Editorial

Air pollution and dementia

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Alzheimer's disease (AD) is today recognized as being one of the leading causes of mortality, and the prevalence is expected to quadruple globally by 2050 (1). Dementia not only takes a heavy toll on the afflicted persons and his/her close relatives, but is also associated with high economic costs to society, making dementia on of the most feared chronic diseases. Given the substantial personal and societal burden from dementia, it is imperative to identify modifiable risk factors. The etiology of AD, dementia and its mechanisms are not yet fully understood. Age, heredity, head injury and cardiovascular disease are important risk factors, but environmental factors have been suggested to be important on a population-level.

In the *Lancet*, Chen and colleagues recently concluded that living close to heavy traffic was associated with a higher incidence of dementia (2). They used a large population-based cohort including all adults who resided in Ontario, Canada and were between 55 and 85 years (about 2.2 million people). Individual proximity to major roadways was based on the cohort members' residential postal-code addresses. Associations between traffic proximity and incident dementia were estimated adjusting for individual and group-level factors. The adjusted hazard ratio (HR) of incident dementia was 1.07 (95% CI: 1.06–1.08) for people living less than 50 m from a major traffic road versus further than 300 m. The associations were even stronger among residents in major cities (HR 1.12; 95% CI: 1.10–1.14) and among people who did not change residential address during follow-up (1.12; 95% CI: 1.10–1.14) The fact that no associations were observed between air pollution and the other outcomes (multiple sclerosis or Parkinson's disease which was investigated in the same study, partly in the same cohort), together with various sensitivity analyses, strengthen their results. Air pollution concentrations were rather low in an international perspective in the study of Chen and colleagues, the average concentration of PM was 9.7 μg/m³ (range 1.3–19.8 μg/m³) and the average concentration of NO was 15.4 ppb (range 2.2–62.0 ppb). Given the ubiquitous nature of air pollution, and the heavy toll of dementia on society, their results implicate a major global public health concern.

During recent years substantial evidence has been published suggesting a potential role for air pollution in cognitive impairment and diseases of the central nervous system (Block *et al.*, 2012). A link between exposure to air pollution and AD was first observed by Jung and colleagues, in a Taiwanese cohort of 95,690 individuals aged 65 years or older. A HR for AD of 2.11 was observed per increase of 10.91 ppb in area-level O_3 over the follow-up period (95% CI: 2.92–3.33) (3). Two studies of neurodegenerative diseases from Sweden and Denmark used a much finer spatial resolution of the air pollution exposure variables. AD and vascular dementia (4), as well as Parkinson's disease (5) were found to be associated with air pollution exposure. Both these Scandinavian studies used home addresses and traffic data to estimate long-term exposure to nitrogen dioxide (NO_2) outside the home. NO_2 is a commonly used indicator of motor vehicle exhaust. The dementia study from Sweden estimated the etiologic fraction of dementia incidence attributed to exposure to 16%, indicating that local traffic pollution could be one of the most important risk factors identified (4). Recently, neurodegenerative effects of particulate air pollutants were also examined in a US cohort of older women from the Women's Health Initiative Memory Study. Residing in places with $PM_{2.5}$ exceeding EPA standards increased the risks for global

cognitive decline and all-cause dementia by 81% and 92% respectively, with stronger adverse effects in APOE ε4/4 carriers (6). In a review from 2016, Power and colleagues conclude that evidence provide support for a relation of air pollution exposure to dementia (7).

Furthermore, the number of studies suggesting an association between traffic pollution and cognitive function in adults is increasing. In a cross-sectional study of 399 elderly women in Germany, consistent associations between traffic-related particle exposure and mild cognitive impairment were found (8). In another cross-sectional study of 1,764 adults in the United States, ozone levels in the participants' home counties were associated with inferior performance on neurobehavioral tests (9). In a third cross-sectional study (of 680 elderly men in the United States), long-term exposure to traffic-related air pollution was associated with lower Mini Mental State Examination (MMSE) scores as well as with lower global cognitive function (10). A similar study of 765 community-dwelling senior citizens showed residential proximity to a major roadway to be associated with poorer performance on cognitive tests, but weaker associations with modeled outdoor levels of black carbon were observed (11). In the Nurses' Health Study Cognitive Cohort, which included 19,409 elderly women in the United States, long-term exposure to particles preceding baseline cognitive testing was assessed (12). Long-term exposure was found to be associated with faster cognitive decline, and a 10 μg/m^3 increment in long-term particulate matter (both $PM_{2.5}$ and $PM_{2.5-10}$) exposure was cognitively equivalent to aging by approximately 2 years. A cross-sectional study conducted in the Los Angeles Basin in southern California examined the associations between modeled air pollution levels at home and cognitive function in middle-aged and older persons, but no significant associations were found between NO_2 levels and cognitive function (13). In the Whitehall II longitudinal cohort study, PM exposure in London was modeled according to postcode for the years 2003–2009. Cross-sectional associations were observed between PM exposure and reasoning and memory, but not with verbal fluency. PM was also associated with a decline in cognition over time (14). The results from two large cross-sectional studies in older adults in the United States suggested associations between fine particulate matter ($PM_{2.5}$) and both cognitive function—primarily episodic memory (15)—and error rates in cognitive assessments (16). Long-term exposure to fine particles (particulate matter ≤2.5 μm; $PM_{2.5}$) was associated with time to first hospitalization for common neurodegenerative diseases in a register-based (Medicare) study of elderly (65+ years of age) in 50 towns and cities in Northeastern USA (17). Furthermore, epidemiologic studies have shown that air pollution can be linked to decreased cognitive function in children (18,19).

Experimental studies show brain deposition of particles, which may lead to inflammation (20,21). Exposure to diesel particles has been shown to activate microglia, which can produce neurotoxicity via oxidative stress (20). Oxidative stress (22,23) and systemic inflammation (24) may induce anxiety-like behaviors in mice and rats. Furthermore experimental data suggest air pollution causes severe vascular damage in the brain (25) and that PM can infiltrate the brain via circulation or via the olfactory bulb (20). Very recently, results from a study on 428 older men in the Veterans Affairs (VA) Normative Aging Study suggested that telomere length may modify the association between cognitive function, measures as MMSE Score and Black Carbon (an indicator for traffic-related air pollution) (26).

We know very little about which individuals may be more susceptible to develop dementia due to air pollution exposure. We also need to know more about different putative sources. Are some particles more harmful than others? For example, are particles stemming from vehicle exhaust more harmful than for example wear particles, or particles from domestic wood burning? It is also important to investigate if the link between air pollution and dementia is confounded by noise or access to green space.

Given that little is known about modifiable risk factors and that there has been limited progress in pathogenesis, if the study from Chen and colleagues (2) reflect causality, air pollution exposure would be one of few risk factors for dementia that are ubiquitous and can be modified at the population level. When regulatory measures are decided upon, the health costs attributed to air pollution concentrations are central. If there is a causal link between air pollution and dementia, the health costs attributed to air pollution have been grossly underestimated. The severe impact of dementia and AD on society, together with the plausible and preventable association of exposure to air pollution, deserves special attention.

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