

## Invited commentary: The importance of studying environmental risk factors for dementia

In this issue, Chen and colleagues report a significant association between Alzheimer's disease (AD) and vascular dementia (VaD), and long-term exposure to particulate matter (PM<sub>10</sub>) and ozone, in a retrospective case-control study in the Taipei-Keelung metropolitan area [1]. The authors identified 249 AD cases, 125 VaD cases, and 497 controls aged 60 and older from neurology clinics and teaching hospitals in the area. Air quality data were drawn from 24 air quality monitoring stations in the Taipei-Keelung metropolitan area. The adjusted odd ratios (AOR) they report for AD associated with PM<sub>10</sub> (AOR = 4.17, 95% confidence interval or CI 2.31–7.54) is higher than what is typically reported as the risk associated between having one or more apolipoprotein E (*APOE*) 4 allele(s), one of the strongest genetic risk factors for AD. Findings must be interpreted with caution, however. The study is not without limitations, as assumptions about duration of residence were made and temporality cannot be established.

Although a number of studies have related air pollution to health [2–4] and mortality [5,6], recent work has begun to tie air pollution to cognitive impairment [7,8] and structural brain aging [9]. This is one of the first studies to show an association between air quality and significantly increased risk for the two most common forms of dementing illnesses. As our ability to test associations between air pollution and AD improves (i.e., with the emergence of geospatial analysis and the ability to tie historical pollution data to large epidemiological studies of incident dementia), this should become an area of intense research interest in the United States and elsewhere. It will be important to evaluate these associations prospectively, in population-based studies, and across a wide range of geographical areas to establish the elements of causality including; temporality, strength, evidence of a dose response, consistency, plausibility, and specificity.

There are a number of reasons why this work is important. First, as dementia researchers are well aware, the numbers of new cases—and the financial burden of disease—is increasing. According to the 2015 Facts and Figures report [10], the cost of AD has risen to \$226 billion dollars annually; the cost of VaD is likely higher on a per patient basis [11] although the prevalence of VaD is lower. Second, as

we are also painfully aware, no treatments to stop or slow the progression of AD have been found. Recent failures of AD clinical trials suggest that earlier intervention is necessary. Third, in the absence of treatment, prevention becomes paramount; and randomized controlled clinical trials of preventive interventions are in their infancy. Fourth, if a significant risk of exposure can be controlled on a societal level, then the society has a responsibility to act. Published studies on the health effects of air pollution are considered by the Environmental Protection Agency (EPA) when determining standards. In the provisional assessment of “new” science for the evaluation of air quality standards, which occurs every 5 years, the EPA found that there was “no evidence of an association between long-term PM<sub>10-2.5</sub> exposure and mortality” [12]. This indicates that at the time of the last review, not enough new evidence in support of changing the standards had been published. There was no mention of the effects of air pollution on cognition. A recent Cochrane Review [13] highlighted the importance of studying this issue, and the need for more data. They cited the EPA's report noting that the costs of public and private efforts in the United States to meet the 1990 Clean Air Act Amendment requirements are estimated at \$65 billion annually [14]. That is less than 1/3 the cost of AD per year in the United States, not including the cost of VaD, unpaid care, and the burden on families imposed by dementia. Acknowledging that air pollution affects human health in countless other ways, many of them very costly, one might speculate that we can afford to do more.

With the exception of rare familial variants (*APP*, *PS1*, *PS2*) and one risk gene (*APOE*), AD does not appear to be primarily due to genetic risk factors. Although there are a number of other genes with relatively small effects, and genes most certainly contribute significantly to AD risk, we have known for some time that genes account for only a portion of the risk for AD. Other common risk or protective factors have been studied including type 2 diabetes, hypertension, diet, exercise, obesity, and cardiovascular disease. To date, there has been relatively little study of the effects of our environment on AD risk. Of all the factors that contribute to AD, environmental exposures are one of very few, if any, risk factors that can be addressed by societal or

Federal government intervention. As a matter of public health, when a problem is life-threatening, affects a significant portion of the population, and has a substantial societal cost, the government has a duty to step in. As Newt Gingrich noted in his recent *op ed* in the *New York Times*, "...when it comes to breakthroughs that could cure—not just treat—the most expensive diseases, government is unique. It alone can bring the necessary resources to bear. (The federal government funds roughly a third of all medical research in the United States.) And it is ultimately on the hook for the costs of illness" [15]. This study is just a starting point for the work that needs to be done to build a case for action regarding the effects of pollution on dementia risk. We need to rigorously investigate the problem and build a body of supporting evidence (if indeed the evidence support) to effect change. The next EPA review of standards has begun; a call for information on recent research was issued in December 2014 and review should run through December 2017.

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