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Critical Review

Mortality Attributable to Long-Term Exposure to Ambient Fine Particulate Matter: Insights from the Epidemiologic Evidence for Understudied Locations

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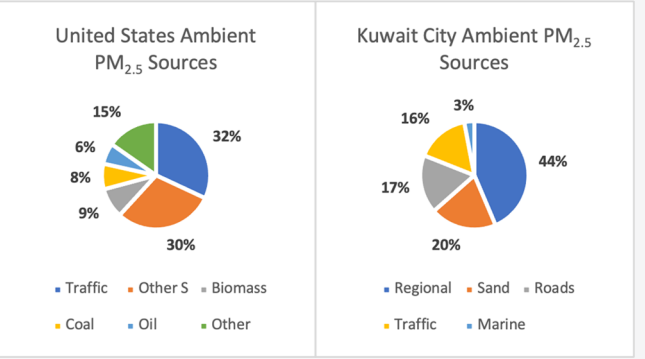
ABSTRACT: Epidemiologic cohort studies have consistently demonstrated that long-term exposure to ambient fine particles ($PM_{2.5}$) is associated with mortality. Nevertheless, extrapolating results to understudied locations may involve considerable uncertainty. To explore this issue, this review discusses the evidence for (i) the associated risk of mortality, (ii) the shape of the concentration–response function, (iii) a causal interpretation, and (iv) how the source mix/composition of $PM_{2.5}$ and population characteristics may alter the effect. The accumulated evidence suggests the following: (i) In the United States, the change in all-cause mortality risk per $\mu g/m^3$ is about 0.8%. (ii) The concentration–response function appears nonlinear. (iii) Causation is overwhelmingly supported. (iv) Fossil fuel combustion-related sources are likely more toxic than others, and age, race, and income may modify the effect. To illustrate the use of our findings in support of a risk assessment in an understudied setting, we consider Kuwait. However, given the complexity of this relationship and the heterogeneity in reported effects, it is unreasonable to think that, in such circumstances, point estimates can be meaningful. Consequently, quantitative probabilistic estimates, which cannot be derived objectively, become essential. Formally elicited expert judgment can provide such estimates, and this review provides the evidence to support an elicitation.



KEYWORDS: *Ambient Air Quality, $PM_{2.5}$, Mortality Risk, Uncertainty, Differential Toxicity, Effect Modification, Causal Inference, Kuwait*

INTRODUCTION

Long-term exposure to ambient fine particulate matter (particles < 2.5 μm in aerodynamic diameter; $PM_{2.5}$) has been recognized as a major environmental health concern around the world.[1−3] While such exposures have been found to increase the incidence of numerous heart and lung diseases and increase the rate and severity of hospital admissions, their impact on mortality is thought to be the most important factor when estimating the public benefits of regulatory policies.[4−7] The Global Burden of Disease (GBD) Results Tool has estimated that exposure to ambient $PM_{2.5}$ pollution was responsible for about 4.2 million global all-cause deaths in 2019, approximately 12% of all deaths.[8] Across the world, regulatory authorities responsible for public health and the environment have been concerned about this impact and have been designing and implementing policies to reduce $PM_{2.5}$ emissions and exposures.[9−11] When considering how to most effectively develop policy that aims to reduce the mortality impacts associated with long-term ambient $PM_{2.5}$ exposure, agencies must first review and synthesize the epidemiologic literature.

Over the past 30 years, epidemiologic studies of over 38 cohorts have consistently shown that long-term exposure to ambient $PM_{2.5}$ is associated with all-cause and cause-specific mortality (i.e., ischemic heart disease [IHD], stroke, chronic obstructive pulmonary disease [COPD], and lung cancer in adults as well as lower respiratory infections in children).[12−14] While most epidemiologists accept this relationship to be causal,[15,16] varying methodologies have been employed by cohort studies, and those methodologies do not themselves provide direct support for causality.[17] Additionally, although there have been many studies to investigate this exposure–mortality relationship, there is still substantial uncertainty as to the actual risk for any given exposure.[12−14,18] Most of this uncertainty is thought to be related to the extrapolation of results from one setting to another, due to differences in ambient levels of $PM_{2.5}$, differential toxicity depending on the source/

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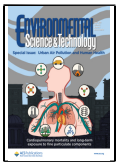

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composition of $PM_{2.5}$, and effect modification by study population characteristics.[14,15,18] Of course, methodological differences and many other unrecognized/unappreciated factors may also contribute to the observed heterogeneity. For example, Cakmak et al. has recently argued that climatic zones account, in part, for the heterogeneity seen across cohorts in Canada.[19]

Unfortunately, many of the regions that have the highest ambient $PM_{2.5}$ levels (e.g., China, India, the Middle East), and therefore are likely have the highest mortality impacts,[8] have very few or no studies that have directly investigated this relationship.[14] Thus, one must rely on this process of extrapolation. If $PM_{2.5}$ is truly differentially toxic depending on its source/composition and/or has differential effects depending on the characteristics of the exposed population, then this must be accounted for when quantitatively estimating risks based on results from cohort studies set in other regions. This is especially true when these estimates are used as inputs for analyses that look at the benefits and costs of control strategies.

The GBD's models for ambient $PM_{2.5}$ and mortality assume that particles are equally toxic and that there is no effect modification by study population characteristics, other than age.[2,20] Still, several analyses have illustrated the potential impact of differentially toxic $PM_{2.5}$ and effect modifying study population covariates. One well-cited study by Lelieveld et al. found that, after considering the potential for the differential toxicity of particles based on findings from other studies, their results were significantly altered.[21] However, the authors also had to rely on studies that are now nearly 10−15 years old.[21−23]

Therefore, the objective of this review is to discuss the available evidence on the long-term ambient $PM_{2.5}$ exposure−mortality relationship and explore how this evidence could be best used to estimate the attributable mortality in regions that have not been studied extensively, using Kuwait as an example, while properly characterizing the uncertainty in such estimates. Our goal is to inform policy that is concerned with more targeted approaches for reducing ambient $PM_{2.5}$ exposure, as well as provide information that can be used to evaluate various research strategies that aim to reduce uncertainty in estimates of attributable mortality.

EVIDENCE FOR THE EFFECT OF LONG-TERM AMBIENT $PM_{2.5}$ EXPOSURE ON MORTALITY

The Harvard Six Cities Study (SCS) by Dockery et al., the first prospective cohort study to investigate this long-term ambient $PM_{2.5}$ exposure−mortality relationship, found the risk of all-cause mortality in the dirtiest city in the United States (Steubenville, Ohio; 30 $\mu g/m^3$) to be 26% larger than in the cleanest city (Portage, Wisconsin; 11 $\mu g/m^3$), an approximate 1.4% increase in risk per $\mu g/m^3$ of ambient $PM_{2.5}$.[24] A study of the American Cancer Society (ACS) cohort by Pope et al. examined this relationship across 50 metropolitan areas that had median levels of ambient $PM_{2.5}$ ranging from 9 to 34 $\mu g/m^3$ and found an all-cause mortality effect about 1/2 as large per $\mu g/m^3$.[25] The difference in the effect estimates from these two studies was too great to be explained by chance and suggested some poorly understood cause of heterogeneity.[26] As a result, for years regulatory agencies in the United States (US) would use the smaller ACS estimate as their "central estimates" of the effect and would conduct sensitivity analyses based on the higher value from the SCS.[27]

As more studies became available, this pattern continued. Cohort studies produced a range of effect estimates; the all-male US Health Professionals Follow-Up Study (HPFS) found a protective all-cause mortality effect from exposure to ambient $PM_{2.5}$ (−1.4% per $\mu g/m^3$; although this was not statistically significant),[28] while the Canadian Community Health Survey (CCHS) study found that the risk of all-cause mortality substantially increased with increasing exposure (2.6% per $\mu g/m^3$).[29]

This raised the question of how to best synthesize the results from cohort studies. Hoek et al. conducted a systematic review and meta-analysis of 11 cohorts assessing all-cause mortality risks and 10 cohorts assessing cardiovascular mortality risks.[12] The authors found all-cause mortality effect estimates ranging from −1.4% to 2.6% per $\mu g/m^3$ of ambient $PM_{2.5}$ (HPFS vs the 2009 Nurse's Health Study),[28,30] with a central estimate of 0.6% per $\mu g/m^3$ (95% confidence interval [CI]: 0.4%, 0.8%) but noted that the collection of study results failed a test for homogeneity and needed to be treated as heterogeneous.[12]

More recently, Chen and Hoek, as an update to the previous review, found that the evidence base increased substantially.[31] They estimated an approximate 0.8% increase in risk for all-cause mortality per $\mu g/m^3$ (95% CI: 0.6%, 0.9%; based on 25 studies).[31] However, they again noted a large degree of heterogeneity across studies.[31] Pope et al. conducted a meta-analysis on the findings of over 25 years of cohort studies.[14] The authors found the same range of all-cause mortality effect estimates as Hoek et al. (−1.4% to 2.6% per $\mu g/m^3$; HPFS vs CCHS cohorts, respectively),[12] and the same central estimate as Chen and Hoek (0.8% per $\mu g/m^3$; 95% CI: 0.6%, 1.1%).[31] Once again, the authors noted that the collection of study results failed the test for homogeneity.[14]

Although a systematic review followed by a meta-analysis has great appeal, it is not the only available approach for synthesizing the evidence. Other approaches that have been considered include (i) the hybrid modeling approach underlying the GBD project's integrated exposure-response (IER) function,[32] (ii) the ensemble modeling approach underlying the Global Exposure Mortality Model (GEMM),[13] (iii) the meta-regression modeling approach used by Vodonos et al.,[18] and (iv) a formal elicitation of expert judgment, as illustrated by Cooke et al. and Roman et al.[15,16]

The purpose of the IER model, first developed by Burnett et al. for the Institute for Health Metrics and Evaluation's (IHME's) GBD project, was to identify the shape of the concentration−response function at high ambient concentrations prevalent in many places outside the Western world.[32] Prior to the IHME's GBD project, estimates of mortality attributable to ambient $PM_{2.5}$ were often constrained. Many simply assumed that relative risk (RR) stabilized at concentrations around 30 or 50 $\mu g/m^3$, implying that there was no further increase in risk above this value.[33−35] This created a major problem for agencies in highly polluted areas, since there would be no projected benefits of improving pollution unless levels were reduced to less than 30 or 50 $\mu g/m^3$. To solve this issue, based on a suggestion from Pope and co-workers, studies of long-term exposure to $PM_{2.5}$ from active smoking, second-hand tobacco smoke, and household air pollution were integrated into long-term ambient $PM_{2.5}$ exposure−mortality risk models.[32,36] This allowed for estimation of the population attributable fraction (PAF) associated with exposure to ambient $PM_{2.5}$ for all countries in the GBD project.[32] However, the IER model made some strong assumptions.[32,37] It assumed equal toxicity per unit of exposure across the all particle sources and that the estimated effects were independent of the dose rate.[13,32] Additionally, since confidentiality agreements restrict the

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sharing of cohort data, the model could only utilize the summary statistics (i.e., central estimates and 95% CIs) of individual studies.[32]

The GEMM, developed by Burnett et al., sought to relax some of the strong assumptions required by the IER model.[13] Since the IER model was first developed, some studies in East Asia examined this relationship at higher exposures.[38−40] Thus, rather than having to rely on other types of exposures, the GEMM was able to rely solely on studies of ambient $PM_{2.5}$.[13] To avoid the problem of simply fitting models based on summary statistics, Burnett and coworkers provided their model to 15 research groups to use with their own cohort data.[13,41] As an additional benefit of these within-cohort analyses, Burnett et al. were able to elucidate the risk of mortality at lower concentrations.[13] For the 26 other studies where subject-level information was not available, a linear association between exposure and the logarithm of the baseline mortality hazard ratio (HR) was assumed.[13] The GEMM was then developed by pooling predictions of the HR among the 41 cohorts over their ranges of exposure.[13] Its predicted HRs were consistently larger than those of the IER model, with much larger risks observed at higher ambient $PM_{2.5}$ concentrations (e.g., a 20% reduction in exposure yielded about four times as many attributable deaths in the Middle East and twice as many in the US and Canada when compared with the original results from the IER model).[13] However, while the GEMM made fewer strong assumptions, the model was somewhat sensitive to the exclusion of the cohort of Chinese men, which experienced a high exposure range (15−84 $\mu g/m^3$).[13,40] Burnett et al. expressed a need for additional cohort studies to corroborate the results of the Chinese cohort.[13]

Vodonos et al. conducted a meta-analysis based on 53 studies that provided 135 estimates for the long-term ambient $PM_{2.5}$ exposure−mortality relationship.[18] They applied meta-regression techniques with random effects, due to the observed heterogeneity between studies, to test whether study population characteristics (i.e., age, gender, smoking, education, income, and area-level socioeconomic status [SES]) modify the association and to estimate the shape of the concentration−response curve.[18] Since the toxicity of $PM_{2.5}$ mass may vary by its composition, the authors also examined whether the source of ambient $PM_{2.5}$ (i.e., natural sources, traffic, industry, biomass burning and other sources) modifies the relationship.[18] The curve produced by this meta-regression was steeper than the IER model, particularly at higher concentrations, in part due to the incorporation of the newer Asian studies with expanded exposure ranges.[18] However, their examination of effect modification by study population characteristics and particle composition was limited by data availability and power issues.[18]

Thus, there is still uncertainty as to how particle source/composition and population characteristics may modify the mortality risk. This illustrates a key question for risk assessors: how do we properly characterize the uncertainty in estimates of the slope of the concentration−response function for application in settings which lack direct epidemiological evidence? One option is to borrow an effect estimate from a large and well-established cohort study, like the SCS or ACS study.[24,25] However, the CIs reported by these studies are often quite narrow and reflect only parameter uncertainty. A second option is to borrow the pooled effect estimate from a recent systematic review and meta-analysis, like Chen and Hoek or Pope et al.[14,31] This typically yields a somewhat broader CI, which reflects both the parameter uncertainty from individual studies and the variation in central estimates from one study to another. Unfortunately, neither of these approaches reflect the full uncertainty inherent in applying an effect estimate derived in one location, with its own $PM_{2.5}$ source mix/composition and study population characteristics, to another location.

An approach that has the potential to properly characterize this uncertainty is formal structured expert judgment.[42] When such elicitations have been conducted, they typically have resulted in substantially broader CIs for the effect estimate than either of the other two approaches.[15,16] This is because experts consider not only objective uncertainties (such as parameter uncertainty) but also issues which are inherently subjective (such as the uncertainty inherent in borrowing evidence collected in one setting and applying it to another). As a result, the uncertainty intervals provided by individual experts are typically larger than uncertainty intervals obtained through meta-analysis. In addition, since subjective probability by its nature depends on the subject (i.e., the expert), these estimates may vary from expert to expert reflecting the heterogeneity of views held by individual experts.

Cooke et al. and Roman et al. explored this long-term ambient $PM_{2.5}$ exposure−mortality relationship with formally elicited expert judgment.[15,16] Both author groups elicited experts for the percentage estimates of the decrease in mortality following a permanent 1 $\mu g/m^3$ reduction in ambient $PM_{2.5}$ levels for the US, and Cooke et al. also did so for the European Union.[15,16] Most of the experts' mortality effect distributions were substantially broader than the distribution reported by the ACS follow-up in 2002.[15,16,43] Additionally, all but one expert gave central estimates higher than that study.[15,16,43] The 95% upper confidence estimates provided by all of the experts were greater than the central estimate derived from the SCS reanalysis in 2000.[15,16,26] Lastly, although two experts in Cooke's study gave 5% lower confidence estimates that were lower than that provided by the 2002 ACS study,[43] no expert assigned as much as a 5% probability to zero impact.[15,16] All experts agreed that there was some mortality effect of ambient $PM_{2.5}$ exposure, although there was still great collective uncertainty among them as to the true impact.[15,16]

EVIDENCE FOR THE DIFFERENTIAL TOXICITY OF AMBIENT $PM_{2.5}$ BY SOURCE AND COMPOSITION

While there is considerable evidence that long-term exposure to ambient $PM_{2.5}$ is associated with some mortality risk, there is still substantial uncertainty as to the actual risk for any given exposure. Contributors to this uncertainty include the sources and elemental components of the particles themselves, which may be differentially toxic and vary by place of study.

Ambient PM is a heterogeneous mix of particles with different physical and chemical characteristics, which depend on factors like nearby sources, atmospheric dispersion and transformation, and seasonality. Over the past two decades, there has been an increased effort to understand the health impacts of particles that originate from different sources and have varying compositions. While results from studies have been inconsistent,[44,45] in order to characterize the mortality risk in Kuwait, it is necessary to review the epidemiologic literature, postulate which components and sources may be most and least toxic, and acknowledge the limitations in the evidence.

Early on, the SCS (1993) and ACS (1995) studies investigated the risk of mortality associated with exposure to ambient $PM_{2.5}$, which has been mainly derived from anthropogenic combustion sources.[24,25] At the time, sulfate made up the largest fraction of mass for ambient $PM_{2.5}$ in the US

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(about 40%−60% for locations in both studies).[24,25] However, while both studies found that there were significant associations with mortality from ambient $PM_{2.5}$ exposure, sulfate and ambient $PM_{2.5}$ concentrations were highly correlated, making it impossible to determine whether sulfate or nonsulfate ambient $PM_{2.5}$ was responsible for these effects.[24,25]

The original SCS and ACS studies were able to investigate the effect of ambient $PM_{2.5}$ due to the US Environmental Protection Agency's (USEPA's) efforts to set up its dichotomous sampler network in 56 cities across the US beginning in 1979.[46] While there have been concerns about the differential toxicity of various components of $PM_{2.5}$ for many years, detailed information on the composition of ambient $PM_{2.5}$ across the US only began to be collected systematically in 1999 when the USEPA established what is now called the Chemical Speciation Network.[47]

One of the most notable and influential systematic investigations to take advantage of this network was the Health Effects Institute's National Particle Component Toxicity (NPACT) Initiative that launched in 2013.[23] As one element of this initiative, Thurston et al. expanded upon the ACS study to evaluate associations between long-term exposure to speciated components of ambient $PM_{2.5}$ and all-cause, cardiovascular, and pulmonary mortality.[48] The authors found the strongest associations for mortality with the coal combustion components (i.e., As, Se, and S) and, to a more sensitive and less robust extent, traffic components (i.e., elemental carbon [EC], Cu, nitrates, and S).[48] They also found that soil and biomass combustion were generally less associated with mortality.[48] Conversely, an NPACT study by Ito et al. performed time series analyses of associations of daily mortality and hospital admissions with the same data and found the traffic source category to have the most consistent associations.[49] Vedal et al., another NPACT study, used data from the Women's Health Initiative Observational Study to investigate the differential toxicity of EC, organic carbon (OC), S, and Si components on cardiovascular end points.[50] The authors found a statistically significant increase in the HR for cardiovascular disease (CVD) mortality per $\mu g/m^3$ increase in OC but nonsignificant elevated effects for the other components (S seemed to be more associated with CVD events rather than CVD mortality).[50]

Since the turn of the millennium, numerous cohort studies have investigated the differential toxicity of ambient $PM_{2.5}$ sources and/or components (Table S1), and these studies have a range of findings that often conflict with one another. For example, the NPACT studies found associations with secondary sulfates;[23,51] however, Lipfert et al.'s analysis of the all-male Veterans cohort in 2009 found that, in contrast to multiple other traffic-related components, exposure to sulfate aerosol reduced the risk of all-cause mortality (−2% per $\mu g/m^3$; 95% CI: −3%, −1%).[52] Meanwhile, an analysis by Beelen et al. of 19 European cohort projects found that exposure to sulfates greatly increased the rate of all-cause mortality (24% per $\mu g/m^3$; 95% CI: 10%, 41%).[53]

This lack of consensus has been emphasized in several recent reviews and meta-analyses of these component/source-mortality relationships. Hime, Marks, and Cowie reviewed the evidence for health effects associated with exposure to ambient PM from five common outdoor emission sources: traffic, coal-fired power stations, diesel exhaust, domestic wood combustion heaters, and crustal dust.[44] From just nine epidemiological studies that investigated health outcomes from at least two of these five emission sources, they concluded that while there is some evidence that traffic and coal-fired power station emissions may elicit relatively greater health effects compared to other sources, the evidence to date does not indicate a clear "hierarchy" of harmfulness.[44]

The first meta-analysis to examine the relationship between long-term exposure to ambient $PM_{2.5}$ chemical components and natural, cardiovascular, or respiratory outcomes was conducted by Yang et al. in 2019.[45] After restricting their analysis to 10 studies that adjusted for $PM_{2.5}$ mass, the authors found significant increases in risks for all-cause and cardiovascular mortality per $\mu g/m^3$ increase in EC (only for all-cause, but substantially so), nitrates, Zn, and Si.[45] Unfortunately, the pooled effect estimates only incorporate between one to four studies for each component−mortality relationship; thus, their findings have substantial uncertainty.[45] It also remains unclear from their report which cohort studies were eventually excluded from their meta-analyses and why (e.g., only one study was included in the meta-estimate for K and all-cause mortality, but the Supporting Information shows four studies that investigate this relationship).[45] Thus, their results should be regarded more as suggestive than conclusive.

While this review focuses on the effects of long-term exposure on mortality, short-term exposure studies may still provide insight. The first meta-analysis to examine the relationship between short-term exposure to ambient $PM_{2.5}$ components and mortality was conducted by Achilleos et al. in 2017.[54] After restricting to 38 studies that controlled for $PM_{2.5}$ mass, the authors reported significant increases in risk per $\mu g/m^3$ increase in EC and K for all-cause mortality.[54] However, much like the other meta-analyses already discussed, the observed variability across component effect estimates remained a key concern.[54]

Most epidemiologic studies that attempt to examine multiple components simultaneously also encounter a common problem—that there are often large correlations among concentrations of components of $PM_{2.5}$. This is especially true for time series studies, since temporal variations in pollution are driven mainly by meteorology, which affects all components. Additionally, many studies attempt to control for PM mass by including it simultaneously with component or source contributions, which exacerbates the issue of multicollinearity and can only explain health effects not associated with PM mass. In the absence of modeling that appropriately accounts for any multicollinearities, it is impossible to avoid bias when estimating mortality effect estimates. Therefore, toxicologic, rather than epidemiologic, studies are potentially more informative when concerned with the differential toxicity of $PM_{2.5}$ components as individual components are isolated in analyses. Additionally, establishing biological plausibility is important for inferring causality.[55,56]

One such study, by Park et al., was able to explore multiple biological and chemical end points for various source-specific aerosol exposures via several bioassays.[57] Particles from diesel engine exhaust, followed by gasoline engine exhaust, biomass burning, coal combustion, and road dust had the highest "toxicity scores" (based on multiple biological and chemical end points).[57] The results suggest that traffic plays the most critical role in enhancing toxic effects and that noncombustion sources (i.e., desert dust, sea spray aerosols, ammonium sulfate, ammonium nitrate), besides road dust, are likely less toxic.[57] However, this analysis did not include secondary pollutants (i.e., sulfates and nitrates) or evaluate interactive effects among component species.[57] Additionally, in vitro to in vivo extrapolation is necessary to predict phenomena in vivo.[57]

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Other toxicological studies have also found relatively lower effects from particles derived from sources other than fossil fuels.[58,59]

While rare, one recent epidemiological study did evaluate the potential for interactive effects among certain components. Weichenthal et al. determined that the oxidative potential of ambient $PM_{2.5}$ is associated with acute cardiovascular events, and a combined exposure to transition metals (i.e., Cu, Fe, Ni, Mn, and Zn) and sulfate increases the risk of such events.[60] According to Fang et al., sulfates increase particle acidity, which increases metal dissolution and solubility.[61] This allows metals to participate in redox reactions that contribute to oxidative stress and adverse health effects.[61] A recent review by Maciejczyk, Chen, and Thurston further discusses this relationship and concludes that fossil fuel combustion emissions are among the greatest contributors to adverse health effects.[62]

Studies of indoor/household $PM_{2.5}$ could provide some additional insights. A large cohort study in rural China by Yu et al., for example, found that household cooking and heating with wood (including charcoal) was more toxic than coal.[63] However, after comparing their results with the ambient $PM_{2.5}$ study from Yin et al., the all-cause mortality risk per $\mu g/m^3$ was about 8 times higher for outdoor $PM_{2.5}$ compared to indoor $PM_{2.5}$ from wood combustion.[40,63] The literature concerning indoor $PM_{2.5}$ exposure from solid fuel use is vast, and comparing the health effects associated with indoor versus outdoor $PM_{2.5}$ involves additional uncertainty.[13] The GBD project relies on an entirely different process to derive risk coefficients for "household air pollution from solid fuels" and "ambient particulate matter".[8] Therefore, it is difficult to draw conclusions from this literature.

It has also been hypothesized that particle toxicity may be mediated by local concentrations of ambient radon. The radioactive progeny of radon reacts with water vapor and atmospheric gases to form highly mobile clusters, which then rapidly attach to aerosols, like $PM_{2.5}$.[64−66] Blomberg et al. assessed this potential modification with daily mortality in a time series analysis in 108 US cities and found that higher mean city-level ambient radon concentrations increased ambient $PM_{2.5}$-associated mortality in the spring and fall.[66] Yitshak-Sade et al. explored the potential modification of ambient $PM_{2.5}$ on the all-cause mortality associated with long-term ambient radon exposure in a portion of the Medicare cohort, and they found a negative interaction (i.e., higher ambient $PM_{2.5}$ concentrations decreased the mortality associated with ambient radon exposure).[67] Other studies have found associations between particle radioactivity and nonfatal health outcomes like higher levels of oxidative stress and inflammation biomarkers,[68,69] high blood pressure,[70] and decreased lung function.[71]

From this body of evidence, fossil fuel combustion-related sources and components seem to be the most toxic while natural noncombustion sources and components seem to be the least toxic. However, there is a general lack of consensus among epidemiologic cohort studies, particularly when considering the relative toxicity of particle components, and it remains difficult to account for large correlations in the concentrations of components of $PM_{2.5}$. Toxicologic studies may be able to fill some of the evidence gaps; however, interpretation is hampered by the need for in vitro to in vivo or animal to human extrapolation. Most studies do not consider interactive effects among chemical species in different particle mixtures; however, recent findings on the relationship between transition metals and acidic sulfur are particularly interesting. Lastly, heterogeneity in particle sources, compositions, and study populations can further influence study comparisons.

EVIDENCE FOR EFFECT MODIFICATION BY STUDY POPULATION COVARIATES

It is possible that certain characteristics of study populations (e.g., age, sex, race, etc.) may influence the mortality risk associated with long-term exposure to ambient $PM_{2.5}$. These modifying study population covariates may serve as another cause for the observed heterogeneity in effect estimates from cohort studies. In addition to the studies where the main objective was to investigate the potential for effect modification by certain covariates, many cohort studies, while estimating all-cause and cause-specific mortality effects from long-term ambient $PM_{2.5}$ exposure, have also formally considered this possibility. To characterize the mortality risk in Kuwait, we must review the literature, posit the likelihood and level of effect modification by certain study population covariates, and acknowledge the limitations in the evidence. It is also important to acknowledge that some covariates (e.g., race/ethnicity or income) may be defined or behave differently depending on the region of interest.

For both the first SCS by Dockery et al. and the initial ACS study by Pope et al., estimates of the association between ambient $PM_{2.5}$ and mortality, when stratified by sex or smoking status, showed only small and nonsignificant differences.[24,25] In the most recent extended follow-up of the SCS cohort by Lepeule et al., there was a stronger effect in current and former smokers than in nonsmokers, but the difference was not statistically significant.[72] The most recent extended follow-up of the ACS cohort by Pope et al. showed no consistent evidence of effect modification from sex, smoking status, BMI, diabetes, blood pressure, heart disease, exercise, fat, diet, aspirin, heart medication, or diuretics.[73] This result is particularly notable as the ACS studies have been heavily weighted in both the Hoek et al. and Pope et al. meta-analyses,[12,14] although other cohorts, like the Medicare or Canadian Census Health and Environment (CanCHEC) cohorts, are now larger.[74,75]

Beyond the SCS and ACS cohorts, there have been many cohort studies that have explored potential effect modification by study population covariates with the long-term ambient $PM_{2.5}$ exposure−mortality relationship. Unlike the Six Cities and ACS studies, many of these studies have found significant and/or substantial effect modification by certain study population covariates (Table S2).

Multiple studies have reported significant and/or elevated effects based on differences in age; however, the direction of effect modification has not been consistent across studies.[29,39,74−81] Most studies reported that those of younger age groups had increased RRs/HRs compared to those of older age groups;[39,74−76,80,81] however, both Hart et al. and Kioumourtzoglou et al. reported increased HRs in populations with increased age.[78,79] Additionally, the age groups varied by study, making any synthesis of the magnitude of effect modification difficult. Despite this, it seems that the consensus among researchers is that age is an effect modifier and that younger age groups experience increased RRs/HRs for mortality. Studies of risk factors for both IHD and stroke mortality have indicated that RRs decline with the logarithm of age, with an age between 100 to 120 years serving as the reference group.[82] This effect modification has been implemented in both the IER and GEMM concentration−response models for IHD and stroke mortality.[13,32]

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Several studies have also reported significant and/or elevated effects based on differences in race/ethnicity,[74,79,81,83,84] as well as income.[75,79,81,85] Unlike age, study populations have been more consistently stratified by race/ethnicity (i.e., Black, White, Asian, Hispanic), and the observed direction of effect modification has been consistent (i.e., subjects of minority races have higher RRs/HRs compared to the majority race subjects).[74,79,81,83,84] It is also important to note that, unlike age, which is more concerned with the biological effects of aging (i.e., age is typically considered a biological determinant of health), race/ethnicity serves as a proxy for the complex social and behavioral factors that lead to varying health impacts (i.e., race/ethnicity is typically considered to be a proxy for social determinants of health).[86,87] For income, the direction of effect modification varies by study, but most studies reported increased RRs/HRs for those in lower income groups.[75,79,85] Like race/ethnicity, income is not a biological determinant of health but rather a social determinant. Additionally, income serves as a component, or proxy, for SES, which can be measured in numerous ways.[88,89] One study, Di et al., stratified its study population by eligibility for Medicaid,[74] which is based on income as well as family size and other variables.[90] However, income stratification has been inconsistent across studies.[75,79,81,85]

There have been mixed study results for other covariates (like smoking, sex, BMI, diabetes, diet, education, and urbanicity). Smoking, in particular, has been well researched, but only Pope et al. reported a significantly modified effect (in this case, never smokers were at increased relative risk for all-cause and cardiopulmonary mortality),[80] and many studies have reported there being no significant modifying effect.[24,25,29,40,72,73,78,79,85,91−94] Many covariates (i.e., diabetes, blood pressure, pre-existing IHD, exercise) have seemingly very few studies investigating their potential for effect modification (Table S2).

There are no systematic reviews and/or meta-analyses summarizing effect modification results across all studies of long-term ambient $PM_{2.5}$ exposure and mortality. The only meta-analysis of effect modification for ambient PM is that of Bell et al., which reviewed the evidence from short-term ambient PM_{10} exposure−mortality studies.[95] They found that age was a strong effect modifier, with older persons experiencing higher absolute risk of mortality (which is not inconsistent with a decreasing RR/HR with age, because of the strong age dependence of mortality).[95] Higher risks of mortality for women, those with low education, low income, and those unemployed were suggested, while race was not an effect modifier.[95] However, these findings may not apply for long-term ambient $PM_{2.5}$ exposures.

While the published studies have produced a range of results, it seems that age, race, and income are most likely to be effect-modifying covariates, and smoking is not likely to be an effect-modifying covariate. However, these conclusions are far from definitive. For most of the individual covariates, only a few studies have investigated their potential for effect modification. There also remains the issue of the inconsistent stratification of study populations by certain covariates (like age, income, smoking). While one study conducted a factor analysis to understand if and how variables have a combined impact,[79] it remains difficult to account for the interactive effects of covariates. Additionally, certain covariates might be defined or behave differently depending on the region of interest (like race/ethnicity or income in Kuwait).

EVIDENCE FOR A CAUSAL INTERPRETATION OF THE LONG-TERM AMBIENT $PM_{2.5}$ EXPOSURE AND MORTALITY RELATIONSHIP

Generally, cohort studies have demonstrated an association between long-term exposure to ambient $PM_{2.5}$ and mortality that persists even after controlling for various known risk factors (e.g., age, sex, race, marital status, education, occupation, income, smoking, alcohol consumption, diet, obesity).[14] However, this alone does not rule out the possibility for residual confounding or guarantee exchangeability between subjects. Methods that are designed to infer causality have been developed, and several studies investigating this relationship have recently addressed these concerns using causal methods. To characterize the likelihood that long-term exposure to ambient $PM_{2.5}$ causes mortality in Kuwait, we must review the relevant epidemiological evidence and comprehend the limitations of the employed causal methods.

In recent reanalyses of well-established cohorts, authors have started to implement causal inference methods to provide stronger conclusions. Over the past half-decade, many studies were published that utilize these methods.[79,96−102] These studies have all concluded that ambient $PM_{2.5}$ is causally associated with mortality, even at levels below national standards.[79,96−102]

While each of these studies produces similarly significant and positive effects, they employ a range of causal inference methodologies. Kioumourtzoglou et al., Wang et al., Yitshak-Sade et al., and Schwartz et al. used difference-in-differences (DID) to analyze this relationship within the Medicare population.[79,96,101,102] Kioumourtzoglu et al. utilized city-specific analyses across time, which eliminated confounding by factors that do not vary across time or that vary across cities, and then, the city-specific health effect estimates were combined using a random effects meta-analysis.[79] Wang et al., Yitshak-Sade et al., and Schwartz et al. implemented similar DID methods using census tracts or Zone Improvement Plan (ZIP) codes within their study populations.[96,101,102] Wang et al., Awad et al., Danesh Yazdi et al., Higbee et al., and Dominici et al. utilized inverse probability weighting (IPW) to adjust their models.[97−100,103] Wang et al. applied two additive hazards models with IPW applied to propensity scores, another method that is commonly employed for causal inference.[97] Awad et al. utilized IPW in a subpopulation of Medicare enrollees who moved their residence from one ZIP code to another, which they claim essentially randomized exposure as the new ZIP code is unlikely to be related with any confounders.[98] Danesh Yazdi et al. and Higbee et al. applied IPW within their marginal structural models, yet another method for causal inference.[99,100] Dominici et al. applied matching, weighting and adjustment to their estimated generalized propensity scores.[103] More about these methods is detailed in Hernan and Robins.[17]

While the use of causal methods can support causal interpretations, it does not guarantee causal results. All methods that have been designed to account for the lack of counterfactual outcomes in observational (i.e., nonrandomized) studies have required assumptions. More detail about these assumptions can again be found in Hernan and Robins.[17] However, if these causal methods are utilized appropriately, the potential bias will be reduced when compared with effect estimates from noncausal methods.

Although some remain unconvinced,[104−107] the body of evidence, i.e., the consistent epidemiological findings,[14,79,96−102]

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the linked biological mechanisms,[57,108,109] and results from real-world interventions,[110] overwhelmingly supports the conclusion that long-term exposure to ambient $PM_{2.5}$ causes mortality. The World Health Organization (WHO) and USEPA concluded that there was enough evidence to infer a causal link between ambient $PM_{2.5}$ and adverse health outcomes before studies using causal methods were published.[111,112] These latest study results only serve to strengthen the evidence base for such a conclusion.

APPLYING THE EVIDENCE IN UNDERSTUDIED LOCATIONS

As we have seen, extrapolating study results to estimate the mortality impacts associated with long-term ambient exposure to $PM_{2.5}$ for understudied locations, like Kuwait, requires numerous uncertain adjustments (i.e., accounting for the change in concentration and the nonlinear exposure−mortality function, the local source mix/elemental composition of $PM_{2.5}$, and the characteristics of the study population). Therefore, we propose that a formal elicitation of expert judgment be conducted.

To apply this approach to Kuwait, experts will first be asked to provide subjective probabilistic answers to questions of interest regarding the US. This serves as an effort to decompose, or disaggregate, the complex Kuwait problem by first asking questions that the experts may be generally more familiar with and that are easier to answer. For example, questions relevant to our example regarding the overall slope in the US and differential toxicity of $PM_{2.5}$ might include the following:

- Q1: What is your estimate of the true, but unknown, percent change in the annual all-cause mortality rate for adults (ages 30 and older) in the United States resulting from a permanent 1 $\mu g/m^3$ reduction in the long term annual average ambient $PM_{2.5}$ (with proportional reduction in all $PM_{2.5}$ components), from a population-weighted national baseline concentration of 7.7 $\mu g/m^3$?
- Q2a: Please rank fine particulate matter originating from each of the following sources (coal combustion, crustal, industrial, oil combustion, traffic-related, all other) in terms of their inherent human toxicity (i.e., the slope of the concentration−response function for all-cause mortality in adults [ages 30 and older]).
- Q2b: On the basis of your ranking, what is your estimate of the true, but unknown, ratio of the percent change in the annual all-cause mortality in the adult (ages 30 and older) population in the United States resulting from a permanent 1 $\mu g/m^3$ reduction in the long term annual average ambient $PM_{2.5}$ emitted from (most/least/all other toxic source[s]) to the effect that would be seen from a permanent 1 $\mu g/m^3$ reduction in the long term annual average United States ambient mix of $PM_{2.5}$, from a population-weighted national baseline concentration of 7.7 $\mu g/m^3$?

While the final versions of the questions of interest have not yet been designed, many of the questions will follow the general format of the questions used by Cooke et al. and Roman et al.[15,16] Experts will also be asked to quantify their uncertainty in providing answers to questions like Q1 and Q2b by giving 5th, 25th, 50th, 75th, and 95th percentiles of their distributions.

For experts to be able to establish rationales and appropriately answer these questions of interest regarding the US, and then later adjust their answers for Kuwait, information on the overall concentration of ambient $PM_{2.5}$ and the source mix/composition of ambient $PM_{2.5}$ for both Kuwait and the US should be made available. This information is characterized briefly below.

For the US, the following information is given: (i) The typical annual average $PM_{2.5}$ concentrations in cities are around 5−15 $\mu g/m^3$.[113,114] (ii) The major sources of ambient $PM_{2.5}$ appear to be traffic, biomass burning, and coal combustion (Figure S1), leading to an elemental composition rich in OC, nitrates, S, and EC.[115] For Kuwait, the following information is given: (i) The annual average $PM_{2.5}$ concentrations in Kuwait City are about 40−50 $\mu g/m^3$.[116−119] (ii) The leading sources of ambient $PM_{2.5}$ in Kuwait appear to be sand dust, oil combustion, and petrochemical industrial activity (Figures S2 and S3) resulting in an elemental composition dominated by S, OC, Si, EC, and Ca.[117,119] More information on the source mix/composition differences is provided in Text S1.

With the necessary background information outlined, experts can begin to estimate and adjust $PM_{2.5}$−mortality effect estimates. The proposed approach for adjusting effect estimates, borrowed from Lelieveld et al.,[21] is outlined briefly below and illustrated with an example involving differential toxicity.

Imagine that an expert identifies $PM_{2.5}$ source A (or $PM_{2.5}$ chemical constituent A) as 2 times as toxic as the ambient mix, i.e., $\beta_A = 2 \times \beta$, where β_A is the slope for source or constituent A (% increase in mortality risk per $\mu g/m^3$ of $PM_{2.5}$ from source or constituent A), and β is the slope of the ambient mix of $PM_{2.5}$. If the expert's estimate of β was 0.5% per $\mu g/m^3$, we would estimate β_A as 1% per $\mu g/m^3$. To use this knowledge to adjust the effect estimate for Kuwait, we would need to know the fraction, $f_{A\text{-}US}$, of the ambient mix in the US made up of source or constituent A and the fraction, $f_{A\text{-}K}$, of the ambient mix in Kuwait contributed by the same source or constituent.

Assume that source or constituent A was responsible for one-third of the $PM_{2.5}$ mass in the US and one-tenth of the $PM_{2.5}$ mass in Kuwait. With this known, we would estimate the slope of all other constituents of ambient $PM_{2.5}$ by solving the following equation for β_{notA}:

$$f_{A\text{-}US} \times \beta_A + (1 - f_{A\text{-}US}) \times \beta_{notA} = \beta$$

$$\beta_{notA} = \frac{1 - (f_{A\text{-}US} \times (\beta_A/\beta))}{1 - f_{A\text{-}US}} \times \beta$$

$$\beta_{notA} = \frac{1 - (0.\overline{3} \times (1/0.5))}{1 - 0.\overline{3}} \times 0.5 = 0.25\%\ \text{per}\ \mu g/m^3$$

From this, the effect estimate for the Kuwait mix, β_K, can readily be estimated as

$$\beta_K = f_{A\text{-}K} \times \beta_A + (1 - f_{A\text{-}K}) \times \beta_{notA}$$

$$\beta_K = 0.1 \times 1 + (1 - 0.1) \times 0.25 = 0.325\%\ \text{per}\ \mu g/m^3$$

A similar approach would be used to account for differences in levels of effect modifying attributes of the populations of the US and Kuwait.

To ensure that each expert gives answers which are logically coherent (i.e., do not imply that some sources or constituents have beneficial effects on health/mortality risk), these equations will be used during the elicitation to allow the expert to immediately see the implications of their choices.

Of course, these estimation procedures will also need to account for both β and β_A/β being probabilistic. Further details on this, as well as how to formally elicit, validate, and potentially

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aggregate expert judgments, will be fully explored in a subsequent paper describing the methods, data, and interpretation of results from the expert elicitation study.

DISCUSSION

Our study has several strengths. To our knowledge, this is the first review to comprehensively consider the evidence for (i) the mortality risk associated with long-term exposure to ambient $PM_{2.5}$, (ii) the shape of the concentration−response function, (iii) differential toxicity of $PM_{2.5}$, (iv) effect modification due to differences in population attributes, and (v) support for causal conclusions. In the process, we emphasized the complexity of the ambient $PM_{2.5}$−mortality relationship, characterized the heterogeneity in reported effects from large cohort studies and identified gaps in the research.

Of course, our study also has limitations. Arguably the most important of these is that the studies included in our review were not selected by a formal systematic review of the literature and therefore could be criticized as idiosyncratic.

This review makes clear that effect estimates from meta-analysis if applied directly to understudied locations, such as Kuwait, may yield implausible and potentially misleading results. It seems unlikely that exposure of Kuwaitis to ambient $PM_{2.5}$ levels of 40 to 50 $\mu g/m^3$ is responsible for 25% or 30% of all mortality in the country—as would be suggested by direct application of a coefficient of 0.8% per $\mu g/m^3$ to the levels of exposure prevalent in Kuwait.[31]

This may lead some to conclude that meaningful risk estimates cannot be made in such circumstances until local cohort studies of $PM_{2.5}$ mortality are conducted. While this view is understandable, it provides no guidance about how policy decisions should be made without estimates of risk and ignores the societal costs of deferring control decisions until epidemiological studies can be conducted, analyzed, and interpreted. It also fails to recognize the nature of risk assessment.

Risk assessment is the art and science of estimating risk based on the evidence which is currently available. It seeks to characterize the state of knowledge and, to the extent possible, produce probabilistic estimates of risk which provide decision makers with a sense of what is known and how well it is known. Such information allows decision makers to formally consider the trade-offs between acting now based on imperfect information and delaying decisions to allow research studies (with the potential for reducing uncertainty) to be designed, conducted, and interpreted.

Uncertainty may exist because of limited sample size (parameter or aleatory uncertainty) and/or because of more fundamental questions of basic science (model or epistemic uncertainty). In the first case, characterization of uncertainty using well-developed methods of frequentist statistics is relatively straightforward, objective, and uncontroversial. In the latter case, it becomes necessary to rely on formally elicited subjective judgments of leading experts in relevant fields.

Our review of the epidemiological evidence on mortality attributable to ambient $PM_{2.5}$ exposure leads us to suggest that the dominant uncertainties faced in efforts to estimate risk in understudied locations are epistemic in nature, for example, what to think about the differential toxicity of $PM_{2.5}$ from various sources, what to think about the effect modification induced by various population characteristics, and what to conclude about the sufficiency of evidence that the observed associations reflect causal relationships. For this reason, we see no realistic alternative to formal elicitation of expert judgment.

Fann et al. have argued that the current evidence is sufficient to support policy decisions in the US and that further expert judgment studies are not necessary.[120] While this may be true in the US, it is certainly not true in efforts to estimate risks in understudied locations.[121,122]

It is important to allay the fears of those who believe that conducting an expert elicitation obviates the need for conducting future epidemiological research. Nothing could be further from the truth. Properly conducted expert judgment studies can provide the information needed by risk assessors to answer two questions: (i) how to make the "best" control decisions under uncertainty and (ii) how to make good decisions about the value of further research. Nearly 20 years ago, using this approach, Wilson demonstrated that it would be worth approximately 10 billion US dollars/year to eliminate the then-current uncertainty about mortality risks posed by exposure to ambient $PM_{2.5}$.[123]

Finally, we note that the results of the proposed expert elicitation may have implications for policy and standard setting in Kuwait, in other understudied locations, and more broadly. Some impications are now given. (i) If fine particulate matter from one or more sources is appreciably more or less toxic than that from other sources, then the following may occur: (a) It may be appropriate to derive source−class specific effect estimates to support policy analysis.[124] (b) Emissions from those sources may need to be regulated more or less stringently than emissions from other sources. (c) As Li et al. suggested, ambient air quality standards for fine particulate matter may need to be adjusted to reflect local source mix and/or disaggregated/supplemented by ambient standards for fine particulate matter originating from specific sources or source classes.[125] (ii) If attributes or health behaviors of the exposed population lead to substantial effect modification, then the following may occur: (a) Estimates of risk from studies in one part of the world may not be transferred directly to other parts of the world without attempting to account for these differences. (b) Ambient air quality standards may need to be similarly adjusted. However, our goal in this review is not to explore the implications of results that we do not yet have but instead to summarize the evidence on which judgments might be based and to clearly outline an approach for utilizing this information.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.1c08343.

> Additional information related to the application of our findings in the context of Kuwait, figures showing the relevant $PM_{2.5}$ source contributions for both Kuwait and the United States, and two tables outlining studies that investigate the potential for the differential toxicity of $PM_{2.5}$ and mortality effect modification (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript. Kyle J. Colonna and John S. Evans: Concept and design; acquisition, analysis, or interpretation of data/evidence; and drafting of the manuscript. All authors: Critical revision of the manuscript for important intellectual content. John S. Evans: Supervision.

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