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Invited Perspective: Air Pollution and Dementia: Challenges and Opportunities

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Alzheimer's disease and related dementias (ADRD) are a major public health challenge in societies with aging populations. ADRD's contributions to increased morbidity in the elderly, a heavy burden on informal caregivers such as family members, high health care costs, loss of health-related quality of life, and a paucity of treatment options make preventive actions urgent (Paul et al. 2019; Wong 2020; Yu et al. 2020). Air pollution exposure is ubiquitous globally. Strong evidence links air pollutants to cardiovascular events and diabetes, both known to affect cognition in elders. However, data in support of the contributions of air pollution to aging-related cognitive decline are only just emerging (Paul et al. 2019). As exposures are chronic and affect large populations, even modest risks result in large numbers of cases (Kuenzli 2002).

In their new study, Shaffer et al. (2021) relied on the Adult Changes in Thought (ACT) cohort study based in Seattle to examine associations between exposures to fine particulate matter with an aerodynamic diameter of $\leq$2.5 μm ($PM_{2.5}$) and incident all-cause dementia. Although not the first to report on this subject, this study makes an important contribution to the field, not only due to its size and careful exposure and outcomes assessment, but especially because it suggests that the cognitive health of even a low-risk, low-exposure population may be affected.

For a longitudinal cognitive outcomes study, the ACT study is quite large (5,546 total enrollees as of 2018), and loss to follow-up was minor (14% had no informative follow-up after enrollment), likely because participants were enrolled in a large health maintenance organization. The possibility remains that some ADRD cases were missed because participants with cognitive problems did not return for testing (Kukull et al. 2002). This older population (on average 75 years of age at enrollment) had a very low baseline prevalence of comorbidities related to dementia (such as diabetes and cardiovascular disease), and the cohort thus likely avoided any substantial loss of subjects due to competing risks. A large number (1,267) of subjects were diagnosed with a form of dementia during its average 9.7 years of follow-up. The researchers administered sensitive outcome measures, including the Cognitive Abilities Screen Instrument (CASI) exam and neuropsychological tests. They subsequently employed a consensus conference for diagnosis that distinguished between AD and all-cause dementia. This consensus conference goes well beyond what can be achieved when large administrative health data sets are used to retrieve diagnoses for environmental health studies. Biennial cognitive assessment allowed the investigators to identify cases with high accuracy and in a timely manner.

The researchers estimated $PM_{2.5}$ exposures at participants' residential addresses using a sophisticated and fine-grained spatiotemporal model developed for 1978–2018, a 40-y period that also coincided with an impressively complete address history for most participants. They relied on multiple sources of $PM_{2.5}$ monitoring—long-term routine monitoring combined with shorter-term but spatially denser research monitoring campaigns—as well as extensive land use data. They generated individual-level time-varying 10-y average $PM_{2.5}$ exposures prior to diagnosis and were even able to extend this out to 20 y prior in sensitivity analyses.

Remaining Challenges and Opportunities

Assessment of ADRD for large population-based studies is a major challenge due to these disorders' pathological complexity, clinical symptom diversity, and varied latency; individuals with larger cognitive reserves may be able to mask their cognitive decline for much longer than others. In fact, clinical syndromes likely never reflect the type or progression of the underlying pathology perfectly, making an accurate diagnosis of AD and especially ADRD subtypes even more difficult (Corrada et al. 2012; Schneider et al. 2007). If air pollutants such as $PM_{2.5}$ do not contribute to all pathologies (i.e., vascular and inflammatory vs. amyloid-like), underestimation of risk in subgroups may occur. However, in a majority of older persons, neurodegenerative and cerebrovascular disease pathologies likely coexist (Kapasi et al. 2017). These issues are more relevant when secondary data sources (electronic medical records or death certificates) are employed (Buckley et al. 2019), underscoring the value of the ACT study's outcome ascertainment.

Valid and long-term assessment of temporally and spatially varying air pollution exposure is another major challenge in studies of diseases with a long latency period, such as ADRD. This challenge is due to the likelihood of changes in residential addresses and in personal activities (i.e., commuting and physical activity). Thus, the ACT's 10-y average $PM_{2.5}$ estimate was probably less affected by exposure misclassification than estimates in studies without address histories prior to enrollment. It also was helped by the fact that most participants likely were retired at enrollment, spending more time at home than at workplaces. These advantages may be somewhat counterbalanced by the likelihood of enrolling a mostly healthy survivor population and the inability to estimate effects of exposures earlier in life or to adopt a life-course perspective. Valid estimation of exposures during fetal life and childhood, hypothesized to be important for later-life diseases of the brain (de Boo and Harding 2006), however, may remain far from reach in any dementia study for a while. Finally, because this study overwhelmingly enrolled White participants of a narrow socioeconomic background, it avoided some confounding. Unfortunately, this study also precluded

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assessments of increased vulnerability from social or cultural factors and social inequities; such investigations are still urgently needed.

In conclusion, this well-conceived and well-conducted study makes an important contribution to the existing literature due to its exceptional exposure and outcome assessment, sophisticated analytical strategy, and uniquely stable, low-risk population. It adds considerable evidence that ambient air fine particles affect ADRD risk. Although future multidisciplinary collaborations and resources are needed to address some remaining challenges in ADRD–air pollution research, there is no need to delay efforts to reduce environmental air pollution to protect the aging brain from the consequences of exposure. Environmental air pollution reduction will require long-term policies, including standard-setting and collective action at international and local levels.

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