population characteristics that may convey susceptibility (percent of female, age distribution, percent of smoking, percent low educational level, percent low income) and analytic characteristics (whether area level socio socioeconomic status (SES) was controlled for, type of exposure assessment) by including them separately as covariates in the meta-regression models. In addition, since toxicity of $PM_{2.5}$ mass may vary by its composition and source, we examined whether the source of $PM_{2.5}$ (expressed as percent source from natural sources (dust and sea salt), traffic, industry, biomass burning and other sources) modifies the effect of $PM_{2.5}$ and estimates of the mortality. We added to each study information regarding the distribution of $PM_{2.5}$ source based on available information from a detailed systematic review of local source contributions at global level (Karagulian et al., 2015) (Table 2 in supplemental material).

Exposure assessment was classified by categories we felt were representative of different amounts and types of exposure error. Land use regression was used as the reference as it was the most common recent approach. Some studies used fixed site monitors, either close to participants' homes, or with more regional matching which would include more exposure error, and others employed air dispersion or hybrid-space-time models. These additional factors were first examined by being individually added to the baseline model. Variables that were significant predictors of difference in effect size from those analyses were considered in a final model and kept if marginally significant (p-value < 0.10). In addition, because of the substantial number of results in studies with mean exposures below 10 μg/m^3, we also conducted a meta-analysis restricted to those studies to directly assess the evidence below the WHO guideline.

3. Results

A flow diagram of the study selection process is presented in Supplemental Figure 1. Estimates from one cohort study from Norway (Næss et al., 2006) could not be converted to units of 1-μg/m^3, and thus, this study did not contribute to the meta-estimates. Five studies that provided data on only specific subpopulations; a tuberculosis cohort (Peng et al., 2017), myocardial infarction survivors (Tonne et al., 2016; Tonne and Wilkinson, 2013; Chen et al., 2016) and U.S. veterans who were diagnosed as hypertensive (Lipfert et al., 2006), were excluded from the meta-analysis. Finally, total of 53 studies from 29 cohorts that provided 135 estimates of the quantitative association between the risk of mortality and exposure to $PM_{2.5}$ were included in the meta-analysis. There were 39 studies (18 cohorts) from North America, 8 studies (6 cohorts) from Europe, and 6 studies (5 cohorts) from Asia. The studies in the meta-analysis primarily used Cox proportional hazards models, other studies used (Wang et al., 2017; Hao et al., 2015; Kloog et al., 2013; Zeger et al., 2008) relative incidence analysis.

Table 1 summarizes the effect estimates, study population characteristics and $PM_{2.5}$ measurements for the studies included in the meta-analysis. Most of the studies reported positive significant associations between $PM_{2.5}$, while a few studies reported negative association with $PM_{2.5}$ (Ueda et al., 2012; Crouse et al., 2015). The highest association was reported in a study of women residing in 36 U.S. metropolitan areas (Miller et al., 2007).

Reported average $PM_{2.5}$ exposure levels were higher in studies from Asia and varied from 25.8 μg/m^3 to 43.7 μg/m^3, compared to the studies in North America and Europe, with ranges of 4.1–23.4 μg/m^3 and 9.8–28.3, μg/m^3 respectively. The mean $PM_{2.5}$ level across all studies was 15.7 ± 7.9. In addition, exposure assessment techniques differed across studies. Some studies used fixed site monitors, either close to participants' homes (zip-code level =7), or with more regional matching (city level = 6, area level = 7), and others employed modeling techniques, such as land use regression (n = 13), air dispersion (n = 6) or hybrid-space-time models (n = 14). Supplemental table 2 summarizes the regional averages of sources of ambient $PM_{2.5}$ with matched studies in the current meta-analysis based on their geographical area. Based on the available information, in USA 24% of urban ambient air pollution from $PM_{2.5}$ is contributed by traffic, compared to 22.6% in Europe and 23.5% in China. Percent of $PM_{2.5}$ originating from industry was higher in the Asia countries with 34% in Japan and 17.1% in China, compared to 5.2% in USA and 10.3% in Europe.

Table 2 present the results of the baseline meta-analyses estimating the overall and specific cause mortality. In our basic model, we found that the inverse transform of average $PM_{2.5}$ fit best among the parametric models, as judged by AIC (Fig. 1). That is, the $PM_{2.5}$ coefficient decreased inversely proportional to the mean concentration. This was also consistent with our penalized spline model (Fig. 2). Using this $PM_{2.5}$ term, and the indicators for cause of death, we found that for all-cause all-age mortality, a 1 μg/m^3 increase in $PM_{2.5}$ was associated with a 1.29% increase in all-age all-cause mortality (95%CI 1.09-1.50) at a mean exposure of 10 μg/m^3, which decreased to 1.03% (95%CI 0.97-1.11) at a mean exposure of 15.7 μg/m^3 (the mean level across all studies), and to 0.82% (95%CI-0.52-1.12) at 30 μg/m^3. The percent

Table 1
Summary of the effect estimates (beta coefficient and standard error) from cohort studies on $PM_{2.5}$ and the mortality from all-causes, cardiovascular, respiratory diseases and lung cancer.

Reference	Publish Year	Cohort	Mortality	B	SE	% Low education	% Married	% Female	% Smoking	% Low income	Mean age	$PM_{2.5}$ exposure environmental assessment	Mean $PM_{2.5}$
NorthAmerica													
Di et al. (Di et al., 2017)	2017	Medicare	All-cause, elderly	0.007	0.0001	31.7	56.2	56.0	45.8	11.5	71.0	Hybrid Space Time model	12.4
			All-cause, elderly, female	0.006	0.0001								
Wang, Y., et al. (Wang et al., 2017)	2017	Medicare	All-cause, elderly	0.021	0.002			58.0		15.0		Hybrid Space Time model	10.7
Shi, Liuhua, et al. (Shi et al., 2016)	2016	Medicare	All-cause, elderly	0.007	0.003							Hybrid Space Time model	8.1
Zeger, Scott L., et al. (Zeger et al., 2008)	2008	Medicare	All-cause, elderly	0.007	0.001							Fixed-cite monitor (Zip-code)	13.2
Pope, C. Arden, et al. (Pope et al., 2014)	2014	ACS	Cardiovascular	0.012	0.001	12.5	83.7	56.4	21.6		56.6	Land-use regression	12.6
			All-cause	0.007	0.001								
			Respiratory	-0.001	0.003								
Jerrett, M., et al. (Jerrett et al., 2013)	2013	ACS	All-cause	0.006	0.003	8.7		56.2	19.4		57.4	Land-use regression	14.1
			Cardiovascular	0.011	0.004								
			Respiratory	0.008	0.009								
			Lung cancer	0.011	0.010								
Turner, Michelle C., et al. (Turner et al., 2016)	2016	ACS	Cardiovascular	0.007	0.001	11.7	84.3	56.2	19.4			Land-use regression	12.6
			All-cause	0.007	0.001								
			Lung cancer	0.009	0.003								
			Respiratory	0.016	0.003								
Turner, Michelle C., et al. (Turner et al., 2011)	2011	ACS	Lung cancer	0.019	0.013	11.2	81.1	71.4	0.0		65.0	Fixed-cite monitor (Zip-code)	17.6
Krewski, Daniel., et al. (Krewski et al., 2009)	2009	ACS	All-cause	0.003	0.001							Fixed-cite monitor (Zip-code)	14.0
			Lung cancer	0.010	0.003								
			Cardiopulmonary	0.014	0.002								
Jerrett, M., et al. (Jerrett et al., 2009)	2009	ACS	All-cause	0.005	0.001	12.1	83.5	56.6	22.4		56.6	Fixed-cite monitor (Area)	13.8
			Cardiopulmonary	0.012	0.002								
			Cardiovascular	0.003	0.004								
			Cardiovascular, elderly	0.014	0.001								
Jerrett, M., et al. (Jerrett et al., 2005)	2005	ACS	All-cause	0.016	0.005	8.2	80.9	43.0	21.3		57.0	Dispersion models	12.6
			Lung cancer	0.036	0.020								
			Cardiopulmonary	0.012	0.007								
Pope, C. Arden, et al. (Pope et al., 2004)	2004	ACS	Cardiovascular	0.012	0.002	12.5	83.7	56.4	21.6		56.6	Fixed-cite monitor (Area)	17.1
			Respiratory	-0.008	0.003								
Pope III, C. Arden, et al. (Pope III et al., 2002)	2002	ACS	All-cause	0.006	0.002	12.5	83.7	56.4	21.6		56.6	Fixed-cite monitor (Area)	17.7
			Cardiopulmonary	0.009	0.003								
			Lung cancer	0.013	0.004								
Weichenthal, Scott, et al. (Weichenthal et al., 2014)	2014	AHS	All-cause	0.005	0.022		89.0	38.0	14.0		46.0	Hybrid Space Time model	9.5
			All-cause, female	-0.005	0.012								
			Cardiovascular	0.014	0.021								
			Cardiovascular, female	-0.050	0.023								
Gan, Wen Qi, et al. (Gan et al., 2013)	2013	Canada British Colombia	Respiratory	0.013	0.025			53.0		18.3	60.0	Land-use regression	4.1
Gan, Wenqi, et al. (Gan et al., 2011)	2011	Canada British Colombia	Cardiovascular	0.006	0.011	36.9		54.1			58.9	Land-use regression	4.1
Crouse, Dan L., et al. (Crouse et al., 2012)	2012	Canadian census mortality	All-cause	0.014	0.001	35.0	73.0	51.0			45.3	Fixed-cite monitor (Area)	8.7
			Cardiovascular	0.015	0.001								
Pinault, Lauren, et al. (Pinault et al., 2016)	2016	Canadian Community Health Survey	All-cause	0.023	0.003	23.9	61.3	54.0	25.3	6.5		Hybrid Space Time model	6.3
			Cardiovascular	0.017	0.005								
			Lung cancer	0.015	0.009								
			Respiratory	0.042	0.010								

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Table 1 (*continued*)

Reference	Publish Year	Cohort	Mortality	B	SE	% Low education	% Married	% Female	% Smoking	% Low income	Mean age	$PM_{2.5}$ exposure environmental assessment	Mean $PM_{2.5}$
Pinault, Lauren, et al. (Pinault et al., 2017)	2017	CanCHEC	All-cause	0.016	0.001	28.7				15.3	48.4	Hybrid Space Time model	7.4
			Cardiovascular	0.021	0.002								
			Respiratory	0.019	0.004								
			Lung cancer	0.015	0.004								
Crouse, Dan L., et al. (Crouse et al., 2016)	2016	CanCHEC	All-cause	0.008	0.012	34.5	74.8	50.2		15.6		Hybrid Space Time model	8.3
Weichenthal, Scott, et al. (Weichenthal et al., 2016)	2016	CanCHEC	All-cause	0.012	0.003	32.6	64.9	51.5		14.9	45.3	Fixed-cite monitor (Zip-code)	9.8
			Cardiovascular	0.007	0.005								
			Lung cancer	0.022	0.011								
			Respiratory	0.015	0.011								
Crouse, Dan L., et al. (Crouse et al., 2015)	2015	CanCHEC	All-cause	0.007	0.001	35.0	73.0	51.0			45.3	Hybrid Space Time model	8.9
			Cardiovascular	0.006	0.001								
			Lung cancer	0.006	0.002								
			Respiratory	-0.005	0.002								
Villeneuve, Paul J., et al. (Villeneuve et al., 2015)	2015	CNBSS	All-cause, female	0.011	0.003	26.1	79.8	100.0			48.5	Hybrid Space Time model	9.1
			Cardiovascular, female	0.027	0.007								
			Lung cancer, female	-0.003	0.009								
Ostro, Bart, et al. (Ostro et al., 2015)	2015	CTS	Cardiovascular, female	0.017	0.005		46.6	100.0	4.7		57.3	Dispersion models	17.9
Ostro, Bart, et al. (Ostro et al., 2010)	2010	CTS	All-cause, female	0.065	0.013		45.1	100.0	5.2		53.4	Fixed-cite monitor (Zip-code)	17.0
			Cardiopulmonary, female	0.074	0.017								
Lipsett, Michael J., et al. (Lipsett et al., 2011)	2011	CTS	All-cause, female	0.001	0.004			100.0	5.0			Dispersion models	15.6
			Cardiovascular, female	0.007	0.006								
			Lung cancer, female	-0.005	0.015								
			Respiratory, female	0.019	0.013								
Lepeule, Johanna, et al. (Lepeule et al., 2012)	2012	Harvard Six Cities	All-cause	0.013	0.003			54.7	35.8		49.6	Fixed-cite monitor (City)	15.9
			Cardiovascular	0.023	0.005								
			Lung cancer	0.031	0.013								
Laden, Francine, et al. (Laden et al., 2006)	2006	Harvard Six Cities	All-cause	0.015	0.004			55.0	36.5		50.0	Fixed-cite monitor (City)	16.4
			Cardiovascular	0.025	0.006								
			Lung cancer	0.024	0.014								
			Respiratory	0.008	0.016								
Krewski, Daniel, et al. (Krewski et al., 2000)	2000	Harvard Six Cities	All-cause	0.013	0.004							Fixed-cite monitor (City)	17.9
			Cardiovascular	0.017	0.006								
			Cardiopulmonary	0.015	0.006								
			Respiratory	-0.007	0.017								
			Lung cancer	0.013	0.014								
Dockery, Douglas W., et al. (Dockery et al., 1993)	1993	Harvard Six Cities	All-cause	0.012	0.004	28.0		54.8	36.0		49.6	Fixed-cite monitor (City)	17.9
			Lung cancer	0.017	0.014								
			Cardiopulmonary	0.017	0.006								
Puett, Robin C., et al. (Puett et al., 2011)	2011	Health Professionals	All-cause, male	-0.015	0.010			0.0	9.5		57.4	Land-use regression	17.8
Kloog, Itai, et al. (Kloog et al., 2013)	2013	Massachusetts census	Respiratory and Cardiovascular	0.047	0.005			54.0				Hybrid Space Time model	9.9
Hao, Yongping, et al. (Hao et al., 2015)	2015	NCHS	Respiratory	0.014	0.007							Fixed-cite monitor (Area)	10.7
Wang, Y., et al. (Wang et al., 2016)	2016	New Jersey US	All-cause	0.015	0.007							Hybrid Space Time model	11.3
			All-cause, elderly	0.017	0.008								

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Table 1 (*continued*)

Reference	Publish Year	Cohort	Mortality	B	SE	% Low education	% Married	% Female	% Smoking	% Low income	Mean age	$PM_{2.5}$ exposure environmental assessment	Mean $PM_{2.5}$
Thurston, George D., et al. (Thurston et al., 2016)	2016	NIH-AARP	All-cause	0.003	0.001	5.9	68.1	41.3	13.4		65.7	Land-use regression	12.6
			Cardiovascular, elderly	0.010	0.002								
			All-cause, elderly	0.002	0.002								
			Cardiovascular	0.010	0.002								
			Respiratory	0.005	0.004								
			All-cause, elderly, female	0.002	0.002								
			Cardiovascular, female	0.009	0.004								
			Cardiovascular, elderly, female	0.009	0.004								
			Respiratory, elderly	0.006	0.004								
			Respiratory, female	0.009	0.006								
			Respiratory, elderly, female	0.011	0.006								
Hart, Jaime E., et al. (Hart et al., 2015)	2015	Nurses Health Study	All-cause, female	0.017	0.007	4.0	64.0	100.0	10.0		69.0	Hybrid Space Time model	12.0
Puett, Robin C., et al. (Puett et al., 2009)	2009	Nurses Health Study	All-cause, female	0.023	0.011			100.0	13.5		62.4	Land-use regression	13.9
Hart, Jaime E., et al. (Hart et al., 2011)	2011	US trucking companies	All-cause, male	0.010	0.004			0.0			42.1	Fixed-cite monitor (Zip-code)	14.1
Miller, Kristin A., et al. (Miller et al., 2007)	2007	WHI	Cardiovascular, female	0.057	0.017	4.7	63.0	100.0	6.1		63.2	Fixed-cite monitor (Zip-code)	13.5
Europe													
Dehbi, Hakim-Moulay, et al. (Dehbi et al., 2017)	2016	NSHD &SABRE	Cardiovascular	0.026	0.061			34.4	26.2		48.5	Land-use regression	9.8
Bentayeb, Malek, et al. (Bentayeb et al., 2015)	2015	French electricity gas company	All-cause	0.013	0.012	6.8	90.2	27.2	27.6	18.4	43.7	Dispersion models	17.2
			Respiratory	-0.010	0.028								
			Cardiovascular	0.013	0.034								
Beelen, Rob, et al. (Beelen et al., 2014a)	2014	ESCAPE	All-cause	0.014	0.005			62.9	52.6		50.5	Land-use regression	13.7
Beelen, Rob, et al. (Beelen et al., 2014b)	2014	ESCAPE	Cardiovascular	-0.002	0.009	29.0	75.0	63.0	53.0		50.5	Land-use regression	13.7
Dimakopoulou, Konstantina, et al. (Dimakopoulou et al., 2014)	2014	ESCAPE	Respiratory	-0.023	0.027	27.6	65.2	66.1			52.3	Land-use regression	13.6
Carey, Iain M., et al. (Carey et al., 2013)	2013	National English Cohort	All-cause	0.021	0.005	14.5		51.6	19.3	12.5		Dispersion models	12.9
			Cardiovascular	0.010	0.007								
			Respiratory	0.060	0.010								
			Lung cancer	0.021	0.013								
Cesaroni, Giulia, et al. (Cesaroni et al., 2013)	2013	RoLS	All-cause	0.004	0.001							Dispersion models	23.0
			Cardiovascular	0.006	0.001								
			Lung cancer	0.005	0.002								
			Respiratory	0.003	0.003								
Beelen, Rob, et al. (Beelen et al., 2008)	2008	NLCS-AIR	All-cause	0.006	0.005			51.7	26.0		61.4	Land-use regression	28.3
			Cardiovascular	0.004	0.008								
			Lung cancer	0.006	0.018								
			Respiratory	0.007	0.013								
Asia													
Yin, Peng, et al. (Yin et al., 2017)	2017	China	All-cause	0.009	0.000	72.3	91.0	0.0	68.2		54.8	Hybrid Space Time model	43.7
			Cardiovascular	0.009	0.000								
			Lung cancer	0.011	0.002								

(*continued on next page*)

Table 1 (*continued*)

Reference	Publish Year	Cohort	Mortality	B	SE	% Low education	% Married	% Female	% Smoking	% Low income	Mean age	$PM_{2.5}$ exposure environmental assessment	Mean $PM_{2.5}$
Wong, Chit Ming, et al. (Wong et al., 2016)	2016	Hong Kong	All-cause, elderly	0.012	0.002	3.5		66.6	9.5			Fixed-cite monitor (Area)	33.7
			Lung cancer, elderly	0.013	0.009								
			Lung cancer, elderly, female	-0.001	0.013								
Tseng, Eva, et al. (Tseng et al., 2015)	2015	Taipei	All-cause	-0.008	0.012	2.1	40.6	43.0	43.2	9.5	41.3	Fixed-cite monitor (Area)	29.7
			Cardiovascular	-0.022	0.032								
Wong, Chit Ming, et al. (Wong et al., 2015)	2015	Hong Kong	All-cause, elderly	0.013	0.003	45.5		65.8	9.6	14.7	71.9	Hybrid Space Time model	34.6
			Cardiovascular, elderly	0.020	0.006								
Ueda, Kayo, et al. (Ueda et al., 2012)	2012	NIPPON, Jappan	All-cause	-0.002	0.003			56.7	33.6		48.9	Fixed-cite monitor (City)	30.2
			Cardiovascular	-0.011	0.005								
Katanoda, Kota, et al. (Katanoda et al., 2011)	2011	Japan	Lung cancer	0.021	0.006			57.0	45.7		57.0	Fixed-cite monitor (City)	27.6
			Respiratory	0.015	0.006								

Abbreviations: **CanCHEC**; Canadian Census Health and Environment Cohort, **CNBSS**; Canadian National Breast Screening Study (CNBSS), **EFFECT**; Enhanced Feedback For Effective Cardiac Treatment, **WHI**; Women's Health Initiative, **NIH-AARP**; National Institutes of Health AARP Diet &Health, **ACS**; American Cancer Society, **AHS**; agricultural health study, **CA CPS I**; The California Cancer Prevention Study I, **ESCAPE**; European Study of Cohorts for Air Pollution Effects, **NSHD**; National Survey of Health and Development, **SABRE**; Southall And Brent Revisited, **MINAP**; Myocardial Ischemia National Audit Project, **NIPPON**; National Integrated Project for prospective Observation of Non-communicable diseases, **CTS**; California Teachers Study, **NLCS**; Netherlands Cohort Study on Diet and Cancer, **RoLS**; Rome Longitudinal Study.

[a]Non-accidental mortality reported if all-cause mortality was not available.

Table 2
Estimates from meta-regression for the association between long term $PM_{2.5}$ exposure on Overall and Specific Mortality risk.

Mortality	Coefficient	SE	p-value	Percent increase at $PM_{2.5}=10$, (%)
Inverse transform of average $PM_{2.5}$ $=\frac{1}{PM_{2.5}}$	0.071	0.038	0.060	–
Intercept (All-cause mortality)[a]	0.006	0.003	0.033	1.29(1.09–1.50)
Cause specific mortality				
Cardiovascular mortality	0.002	0.001	< 0.001	1.46 (1.25–1.67)
Lung cancer mortality	0.002	0.001	0.008	1.22 (0.87–1.39)
Respiratory mortality	− 0.002	0.001	0.139	1.13 (0.85–1.41)
Cardiopulmonary mortality	0.006	0.001	< 0.001	1.92 (1.59–2.25)
Elderly studies only (yes/no)	0.003	0.001	< 0.001	1.61 (1.35–1.85)
Female studies only (yes/no)	0.0002	0.001	0.892	1.31 (1.01–1.62)

[a] All-cause, all-ages mortality represents the reference group to indicators for cause specific mortality.

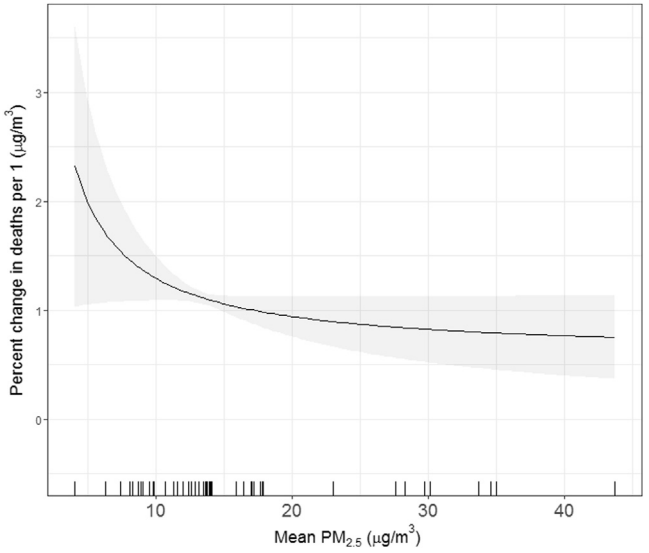

Fig. 1. Meta-regression analysis of long-term $PM_{2.5}$ exposure and percent change in mortality.

increase was larger for cardiopulmonary, cardiovascular and elderly mortality with 1.92% (95%CI1.59–2.25),1.46% (95%CI 1.25–1.67) and 1.61% (95%CI 1.35–1.85), respectively at a mean exposure of 10 μg/m^3, but smaller for respiratory and lung cancer deaths with 1.13% (95%CI 0.85–1.41) and 1.22% (95%CI 0.87–1.39), respectively.

We further examined the effect modifiers described above. Since some of the studies did not report on study population characteristics, studies with missing information were excluded from the analysis. We found several additional modifiers of effect size. Table 3 shows the meta-regression results of $PM_{2.5}$–mortality estimates on selected modifiers, and the number of the studies excluded due to the missing information. $PM_{2.5}$ exposure assessment with a hybrid space time model (i.e. using combinations of satellite remote sensing, chemical transport models, land use and meteorological variables) and fixed monitors at Zip-code scale (as compared to land use regression method as our reference) were significantly associated with higher $PM_{2.5}$ effect size estimates. The percent increase in mortality rates per 1 μg/m^3 at a mean exposure of 10 μg/m^3 was estimated to be 1.61% (95%CI 1.18–2.04) and 1.67% (95%CI 0.85–2.49), respectively when those exposure assessments were used. In addition, we found that controlling for area SES

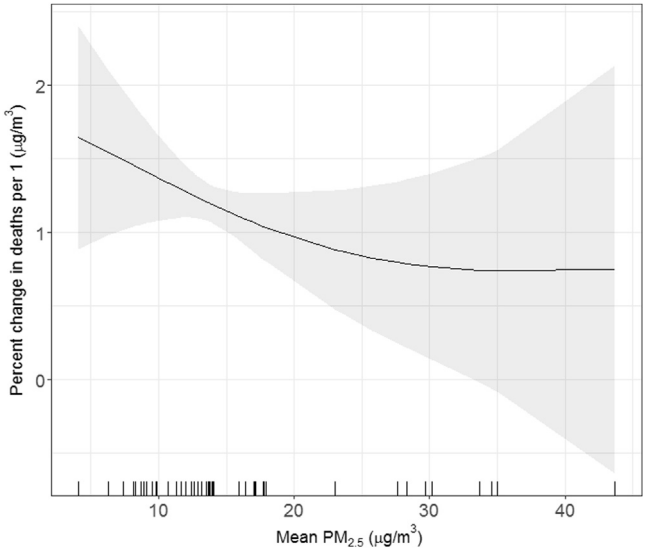

Fig. 2. Penalized spline model plot of long-term $PM_{2.5}$ exposure and percent change in mortality.

(additionally to the individual level SES) was significantly associated with higher effect size estimates with 1.43% (95%CI 1.20–1.66) at mean exposure of 10 μg/m^3. Moreover, geographical locations with higher percent of $PM_{2.5}$ sourced from traffic was significantly associated with higher estimates with a 2.05% increase in mortality rate (95%CI 1.89–2.81) per μg/$m^{3.}$. Other variables in the meta-regression (percent of female, percent low income and percent low education or age distribution) were not significantly associated with the mortality estimates. We then fit a combined model with all the significant variables from the separate analysis (Area level SES and fixed monitors at Zip-code scale, hybrid space time model and particles from traffic source). Only Area level SES variable remained significant in our final model, however the effect estimates for the other modifiers did not changed in the combined model, suggesting this is a power issue rather than confounding by other modifiers. Assuming that the space time models have higher effect estimates because of smaller exposure error, the best estimated all-cause mortality effect size at 10 μg/m^3 would be 1.61% (95%CI1.18–2.04). In addition, our meta-regression restricted to studies with mean concentrations below 10 μg/m^3 was significant with a 2.4% increase per 1 μg/m^3, 95% (95%CI 0.8–4.0).

4. Discussion

This comprehensive meta-analysis assessed the associations between exposure to chronic fine particulate matter pollution and all-cause mortality. It advances on previous ones (Hoek et al., 2013; Chen et al., 2015; Hamra et al., 2014; Pelucchi et al., 2009) in several ways, in addition to incorporating more studies. First, by including the association between e.g. the coefficients of all-cause mortality and the coefficients of mortality among persons aged 65 or more in a meta-regression framework, we are able to incorporate many more studies than previous meta-analyses, which dealt with outcomes individually. This, in turn gives us more power to examine effect modification by both exposure concentration as well as other potential modifiers. For example, the most recent meta-analysis by Hoek et al. (2013) used 11 coefficients of all-cause all-age mortality and 10 coefficients of cardiovascular mortality whereas we were able to use 135 coefficients from 53 cohort studies. Second, by taking advantage of newer studies at higher and lower exposure concentrations we were able to estimate how the effect size estimate changes across the range of exposure concentrations, showing both evidence of effects below the WHO guideline of 10 μg/m^3 and providing, for the first time, estimates at

Table 3
Meta-regression results of $PM_{2.5}$–mortality estimates on selected modifiers.

		Percent increase in mortality at $PM_{2.5}$ = 10, (%)	Percent increase in mortality at $PM_{2.5}$ =10, (%) at the 25th percentile of the modifier[a]	Percent increase at $PM_{2.5}$ =10, (%) at the 75th percentile of the modifier[a]	p-value for modifier
Baseline model		1.29% (1.09–1.50)			
Population characteristics	Baseline model + Percent Female[b]		1.12 (1.09–1.23)	1.48 (1.22–1.75)	0.826
	Baseline model + Percent Smoking[b]		1.34 (0.87–1.81)	1.14 (0.67–1.60)	0.467
	Baseline model +Age Distribution[b]		0.93 (0.69–1.17)	1.06 (0.71–1.41)	0.475
	Baseline model +Percent low income[b]		1.41 (0.76–2.06)	2.11 (0.72–3.48)	0.291
	Baseline model +Percent low education[b]		1.17 (0.82–1.53)	1.39 (1.23–1.55)	0.419
Different sources of ambient $PM_{2.5}$	Baseline model + %Natural sources (dust and sea salt)		1.32 (1.06–1.57)	1.35 (1.16–1.54)	0.788
	Baseline model + %Traffic particles		1.04 (0.72–1.36)	1.33 (1.22–1.53)	0.043
	Baseline model + % Industry		1.26 (0.92–1.56)	1.26 (1.04–1.45)	0.833
	Baseline model + % Biomass burning		1.32 (0.83–1.81)	1.32 (0.99–1.64)	0.854
Categorical variable for exposure assessment method (Reference LUR; Land Use Regression	Baseline model +local Monitors (Zip-code)	1.67 (0.85–2.49)			0.060
	Baseline model +city level Monitors	1.45 (0.56–2.34)			0.144
	Baseline model +Area level Monitors	0.90 (0.18–1.62)			0.606
	Baseline model +Dispersion models	1.10 (0.19–2.01)			0.421
	Baseline model +Hybrid Space Time models	1.61 (1.18–2.04)			0.024
Area level SES Controlled (yes/no)		1.43 (1.20–1.66)			< 0.001

All the adjusted terms were entered in to the model separately.

[a] Percent increase in mortality at $PM_{2.5}$ = 10 μg/m^3, calculated based on the, 25th and 75th percentile levels of the continuous variables; percent female = 41.7,56.4, percent smoking = 13.5,33.6, age distribution = ,48.4,61.4; percent low income= 11.9,15.3, percent low education = 7.2,28.7, percent natural sources= 6.5,10.0, percent traffic= 19.3,26.5, percent industry= 5.0,13.0, percent biomass burning= 6.2,21.7.

[b] The number (%) of the studies excluded due to the missing information are the following: percent female; 8 (15.1%), percent smoking; 17 (32.1%), age distribution; 16 (30.2%), percent low income; 42 (79.2%), percent low education; 23 (46.4%).

higher concentrations that do not rely on extrapolation from other exposures (e.g. secondhand smoke). Third, this is the first meta-analysis to examine how the nature of the exposure assessment in published studies impacts effect size estimates. We found that less error prone exposure assessments tended to produce higher effect estimates, suggesting that meta-analyses that ignore exposure error will likely underestimate effect sizes, since the studies with more exposure error are producing downwardly biased effect size estimates. Importantly, we show that more control for SES is associated with larger effect size estimates, indicating that confounding by SES is unlikely to be a source of upward bias in $PM_{2.5}$ effect estimates. Finally, we identified traffic particles as likely to be more toxic than average, on a unit mass basis.

Our baseline analysis found a percent increase in all-cause mortality per 1 μg/m^3 in $PM_{2.5}$ of 1.03% (95%CI 0.97-1.11) at a mean exposure of 15.7 μg/m^3 as compared to 0.6% (95% 0.4–0.8) in the previous Hoek meta-analysis. This likely reflects our ability to account for the smaller effect size estimates at higher exposures by including mean $PM_{2.5}$ concentration as a modifier. Those smaller number pull down the average effect size estimate in a meta-analysis, while a meta-regression that accounts for that variation will avoid a downward bias in the effect at lower exposures. However, we confirm the results of the meta-analysis by Hoek et al. (2013), which found a higher effect size for $PM_{2.5}$ for deaths from cardiovascular disease than from respiratory diseases.

The findings from the current meta-analysis indicated that the effect size decreased with increasing $PM_{2.5}$ concentrations across the studies, providing evidence of a nonlinear concentration response association. This has been noted previously. To estimate the concentration-response association at the higher ambient exposures, Geng et al. (2015), Burnett et al. (2014), fitted an integrated exposure–response (IER) model where active smoking and secondhand exposures were converted to estimated annual $PM_{2.5}$ exposure equivalents using inhaled doses of particle mass. This function was updated and utilized in several recent assessments of global mortality from $PM_{2.5}$ (Apte et al., 2015; Song et al., 2017; Cohen et al., 2017). There are three main differences between the approach in IER function and the approach in the current meta-analysis; (1) rather than trying to convert cigarette smoke exposure to $PM_{2.5}$ our analysis was able to rely on actual studies of ambient $PM_{2.5}$; (2)whereas the IER model specified an a priori functional form that required predicted estimates to flatten out in high exposures, the current analysis first used an agnostic fit based on penalized splines and then chose a functional form that was very close to the spline and minimized AIC; (3) in the IER function, RR estimates were weighted by the inverse of the variance estimate, assuming no heterogeneity between the studies. In our analysis we consider a random effect for each study and cohort. By using newer $PM_{2.5}$ studies at high (and low) concentrations we were able to provide insight into the shape of the concentration–response using only ambient $PM_{2.5}$ exposure studies which should provide a more reliable estimate of what the impact is at those concentrations. As is clear from Fig. 2, our empirical concentration-response curve flattens out at higher concentrations, as does the IER curve. However, this flattening is not as steep as the IER, as Asian studies at high concentration report larger effect size estimates than would be expected from the IER. Hence estimates of the global attributable fraction of deaths due to air pollution using the current study would be higher than the estimates using the IER function. Importantly for the developed world, we also find a larger effect at concentrations below 10 μg/m^3 as well.

In addition, our meta-regression analysis showed that exposure assessment with hybrid space time model, or nearby fixed monitors (as compared to land use regression method) resulted in higher estimates. This suggests that the lack of time resolution in many of the land use regression exposure estimates may result in exposure error, such as different spatial patterns in years not sampled in the exposure model, and consequently downwardly bias the effect size. Moreover, our results show a clear pattern of effect estimates decreasing as the exposure measurement error increases; i.e the lowest effect estimate was found using the monitor information within area scale as compared to the land use regression method, then dispersion models, monitors within city scale, monitors within zip-code scale and finally the highest effect estimate observed using the hybrid space time model. Thus, since the exposure assessment measurement method matters, the latter should be considered while estimating the effect of health outcomes associated with air pollution. In particular, the effect size estimates from using area level monitors produce estimates 30% lower than those from land use regression, and 44–46% lower than those using the most accurate exposure models. Hence future systematic reviews may wish to discard such studies as too subject to bias due to exposure error, or, as we have done, provide a means to correct the estimate to what would have been seen had all studies used better exposure estimates. Previous meta-analyses did not assess the impact of different exposure assessment methods but rather estimated the mean of $PM_{2.5}$-mortality estimates from all the methods.

An important finding is that studies that controlled for area level SES were associated with higher mortality effect estimates. This provides assurance that the lack of such variables in some studies did not result in upward bias in effect sizes, but likely in a downward bias. This is an important finding as some air pollution studies have been criticized for not including enough SES control. Higher percentage of $PM_{2.5}$ sourced from traffic was associated with higher estimates of mortality in our current meta-analysis. This supports the evidence from recent studies showing that toxicity of $PM_{2.5}$ mass vary from place to place, depending on their respective source mixtures (Ostro et al., 2015; Thurston et al., 2016; Laden et al., 2000). However, the composition data from the individual cohorts was not available in the publications, thus our ability to identify $PM_{2.5}$ composition was limited by data availability (Karagulian et al., 2015), and variations within countries and over years in particle composition that we were unable to capture added considerable error to our classification of relative sources. Further work is clearly warranted.

We also took advantage of the relationship between meta-regression and mixed models to nonparametrically estimate the concentration-response relationship, which confirmed a shape of lower slopes at higher exposures, but also a leveling off of that decline to an asymptote. That is, at some point the slope ceased falling. This pattern, in addition to the higher AIC, justifies the use of an inverse relationship in our parametric model. Our results of the nonlinear $PM_{2.5}$-mortality concentration- response association support the evidence for the association found between $PM_{2.5}$ and cardiovascular mortality, where the concentration-response function increased more rapidly at lower concentrations and the marginal increase in the excess relative risk decreases at higher exposures (Pope et al., 2002, 2011).

Our meta-analysis also takes advantage of new studies at lower concentrations to learn more about the effect size at levels below current standards or guidelines. With 14 studies conducted on populations with mean exposure below 10 μg/m^3, we had ample power to demonstrate effects below the WHO standard. A further analysis of the Harvard Six City Study used smooth functions to explore the concentration–response relation between $PM_{2.5}$ and daily deaths at lower exposures (Schwartz et al., 2002) and found the estimated concentration-response relation was near linear with no evidence of a threshold. In a reanalysis of the data derived from the American Cancer Society (ACS), the adjusted effect of fine particles on mortality showed a stronger relationship in the lower (up to about 16 μg/m^3) than in the higher range of their values. The recent analysis from Canadian Census Health and Environment Cohort, showed that the shape of the concentration response curve for various causes of death were supra-linear, with greatest increase in the lower ranges of $PM_{2.5}$ exposure (Pinault et al., 2017). Notably, the average exposure in that cohort was only 8 μg/m^3, and the lowest measured level was 1 μg/m^3. Our meta-analysis was able to take advantage of these more recent studies to estimate the slope at lower concentrations and find significant and higher estimates. Consistent with this, even low levels of exposure from ambient air pollution have been associated with pulmonary and systemic

oxidative stress, inflammatory vascular dysfunction, increased platelet activation and blood viscosity, atherosclerosis, IHD, and altered cardiac autonomic function (Brook et al., 2010; Pope et al., 2004).

There are a number of limitations that must be acknowledged. We have assumed that the estimated coefficients from the studies were normally distributed, and that the random intercepts for cohort and study within cohort were also normally distributed. These are standard assumptions in all meta-analyses. The large sample sizes of the cohorts suggest that the first assumption is likely to have been met, and the large number of cohorts and studies used in this analysis suggests that the central limit theorem makes the second likely. The assessment of particle composition as a fraction of total was crude and may have limited our ability to detect different toxicity. While we were able to include Asian cohorts with higher exposures there are still cities whose exposure remains outside of the range of our study, and extrapolation is required to do a Health Impact Assessment there. That our evidence indicates the fall of the slope with higher concentrations seems to asymptote provides support for that extrapolation, but it remains an important uncertainty. Further, the locations of the cohort studies are not representative of the world. Hence the application of the does-response curve to populations with substantially different characteristics, or with exposure to different mixes of particle types creates additional uncertainty. This is also true for all previous attempts to generate a universal concentration-response to apply globally. We have tried to address this limitation using meta-regression methods, looking at population and particle characteristics as predictors of differences in the effect size for particles. Finally, the examination of the effect modification by study population characteristics was limited because all studies did not include all characteristics; thus caution should be applied in applying these results. In addition, percent low income was characterized differently across studies from different areas. However, we believe that while different methods were used to define percent low income they do reflects the socio-economic status in the specific locations of the study and provide information about relative, but not absolute, socio-economic position.

5. Conclusion

In conclusion, this meta-analysis provides a strong evidence for the adverse effect of long-term exposure to air pollution and mortality. There are a significant number of new studies on long-term air pollution exposure, covering wider geographic areas, and both studies where exposures were predominantly at concentrations $< 10\,\mu g/m^3$ and predominantly at concentrations $> 20\,\mu g/m^3$. The empirical findings of this analysis have important public health implications, including that the marginal benefits of $PM_{2.5}$ reduction increase as the concentrations fall, and that more SES control does not decrease effect size. Our analyses contribute to the empirical evidence on the overall mortality estimate and suggest an alternative function for further applied to global health risk assessment of air particulate matter.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2018.06.021.

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