COMMENTS OF THE ATTORNEYS GENERAL OF NEW YORK, CALIFORNIA, CONNECTICUT, DELAWARE, ILLINOIS, MARYLAND, MASSACHUSETTS, MICHIGAN, MINNESOTA, NEW JERSEY, OREGON, PENNSYLVANIA, RHODE ISLAND, VERMONT, VIRGINIA, AND WASHINGTON

November 20, 2020

Comments submitted via email: a-and-r-docket@epa.gov

Re: Docket ID No. EPA-HQ-OAR-2015-0072/Supplemental Comments re. Particulate Matter Studies

Dear Environmental Protection Agency:

The undersigned State Attorneys General (the States) respectfully submit this letter along with copies of three scientific studies published after the close of the public comment period concerning the harms of fine particulate matter ($PM_{2.5}$) exposure, including links between mortality from COVID-19 and particulate matter exposure. These studies provide important supplemental information regarding why it is necessary for EPA to strengthen the national ambient air quality standards for particulate matter to provide the "margin of safety" to protect human health and the public welfare required by the Clean Air Act. [1] We request that EPA reopen its review of the national ambient air quality standards for particulate matter to consider this significant new information.[2]

In our June 29, 2020 comments on EPA's review of the national ambient air quality standards, we emphasized that EPA must strengthen the standards to protect the public. [3] We first noted that EPA employed a flawed process when reviewing the standards for particulate matter because it had disbanded the particulate matter scientific expert review panel. We then cited numerous studies indicating that exposure to $PM_{2.5}$ causes premature mortality, cardiovascular impacts, respiratory impairments, lung cancer, and cognitive impairments. We asked EPA to reconstitute the particulate matter review panel to evaluate this information.

In the five months since submitting those comments, scientists have published additional studies that further demonstrate the harmful impacts of exposure to $PM_{2.5}$. First, multiple studies found links between mortality from COVID-19 and particulate matter exposure. For example, one study "found that an increase of 1 $\mu g/m^3$ in the long-term average $PM_{2.5}$ is associated with a

[1] *See* 42 U.S.C. § 7409(b).

[2] *See id.* § 7607.

[3] Comment submitted by Letitia James, Attorney General, State of New York *et al.*, *Review of the National Ambient Air Quality Standards for Particulate Matter*, June 29, 2020, *available at*: https://www.regulations.gov/document?D=EPA-HQ-OAR-2015-0072-0972.

statistically significant 11%. . . increase in [a] county's COVID-19 mortality rate." [4] Another study found that particulate matter exposures are positively correlated with higher mortality from COVID-19. [5] As the number of COVID-19 cases reaches new peaks and the impacts of the pandemic continue to devastate communities across the country, it is even more imperative that EPA should set standards that protect lungs and decrease mortality from respiratory diseases.

The negative health impacts of exposure to $PM_{2.5}$ is not limited to respiratory harms. Researchers conducted a long-term study of the effects of $PM_{2.5}$ on neurological disorders in older Americans. [6] The researchers found an increased risk of Parkinson's disease, Alzheimer's disease, and related dementias based on long-term exposure to particulate matter, even at levels lower than EPA's current air quality standards. [7] Moreover, the risks increased as the concentration of particulate matter increased. [8] Thus, fine particulate matter negatively impacts many areas of public health.

These new studies document both the immediate harms of exposure to particulate matter during a respiratory disease pandemic and the long-term cognitive impacts of exposure. We therefore reiterate our request that EPA reconstitute its particulate matter review panel and reopen its rulemaking to consider the new information presented in these supplemental comments.

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[4] *See* A. Pozzer *et al.*, *Regional and Global Contributions of Air Pollution to Risk of Death from COVID-19*, Cardiovascular Research, Sept. 30, 2020, at 1, *available at*: https://academic.oup.com/cardiovascres/advance-article/doi/10.1093/cvr/cvaa288/5940460.

[5] X. Wu *et al.*, *Air Pollution and COVID-19 Mortality in the United States: Strengths and Limitations of an Ecological Regression Analysis*, *Science Advances*, Nov. 4, 2020, at 1, *available at:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7277007/.

[6] *See* L. Shi *et al.*, *Long-term Effects of $PM_{2.5}$ on Neurological Disorders in the American Medicare Population: A Longitudinal Cohort Study*, The Lancet, Oct. 19, 2020, at 1, *available at*: https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196(20)30227-8/fulltext.

[7] *Id.* at 6.

[8] *Id.*

Respectfully submitted,

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Regional and global contributions of air pollution to risk of death from COVID-19

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Aims The risk of mortality from the coronavirus disease that emerged in 2019 (COVID-19) is increased by comorbidity from cardiovascular and pulmonary diseases. Air pollution also causes excess mortality from these conditions. Analysis of the first severe acute respiratory syndrome coronavirus (SARS-CoV-1) outcomes in 2003, and preliminary investigations of those for SARS-CoV-2 since 2019, provide evidence that the incidence and severity are related to ambient air pollution. We estimated the fraction of COVID-19 mortality that is attributable to the long-term exposure to ambient fine particulate air pollution.

Methods and results We characterized global exposure to fine particulates based on satellite data, and calculated the anthropogenic fraction with an atmospheric chemistry model. The degree to which air pollution influences COVID-19 mortality was derived from epidemiological data in the USA and China. We estimate that particulate air pollution contributed ~15% (95% confidence interval 7–33%) to COVID-19 mortality worldwide, 27% (13 – 46%) in East Asia, 19% (8–41%) in Europe, and 17% (6–39%) in North America. Globally, ~50–60% of the attributable, anthropogenic fraction is related to fossil fuel use, up to 70–80% in Europe, West Asia, and North America.

Conclusion Our results suggest that air pollution is an important cofactor increasing the risk of mortality from COVID-19. This provides extra motivation for combining ambitious policies to reduce air pollution with measures to control the transmission of COVID-19.

Keywords COVID-19 • Air pollution • Fine particulate matter • comorbidity • mortality

1. Introduction

Poor air quality, especially from fine particulate matter with a diameter <2.5 μm ($PM_{2.5}$), is one of the leading risk factors, and responsible for many excess deaths.[1,2] The global loss of life expectancy from long-term exposure to ambient air pollution exceeds that of infectious diseases, and is comparable with that of tobacco smoking.[1–3] The mortality from COVID-19 depends on comorbidities, including conditions that increase cardiovascular risks such as arterial hypertension, diabetes mellitus, obesity, and established coronary artery disease, as well as respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD), being similar to those that are influenced by air pollution.[3–6] The risk of death is strongly related to age, being particularly high in those aged >70. It is also higher amongst males, economically disadvantaged populations, and in some ethnic groups. In assessing the relationships between exposures to risk factors and outcomes, potential confounders therefore need to be accounted for in the design of studies and in data analysis. These include the age distribution of the population, availability of hospital beds (and intensive care capacity), and the proportion of the population living in poverty.

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A recent study, using an ecological design, assessed how environmental influences modify the severity of COVID-19 outcomes in the USA.[7] Potential confounders were identified, and statistical models were used to relate long-term exposure to ambient $PM_{2.5}$ to COVID-19 deaths. The computed mortality rate ratios (MRRs) express the relative increase in COVID-19 deaths for each microgram per cubic meter increment of $PM_{2.5}$ in ambient air. The $PM_{2.5}$ data were derived from satellite and ground-based measurements combined with atmospheric modelling,[8] and the confounders were determined from county-level censuses, homeland infrastructure, and meteorological data. Here we test the assumption that the derived MRRs are representative for the populations of other countries (China) and consider the global impact. In the present study, we apply the MRRs to estimate the excess mortality, i.e. the fraction of COVID-19 deaths that could be avoided if the population were exposed to lower counterfactual air pollution levels without fossil fuel-related and other anthropogenic emissions. We emphasize that our results are provisional, based on epidemiological data collected up to the third week of June 2020, and a comprehensive evaluation will need to follow after the COVID-19 pandemic.

1.1 SARS and air pollution

In the early 2000s, the first severe acute respiratory syndrome coronavirus (SARS-CoV-1) appeared in China (Guangdong Province). The virus was zoonotic, as it originally developed in bats.[9] The World Health Organization (WHO) reported that it resulted in a SARS epidemic with >8000 cases in 26 countries, mostly in south-east Asia and in Canada.[8] The disease emerged in November 2002 and was contained in July 2003. SARS-CoV-1 and SARS-CoV-2 have many similarities, as their RNA genomes are closely related and the viruses enter the host cells by binding to the same entry receptor angiotensin-converting enzyme 2 (ACE2).[10–12] About 2–14 days after infection, the systemic symptoms of both diseases are alike, and a similar fraction of patients develops severe symptoms with a mortality rate that increases strongly with advanced age.[13–16] In China alone, >5000 cases of SARS-CoV-1 were reported, leading to nearly 350 fatalities. Since the exposure to ambient air pollution is associated with respiratory and cardiovascular diseases, it was hypothesized that health outcomes of SARS were aggravated by poor air quality. A study in 2003 corroborated that in parts of China with moderate levels of air pollution, the risk of dying from the disease was >80% higher compared with areas with relatively clean air, while in heavily polluted regions the risk was twice as high.[17]

1.2 COVID-19 and air pollution

In 2019, the related second virus strain appeared (SARS-CoV-2) in China (Hubei Province), which also developed in bats,[4] causing COVID-19, which grew from an epidemic into a pandemic in the early part of 2020. A Chinese analysis indicated that the risk of symptomatic infection typically increases by ~4% for each year of age between 30 and 60, and that the lethality is highest for individuals >60 years.[15]COVID-19 is associated with a combination of respiratory and cardiovascular complications, which may comprise myocardial infarction, heart failure, venous thrombo-embolisms, and increases in biomarkers,[18] which are also found in connection with high levels of air pollutants.[5] In a recent analysis of 5700 patients hospitalized with COVID-19 in the New York City area, the most common comorbidities were hypertension (57%), obesity (42%), and diabetes (34%),[19] representing cardiovascular risk factors that are also observed in relation to elevated $PM_{2.5}$ concentrations,[5,20] suggesting additive or synergistic effects on the cardiovascular system. In addition, advanced age is a strong risk factor for cardiovascular disease, and the effects on immune function may be equally important for COVID-19 susceptibility. The age dependency coincides with that of excess mortality from $PM_{2.5}$.[3,15] The COVID-19 mortality rate has been estimated to be ~4% in symptomatic cases, in part because pre-existing conditions such as cardiovascular and respiratory disorders increase the risk.[21]

Considering the cardiovascular and respiratory health impacts of air pollution, the relationship to COVID-19 mortality is not unexpected. Preliminary studies addressed the influence of air pollution on COVID-19 in different regions. In China, the incidence of COVID-19 was found to be significantly enhanced by $PM_{2.5}$,[22] while a correlation between ambient $PM_{2.5}$ and the mortality rate was also established.[23] In Italy, it was found that the high pollution concentrations that are typical for the Po valley, especially in the Lombardy region of which Milan is the capital, were associated with a high mortality rate.[24] As mentioned above, in the USA the severity of COVID-19 outcomes was linked to $PM_{2.5}$ exposure, making use of Medicare data for >60 million people and nationwide air quality measurements.[7] Data were collected for 98% of the population in 3087 of the total number of 3142 counties, of which ~42% had reported COVID-19 deaths up to the third week of April 2020. The death counts relied on data from the Coronavirus Resource Center of the Johns Hopkins University.[25] The study accounted for 20 potential confounding factors including population size, age distribution, population density, time period since the beginning of the outbreak, time elapsed since the home confinements, hospital beds, number of individuals tested, meteorological conditions, and socioeconomic and risk factors such as obesity and smoking.[7] The results showed significant overlap between the causes of death in COVID-19 patients and those that lead to mortality from $PM_{2.5}$. The MRR, i.e. the percentage increase of COVID-19 mortality risk per $\mu g/m^3$ increase of exposure to $PM_{2.5}$, was found to be 8%, with a 95% confidence interval of 2–15%.[7] The calculations are continually updated based on the most recent data (up to 18 June at the time of writing), showing no significant changes in the MRR in the preceding 4 months.

2. Methods

2.1 Global model and data

We applied a global atmospheric chemistry general circulation model (EMAC) which comprehensively simulates atmospheric chemical and meteorological processes and interactions with the oceans and the biosphere, in the same set-up as in recent studies on climate change, air pollution, and public health.[3,26] In addition to the standard simulation, we performed two sensitivity calculations: (i) with fossil fuel-related emissions removed and (ii) with all anthropogenic emissions removed. The model results were used to estimate the ratio of fine particulates in simulation (i) and (ii) and the standard simulation. The annual atmospheric near-surface $PM_{2.5}$ concentrations were taken from model-integrated satellite data, for the year 2019.[8,27] The horizontal resolution is 0.01 by 0.01 degrees, corresponding to a grid size of ~1 km 1 km. The near-surface concentrations of $PM_{2.5}$ for fossil fuel-related and all anthropogenic emissions are estimated by scaling this data set to the ratios (i) and (ii) obtained with the EMAC model simulations.

2.2 Relative risk

To estimate the relative risk (RR or hazard ratio) of excess COVID-19 mortality from the long-term exposure to air pollution, we used the exposure–response function of the WHO,[28]

$$RR = \left(\frac{X+1}{X_0+1}\right)^{\beta},$$

RR is a function of the concentration of air pollutants, which specifies annual average exposure dependent on location (grid cell) derived from the data mentioned above. X is the pollutant ($PM_{2.5}$) and X_0 is the pollutant threshold concentration below which exposure does not have implications for public health. Both β and X_0 are estimated by fitting to data from the literature with a least square method (*Figure 1*). We adopted the threshold $PM_{2.5}$ concentration (X_0) from Burnett *et al.*[2] (i.e. < 2.4 μg/m^3 $PM_{2.5}$), forcing the curve fitting into this range. We tested different exposure–response functions, e.g. of Burnett *et al.*,[2] and values for X_0, and find that the results are not sensitive to these assumptions.

Because the COVID-19 mortality rate ratio due to air pollution, based on data in the USA alone,[7] may not represent countries with very high fine particle concentrations (associated with a lack of observations in such regions), we investigated the effect of including data from the enhanced mortality rate derived for the Chinese SARS epidemic in 2003.[17] We make the assumption that SARS and COVID-19 mortality are similarly affected by long-term exposure to air pollution. Since the analysis for SARS was based on the Chinese Air Pollution Index (API), we converted the API to $PM_{2.5}$ concentrations following empirical relationships from the literature.[29,30] The large uncertainty range in the fitting function to a large degree derives from those in these relationships (black squares and ranges in *Figure 1*). In spite of uncertainties, the curves for the USA only and those that include the Chinese results are almost identical, providing confidence in the function derived for conditions in the USA only.

2.3 Attributable fraction

We calculated RR globally using $PM_{2.5}$ distributions calculated under the standard scenario. The attributable fraction (AF) of COVID-19 mortality to air pollution is calculated from the RR by AF = 1 – 1/RR. From the globally distributed, gridded AFs, we aggregated into regional and country-level AFs, weighted according to the population density, in order to account for the varying population distributions within regions and countries. The population data for the year 2020 were obtained from the NASA Socioeconomic Data and Applications Center (SEDAC), hosted by the Columbia University Center for International Earth Science Information Network (CIESIN).[31] Our definition of AF does not imply a direct cause–effect relationship between air pollution and COVID-19 mortality (although it is possible). Instead it refers to relationships between the two, direct and indirect, i.e. by aggravating comorbidities that could lead to fatal health outcomes of the virus infection.

3. Results

3.1 Attribution of COVID-19 mortality

To estimate the AF from exposure to ambient $PM_{2.5}$ to COVID-19 mortality, we used the epidemiological data from the USA (red curve in *Figure 1*). The chronic exposure to $PM_{2.5}$ in the years prior to the COVID-19 outbreak was estimated on the basis of satellite observations over the year 2019. The anthropogenic and fossil fuel-related fractions were calculated with the global EMAC model. Here we focus on anthropogenic and fossil fuel-related $PM_{2.5}$ to determine the impact of potentially avoidable air pollution on COVID-19 mortality. *Figure 2* and *Table 1* present the average fractions of COVID-19 mortality attributed to the exposure to $PM_{2.5}$ pollution, both globally and regionally. *Table S1* (available as Supplementary material online) lists the results for all countries. To account for the different population distributions within countries, e.g. between rural and urban areas, the averages have been weighted accordingly.

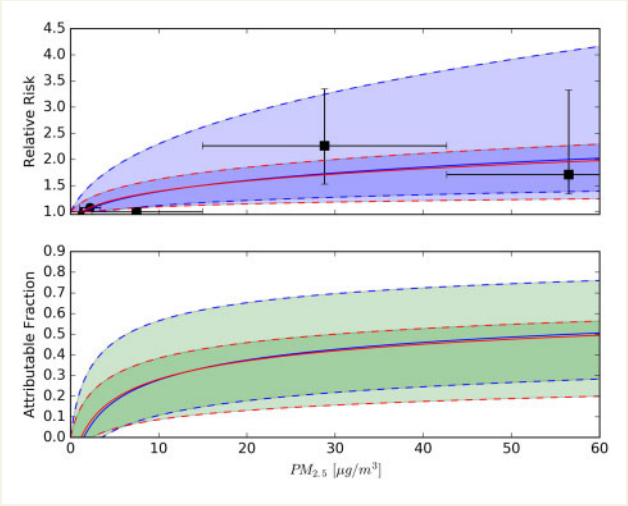

Figure 1 Exposure-response dependencies, based on a log-normal relationship[28]. The relative risk (or hazard ratio), from which the attributable fraction has been derived, is based on mortality rate ratios attributed to air pollution in the COVID-19 pandemic[7] and the SARS epidemic[17], indicated by the black bullet and squares, respectively. The triangle represents the threshold concentration below which $PM_{2.5}$does not have health implications[2]. The red curves depict the function fitted to the data from COVID-19 in the USA only[7], plus the threshold[2] (triangle and bullet). The blue curves depict the function fitted to all data[2,7,17]. The colored ranges show the 95% confidence intervals, which are wider after including the SARS-related results (blue), mostly due to uncertainty from converting Chinese API's into $PM_{2.5}$concentrations (black squares).

In regions with strict air quality standards and relatively low levels of air pollution, such as Australia, the attributable fraction by human-made air pollution to COVID-19 mortality is found to be a few percent only. Relatively high fractions occur in parts of east Asia (∼35%), central Europe (∼25%), and eastern USA (∼25%). The country-level contribution to COVID-19 that we find for China, i.e. 27% (95% confidence interval 13 – 47%), agrees well with that found for the SARS epidemic in 2003.[17] The largest country-average fractions are found in the Czech Republic, Poland, China, North Korea, Slovakia, Austria, Belarus, and Germany, all above 25% (Supplementary material, *Table S1*). Globally, anthropogenic air pollution contributes ∼15% (7 – 33%) to COVID-19 mortality, which could have been largely prevented, for example by adopting the air quality regulations applied in Australia (annual $PM_{2.5}$ limit of 8 μg/m^3). The global mean contribution of fossil fuel use to the anthropogenic fraction is ∼56%, being highest in North America (83%), West Asia (75%), and Europe (68%) (*Table 1*).

4. Discussion

4.1 Pathophysiological aspects

Both the air pollutant $PM_{2.5}$ and the SARS-CoV-2 virus enter the lungs via the bronchial system (portal organ), with potential systemic health impacts through the blood circulation. Both $PM_{2.5}$ and SARS-CoV-2 cause vascular endothelial dysfunction, oxidative stress, inflammatory responses, thrombosis, and an increase in immune cells.[32–36] The SARS-CoV-2 infection facilitates the induction of endothelial inflammation in

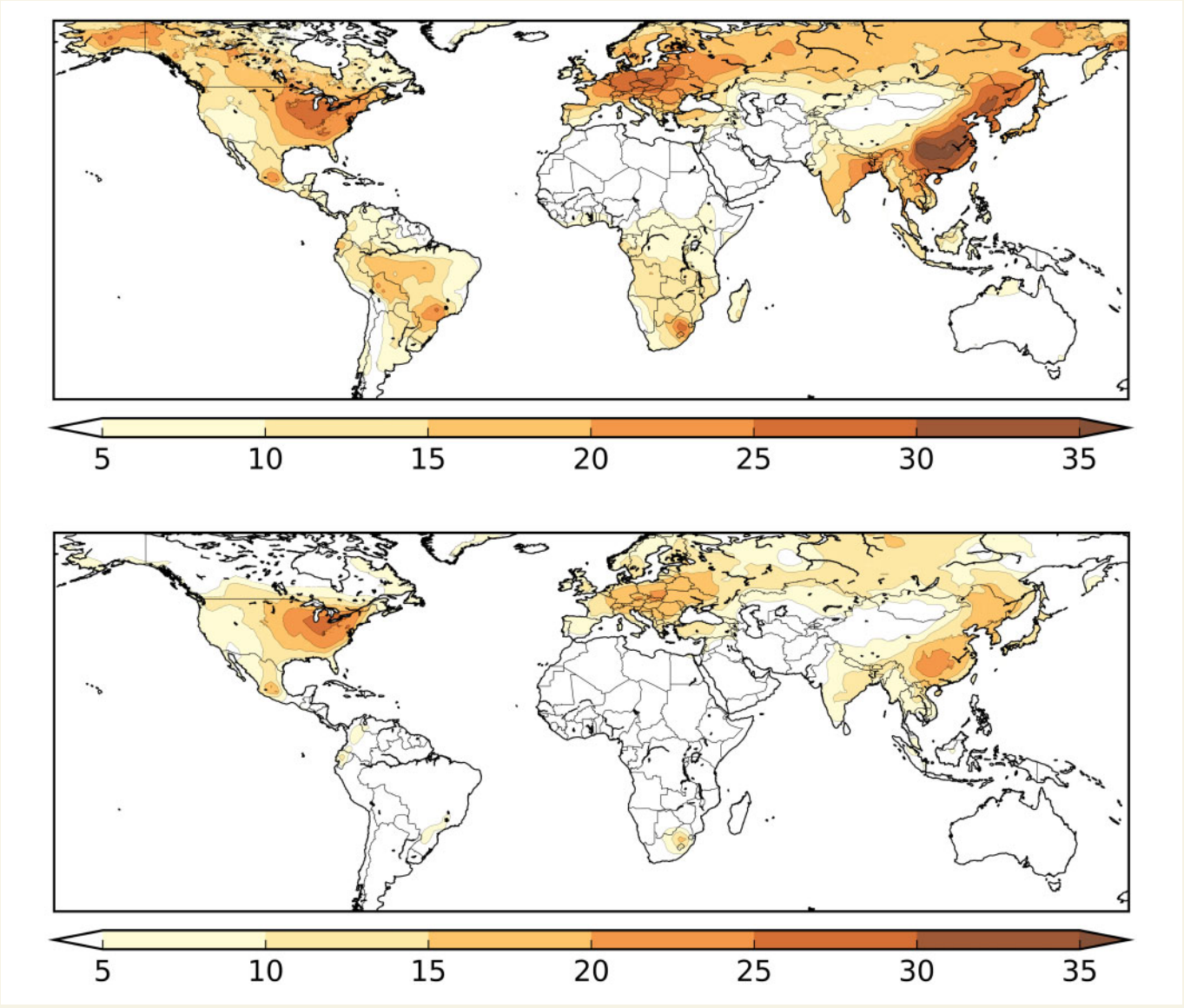

Figure 2 Estimated percentages of COVID-19 mortality attributed to air pollution from all anthropogenic sources (top), and from fossil fuel use only (bottom). The regions with high attributable fractions coincide with high levels of air pollution. The mapped results account for population density, thus reflecting population weighted exposure to $PM_{2.5}$.

several organs as a direct consequence of viral cytotoxic effects and the host inflammatory response, which can aggravate pre-existing chronic respiratory and vascular (coronary) dysfunction, and cause lung injury by alveolar damage, as well as stroke and myocardial infarction by inducing plaque rupture.[37] Potential common pathophysiological mechanisms of increased risk thus relate to endothelial injury[33,38] and pathways that regulate immune function.[39,40] Further, there are strong indications of increased susceptibility to viral infections from exposure to air pollution.[41–46]

Lung injuries, including the life-threatening acute respiratory distress syndrome and respiratory failure, as well as acute coronary syndrome, arrhythmia, myocarditis, and heart failure, were shown to be clinically dominant, leading to critical complications of COVID-19.[47,48] Recent studies in China, the USA, as well as Europe indicate that patients with cardiovascular risk factors or established cardiovascular disease and other comorbid conditions are predisposed to myocardial injury during the course of COVID-19.[19,46,49–52] From the available information, it thus follows that air pollution-induced inflammation leads to greater vulnerability and less resiliency, and the pre-conditions increase the host vulnerability. Air pollution causes adverse events through myocardial infarction and stroke, and it is an additional factor capable of increasing blood pressure, while there is emerging evidence for a link with type 2 diabetes and a possible contribution to obesity and enhanced insulin resistance.[36] Bronchopulmonary and cardiovascular pre-conditions, including hypertension, diabetes, coronary artery disease, cardiomyopathy, asthma, COPD, and acute lower respiratory illness, all negatively influenced by air pollution, lead to a substantially higher mortality risk in COVID-19. Furthermore, it seems likely that fine particulates prolong the atmospheric lifetime of infectious viruses, thus favouring transmission.[53] It is possible that future research will reveal additional pathways that mediate the relationship between air pollution and the risk of death from COVID-19.

Table 1 Regional percentages of COVID-19 mortality attributed to fossil fuel-related and all anthropogenic sources of air pollution

Region	Population (million)	COVID-19 mortality fraction attributed to air pollution (%)	
		Fossil fuel-related emissions	All anthropogenic emissions
Europe	628	13 (6–33)	19 (8–41)
Africa	1345	2 (1–19)	7 (3–25)
West Asia	627	6 (3–25)	8 (4–27)
South Asia	2565	7 (3–22)	15 (8–31)
East Asia	1685	15 (8–32)	27 (13–46)
North America	525	14 (6–36)	17 (6–39)
South America	547	3 (1–23)	9 (4–30)
Oceania	28	1 (0–20)	3 (1–23)
World	7950	8 (4–25)	15 (7–33)

4.2 Limitations

Our results indicate that the long-term exposure to high levels of fine particulate matter is a significant cofactor that influences the severity of COVID-19 outcomes. Since $PM_{2.5}$ in China and the USA, from which epidemiological data have been used, is dominated by anthropogenic sources that are potentially preventable, we focus our analysis on this fraction of $PM_{2.5}$. The good agreement of our results for the USA and China is in line with recent studies, showing that the association between air pollution and excess mortality is valid for many different countries.[2,55] Nevertheless, the calculations of RRs (hazard ratios) and the AF to mortality rely on the use of data from an ecological study design that has limitations, even though 19 county-level variables and one state-level variable, some of which are more important than air pollution, were considered as potential confounders in the analysis—and the $PM_{2.5}$ exposure data have been extensively cross-validated.[7] However, we acknowledge that residual confounding cannot be excluded. While cross-sectional ecological studies do not allow conclusions about cause–effect relationships, the biological mechanisms of air pollution-related disorders, acting as comorbidities in COVID-19, are well documented.[56,57] Recent studies in England and The Netherlands corroborate the positive relationships between air pollution and the number of COVID-19 cases, hospital admissions, and mortality.[58–60] The reported MRRs for $PM_{2.5}$ range from 1–7% to 13–21% (we applied 2–15%), which confirms the significant role of air pollution but emphasizes the large uncertainty ranges. Furthermore, our approach is likely to realistically approximate the contribution of fossil fuels and other anthropogenic sources to the total excess deaths through long-term ambient $PM_{2.5}$ air pollution exposure.

We reiterate that the data used for China are associated with substantial uncertainty, and underly the assumption that comorbidity and mortality from air pollution in COVID-19 are the same as in SARS. Nonetheless, using these data does not change the results, providing confidence in the robustness of our findings. We emphasize that the data relevant to the present study are from upper-middle and high-income countries, and the representativeness of our results for low-income countries may be limited, and uncertainties are likely to exceed the 95% confidence intervals. It is expected that in countries with high levels of aeolian dust, e.g. in Africa and West Asia, $PM_{2.5}$ pollution is also a cofactor but with less contribution from human activities. Household air pollution is also likely to be important, being of particular relevance in low-income countries.[61] It will be critical to collect epidemiological evidence from many regions with different socio-economic and environmental conditions, to support analyses of the COVID-19 pandemic and investigate the role of environmental factors. The uncertainty ranges that accompany our results are considerable but, taking into account the biological plausibility of the relationship and the strong evidence of the impact of air pollution on conditions that are known to increase COVID-19 mortality, they can nevertheless inform policy decisions.

4.3 Short- and long-term health impacts

A new, though preliminary, finding of the present study is that a significant fraction of worldwide COVID-19 mortality is attributable to anthropogenic air pollution, of which ~50 – 60% is related to fossil fuel use (~70 – 80% in Europe, West Asia, and North America). This represents potentially avoidable, excess mortality. The links between economic activity, traffic, energy use, and public health have been illustrated by the strong reduction of air pollution in many locations during the lockdown measures.[62,63] There is ample evidence for a relationship between short-term exposure to $PM_{2.5}$ and adverse health effects, including excess mortality from cardiovascular and respiratory diseases.[55] While it is in principle possible to disentangle the acute from the chronic outcomes from short- and long-term exposure to air pollution,[64] at this stage it is difficult to make that distinction for $PM_{2.5}$-induced comorbidity and mortality from COVID-19. Generally, short-term associations between air pollution and mortality are substantially less than those from long-term exposure, due to the more persistent, cumulative effects from the latter.[65] By relating air pollution anomalies to short-term health outcomes during the COVID-19-induced societal lockdown, it was found that in China alone >4600 excess deaths may have been avoided.[62] This can be viewed as a health co-benefit from the containment measures, which may reduce air pollution-induced COVID-19 mortality. Such benefits could also be achieved after the COVID-19 lockdown. Both perspectives of air pollution during the pandemic underscore the important role of fossil fuel-related and other anthropogenic emissions.

4.3 Future directions

Our results suggest the potential for substantial benefits from reducing air pollution exposure even at relatively low $PM_{2.5}$ levels. Refinement of the exposure–response relationship and reducing uncertainties will require additional data analyses, including from large cohort studies as the COVID-19 pandemic evolves, but may appear too late to guide

decision-making. A lesson from our environmental perspective of the COVID-19 pandemic is that the quest for effective policies to reduce anthropogenic emissions, which cause both air pollution and climate change, needs to be accelerated. The pandemic ends with the vaccination of the population or with herd immunity through extensive infection of the population. However, there are no vaccines against poor air quality and climate change. The remedy is to mitigate emissions. The transition to a green economy with clean, renewable energy sources will further both environmental and public health locally through improved air quality and globally by limiting climate change.

Supplementary material

Supplementary material is available at *Cardiovascular Reseach* online.

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Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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Translational perspective

COVID-19 infections and air pollution cause excess mortality from cardiovascular and pulmonary diseases. We estimated the fraction of COVID-19 mortality attributable to the long-term exposure to ambient fine particulate air pollution ($PM_{2.5}$). Global exposure to $PM_{2.5}$ was characterized based on satellite data, and the anthropogenic fraction was calculated with an atmospheric chemistry model. $PM_{2.5}$ contributed ~15% to COVID-19 mortality worldwide, 27% in East Asia, 19% in Europe, and 17% in North America. Globally ~50–60% of the attributable, anthropogenic fraction is related to fossil fuel use, and 70–80% in Europe/West Asia/North America, indicating the potential for substantial health benefits from reducing air pollution exposure.

CORONAVIRUS

Air pollution and COVID-19 mortality in the United States: Strengths and limitations of an ecological regression analysis

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Assessing whether long-term exposure to air pollution increases the severity of COVID-19 health outcomes, including death, is an important public health objective. Limitations in COVID-19 data availability and quality remain obstacles to conducting conclusive studies on this topic. At present, publicly available COVID-19 outcome data for representative populations are available only as area-level counts. Therefore, studies of long-term exposure to air pollution and COVID-19 outcomes using these data must use an ecological regression analysis, which precludes controlling for individual-level COVID-19 risk factors. We describe these challenges in the context of one of the first preliminary investigations of this question in the United States, where we found that higher historical $PM_{2.5}$ exposures are positively associated with higher county-level COVID-19 mortality rates after accounting for many area-level confounders. Motivated by this study, we lay the groundwork for future research on this important topic, describe the challenges, and outline promising directions and opportunities.

INTRODUCTION

The suddenness and global scope of the coronavirus disease 2019 (COVID-19) pandemic have raised urgent questions that require coordinated investigation to slow the disease's devastation. A critically important public health objective is to identify key modifiable environmental factors that may contribute to the severity of health outcomes [e.g., intensive care unit (ICU) hospitalization and death] among individuals with COVID-19. Numerous scientific studies reviewed by the U.S. Environmental Protection Agency (EPA) have linked fine particles ($PM_{2.5}$; particles with diameter, ≤ 2.5 μm) to a variety of adverse health events (*1*) including death (*2*). It has been hypothesized that because long-term exposure to $PM_{2.5}$ adversely affects the respiratory and cardiovascular systems and increases mortality risk (*3*–*5*), it may also exacerbate the severity of COVID-19 symptoms and worsen the prognosis of this disease (*6*).

Epidemiological studies to estimate the association between long-term exposure to air pollution and COVID-19 hospitalization and death is a rapidly expanding area of research that is attracting attention around the world. Two studies have been published using data from European countries (*7*, *8*), and many more are available as preprints. However, because of the unprecedented nature of the pandemic, researchers face serious challenges when conducting these studies. One key challenge is that, to our knowledge, individual-level data on COVID-19 health outcomes for large, representative populations are not publicly available or accessible to the scientific community. Therefore, the only way to generate preliminary evidence on the link between $PM_{2.5}$ and COVID-19 severity and outcomes using these aggregate data is to use an ecological regression analysis. With this study design, publicly available area-level COVID-19 mortality rates are regressed against area-level air pollution concentrations while accounting for area-level potential confounding factors. Here, we discuss the strengths and limitations of conducting ecological regression analyses of air pollution and COVID-19 health outcomes and describe additional challenges related to evolving data quality, statistical modeling, and control of measured and unmeasured confounding, paving the way for future research on this topic. We discuss these challenges and illustrate them in the context of a specific study, in which we investigated the impact of long-term $PM_{2.5}$ exposure on COVID-19 mortality rates in 3089 counties in the United States, covering 98% of the population.

Illustration of an ecological regression analysis of historical exposure to $PM_{2.5}$ and COVID-19 mortality rate

We begin by describing how to conduct an ecological regression analysis in this setting. COVID-19 death counts (a total of 116,747 deaths) were obtained from the Johns Hopkins University Coronavirus Resource Center and were cumulative up to 18 June 2020. We used data from 3089 counties, of which 1244 (40.3%) had reported zero COVID-19 deaths at the time of our analysis. Daily $PM_{2.5}$ concentrations were estimated across the United States on a $0.01° \times 0.01°$ grid for the period 2000–2016 using well-validated atmospheric chemistry and machine learning models (*9*). We used zonal statistics to aggregate $PM_{2.5}$ concentration estimates to the county level and then averaged across the period 2000–2016 to perform health outcome analyses. Figure 1 illustrates the spatial variation in 2000–2016 average (hereafter referred to as "long-term average") $PM_{2.5}$ concentrations and COVID-19 mortality rates (per 1 million population) by county.

We fit a negative binomial mixed model using COVID-19 mortality rates as the outcome and long-term average $PM_{2.5}$ as the exposure of interest, adjusting for 20 county-level covariates. We conducted more than 80 sensitivity analyses to assess the robustness of the findings to various modeling assumptions. We found that an increase of 1 $\mu g/m^3$ in the long-term average $PM_{2.5}$ is associated with a statistically significant 11% (95% CI, 6 to 17%) increase in the county's COVID-19 mortality rate (see Table 1); this association continues to be stable as more data accumulate (fig. S3). We also found that population density, days since the first COVID-19 case was reported, median household income, percent of owner-occupied housing, percent of the adult population with less than high school

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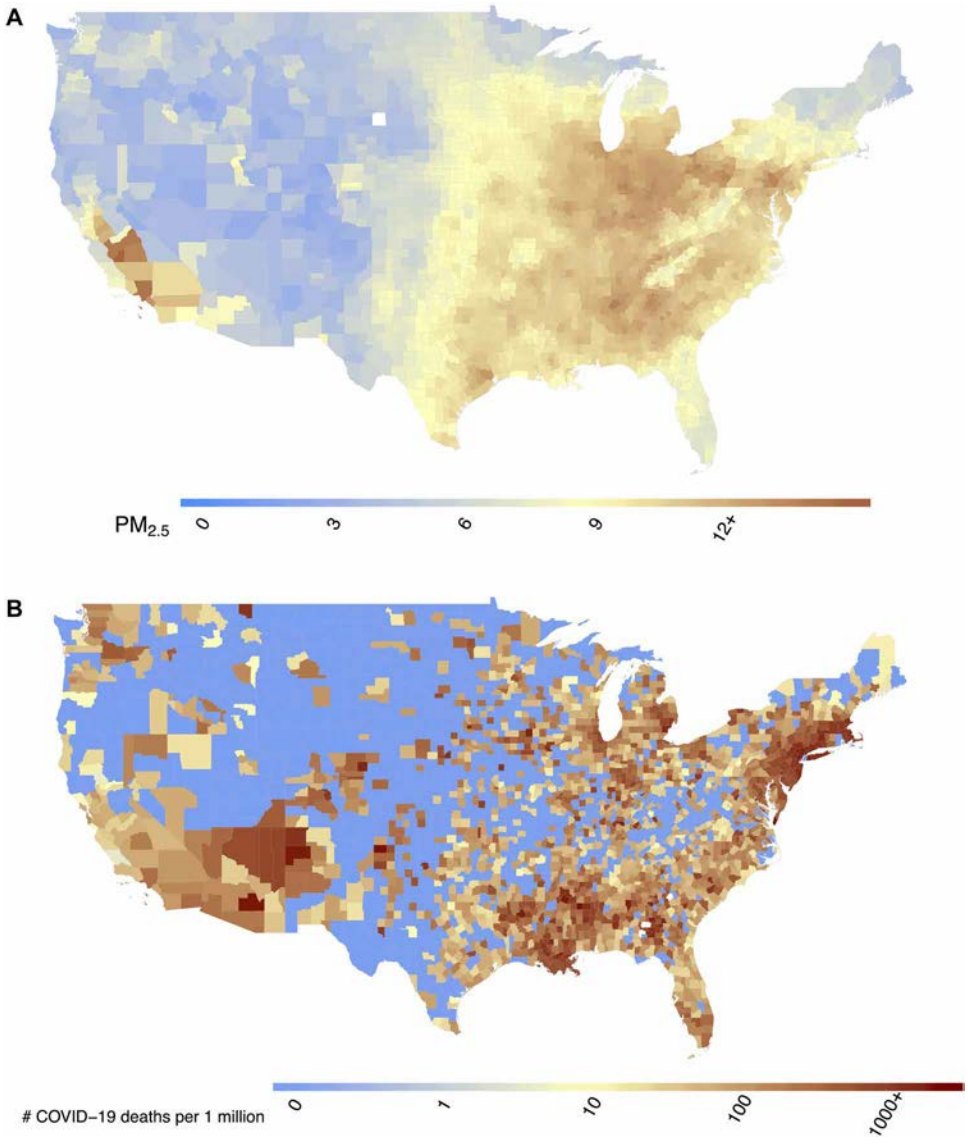

Fig. 1. National maps of historical $PM_{2.5}$ concentrations and COVID-19 deaths. Maps show (**A**) county-level 17-year long-term average of $PM_{2.5}$ concentrations (2000–2016) in the United States in $\mu g/m^3$ and (**B**) county-level number of COVID-19 deaths per 1 million population in the United States up to and including 18 June 2020.

education, age distribution, and percent of Black residents are important predictors of the COVID-19 mortality rate in the model. We found a 49% (95% CI, 38 and 61%) increase in COVID-19 mortality rate associated with a 1-SD (per 14.1%) increase in percent Black residents of the county. Details on the data sources, statistical methods, and analyses are summarized in the Supplementary Materials. All data sources used in the analyses, along with fully reproducible code, are publicly available at https://github.com/wxwx1993/PM_COVID.

Strengths and limitations of an ecological regression analysis

Ecological regression analysis provides a simple and cost-effective approach for studying potential associations between historical exposure to air pollution and increased vulnerability to COVID-19 in large representative populations, as illustrated in our study in the previous section. This approach is regularly applied in many areas of research (*10*). Using our study as an example, we summarize in Table 2 the strengths, limitations, and opportunities considering (i) study design, (ii) COVID-19 health outcome data, (iii) historical exposure to air pollution, and (iv) measured and unmeasured confounders, with the goal of paving the way for future research.

Among the key limitations, by design, ecological regression analyses are unable to adjust for individual-level risk factors (e.g., age, race, and smoking status); when individual-level data are unavailable, this approach leaves us unable to make conclusions regarding individual-level associations. In the context of COVID-19 health outcomes, this is a severe limitation, as individual-level risk factors are known to affect COVID-19 health outcomes. It is important to note that confusion between ecological associations and individual associations may present an ecological fallacy. In extreme

cases, this fallacy can lead to associations detected in ecological regression that do not exist or are in the opposite direction of true associations at the individual level. However, ecological regression analyses still allow us to make conclusions at the area level, which can be useful for policy-making (*11*). For the association between COVID-19 health outcomes and $PM_{2.5}$ exposure, we argue that area-level conclusions are valuable, as they can inform important immediate policy actions that will benefit public health, such as (i) prioritization of precautionary measures [e.g., personal protective equipment (PPE) allocations and hospital beds] to areas with historical higher air pollution and (ii) further strengthening the scientific argument for lowering the U.S. National Ambient Air Quality Standards for $PM_{2.5}$ and other pollutants. To completely avoid potential ecological bias, a representative sample of individual-level data is necessary. While this may not be feasible in the near future, as some COVID-19 outcome data become available at the individual level, existing approaches that augment county-level data with individual-level data (*12*) could be used to correct for ecological bias.

Furthermore, air pollution exposure misclassification, due to between-area mobility and within-area variation, is another potential source of bias that could affect the ecological regression results described in our example study. Methods to account for the propagation of exposure error into the ecological regression model (*13*) could be applied to help mitigate the impact of measurement error. Outcome misclassification is another limitation that can be partially overcome by accessing nationwide registry data with the validated cause of death (*14*). As in all observational studies, adjustment for measured and unmeasured confounding presents another key challenge in ecological regression analyses, which may be exacerbated when dealing with dynamic pandemic data, as in our study. Conducting studies using both traditional regressions and methods for causal inference as in Wu *et al.* (*2*) is necessary to assess the robustness of the findings.

Increasing the scientific rigor of research in this area requires access to representative, individual-level data on COVID-19 health outcomes, including information about patients' residential address, demographics, and individual-level confounders. This is an enormous challenge that will require consideration of many privacy, legal, and ethical trade-offs (*14*). Future areas of research also include the application of statistical methods to quantify and correct for ecological bias and measurement error, reproducible methods for causal inference, and sensitivity analysis of measured and unmeasured confounding bias as suggested above. These strengths and limitations are illustrated further in the context of our own study (see the Supplementary Materials).

Table 1. Mortality rate ratios (MRR), 95% confidence intervals (CI), and *P* values for all variables in the main analysis. Details of the statistical models are available in section S2. Q, quintile.

	MRR	95% CI	*P* value
$PM_{2.5}$	1.11	(1.06–1.17)	0.00
Population density (Q2)	0.91	(0.71–1.15)	0.42
Population density (Q3)	0.91	(0.71–1.16)	0.45
Population density (Q4)	0.74	(0.57–0.95)	0.02
Population density (Q5)	0.92	(0.69–1.23)	0.56
% In poverty	1.04	(0.96–1.12)	0.31
Log(median house value)	1.13	(0.99–1.29)	0.07
Log(median household income)	1.19	(1.04–1.35)	0.01
% Owner-occupied housing	1.12	(1.04–1.20)	0.00
% Less than high school education	1.20	(1.10–1.32)	0.00
% Black	1.49	(1.38–1.61)	0.00
% Hispanic	1.06	(0.97–1.16)	0.23
% ≥ 65 years of age	1.04	(0.93–1.17)	0.46
% 45–64 years of age	0.77	(0.67–0.90)	0.00
% 15–44 years of age	0.76	(0.68–0.85)	0.00
Days since stay-at-home order	1.18	(0.92–1.52)	0.20
Days since first case	2.40	(2.05–2.80)	0.00
Rate of hospital beds	1.00	(0.93–1.08)	0.95
% Obese	0.96	(0.90–1.03)	0.32
% Smokers	1.13	(1.00–1.28)	0.05
Average summer temperature (°F)	1.11	(0.95–1.30)	0.20
Average winter temperature (°F)	0.86	(0.69–1.07)	0.19
Average summer relative humidity (%)	0.93	(0.80–1.09)	0.38
Average winter relative humidity (%)	0.97	(0.87–1.07)	0.52

DISCUSSION

Ecological regression analyses are crucial to stimulate innovations in a rapidly evolving area of research. Ongoing research has already focused on overcoming some aspects of these limitations (*8*, *15*). For example, ecological regression analysis of air pollution and COVID-19, using data with finer geographic resolution, is being conducted for different countries and regions around the world. Cole *et al.* (*8*) published an ecological regression analysis using data in Dutch municipalities and found results consistent with our own investigation; the California Air Resources Board (CARB) is planning to conduct a similar study at the census tract level (*15*). Although an ecological regression analysis cannot provide insight into the mechanisms underlying the relationship between $PM_{2.5}$ exposure and COVID-19 mortality, studies are starting to shed light on the potential biological mechanisms that may explain the relationship between air pollution and viral infection outcomes (*16*). For example, it has been hypothesized that chronic exposure to $PM_{2.5}$ causes alveolar angiotensin-converting enzyme 2 (ACE-2) receptor overexpression and impairs host defenses (*17*). This could cause a more severe form

Table 2. Strengths and limitations of ecological regression analyses applied to research on air pollution and COVID-19 and opportunities for future research.

	Strengths	Limitations	Future research
Study design: ecological regression	Feasible, timely, and cost-effective	Cannot be used to make inference about individual-level associations, doing so leads to ecological fallacy	Augment county-level data with individual-level data to adjust for ecological bias (*12*)
	Data are representative of the entire U.S. population	Cannot adjust for individual-level risk factors such as age, gender, and race (*19*–*21*)	Conduct studies of individual-level health records using traditional regression and causal inference methods as in Wu *et al.* (*2*)
	Allows inference at the area level, which can be useful for policy-making (*11*)	Results are sensitive to the assumptions of the statistical model (*11*)	
	Computationally efficient and can be conducted daily to allow for the dynamic nature of the data and observe temporal trends; see fig. S3		
	Facilitates comparison of results across countries		
Outcome: COVID-19 deaths aggregated at the county level	Publicly available data updated almost daily	Potential for outcome misclassification (*22*), particularly differential misclassification over time and space, which could bias results	Access to nationwide registry data with the validated cause of death (*14*)
			Analyses using county excess deaths as the outcome (*23*)
Exposure: 2000–2016 average exposure to $PM_{2.5}$ at the county level	Use of well-validated atmospheric chemistry models and machine learning models (*9*, *24*)	Aggregation assumes that everyone in a county experiences the same exposures, leading to exposure misclassification, especially for the largest counties	Individual-level data on COVID-19 deaths with geocoded addresses to link to air pollution data at the place of residence
	$PM_{2.5}$ exposure estimated at fine grids, which can be aggregated to the county level to assess exposure even in unmonitored areas (*24*)	Can be used to assess historical exposures to air pollution but not real-time exposures	Additional statistical methods to account for the propagation of exposure error into the ecological regression model (*13*)
	As opposed to using monitor data, aggregation of modeled estimates ensures that county $PM_{2.5}$ exposure estimates represent the distribution across the entire area		
Measured confounders	More than 20 area-level variables capture age distribution, race distribution, socioeconomic status, population density, behavioral risk factors, epidemic stage, and stay-at-home orders (see tables S1 and S2)	County average features may not represent the features of COVID-19 patients, leading to inadequate adjustment	Causal inference approaches to adjust for measured confounding bias, producing results that are less sensitive to statistical modeling assumptions
	These overlap with the confounder sets used in much of the previous literature on air pollution and health (*25*, *26*)	Difficult to formalize the notion of "epidemic stage," which may be an important confounder	
		The threat of unmeasured confounding bias still present	Causal inference approaches to assess covariate balance (*2*)
		Sensitive to the form of the statistical model specified (i.e., assumptions of linearity and no effect modification)	Individual-level data on key measured confounders such as smoking and body mass index
Unmeasured confounders	Leverage existing approaches, such as the calculation of the E-value (*27*), to assess how strong the effect of an unmeasured confounder would need to be to explain away the associations detected (see section S3)	The most important threat to the validity of any observational study Even measures like the E-value cannot inform us about the likelihood that a strong unmeasured confounder exists; this must be evaluated on the basis of subject matter knowledge	Natural experiment designs and instrumental variables can be used to reduce the threat of unmeasured confounding but are less common

of COVID-19 in ACE-2–depleted lungs, increasing the likelihood of poor outcomes, including death (*18*).

The associations detected in ecological regression analyses provide strong justification for follow-up investigations as more and higher-quality COVID-19 data become available. Such studies would include validation of our findings with other data sources and study types, as well as investigations into mediating factors and effect modifiers, biological mechanisms, impacts of $PM_{2.5}$ exposure timing, and relationships between $PM_{2.5}$ and other COVID-19 outcomes such as hospitalization. Research on how modifiable factors may exacerbate COVID-19 symptoms and increase mortality risk is essential to guide policies and behaviors to minimize fatality related to the pandemic. Such research could also provide a strong scientific argument for revision of the U.S. Ambient Air Quality Standards for $PM_{2.5}$ and other environmental policies in the midst of a pandemic.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/6/45/eabd4049/DC1

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Science Advances

Air pollution and COVID-19 mortality in the United States: Strengths and limitations of an ecological regression analysis

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Long-term effects of $PM_{2.5}$ on neurological disorders in the American Medicare population: a longitudinal cohort study

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Summary

Background Accumulating evidence links fine particulate matter ($PM_{2.5}$) to premature mortality, cardiovascular disease, and respiratory disease. However, less is known about the influence of $PM_{2.5}$ on neurological disorders. We aimed to investigate the effect of long-term $PM_{2.5}$ exposure on development of Parkinson's disease or Alzheimer's disease and related dementias.

Methods We did a longitudinal cohort study in which we constructed a population-based nationwide open cohort including all fee-for-service Medicare beneficiaries (aged ≥65 years) in the contiguous United States (2000–16) with no exclusions. We assigned $PM_{2.5}$ postal code (ie, ZIP code) concentrations based on mean annual predictions from a high-resolution model. To accommodate our very large dataset, we applied Cox-equivalent Poisson models with parallel computing to estimate hazard ratios (HRs) for first hospital admission for Parkinson's disease or Alzheimer's disease and related dementias, adjusting for potential confounders in the health models.

Findings Between Jan 1, 2000, and Dec 31, 2016, of 63 038 019 individuals who were aged 65 years or older during the study period, we identified 1·0 million cases of Parkinson's disease and 3·4 million cases of Alzheimer's disease and related dementias based on primary and secondary diagnosis billing codes. For each 5 μg/m³ increase in annual $PM_{2.5}$ concentrations, the HR was 1·13 (95% CI 1·12–1·14) for first hospital admission for Parkinson's disease and 1·13 (1·12–1·14) for first hospital admission for Alzheimer's disease and related dementias. For both outcomes, there was strong evidence of linearity at $PM_{2.5}$ concentrations less than 16 μg/m³ (95th percentile of the $PM_{2.5}$ distribution), followed by a plateaued association with increasingly larger confidence bands.

Interpretation We provide evidence that exposure to annual mean $PM_{2.5}$ in the USA is significantly associated with an increased hazard of first hospital admission with Parkinson's disease and Alzheimer's disease and related dementias. For the ageing American population, improving air quality to reduce $PM_{2.5}$ concentrations to less than current national standards could yield substantial health benefits by reducing the burden of neurological disorders.

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Introduction

Globally, neurological disorders are the leading group-cause of disability and the second leading group-cause of death, posing an urgent and substantial worldwide public health challenge.[1] Parkinson's disease and Alzheimer's disease and related dementias are the most prevalent neurodegenerative diseases.[2] Worldwide, an estimated 6 million people have Parkinson's disease and 44 million people have Alzheimer's disease and related dementias.[1] The Global Burden of Diseases, Injuries, and Risk Factors Study 2016 analysis estimated that, since 1990, the prevalence of Parkinson's disease has increased by 145% and Alzheimer's disease and related dementias have increased by 117%. The prevalence of these conditions is expected to continue to increase due to lengthening life expectancy.[1] As no cure exists yet for these conditions, the identification of modifiable risk factors, such as environmental exposures, should be a top research priority.

Concern is mounting that air pollution increases the risk for neurological disorders. Emerging evidence has shown that particulate air pollution is associated with impaired cognitive function,[3,4] accelerated cognitive decline,[5,6] Parkinson's disease, Alzheimer's disease, and dementia.[7–9] Research suggests that air pollution might contribute to the potential onset of neurodegeneration via mechanisms such as oxidative stress, systemic inflammation, and neuroinflammation, among others.[10–12] There is also evidence that air pollution might exacerbate disease progression by accelerating these biological pathways or worsening intermediate processes.[13,14] Therefore, the first hospital admission with a relevant diagnosis code is occurring sooner than expected. Previous studies that used hospital admission data to assess the effect of air pollution exposure on progression of Parkinson's disease and Alzheimer's disease and related dementias included populations residing in the southeastern US region,[7,15] the

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Research in context

Evidence before this study

Air pollution is a known risk factor for poorer human health. Concern is mounting that air pollution increases the risk for neurological disorders, the leading group-cause of disability and the second leading group-cause of death according to the Global Burden of Diseases, Injuries, and Risk Factors Study 2016. We searched PubMed and Google Scholar for studies examining associations of air pollution exposure with neurological disorders published from database inception until Aug 25, 2020. We used the keywords: ("PM2.5" OR "fine particulate matter" OR "fine particles" OR "air pollution" OR "air pollutants") AND ("neurological" OR "neurodegeneration" OR "neurodegenerative" OR "cognitive" OR "Parkinson's disease" OR "Alzheimer's disease" OR "dementia"). Although toxicological evidence links long-term $PM_{2·5}$ exposure with adverse effects on the nervous system, the epidemiological evidence remains scarce. Emerging evidence has shown that particulate matter air pollution is associated with impaired cognitive function, accelerated cognitive decline, Parkinson's disease, Alzheimer's disease, and dementia. The studies using hospital admission data to look at the effect of particulate matter air pollution on these conditions generally included populations residing in well monitored urban areas, or in a single region of the USA, or in a province of Canada. To date, no study has been done nationwide in the USA. Previous studies also focused on older data; air pollution concentrations in the USA have been steadily decreasing, so it is essential to establish whether these associations persist even at lower concentrations.

Added value of this study

To our knowledge, this is the first nationwide cohort study of the association between $PM_{2·5}$ exposures and neurodegenerative disease in the USA. Our findings provide strong epidemiological evidence for the association between air pollution and neurological disorders. We showed that long-term $PM_{2·5}$ exposures were significantly associated with an increased risk of first hospital admission with primary or secondary diagnosis codes for Parkinson's disease and Alzheimer's disease and related dementias. In addition, we observed that risk of first hospital admission with a diagnosis code for these conditions, as a proxy for neurodegeneration, linearly increased with increasing $PM_{2·5}$ concentrations less than the current national standards (annual mean 12 $\mu g/m^3$), suggesting that no safe threshold exists for health-harming pollution concentrations. One highlight of this paper is that we are leveraging an unparalleled amount of data compared with any previous air pollution study to our knowledge, to provide robust epidemiological evidence with the highest possible scientific rigour. Another key feature is the use of innovative computational approaches to accommodate our very large datasets, which can be applicable to other epidemiological studies that face similar challenges in the era of big data.

Implications of all the available evidence

Our study adds to the small but emerging evidence base indicating that long-term air pollution exposures are linked to an increased risk of neurological health deterioration, even at $PM_{2·5}$ concentrations less than the current national standards. Our findings suggest that policies that result in further reductions in ambient $PM_{2·5}$ concentrations can yield substantial health benefits in the ageing American population, even for those already exposed to low $PM_{2·5}$ concentrations.

Ontario province of Canada,[8] and well monitored urban areas in the northeastern USA.[9] To the best of our knowledge, no study to date has been done in the whole US population. Previous studies also focused on older data; as air pollution concentrations have been steadily decreasing in the past few decades in the USA although increases have been seen in some regions, it is essential to establish whether these associations persist even at low concentrations. Hence, evidence remains scarce for the health effects of long-term exposure to low amounts of air pollution across the USA, including locations with sparse or no monitoring.

We aimed to investigate the effect of long-term exposure to fine particulate matter ($PM_{2·5}$) on hospital admissions with a Parkinson's disease or an Alzheimer's disease and related dementias diagnosis code. We leveraged a nationwide comprehensive dataset integrating highly accurate and well validated high-resolution $PM_{2·5}$ prediction models and health data for all fee-for-service Medicare beneficiaries across the contiguous United States (2000–16). To address the computational challenges, we applied a novel computationally scalable re-parameterised Cox-equivalent Poisson model.

Methods

Study design and participants

We did a longitudinal cohort study in which we constructed a cohort including all Medicare-fee-for-service beneficiaries who were aged 65 years or older in the USA from Jan 1, 2000, to Dec 31, 2016, using the Medicare part A data. We obtained the Medicare inpatient hospital claims from the Medicare Provider and Analysis Review files, which include one record per hospital admission. People are eligible to enter Medicare after they turn 65 years of age, and for each beneficiary, follow-up started on Jan 1, 2000, or Jan 1 of the year following entry into the cohort, until first admission with diagnosis codes for each outcome separately (ie, Parkinson's disease or Alzheimer's disease and related dementias), death, or the end of the study period, whichever came first. We extracted age, sex, race, postal code (ie, ZIP code) of residence, and Medicaid eligibility for each

code means and assigned the postal code-wide annual $PM_{2.5}$ concentration means to Medicare enrollees according to the postal code of residence and calendar year. In the USA, the mean population per postal code is around 7500. Each postal code can cover a small area in cities but can be larger in rural areas. The median land area of a postal code is around 92 km².

Statistical analysis

We collected neighbourhood-level socioeconomic status variables, available at county level or postal code tabulation areas level, which have both been associated with ambient air pollution and implicated in neurological health.[17,18] These variables were derived from the 2000–16 Behavioral Risk Factor Surveillance System, the 2000 and 2010 US Census, and the American Community Survey for each year from 2005 to 2016 (appendix pp 3–4). Region was classified as northeast, southeast, midwest, southwest, and west.

Given the very large dataset, we applied a Cox-equivalent reparameterised Poisson approach for each of the two outcomes, coupled with parallel computing, to address the computational challenges (eg, inadequate memory size and lengthy computational time) faced by the conventional Cox proportional hazards model. Specifically, we proposed and fit a stratified quasi-Poisson model to estimate associations between the rate of first hospital admissions with neurological-related diagnosis codes (Parkinson's disease or Alzheimer's disease and related dementias) and time-varying annual mean $PM_{2.5}$ concentrations. The dependent variable was the count of outcomes (first hospital admissions) in each follow-up year, calendar year, and postal code location within strata specified by individual characteristics, using the corresponding total person-time of Medicare-fee-for-service beneficiaries as the offset. By stratifying on individual characteristics—ie, sex, race, Medicaid eligibility, and age at study entry (5-year categories)—we allowed for flexible strata-specific baseline rates.

See Online for appendix

For the **Environmental Protection Agency's air quality data** see https://www.epa.gov/outdoor-air-quality-data

(ie, 12 μg/m³) over the study period (low-exposure analysis). Finally, to evaluate any potential deviations from linearity in the concentration–response curves, we included penalised splines for the $PM_{2·5}$ term in the models.

	Full cohort (n=63 038 019)	Low-exposure cohort (n=21 928 573)
Age at entry, years		
65–74	48 784 857 (77·4%)	17 010 757 (77·6%)
75–84	10 550 039 (16·7%)	3 673 343 (16·8%)
85–94	3 327 268 (5·3%)	1 134 507 (5·2%)
95–104	375 708 (0·6%)	109 934 (0·5%)
105–114	147 (<0·1%)	32 (<0·1%)
Mean (SD)	69·9 (7·2)	69·8 (7·1)
Sex		
Men	28 295 987 (44·9%)	10 084 588 (46·0%)
Women	34 742 032 (55·1%)	11 843 985 (54·0%)
Race		
White	53 229 370 (84·4%)	19 776 603 (90·2%)
Black	5 513 530 (8·7%)	663 313 (3·0%)
Other*	4 295 119 (6·8%)	1 488 657 (6·8%)
Medicaid eligibility		
Eligible	7 853 739 (12·5%)	2 405 354 (11·0%)
Ineligible	55 184 280 (87·5%)	19 523 219 (89·0%)
$PM_{2·5}$ concentration, μg/m³	9·7 (3·2)	7·2 (2·3)
Body-mass index, kg/m²	27·5 (1·1)	27·3 (1·0)
Ever smoked, %	47·1 (7·7)	48·1 (7·8)
Hispanic, %	9·2 (16·7)	9·2 (16·3)
Black, %	9·1 (17·3)	2·7 (7·5)
Median household income, US$1000	48·0 (21·7)	47·5 (18·9)
Median home value, $1000	159·0 (141·9)	153·9 (131·8)
Below poverty level, %	11·0 (10·9)	9·7 (10·2)
Not graduated from high school, %	28·7 (18·8)	24·2 (17·1)
Owner-occupied housing, %	71·1 (18·8)	75·2 (14·8)
Population density, people per mile²	1601·2 (5233·1)	595·1 (1595·8)

Data are n (%) or mean (SD). *Other included Asian, Hispanic, American Indian or Alaskan Native, and unknown.

Table 1: **Cohort characteristics**

	Parkinson's disease	Alzheimer's disease and related dementias
Main analyses		
Number of admissions	1 033 669	3 425 102
Total person-years	478 335 593	473 696 618
Median follow-up year	7	7
HR per 5 μg/m³ $PM_{2·5}$	1·13 (1·12–1·14)	1·13 (1·12–1·14)
Low-exposure analyses (<12 μg/m³)		
Number of admissions	301 227	939 035
Total person-years	156 287 478	155 139 930
Median follow-up year	6	6
HR per 5 μg/m³ $PM_{2·5}$	1·14 (1·12–1·16)	1·18 (1·15–1·21)

Data are n or HR (95% CI). HR=hazard ratio.

Table 2: **Cause-specific admissions for Parkinson's disease and Alzheimer's disease and related dementias, 2000–16**

To identify subpopulations who might be particularly susceptible, we assessed potential effect modification by sex (men *vs* women), race (white people *vs* Black people *vs* other [Asian, Hispanic, American Indian or Alaskan Native, and unknown]), age (≥80 years *vs* <80 years), Medicaid eligibility (dual *vs* non-dual eligibility) as a surrogate for individual-level socioeconomic status, and urbanicity (quartiles of population density), by including interaction terms between these potential modifiers and $PM_{2·5}$. Specifically, we calculated the effect of $PM_{2·5}$ in each category of the effect modifier and assessed significance of the interaction term. We chose the age of 80 years as a cutoff to distinguish the young and middle-old from the old-old.[21]

We did a series of sensitivity analyses to assess the robustness of our results to confounding, inclusion of prevalent cases, potential outcome misclassification, and exposure time window (appendix pp 5–8). Given that these neurodegenerative diseases are age-dependent, as additional sensitivity analysis we also considered stratification by age at entry using 1-year intervals. To remove potentially prevalent cases, we ran additional analyses excluding anyone who had a first admission for these outcomes in their first 2 years of follow-up and repeated our analyses. As information in Medicare is only available after beneficiaries turn 65 years old, it is possible that some study participants had a Parkinson's disease or Alzheimer's disease and related dementias hospital admission before enrolling to Medicare. This sensitivity analysis—excluding cases with an admission during their first 2 years of enrolment—increases the probability that we are capturing the first admission with a related code. To evaluate whether the associations we observed can be attributed to a different outcome also linked to air pollution, we excluded the subset of Parkinson's disease and Alzheimer's disease and related dementias cases with the most frequent category of primary discharge codes (ie, circulatory system disease [ICD-9: 390–459; ICD-10: I00–I99]) from analyses. The primary discharge code appeared in 392 588 (41·1%) cases of Parkinson's disease and 1 323 044 (45·3%) cases of Alzheimer's disease and related dementias. Additionally, we added a sensitivity analysis restricting cases only to those with primary diagnoses codes for Parkinson's disease or Alzheimer's disease and related dementias. Finally, we considered an alternative exposure window with 1-year lag period (ie, using the annual mean exposure during the year preceding the outcome). Considering that chemical composition of $PM_{2·5}$ mass (and thus relative toxicity) can vary markedly among different regions in the USA, we also did a subgroup analysis by region.

The computations of the analyses of this study were done on the Research Computing Environment, which is supported by the Institute for Quantitative Social Science at Harvard University. We used R software, version 3.3.2 for all analyses.

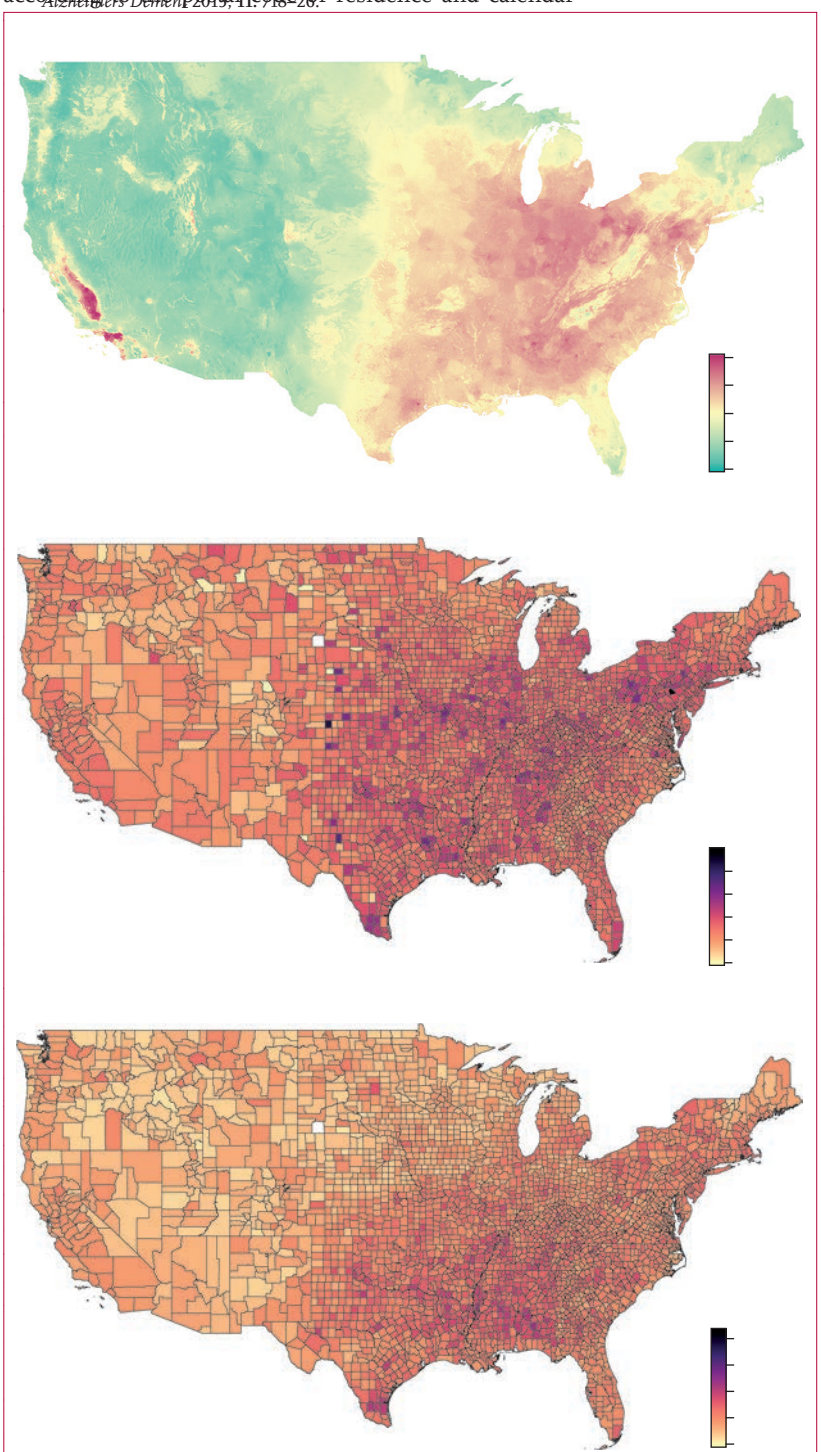


Figure 1: Nationwide geographical distribution of PM$_{2.5}$ and occurrence of Parkinson's disease and Alzheimer's disease and related dementias across the contiguous United States
(A) 17-year mean of annual PM$_{2.5}$ concentrations (μg/m^3). (B) Occurrence of first Parkinson's disease hospital admissions per 100 000 Medicare beneficiaries. (C) Occurrence of first Alzheimer's disease and related dementias hospital admissions per 100 000 Medicare beneficiaries (2000–16).

Figure 2 shows the concentration–response relationships for Parkinson's disease and Alzheimer's disease and related dementias. We observed a strong linear relationship for annual mean $PM_{2·5}$ concentrations less than 16 μg/m³, followed by a plateaued association with increasingly larger confidence bands for both outcomes. However, less than 5% of the distribution of the $PM_{2·5}$ concentrations were greater than 16 μg/m³.

Among the effect modifiers, we found $PM_{2·5}$ effect estimates that were significantly larger in magnitude among individuals in more urban areas versus those in less urban areas (as expressed in quartiles of population density). We also observed higher HRs among those who identified as white than those who identified as Black or Asian, Hispanic, American Indian or Alaskan Native, and unknown, and for women compared with men (figure 3).

For both Parkinson's disease and Alzheimer's disease and related dementias, all sensitivity analyses yielded similar results to the main analyses (appendix pp 5–8). When excluding potentially prevalent cases (ie, excluding those who had a first admission in the first 2 years of follow-up), both effect estimates were slightly elevated. The sensitivity analysis in which Alzheimer's disease and dementia were treated as separate outcomes also yielded significant and positive associations between $PM_{2·5}$ and the two separate outcomes of interest. However, the effect estimates for Alzheimer's disease (HR 1·17, 95% CI 1·16–1·18) were higher than those for dementia (HR 1·06, 1·05–1·07). Our results were robust to confounding adjustment—ie, the results were almost unchanged when we excluded different sets of covariates in alternative models compared with the main one. Additionally, both exclusion of all cases identified through secondary diagnostic codes and exclusion of those secondary diagnostic cases with circulatory system disease as the primary diagnosis code did not change the main results. Finally, our results were robust to the use of a different exposure window. The 1-year lagged exposure analysis (eg, using annual mean $PM_{2·5}$ in 2005 to link the outcome in 2006) yielded results nearly identical to the findings from our main analysis.

All region-specific results consistently suggested a link between $PM_{2·5}$ and first Parkinson's disease and Alzheimer's disease and related dementias hospital admissions, although effect estimates varied by geographical region. In summary, we observed the highest HR for first Parkinson's disease hospital admission among Medicare enrollees in the northeastern USA and for first Alzheimer's disease and related dementias hospital admissions in the midwestern USA.

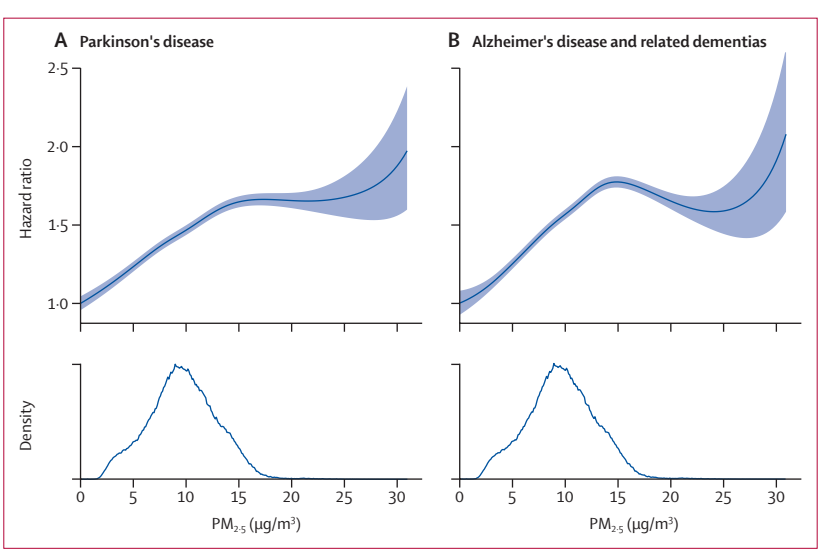


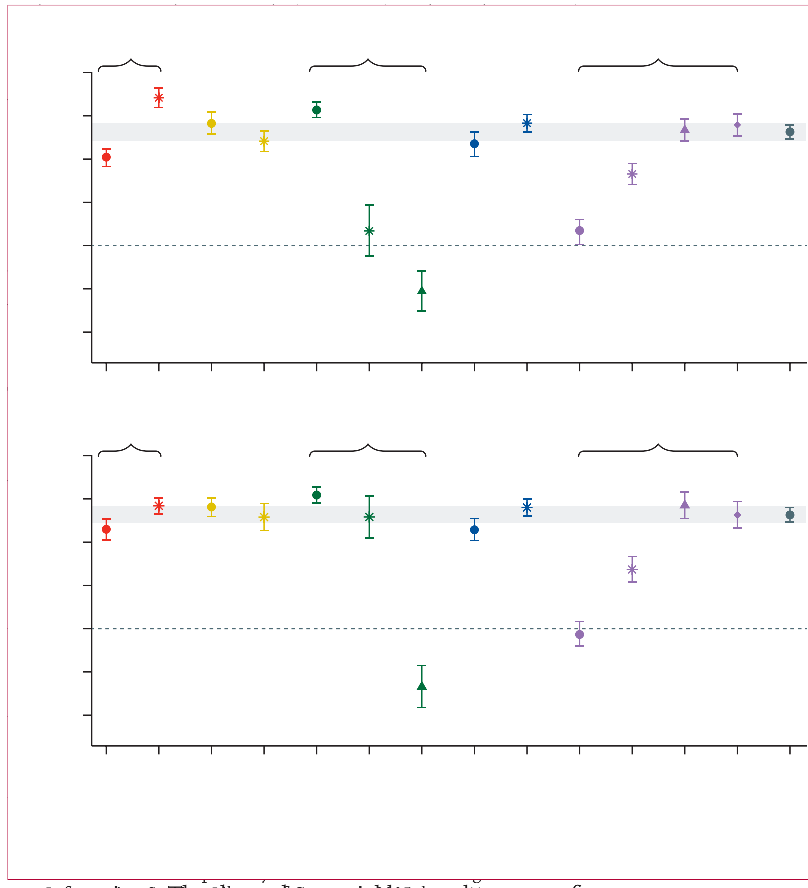
Figure 2: **Concentration–response curves of the association between long-term $PM_{2·5}$ exposure and neurological disorders**
Parkinson's disease (A) and Alzheimer's disease and related dementias (B).

Discussion

In this large, nationwide prospective cohort of all Medicare-fee-for-service beneficiaries, long-term exposure to $PM_{2·5}$, an indicator for the air pollution mixture at each postal code, was associated with an increased risk of first hospital admission with a Parkinson's disease or an Alzheimer's disease and related dementias diagnosis code, even at concentrations less than the current annual national standards (12 μg/m³). We also identified women, white people, and more urbanised populations as particularly susceptible subgroups. These findings suggest that improving air quality, with $PM_{2·5}$ concentrations even lower than current national standards, could yield public health benefits.

The shape of the concentration–response relationship between air pollution and neurodegeneration has rarely been assessed in the literature. Only one previous study simply assessed non-linearity using quartiles and found no evidence of deviation.[9] This result was in agreement with our results, had we used quartiles. Use of splines allowed for a more detailed characterisation of the shape across the $PM_{2·5}$ concentration range. Risk of first hospital admission with a Parkinson's disease or an Alzheimer's disease and related dementias diagnosis code, as a proxy for neurodegeneration progression, linearly increased with increasing $PM_{2·5}$ concentrations less than the current annual standards (12 μg/m³), suggesting no safe threshold for harmful pollution. Although we detected some deviations from linearity at concentrations greater than 16 μg/m³, less than 5% of the observations were higher than that. It is possible that any deviation at such high concentrations could indicate that the flexible penalised splines are sensitive to potential outlying observations with high leverage.

Our findings regarding associations between $PM_{2·5}$ and Alzheimer's disease and related dementias are consistent with previous research, both in terms of direction and magnitude; of these, one was done in Ontario's Canadian population,[8] and the other two were done in regional subpopulations of US Medicare enrollees.[7,9] Mixed results,



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Alzheimer's disease and Parkinson's disease pathology and concomitant neurobehavioural deficits. For all neurological outcomes, we observed significantly higher effects of $PM_{2·5}$ among individuals in urban areas versus rural areas. One possible reason might be the abundance of metal-bearing nanoparticles in the urban atmosphere, which have very small diameters and can access the brain directly.[28] The higher estimates among white people and women could be attributed to a longer life expectancy in these groups—ie, the chance of competing risks among non-white individuals or men is greater, including the probability of death before developing Parkinson's disease or Alzheimer's disease and related dementias.[29]

Our study data and methods have several advantages. First, our study population of all Medicare-fee-for-service beneficiaries in the USA gives us ample power to detect effects. This statistical power is particularly useful in environmental studies in which exposures are highly prevalent but effect estimate sizes are often small. Second, our study assessed the whole of the USA, which has greater generalisability than previous smaller cohort studies that were geographically restricted, although our study might not be generalisable to other countries. Furthermore, the aggregation of data into strata of shared individual characteristics not only allowed us to create a more efficient model but also allowed us to analyse a very large dataset with a far smaller computational burden. Given the increase in the use of very large datasets, this novel analytical approach might be useful in other research as well.

Our findings, however, should be interpreted in light of some potential limitations. First, reliance on an administrative cohort did not allow us to examine the relationship between $PM_{2·5}$ and disease onset. Parkinson's disease and Alzheimer's disease and related dementias are diseases that do not require hospital admission for diagnosis and treatment; usually, hospital admission occurs at more advanced stages of the disease for treating complications or for adjusting the therapeutic plan. Thus, the hospital admission records cannot represent disease incidence and we probably underestimate the case number when using first hospital admission as a proxy for neurodegeneration. In addition, a positive predictive value of 0·65 for Parkinson's disease[30] and about 0·75 for Alzheimer's disease and related dementias[31] has been reported when Medicare claims were used, indicating the under-diagnosed nature of neurological conditions using claims records. Furthermore, our results only represent the Medicare-fee-for-service population, which does not include all Medicare beneficiaries. Specifically, earlier in our study period (eg, in 2003), the Medicare-fee-for-service population covered up to 29 230 838 (84·9%) of 34 423 305 Medicare beneficiaries, while in 2016 it was 30 974 063 (65·8%) of 47 099 370 Medicare beneficiaries. It is possible that Medicare-fee-for-service beneficiaries switched to Medicare-HMO (Medicare managed care plan) and back, potentially resulting in some missed cases in our data, as we have no information on Medicare-HMO claims records. Our findings, thus, might not be generalisable to the entire Medicare population. Second, the use of predicted concentrations for exposure assessment might have resulted in some exposure measurement error. However, the prediction model we used is considered to have excellent predictive accuracy,[16] substantially reducing potential exposure measurement error. In our study, exposure measurement error is likely to be non-differential because the error in the predicted ambient $PM_{2·5}$ concentrations is probably independent of outcome status. Thus, any resulting bias would be towards the null.[32] Third, we cannot exclude the possibility of potential residual confounding bias. We did, however, adjust all our models for multiple neighbourhood-level socioeconomic status variables, and thus any potential residual bias is expected to be very small. Individual-level risk factors for neurological disorders, such as smoking, are not available in Medicare. However, we used postal code mean predicted $PM_{2·5}$ to assign exposures, which could only covary with individual-level factors through postal code-level socioeconomic status,[33] for which we carefully adjusted, thus effectively minimising this potential source of bias. Fourth, our ensemble model predicts total $PM_{2·5}$ mass concentrations, but not all particles have the same toxicity; some studies have shown that traffic-related pollution might be particularly toxic.[34] Future studies should aim to disentangle specific effects of regional versus local particles.

In conclusion, our study provides strong epidemiological evidence that long-term exposure to air pollution is significantly associated with a higher risk of neurological health deterioration, even at concentrations less than the current national standards. Our findings suggest that policies that result in further reductions in ambient $PM_{2·5}$ concentrations can yield substantial health benefits in the ageing US population, even for those already exposed to low $PM_{2·5}$ concentrations.

Contributors

AZ and M-AK designed the research and directed its implementation. MDY, DB, YAA, YWe, YWa, PL, QD, JS, and FD prepared datasets. LS and XW analysed data. LS, XW, and PL made the figures. LS, XW, M-AK, and AZ wrote the paper, and all authors contributed to the revision of the manuscript.

Declaration of interests

We declare no competing interests.

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code means and assigned the postal code-wide annual $PM_{2.5}$ concentration means to Medicare enrollees according to the postal code of residence and calendar year. In the USA, the mean population per postal code is around 7500. Each postal code can cover a small area in cities but can be larger in rural areas. The median land area of a postal code is around 92 km².

Statistical analysis

We collected neighbourhood-level socioeconomic status variables, available at county level or postal code tabulation areas level, which have both been associated with ambient air pollution and implicated in neurological health.[17,18] These variables were derived from the 2000–16 Behavioral Risk Factor Surveillance System, the 2000 and 2010 US Census, and the American Community Survey for each year from 2005 to 2016 (appendix pp 3–4). Region was classified as northeast, southeast, midwest, southwest, and west.

Given the very large dataset, we applied a Cox-equivalent reparameterised Poisson approach for each of the two outcomes, coupled with parallel computing, to address the computational challenges (eg, inadequate memory size and lengthy computational time) faced by the conventional Cox proportional hazards model. Specifically, we proposed and fit a stratified quasi-Poisson model to estimate associations between the rate of first hospital admission with neurological-related diagnosis codes (Parkinson's disease or Alzheimer's disease and related dementias) and time-varying annual mean $PM_{2.5}$ concentrations. The dependent variable was the count of outcomes (first hospital admissions) in each follow-up year, calendar year, and postal code location within strata specified by individual characteristics, using the corresponding total person-time of Medicare-for-service beneficiaries as the offset. By stratifying on individual characteristics—ie, sex, race, Medicaid eligibility, and age at study entry (5-year categories)—we allowed for flexible strata-specific baseline hazards. Mathematically, this stratified Poisson model is equivalent to a time-varying Cox proportional hazard model for clustered data (Andersen-Gill) (appendix pp 4–5).

See Online for appendix

For the Environmental Protection Agency's air quality data see https://www.epa.gov/outdoor-air-quality-data

Figure 3: Identification of vulnerable subpopulations

Figure 1: Nationwide spatial distribution of $PM_{2.5}$ and occurrence of first Parkinson's disease and Alzheimer's disease and related dementias across the contiguous United States
(A) 17-year mean of annual $PM_{2.5}$ concentrations (μg/m³). (B) Occurrence of first Parkinson's disease hospital admissions per 100 000 Medicare beneficiaries. (C) Occurrence of first Alzheimer's disease and related dementias