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OCTOBER 23, 2019

TO: Tony Cox, PhD, CASAC Chair

CC: All CASAC members

FROM: Giffe Johnson, PhD

SUBJECT: Request for Information: Unmeasured Confounding

Dr. Cox,

Please review my response to your request for further information regarding the potential presence of unmeasured confounding in observational studies, how that confounding may impact the interpretation of observational studies, and various methods that can be used to detect and account for the presence of unmeasured confounding. Attached to this letter are 5 publications that examine the presence of unmeasured confounding in observational studies:

1. Janes H, Dominici F, Zeger SL. Trends in air pollution and mortality: an approach to the assessment of unmeasured confounding. Epidemiology. 2007 Jul;18(4):416-23

2. Greven S, Dominici F, Zeger S. An Approach to the Estimation of Chronic Air Pollution Effects Using Spatio-Temporal Information. J Am Stat Assoc. 2011;106(494):396-406.

3. Pun VC, Kazemiparkouhi F, Manjourides J, Suh HH. Long-Term PM2.5 Exposure and Respiratory, Cancer, and Cardiovascular Mortality in Older US Adults. Am J Epidemiol. 2017 Oct 15;186(8):961-969.

4. Eum K, Suh HH, Chit V, Manjourides J. Impact of long-term temporal trends in fine particulate matter (PM2.5) on associations of annual PM2.5 exposure and mortality: An analysis of over 20 million Medicare beneficiaries. Environmental Epidemiology. June 2018 2:2 pe009

5. Zhang X, Faries DE, Li H, Stamey JD, Imbens GW. Addressing unmeasured confounding in comparative observational research. Pharmacoepidemiol Drug Saf. 2018 Apr;27(4):373-382.

The first four publications specifically examine spatio-temporal methods

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of identifying unmeasured confounding in observational studies evaluating the potential association between low levels of PM2.5 exposure and adverse health effects. The fifth is a more general review of the manifestation of unmeasured confounding in observational studies and various approaches that could potentially detect and account for this confounding. These articles demonstrate the presence of unmeasured confounding in large data sets examining the relationship between low levels of PM2.5 exposure and adverse health effects. The impact of the presence of unmeasured confounding in studies that find magnitudes of association that are very small is severe; in the examples shown, positive measures of association frequently revert back to the null when adjusted for this confounding. In the field of low concentration PM2.5 observational studies and the related body of literature, associations are seldom reported above a relatively small percentage change over controls for most health outcomes. The need for understanding and accounting for unmeasured confounding becomes an imperative feature in this body of evidence for the evaluation of risk of bias and the integration of evidence.

I hope you find these articles helpful in conducting your independent review of the PM NAAQS. In the Pun et al. 2017 article, be sure to review the supplemental material provided as that is where the relevant data for this issue is presented. Feel free to contact me about this or other resources regarding NCASI's technical work on particulate matter.

Submitted respectfully,

Giffe Johnson, PhD
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Toxicology, Epidemiology, and Risk Assessment
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