EDITORIAL

Air Pollution and Parkinson Disease

Increasing Our Risk Each Breath We Take?

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Page 928

The etiology of Parkinson disease (PD) is multifactorial and involves both genetic and nongenetic factors. Only approximately 10%–20% of the incidence of PD can be attributed to genetics, implying a larger role for nongenetic factors, including—but not limited to—environmental toxins. There is currently broad interest in the identification of environmental toxins that may increase the risk of PD because such factors are potentially modifiable and could therefore be targeted as part of a public health campaign aimed to prevent PD.

The putative leading known environmental cause of mortality worldwide is air pollution.[1] Air pollution is primarily composed of gases, such as ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide.[2] It also contains aerosolized particulate matter, including particles of 2.5 μm or smaller ($PM_{2.5}$), which can be inhaled through the respiratory tract. In fact, ultrafine particles (i.e., particles of 0.1 μm or smaller) have been shown to cross the blood-brain barrier in humans. More than 90% of the world's population currently lives in areas that exceed the World Health Organization's guideline for $PM_{2.5}$.[3] Previous studies have linked $PM_{2.5}$ to various adverse health outcomes, including cancer, cardiovascular disease, stroke, dementia, and all-cause mortality.[2] The ubiquitous nature of air pollution exposure and the ability of ultrafine particles to cross the blood-brain barrier have motivated investigations into a possible role of $PM_{2.5}$ in the etiology of PD. To date, however, studies on the association between $PM_{2.5}$ and PD have yielded equivocal results.[4] One possible explanation is that air pollution has no meaningful role in the etiology of PD, but—alternatively—it is also conceivable that the detection of a robust association in previous studies was precluded by methodologic limitations, particularly on the assessment of exposure to air pollution and on the timing of $PM_{2.5}$ exposure in relation to the onset of PD.

To expand on previous studies, in this issue of *Neurology*®, Krzyzanowski et al.[5] publish a study in which they assessed the association between ambient $PM_{2.5}$ levels and incident PD among 21.6 million Medicare beneficiaries. Exposure to $PM_{2.5}$ was estimated based on modeled $PM_{2.5}$ levels at the level of geographic residence code (zip + 4) from 1998 to 2000. Cases with incident PD were identified based on the presence of a first diagnostic code of PD in 2009, which occurred in 89,390 individuals. Analyses were adjusted for age, sex, race, estimated smoking, and health care utilization. Their main finding was that higher annual $PM_{2.5}$ levels were associated with an increased risk of PD. The relative risk of PD was 56% (95% CI 47–66) greater for those exposed to the median level of $PM_{2.5}$ and was slightly attenuated after accounting for airborne levels of trichloroethylene, which is another suspected risk factor of PD.

A key strength of this study was the inclusion of a 10-year lag between the assessment of $PM_{2.5}$ exposure and the incidence of PD because the relevant period of exposure precedes the clinical manifestation of PD likely by many years. Furthermore, the county-level assessment of exposure to fine particle matter was supplemented by model-derived individual-level measures in a representative subsample. In addition, this is the largest study on this topic to date, and the study included a comprehensive population-based capture of beneficiaries (instead of recruitment through hospitals), resulting in more complete counting of cases with incident PD overall, including those from groups that were underrepresented in previous studies.

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A specific methodologic concern is that the geographic location of Medicare beneficiaries in 2009 may not fully reflect where they lived 10 years earlier, resulting in possible misclassification of exposure to $PM_{2.5}$ in the most relevant period. There was also no clear exposure-response relation between $PM_{2.5}$ and the incidence of PD beyond $PM_{2.5}$ levels of 13 $\mu g/m^3$, and the analyses in this study did not differentiate between subcomponents of $PM_{2.5}$, which may have differential associations with the risk of PD.[6] Furthermore, there is the possibility of residual confounding by other air pollutants, which have previously been implicated as possible risk factors of PD, such as nitrogen dioxide. This is a relevant limitation because previous research has demonstrated that associations of $PM_{2.5}$ with other health outcomes may attenuate considerably after adjustment for other air pollutants.[7] Similarly, aside from the slight attenuation of the results after adjustment for trichloroethylene, residual confounding may have occurred by other possible environmental risk factors of PD, such as pesticides, metals, or extremely low-frequency magnetic fields.

More generally, a degree of caution is always needed when drawing causal inferences from associations, even for well-conducted studies. While there are plausible biologic mechanisms linking $PM_{2.5}$ to PD, there are also many possible noncausal pathways, including biases in the $PM_{2.5}$ measurement system[8] and concerns for unmeasured or residual confounding. Confounding is a considerable concern given the strong associations between both $PM_{2.5}$ and social determinants of health[9] and social determinants and health outcomes. Regardless, $PM_{2.5}$ is unlikely to be a potent cause of PD because there is some evidence that the incidence of PD has been increasing[10] over the same interval where $PM_{2.5}$ levels have substantially declined in the United States (the 90th percentile $PM_{2.5}$ level in 2016 is less than the 10th percentile level in the early 1990s[9]).

The study by Krzyzanowski and colleagues has provided additional insight on the association between $PM_{2.5}$ and PD, while also highlighting several key remaining gaps in knowledge. The study has thus helped to set the agenda for future research to elucidate the role of $PM_{2.5}$ and other environmental toxins in the etiology of PD, which are warranted to determine the robustness of the observed associations and to scrutinize whether these associations are causal. This will likely require a combination of different study designs and statistical approaches to account for the above-highlighted potential sources of bias (including confounding) and measurement error. Ultimately, such studies could facilitate public health strategies that target $PM_{2.5}$ and other environmental toxins with the aim to prevent PD.

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