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Anti-hypertensive drugs, occupational metal exposure, and arterial stiffness: structural confounders vs. precision covariates

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We would like to thank Dr. Varol for his interest in our manuscript, "The relationship between occupational metal exposure and arterial compliance." We are delighted that our research has reached a wide audience. Dr. Varol suggests that use of anti-hypertensive drugs is a confounder in the relationship between occupational exposure to metals (as reflected in toenail levels of Ni, Pb, Cd, Mn, and As) and arterial stiffness using augmentation index as a proxy. He also recommends that data on anti-hypertensive drug use should be presented and considered in arterial stiffness evaluation (regression modeling).

From a causal inference perspective, a structural confounder is defined as an extraneous variable that: 1) is associated with the exposure, 2) is associated with the outcome, 3) temporally precedes both the exposure and outcome, 4) is not a causal intermediate between the exposure and outcome, and 5) when controlled or conditioned upon, can block a backdoor path of association between the exposure and outcome (1, 2).

Anti-hypertensive drug use is undoubtedly associated with the outcome of arterial stiffness. However, no studies to our knowledge have implicated the use of anti-hypertensive drugs with biological accumulation of metals such as Ni, Pb, Cd, Mn, and As. Furthermore, we are not aware of any substantial research demonstrating that the mechanism of action of anti-hypertensive drugs operates through circulating levels of these metals. In addition, it is unlikely the use of anti-hypertensive drugs affects environmental exposure to metals through welding fumes. Given the lack of association between anti-hypertensive drug use and the exposure, it does not fit the criteria of being a confounder and should not be controlled in the analysis. However, given the drugs' association with the outcome of arterial stiffness, it may be considered a "precision variable", in which controlling would reduce the variance of the estimates. Omitting a precision variable will not bias the association, but rather increases the variance to some degree. However, statistically significant findings were still found for Ni.

The sample size of our study was limited given the nature of this particular occupational cohort of welders from a union in Quincy, MA. Of the 25 participants in the current analysis, there were only 4 who reported current use anti-hypertensive drugs (Lisinopril)

Invited Response to Letter to Editor (Response to: JOEM-15-5343. Aortic stiffness in patients with occupational metal exposure; role of antihypertensive drugs and statins)

during the follow-up, and 1 who reported past use. Even under the assumption that anti-hypertensive drug use is a structural confounder in the relationship (which it is most likely not), there was not enough variability to warrant its adjustment in the regression model given the sample size. In order for a confounder to significantly bias an estimate, it must have sufficient statistical variability. Additionally, the degree of bias would depend on its strength and direction of association with the exposure and outcome. Other stronger and more pertinent confounders need to take priority in the model to account for bias.

In summary, presenting the descriptive data on anti-hypertensive use is helpful when examining arterial stiffness. However, anti-hypertensive use does not meet the criteria of being a structural confounder based on the body of literature. As such, omission of the variable from the analysis will not bias the associations.

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