Imperial College London

Environmental Research Group

30th Anniversary Series

How Does Air Pollution Affect the Brain?

Exploring the evidence between air pollution and incidences of declining cognition and increasing dementia

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IMPERIAL POLICY FORUM

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Introduction

Over the last decade there has been increased interest in the potential role long-term air pollution plays in age-related declines in cognitive function, and the risk of developing dementia. We addressed this emerging research field in the third of our series of seminars to celebrate the 30th anniversary of the Environmental Research Group, in partnership with Imperial College London's Policy Form: How Does Air Pollution Affect the brain? The seminar was hosted by Dr Ian Mudway, Senior Lecturer within the School of Public Health and lead of the ERG's Environmental Toxicology Group, and featured talks from Professor Klea Katsouyanni (Lead of the ERG's Air Pollution Epidemiology Team), Professor Paul Matthew (Head of the UK the Dementia Institute at Imperial) and Professor Roland Wolf (Division of Systems Medicine at the University of Dundee). The event reviewed the evidence that has accumulated from epidemiological studies, the latest research on air pollution linkages with Alzheimer's disease and explored how we can use experimental toxicology to understand how the pollutants we breath cause harm to the brain.

Exposure to air pollution, cognitive function and incidence of dementia: evidence from epidemiological studies

In 2022 the Committee on the Medical Effects of Air Pollution (COMEAP) published a review of the emerging evidence concerning the potential impact of air pollution on the ageing brain. They concluded that there was sufficient evidence to support an association between long-term air pollution exposures, particularly to PM2.5, PM10 and NO2, with the rate of cognitive decline, and increased risk of developing dementia (COMEAP, 2022). However, understanding the impact of air pollution on cognitive function and dementia at a population level is challenging. Firstly, studies need to be of a sufficient size for them to be applicable to the wider population. Secondly, in longitudinal analysis of population health the very nature of cognitive decline and dementia makes sufferers more likely to withdraw from the study which may lead to a bias in the results. Lastly, dementia itself is an umbrella term for a number of conditions associated with accelerated loss of cognitive function, which is now known to have long prodromal period of underlying pathological changes,

Alzheimer's disease is the most common form of dementia, accounting for approximately 60% of all dementia cases in the UK

Dementia UK

prior to the development of symptoms, which means there needs to be an understanding of historic exposures going back decades. Whilst past research has provided evidence supporting a negative impact of air pollution on cognitive decline and dementia, more work is required to address these points. In addition, much of the current evidence is based on research in high income countries and more work is therefore needed in South America, Africa, South Asia and Australasia, to gauge the likely burden of poor air quality on their populations. Given the chronicity of dementia more longitudinal studies are required, incorporating repeated measurements, to deepen our understanding of cognitive changes and their relationship to dementia onset. In these studies, more emphasis should be placed on the different source contributions and chemical components within particulate matter, as well as other gaseous and volatile pollutants. Finally, more research is required to investigate whether early life impacts if air pollution on cognitive development, contribute to increased risks of dementia as the population ages.

How does air pollution contribute to the risk of Alzheimer's disease?

One new case of Alzheimer's disease is diagnosed in the UK every three minutes, and this will continue to increase as the UK population grows older. Professor Paul Matthews, head of the Dementia Research Institute at Imperial College London, highlighted that this is a global problem, which is even more serious in countries with greater air pollution problems.

Dementia is loosely defined as cognitive impairment sufficient to impact on daily life. However, the cause is not specified, and it is an intrinsically poor endpoint in most research studies. Alzheimer's disease makes up 60% of all dementias in the UK, with vascular dementia being the other predominant presentation. The symptoms and signs of these dementias, such as memory impairment and loss of language, are progressive and occur at different rates in different people, dependent on an individual's underlying genetics.

The time between diagnosis of Alzheimer's disease and death is about ten years, however, diagnoses are difficult to make, as symptoms are often weak and confounded by various factors. In fact, some diagnoses are not made until symptoms become very severe. What is now apparent however is that the underlying disease processes occur pre-clinically for decades before a medical diagnosis can be made. Therefore, when developing new therapies, or lifestyle interventions that can either prevent or cure Alzheimer's there is a need to address cellular events that occur during the pre-clinical phase.

However, knowing where to start can be difficult, as the root causes of dementia are multiple, often overlapping, or secondary to other chronic health conditions. Linking population changes to changes in cells and molecules requires a holistic approach which crosses scientific boundaries. It must relate population exposures to human behaviours, brain network function, cellular responses, and the underlying molecular changes driving brain inflammation and neuronal cell death. Ultimately, we need to aggressively research the causes and mechanisms contributing to the onset of dementia and begin to control them on a population level. To ensure this research field continues to move forward quickly, clinical, pathological and epidemiological studies need to work together with molecular and cellular studies in a hypothesis guided framework.

Application of humanised and reporter mouse models to study mechanisms of environmentally induced disease and in drug development

Understanding the mechanisms by which exposure to air pollution causes harm is vital to maintaining human health. Professor Wolf's presentation focused on this subject by detailing his research in understanding the regulation of pathways that have evolved to protect us from toxic environments, which come into effect when we are exposed to toxins in air pollution.

Cells in the human body have adapted to metabolic and environmental stress. When they detect certain substances, they express enzymes that protect the cell. Different pathways are activated in response to different stresses, which are fundamental to ensure that humans can maintain normal functions. However, these pathways can be overwhelmed by high or chronic doses of environmental stressors (e.g., NO2, PM2.5 or PM10), which can result in tissue degeneration, disease pathogenesis and aging. Developing an in-depth understanding of these complex processes and their relationship to disease provides exciting possibilities for the development of new therapies.

If a researcher attempted to study pathways activated by environmental stressors in patients, it would be very difficult to isolate what caused an effect. So, Professor Wolf investigates these important pathways using reporter mouse models. These are mice that have had a gene substituted with a reporter gene so that a marker, such as a colour, is produced when an enzyme is activated. These markers can be measured easily from tissue samples or non-invasive imagery to enable researchers to see when enzymes that form part of these pathways are activated. Using these animal models is a powerful approach for researchers to achieve a detailed analysis of where and when receptors are activated and in doing so, determine complex mechanisms underlying disease.

These models can be combined with intervention strategies to gain further mechanistic insights and they dramatically reduce the timeframes required because observed changes in the models occur before any physiological or pathological changes. In the future, the application of these models will aim to identify specific biomarkers of the toxicological effects caused by exposure to air pollution, which will provide invaluable measurable evidence for explaining associations in epidemiological studies.

Summary

While the areas of research surrounding the links between air pollution, cognitive decline and incidences of dementia are still developing, progress has undoubtedly been made in the understanding of how environmental exposure to airborne pollutants may impact brain health. By examining the issue simultaneously from clinical, epidemiological, and physiological perspectives, researchers are beginning to gain a holistic view of the ways air pollution may affect the brain which, ultimately, may bring about intervention strategies, be they treatments or preventative measures. human health. Significant action is needed from stakeholders in industry and policy.

Photo: Dr An invigorated audience during the *How Does Air Pollution Affect the Brain?* seminar panel discussion.

About the ERG & the 30th Anniversary Seminar Series

Founded in 1993, the **Environmental Research Group** initially consisted of measurement, modelling, and toxicology teams. 2023 is the ERG's 30th anniversary. The group is now located at Imperial College London, and is nine teams strong, with over 100 members of staff studying air pollution, water pollution, and microplastics to better understand the impact of these stressors on our environment and health.

This seminar was the third of six, as part of the ERG's 30th Anniversary Seminar Series. More information on the ERG and the 30th Anniversary celebrations can be found at on the Environmental Research Group website here.

The ERG 30th Anniversary Seminar Series is hosted in partnership with Imperial Policy Forum, the College's policy engagement unit. More information about the Environmental Toxicology team's research is linked here. More information about the Air Pollution Epidemiology team's research is linked here.