Do not ignore environmental contaminants as risk factors for PAD, CLTI, and lower extremity amputations

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The timely American Heart Association (AHA) policy statement 'Reducing nontraumatic lower-extremity amputation by 20% by 2030: Time to get to our feet' proposes a multi-pronged approach to identify and prevent progression of peripheral artery disease (PAD)[1]. This statement, however, misses the opportunity to highlight the growing understanding of environmental risk factors in cardiovascular disease, including PAD.

There are 2 modifiable environmental risk factors that, if intervened upon, might lead to a reduction of PAD, and potentially reduce lower extremity vascular events: fine particulate air pollution ($PM_{2.5}$) and contaminant metals.

Particulate air pollutants consist of a complex mixture classified by its size in microns. $PM_{2.5}$, corresponding to particles 2.5 microns and smaller, is a complex mixture of carbon species, sulfates, nitrates, and variable proportions of metal contaminants such as cadmium, lead, arsenic, aluminum, nickel, vanadium, zinc, and iron. A recent review in the Journal of the American College of Cardiology highlights $PM_{2.5}$ as a leading risk factor for global morbidity and mortality, with cardiovascular events being the largest contributor. Numerous studies support the association between ambient air $PM_{2.5}$ and cardiovascular disease, including PAD. In a population-based community study in northeastern United States, every 10 $\mu g/m^3$ increase in average daily $PM_{2.5}$ levels between 2000-2008 was associated with a significant 4.4% (95% CI: 3.5-5.35%) increase in PAD hospitalizations; while a 10 $\mu g/m^3$ increase in daily $PM_{2.5}$ levels was associated with an increase of 0.26% (95% CI: 0.08-0.45%) of PAD hospitalization over the following 24h[2].

Contaminant metals have been identified by the AHA as cardiovascular risk factors in American Indians and Alaska Natives and as non-conventional risk factors for PAD. In NHANES 1999-2000 (N=2,125), the odds ratio for PAD comparing the highest to the lowest

quartile of blood cadmium levels was 2.42 (95% CI 1.13-5.15).[3] For blood lead, although the odds ratio comparing the highest to lowest quartile was not significant (2.88, 95% CI 0.87, 9.47), there was a positive trend across all quartiles (p for linear trend 0.01). In the Strong Heart study, a prospective cohort study in American Indian communities ongoing since 1989-91, the hazard ratio (95% CI) for incident PAD comparing the highest to the lowest tertile of urinary cadmium was 1.96 (1.32, 2.81), after adjustment for smoking status and pack-years. In a small study of patients with PAD (N=22), higher urine cadmium was associated with an increase in PAD severity, with the highest urine cadmium levels found in patients with critical limb threatening ischemia[4]. An environment-wide association study evaluating 417 risk factors with PAD in NHANES 1999-2004 identified blood cadmium as one of the four key predictors of PAD[5]. Despite this evidence, most cohort studies of PAD do not include information on contaminant metal levels or air pollution exposures.

Thus, we propose that to meet the 20% reduction of lower extremity amputation by 2030, recognition, measurement, and reduction of environmental pollutants must be part of the formula.

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