



Ambient air pollution and Alzheimer's disease: the role of the composition of fine particles

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Ambient air pollution is the most important environmental risk factor globally due to its well-established burden of respiratory and cardiovascular diseases (1). Within the complex mixture of polluted ambient air, fine ambient particles defined as mass of particles smaller or equal to 2.5 μm in aerodynamic diameter (PM_{2.5}) are an established causal factor. Epidemiological evidence is accumulating that PM_{2.5} is linked to cognitive decline (2, 3). Recent evidence highlighted that PM_{2.5} is also associated with neurodegenerative diseases, specifically with Alzheimer's and Parkinson's disease (4). In this issue of the journal, Shi et al. investigated the association between constituents of PM_{2.5} and the incidence of dementia and Alzheimer's disease (5). Their analyses are based on a cohort assembled from the Medicare and Medicaid records including all inhabitants of the contiguous United States aged 65 y and older for the time period 2000 to 2017. They constructed two separate cohorts: They identified 5.8 Mio cases of incident dementia among 18.5 Mio individuals and 2.8 Mio cases of incident Alzheimer's disease among 19.2 Mio individuals. They report consistent associations for constituents of PM_{2.5}, namely black carbon, organic matter, sulfates (SO_4^{2-}), and ammonium (NH_4^+). They conclude that annual average PM_{2.5} concentrations from traffic and fossil fuel combustion are significantly associated with the development of dementia and Alzheimer's disease (5).

PM_{2.5} is a complex mixture both with respect to their size ranging down to several nanometers and their composition (6). The composition of combustion-related particles is determined by three factors, the composition of the fuel, the chemical reactions when forming the primary particles, and the substances that are absorbed on the particle surfaces while being dispersed in air. The constituents of PM_{2.5} assessed by Shi et al. (5) describe the sources of the particles and the toxicological properties. Black carbon is a measure of soot particles produced in combustion processes. As primary particles, they are part of the ultrafine particles (UFP) defined as particles smaller than 100 nm. In this size range, they are characterized by high number concentration and surface area. Particles agglomerate as they age, so that primary ultrafine particles grow into the fine particle fraction. The majority of sulfates, nitrates, and ammonium in PM_{2.5} are secondary constituents formed from their gaseous precursors and absorbed on the particles. Their concentrations have been consistently associated with adverse health effects, while the toxicity of these constituents is low (6). They are indicators for combustion-related, aged, and regionally transported PM_{2.5}.

Shi et al. have used two independent approaches to characterize the spatial variation of annual averages of PM_{2.5} constituents (5). First, they estimated the annual averages based on an integrated approach combining satellite data, chemical transport models, and ground-based observation with a resolution

of 1 km by 1 km. Second, they estimated the annual averages based on nearly 1,000 measurement stations and hundreds of additional predictor variables with a resolution of 50 m by 50 m in urban areas and 1 km by 1 km in rural areas. Both methods yielded comparable correlations between the PM_{2.5} constituents and PM_{2.5} mass. The resulting spatial maps provide comparable spatial distributions for all constituents but black carbon. For black carbon, the method relying on chemical transport models assigned the largest values to the industrial southeast and suggests long-range transport of soot-containing particles. In contrast, the method putting most weight on measured constituents implicated that the metropolitan areas had the highest annual averages of black carbon.

A key finding of the study by Shi et al. (5) is that the hazard ratio for dementia increased 12% (95% CI: 11 to 14%) per 1 $\mu\text{g}/\text{m}^3$ black carbon for the chemical transport-based model and 25% (95% CI: 22 to 27%) per 1 $\mu\text{g}/\text{m}^3$ black carbon for the second model with finer spatial resolution. The hazard ratio for Alzheimer's disease increased 23% (95% CI: 21 to 25%) per 1 $\mu\text{g}/\text{m}^3$ black carbon for the for the chemical transport-based model and 39% (95% CI: 36 to 43%) based on the second model with finer spatial resolution. The estimates based on the second model with finer resolution are robust against adjustments for the remaining variation in PM_{2.5} mass. The estimates based on chemical transport-based model are reduced to a null effect when adjusting for the remaining variation in PM_{2.5} mass. This highlights two important points: First, the observed associations are to a large degree driven by Alzheimer's disease, and second, the second model captures the role of locally emitted soot particles better than the chemical transport-based model.

Considering sulfates as a key indicator for regionally transported, aged PM_{2.5}, the differences are less striking. One $\mu\text{g}/\text{m}^3$ SO_4^{2-} is associated with an increased hazard ratio for dementia of 5.9 % (95% CI: 5.6 to 6.2%) based on the chemical transport-based model and of 6.2 % (95%

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CI: 5.8 to 6.5%) based on the second model with finer spatial resolution. The risk for Alzheimer's disease associated with an increase of $1 \mu\text{g}/\text{m}^3 \text{SO}_4^{2-}$ was estimated to be 7.4 % (95% CI: 6.9 to 7.9%) based on the chemical transport-based model and 8.4 % (95% CI: 7.9 to 9.0%) based on the second model with finer resolution. These findings imply that first, the observed increased risks are attributable to Alzheimer's disease and other dementias and second, both models derive consistent results for regionally transported fine particles.

There are multiple ways how fine particles and their constituents are hypothesized to impact the brain and initiate and promote neurodegenerative diseases (Fig. 1). Particles are deposited in the upper and lower airways and reach the lung as well as the gastrointestinal tract (Fig. 1: 1 to 4). UFP are able to enter into cells (7, 8) and to reach the brain via the olfactory nerve (8) (Fig. 1:1). Consequently, UFP could contribute to Alzheimer's disease development by translocation to the cortex regions where Alzheimer's disease is initiated (9, 10) (Fig. 1:8). Alzheimer's disease is characterized by progression of protein miss-folding and plaques that start to develop in distinct brain regions before the entire cortex is affected. Indeed, animal experiments with diesel exhaust containing high numbers of UFP showed protein miss-folding and plaques in addition to oxidative stress (11). By these

mechanisms, UFP could contribute to the observed Alzheimer's disease-specific associations of black carbon by Shi et al. (5). Furthermore, UFP and other constituents of PM_{2.5} such as transition metals or semivolatile organic compounds translocate from the lung or the gastrointestinal tract to the bloodstream and reach the brain vasculature (Fig. 1:5 to 8). It has been demonstrated by experimental studies that UFP are able to pass the blood-brain-barrier (12). Thereby, more diffuse impacts including microglia activation and reactive astrocytes inducing neuronal inflammation and degeneration as well as oligodendrocyte dysfunction have been described (13). Promotion of neurodegeneration in the entire brain including the cortex would be a consequence (Fig. 1:8). This would be consistent with the finding that aged and regionally transported PM_{2.5} is robustly associated with dementia and Alzheimer's disease (5). Further support is provided by a study in children and young adults from Mexico City. (14). UFP were detected along with evidence for neurovascular damage in several brain regions using imaging modalities such as transmission electron microscopy. Furthermore, inflammatory processes induced by PM_{2.5} in multiple barrier organs could result in systemic oxidative stress and inflammation (Fig. 1:5). Systemic oxidative stress and inflammation are among the hallmarks of

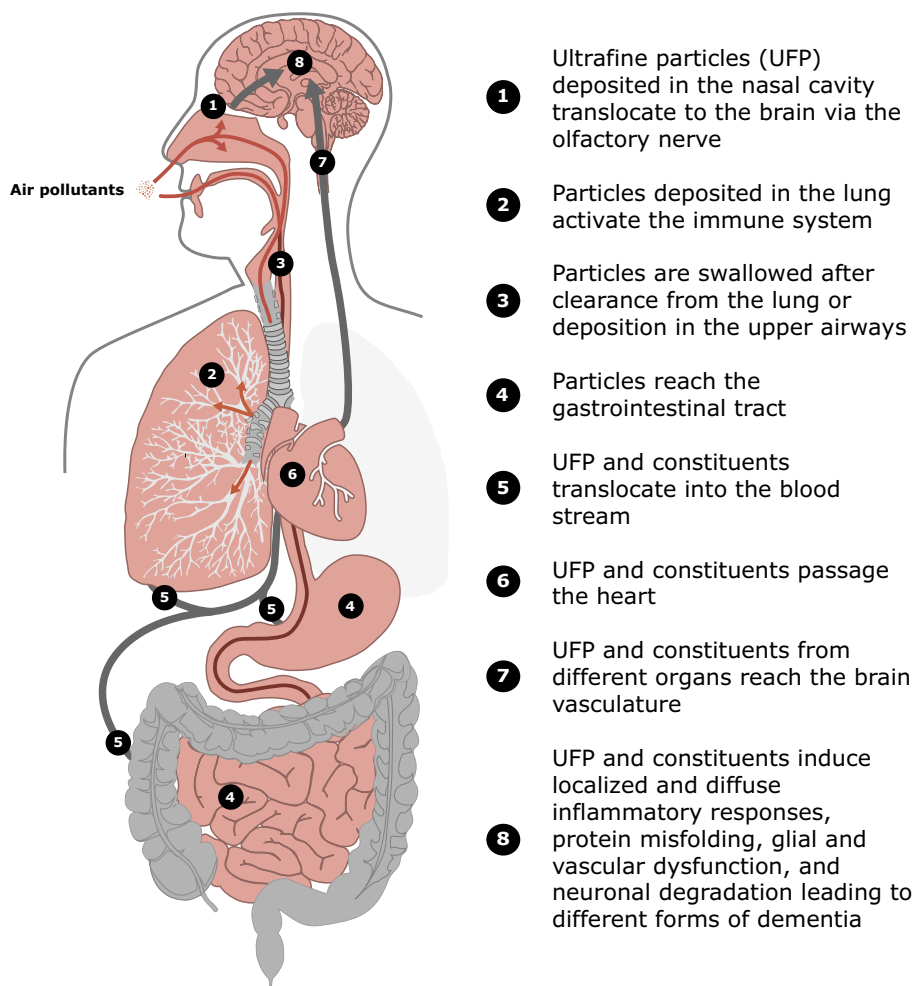


Fig. 1. Schematic overview on ambient fine and ultrafine particle deposition and interaction with organs and the circulation contributing to the development and progression of dementia and neurodegeneration. Orange lines and arrows: Particle paths through the upper airways into the lung. Dark red lines: Particle paths through the esophagus into the gastrointestinal tract. Gray lines and arrows: Paths of ultrafine particles and constituents from the barrier organs to the brain.

environmental insults (15) and could thereby contribute to the progression of dementia. We recently demonstrated the impact of PM_{2.5} on the gut microbiome (16) (Fig. 1:4), and in general, the gut-brain axis is discussed as relevant for dementia development and progression (17). Finally, a robust association has been documented between PM_{2.5} and vascular dysfunction (18). Therefore, it is also plausible that PM_{2.5} impairs endothelia in the brain and induces vascular dementia (Fig. 1:8). Taken together, the hypothesized pathways could promote various types of dementia (10, 17).

“In PNAS, Shi et al. investigated the association between constituents of PM_{2.5} and the incidence of dementia and Alzheimer’s disease.”

There is the need for experimental studies to pursue these aspects further. In particular, toxicological studies are needed to understand the role of UFP and constituents of PM_{2.5} for initiation and progression of dementia including Alzheimer’s disease. Within epidemiological studies, measuring the incidence of Alzheimer’s disease and related dementia is a challenge. There is evidence for substantial misclassification and late detection of the disease. However, using the nationwide Medicare and Medicaid data provides a comprehensive and consistent approach. It is unlikely

that a large proportion of the early stages of Alzheimer’s disease are captured. To further advance the understanding, large prospective population-based cohorts are needed including longitudinal brain imaging, cognitive function assessments, biomarker measurements, and genotyping to advance the understanding of Alzheimer’s disease initiation and progression by environmental factors such as air pollution.

The population around the world is growing and aging. Consequently, age-related diseases are increasing globally.

Today, Alzheimer’s disease and other dementias are globally the seventh leading cause of mortality according to the World Health Organization (19). Of the approximately 55 Mio cases, 60 to 70% are Alzheimer’s disease. These numbers highlight that the paper by Shi et al. (5) has important implications for regulatory action. The finding that black carbon particles per $\mu\text{g}/\text{m}^3$ have an approximately 10-fold larger effect size than the PM_{2.5} mixture calls for action to further limit emissions of soot particles from their sources. It also calls in my mind for intensified monitoring of ultrafine particles. The finding that aged regional transported particles are associated with dementia including Alzheimer’s disease strongly highlights that air pollution mitigation strategies need to be part of regional and national agendas.

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