LETTER

REPLY TO LUCOCK ET AL.:

Significance of interpretation and misinterpretation of a small mechanistic study

Jia Zhong[a,1], Mary Speck[b], Bruce Urch[b,c,d,e], Frances Silverman[b,c,d,e], Diane R. Gold[f,g], Petros Koutrakis[f], and Andrea A. Baccarelli[a]

The aim of our small mechanistic study (1) was to test the biologic plausibility that ambient particle pollution might have epigenetic effects on DNA methylation that could be modulated by methyl donor supplements. We acknowledge in this letter and in our paper that generalizability of our results is limited not only by study size, but also by the characteristics of healthy study participants. In contributing to the body of literature used for scientific assessment and consequent policy decision making, carefully controlled mechanistic studies like ours complement the large epidemiologic studies that, as Lucock et al. (2) suggest, show that reduction in ambient particle levels have led to improvement in health and reduction in morbidity and mortality (3–6). Studies like ours cannot diminish—nor be used to underemphasize—the urgent need to lower air pollution levels to—at a minimum—meet the air-quality standards set forth in the United States and other countries.

We agree that in the ethical conduct of clinical trials, consideration of potential toxicity of a study medication is paramount (2). As investigators, we reviewed the available published peer-reviewed literature for evidence of toxicity of the supplements, consulted nutrition experts, and concluded that our protocol—with 4 wk of supplementation with a dose and formulation that had previously been used for a large 5-y clinical trial (7)—presented no clinical risks that we could anticipate for healthy adults not pregnant and on no other medications. The protocol, including the dosage, was reviewed and approved by two Canadian institutional review boards and Health Canada's Clinical Trials Therapeutic Product Directorate, was registered with https://ClinicalTrials.gov, and was reviewed before implementation and monitored for safety at regular intervals during the trial by our study's Data Safety Monitoring Board. There were no reports of intolerance to the methyl donor supplements and there were no adverse events during the study.

We acknowledge that there is an important ongoing discussion in the scientific community about potential risks of vitamin supplementation above the recommended dietary intake of nutrients, particularly in potentially vulnerable populations (e.g., those who are pregnant, have cancer, or are on specific medications that may interact with the supplements). We agree that concerns about the potential toxicity and questions about health benefits of high-dose vitamin supplementation beyond recommended dietary intake should be considered, along with thorough up-to-date review of peer-reviewed scientific literature, and together should inform future study design as well as public policy nutritional recommendations, which are beyond the scope of our small mechanistic study (1).

We are also aware that there is ongoing concern that malnutrition, highly prevalent world-wide, may compound vulnerability to environmental insults, such as ambient pollution. In that context we think that mechanistic studies such as ours, with all of their limitations, contribute to generation of potentially testable hypotheses that adequate nutrition may buffer effects of environmental insults (8–11). That is not in contradiction with our understanding that in the hierarchy of hazard control, elimination or reduction of exposure is usually more effective than use of personal protection measures in protecting human health.

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[a]Mailman School of Public Health, Columbia University, New York, NY 10032; [b]Division of Occupational & Environmental Health, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada M5S 1AB; [c]Department of Medicine, University of Toronto, Toronto, ON, Canada M5S 1AB; [d]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada M5B 1W8; [e]Southern Ontario Centre for Atmospheric Aerosol Research, Toronto, ON, Canada M5S 3E5; [f]Department of Environmental Health, T. H. Chan School of Public Health, Harvard University, Boston, MA 02115; and [g]Channing Laboratory, Brigham and Women's Hosptial, Harvard Medical School, Boston, MA 02115

Author contributions: J.Z., M.S., B.U., F.S., D.R.G., P.K., and A.A.B. designed research; J.Z., M.S., B.U., P.K., and A.A.B. performed research; J.Z., M.S., and B.U. analyzed data; and J.Z., D.R.G., and A.A.B. wrote the paper.

The authors declare no conflict of interest.

[1]To whom correspondence should be addressed. Email: jiazhong@mail.harvard.edu.

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