

Letters to the Editor

RE: "CONFOUNDING OF THE RELATION BETWEEN HOMOCYSTEINE AND PERIPHERAL ARTERIAL DISEASE BY LEAD, CADMIUM, AND RENAL FUNCTION"

This is a well-constructed and thoughtful analysis of the complex interrelations among exogenous exposure factors (lead, cadmium), endogenous metabolic markers (homocysteine), and peripheral arterial disease (PAD) (1). However, the characterization of the homocysteine/PAD association as confounded may be inappropriate. The authors claim that "impaired renal function is likely to be an intermediate variable, rather than a confounder, for the association of lead or cadmium with PAD" (1, p. 705). A similar statistical machination may exist with homocysteine.

The authors offer a thoughtful discussion of how exposure to lead and/or cadmium may perturb metabolic processes affecting homocysteine levels, or homocysteine itself may act in a chelating role, thereby affecting the observed lead/cadmium blood levels. If either or both of these mechanistic explanations are operating as the cause of the observed associations, then the attenuation of measures of association following the addition of covariates to statistical models may be more appropriately attributed to a process of multicollinearity. This process would be driven by covariates' being connected to each other as a collection of correlated measures of a common syndrome. If true, then it would be inappropriate to infer that the nature of homocysteine's association with PAD is confounded and thus spurious. Its role would require a different interpretational framework. This framework would be based on how various indirect

measures of exogenous exposure and various markers of perturbed metabolic pathways are mechanistically linked to the pathologies leading to clinically measured PAD.

ACKNOWLEDGMENTS

Conflict of interest: none declared.

REFERENCE

1. Guallar E, Silbergeld EK, Navas-Acien A, et al. Confounding of the relation between homocysteine and peripheral arterial disease by lead, cadmium, and renal function. *Am J Epidemiol* 2006;163:700–8.

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Editor's note: In accordance with Journal policy, Guallar et al. were asked whether they wanted to respond to this letter, but they chose not to do so.

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