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Low-concentration air pollution and mortality in American older adults: A national cohort analysis (2001-2017)

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Lack of Epidemiologic Qualifications of Authors

Lead co-author Dr. Liuhua Shi is Emory University Research Assistant Professor of Environmental Health (https://sph.emory.edu/faculty/profile/index.php?FID=liuhua-shi-10928). She has a 2016 ScD in Environmental Health from Harvard TH Chan School of Public Health (HTHCSPH) and a 2009 BS and 2012 MS in Geography from Beijing Normal University in China. Her 2016 ScD Dissertation, "Estimating Health Effects of Temperature and pm2.5 Using Satellite-Retrieved High-Resolution Exposures," was apparently obtained under the direction of Senior Author and HTHCSPH Professor Joel D. Schwartz. She states "My research focuses on employing massive datasets, including satellite-retrieved high resolution exposures and health data of all Medicare beneficiaries, to investigate how climate change and air pollution influence seniors' health." However, she lists no formal training in Epidemiology, the discipline most relevant to the above manuscript.

Lead co-author Mr. Andrew Rosenberg has a 2021 MPH in Environmental Health from Emory University and is a "Master Student" member of Dr. Shi's "The Environment and Seniors' Health Research Group" (https://www.liuhuashi.com/people/). He lists no formal training in Epidemiology. The stated goal of this Group "is to leverage massive nationwide datasets, including satellite-retrieved high-resolution environmental exposure data and individual-level longitudinal health records, to better understand the influence of environmental risk factors on older adults' health and better frame environmental policy." The Group website does not cite any of the severe flaws of ecological epidemiology used in the Group publications (https://www.liuhuashi.com/publications/).

Based on an initial examination of backgrounds of the ten other authors, they have little or no formal training in epidemiology.

Lack of Public Health Basis for Study Because Current Air Pollution Levels in the US are Very Low

There is NO public health basis for this study because the US already has very low levels of air pollution. Indeed, several of these levels are not much higher than natural background levels. In recent years, the US has had far lower PM2.5 than most other countries. At present, PM2.5 levels in the US are about one-sixth the global average, one-seventh of the China average, and one half of the continental Europe average, as per the 2019 State of Global Air Map (https://www.stateofglobalair.org/data/#/air/map), which is shown on page 30 of this review. In 2019, the average annual population-weighted PM2.5 level was **7.7 µg/m3 in the US** and **48 µg/m3 in China**. The lowest PM2.5 level anywhere in the world was about 6 µg/m3, which must be considered as a realistic minimum level.

Specific Criticism of Manuscript

1. The Abstract makes unjustified scientific and policy claims about air pollution.

Abstract Claims (Line 45): "There was strong evidence of linearity in concentration-response relationships for PM2.5 and NO2 at levels below the current NAAQS, suggesting that no safe threshold exists for health-harmful pollution levels. For O3, the concentration-response relationship shows an increasingly positive association at levels above 30-ppb. In conclusion, long-term exposures to PM2.5, NO2, and O3 were significantly associated with an increased risk of all-cause mortality, particularly at levels below the current NAAQS standards, suggesting that implementing more stringent regulations in air quality may yield substantial health benefits."

There is extensive peer-reviewed evidence that does not support the validity of the EPA NAAQS and the authors have not cited any of this evidence. Instead, the authors suggest "implementing more stringent regulations in air quality" based on their selective and biased analysis of Medicare data that was never intended for this type of analysis. The manuscript completely ignores 30+ years of severe criticism of the ecologic epidemiology used to relate air pollution to mortality. The Senior Author Joel Schwartz is WELL AWARE of this criticism and he continues to deliberately ignore it. A sample of the criticism is shown on pages 6-29 of this review: the classic 1988 AJE "The Ecological Fallacy" (doi:10.1093/oxfordjournals.aje.a114892); the 2002 RTP critique of the PM2.5 NAAQS by Green and Lash (doi:10.1006/rtph.2002.1548); the 2017 and 2018 D-R Reanalysis articles by Enstrom, and the June 29, 2020 Enstrom Comment to EPA on the PM2.5 NAAQS (Enstrom 2020) (http://www.scientificintegrityinstitute.org/EPAPM25JEE062920.pdf).

Note that the 2002 RTP critique, co-authored by Dr. Timothy Lash, current Chair of the Emory University Department of Epidemiology, states: "Associations between airborne concentrations of fine particulate matter (PM2.5) and mortality rates have been investigated primarily by ecologic or semiecologic epidemiology studies. Many investigators and regulatory agencies have inferred that the weak, positive association often observed is causal, that it applies to all forms of airborne PM2.5, and that current ambient levels of PM2.5 require reduction. Before implementing stringent regulations of ambient PM2.5, analysts should pause to consider whether the accumulated evidence is sufficient, and sufficiently detailed, to support the PM2.5 National Ambient Air Quality Standard. . . . Taken together, the toxicologic evidence and lessons learned from analogous epidemiologic associations should encourage further investigation of the association between particulate matter and mortality rates before additional regulation is implemented, and certainly before the association is characterized as causal and applicable to all PM2.5." The PM2.5 death associations have been continuously challenged

since the PM2.5 NAAQS was established in 1997, as documented in Enstrom 2020 (pages 10-29 of this review).

2. The Introduction falsifies the research record regarding PM2.5 and mortality in the US

Introduction Claims (Line 62): "Increasing epidemiological evidence has documented the associations between long-term exposure to fine particulate matter (particles with a mass aerodynamic diameter below 2.5 µm (PM2.5) and reduced life expectancy among adults.(3-7)" References 3 to 7 do not objectively describe the existing US evidence on PM2.5 deaths. Reference 3 (Wu 2020, line 373), Reference 4 (Di 2017, line 376), Reference 7 (Wang 2020, line 384) cite other PM2.5 death findings by Senior Author Schwartz based on Medicare records. These various overlapping findings involve tiny relative risks that do not establish a causal connection between PM2.5 and mortality. The claims of PM2.5 deaths in the ACS CPS II cohort in Reference 5 (Krewski 2009, line 379) were shown to be seriously flawed by Enstrom 2017 and Enstrom 2018. Reference 6 (Ostro 2015, line 381) actually found NO relationship between PM2.5 and total mortality in the CTA cohort, as shown in Enstrom 2017. Enstrom 2020 presents strong evidence that there is NO significant relationship between PM2.5 and total mortality in the US. Furthermore, this current review challenges the validity of all claims of a causal relation between PM2.5 and total deaths based on the multiple ecological epidemiologic analyses of Medicare records by these authors.

3. The Materials *Study Population* section involves likely violations of NIH Human Subjects Research Regulations

Line 98: "Health data were obtained from the Centers for Medicare and Medicaid Services (CMS), including all [68.7 million] Medicare beneficiaries, aged 65 years or older, in the contiguous United States from 2001-2017. We extracted data including age and year of Medicare entry, sex, race, Medicaid eligibility (a proxy for SES), the date of death, and ZIP code of residence **for each beneficiary**. Medicaid eligibility and ZIP code were updated annually. We constructed an open, full cohort containing all Medicare beneficiaries who were alive on January 1 of the year following enrollment into Medicare, through each calendar year of follow-up, with all-cause mortality as the outcome of interest."

I contend that the authors of this manuscript have made unethical use of personal and medical data on 68.7 million Medicare beneficiaries. These beneficiaries include me, many of my extended family members, and many of my scientific colleagues. Consent was never given my me or my family members or my scientific colleagues to have our personal Medicare data used for ecologic epidemiology that I am explaining in this review is bad science. The age and year of Medicare entry, sex, race, Zip code of residence, and date of death is sufficient to identify many beneficiaries, even without their name or exact address. I can identify specific beneficiaries if the investigators produce the deidentified Medicare records for beneficiaries who died during 2001-2005 in a Zip Code that I specify. If the investigators refuse to produce the requested Medicare records, I will use their refusal as evidence that they do not support transparent and reproducible research.

I contend that this NIEHS-funded research violates NIH Human Subjects Research Regulations (https://grants.nih.gov/policy/humansubjects.htm). This research does not satisfy NIH Human Subjects

Exemption Categories (https://grants.nih.gov/sites/default/files/exemption_infographic_v8_508c_1-15-2020.pdf) and does not satisfy the NIH Requirements for Waiver of Informed Consent (https://policymanual.nih.gov/3014-301). Exemption Categories are shown on page 31 of this review. Thus, the authors must provide the evidence that substantiates their claim (Line 110) "This study was approved by the Institutional Review Board of Emory University and a waiver of informed consent was granted." Because of the seriousness of these violations, I am currently pursuing the matter with the appropriate officials at Emory University and the Centers for Medicare and Medicaid Services.

4. The Results section misrepresents full analysis of PM2.5 and deaths in Medicare cohort

Line 208: "Our findings indicate that long-term exposure to PM2.5, NO2, and O3 was significantly associated with an increased risk of all-cause mortality, particularly at levels below the current NAAQS standards for each pollutant (Fig. 2). Line 213: "Assessing each pollutant individually in the full cohort analysis, a 10-µg/m3 increase in PM2.5 . . . was associated with an increase in mortality rate (i.e., HR-1) ranging between 5-7% . . . . In contrast, the low exposure analysis yielded larger effect estimates, with corresponding increases in mortality rate ranging between 10-13% . . . ."

The focus in the Results and the Abstract is on the "low exposure" Medicare beneficiaries, where the HR for PM2.5 has a maximum value of 1.13. But for the full cohort, the HR for PM2.5 averages 1.06 for single-pollutant models and 1.02 for the three-pollutant models, as shown in Figure 2 (Line 253). These HRs are etiologically insignificant and the most likely reason that they are slightly positive is because of selective analysis, the ecological fallacy, and lack of proper control of confounders.

In addition, the authors have not mentioned the large geographic variation found in the first major analysis of Medicare data, the 2008 *EHP* article "Mortality in the Medicare Population and Chronic Exposure to Fine Particulate Air Pollution in Urban Centers (2000–2005)" (doi:10.1289/ehp.11449). Table 3 of the *EHP* article shows large unexplained geographic variation in PM2.5 mortality risk in the Eastern, Central, and Western portions of the US. There was NO relationship in the Western US (mainly CA) and CA is the state which has been subjected to the most restrictive PM2.5 regulations.

The geographic variation in HR (RR) from the *EHP* Table 3 is shown below.

	Eastern US	Central US	Western US	Total US
Age-adjusted HR:	1.155 (1.130-1.180)	1.178 (1.133-1.222)	1.003 (0.981-1.025)	1.091 (1.076-1.107)
Age+SES-adjusted HR:	1.105 (1.084-1.125)	1.089 (1.052-1.125)	0.997 (0.978-1.016)	1.056 (1.043-1.069)
Age+SES+COPD-adjusted HR:	1.068 (1.049-1.087)	1.132 (1.095-1.169)	0.989 (0.970-1.008)	1.044 (1.032-1.057)

The authors must acknowledge this large unexplained geographic variation in their current manuscript. Indeed, the authors must acknowledge that the US HR in the total Medicare cohort may be NULL if it could be fully and properly adjusted on the individual level to account for sex, race, cigarette smoking, education level, co-pollutants, and other relevant confounders. Enstrom 2020 documents that the HR is NULL for nine US cohorts, including the 2008 Medicare cohort, as shown on page 14 of this review.

5. Conclusion is not justified because of all criticisms in this review.

Line 346: "Using a large nationwide cohort and robust epidemiological analyses, we provide strong evidence that long-term exposure to PM2.5, NO2, and O3, at levels below the current national standards, is significantly and independently associated with increased mortality. Amending national standards in the future may pose substantial public health benefits."

This Conclusion is a complete distortion of their own analysis of the Medicare cohort, for the reasons described throughout this entire review. The authors provide NO evidence that "Amending national standards in the future may pose substantial public health benefits."

Manuscript Decision: Unequivocally, do not publish this manuscript .

Potential Alternative: A point-counterpoint on the air pollution epidemiology, where Enstrom makes the point criticizing air pollution epidemiology and Schwartz makes the counterpoint promoting air pollution epidemiology.