The number of Americans with Alzheimer’s disease (AD) dementia is expected to triple by 2050. No effective treatments exist, and prevention research has focused on behaviors and medical conditions, which have been difficult to modify at the population level. Cardiovascular disease epidemiology can inform the search for AD risk factors; exposure to fine particulate matter (PM) air pollution increases cardiovascular risk, pollutant regulations appear to reduce cardiovascular deaths, and vascular pathology influences dementia risk. In this issue of the Journal, Ailshire and Crimmins (Am J Epidemiol. 2014;180(4):359–366) report analyses of data from 14,000 older adults living across the United States, indicating an inverse association between exposure to PM and cognitive function, an outcome related to AD by virtue of the long period of cognitive decline that precedes clinical disease. Their work joins a growing body of data linking PM exposure to AD risk. If these data reflect causality, PM exposure would be 1 of few AD risk factors that are not only widespread, but that also can be modified at the population level using regulatory intervention. Active collaboration between air pollution and dementia epidemiologists will be critical for refining the available evidence and filling fundamental gaps, including the lack of studies on AD itself.

Abbreviations: AD, Alzheimer’s disease; PM, particulate matter; PM$_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 $\mu$m.

ALZHEIMER’S DISEASE: AN EPIDEMIOLOGIC NIGHTMARE

The impending surge in the number of people expected to have Alzheimer’s disease (AD) or other dementias in coming decades is so ominous and so frequently cited that it has taken on a similarly ominous drumbeat quality. By 2050, 13.8 million older adults in the United States are expected to have AD, the most common cause of dementia, which is nearly triple the number in 2010 (4.7 million adults) (1). Embedded in this dire forecast is the assumption that, over that period, we will make little progress in treating or preventing the condition. Unfortunately, the bar for progress is low: there are no treatments that alter the course of AD and, increasingly, focus is shifting to prevention (2).

Among the putative modifiable risk factors for AD supported by the most robust evidence are physical activity (3) (beneficial) and diabetes (4) (harmful). Therefore, intervening in them should, theoretically, reduce the burden of AD in the population. One model predicted that an intervention that merely delayed the onset of AD by 2 years could translate 50 years later into approximately 2 million fewer cases than originally forecasted (5). This intervention’s impact equates to an average reduction in AD risk of 25%, which might be possible in a world in which most people at risk are in need of the intervention (e.g., all are inactive), or if the intervention strikes a powerful punch on AD risk. A less omnipotent intervention (e.g., 10% reduction in risk factor prevalence) on a less prevalent risk factor (e.g., diabetes) will make a comparably small dent in the AD epidemic (6). Although intensive
programs that focus on individual behaviors can increase engagement in physical activity and reduce the risk of diabetes, these results have proven challenging to achieve on the population level. Over the past 2 decades, physical activity levels in the United States have not demonstrably increased, and diabetes has grown more prevalent (7–10). Of course, targeting medical and behavior-oriented risk factors should remain integral to AD prevention. This strategy happens to overlap with that for cardiovascular disease prevention. Yet, if cardiovascular epidemiology has anything to teach us, it is that we should look to toxicants in the environment for additional AD risk factors—risk factors that are highly prevalent and that are amenable to modification at the population level.

**CARDIOVASCULAR TIES**

Large-scale studies that implicated exposure to air pollution as a cause of cardiovascular disease (11) began to emerge in the 1990s, well after smoking, hypertension, and sloth had entered the realm of established risk factors. One bad actor appears to be suspended particulate matter (PM), a mixture of liquid and solid particles of varying chemical composition; fine particulate matter with aerodynamic diameter less than 2.5 μm (PM2.5) seems especially noxious. The risk of cardiovascular death increases both with higher short-term and long-term exposures (12, 13), with most studies reporting 10%–40% increases in risk per 10-μg/m3 increment in long-term exposure (13). This magnitude, in its absolute, places this exposure in the company of cardiovascular risk factors such as physical activity (14) and lowering blood pressure by 10 mm Hg using medication (15). The association is especially pronounced at the lower end of the exposure spectrum (16, 17), suggesting that a large swath of the population is exposed at meaningful levels. Possibly because these exposures are so widespread, intervening in PM exposure within the regulatory framework appears to result in measurable decreases in cardiovascular deaths (18, 19).

Accompanying the extensive data linking PM exposure to cardiovascular disease are data linking PM exposure to stroke (13, 20). PM exposure is also associated with cardiovascular and cerebrovascular risk factors that have been found to predict cognitive deficits, cognitive decline, dementia, and/or AD pathology (13, 21–23). Critically, for a given level of AD-related neuropathological burden, the presence of cerebrovascular injury—even subacute injury—increases the likelihood of cognitive deficits (24). Consider the convergence of the looming AD epidemic, the seeming success of increasingly stringent air pollution regulation in reducing the population burden of cardiovascular disease, and the ties extending from PM exposure to vascular disease to AD. Together, these hint at substantial potential to influence the population burden of AD by reducing PM exposure. However, we need evidence. Fortunately, it has been accruing.

**PATHS TO THE BRAIN AND AD**

Data from controlled animal experiments and postmortem studies suggest that not only does PM exposure wreak havoc in the brain’s vascular domain (25, 26), but it can infiltrate the brain via circulation or translocation via the olfactory nerve (26) and induce changes that are consistent with the development and progression of AD (27, 28), including elevated levels of amyloid-β42, the presence of hyperphosphorylated τ and neurofibrillary tangles, neuroinflammation, and neural degeneration (26, 29). Although these data are compelling, observational epidemiologic studies can provide important complementary information. Human postmortem studies have contributed detailed neuropathological data on long-term exposures, but these studies entail crude measures of exposure and cannot disentangle the temporal order of exposure and pathology. Controlled animal studies offer the exquisite ability to manipulate and measure PM exposures and to expediently examine postexposure behavior and neuropathology, but animal models do not necessarily translate uniformly to the human exposure and response experience (30–32). Randomized controlled studies can characterize the acute neurological effects of short-term exposures, but we cannot turn to this study design to investigate long-term exposure in relation to dementia.

In this issue of the *Journal of Alzheimer’s Disease*, Hurlin and colleagues (33) bridge epidemiologic findings to the conversation. They examined PM2.5 exposure in relation to cognition, an outcome of interest because a long period of decline in cognition often precedes dementia (34, 35), and worse performance on cognitive tests can reflect this decline. The investigators capitalized on data from the Health and Retirement Study, a study designed to represent the population of US adults aged 50 years or older. In analyses of nearly 14,000 Health and Retirement Study participants, higher estimated annual exposure to PM2.5 was associated with worse performance during that same year on a test of cognitive function, particularly the test component evaluating episodic memory, a cognitive function that declines in the earlier stages of AD. The authors observed these associations after adjusting for numerous potential sources of confounding, including several individual- and area-based measures of socioeconomic position, but, fittingly, not plausible cardiovascular intermediates. The pattern of cognitive differences across quartiles of exposure was not linear: those in the 2 highest quartiles of exposure performed significantly worse on the cognitive test than those in the lowest quartile, but participants in the third quartile performed especially poorly. The estimated PM2.5 exposures in these 2 quartiles—representing half of the population—exceeded the current US Environmental Protection Agency (Washington, DC) primary annual standard of 12 μg/m3, but in the case of the third quartile (12.2–13.8 μg/m3), not by much.

This study adds to the small group of studies that have examined PM exposures occurring in the past decade or so. With the Environmental Protection Agency’s lowering of the PM2.5 standard in 2013 and PM concentrations falling in many areas, characterizing the association of cognitive outcomes with exposure on the lower end of the exposure range—where the PM2.5 association with cardiovascular death is steeper than on the higher end of the exposure range—will bear directly on future air pollution policy deliberations.

**WHAT EPIDEMIOLOGY CAN STILL CONTRIBUTE**

Seven other epidemiologic studies have evaluated exposures to air pollutants in relation to cognition in middle-aged
and older adults (36–42). Ailshire and Crimmins’s study (33) joins 2 others that examined PM$_{2.5}$ averaged over the 1–2 years around cognitive testing. One observed worse cognition with higher exposure (37), whereas the second, a nationwide study that included younger adults (≥45 years of age), found no association between exposure and incident cognitive impairment as measured by a telephone-based screening test (42). Complementing this work on PM$_{2.5}$ are studies of other air pollutants. Those studies have found worse cognition with higher exposure to black carbon (a marker of traffic-generated PM) (39, 40), closer residential proximity to a busy road (a source of traffic-generated PM) (40, 41), and worse air pollution index (38). Exposure to particulate matter with aerodynamic diameter less than 10 μm was not associated with cognition in 2 studies (36, 41). An eighth study evaluated longitudinal change in cognitive function over 4 years, finding faster rates of decline associated with higher exposure to PM$_{2.5}$, as well as higher exposures to coarse fraction PM (with aerodynamic diameter of 2.5–10 μm) and, in contrast to previous studies, particulate matter with aerodynamic diameter less than 10 μm (43). In evaluations of gaseous pollutants, higher ozone exposure corresponded to worse cognitive performance in 1 study (36), but results were mixed in another study (37); exposure to nitrogen dioxide, in the single study that evaluated it (37), was not associated with cognition.

Even with this accumulated evidence, epidemiologic studies can still contribute important information, including insights on a wide range of air pollutants and interactions of exposure with the genome and epigenome in affecting cognitive risk. Epidemiologic studies can fill even more fundamental needs, which are most likely to be recognized and met by exploiting the expertise and collaboration of experts from both sides of the “hypothesis equation.” The disciplines of air pollution epidemiology and dementia epidemiology have evolved over decades, developing extensive scholarship in study design, measurement, and interpretation of analyses specific to their realms. However, their evolutions have occurred largely in parallel; without input from both disciplines, merely pasting cognitive measurements onto an existing study of air pollution or vice versa does not necessarily make for the best science. The examples below illustrate how combined disciplinary knowledge can refine this line of inquiry.

First, all but 1 (43) of the 9 aforementioned epidemiologic studies examined cognitive level as the outcome, rather than cognitive decline or risk of AD. Sociocultural background and other factors can influence performance on cognitive tests in ways unrelated to underlying ability or neuropathology (e.g., familiarity with test taking) (44–47). If these factors are associated with exposure, as is often the case (36, 37, 43), failure to account for them can bias estimates of association between exposure and cognition. By contrast, these factors often do not strongly influence change in cognition over time (35, 48). Though it is possible that many previous studies generated unbiased estimates, studies of cognitive change would provide reassurance. Moreover, whereas studies of air pollution exposure and cognitive decline are rare, comparable studies of dementia risk are completely absent.

Measurement decisions alone can stymie. A stumbling block that may trip investigations of AD is the identification of cases. There are no surveillance systems for AD, and AD remains poorly documented in medical records and death certificates; thus, study participants must regularly undergo diagnostic assessments. On the exposure side, epidemiologic studies thus far have appropriately targeted long-term exposure. The total effect of exposure on cognitive aging is probably a mixture of chronic effects from long-term exposure and acute effects (clinical and subclinical) from repeated short-term exposures. (Pragmatically speaking, even if short-term exposures influence cognition, large-scale studies are not well suited to discern this phenomenon.) Measured exposures should also represent exposures occurring prior to the cognitive outcomes. The closer the outcome is to being AD, the more critical this prospective relationship becomes, because AD’s pathogenesis may span decades (34). Exposures estimated from data collected the year prior to diagnosis may be excellent measures for that year and correlate reasonably well with exposures in previous years, but they may imperfectly measure long-term exposure and/or the relevant window of risk. The resulting threat of attenuated statistical power and effect estimation becomes consequential when sample sizes and case numbers are small, cognitive measurement itself is imperfect, and regulatory decisions lie in the balance (49). In addition, many air pollution exposure estimates are based on study participants’ residential locations, which can be an advantage in a study of individuals who are largely retired. But this approach may introduce reverse causation into study estimates if some participants live in nursing homes, where many residents live because they are cognitively impaired.

Combined knowledge of air pollution and cognitive aging informs a causal framework that, in turn, informs analyses. Socioeconomic variables warrant attention as sources of confounding, but apolipoprotein E genotype does not, unless, through some circuitous pathway, this genotype influences exposure. Cardiovascular and cerebrovascular variables could justifiably be intermediates and should be handled as such. Further, attrition because of death is exceedingly common in studies of older adults. A study of older adults can easily lose half of its participants over a decade of follow-up; moreover, death and illness prior to enrollment limit the types of individuals who are included in a study. Both exposure to air pollution and poor cognition may curtail participation and certainly predict death (16, 50). The resulting differential selection can bias estimates of the association between exposure to air pollution and cognitive aging outcomes. Understanding whether differential selection is present, the approaches for managing it, and the limitations of those approaches underlies key analytical decisions and the interpretation of results.

Evidence supporting air pollution as an AD risk factor could buttress public support for continuing regulatory action in the United States and worldwide, with the potential to alter the epidemic at the population level. To those still personally untouched by AD, the projected trajectories in AD prevalence and its attendant public health burden are abstractions. But, behind cancer, AD is the most feared chronic disease (51). After my colleagues and I reported an association of PM exposure with cognitive decline, the question I fielded most was, “Should I move?”
ACKNOWLEDGMENTS

Author affiliation: Rush Institute for Healthy Aging, Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois (Jennifer Weuve).

J.W. is supported by the National Institute of Environmental Health Sciences (grant R21ES020404) and the Alzheimer’s Association (grant NIRG-12-242395).

The author thanks Dr. Denis A. Evans for his thoughtful guidance on writing this manuscript.

Conflict of interest: none declared.

REFERENCES


