Air pollution is a ubiquitous environmental exposure that threatens the health of people worldwide, in no small part due to the development and exacerbation of cardiovascular diseases. Daily fluctuations in pollution have been associated with acute changes in subclinical measures of disease (eg, systemic inflammation, endothelial dysfunction, and vasoconstriction), and increases in risk of overt cardiovascular events (eg, myocardial infarction, stroke, and mortality), as well. Moreover, living in a more polluted area over a long period of time has been shown to elevate risks of cardiovascular morbidity and mortality.1–3 With no evidence of a safe threshold, health impacts are detectable even in areas with concentrations below current regulatory standards of the United States and abroad. In fact, the World Health Organization has estimated that more than one million deaths per year are attributable to outdoor air pollution.4

The primary finding was that young adults who had lived in areas with 10 ppb higher concentrations of O3 throughout their childhood had ~10 μm larger intima-medial thicknesses after controlling for individual-level risk factors and other measured pollutants. This is an important result, because it is the first nonoccupational study to report an association between O3 and atherosclerosis in humans. Although the small epidemiological literature on the cardiovascular impacts of long-term O3 exposure has mixed results, recent toxicological studies support the plausibility of these human findings with evidence of increased aortic atherogenesis, oxidative stress, vascular inflammation, vasoconstriction, and thrombosis among animals exposed to O3.3

The findings of this article are especially novel in that they indicate that childhood exposure to O3 may play a role in potentiating early atherosclerotic processes, even among young adults. As some evidence suggests that higher intima-medial thickness is associated with greater cardiovascular risk,10,11 this suggests that early life exposure to O3 may increase the proportion of people at risk for cardiovascular events both because of normal disease progression and because of the exacerbation of disease by short-term exposures to air pollution, as well. In fact, one could speculate that a lifetime of exposure to higher O3 levels could potentially pose cardiovascular risks far greater than are conveyed by a few years of higher concentrations during adulthood. Such a scenario represents an extension of the Barker hypothesis, which states that the earliest experiences of life can have important impacts on cardiovascular risk.12 Although little is currently known about air pollution as an early origin of disease, in utero exposure to cigarette smoke has been linked with higher blood pressure in adolescence, and early exposures to air pollution have been linked with greater childhood asthma risks.13,14

In as much as the findings with O3 are interesting, another intriguing aspect of this work is what was not observed. Contrary to many, but not all, of the other studies of air pollution and atherosclerosis prevalence15 and progression,16,17 null and slightly inverse associations were identified for particulate matter and NO2. The reasons for these differences are not obvious; however, several factors may have contributed. One possible explanation is that PM2.5 and/or NO2 may play larger roles in exacerbating advanced athero-

Editorial

Childhood Exposures to Ozone
The Fast Track to Cardiovascular Disease?

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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1570
sclerotic lesions (>1.0–1.3 mm) rather than early atherosclerotic processes. Another, perhaps more likely, explanation relates to this study’s focus on regional differences in air pollution as opposed to smaller spatial scale concentration gradients. Evidence suggests that traffic pollution may be important for cardiovascular disease, and traffic pollution varies considerably over small distances. As such, it is likely that most of the critical variation in PM$_{2.5}$ and NO$_2$, especially, was not captured by the current design. In contrast, Breton and colleagues may have been better positioned to detect associations with O$_3$ for 2 reasons. First, the ratio of personal exposures to outdoor O$_3$ concentrations should be substantially higher in this study than in those of older adults, because youths spend more time outdoors, and O$_3$ is a highly reactive gas that is removed by indoor surfaces. Second, more complete monitoring data were available for O$_3$ than for particles and NO$_2$ in this study, likely resulting in less exposure misclassification for this pollutant.

This study’s focus on regional air pollution contrasts raises another issue of potential confounding by regional differences in personal characteristics. As in all air pollution cohort studies, it is critical to ask if there are confounding factors that are associated both with living in more polluted neighborhoods, and with cardiovascular disease risk, as well. Although this is somewhat difficult to assess without additional details on the cohort’s spatial distribution of exposures, it appears as though very large scale regional differences likely do not explain the primary findings because results were still found after restriction to Southern California participants. Nevertheless, residual confounding on smaller spatial gradients is still possible, especially within a large and diverse area such as Southern California. Important personal-level confounders, including body mass index, family history of disease, physical activity, childhood outdoor activity, and secondhand smoke exposures, were included in this analysis, but unmeasured factors such as diet or access to resources are often possible culprits for residual confounding in chronic air pollution studies. In this study, race/ethnicity and maternal education levels were included to capture socioeconomic effects, and some homogeneity is expected among students of the same university.

Future studies of early life exposures to air pollution are clearly warranted to better understand the potentially large clinical health implications of this work and identify the critical periods of exposure. Although high correlations ($\rho$: 0.8–0.98) prevented the authors from isolating any key exposure period (ie, age 0–5, 6–12, or 0–20+), this study did showcase college students as an interesting group for future research by demonstrating detectable associations with intima-medial thickness levels well within normal ranges. Because students typically move away from their childhood homes for 4 or more years and often move again after schooling, their longitudinal follow-up could provide interesting insight as to the relative importance of recent versus early exposures. This is exciting because the older populations that are studied most often are typically more residentially stable, and a well-conducted study from Canada recently identified differential risks of coronary heart disease mortality based on changing residential proximity to roadways within a 4-year follow-up period.

In summary, the work by Breton and colleagues in this issue of *Circulation* presents important new evidence of an association between long-term exposures to O$_3$ and atherosclerosis in young adults. These data suggest that, even at levels regularly experienced in the environment, childhood exposures can increase a young person’s atherosclerotic burden, thus increasing the risk of cardiovascular disease events in the future. As a novel finding, additional confirmatory research is needed, but, if corroborated, the implications could be large. Even now, this work provides further evidence to support recent efforts by the Environmental Protection Agency to lower the national ambient air quality standard to protect human health.

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**Disclosures**

None.

**References**


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