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Letter to the Editor

More on peripheral artery disease and air pollution. Author's reply

Dear Editor,

We appreciate that our article on ambient air pollution and peripheral artery disease (PAD) [1] has been read with interest and triggered the submission and publication [2,3] of two responses. We enclose herewith our answers and comments.

In their revisitation of the association PAD-pollution, Deng et al. [2] employed a Mendelian randomization analysis to establish that the association was not causal, as overtly recognized by us owing to the observational and retrospective design of the study. Mendelian randomization is a method of study of the causal effect of exposures using genetic variants associated with the exposure of interest. However, the evidence that genetic variants are associated with exposure to air pollution is quite elusive and uncertain, as recognized by the authors. Thus, we concur with Deng et al. [2] that the issue of causality between PAD and air pollution is still unsettled.

In their comment to our article Mayntz and Rosenbech [3] offered several different points of criticism. Whilst we agree that our study fails to have a marked clinical impact regarding the association between air pollution and PAD owing to the absence of a clear dose-response trend (at least for some pollutants), we disagree that lack of adjustment for smoking is a limitation of the findings, and thus we also disagree with their strong final statement that our study has the snag of shedding statistical shadows rather than addressing the true drivers of PAD incidence. We definitely agree on the key mechanistic role of diabetes and high blood pressure: these confounders were indeed taken into consideration as covariates by us but had no effect on the strength of association between PAD and air pollution. Regarding smoking, while we acknowledge the limitations of our dataset, we adjusted our models for an area-level socio-economic index. This index serves as a proxy for several individual lifestyle habits, such as smoking and diet, because it reflects the social deprivation of census blocks [4,5]. Moreover, from an epidemiological perspective, a confounder should be associated with both the exposure and the outcome: smoking is undoubtedly linked to PAD, but there is no evidence of an association with air pollutants.

We recognize the lack of statistical significance in the estimates obtained in our study. However, the positive estimates, with only a marginal overlap of the null value, suggest a potential positive association between exposure and outcome. While the p value is a valuable tool for reinforcing evidence and facilitating communication within the public health community, we acknowledge the importance of maintaining an unbiased perspective, as highlighted by numerous studies in the past decade [6,7]. Furthermore, our approach prioritizes the magnitude of the effect in relation to the large sample size of the study. In particular, although our estimates may not be considered clinically significant at an individual level, they hold substantial relevance from a public health perspective, which remains our primary focus. Given the limited evidence available in the epidemiological literature and the significant public health burden of PAD, we believe that our findings provide valuable insights for decision makers. Regarding the absence of the absolute risk difference in our cohort, we deliberately chose not to report this metric. Instead, we focused on presenting the association results using hazard ratios. The interpretation of both indicators is similar; however, to ensure consistency with the broader body of research in environmental epidemiology, we opted to report hazard ratios, i.e., the standard approach in this field.

In conclusion, we conceived and designed this study because we have always been puzzled to notice that the majority of the multiple studies that did evaluate so far the association of air pollution with cardiovascular diseases did focus on coronary artery and cerebrovascular disease but mostly ignored the association with PAD (and, incidentally, also venous thromboembolism) [4,5], notwithstanding that they are frequent and important cardiovascular diseases. We certainly welcome more and larger epidemiological studies, perhaps taking into account also other potential confounders such as alcohol intake, car traffic and exposure to greenness, not by us nor by Mayntz and Rosenbech [3]. Yet, it is definitely plausible that an atherothrombotic disease such as PAD, so closely linked to coronary artery disease, is associated with air pollution, considering the strong and undiscussed evidence of the association between air pollution and atherothrombotic cardiovascular disease.

Conflict of interest

The authors declare no conflict of interest.

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