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Citation for published version:

Russ, TC, Reis, S & Van Tongeren, M 2018, 'Air pollution and brain health: defining the research agenda', *Current Opinion in Psychiatry*, pp. 1. <https://doi.org/10.1097/YCO.0000000000000480>

Digital Object Identifier (DOI):

[10.1097/YCO.0000000000000480](https://doi.org/10.1097/YCO.0000000000000480)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Current Opinion in Psychiatry

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Air pollution and brain health: defining the research agenda

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Word count: 2941

Abstract word count: 198

ABSTRACT

Purpose of review: The literature on air pollution and brain health is rapidly expanding and it is a universal finding that greater exposure to air pollution is associated with worse outcomes, whatever the measure of brain health used (clinical dementia, neuroimaging correlates, or cognitive impairment). However, there are a number of important questions which the studies currently published are not able to answer: (A) when in the life course does exposure to air pollution most have the most impact?; (B) which pollutant(s) or components are most important?; and (C) since dementia describes a heterogeneous group of conditions, which is most affected by exposure to air pollution?

Recent findings: We briefly review and discuss the nine articles which have been published so far in 2018, so recently that they were not included in the four review articles also published this year. We highlight the variation in estimates of air pollution used but the consistency in deriving them from residential address (with or without some knowledge of an individual's previous home locations).

Summary: We are now at the stage when the research agenda needs to be agreed and we believe these three questions should be the focus of future research.

KEY WORDS

Dementia, Alzheimer's disease, Ageing, Epidemiology, Risk factors, Air pollution, Environment, Life course

INTRODUCTION

The detrimental effects of a variety of types of air pollution on human health has long been known. The importance of brain-specific health effects has recently been getting increasing attention, both in the scientific literature and the media.[1] A number of researchers, notably Dr Lilian Calderón-Garcidueñas, have focused on this area for many years,[2] but the volume of literature has recently been rapidly expanding. So far in 2018 there have been four review articles[3-6] published and another nine scientific articles[7-15] which were published too recently for inclusion in those review articles.

The authors were part of a pilot project funded by the Natural Environment Research Council “Improving Health with Environmental Data” call to link modelled historical air pollution data with cognitive ageing in the Lothian Birth Cohort 1936.[16] At the end of this project, we held a workshop at the University of Manchester to begin to form a consensus about how research in this area should move forward (attendees are listed in the acknowledgements). Thus, in this article we will summarise some of the recent literature but focus on three questions which emerged from the workshop which we feel are fundamental to advancing knowledge in this area but which remain unanswered to date.

THE STATE OF THE LITERATURE

The nine articles not cited in the most recent systematic reviews include findings from research involving a total of 7.2 million participants and encompass up to 25 years of exposure to air pollution or more (**Table**). Two reports emerged from the longitudinal Betula study in Sweden using a clinical diagnosis of dementia, with accurate subtyping (i.e. differentiating Alzheimer’s dementia, vascular dementia, etc.), as the outcome of interest investigating the effects of traffic-derived nitrogen oxides (NO_x) and traffic noise[7] and fine particulate matter (with an aerodynamic diameter of less than 2.5µm [PM_{2.5}], in this case from residential wood burning).[12]

Both studies found a detrimental effect of exposure to air pollution – HR for highest:lowest NO_x quartile, 95%CI 1.41, 0.97-2.03; HR per 1µg/m³ increase in PM_{2.5}, 95%CI 1.55, 1.00-2.41 – but no additional effect of traffic noise on the NO_x association. Participants’ residential addresses for the period from 1993 to 1995 were obtained from the Swedish population register and these were used to derive exposure to air pollution based on a 50m×50m land-use regression (LUR) model for NO_x and a model deriving annual average PM_{2.5} concentrations in 1990, 2000, and 2010 from the Swedish Meteorological and Hydrological Institute.

Investigators in one imaging study linked air pollution with 3T brain MRI in a subset of the Atherosclerosis Risk in Communities Study (ARIC) study.[13] This was essentially a cross-sectional study as only one structural imaging measure was available per participant, though long term exposure to air pollution was estimated. Participants’ residential addresses, recorded at each study visit, were again used to estimate monthly exposure to PM₁₀ and PM_{2.5} using spatiotemporal models. The availability of national ambient air pollution monitoring data varied during the period of exposure and so separate models were fit for the periods 1988-1998 and 1999-2007. Exposure to both size fractions of PM was found to be associated with smaller deep grey matter volume but not with other structural measures. Findings varied somewhat across the four sites assessed in this study, perhaps suggesting some variation between the samples. No study to date has reported on the association between air pollution and change in neuroimaging markers over time.[5]

Studies in the US and UK have focused on a dementia outcome derived from electronic health records, in Medicare and the Clinical Practice Research Database (CPRD).[8,9] The large scale Medicare study included 6.9 million older adults who were followed up for 55.4 million person-years of whom 23% were recorded as having developed dementia at some stage; this required the recording of dementia using an insurance claim code.[8] Investigators obtained ZIP+4 codes

from Social Security records, corresponding to a single mail delivery segment (but not unique address) for the follow up period. The latitude and longitude of the centroid of each ZIP+4 code was derived and the square of the inverse distance to each air pollution monitor was used to calculate a weighted average of PM_{2.5} exposure for each location. The authors concluded that a 1µg/m³ increase in decadal PM_{2.5} exposure was associated with an increased probability of dementia diagnosis of 1.3% (95%CI 0.4-2.2). The UK investigators using primary care data derived their dementia outcome from the use of Read codes for dementia within the Quality and Outcomes Framework (NHS Digital).[9] Annual concentrations of nitrogen dioxide (NO₂), PM_{2.5}, and tropospheric ozone (O₃) were derived at 20m×20m spatial resolution from urban dispersion models developed by King's College London incorporating London Atmospheric Emissions Inventory (LAEI) data, but only for one year. Traffic proximity measures were estimated from the distance to the nearest road of heavy vehicle intensity (top quartile) and average annual road traffic noise was estimated from a TRAffic Noise EXposure model. All these data were linked with centroids of residential postcodes. The authors concluded that increasing NO₂ exposure was associated with an increased risk of dementia (HR highest:lowest quintile, 95%CI 1.40, 1.12-1.74), as was exposure to PM_{2.5} and traffic noise. In multipollutant models, only NO₂ and PM_{2.5} remained independent predictors.

Three studies reported a measure of cognitive change (based on two measurements)[10,11,14] and one study reported a measure of cognition at one point in time.[15] UK Biobank included several cognitive tests performed on a tablet computer at recruitment: reasoning; reaction time; numeric memory; visuospatial memory; and prospective memory.[10] Participants' residential addresses at baseline were used to derive estimated exposure to PM₁₀ and NO₂ concentrations derived from EU-wide air pollution maps with 100m×100m spatial resolution based on a LUR model combining data from >1,500 monitoring sites and satellite-derived ground-level concentration estimates. Some data on historical residence locations at 1km×1km resolution

were available and used for sensitivity analyses. Cross-sectional associations were observed with exposure to higher levels of air pollution but no associations were seen which reached conventional levels of statistical significance between air pollution exposure and cognitive change.

Investigators from the China Family Panel Study reported an association between long-term exposure to air pollution and poorer performance on mathematics and word-recognition questions.[15] Air pollution data were derived from daily readings of sulphur dioxide (SO₂), NO₂, and PM₁₀ aggregated to an Air Pollution Index (API), which ranged from 0 to 500. API values were linked to “exact information about the geographic location” (supplementary material) along with meteorological parameters on the specific test date derived from 402 monitoring stations across China. In fact, it seemed that the resolution of the air pollution data was at the city level, or nearest city if a study county was in a city with no local air pollution monitoring data available.

A report from the Boston Puerto Rican Health Study linked higher exposure to PM_{2.5} and its components Black Carbon and Nickel with decline in four cognitive domains (verbal memory, recognition, mental processing, and executive function) but not visuospatial function.[14]

Associations with other components of PM_{2.5} (Sulphur and Silicon) and cognition were mostly null, apart from recognition. Air pollution data were derived from a single monitoring supersite measuring ambient PM_{2.5} concentrations and its components which were regarded as tracers for traffic, regional contributions or oil combustion, coal combustion, and crustal PM_{2.5} sources.

Finally, investigators from the Study on the Influence of Air Pollution on Lung, Inflammation and Ageing (SALIA) cohort linked exposure to air pollution with poorer visuo-construction performance and concluded that part of this association was mediated by poorer lung function.[11] Study participants completed the Consortium to Establish a Registry for

Alzheimer's Disease (CERAD) test battery at each wave but investigators focused on visuo-construction performance because it had previously been linked with air pollution. NO₂ and PM were estimated using the European Study of Cohorts for Air Pollution Effects (ESCAPE) protocol on data from up to 40 measurement sites at three time points (to assess seasonality) over one year. These monitoring data were used in a LUR model incorporating information on nearby traffic, ports, industry, and population density and linked to participant's home addresses.

Overall, these studies share a number of limitations, in particular in relation to the estimation of air pollution exposure. Median (IQR) NO₂ values varied from 33.20µg/m³ (26.20-39.91) in UK Biobank to 36.4µg/m³ (32.9-40.4) in London.[9,10] PM_{2.5} was much more variably reported and only two papers reported values allowing comparisons, with median (IQR) values of 15.6µg/m³ (15.2-16.1) in London and 33.0µg/m³ (4.9) in the SALIA cohort.[9,11] All the studies used residential address as a proxy for exposure to some extent, but one study used a single air pollution measurement source to assign personal exposure values to everyone in the study.[14] Furthermore, some studies use a very limited period of measurement, for example one year's air pollution data being extrapolated to fifteen years of follow up.[7] Added to this are the uncertainties associated with the various environmental modelling approaches used which means that few of the studies presented here are readily comparable.

SAME OLD SAME OLD?

In spite of the limitations just outlined, we now have a large literature linking air pollution with poorer brain health and there have been no studies suggesting a null or protective effect.[17-22] However, there are limitations in the conclusions which can be drawn from observational research and so we must be circumspect in our interpretation of the literature. In particular, there is variability in the extent to which potential confounders or mediating factors – including

socioeconomic position, smoking, respiratory illness, and lung function – are taken into account.[1]

There is a marked contrast with the literature linking air pollution with cardiovascular disease where experimental work in humans has clarified the mechanisms underlying this association – direct effects of particulate matter on the vasculature and indirect inflammatory effects.[23]

However, it is important to remember that combustion-derived (in particular, ultrafine) particles have been identified in brain tissue suggesting that direct effects on the brain are possible.[24]

This area of research needs to avoid the trap of simply replicating previous findings – with perhaps minor variations, such as identifying particular aspects of cognition which are affected by exposure to air pollution in a particular study.[15] Taking a step back, there are a number of important questions which require answers in order to progress this field and understand whether and how air pollution might have a detrimental effect on the brain. In our opinion, these questions relate to (A) when in the life course does exposure to air pollution have most impact – or is it an accumulation of exposure which conveys risk?; (B) which pollutant(s) or components are responsible for detrimental health effects?; and (C) which aspect of brain health is affected? We will elaborate on these questions in a little more detail below.

Life course epidemiology

It is now clear that neurodegenerative diseases such as Alzheimer's dementia have a long asymptomatic so-called 'preclinical' period when the disease is present but without any overt symptoms. The initial origins of the disease begin decades before any symptoms become apparent.[25-28] Indeed, much research attention is now focused on mid-life when the possibility of modifying the disease course and potentially preventing or delaying the appearance

of symptoms, for example the European Prevention of Alzheimer's Dementia (EPAD) consortium.[29]

Life course epidemiology has been developing over the last two decades and provides a helpful paradigm for considering the origins of conditions – such as dementia – which are influenced by risk and protective factors at all stages of life.[30] The three models of exposure across the life course are: (i) accumulation of risk through prolonged exposure; (ii) sensitive periods when an exposure is more influential than at other times, though it also affects the individual – to a lesser extent – at other times; and (iii) critical periods during which an exposure is influential, not having an effect at other periods of life. It is still an open question which of these models applies to the association between air pollution and poorer brain health and datasets which could answer this question are rare – requiring both lifetime residential history for participants and access to historical air pollution data.

Exposure assessment

Air pollution consists of particulate matter (PM, classified by aerodynamic diameter: $PM_{10} < 10\mu m$, $PM_{2.5} < 2.5\mu m$, and ultrafine particles, $UFP < 100nm$) and gaseous pollutants, including O_3 , NO_x , and SO_2 . Different studies have focussed on different – often multiple – pollutants but, interestingly, there have been no null associations identified between any air pollutant and any measure of impaired brain health; every study has concluded that the association observed is a detrimental one.

A particular challenge is exposure misclassification – for instance, someone erroneously thought to live in one location but having moved elsewhere or that individual spending substantial periods of time away from home due to commuting and personal mobility. It is possible to incorporate the difference between time spent at residential and work locations into modelled

exposure assessments at a national scale for the UK.[31,32] While the overall differences in calculating aggregated exposure did not substantially differ at a *population* level – modelled PM_{2.5} was similar and modelled NO₂ was slightly higher – at an *individual* level, additionally including workplace location led to large variations in actual exposure compared to an assessment based on residence only. Hence, including mobility when assessing individual exposure will reduce exposure misclassification. The use of modelled concentration data for exposure assessments is often controversial due to the inherent model uncertainties. However, the potential exposure misclassification due to using one or few monitoring sites, which are not representative for their respective populations, needs to be carefully evaluated against the whole range of uncertainties introduced by using different datasets.

This applies equally to assessment of interventions, where identifying the sources of ambient pollutant concentrations is paramount. In this context, one research group attempted to identify the components of PM_{2.5} concentrations and infer its sources, using a suite of different instruments to determine particle composition to assess which of the components are associated with cognition and to identify potential contributing sources.[14] While they found stronger associations with Black Carbon (an indicator of traffic-related combustion emissions) than with other components, composition measured at one location only represents population-wide exposure to a very limited extent. If one pollutant from a particular source were found to be especially toxic to brain health, this would point to the most valuable public health intervention to ameliorate this. However, being able to draw secure conclusions about this would require much better data than we currently have.

Which dementia?

Dementia is not a unitary entity, but rather a syndrome describing the combination of progressive cognitive decline and consequent functional impairment. However, we often speak

of it as if it were not a heterogeneous mixture of different neurodegenerative and neurological diseases, but rather one thing. This sometimes reflects the methodology used in a study to ascertain dementia status – in many cases, electronic medical records do not provide sufficient detail to allow one to identify specific dementia subtypes with any certainty (though this is improving) and completers of death certificates, in particular, have been guilty of merely stating ‘dementia’ as one of the causes of death, when indeed it is recorded at all.[33-35]

However, there is evidence of differential effects of air pollution on different subtypes of dementia. The conclusions we draw regarding this must be informed by the certainty we can place on the differential diagnosis within dementia in each study; only when diagnoses are truly robust can we be anything other than circumspect. Furthermore, in multi-site studies, varying levels of skill in diagnosing dementia or service provision may influence accuracy of diagnosis at different sites which again could influence the observed associations. Most recently, investigators using CPRD found a more consistent association between air pollution and Alzheimer’s disease than vascular dementia.[9] However, a primary care diagnosis of a dementia subtype based on Read codes will not be as robust as a clinical diagnosis based on multidisciplinary assessment. Indeed, there is evidence from an imaging study by the AirPollBrain group at the University of Southern California that $PM_{2.5}$ was associated with changes in white matter volume but not volume of the hippocampus which is characteristically affected by Alzheimer’s disease pathology.[36] On the other hand, further research from the same group identified that $\epsilon 4/\epsilon 4$ homozygotes for *APOE* were particularly susceptible to the effects of air pollution and complementary research reported in the same article identified selective atrophy of hippocampal CA1 neurites, suggesting that a differential effect on Alzheimer’s disease pathology might, after all, be plausible.[37,38]

CONCLUSION

There is now ample evidence for an association between exposure to air pollution and poorer brain health, measured a variety of ways. It would seem unnecessary to further accumulate studies reporting the same findings without attempting to overcome some of the limitations of the extant literature. Thus, we suggest three important questions which require answers in order to define the research agenda in this field. In order to examine life course associations we need high quality longitudinal cohort studies with large sample size (conferring statistical power) which have detailed residential histories as well as information on employment and mobility and important confounders/mediators. In order to investigate which pollutants (or combinations of pollutants) are most harmful we need good information on emission sources and measurement data to allow accurate historical exposure modelling. And finally, to clarify which aspect of brain health and/or type of dementia is most affected we need either repeated measures of cognition or other measures of brain health, and/or identification of clinical cases of dementia (with accurate subtyping) using high quality diagnostic processes and accepted criteria. If we can find the necessary data to answer these three questions we will move closer to being able to conclude that the observed associations are causal and be in a position to plan effective preventive strategies.

ACKNOWLEDGEMENTS

Acknowledgments: The following people attended the consensus workshop held at the Manchester Environment Research Institute (University of Manchester) on 14th September 2018: Carmel Armon, Ed Carnell, JC Chen, Ruoling Chen, John Cherrie, Angela Clifford, Hugh Coe, Eirini Dimakakou, Chloe Fawns-Ritchie, Giulia Grande, Sabina Hawthornthwaite, James Jie Tang, Lewis Killin, Sarah Lindley, Miranda Loh, Gordon McFiggans, Ian Mudway, Neil Pendleton, Radka Prichystalova, Stefan Reis, Debora Rizzito, Tom Russ, Sam Tomlinson, Martie van Tongeren, Massimo Vieno, Stephanie von Hinke Kessler Scholder, Yuhui Wan, and Yuyou Yao.

Financial support: All three authors were until recently supported by a grant from the NERC-MRC-CSO Improving Health with Environmental Data call (NE/P010849/1).

TCR is employed by NHS Lothian and is a member of both the Alzheimer Scotland Dementia Research Centre funded by Alzheimer Scotland and the University of Edinburgh Centre for Cognitive Ageing & Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (G0700704/ 84698). Funding from the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, and Medical Research Council is gratefully acknowledged for the latter. SR's work is supported by the Natural Environment Research Council award number NE/R016429/1 as part of the UK-SCAPE programme delivering UK National Capability.

Conflicts of Interest: None

KEY POINTS

- The research agenda for air pollution and brain health must now be agreed.
- When in the life course air pollution has most impact is a fundamental question.
- Which pollutant – or group of pollutants – are detrimental to brain health is also unclear.
- Whether there is more of an effect on one subtype of dementia than others is also unknown.

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Table. Scientific articles on air pollution and brain health published so far in 2018

	Setting	N	Design	Duration	When in life course?	Exposure modelling	Outcome
Andersson <i>et al.</i> [7]	Betula	1721	Longitudinal	15 years	>54 years at baseline	LUR based on annual average of NO _x measurements. Modelled road traffic noise. Based on residential address at baseline.	Clinical diagnosis of dementia, with subtyping
Bishop <i>et al.</i> [8]	Medicare	6.9 million	Longitudinal	15 years	>64 years at baseline	Annual PM _{2.5} weighted average based on the distance between each person's location and every monitors each year. Based on annual residential ZIP+4 code (centroid).	Dementia NOS, as recorded in Medicare
Carey <i>et al.</i> [9]	CPRD	130,978	Longitudinal	14 years	50-79 years at baseline	Dispersion models of NO ₂ , PM _{2.5} , and O ₃ as well as traffic intensity, distance from major road, and night-time noise (2004 only). Based on postcode address centroid. 2005 NO ₂ and 2007 PM ₁₀ estimates used LUR for Western Europe with satellite monitoring. 2010 PM _{2.5} & 2.5-10 and NO _x estimates used ESCAPE data which are only valid within 400km of London. Based on residential address.	Primary care record of dementia, with subtyping
Cullen <i>et al.</i> [10]	UK Biobank	86,759	Cross-sectional/ Longitudinal	2.8 years	40-69 years at baseline	ESCAPE protocol. Annual average NO ₂ and PM based on monitoring in study area in 2008-9 (three times) and LUR, traffic/ports/industry, and population density. Previous years' data were derived by comparing with average annual monitored concentrations in each year.	UK Biobank cognitive test battery (two measurements)
Hüls <i>et al.</i> [11]	SALIA cohort	587	Longitudinal	19 years	55 years at baseline	Annual mean PM _{2.5} concentrations modelled for 1990, 2000, and 2010. Data included road networks, vehicle types, residential heating. Based on geocoded home address. Monthly exposure to PM _{2.5} & 10 estimated from modelling (different models used for 1988-98 and 1999-2007). Based on residential address.	Visuo-construction performance from CERAD battery (two measurements)
Oudin <i>et al.</i> [12]	Betula	1806	Longitudinal	>25 years	35-80 years at baseline	Daily concentrations of BC, nickel, sulphur, silicon, and PM _{2.5} averaged to give one and two year average exposures. Based on measurement at a single monitor.	Clinical diagnosis of dementia, with subtyping
Power <i>et al.</i> [13]	ARIC	1753	Cross-sectional (but long-term exposure)	-	Participants in mid-50s at baseline	Air Pollution Index based on daily readings for SO ₂ , NO ₂ , and PM ₁₀ . Weather also included in models. Based on "exact information about the geographic location."	3T brain MRI
Wurth <i>et al.</i> [14]	BPRHS	1255	Longitudinal	2 years (median)	45-75 years at baseline		Cognitive function in five domains (two measurements)
Zhang <i>et al.</i> [15]	CFPS	31,955	Cross-sectional	-	Aged over 10 at baseline		Mathematics and word-recognition questions

ARIC: Atherosclerosis Risk in Communities; BC: black carbon; BPRHS: Boston Puerto Rican Health Study; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CFPS: China Family Panel Study; CPRD: Clinical Practice Research Database ; ESCAPE: European Study of Cohorts for Air Pollution Effects; LUR: Land Use Regression; NOS: Not Otherwise Specified ; SALIA: Study on the influence of Air pollution on Lung function, Inflammation, and Ageing