Growing Evidence Links Air Pollution Exposure to Risk of Alzheimer's Disease and Related Dementia

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Given the ageing of the global population, the number of individuals with Alzheimer's disease and related dementia (ADRD) is expected to double approximately every 20 years, to an estimated 115 million people by 2050 (Prince *et al.*, 2013). As there are no disease-modifying treatments for the most common types of dementia, identification of modifiable risk factors for ADRD is of paramount importance.

As a class, environmental risk factors for cognitive decline and ADRD have received relatively little attention, despite established neurotoxicity of many pollutants. The exception to this is the small but growing literature suggesting that higher air pollution exposure is associated with worse cognitive performance, faster cognitive decline, and increased risk of cognitive impairment or dementia (Power *et al.*, 2016). Almost all studies to date that examine the association between exposure to air pollution and cognition or dementia suggest a link between the two. However, this literature has met with scepticism, despite evidence that common sources of bias are unlikely to account for the observed associations (Power *et al.*, 2016). Additional evidence linking air pollution to ADRD-related markers of brain pathology is needed both to strengthen the evidence base and to provide insight into the mechanisms by which air pollution exposures may be related to ADRD. In this issue of *Brain*, Younan *et al.* present evidence linking particulate matter (PM) air pollution to late-life cognition and explore whether this association is mediated by changes in brain structure using data from a subset of participants of the Women's Health Initiative (WHI) study (Younan *et al.*, 2020).

Younan *et al.* leverage existing cognitive test score and MRI data from sub-studies of the parent WHI study. Air pollution exposures are highly related to time and space. Based on geocoded participant addresses, the authors estimated exposure to one air pollutant, $PM_{2.5}$, at each eligible participant's residential address in the 3 years prior to their first MRI as a proxy for long-term personal exposures. Use of residential address to assign individual-level exposures is a common choice in air pollution research, in part because regulatory efforts to curb air pollution exposures rely on regulating ambient levels. The authors were then able to link the new $PM_{2.5}$ air pollution estimates to existing cognitive and

MRI data in order to test hypotheses about the link between PM$_{2.5}$ exposures and late-life cognitive change. The time of the first MRI is considered 'baseline' for the purposes of this study.

First, the authors consider the association between PM$_{2.5}$ and both baseline performance and longitudinal change in episodic memory, as measured by the California Verbal Learning Test (CVLT). The CVLT measures both verbal learning and verbal memory. Verbal learning is assessed through performance on immediate recall of word lists and yields two measures (CVLT Trials 1–3 and CVLT List B). Verbal memory is assessed through delayed recall of word lists and yields two additional measures (CVLT List A Short-Delay Recall, CVLT List A Long-Delay Recall). The authors also considered a summary measure that was the average of the Trials 1–3, Short-Delay Recall, and Long-Delay Recall scores. Notably, the authors did not find an association between long-term PM$_{2.5}$ exposure and baseline performance on the CVLT using any measure. While PM$_{2.5}$ exposure was associated with greater decline in CVLT-based measures of verbal learning (CVLT Trials 1–3 and CVLT List B), there was no association between PM$_{2.5}$ and change in the CVLT-based measures of verbal memory (CVLT List A Short-Delay Recall and CVLT List A Long-Delay Recall) or the composite score.

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Next, the authors used a separate statistical mediation model to examine whether the associations observed between PM$_{2.5}$ and verbal learning (CVLT Trials 1–3 and CVLT List B), were mediated by simultaneous change in a neuroimaging-based marker of ADRD-related brain atrophy, the Alzheimer's Disease Pattern Similarity (AD-PS) score. Using this model, the authors report that individuals with greater exposure to PM$_{2.5}$ have greater change in the AD-PS score and that change in AD-PS score is itself associated with greater cognitive decline in the CVLT-based measures of verbal learning. This was interpreted as evidence that the association between PM$_{2.5}$ and change in verbal learning scores was mediated by increasing grey matter atrophy in selected brain regions. The path through the AD-PS score explained 11% (CVLT Trials 1–3) or 23% (CVLT List B) of the adverse association observed between higher PM$_{2.5}$ and decline on these measures of verbal learning. While the findings were robust to most sensitivity analyses, the authors did not find evidence of mediation using change in total grey matter, rather than change in the AD-PS. These findings suggest that the observed associations between PM$_{2.5}$ exposures and cognitive decline in verbal memory are partially, but not primarily attributable to exposure-related atrophy in specific regions of the brain.

This study must be interpreted within the context of its limitations. While the focus on episodic memory is justified, this study cannot provide insight into whether PM$_{2.5}$ may affect other areas of cognition or whether any effects of PM$_{2.5}$ on other domains in cognition are mediated by similar changes in the brain. The participants included in the sample were healthier and generally of higher socioeconomic status than the overall WHI sub-study population with available cognitive or MRI data. Similarly, those who returned for a second MRI were healthier and of higher socioeconomic status than those who did not. In addition, the participants were all female, and the vast majority were white and well-educated. Whether and how these factors affect the validity and generalizability of the findings is unclear. Another potential

limitation is that the authors use PM$_{2.5}$ exposures over the 3 years prior to the first MRI as their estimate of exposure; this may not represent the relevant window of exposure. Finally, other air pollutants may also exert independent effects on ADRD and related outcomes.

Overall, the Younan *et al.* study is consistent with the broader literature linking PM$_{2.5}$ air pollution exposures to worse late-life cognitive outcomes. However, the current body of literature considering neuroimaging outcomes is both sparse and heterogeneous. These differences may be related to differences in study design. While the evidence suggesting mediation by progression of brain atrophy in selected areas of the brain is novel, it relies on demonstrating an association between PM$_{2.5}$ exposures and atrophy of selected brain areas. A prior study using a summary measure for volumes of structures known to atrophy in Alzheimer's disease failed to show associations between PM$_{2.5}$ exposure and this summary measure (Power *et al.*, 2018). To the contrary, the current study and a second study using the same WHI MRI data demonstrate associations between PM$_{2.5}$ exposures and grey matter structures based on methods using a voxel-wide analysis (Casanova *et al.*, 2016; Younan *et al.* 2020). In addition, most of the prior studies assessing the link between air pollution and neuroimaging markers of brain pathology considered data from a single MRI, whereas Younan *et al.* considered change across two MRI scans. Further work is needed to replicate the mediation results observed here and to examine whether these study design differences account for the heterogeneous findings.

Within the context of the existing literature, the Younan *et al.* paper in this issue of *Brain* provides additional support for the hypothesis that higher exposure to PM$_{2.5}$ is related to increased risk of ADRD and related outcomes, and suggests that this is mediated by observable changes to the grey matter. However, the implications of this investigation and the growing body of similar work on air pollution and late-life cognitive health go beyond whether air pollution is a modifiable risk factor for ADRD and related outcomes. As a class, environmental exposures represent an understudied set of potential risk factors for neurological conditions. Further consideration of the impact of an expanded set of exposures on the brain is warranted.

References

Glossary
AD-PS score: Alzheimer's Disease Pattern Similarity score. Using a statistical process, the investigators quantify the extent to which participant structural MRI scans have patterns of grey matter atrophy that resemble those derived from patients known to have Alzheimer's disease dementia.
PM$_{2.5}$: Particulate matter with aerodynamic diameter <2.5 μm. PM$_{2.5}$ exposures have been consistently linked to adverse health outcomes, including cardiovascular disease, respiratory problems, and mortality. As such, PM$_{2.5}$ levels are regulated by many countries around the world, including the USA, where PM$_{2.5}$ standards are part of the National Ambient Air Quality Standards (NAAQS), which specify a maximum amount of particulate matter to be present in outdoor air.
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