See related article, pages 869–877.

W here survivors of stroke live may make a difference in their clinical outcomes, including long-term mortality. A large body of supportive evidence from epidemiological studies has demonstrated that a geographic difference in stroke mortality is nonartifactual, although both its presence and magnitude are likely scale dependent at different population levels.1 For instance, since at least the 1940s, there has been a consistent pattern of marked geographic variation in stroke mortality within the United States, with very high rates reported in the southeast Atlantic coastal plain and very low rates in the mountain census division.2 By the mid 1990s, despite minor geographic shifts, such regional differences in stroke mortality had persisted for more than half a century, yet the underlying causes of geographic disparities remained elusive.3 In 2001, the REasons for Geographic And Racial Differences in Stroke study was launched.4 This landmark study aimed to examine whether the spatial variations in stroke risk factors, sociodemographic features, lifestyle variables, and psychosocial characteristics explain geographic differences in stroke. Although more definitive answers are pending, recent reports by the REasons for Geographic And Racial Differences in Stroke investigators5–7 and others using the Cardiovascular Health Study cohort data8 did not provide persuasive evidence to support the concept that the geographic variations in stroke mortality are largely attributable to variations in conventional cerebrovascular risk factors.

As the search for the spatial determinants of the nonrandom distribution of stroke mortality continues, accumulating knowledge in the science of the effects of air pollution on health is opening a promising avenue for studying the geographic determinants of stroke mortality. During the last 2 decades, epidemiological studies conducted worldwide have shown a consistent, increased risk for cardiovascular events.9 These include heart disease and stroke deaths in relation to short- and long-term exposures to present-day concentrations of ambient air pollution, especially particulate matter (PM).

This new wave of environmental health sciences started in the early 1990s, with several reports showing excessive mortality unexpectedly associated with low PM concentrations. Recent meta-analyses confirmed that short-term exposure to ambient ozone increases cardiovascular mortality.10 Short-term elevations of PM and ozone can increase ischemic stroke mortality,11 hospitalizations, and emergency visits.12 Beyond these acute effects, large cohort studies have consistently shown that long-term exposure to air pollution is associated with increased cardiovascular mortality13,14; PM exposure also increases the incidence of coronary heart diseases and stroke.15 Parallelled with this mounting epidemiological literature are intriguing findings from human exposure experiments16,17 and in vivo animal models,18,19 all pointing to the possibility that exposure to ambient air pollutants can induce oxidative stress, provoke inflammatory responses, perturb endothelial function, damage the microvasculature, and cause progression of atherosclerosis.20

In this issue of Stroke, Maheswaran et al21 have added another dimension to the fast-moving field of air pollution–cardiovascular epidemiology by studying whether exposure to outdoor air pollution affects long-term mortality in stroke survivors. The investigators conducted a retrospective, cohort study of patients who had experienced but survived a first stroke in 1995 to 2005 and all of whom resided in South London communities. The authors reported positive associations between estimated exposure to ambient air pollution and increased poststroke mortality; each 10-µg/m³ increment of exposure was associated with an increase in mortality of 28% (95% CI, 11% to 48%) and 52% (95% CI, 6% to 118%), respectively, for nitrogen dioxide (NO₂) and PM with an aerodynamic diameter <10 μm (PM₁₀).

Compared with other air pollution–mortality cohort analyses that also drew their study populations from existing health databases, this study has several obvious strengths, despite its much smaller size. First, unlike those cohorts reconstructed from large, medical-claims databases, wherein information on most individual-level confounders is often unavailable,22–24 this study leveraged the South London Stroke Register, in which patient interviews were conducted, thus allowing for assessment of and adjustment for potential confounding by individual-level socioeconomic position and lifestyle/behavioral factors. Second, because the reported difference in survival was compared across the spatially referenced residential postal codes within a small area, this study was less subject to temporal confounding.25 Such temporal confounding in long-term studies of air pollution and mortality is more of a concern when one relates time-varying and overall declining air pollution exposure with a largely rising survival rate, possibly driven by other factors.
(eg, access to health care, treatment efficacy) that also change over time.

The reported point estimates for air pollution–associated increase in nonspecific mortality (28% and 52%, respectively, for each 10-μg/m³ difference in NO₂ and PM₁₀) were larger than those (~10% to 14% for NO₂ and ~10% to 16% for PM₁₀) published before. Among several legitimate reasons for this observed difference, 2 possibilities are worth attention. First, unlike other studies, in which all-cause mortalities were correlated with between-city differences in ambient air pollution or estimated exposures across large geographic regions, the present study was based in the single and small geographic area of South London, where the primary source of outdoor air pollution is road traffic, as depicted clearly in Figure 1 in the article of Maheswaran et al. Also noted by the authors, larger effect estimates have been found in within-city than in between-city exposure contrasts for long-term air pollution–mortality studies, suggesting a profile of higher toxicity in traffic-related pollutants within urban areas. One ecological study in the United Kingdom and 1 cohort analysis in Ontario, Canada, also linked traffic proximity with increased stroke mortality. More recently, progression of subclinical atherosclerosis associated with traffic-related pollutants was also found in humans.

Second, regardless of other possible differences in personal attributes and/or clinical characteristics, the stronger associations observed in this study suggest that patients with stroke may be biologically more vulnerable than is the general population to the adverse long-term effects of air pollution. It has been found that stroke patients are also more sensitive to the effects of short-term PM₁₀ exposure or extremely high ambient temperature, although the underlying mechanisms are unclear. One interesting hypothesis to test, perhaps, is that the neurovascular system represents a sensitive target of vascular or systemic toxicity imparted by exposure to traffic-related air pollution. In the first cohort study on air pollution–vascular or systemic disease incidence, Mill et al found very sizable differences in the effect estimates that compared stroke and coronary heart disease risks. For each 10-μg/m³ within-city difference in fine particles, the incidence rate increased by 108% for first stroke and by 56% for first coronary heart disease events (with a 193% increase in fatal stroke and a 117% increase in fatal coronary heart disease events).

Maheswaran et al also left several important questions unanswered. For instance, cause-specific mortality associated with air pollution was not investigated, although it is arguable that the major causes of death (cerebrovascular diseases, pneumonia, heart diseases) after hospital discharge in stroke patients could all be triggered or aggravated by exposure to air pollution. Whether the increased (overall or cause specific) mortality depends on stroke subtypes (hemorrhagic versus ischemic, ischemic subtypes) should also be studied. When geocoded individual location data are unavailable and one has to rely on spatial aggregates (eg, residential postal codes in this study) for exposure assignment, the degree of resulting estimation errors and its influence on statistical inference may not be obvious. The better we could answer these questions and address remaining uncertainties, the closer we are to call ambient air pollution an environmental determinant of clinical outcomes in vascular neurologic diseases.

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Jiu-Chiuan Chen

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