COMMENTS OF THE ELECTRIC POWER RESEARCH INSTITUTE ON

ENVIRONMENTAL PROTECTION AGENCY

83 FR 53471

[EPA-HQ-ORD-2014-0859; FRL-9985-68-ORD]

Integrated Science Assessment for Particulate Matter (External Review Draft)

December 10, 2018

The Electric Power Research Institute, Inc. (EPRI) respectfully submits the enclosed comments on the U.S. Environmental Protection Agency's (EPA's or the Agency's) *Integrated Science Assessment for Particulate Matter (External Review Draft)*. EPRI appreciates the opportunity to comment on this Integrated Science Assessment (ISA).

EPRI is a nonprofit corporation organized under the laws of the District of Columbia Nonprofit Corporation Act and recognized as a tax-exempt organization under Section 501(c)(3) of the U.S. Internal Revenue Code of 1986, as amended, and acts in furtherance of its public benefit mission. EPRI was established in 1972 and has principal offices and laboratories located in Palo Alto, Calif.; Charlotte, N.C.; Knoxville, Tenn.; and Lenox, Mass. EPRI conducts research and development relating to the generation, delivery, and use of electricity for the benefit of the public. As an independent, nonprofit organization, EPRI brings together its scientists and engineers as well as experts from academia and industry to help address challenges in electricity, including reliability, efficiency, health, safety, and the environment. EPRI also provides technology, policy and economic analyses to inform long-range research and development planning, as well as supports research in emerging technologies. As a tax-exempt research organization, EPRI makes its research results widely available to the interested public through license, purchase or other dissemination.

These comments on the ISA reflect EPRI's opinions derived from its research and development experience related to the study of air quality health effects, including extensive epidemiological, toxicological, and exposure research on particulate matter. These comments reflect EPRI's research activities in that they are technical rather than legal in nature. The enclosed comments reflect only EPRI's opinion and expertise and do not necessarily reflect the opinions of those supporting and working with EPRI to conduct collaborative research and development.

EPRI hopes its comments and technical feedback will be valuable to EPA.

Sincerely,

Robert Chapman
Vice President, Energy and Environment

COMMENTS

ENVIRONMENTAL PROTECTION AGENCY

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Integrated Science Assessment for Particulate Matter (External Review Draft)

Submitted by:

ELECTRIC POWER RESEARCH INSTITUTE

3420 Hillview Avenue

Palo Alto, CA 94304

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The Electric Power Research Institute, Inc. (EPRI) respectfully submits the enclosed comments on the U.S. Environmental Protection Agency's (EPA's or the Agency's) *Integrated Science Assessment for Particulate Matter (External Review Draft)*. EPRI appreciates the opportunity to comment on this ISA.

We first discuss four primary comments, and then follow with secondary comments organized by chapter.

Primary Comments

1. Confounding in epidemiological studies on PM is a critical issue, and since the last ISA many studies have focused on the evaluation and/or control of confounding in air pollution epidemiology studies. While most of these studies are discussed in the current ISA, there are several papers related to the evaluation of confounding, centered around a method developed by Greven et al. (2011), that were not included.

   Since 2014, EPRI has been supporting research to better understand confounding in long-term air pollution epidemiology studies. As such, a large Medicare dataset of over 60 million beneficiaries was obtained from the Centers for Medicare and Medicaid Services (2000-2012); these data also included cause of death for the years 2000-2008. The method of Greven et al. (2011) was applied to decompose $PM_{2.5}$ into temporal and spatio-temporal components. This approach posits that if the associations for these two independent components of $PM_{2.5}$ differ, unmeasured confounding is present. Pun et al. (2017) conducted an analysis of 20 million beneficiaries living within 6 miles of a $PM_{2.5}$

monitor and found that the temporal and spatio-temporal coefficients were different; the authors concluded that unmeasured confounding was present.

Eum et al. (2018) applied three different methods to evaluate temporal confounding in the same dataset: (1) assessing exposures using the residual of $PM_{2.5}$ regressed on time; (2) adding a penalized spline term for time to the health model; and (3) including a term that describes temporal variability in $PM_{2.5}$ into the health model, with this term estimated using the Greven et al. decomposition approach. Results showed that a 10 µg/m3 increase in $PM_{2.5}$ exposure was associated with a mortality rate ratio of 1.20 (1.20, 1.21) over the 13-year study period. However, when models adjusted for long-term time trends in $PM_{2.5}$, the associations were significantly attenuated. The most stable result was observed for the residual-based approach, and that association was reduced by approximately 50% from the unadjusted model. The authors concluded that epidemiological studies of long-term $PM_{2.5}$ can be confounded by long-term time trends, and this confounding can be controlled using the residuals of $PM_{2.5}$ regressed on time. The paper by Eum et al. (2018) is included in this comment document as Appendix A.

In light of the importance of the original Greven et al. (2011) findings, EPRI convened an expert panel in June 2017 to discuss the method and implications for its use. The panel consisted of Adam Szpiro (University of Washington), Rick Bilonick (University of Pittsburgh), and Garrett Glasgow (NERA Economic Consulting). A paper describing the meeting has been submitted (Glasgow, submitted). In light of the importance of confounding in long-term PM epidemiology studies, EPRI recommends that the work began by Greven et al. (2011) and continued by Pun et al. (2017) and Eum et al. (2018) be included and discussed in the ISA.

2. EPRI finds that the classification of the relationship between long-term exposures to $PM_{2.5}$ and ultrafine particles (UFP) and nervous system effects as “likely to be causal” is not supported by the evidence.

   The strongest evidence of the causal relationship between long-term $PM_{2.5}$ exposure and nervous system outcomes come from toxicological studies using animal models. Although these studies can provide valuable information, they have substantial limitations in offering evidence to determine the causal relationship between long-term $PM_{2.5}$ and human health. The animal toxicological studies tend to use high $PM_{2.5}$ concentrations; rodents were exposed to >100 µg/m^3 in Bhatt et al. (2015), Ljubimova et al. (2013), Tyler et al. (2016), and other studies. These high levels of PM are unrealistic compared to the long-term ambient levels that human populations experience in the US. In addition, uncertainties exist regarding animal-to-human extrapolation.

   Among the epidemiological studies based on real-world human cohorts and $PM_{2.5}$ exposure, there is considerable inconsistency in results for most of the nervous system outcomes. For cognitive effects, two epidemiological studies out of ten found statistically significant positive changes associated with long-term $PM_{2.5}$ exposure, two found significant negative changes, and the remaining six found null effects (Figure 8-3 and 8-4). For neurodegenerative diseases, four out of the eight studies found significant results; the remainder were null (Figure 8-6). For autism, four out of five found significant associations, but the small number of studies and limitations in their study methods may

constrain the interpretation of the results (Section 8.2.7.2). The results for other nervous system outcomes are largely null. Considering the results from animal toxicological studies and epidemiological studies, concluding that there is likely to be a causal relationship between long-term $PM_{2.5}$ and nervous system effects based on the studies included in this chapter appears to be an overstatement.

For long-term UFP, the animal toxicological studies have similar limitations as those related to the $PM_{2.5}$ studies. There is only one epidemiological study that investigated the association between UFP and nervous system outcomes; this study did report a significant positive association. The extremely limited epidemiological evidence does not support the "likely to be causal" relationship concluded in the ISA.

3. In some cases, presentation and discussion of the results are not consistent with respect to the direction, magnitude, and significance of epidemiological effect estimates. This unbalanced presentation could lead the reader to biased conclusions. For example, in Section 5.1.4.1.1 and Section 5.1.4.1.2, the results with positive coefficients and confidence intervals covering zero are reported as increases in effects (in page 5-57, line 29 and page 5-58, line 8), but results with negative coefficients, or estimates less than 1 in the case of RR, and confidence intervals covering zero are reported as null effects (in page 5-58, line 19). The sentence at page 5-57, line 18 states that single-city studies "reported inconsistent evidence", but all the results reported in this paragraph are null results at the confidence level the authors chose. The description of studies and the discussion of the results would be more objective if the reporting of direction and significance is consistent.

   In addition, potential bias in readers' interpretations may appear from selective reporting of estimates from some studies. For example, in Figure 5-44, Peng et al. (2008) estimated effects for lag 0, 1, and 2, and while the estimate for lag 0 is positive, the other two estimates are negative (all non-significant at 95% confidence level). The figure only included the positive estimate from this paper.

4. There are a number of studies missing from the document in multiple chapters. Some of these were published in late 2017 and 2018, after the cutoff period for the document; however, many were published prior to this date. A detailed list of missing studies in each chapter can be found in the Secondary Comments section.

Secondary Comments

EPRI's secondary comments on the ISA are categorized by chapter below.

Chapter 5: Respiratory Effects

Page 5-50: The following study should be added:

Magzamen, S., Oron, A.P., Locke, E.R., Fan, V.S. 2018. Association of ambient pollution with inhaler use among patients with COPD: a panel study. *Occup Environ Med* 75.5: 382-388.

Page 5-85: The following study should be added:

Makar, M., Antonelli, J., Di, Q., Cutler, D., Schwartz, J., Dominici, F. 2017. Estimating the causal effect of low levels of fine particulate matter on hospitalization. *Epidemiology* 28(5):627-634.

Page 5-87, line 25: Prevalence of using air conditioners may be one of the contributors to the observed geographic variability in $PM_{2.5}$ associations with respiratory-related diseases. The role of air conditioning was the main topic of the literature cited at the end of the statement, i.e., Bell et al., 2009a.

Page 5-117, line 8: Consider adding references.

Page 5-119: The following study should be added:

Lall, R., Ito, K., Thurston, G.D. 2010. Distributed lag analyses of daily hospital admissions and source-apportioned fine particle air pollution. *Environ Health Perspect* 119(4):455-460.

Page 5-131, line 8: Consider explaining what a "scripted" exposure is.

Page 5-138: The following studies should be added:

Fang, T., Verma, V., Bates, J.T., Abrams, J., Klein, M., Strickland, M.J., et al. 2016. Oxidative potential of ambient water-soluble $PM_{2.5}$ in the southeastern United States: contrasts in sources and health associations between ascorbic acid (AA) and dithiothreitol (DTT) assays. *Atmos Chem Phys* 16(6):3865-3879.

Luttmann-Gibson, H., Sarnat, S.E., Suh, H.H., Coull, B.A., Schwartz, J., Zanobetti, A., et al. 2014. Short-term effects of air pollution on oxygen saturation in a cohort of senior adults in Steubenville, OH. *J Occup Environ Med* 56(2):149.

Page 5-140, line 21: The pairwise posterior probability that elemental carbon had greater toxicity than $PM_{2.5}$ in the East is about 0.7 for respiratory hospital admissions. Consider modifying the statement "The recent analysis by Levy et al. (2012) indicated the likelihood of greater risk for EC than $PM_{2.5}$ in the East" to "The recent analysis by Levy et al. (2012) indicated a suggestive likelihood of greater risk of respiratory hospital admissions for EC than $PM_{2.5}$ in the East".

Page 5-183, Table 5-22: In Column titled "Exposure assessment", consider adding the exposure metric, i.e., whether the authors used annual averages or monthly averages.

Page 5-246: The following study should be added. It looks like a statistics paper but it estimated respiratory effects in Medicare patients:

Chang, H.H., Peng, R.D., Dominici, F. 2011. Estimating the acute health effects of coarse particulate matter accounting for exposure measurement error. *Biostatistics* 12.4: 637-652.

Page 5-5, line 16 and other locations in this chapter: Please define "Section 0".

Page 5-112 to 114, all figures: Please clarify the differences between solid circles and open circles.

Page 5-141, Figure 5-24: Consider mentioning in the figure caption that the bars of asthma, COPD, etc. in each section would add up to the first bar to add clarity.

Page 5-259, Figure 5-46: Please clarify the differences between solid and open red circles.

Page 5-310: Please clarify which section is "Section 0". Clicking on the "section 0" hyperlink in the pdf of this report takes to Ostro et al. (2015), which does not seem to be relevant to the content.

Chapter 6: Cardiovascular Effects

Overall, several studies are omitted that should have been included in the tables and discussion. The tables highlight papers published since the last PM review, but key findings of the earlier papers should have been included in the figures and discussion so that the discussion and conclusion are not based only on the most recent studies.

Pages 6-8-6-10; Table 6-1: The following studies should be added, which should also be incorporated into the discussion and Figure 6-2.

> Sarnat, S.E., Winquist, A., Schauer, J.J., Turner, J.T., Sarnat, J.A. 2015. Fine particulate matter components and emergency department visits for cardiovascular and respiratory diseases in the St. Louis, Missouri-Illinois Metropolitan Area. *Environ Health Perspect* 123(5):437-444.
>
> Kioumourtzoglou, M-A, Zanobetti, A., Schwartz, J., Coull, B.A., Dominici, F., Suh, H. 2013. The effect of primary organic particles on emergency hospital admissions among the elderly in 3 US cities. *Environ Health* 12:68.
>
> Atkinson, R.W., Fuller, G.W., Anderson, H.R., Harrison, R.M., Armstrong, B. 2010. Urban ambient particle metrics and health: a time-series analysis. *Epidemiology* 21:501-511.
>
> Bell, M.L., Ebisu, K., Peng, R.D., Samet, J.M., Dominici, F. 2009. Hospital admissions and chemical composition of fine particle air pollution. *Am J Respir Crit Care Med* 179:1115-1120.
>
> Ito, K., Mathes, R., Ross, Z., Nadas, A., Thurston, G., Matte, T. 2011. Fine particulate matter constituents associated with cardiovascular hospitalizations and mortality in New York City. *Environ Health Perspect* 119:467-473.
>
> Lall, K., Ito, K., Thurston, G.D. 2011. Distributed lag analyses of daily admissions and source-apportioned fine particulate air pollution. *Environ Health Perspect* 119:455-460.
>
> Peng R.D., Bell, M.L., Geyh, A.S., McDermott, A., Zeger, S.L., Samet, J.M. 2009. Emergency admissions for cardiovascular and respiratory diseases and the chemical composition of fine particle air pollution. *Environ Health Perspect* 117:957-963.

Page 6-15, Table 6-2: The following studies should be added to the table and accompanying discussion:

> Suh, H., Zanobetti, A. 2010. Exposure error masks the relationship between traffic-related air pollution and heart rate variability. *J Occup Environ Med* 52:685-692.

Weichenthal, S., Kulka, R., Debeau, A., Martin, C., Wang, D., Dales, R. 2011. Traffic-related air pollution and acute changes in heart rate variability and respiratory function in urban cyclists. *Environ Health Perspect* 119:1173-1178.

Page 6-28, Table 6-7: The following paper should be added to the table and ensuing discussion:

Sarnat, S.E., Winquist, A., Schauer, J.J., Turner, J.T., Sarnat, J.A. 2015. Fine particulate matter components and emergency department visits for cardiovascular and respiratory diseases in the St. Louis, Missouri-Illinois Metropolitan Area. *Environ Health Perspect* 123(5):437-444.

Page 6-33, Table 6-8: This table is inconsistent from others in that it also includes some earlier studies considered in the previous ISA. If earlier studies are to be included, the tables should also include this paper, which reports on the largest study ever undertaken on air pollution and arrhythmia.

Metzger, K.B., Klein, M., Flanders, W.D., Peel, J.L., Mulholland, J.A., Langberg, J.J., Tolbert, P.E. 2007. Ambient air pollution and cardiac arrhythmias in patients with implantable defibrillators. *Epidemiology* 18(5):585-592.

Page 6-42, Table 6-12: This table and ensuing discussion should include the following study:

Sarnat, S.E., Winquist, A., Schauer, J.J., Turner, J.T., Sarnat, J.A. 2015. Fine particulate matter components and emergency department visits for cardiovascular and respiratory diseases in the St. Louis, Missouri-Illinois Metropolitan Area. *Environ Health Perspect* 123(5):437-444.

Page 6-65, Table 6-19: Several studies should be added to the table. They include:

Sarnat, S.E., Winquist, A., Schauer, J.J., Turner, J.T., Sarnat, J.A. 2015. Fine particulate matter components and emergency department visits for cardiovascular and respiratory diseases in the St. Louis, Missouri-Illinois Metropolitan Area. *Environ Health Perspect* 123(5):437-444.

Kioumourtzoglou, M-A, Zanobetti, A., Schwartz, J., Coull, B.A., Dominici, F., Suh, H. 2013. The effect of primary organic particles on emergency hospital admissions among the elderly in 3 US cities. *Environ Health* 12:68.

Atkinson, R.W., Fuller, G.W., Anderson, H.R., Harrison, R.M., Armstrong, B. 2010. Urban ambient particle metrics and health: a time-series analysis. *Epidemiology* 21:501-511.

Bell, M.L., Ebisu, K., Peng, R.D., Samet, J.M., Dominici, F. 2009. Hospital admissions and chemical composition of fine particle air pollution. *Am J Respir Crit Care Med* 179:1115-1120.

Ito, K., Mathes, R., Ross, Z., Nadas, A., Thurston, G., Matte, T. 2011. Fine particulate matter constituents associated with cardiovascular hospitalizations and mortality in New York City. *Environ Health Perspect* 119:467-473.

Lall, K., Ito, K., Thurston, G.D. 2011. Distributed lag analyses of daily admissions and source-apportioned fine particulate air pollution. *Environ Health Perspect* 119:455-460.

Peng R.D., Bell, M.L., Geyh, A.S., McDermott, A., Zeger, S.L., Samet, J.M. 2009. Emergency admissions for cardiovascular and respiratory diseases and the chemical composition of fine particle air pollution. *Environ Health Perspect* 117:957-963.

Page 6-76, Table 6-20: The following paper should be added to the table:

Suh, H., Zanobetti, A. 2010. Exposure error masks the relationship between traffic-related air pollution and heart rate variability. *J Occup Environ Med* 52:685-692.

Page 6-118-6-128: This section would strongly benefit from additional discussion considering several more studies than those listed in Figure 6-14. For a more comprehensive list of studies undertaken through February 2012, see Rohr and Wyzga (Rohr, A.C., Wyzga, R.E. 2012. Attributing health effects to individual particulate matter constituents. *Atmos Environ* 62:130-152.) They reviewed all short-term studies published through February 2012 that considered $PM_{2.5}$ and at least one constituent of $PM_{2.5}$. Although they found that every component of PM was associated with some cardiovascular effect, they did find that EC and OC (elemental and organic carbon), especially OC, showed more significant associations with health effects, especially cardiovascular health effects, than $PM_{2.5}$ mass. We would encourage EPA to undertake a similar examination of results for the broader set of studies that inform the ISA. This is important because it could help EPA decide upon the most appropriate index of PM and to stimulate further research that examines this issue. In the discussion on Page 6-122, EPA should also discuss Suh and Zanobetti (2010) who found that a component of PM was a better predictor of cardiovascular response when personal exposures were considered.

Page 6-125, Section 6.1.15.4: The document should also include and discuss the following paper:

Ye, D., Klein, M., Mulholland, J.A., Russell, A.G., Weber, R., Edgerton, E.S., et al. 2018. Estimating acute cardiovascular effects of ambient $PM_{2.5}$ metals. *Environ Health Perspect* 126:027007.

Page 6-136, Table 6-34: This table should also say something about PM components.

Page 6-143, Table 6-35: The following study should be included:

Vedal, S., Campen, M.J., McDonald, J.D., Kaufman, J.D., Larson, T.V., Sampson, P.D., et al. 2013. NPACT Epidemiologic Study of Components of Fine Particulate Matter and Cardiovascular Disease in the MESA and WHI-OS Cohorts in National Particle Toxicity (NPACT) Initiate report on Cardiovascular Effects. Research Report 178. Health Effects Institute, Boston, MA.

Page 6-186, Table 6-47: The following studies should be incorporated here and in other tables of this chapter; their results should be incorporated into the figures and discussion:

Vedal, S., Campen, M.J., McDonald, J.D., Kaufman, J.D., Larson, T.V., Sampson, P.D., et al. 2013. NPACT Epidemiologic Study of Components of Fine Particulate Matter and Cardiovascular Disease in the MESA and WHI-OS Cohorts in National Particle Toxicity (NPACT) Initiate report on Cardiovascular Effects. Research Report 178. Health Effects Institute, Boston, MA.

Ostro, B., Lipsett, M., Reynolds, P., Goldberg, D., Hertz, A., Garcia, C., et al. 2010. Long-term exposure to constituents of fine particulate matter: results from the California Teachers Study. *Environ Health Perspect* 118:363-369.

Ostro B., Lipsett, M., Reynolds, P., Goldberg, D., Hertz, A., Garcia, C., et al. 2011. Erratum: assessing long-term exposure in the California Teachers Study. *Environ Health Perspect* 119:242-243.

Wang, M., Beelen, R., Stafoggia, M., Raaschou-Nielsen, O., Andersen, Z.J., Hoffmann, B., et al. 2014. Long-term exposure to elemental constituents of particulate matter and cardiovascular mortality in 19 European cohorts: Results from the ESCAPE and TRANSPHORM project. *Environ Int* 66:97-106.

Cesaroni, G., Forastiere, F., Stafoggia, M., Andersen, Z.J., Badaloni, C., Beelen, R., et al. 2014. Long-term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE project. *Brit Med J* 348:1-16.

Gan, W.Q., Koehoorn, M., Davies, H.W., Demers, P.A., Tamburic, L., Brauer, M., et al. 2010. Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. *Environ Health Perspect* 119:501-507.

Lenters, V., Uiterwaal, C.S., Beelen, R., Bots, M.L., Fischer, P., Brunekreef, B., et al. 2010. Long-term exposure to air pollution and vascular damage in young adults. *Epidemiology* 21:512-520.

Stafoggia, M., Cesaroni, G., Peters, A., Andersen, Z.J., Badaloni, C., Beelen, R., et al. 2014. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results form 11 European cohorts within the ESCAPE Project. *Environ Health Perspect* 122:919-925.

Page 6-213, Figure 6-28 and its discussion: Is it noteworthy that BC appears to be a better indicator than $PM_{2.5}$ in the number of positive and significant positive associations with cardiovascular endpoints. There should be some discussion of this issue and a comparison of the findings here with those from the acute studies.

Page 6-220, Table 6-54: Should there be some mention here of the importance of BC as a component of PM?

Page 6-274, Section 6.5: Should there be some discussion of the difficulty of undertaking short-term epidemiological studies for UFPs given their spatial and temporal heterogeneity?

Page 6-277, Section 6.5.2.1: Metzger et al. (2007) examined the associations between emergency department admissions and several pollutants, including UFP and $PM_{2.5}$. It is noteworthy that the results of this study showed a significant negative effect of UFP on these admissions and that $PM_{2.5}$ and UFP were negatively correlated.

Chapter 7: Metabolic Effects

Page 7-30, line 2: May be worth mentioning that many of the studies in this section had exposure levels over 100 $\mu g/m^3$, which are not comparable to average long-term $PM_{2.5}$ levels in the United States.

Page 7-54, line 11: Consider adding references for the "well-conducted studies".

Chapter 8: Nervous System Effects

Page 8-11, line 11: Unclear what the comparison group is in the RR estimate.

Page 8-13, Table 8-5: Concentration is recorded as NA in the 4th column because the paper reported community-specific levels. Consider adding a range of the community-specific concentration in the first row, column #4, to provide more relevant information.

Page 8-35, line 9: Consider adding references.

Page 8-53, line 18 and 20: Please add what the reference group of the OR is: comparing "entire pregnancy exposure" with no exposure during pregnancy, or exposure during one or two trimesters? Also unclear what "entire pregnancy exposure" is: exposed to certain levels of $PM_{2.5}$ every day during pregnancy?

Chapter 9: Reproductive and Developmental Effects

Page 9-7, line 21: Consider changing "mixed effects were seen" to "mixed results were seen" because the phrase "mixed effects" coincides with a specific type of statistical model.

Page 9-16: The following studies should be added:

> Savitz, D.A., Bobb, J.F., Carr, J L., Clougherty, J E., Dominici, F., Elston, B., et al. 2013. Ambient fine particulate matter, nitrogen dioxide, and term birth weight in New York, New York. *Am J Epidemiol* 179(4):457-466.
>
> Kingsley, S.L., Eliot, M.N., Glazer, K., Awad, Y.A., Schwartz, J.D., Savitz, D.A., et al. 2017. Maternal ambient air pollution, preterm birth and markers of fetal growth in Rhode Island: results of a hospital-based linkage study. *J Epidemiol Community Health*. 71:1131-1136.

Page 9-25, line 6: Consider adding some discussion on why examining studies of sex ratio in litters at birth would be relevant to $PM_{2.5}$ regulations that aim to protect human health.

Page 9-39: The following studies should be added:

> Basu, R., Pearson, D., Ebisu, K., Malig, B. 2017. Association between $PM_{2.5}$ and $PM_{2.5}$ constituents and preterm delivery in California, 2000–2006. *Ped Perinatal Epidemiol* 31(5):424-434.
>
> Bell, M.L., Belanger, K., Ebisu, K., Gent, J.F., Leaderer, B.P. 2012. Relationship between birth weight and exposure to airborne fine particulate potassium and titanium during gestation. *Environ Res* 117:83-89.

Chapter 10: Cancer

Page 10-13, line 12: The implication of seasonal variation from Singla et al. (2012) is based on observation instead of statistical analyses, so extra caution is required when interpreting their

findings. Therefore, providing more basic information from which the authors drew their conclusion, such as sample size, would be helpful.

Page 10-19, Section 10.2.2.2.3 and Table 10-1: The first paragraph of the section indicated that this section aims to examine studies of long-term exposure. The fourth study in the Table (Ma et al., 2015) only measured 2 weeks of exposure. It may be helpful to describe what type of exposure window is considered long-term in this context.

Page 10-37, Table 10-4: Inconsistent reporting of exposure assessment. Some cells reported temporal resolution and measurement/modeling methods, some cells only reported measurement/modeling methods. Consider adding temporal resolution to all cells.

Page 10-45 to 47: About half the studies described on these pages had HR estimates with large confidence intervals covering null estimates. Consider changing the statement "provide evidence for a relationship between $PM_{2.5}$ and lung-cancer mortality" to "provide evidence for a suggestive relationship between $PM_{2.5}$ and lung-cancer mortality" for the conclusions on these pages.

Page 10-72, line 8: Consider adding a section number or references to support the statement "$PM_{2.5}$ has been shown to act as a tumor promoter…".

Chapter 11: Mortality

Page 11-38, Section 11.1.10: The following paper is missing from this section and should be added:

> Schwartz J., Bind, M.A., Koutrakis, P. 2017. Estimating causal effects of local air pollution on daily deaths: effect of low levels. *Environ Health Perspect* 125(1):23-29.

This paper found that when only days with $PM_{2.5}$ estimated to be < 30 $\mu g/m^3$ were considered, the RR was slightly lower than when all days were included.

Page 11-41, Section 11.1.11.1: Rohr and Wyzga (2012) conducted a semi-quantitative review of the available literature as it relates to $PM_{2.5}$ components and short-term health effects, including mortality. While the authors concluded that no major component of $PM_{2.5}$ was exonerated, the literature did suggest a need to systematically consider the role of carbonaceous components. The review identified EC and/or OC as being potentially more important than other $PM_{2.5}$ components, and this finding was consistent across disciplines. Also of note, the majority of the studies examined yielded significant findings for specific components of $PM_{2.5}$, but not for $PM_{2.5}$ mass concentration, demonstrating that $PM_{2.5}$ alone does not drive health responses. For example, among the epidemiology studies, 39 studies considered both $PM_{2.5}$ and at least two components. Of these 39 studies, 21 reported significant associations between a health response and both $PM_{2.5}$ and at least one component; 1/39 found significant associations with $PM_{2.5}$ but with no components, and 17/39 found significant responses with at least one component but not with $PM_{2.5}$. Similarly, in the toxicology arena, while 5/20 studies reported at least one association with $PM_{2.5}$ mass concentration, 15/20 studies did not.

Also related to Section 11.1.11.1, a number of studies are missing. These include:

Franklin, M., Koutrakis, P., Schwartz, J. 2008. The role of particle composition on the association between $PM_{2.5}$ and mortality. *Epidemiology* 19(5):1-10.

Klemm, R.J., Lipfert, F.W.,Wyzga, R.E.,Gust, C. 2004. Daily mortality and air pollution in Atlanta: two years of data from ARIES. *Inhal Toxicol* 16 (Suppl. 1):131-141.

Klemm, R.J., Thomas, E.L., Wyzga, R.E. 2011. The impact of frequency and duration of air quality monitoring: Atlanta, GA, data modeling of air pollution and mortality. *J Air Waste Manage Assoc* 61:1281-1291.

Lipfert, F.W., Morris, S.C., Wyzga, R.E. 2000. Daily mortality in the Philadelphia metropolitan area and size-classified particulate matter. *J Air Waste Manage Assoc* 50:1501-1513.

Lippmann, M., Ito, K., Hwang, J.-S., Maciejczyk, P., Chen, L.C. 2006. Cardiovascular effects of nickel in ambient air. *Environ Health Perspect* 114(11):1662-1669.

Mar, T.F., Norris, G.A., Koenig, J.Q., Larson, T.V. 2000. Associations between air pollution and mortality in Phoenix, 1995-1997. *Environ Health Perspect* 108(4):347-353.

Page 11-46: The role played by $PM_{2.5}$ components in mortality should be investigated in single (or preferably multi-) pollutant models using the actual concentration of $PM_{2.5}$ and its components. Other approaches, such as using a deviation from a monthly mean as in Lippmann et al. (2013) or a percent contribution of a given component to overall mass, eliminate the "dose" from the "dose-response". If we assume that it is the actual *concentration* of a particular toxic agent that leads to a response, any approach beyond including that concentration in models does not make biological sense. These approaches could make sense if the objective is to generally differentiate one "type" of $PM_{2.5}$ mixture from another, but that is not the same as evaluating the relative toxicity of components and should not be construed as such.

Page 11-58, Table 11-5: Several studies are missing from this table and the text. These include:

Greven, S., Dominici, F., Zeger, S. 2011. An approach to the estimation of chronic air pollution effects using spatio-temporal information. *J Am Stat Assoc* 106(494):396-406.

Pun, V.C., Kazemiparkouhi, F., Manijourides, J., Suh, H.H. 2017. Long-term $PM_{2.5}$ exposure and respiratory, cancer, and cardiovascular mortality in older US adults. *Am J Epidemiol* 186(8):961-969.

Eum, K., Suh, H.H., Pun, V.C., Manjourides, J. 2018. Impact of long-term temporal trends in fine particulate matter ($PM_{2.5}$) on association of annual $PM_{2.5}$ exposure and mortality: an analysis of over 20 million Medicare beneficiaries. *Environ Epidemiol* 2(2): e009. [included as Appendix A]

Page 11-82, Table 11-7: A number of studies that investigated the shape of the concentration-response function between long-term $PM_{2.5}$ and mortality do not appear in this table and should be added. Some of these did not present a shape *per se*, but they did conduct analyses of effects above and below certain concentration cutpoints. Studies that are missing include:

Pope, C.A. 3rd, Burnett, R.T., Krewski, D., Jerrett, M., Shi, Y., Calle, E.E., et al. 2009. Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure-response relationship. *Circulation* 120(11):941-948.

Pope, C.A. 3rd, Burnett, R.T., Turner, M.C., Cohen, A., Krewski, D., Jerrett, M., et al. 2011. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure–response relationships. *Environ Health Perspect* 119(11):1616-1621.

Brook, R.D., Cakmak, S., Turner, M.C., Brook, J.R., Crouse, D.L., Peters, P.A., et al. 2013. Long-term fine particulate matter exposure and mortality from diabetes in Canada. *Diabetes Care* 36(10):3313-3320.

Weichenthal, S., Villeneuve, P.J., Burnett, R.T., van Donkelaar, A., Martin, R.V., Jones, R.R., et al. 2014. Long-term exposure to fine particulate matter: association with nonaccidental and cardiovascular mortality in the Agricultural Health Study cohort. *Environ Health Perspect* 122(6):609-15.

Crouse, D.L., Philip, S., van Donkelaar, A., Martin, R.V., Jessiman, B., Peters, P.A., et al. 2016. A new method to jointly estimate the mortality risk of long-term exposure to fine particulate matter and its components. *Sci Rep* 6:18916.

Jerrett, M., Turner, M.C., Beckerman, B.S., Pope, C.A., van Donkelaar, A., Martin, R.V., et al. 2017. Comparing the health effects of ambient particulate matter estimated using ground-based versus remote sensing exposure estimates. *Environ Health Perspect* 125(4):552-559.

Weichenthal, S., Pinault, L.L., Burnett, R.T. 2017. Impact of oxidant gases on the relationship between outdoor fine particulate air pollution and nonaccidental, cardiovascular, and respiratory mortality. *Sci Rep* 7:16401.

Pinault LL, Weichenthal S, Crouse DL, Brauer M, Erickson A, Donkelaar AV, et al. 2017. Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment cohort. *Environ Res* 159:406-415.

Deng, H., Eckel, S.P., Liu, L., Lurmann, F.W., Cockburn, M.G., Gilliland, F.D. 2017. Particulate matter air pollution and liver cancer survival. *Int J Cancer* 141(4):744-749.

Makar, M., Antonelli, J., Di, Q., Cutler, D., Schwartz, J., Dominici, F. 2017. Estimating the causal effect of low levels of fine particulate matter on hospitalization. *Epidemiology* 28(5):627-634.

Corrigan, A.E., Becker, M.M., Neas, L.M., Cascio, W.E., Rappold, A.G. 2018. Fine particulate matters: The impact of air quality standards on cardiovascular mortality. *Environ Res* 161:364-369.

EPRI conducted an unpublished review of the long-term mortality literature presenting C-R function shape information. Of the 20 studies identified (including those above), 13 suggested a supralinear shape, 4 suggested a sublinear shape, and 3 suggested a linear or mixed shape. The ISA could be improved by pointing out the multiple factors that may cause or contribute to the observation of a supralinear shape, including:

- The C-R effect is truly supralinear over the range of $PM_{2.5}$ levels observed in the study
- In areas with the lowest $PM_{2.5}$ levels, the fraction of the mass that is the toxic constituent(s) is generally larger than areas with higher $PM_{2.5}$ levels

- Individual susceptibility to $PM_{2.5}$ is not normally distributed across the population, but highly concentrated near the origin, and skewed to the right
- $PM_{2.5}$ associations serve as a proxy for another risk factor, and the other risk factor has not declined proportionately with the recent declines in $PM_{2.5}$ across the nation
- Exposure misclassification (i.e., measurement error) is disproportionately large in areas with higher $PM_{2.5}$ concentrations
- Exposure misclassification (i.e., measurement error) is disproportionately small in areas with higher $PM_{2.5}$ concentrations
- There is a significant latency period for effect, and earlier exposure levels explain a portion of the presently observed risk

Page 11-90: Consider mentioning the following review:

> Wyzga, R.E., Rohr, A.C. 2015. Long-term particulate matter exposure: attributing health effects to individual PM components. *J Air Waste Manage Assoc* 65(5):523–543.

Page 11-90, Section 11.2.6: The same comment made above regarding short-term mortality studies can be made here. Considering $PM_{2.5}$ sources and components must be done in a manner that reflects the quantitative dose of the material. Adjusting for the proportion of a specific component or using residual approaches eliminates the dose concept. This is particularly true for components that have low concentrations, such as BC.

Page 11-91, lines 18-21: Please add a category for "positive associations, regardless of width of the confidence interval." This comment also applies to the short-term mortality section.

Page 11-92, Table 11-14: The following studies are missing from this section and should be added:

> Lipfert, F.W., Wyzga, R.E., Baty, J.D., Miller, J.P. 2009. Air pollution and survival within the Washington University-EPRI Veterans cohort: risks based on modeled estimates of ambient levels of hazardous and criteria air pollutants. *J Air Waste Manage Assoc* 59:473–489.
>
> Wang, M., Beelen, R., Stafoggia, M., Raaschou-Nielsen, O., Andersen, Z.J., et al. 2014. Long-term exposure to elemental constituents of particulate matter and cardiovascular mortality in 19 European cohorts: results from the ESCAPE and TRANSPHORM projects. *Environ Int* 66:97–106.
>
> Jerrett, M., Newbold, K.B., Burnett, R.T., Thurston, G., et al. 2007. Geographies of uncertainty in the health benefits of air quality improvements. *Stoch Environ Res Risk Assess* 21:511–522.
>
> Pope, C.A. III, Burnett, R.T., Thun, M.J., et al. 2002. Lung cancer, cardiopulmonary mortality and long-term exposure to fine particulate air pollution. *J Am Med Assoc* 287:1132–1141.

Chapter 12: Populations and Lifestages Potentially at Increased Risk of a Particulate Matter-Related Health Effect

Page 12-11, line 24: Please clarify "effect estimates were imprecise". Does it mean that the effects are statistically insignificant?

Page 12-18: The following papers should be added:

> Clougherty, J.E., Kubzansky, L.D. 2009. A framework for examining social stress and susceptibility to air pollution in respiratory health. *Environ Health Perspect* 117(9): 1351-1358.
>
> Liu, J.C., Wilson, A., Mickley, L.J., Ebisu, K., Sulprizio, M.P., Wang, Y., et al. 2017. Who among the elderly is most vulnerable to exposure to and health risks of fine particulate matter from wildfire smoke? *Am J Epidemiol* 186(6):730-735.

Page 12-21, line 11: Consider adding some discussion of whether genetic variants in the glutathione pathway are more prevalent in certain ages/regions/races, etc., and how these variants are relevant to air pollution regulation, if any.

Page 12-25, line 7: Please clarify what the comparison group is in the summary sentence of the section. The summary sentence stated "… children are at increased risk for $PM_{2.5}$-related health effects.". Among the studies cited in the section, there are studies that compared children to adults, and studies that compared younger children to older children. Therefore, it is better to specify the comparison group.

Page 12-29: The following study should be added:

> Bell, M.L., Zanobetti, A., Dominici, F. 2013. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: a systematic review and meta-analysis. *Am J Epidemiol* 178(6):865-876.

Page 12-44: The following study should be added:

> Péter, S., Holguin, F., Wood, L., Clougherty, J., Raederstorff, D., Antal, M., et al. 2015. Nutritional solutions to reduce risks of negative health impacts of air pollution. *Nutrients* 7(12):10398-10416.

References

Eum, K., Suh, H.H., Pun, V.C., Manjourides, J. 2018. Impact of long-term temporal trends in fine particulate matter ($PM_{2.5}$) on association of annual $PM_{2.5}$ exposure and mortality: an analysis of over 20 million Medicare beneficiaries. *Environ Epidemiol* 2(2): e009.

Glasgow, G. PM decomposition models and confounding in long-term epidemiology studies. Submitted.

Greven, S., Dominici, F., Zeger, S. 2011. An approach to the estimation of chronic air pollution effects using spatio-temporal information. *J Am Stat Assoc* 106(494):396-406.

Pun, V.C., Kazemiparkouhi, F., Manijourides, J., Suh, H.H. 2017. Long-term $PM_{2.5}$ exposure and respiratory, cancer, and cardiovascular mortality in older US adults. *Am J Epidemiol* 186(8): 961-969.

Rohr, A.C., Wyzga, R.E. 2012. Attributing health effects to individual particulate matter constituents. *Atmos Environ* 62:130-152.

Wyzga, R.E., Rohr, A.C. 2015. Long-term particulate matter exposure: attributing health effects to individual PM components. *J Air Waste Manage Assoc* 65(5):523–543.

APPENDIX A
EUM ET AL. (2018)

Original Research

ENVIRONMENTAL EPIDEMIOLOGY

OPEN

Impact of long-term temporal trends in fine particulate matter ($PM_{2.5}$) on associations of annual $PM_{2.5}$ exposure and mortality

An analysis of over 20 million Medicare beneficiaries

Ki-Do Eum*[a], Helen H. Suh[a], Vivian Chit Pun[b], Justin Manjourides[c]

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Abstract

Decreasing ambient fine particulate matter ($PM_{2.5}$) concentrations over time together with increasing life expectancy raise concerns about temporal confounding of associations between $PM_{2.5}$ and mortality. To address this issue, we examined $PM_{2.5}$-associated mortality risk ratios (MRRs) estimated for approximately 20,000,000 US Medicare beneficiaries, who lived within six miles of an Environmental Protection Agency air quality monitoring site, between December 2000 and December 2012. We assessed temporal confounding by examining whether $PM_{2.5}$-associated MRRs vary by study period length. We then evaluated three approaches to control for temporal confounding: (1) assessing exposures using the residual of $PM_{2.5}$ regressed on time; (2) adding a penalized spline term for time to the health model; and (3) including a term that describes temporal variability in $PM_{2.5}$ into the health model, with this term estimated using decomposition approaches. We found a 10 μg/m^3 increase in $PM_{2.5}$ exposure to be associated with a 1.20 times (95% confidence interval [CI] = 1.20, 1.21) higher risk of mortality across the 13-year study period, with the magnitude of the association decreasing with shorter study periods. MRRs remained statistically significant but were attenuated when models adjusted for long-term time trends in $PM_{2.5}$. The residual-based, time-adjusted MRR equaled 1.12 (95% CI = 1.11, 1.12) per 10 μg/m^3 for the 13-year study period and did not change when shorter study periods were examined. Spline- and decomposition-based approaches produced similar but less-stable MRRs. Our findings suggest that epidemiological studies of long-term $PM_{2.5}$ can be confounded by long-term time trends, and this confounding can be controlled using the residuals of $PM_{2.5}$ regressed on time.

Keywords: Medicare beneficiaries; Residual; Temporal confounding; Mortality; Fine particulate matter ($PM_{2.5}$)

Introduction

Over the last 2 decades, ambient air pollution concentrations have decreased steadily across the United States primarily as the result of emissions controls instituted as part of the Clean Air Act Amendments. In the United States, $PM_{2.5}$, annual concentrations have dropped by 24% from 2001 to 2010, with 2010 mean concentrations ranging, by location, between 3 and 18 μg/m^3.[1] These lower concentrations are projected to result in substantial health benefits. A 2011 US Environmental Protection Agency report, e.g., estimated that the Clean Air Act Amendments will prevent 230,000 early deaths in 2020, with most early deaths attributable to reductions in ambient $PM_{2.5}$.[1]

Despite these reductions, $PM_{2.5}$ concentrations continue to be linked with adverse health impacts.[2–6] Numerous multicity studies, including the American Cancer Society, Six Cities, Women's Health Initiative, Nurses' Health Study, and National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Cohort, have shown positive associations between long-term exposure and mortality.[2–7] The observed associations in these studies vary widely, with null associations in Health Professionals Follow-Up Study prospective cohort[8] and significant effect estimates ranging from a 3% increase (per 10 μg/m^3 in $PM_{2.5}$) in the NIH-AARP cohort[7] to 26% in Nurses' Health Study.[9] Variability in effect sizes has been attributed to differences in cohort characteristics, $PM_{2.5}$ composition, modeling approaches, and confounding by correlated air pollutants or unmeasured covariates.[10–13]

Another possible, but little studied, explanation for the variation in $PM_{2.5}$-associated mortality risks is confounding by long-term time trends in both $PM_{2.5}$ and mortality, where decline in ambient $PM_{2.5}$ concentrations is accompanied by increased life expectancy. Several studies provide evidence of the impact of long-term time trends on $PM_{2.5}$-associated mortality.[14] In a simulation study, Griffin et al[15] showed that the length of the study period may adversely affect the performance of the Cox proportional hazards model, increasing bias and mean and squared error (MSE) and reducing power as the strength of the linear association between exposure and time increases, as may occur with the temporal trends observed for $PM_{2.5}$. Similarly, linear models may also produce biased effect estimate, if linear trends exist between both $PM_{2.5}$ and time, and mortality and time. Consistent with this, Janes et al,[16] Greven et al,[17] and Pun et al[18] found evidence of

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of the article.

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unmeasured confounding of the association of $PM_{2.5}$ and all-cause mortality. They did so by decomposing $PM_{2.5}$ into two orthogonal components describing temporal and spatiotemporal variability, which they term "global" and "local" $PM_{2.5}$, respectively. When both terms were included in the health model, the coefficient for temporal $PM_{2.5}$ was larger and statistically significant compared with the spatiotemporal coefficient, which was null. The unequal temporal and spatiotemporal coefficients led the authors to conclude that $PM_{2.5}$ associations with mortality were confounded by unmeasured variables, such as long-term time trends.

To examine the possibility that temporal confounding is present in the mortality and $PM_{2.5}$ relationship, we analyzed data for over 20 million Medicare enrollees from 2000 to 2012 to assess the impact of long-term time trends on the association between 1-year–averaged $PM_{2.5}$ concentrations and mortality.

Methods

The protocol was reviewed and approved by the Institutional Review Boards of Northeastern University.

Medicare beneficiary and mortality data

We obtained monthly mortality counts for 2000–2012 in the United States (except for Alaska and Hawaii) using data from the Centers for Medicare and Medicaid Services Medicare enrollment file, which provides demographic (age and sex), ZIP code of residence, and survival, including date of death and data for all Medicare enrollees (≥65 years).

$PM_{2.5}$ exposure

We compiled daily $PM_{2.5}$ concentrations from Environmental Protection Agency's Air Quality System from 2000 to 2012. We did so for monitoring sites ("site") with daily measurements for at least eight calendar years, with each year having 9+ months with 4+ daily measurements. For the 798 sites that met these criteria, we calculated long-term concentrations following Greven et al.[17] Briefly, we smoothed the time series at each site using a linear regression with the daily pollutant values as the response, and thin plate splines of time with four degrees of freedom per year as the predictor. For gaps longer than 90 days, we smoothed the $PM_{2.5}$ time series before and after each gap separately. We used the predicted daily values to calculate yearly moving averages for $PM_{2.5}$ each month. Yearly averages were considered valid when 350+ days were available. Sites were classified based on their geographical region: "East" of the Mississippi River, "Center" between the Mississippi River and the Sierra Nevada mountain range, and "West" of the Sierra Nevada mountain range.[17]

Data linkage

We linked data for Medicare beneficiaries (65–120 years) to $PM_{2.5}$ monitors that met the study criteria for each month of the study, which restricted our sample to those beneficiaries living in ZIP codes with centroids within six miles of a valid monitor. We then linked data for beneficiaries living in these ZIP codes to the closest corresponding site's $PM_{2.5}$ concentration for the previous 12-month period ending in that study month. We performed the ZIP code identification and linkage by year to reduce exposure error introduced by residential moves and changes in ZIP code boundaries. For each month, we calculated the total number of Medicare beneficiaries at risk and the number of deaths associated with each site.

Statistical analysis

All analyses were conducted for the entire study population living in the United States as well as separate analyses for Medicare beneficiaries living in each of three US regions (East, Central, and West). In general, we examined the variation in MRR estimates per 10 μg/m^3 increase in exposure; although for analyses comparing MRRs for base to those for time-adjusted models, we make comparisons based on an interquartile range (IQR) increase in exposure given their different variabilities. We further present graphical summaries of this variation using linear regression. SAS statistical software package (SAS Institute Inc., Cary, NC, 2003) and R-Studio, Inc., (Boston, MA) were used for all analyses.

Base models

To examine the association between $PM_{2.5}$ exposure and monthly rate of all-cause mortality, we fit an age-stratified log-linear model including offset terms for the size of the population at risk as our base model:

$$\log E\left(Y_{at}{}^{c}\right)=\log\left(h_0^c(a)\right)+\beta PM_t^c+\beta_c \mathrm{BRFSS} \tag{1}$$

where $(Y_{at}{}^{c})$ is the number of deaths at time t, in age category a, associated with site C. The exposure measure PM_t^c is the 1-year average $PM_{2.5}$ concentration at site C, preceding the month (t) of death. For each age group a and site C, mortality counts are offset by both the baseline hazard of death, $h_0^c(a)$, and the total population at risk at time t, N_{at}^c. The Poisson model was selected (over the quasi-Poisson) as overdispersion parameter values varied from 1.02 to 1.25. To reduce the computational burden of this large dataset, we assumed a constant baseline hazard of death for all age groups above 90 years of age and models were fit via the backfitting algorithm.[17–19]

To adjust for potential, measured confounders, we performed additional analyses adjusting for county-level behavioral covariates from the Selected Metropolitan/Micropolitan Area Risk Trends of the Behavioral Risk Factor Surveillance System (BRFSS), including proportions of non-whites, current smokers, diabetes, asthma, individuals possessing health care plans, and mean income and body mass index.[20] β_c is the vector of BRFSS adjustment variables. Because the BRFSS data are only available for 465 of the 798 sites with $PM_{2.5}$ monitoring data, we performed these analyses using the corresponding subset of the cohort. As appropriate, we converted results from previous studies into percent change per 10 μg/m^3 $PM_{2.5}$ increase to compare with our results.[16–18] Additionally, we assessed whether unmeasured confounding of our base models remained by decomposing $PM_{2.5}$ into two orthogonal components that capture temporal and spatiotemporal variability, following methods described by Greven et al.[17] Briefly,

- The temporal component describes national trends in exposures by centering the average exposure nationally in month t, $\overline{PM_t}$, by the average concentration for all sites over the entire study period, $\overline{PM}$:

$$\mathrm{Temporal}\, PM_t=\overline{PM_t}-\overline{PM}$$

- The spatiotemporal component describes site-specific temporal trends in exposure by centering the exposure in month t at site c, PM_t^C, by the average exposure at site c, $\overline{PM_c}$, and the national trends, $(\overline{PM_t}-\overline{PM})$:

$$\text{Spation-temporal}\, PM_t^C=\left(\overline{PM_t^C}-\overline{PM_c}\right)-\left(\overline{PM_t}-\overline{PM}\right)$$

We included the temporal and spatiotemporal components jointly in our base models and compared their effect estimates, interpreting a difference in their estimates as evidence of unmeasured confounding.[17]

Evaluation of temporal confounding

We evaluated long-term time trends as a potential source of unmeasured confounding. To do so, we ran our base models using data for the entire 13-year study period (2000–2012) and for shorter study periods, ranging between 3 and 12 years in

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length, with each of these study periods ending in 2012 (e.g., 2001–2012, 2002–2012, 2003–2012, etc., to 2009–2012). We compared mortality risk ratios (MRRs) for the entire 13-year period with those from each of these shorter study periods, assuming that in the absence of temporal confounding, MRRs would be uniform irrespective of the study period length.

In addition to fitting our base model, we also examined three approaches to control for long-term time trends in $PM_{2.5}$. In our first approach, we adjusted for long-term time trends in $PM_{2.5}$ using a new exposure measure calculated as the residual r_t^c of the linear regression of $PM_{2.5}$ on time in 4-year intervals December 2000–2004, 2005–2008, and 2009–2012:

$$PM_t^c = \beta_0 + \beta_1 year_{2005-08} + \beta_2 year_{2009-12} + t_t^c$$

The term r_t^c was subsequently used as the exposure measure in the log-linear model:

$$\log E(Y_{at}^c) = \log(h_0^c(a)) + \beta r_t^c \quad (2)$$

Our second approach adjusted for long-term time trends in $PM_{2.5}$ by adding a penalized spline term for time, $\delta^c(t)$, modeled as two knots per study year, to our base log-linear model:

$$\log E(Y_{at}^c) = \log(N_{at}^c) + \log(h_0^c(a)) + \beta_1 PM_t^c + \beta_2 \delta(t) \quad (3)$$

For our third approach, we included the temporal component of decomposed $PM_{2.5}$ into the base model as follows:

$$\log E(Y_{at}^c) = \log(N_{at}^c) + \log(h_0^c(a)) + \beta_1 PM_{2.5} + \beta_2 \text{Temporal} PM_t \quad (4)$$

where "temporal $PM_{2.5}$" was calculated by decomposing $PM_{2.5}$ into its orthogonal temporal and spatiotemporal components as above and in the study by Greven et al.[17]

For each of these time-adjusted approaches, we ran models using data for study periods ranging between 3 and 13 (2000–2012) years in length and examined whether MRRs varied by length of study period.

Sensitivity analyses

We ran several sensitivity analyses to examine alternate specifications of our methods to adjust for long-term time trends in $PM_{2.5}$. Specifically, for the calculation of residuals for our residual-based approach, we adjusted for time as each year rather than for each 4-year interval as in our main analysis:

$$PM_t^c = \beta_0 + \beta_1 year_{2001} + \beta_2 year_{2002} + \cdots + \beta_{12} year_{2012} + r_{t_1}^c$$

as well as for years grouped into 2-, 3-, and 6-year intervals:

$$PM_t^c = \beta_0 + \beta_1 year_{2003-04} + \beta_2 year_{2005-06} + \cdots + \beta_5 year_{2011-12} + r_{t_2}^c$$

$$PM_t^c = \beta_0 + \beta_1 year_{2004-06} + \beta_2 year_{2007-09} + \beta_3 year_{2010-12} + r_{t_3}^c$$

$$PM_t^c = \beta_0 + \beta_1 year_{2007-12} + r_{t_6}^c$$

We subsequently used the residuals from these sensitivity analyses as exposure measures in our log-linear health models and compared their ability to control for confounding by time trends. Additionally, we assessed our ability to account for long-term time trends using penalized splines for time calculated using three, four, or five knots instead of the two knots used in our main analysis.

Results

We examined 20.7 million Medicare enrollees, observing 5.5 million deaths between December 2000 and December 2012 near 798 sites across the contiguous United States (Table 1). Monthly, our analyses include on average over 9 million enrollees. $PM_{2.5}$ concentrations varied regionally, with sites located in the East having the highest mean concentrations. Yearly $PM_{2.5}$ concentrations decreased steadily during our study period (Figure 1), with larger decreases in the East and West as compared to Center. Declines in $PM_{2.5}$ concentrations were steepest between 2000 and 2009, with yearly concentrations more uniform during 2010–2012. The correlation between $PM_{2.5}$ and the residual-based exposure measure equaled 0.92, suggesting that this residual-based exposure measure explained most of the variation in $PM_{2.5}$.

Association of $PM_{2.5}$ and mortality

Base models

We found that a 10 μg/m³ increase in 1-year $PM_{2.5}$ is significantly associated with a 1.20 times (95% CI = 1.20, 1.21 per 10 μg/m³) higher rate of mortality in our Medicare cohort when data from 2000 to 2012 were analyzed (Table 2). Associations varied by geographic region, with MRRs higher in the Central (1.27; 95% CI = 1.26, 1.28) and Eastern (1.26; 95% CI = 1.25, 1.26) regions compared with the Western United States (1.12; 95% CI = 1.11, 1.12). Associations were similar when models additionally adjust for behavioral covariates (Table S1; http://links.lww.com/EE/A4), suggesting that behavioral covariates did not confound associations of $PM_{2.5}$ and mortality.

Despite this, we showed potential confounding of the association of $PM_{2.5}$ and mortality by unmeasured variables. When $PM_{2.5}$ is decomposed into its spatiotemporal and temporal components, we estimated larger MRRs for the temporal as compared to spatiotemporal component of $PM_{2.5}$ (Table S1; http://links.lww.com/EE/A4) for both base and BRFSS-adjusted models, consistent with the previous study.[17] In base models, e.g., a 10 μg/m³ increase in temporal $PM_{2.5}$ corresponded to a 1.54 times (95% CI = 1.52, 1.56) higher rate of mortality, while spatiotemporal $PM_{2.5}$ was associated with only a 1.07 times (95% CI = 1.06, 1.09) higher rate.

Table 1

Descriptive statistics of all-cause mortality for the period of December 2000 to December 2012.[a]

Variable	West	Center	East	United States
No. monitors[a]	93	195	510	798
1-year $PM_{2.5}$ (μg/m³)[b]	11.46 (4.57)	9.87 (2.37)	12.33 (2.68)	11.65 (3.09)
No. Medicare enrollees[a]				
Total	3,931,203	3,112,854	13,832,532	20,744,214
By month[b]	1,739,901 (140,871)	1,254,360 (123,762)	6,062,825 (378,173)	9,057,086 (609,378)
No. deaths				
Total	976,007	769,092	3,739,848	5,484,947
By month[b]	6,731 (703)	5,304 (705)	25,792 (2,409)	37,827 (3,711)

[a]Monitors include those with 8+ calendar years of data, each having 10+ months with 4+ valid measurements. All beneficiaries living in ZIP codes with centroids within 6 miles of a monitor were included in the analysis.

[b]Values are means (SD).

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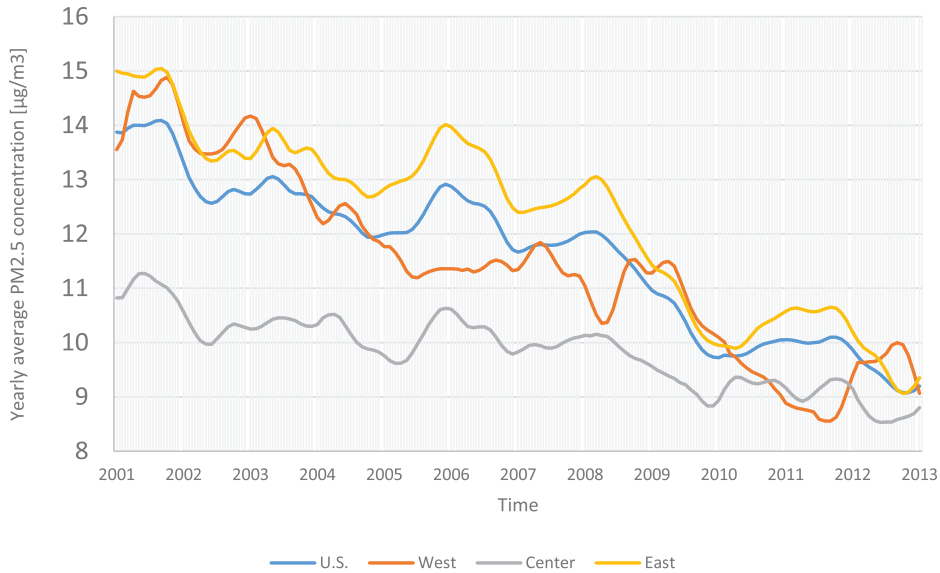

Figure 1. One-year average $PM_{2.5}$ concentrations: December 2000 to December 2012.

Evaluation of temporal confounding

We showed $PM_{2.5}$-associated MRRs increase with the length of the study, consistent with the hypothesis of confounding by long-term time trends in $PM_{2.5}$. MRRs were lowest for the 3-year study periods (1.12; 95% CI = 1.11, 1.14) and increase steadily with longer study periods, resulting in a 0.08 higher MRR for the 13-year as compared to 3-year study period (Figure 2). Similar trends between MRRs and length of study period were observed when analyses were performed by geographic region, although these trends were less pronounced in the Central United States, consistent with the more gradual decline in $PM_{2.5}$ concentrations in the Central Unites States over the 13-year period (Figure S1; http://links.lww.com/EE/A4).

When models were adjusted for long-term time trends, MRRs remain statistically significant (Table 2) but were slightly attenuated (Table S2; http://links.lww.com/EE/A4). For the residual-based approach, we found the MRR to equal 1.04 (95% CI = 1.04, 1.04) per IQR increase in time-adjusted $PM_{2.5}$, as compared to 1.08 (95% CI = 1.08, 1.08) per IQR increase in the base model. MRRs estimated from the penalized spline- and decomposition-based approaches were also attenuated, with MRRs of 1.01 (95% CI = 1.01, 1.02) and 1.03 (95% CI = 1.02, 1.03) per IQR increase, respectively (Table S2; http://links.lww.com/EE/A4). While consistently lower, MRRs for each of the time-adjusted approaches follow the same regional patterns as with the base models, as time-adjusted MRRs were highest in the Central United States and lowest in the Western United States (Table 2; Figures S2–S4; http://links.lww.com/EE/A4).

When analyses were performed across varying study periods, we demonstrated that the residual-based approach produces MRRs that are nearly uniform (Figure 2). The residual-based MRRs for the 13- and 3-year study periods, e.g., were almost identical, with MRRs of 1.12 (95% CI = 1.11, 1.12) and 1.12 (95% CI = 1.11, 1.14) for a 10 µg/m^3 increase in exposure, respectively. In contrast to both the base and residual-based models, MRRs for the spline- and decomposition-based approaches decrease with longer study periods. MRRs from the spline-based approach decrease from 1.09 (95% CI = 1.07, 1.10) for 3-year study period to 1.03 (95% CI = 1.02, 1.04) for 13-year study period. The decomposition-based approach shows a similar decline in MRRs, with MRRs for 3- and 13-year study periods equaling 1.11 (95% CI = 0.10, 1.12) and 1.06 (95% CI = 1.06, 1.07), respectively.

Sensitivity analyses

Sensitivity analyses demonstrated that alternate calculations of residual-based $PM_{2.5}$ exposures and of penalized splines produce similar MRRs. Residual-based exposures calculated by regressing $PM_{2.5}$ concentrations on time as 1-, 2-, or 3-year intervals result in similar MRRs as models controlling for time in 4-year intervals (Figure 3). Residual-based exposure with 6-year intervals showed slightly higher and less-consistent MRRs for longer

Table 2

MRRs (95% confidence intervals) per 10 µg/m^3 increase in 1-year moving average $PM_{2.5}$[a] for base and time-adjusted models: 2000–2012.

			Time-adjusted models		
Region	**Monitors**	**Base model[b]**	**Residual[c]**	**Penalized spline[d]**	**Decomposition[e]**
United States	798	1.20 (1.20, 1.21)	1.12 (1.11, 1.12)	1.03 (1.02, 1.04)	1.06 (1.06, 1.07)
West	93	1.12 (1.11, 1.12)	1.04 (1.04, 1.05)	0.91 (0.90, 0.92)	1.00 (1.00, 1.01)
Center	195	1.27 (1.26, 1.28)	1.20 (1.18, 1.21)	1.15 (1.13, 1.17)	1.18 (1.17, 1.19)
East	510	1.26 (1.25, 1.26)	1.16 (1.15, 1.16)	1.14 (1.13, 1.15)	1.11 (1.10, 1.11)

[a]Exposures estimated as the 1-year moving average $PM_{2.5}$ exposures for all models except for the residual-based time-adjusted model; exposures for the residual-based model estimated as the 1-year moving average of the residuals of $PM_{2.5}$ regressed on year in 4-year intervals.

[b]Log-linear models adjusted for age and regions; all $P < 0.001$.

[c]Model adjusted for long-term time trends in $PM_{2.5}$ using a new exposure measure based on the residuals of $PM_{2.5}$ regressed on year in 4-year intervals.

[d]Model adjusted for long-term time trends in $PM_{2.5}$ by adding a penalized spline term for time to the base model.

[e]Model adjusted for long-term time trends in $PM_{2.5}$ by adding a term that describes only temporal variation in $PM_{2.5}$, which was calculated by decomposing $PM_{2.5}$ into its temporal and spatiotemporal components following Greven et al.[17]

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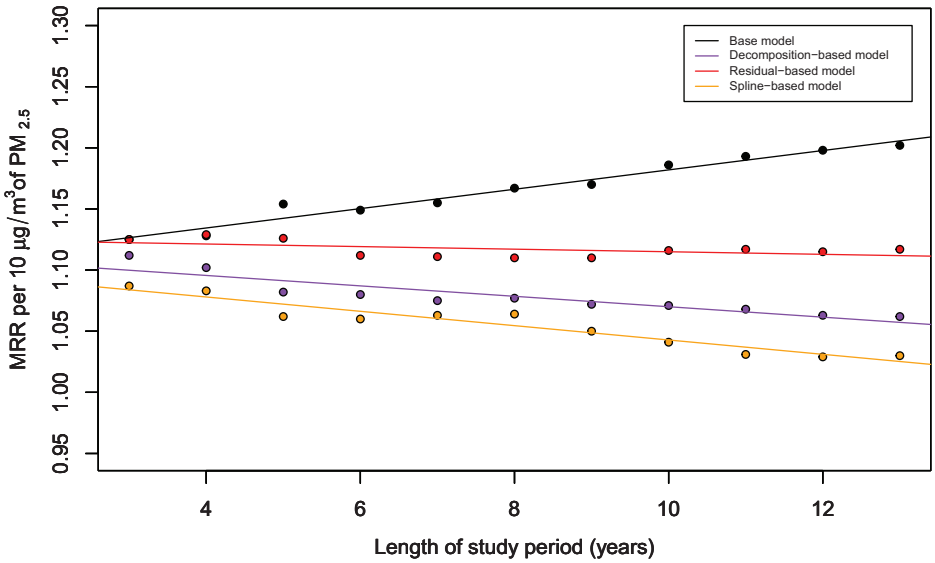

Figure 2. MRRs per 10 µg/m³ increase in $PM_{2.5}$ by length of study period: for base and time-adjusted models.

study periods, suggesting less reliability than with the other intervals. Residual-based exposures calculated using 4-year intervals, however, were more stable, as evidenced by lowest variation in MRRs across study period length. It is also notable that residual-based exposure using 4-year time intervals requires fewer parameters than 1-, 2-, or 3-year intervals, suggesting greater statistical efficiency. For spline-based models, increasing the number of knots per year from two to three or four had little effect on the MRR, thus we selected two knots for better efficiency (results not shown).

Discussion

We showed consistent, statistically significant, and positive associations between 1-year $PM_{2.5}$ exposures and the rate of all-cause mortality among 20.7 million Medicare beneficiaries living across the United States from 2000 to 2012. In our base models, the mortality rate ratio associated with a 10 µg/m³ increase in 1-year average $PM_{2.5}$ equaled 1.20 (95% CI = 1.20, 1.21). Consistent with our hypothesis that long-term time trends in $PM_{2.5}$ positively confound the association between $PM_{2.5}$ and mortality, we found $PM_{2.5}$-associated rates of mortality to be associated with the length of the study period, with higher MRR per 10 µg/m³ for 13-year as compared to 3-year study periods. Of the three examined approaches, we found the residual-based approach to best control for temporal confounding, as evidenced by its statistically significant and uniform MRRs across all study period lengths, with an MRR for the 3- and 13-year study period of 1.12 (95% CI = 1.11, 1.14) and 1.12 (95% CI = 1.11, 1.12) per 10 µg/m³ increase in exposure, respectively. Note, however, that based on our analysis alone, it is not possible to determine which approach is best suited to control for temporal confounding, indicating the need for further examination, possibly through a simulation study.

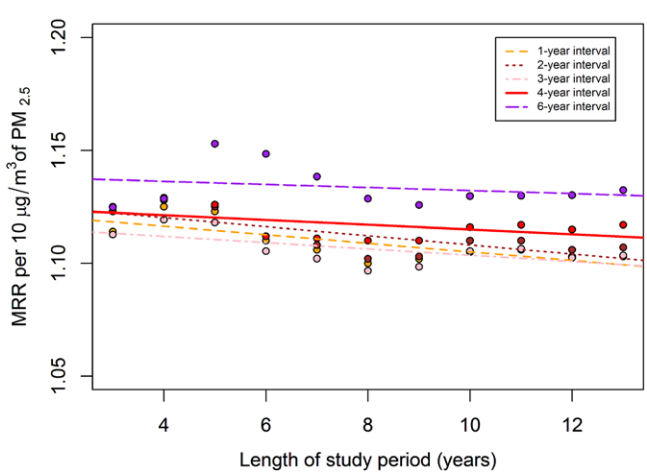

Figure 3. MRRs per 10 µg/m³ increase in $PM_{2.5}$ by length of study period: residual-based model using different time intervals to control for temporal trends.

Our findings add to the body of evidence showing that long-term $PM_{2.5}$ exposures are associated with increased mortality,[2–7,9–13] lending additional support to findings from the American Cancer Society (ACS) cohort,[2] the Nurses' Health Study,[5] and the Medicare cohort.[4] Although no studies to date have explicitly examined the possible impact of temporal confounding on these associations, several studies have indirectly examined this possibility. In a study by Lepeule et al,[6] e.g., the original[21] and initial follow-up[22] of the Six Cities Study were extended to include 11 additional years of follow-up, comprising 36 years in total (1974–2009). MRRs were estimated for the entire 36-year study period and for four, equally divided 9-year time periods. While overall $PM_{2.5}$ concentrations decreased over the 36-year study period, this decrease was uniform neither by city nor over time. $PM_{2.5}$ concentrations exhibited strong downward trends over time in only the three most polluted cities—Steubenville, Kingston-Harriman, and St. Louis, with these trends steepest and most consistent between 1979 and 1992 and to a lesser extent 2000–2009. The authors found an overall MRR for all-cause mortality of 1.14 (95% CI = 1.07, 1.22) for a 10 µg/m³ increase in 1-year $PM_{2.5}$. When data for the four 9-year time periods were analyzed, MRRs varied widely, with values of 1.06 (95% CI = 0.96, 1.17) for 1974–1982, 1.32 (95% CI = 1.16, 1.50) for 1983–1991, 1.11 (95% CI = 0.98, 1.27) for 1992–2000, and 1.19 (95% CI = 0.91, 1.55) for 2001–2009. Notably, MRRs were highest during the period when temporal trends in $PM_{2.5}$ were strongest, providing some, albeit indirect, support for our findings of confounding by long-term temporal trends. The increased MRR for the last 9-year interval compared with the full 36-year MRR may reflect aging of the cohort.

Further support is provided by results from related studies by Janes et al,[16] Greven et al,[17] and Pun et al[18] who decomposed $PM_{2.5}$ into its temporal and spatiotemporal components and found higher and statistically significant MRRs for temporal as compared to spatiotemporal $PM_{2.5}$. The authors concluded that differences in the MRRs associated with temporal and spatiotemporal $PM_{2.5}$ reflected residual confounding by temporally varying covariates.

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Consistent with Greven et al,[17] additional adjustment for county-level BRFSS covariates did not reduce residual confounding, suggesting that the examined behavioral variables do not confound the $PM_{2.5}$ mortality association. This finding, however, differs from that reported by Pun et al,[18] who found that residual confounding decreased after adjustment for BRFSS covariates in models of $PM_{2.5}$ and mortality. This discrepancy likely results from the fact that the Pun et al[18] analysis assessed residual confounding by decomposing both $PM_{2.5}$ and BRFSS data into their temporal and spatiotemporal components, while we decomposed only $PM_{2.5}$ since our time-adjusted models already control indirectly for temporal trends in BRFSS data. Together, these results suggest that temporal trends in confounding variables are important to consider as well.

Our findings of increasing MRRs with longer study periods suggest that long-term temporal trends in $PM_{2.5}$ concentrations may be one source of this unmeasured confounding. We found residual-based exposures to successfully control for these time trends in $PM_{2.5}$. The ability of residual-based exposures to control for these time trends in $PM_{2.5}$ is consistent with previous studies.[23–25] For example, Mostofsky et al[25] used a residual-based approach to estimate the effect of $PM_{2.5}$ constituents while controlling for confounding by total amount of $PM_{2.5}$. To do so, they regressed each constituent of interest on the total $PM_{2.5}$ in a linear model and used the residual to estimate the effect of each individual constituent while holding $PM_{2.5}$ constant. This approach is similar to our residual-based exposure method, with the only difference being our focus on the effect of $PM_{2.5}$ while controlling for the unmeasured variables associated with long-term time trends. Because the unmeasured confounders are not perfectly correlated with time, complete control of time (through indicator functions for each month) would have likely over-adjusted for any potential confounding, as observed when the residual model was based on time controlled in 1-, 2-, and 3-year intervals. On the other hand, using a coarser measure of time (such as 6-year intervals) may not sufficiently control for the unmeasured variables, resulting in a lack of independence between time trends and both $PM_{2.5}$ and mortality. Our results suggest that the residual model controlling for time in 4-year intervals was able to provide MRR estimates that were least affected by study period length.

We found this residual-based method to perform better than the spline and decomposition approaches, both of which showed declining MRRs as study periods increased, suggesting that these methods over-controlled for long-term time trends. Further, by including terms for both $PM_{2.5}$ and some adjustment for time in the model, the spline- and decomposition-based approaches may result in biased effect estimates, given collinearities of $PM_{2.5}$ and time.[26] In our data, the correlations of $PM_{2.5}$ with both the spline of $PM_{2.5}$ and decomposed $PM_{2.5}$ varied with the length of study period, with correlations for $PM_{2.5}$ and the spline of $PM_{2.5}$ equaling 0.15 for 3-year periods and increasing to 0.44 for 12-year periods. Identical correlations were observed for $PM_{2.5}$ and decomposed $PM_{2.5}$. These results suggest that the bias in MRRs derived from the spline and decomposed $PM_{2.5}$ models increases as the study length increases.

Our results are limited by several factors. First, our log-linear models aggregated data by site and limited the number of strata for computational efficiency, thus limiting our ability to control for individual-level covariates. However, when we additionally adjusted for county-level behavioral covariates, we found similar MRRs, suggesting behavioral covariates did not confound associations (Table S1; http://links.lww.com/EE/A4). Second, individual exposure measurement error is unavoidable when using the monitor level air pollution data. This exposure error is likely to be small, given results from studies that show that $PM_{2.5}$ concentrations to be moderately uniform within a given county and ambient $PM_{2.5}$ concentrations to be strong surrogates for personal $PM_{2.5}$ exposure.[27] Thus, we expect any exposure error to bias observed associations toward the null and underestimate mortality risk estimates.[28] Third, although bias may also be introduced by the "healthy worker effect" where subjects less susceptible to $PM_{2.5}$ exposures remain in our study population for longer time periods, this bias would be in the opposite direction of the observed changes. Although our study could not examine the impact of temporal variation of $PM_{2.5}$ composition on MRRs, compositional variability is unlikely to explain our findings given the strong dependence of MRRs on $PM_{2.5}$ time trends and the inconsistent time trends in $PM_{2.5}$-associated total carbon concentrations between 2000 and 2010 in the United States.[29] Finally, while we found the residual model based on 4-year intervals to best control for temporal trends, further study, such as through a simulation study, is needed to confirm our findings.

Summary

We found significant associations between 1-year $PM_{2.5}$ exposures and mortality. These associations were likely confounded by long-term temporal trends in $PM_{2.5}$. We successfully controlled for this confounding by using exposure measures based on the residual of $PM_{2.5}$ regressed on time in 4-year intervals. Controlling for long-term temporal $PM_{2.5}$ trends, we found significant 11.7% increase in all-cause mortality among Medicare beneficiaries for a 10 μg/m^3 increase in $PM_{2.5}$. This MRR was reduced compared to the model without controlling for the temporal confounding. These findings demonstrate the importance and need to account for temporal trends in future air pollution health effect studies.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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