

## Red Flag for Arterial Damage? Early Evidence of a Potential Connection with Ozone

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Fossil fuel combustion emits chemical compounds that undergo sunlight-triggered reactions, producing ground-level ozone (O<sub>3</sub>).<sup>1,2</sup> Short-term exposure to this highly reactive gas can exacerbate respiratory disease,<sup>2,3</sup> and long-term exposure is implicated in multiple cardiovascular and respiratory causes of death.<sup>4,5,6</sup> Investigating the potential health impacts from a new angle, researchers recently reported in *Environmental Health Perspectives* that long-term O<sub>3</sub> exposure was associated with an increase in markers of arterial damage that are known predictors of cardiovascular disease (CVD).<sup>7</sup>

Because of its adverse effects, O<sub>3</sub> has been designated one of six criteria air pollutants for which the federal government has set National Ambient Air Quality Standards (NAAQS).<sup>2</sup> However, these standards center on short-term exposures.<sup>8</sup> Long-term exposures, meanwhile, have been associated with CVD mortality in some studies.<sup>4,5,8</sup>

“Long-term [exposure to] ozone is associated with cardiovascular mortality, but that association is not as well established as short-term ozone exposure and respiratory illnesses,” says Junfeng (Jim) Zhang, a professor of global and environmental health at Duke University, who was not involved in the new study. Even less well understood are the ways in which O<sub>3</sub> may trigger the first steps toward CVD.<sup>7,9</sup>

CVD develops silently over time, with coronary plaque formation, arterial wall thickening, and coronary artery calcification (CAC) serving as early subclinical precursors of disease.<sup>10</sup> In the current study, the researchers assessed changes in these markers over time in a large, representative sample of the U.S. population.

The researchers used data from the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA),<sup>10,11</sup> which enrolled 6,814 U.S. adults without CVD beginning in 2000 and followed them for about 10 years. Study information included participants’ sociodemographic, lifestyle, psychosocial, and CVD risk factors, with each participant undergoing assessments for

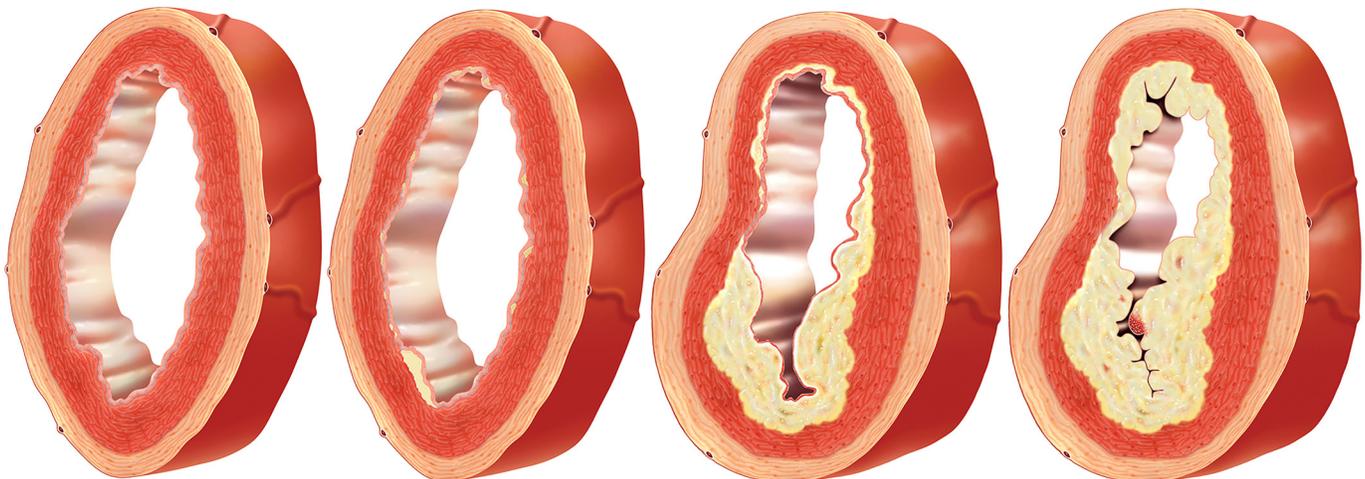
plaque formation, intima-media thickness of the common carotid artery (IMT<sub>CCA</sub>), and CAC.

The current investigation focused on more than 3,000 participants who had received two or more assessments. Those participants’ long-term O<sub>3</sub> exposure was estimated based on their residence, continuous daily O<sub>3</sub> measurements from the U.S. Environmental Protection Agency Air Quality System, and supplementary monitoring data collected through MESA, with adjustments for local factors such as traffic, land use, and geography. The researchers then assessed the longitudinal relationship between O<sub>3</sub> exposure and the progression of IMT<sub>CCA</sub> and CAC scores and numbers of plaques. They also conducted sensitivity analyses to assess whether findings held across different exposure windows (e.g., single-year averages, long-term averages) and with additional adjustments for family history of CVD and biomarkers of risk.

The researchers reported positive associations of O<sub>3</sub> exposure with increased IMT<sub>CCA</sub> and plaque formation but not with CAC. They concluded that chronic O<sub>3</sub> exposure may accelerate the progression of arterial injury.

“The significance of this study is the association that we find between ozone and arterial injury,” says lead author Meng Wang, an assistant professor of epidemiology and environmental health at the University at Buffalo. “So far, few studies [have looked] at chronic exposure and cardiovascular disease. Most studies focus on mortality, but not many really dig into the mechanisms underlying this effect.”

The associations were stronger when exposure was characterized as a long-term average versus average single-year exposures, which suggests that long-term measurements may provide more accurate information about risk. “Ozone association with cardiovascular disease is still relatively new, and this study adds to our knowledge related to ozone and its cardiovascular impact,” says Zhang. “It is quite novel because it is really looking to the subclinical pathological outcomes.”



The path to atherosclerosis begins with the accumulation of fat into plaques between the intima and media layers of the arterial wall, which increases what is known as intima-media thickness. Coronary artery calcification occurs when these plaques harden, stiffening the artery. Image: © iStockphoto/Jfalchetti.

The study was limited in ways that are typical for population-based studies with modeled environmental exposures. Specifically, potential limitations include exposure misclassification, selection bias arising from lack of follow-up data for some participants, and uncontrolled confounding. In addition, the 24-hour continuous measurement is not directly comparable to the 8-hour maximum defined in the O<sub>3</sub> NAAQS.

“The major implication, I think, is the policy implication,” says Zhang. Although the air quality in the United States is perceived as very good, more than 100 million Americans live in areas that do not meet the current O<sub>3</sub> NAAQS,<sup>12</sup> and some evidence suggests that levels below the standard are associated with increased risk of mortality.<sup>5,13</sup> The analysis<sup>11</sup> of another round of assessments completed in MESA participants in 2018 may provide the information for further insights into the association between long-term O<sub>3</sub> exposure and CVD. “This update could provide an opportunity to see if our results persist over time and may allow us to find new results,” says Wang.

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