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1. The method the ISA uses to draw conclusions; by using experts to integrate toxicological studies of cell cultures and in vivo animal studies that provide evidence of pathophysiological changes caused by exposure, mechanisms of action that may or may not support the adverse events, such as deaths, heart attacks and strokes, associated with PM2.5 in epidemiology studies; chamber studies that identify biomarkers that do or do not support the mechanisms of action identified by the toxicology, and are or are not known to be risk factors for deaths, heart attacks and strokes, intervention studies, such as randomized trials of air filtration, that are or are not consistent with those events, and the epidemiology findings of the associations of PM2.5 is the latest scientific method for integrating such data. The ISA methods mirror those recommended by the National Academy of Sciences recent report to the Veterans Administration[1], the World Health Organization[2] in their assessments of the effects of air pollution, the methods used by the American Heart Association in their review of the health effects of PM2.5[3], by the Royal College of Physicians in their latest review[4], the Global Burden of Disease review[5], the recent review published by the European Heart Journal, etc.
   For example,
   In contrast, the methods of causal analysis are applicable to **individual studies**, not reviews, and, contrary to the assertions in the CASAC letter are not limited to causal manipulation studies, but include the application of causal analysis methods to observational data[6].

Nor are such studies absent. For example, Wang and coworkers used a doubly robust propensity score based causal analysis method to demonstrate a causal association between long-term exposure to $PM_{2.5}$ and mortality rates in a study of all of the Medicare participants in the Southeast U.S[7], and a difference in differences analysis in a study of all deaths in New Jersey[8]. A regression discontinuity analysis (another causal analysis method) of data from China also showed that long term particle exposure caused increased mortality rates[9]. The difference in differences study of Kioumourtzoglou looked entirely *within* cities, at whether year-to-year changes in annual average $PM_{2.5}$, controlling for long-term time trends, were associated with year-to-year changes in mortality rates.[10] While some years might be much more polluted than others, generally the $PM_{2.5}$ difference within the same city from one year to the next, after removing long-term time trends, was small. She also found a strong association of $PM_{2.5}$ variations with variations in mortality rates. Another recent study applied the differences in differences approach to a study of the effect of coal and oil burning power plants in California. They compared the rate of preterm births in a neighborhood around the plants before and after the plants shut down. They subtracted from those differences the differences between the years in control locations further from the EGU's to

control for time trends in any predictors. They reported shutting down the coal and oil plants resulted in reduced preterm births[11]. Other recent studies have used instrumental variable analyses and propensity score analyses to examine the causal effects of both long and short term exposure to $PM_{2.5}$ on Mortality[12-14].

However that application of causal modeling methods to individual studies is not the same as an integration of mechanism of action data and epidemiology data. While in principal, Bayesian methods of analysis can be applied, there is no agreed upon method for assigning probabilities of a causal relation to mortality to e.g. an in vivo study showing $PM_{2.5}$ increases atherosclerosis. That is why, worldwide, assessment of causality for toxins by scientific bodies uses the weight of evidence analysis that the ISA applied.

This is important, because such assessments have to integrate toxicology studies of mechanisms. For example, one study exposed mice to filtered air or air with particles from outdoors for six months. They then used MRI scans of the aortic artery to measure the percentage of the artery that was covered by atherosclerotic plaque. They report that the mean composite plaque area of the $PM_{2.5}$ exposed mice was 41.5% vs was vs 26.2% for the filtered air exposed mice (p<.001)[15]. This is a dramatic increase in the amount of atherosclerosis. It is also consistent with epidemiological studies reporting that $PM_{2.5}$ accelerates atherosclerosis in humans. Since atherosclerosis is a major risk factor for cardiovascular disease (CVD) and deaths, this supports the epidemiological findings that $PM_{2.5}$ is associated with those health outcomes.

In yet another study, mice exposed to 20.4 $\mu g/m^3$ of $PM_{2.5}$ of unfiltered air (compared to 1.6 $\mu g/m^3$ of $PM_{2.5}$ after filtering) for four months had higher measures of oxidized low-density lipoprotein (LDL) cholesterol and antibodies against oxidized LDL cholesterol, and thicker arterial walls[16]. A similar study (city air [22.1$\mu g/m^3$] vs filtered-air exposure) reported narrowing of the pulmonary arteries due to thickening of the walls, and increased lung inflammation in the particle-exposed mice[17]. Yet another study confirmed this result and also found thickening of coronary arteries.[18] These studies support the epidemiology.

The randomized intervention trial of Chuang in Taiwan randomized 200 participants to a particle filter vs. a sham (ineffective) filter attached to a window air conditioner for a year.[19] The concentrations of $PM_{2.5}$ in the study averaged 21.4 $\mu g/m^3$ with the sham filter vs. 12.8 $\mu g/m^3$ with the real filter. They reported the sham filter resulted in a 7.8 mmHg higher systolic blood pressure in residents of those homes compared to the people with real particle filters, and a doubling of a measure of DNA damage. Both changes were statistically significant. Elevated blood pressure is a major risk factor for heart attacks and death, and the average impact of antihypertensive drugs is to lower blood pressure by about 7 mmHg, similar to the increase caused by $PM_{2.5}$.

This is why scientific bodies such as the World Health Organization, in a 2016 report entitled "Ambient air pollution: A global assessment of exposure and burden of disease," stated that

"*[a]mbient (outdoor) air pollution alone kills around 3 million people each year, mainly from noncommunicable diseases.*"

The bizarre focus on temperature, based on a single study, is also inapt by CASAC. For example, the case-crossover study matches each person who died to themselves on another day, when they did not die. , The nearby day can be chosen to have the same temperature. If the case day and the control day have the same temperature value, than temperature cannot be explaining any association between particle concentrations and mortality. So confounding is impossible in this design.

the CDC says:

Changes observed in people exposed to $PM_{2.5}$ include: increased airway inflammation and sensitivity, decreased lung function, changes in heart rhythm and blood flow, increased blood pressure, increases in the tendency to form blood clots, and biological markers of inflammation. These health effects cause increases in symptoms, emergency department visits, hospital admissions, and deaths from heart and lung diseases.
(https://ephtracking.cdc.gov/showIndicatorPages.action?selectedContentAreaAbbreviation=11&selectedIndicatorId=75&selectedMeasureId=. Accessed June 2018)

Indeed, WHO's most recent summary on the health effects on ambient air pollution,

2. The use of epidemiology to estimate concentration-response relationships for health impact assessments is consistent with recommendations of the National Academy of Sciences, the EPA Advisory Committee on Clean Air Act Compliance Analysis, the World Health Organization, the International Agency for Research on Cancer, the Global Burden of Disease etc. For example, the Health Effects Subcommittee (HES) of the Advisory Council on Clean Air Compliance Analysis stated that it "*fully supports EPA's use of a no-threshold model to estimate the mortality reductions associated with reduced PM exposure.*"[20] And the Centers for Disease control used a similar method when the stated "*a 10% reduction in $PM_{2.5}$ could prevent:*

more than 400 deaths per year in a highly populated county, like Los Angeles County;"
(https://ephtracking.cdc.gov/showAirHIA.action. Accessed June 2018). Or the World Health Organization when they stated (available online at http://www.who.int/airpollution/ambient/health-impacts/en/),

Ambient (outdoor air pollution) is a major cause of death and disease globally. The health effects range from increased hospital admissions and emergency room visits, to increased risk of premature death.

An estimated 4.2 million premature deaths globally are linked to ambient air pollution, mainly from heart disease, stroke, chronic obstructive pulmonary disease, lung cancer, and acute respiratory infections in children.

Accessed June, 2018

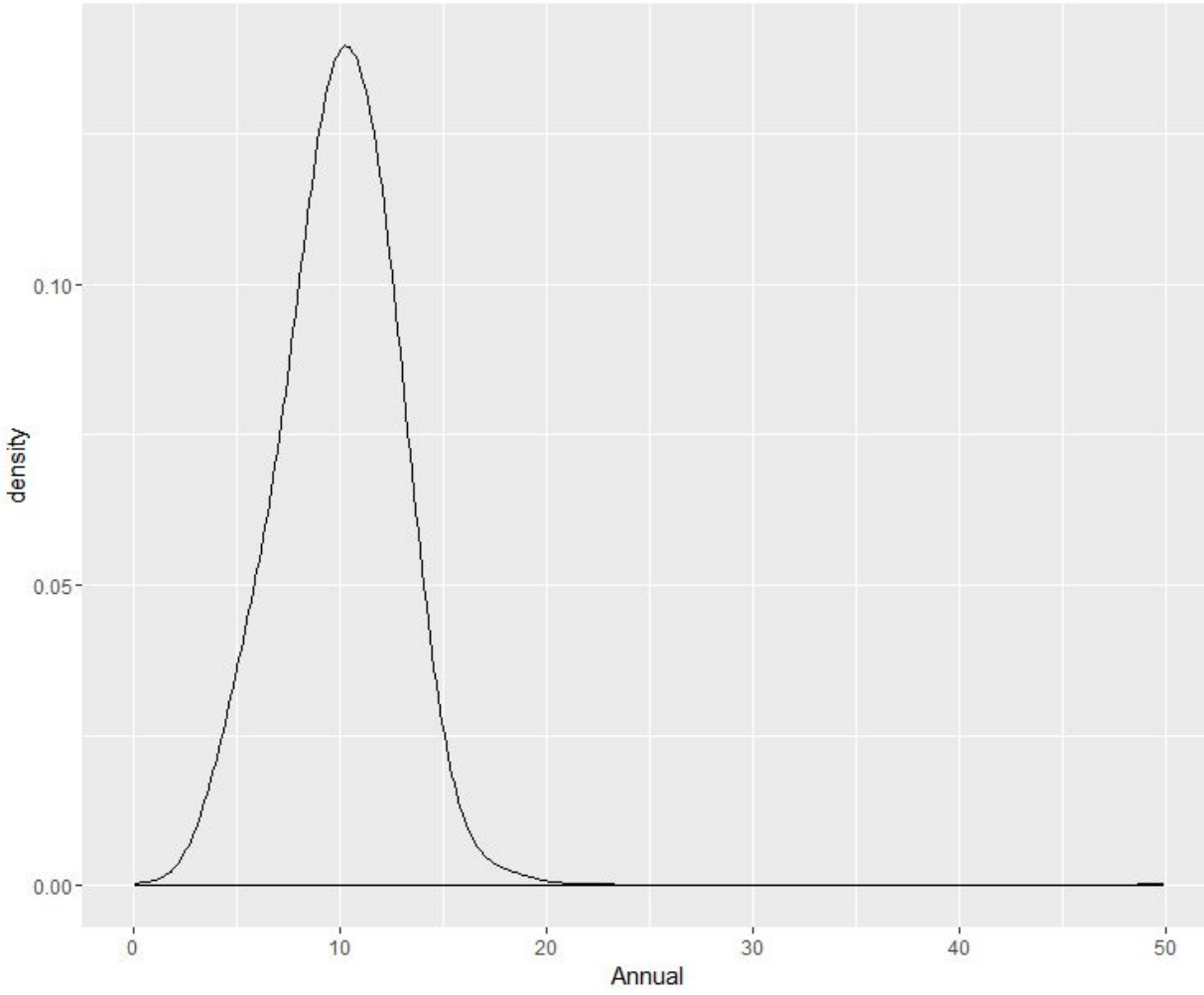
The calculation of the Global Burden of Disease are based on the same approach.

3. The claim that measurement error makes epidemiology studies useless because they can overestimate effects is refuted by empirical data. For example, in a recent meta-analysis of all of the studies of long term effects of PM2.5 on mortality, we examined the impact of the quality of the exposure assignment on the estimated slope of the PM-mortality relationship[21]. We found that the studies with poorer exposure estimates had lower slopes and those with better exposure estimates had steeper slopes, and the meta-regression provided a correction estimate to provide a concentration-response relationship corrected for measurement error. In addition, Hart and coworkers have applied the measurement error correction estimation methods developed by Professor Speigelman, a world expert in the subject[22]. When they used validation studies, which measured both personal $PM_{2.5}$ monitoring and the modeled exposure to examine the nature of the exposure error, and adjusted for that error in the Nurses Health Study Cohort, they found, contrary to the assertion in the CASAC draft letter, that the measurement error corrected slope was higher than the original one, not lower[22]. She further applied this approach in a different cohort, the Netherlands Cohort, to look at the association of $PM_{2.5}$ with lung cancer. Again, correcting for the measurement error increased the slope[23].

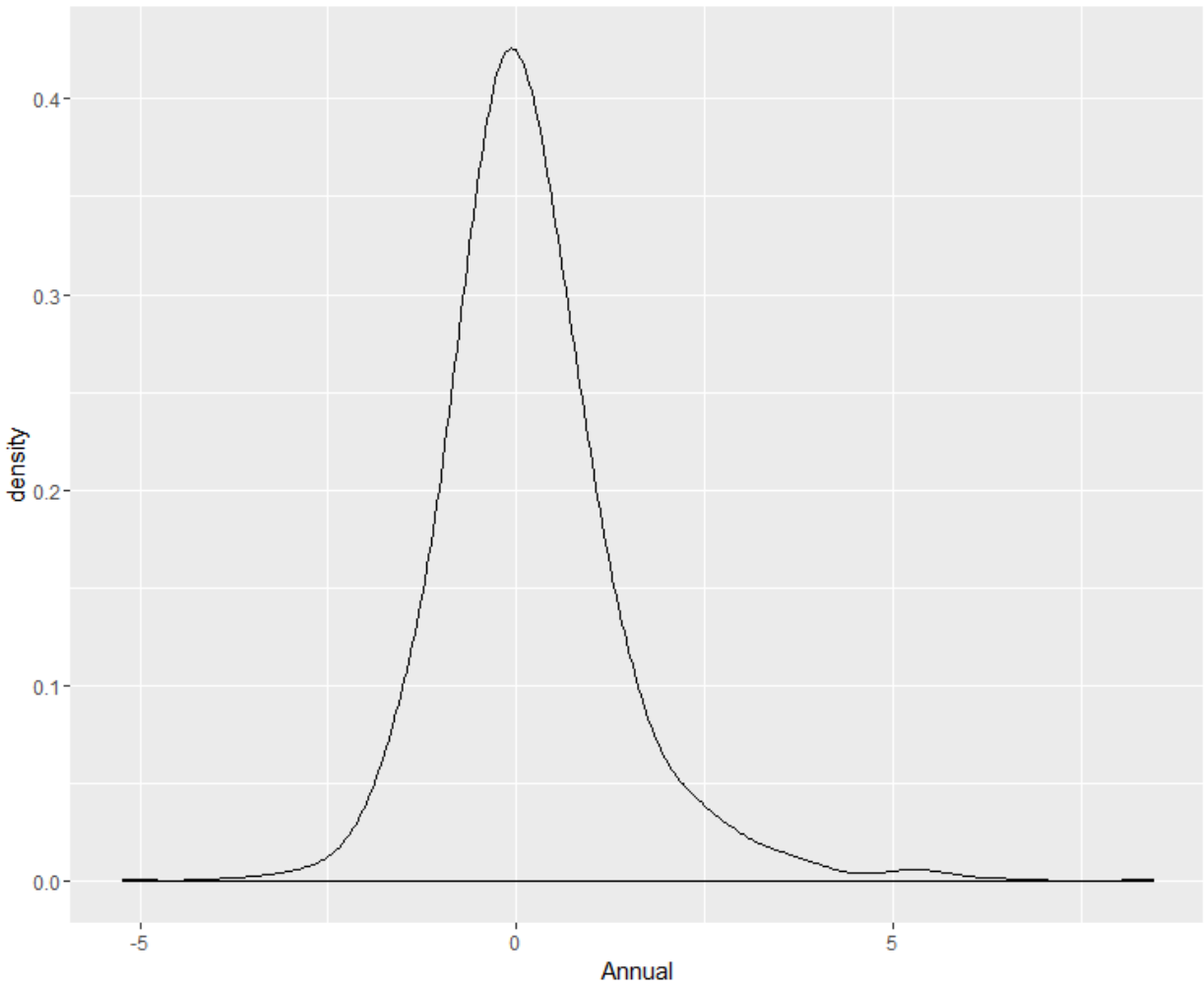
Hence, there is no empirical evidence supporting the assertion of CASAC that the estimates could be biased upward, and therefore should not be used for risk assessment. It is clear that the use of epidemiology to do risk assessment is valid, but is likely biased downward and the ISA should incorporate these new results (e.g. from the Vodonos study) that would allow the risk assessment to correct that downward bias.

Studies that have reported the possibility of upward bias have generally been based on assumptions that are not met by long term studies of $PM_{2.5}$ and mortality. For example, the paper of Krump shows that a concentration response relationship that can be expressed as a power law x^y can be biased upward under certain assumptions, which include a log-normal exposure and multiplicative exposure error. Here is some empirical information on the distribution of exposure, and of exposure error from the study of Di et al. [24] The Figure below shows a plot of the distribution of

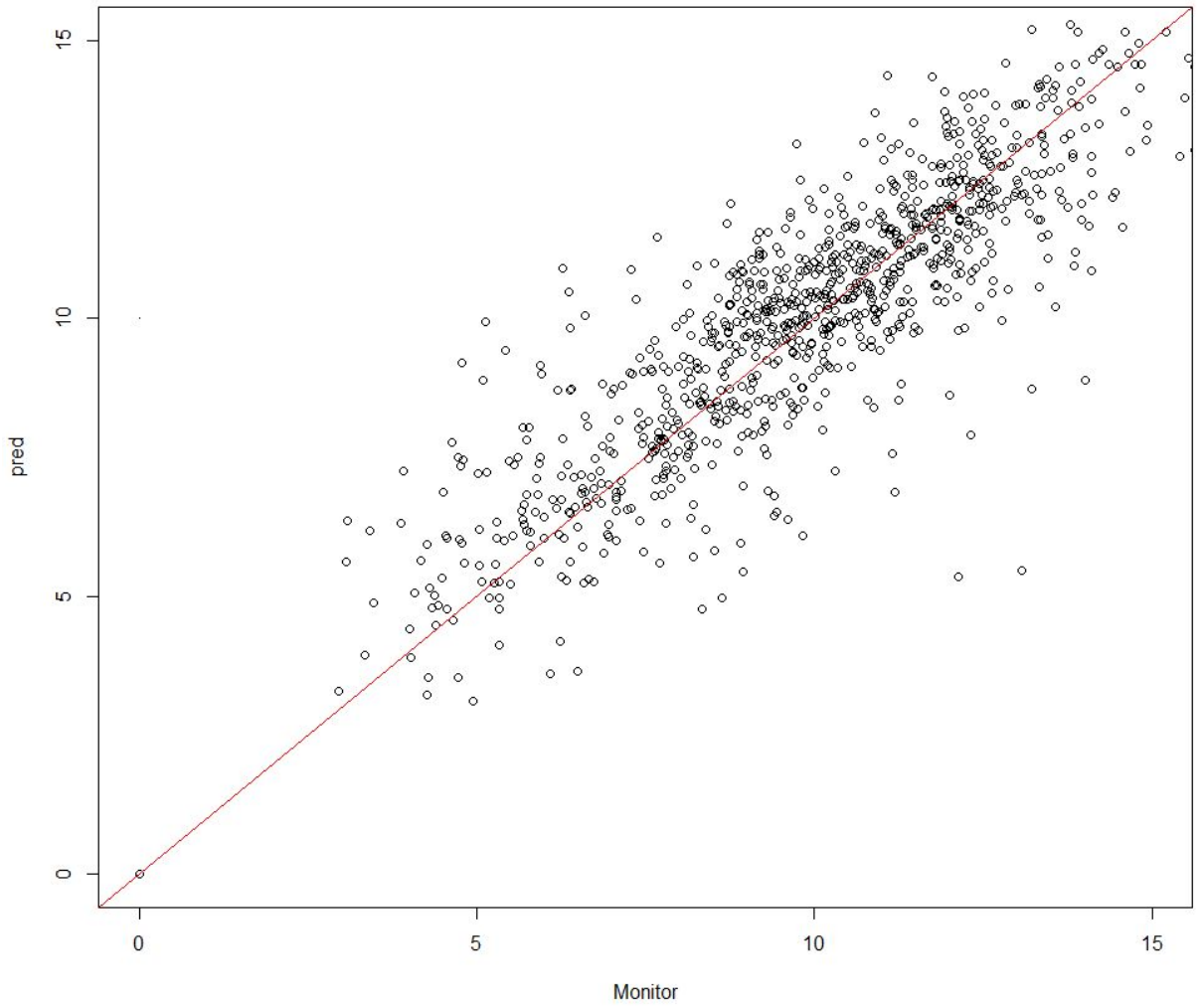
predicted annual $PM_{2.5}$ from the model for every zipcode in the US. It has the characteristic "bell shaped" figure of a normal distribution.



the figure below shows the distribution of the difference between actual measurements at $PM_{2.5}$ monitoring stations and the predicted $PM_{2.5}$ from our model. Once again, this appears normally distributed, and not log-normally distributed.



Finally, consider the assumption of multiplicative error, that in absolute terms, the range of exposure error is three times as large at a $PM_{2.5}$ concentration of 15 μg/m^3 as it is at 5 μg/m^3. We can easily test this by comparing the annual average predictions with the annual average measurements at the 1928 monitoring locations in the U.S. This is shown in the Figure below.



Hence, it is not surprising that the issues Dr. Cox raises are not seen in real data.

1. Medicine, I.o., *Improving the Presumptive Disability Decision-Making Process for Veterans.* 2008: Washington, D.C.
2. World Health Organization, *WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide*. 2006, Geneva, Switzerland: World Health Organization.
3. Brook, R.D., et al., *Particulate Matter Air Pollution and Cardiovascular Disease: An Update to the Scientific Statement From the American Heart Association.* Circulation, 2010. **121**: p. 2331–2378.

4. Royal College of Physicians, *Every breath we take: the lifelong impact of air pollution. Report of a working party.* 2016, Royal College of Physicians: London: .
5. Collaborators, G.B.D.R.F., et al., *Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.* Lancet, 2015.
6. Rubin, D.B., *Estimating causal effects from large data sets using propensity scores.* Ann Intern Med, 1997. **127**(8 Pt 2): p. 757-63.
7. Wang, Y., et al., *Doubly Robust Additive Hazards Models to Estimate Effects of a Continuous Exposure on Survival.* Epidemiology (Cambridge, Mass.), 2017. **28**: p. 771-779.
8. Wang, Y., et al., *Estimating Causal Effects of Long-Term PM2.5 Exposure on Mortality in New Jersey.* Environ Health Perspect, 2016. **124**(8): p. 1182-8.
9. Ebenstein, A., et al., *New evidence on the impact of sustained exposure to air pollution on life expectancy from China's Huai River Policy.* Proceedings of the National Academy of Sciences, 2017. **114**(39): p. 10384-10389.
10. Kioumourtzoglou, M.A., et al., *PM2.5and mortality in 207 US cities: Modification by temperature and city characteristics.* Epidemiology, 2015.
11. Casey, J.A., et al., *Coal and oil power plant retirements in California associated with reduced preterm birth among populations nearby.* American journal of epidemiology, 2018.
12. Schwartz, J., M.A. Bind, and P. Koutrakis, *Estimating Causal Effects of Local Air Pollution on Daily Deaths: Effect of Low Levels.* Environ Health Perspect, 2016.
13. Schwartz, J., K. Fong, and A. Zanobetti, *A National Multi-City Analysis of the Causal Effect of Local Pollution, NO2, and PM2.5 on Mortality.* Environmental Health Perpectives, 2018. **In press**.
14. Schwartz, J.D., et al., *Estimating the Effects of PM2.5 on Life Expectancy Using Causal Modeling Methods.* Environ Health Perspect, 2018. **126**(12): p. 127002.
15. Sun, Q., et al., *Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model.* JAMA : the journal of the American Medical Association, 2005. **294**(23): p. 3003-10.
16. Mauad, T., et al., *Chronic exposure to ambient levels of urban particles affects mouse lung development.* American journal of respiratory and critical care medicine, 2008. **178**(7): p. 721-8.
17. Matsumoto, G., et al., *The time course of vasoconstriction and endothelin receptor A expression in pulmonary arterioles of mice continuously exposed to ambient urban levels of air pollution.* Environmental research, 2010. **110**(3): p. 237-43.
18. Lemos, M., et al., *Chronic Exposure to Urban Air Pollution Induces Structural Alterations in Murine Pulmonary and Coronary Arteries.* Inhalation Toxicology, 2006. **18**(4): p. 247-253.
19. Chuang, H.-C., et al., *Long-term indoor air conditioner filtration and cardiovascular health: A randomized crossover intervention study. .* Environment international, 2017. **106**: p. 91-96.
20. Agency, U.S.E.P., *Summary of Expert Opinions on the Existence of a Threshold in the Concentration-Response Function for PM2.5-related Mortality: Technical Support Document.* , C.b.O.o.A.Q.P.a. Standards, Editor. 2010: Research Triangle Park, NC.

21. Vodonos, A., Y. Abu Awad, and J. Schwartz, *The concentration-response between long-term PM2.5 exposure and mortality; A meta-regression approach.* Environmental Research, 2018(in press).
22. Hart, J.E., et al., *The association of long-term exposure to PM2.5 on all-cause mortality in the Nurses' Health Study and the impact of measurement-error correction.* Environ Health, 2015. **14**: p. 38.
23. Hart, J.E., et al., *Long-term ambient residential traffic–related exposures and measurement error–adjusted risk of incident lung cancer in the Netherlands Cohort Study on Diet and Cancer.* Environ Health Perspect, 2015. **123**: p. 860–866.
24. Di, Q., et al., *Assessing PM2.5 Exposures with High Spatiotemporal Resolution across the Continental United States.* Environ Sci Technol, 2016. **50**(9): p. 4712-21.

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