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Commentary

Local Contrasts in Concentration of Ambient Particulate Air Pollution ($PM_{2.5}$) and Incidence of Alzheimer's Disease and Dementia: Results from the Betula Cohort in Northern Sweden

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Abstract. Exposure to fine particulate air pollution ($PM_{2.5}$) is emerging as a risk factor for Alzheimer's disease (AD), but existing studies are still limited and heterogeneous. We have previously studied the association between dementia (AD and vascular dementia) and $PM_{2.5}$ stemming from vehicle exhaust and wood-smoke in the Betula cohort in Northern Sweden. The aim of this commentary is to estimate the association between total $PM_{2.5}$ and dementia in the Betula cohort, which is more relevant to include in future meta-estimates than the source-specific estimates. The hazard ratio for incident dementia associated with a 1 μg/m3 increase in local $PM_{2.5}$ was 1.38 (95% confidence interval: 0.99 – 1.92). The interpretation of our results is that they indicate an association between local contrasts in concentration of $PM_{2.5}$ at the residential address and incidence of dementia in a low-level setting.

Keywords: Air pollution, Alzheimer's disease, dementia, particulate air pollution, $PM_{2.5}$

Worldwide, Alzheimer's disease (AD) is one of the leading causes of impaired health and mortality and as populations continue to age the share of individuals with AD is projected to increase in the future. Recently, the Lancet Commission of 2020 added air pollution as one of three new modifiable risk factors to the 2017 Lancet Commission on dementia prevention, intervention, and care life-course model, now consisting of twelve factors [1].

We have previously reported results from exposure to air pollutants and dementia from the prospective Betula cohort study from Northern Sweden, in detail described elsewhere [2]. In the Betula cohort, we observed clear associations between traffic-related air pollution (nitrogen oxides) and incidence of AD [3] as well as associations between fine particulate

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air pollution ($PM_{2.5}$) stemming from both vehicle exhaust and domestic wood burning [4]. We also observed that residential noise did not seem to be a risk factor for AD, or confounding the association between air pollution and AD [5], and that adverse effects of air pollution on AD incidence were not limited to, or stronger in, *APOE* ϵ4 carriers than in the total population [6]. We have not yet presented an estimate for the total effect of $PM_{2.5}$ on dementia incidence, however. Such an estimate is important to communicate now, as air pollution is beginning to be an established risk factor for AD and meta-analysis of effect estimates are sought for since substantial heterogeneity in published studies still remain [7, 8].

The aim of this commentary is thus to describe the association between total $PM_{2.5}$ and dementia in the Betula cohort, using the same data and methods as when investigating source-specific exposure [4]. In short, a Cox regression model assuming proportional hazards is used, adjusting for the same individual level factors as previously (physical activity, smoking, sex, body mass index, waist-hip ratio, alcohol, and age) in the Betula study of approximate 1,806 individuals over a 15-year period, where the mean age at start of follow-up was 68 years, 57% were women, and the proportion of *APOE* ϵ4 carriers were 28%. The hazard ratio for incident dementia associated with a 1 $\mu g/m^3$ increase in total $PM_{2.5}$, was 1.38 (95% confidence interval: 0.99 – 1.92). The interpretation of our results is that they indicate an association between total concentration of $PM_{2.5}$ at residential address and incidence of dementia in the Betula cohort. Supported by other epidemiological studies, as well as laboratory studies [1, 9, 10], the results add to already existing evidence for air pollution to increase dementia risk. The estimate is quite high compared to the meta-estimate of a relative risk of 1.08 per 5 $\mu g/m^3$ increase in $PM_{2.5}$ calculated by Yu and colleagues [7]. This is most likely due to the fine spatial resolution in our air pollution model, meaning that we model local contrasts in air pollution concentrations. The study area, Umeå municipality, is furthermore rather small (33.5 km²), and we have not access to any data on possible contrasts in long-range-transported $PM_{2.5}$. Our results should therefore be interpreted as risks associated with differences in local exposures, and may therefore be in line with what has been observed by others in terms of local air pollution having a substantially higher impact on mortality per unit compared to regional air pollution [11]. This could have implications on health impact assessments attributing dementia cases to air pollution exposure, when local models are available, and populations are similar, it might be relevant to consider if a higher dose-response-function should be used than, for example, applied by Rittner and colleagues [12].

Based on strong evidence, the Lancet Commission of 2020 added air pollution as a modifiable risk factor and adding our result in future meta-analyses will help to gain a better understanding of the magnitude and precision on evidence suggesting total air pollution levels to be associated with incident dementia. Our findings further suggest the need to consider ambient air pollution associated with dementia pathology in public health policy decisions.

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