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SYSTEMATIC REVIEW

Is air pollution associated with increased risk of cognitive decline? A systematic review

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Abstract

Introduction: exposure to air pollution has been shown to increase risk of inflammatory processes and risk of cardiovascular mortality. Such exposure may therefore also be a risk factor for cognitive impairment/dementia.
Method: a systematic review of the literature was conducted with databases searched using keywords for air pollution, cognitive decline and dementia. All identified abstracts and potentially relevant articles were double read. For those papers meeting the inclusion criteria, summary tables were prepared and papers quality assessed.
Results: from 1,551 abstracts identified, 10 articles were retrieved of which two were rejected. Of the eight remaining six reported prevalent cognitive assessment with historical pollution exposure and two incident cognitive decline, also with historical pollution exposure. In general, an association was reported between exposure and poorer prevalent measures of cognitive function. Data were mixed for incident cognitive decline with one study finding an association and the other not. Reports were limited by a lack of detailed reporting, use of proxy measures of pollution exposure and a lack of clarity regarding cognitive testing methodology and analysis.
Conclusion: this systematic review highlights that there is some evidence of a potential association between air pollution and subsequent cognitive decline. Further work is clearly required and longitudinal analysis of ongoing cohort studies or new research would add much needed clarity to this area.

Keywords: *dementia, cognitive decline, air pollution, particulate matter, black carbon, older people, systematic review*

Background

Modification of risk factors currently offers the best hope of reducing the global burden of dementia. In addition to lifestyle and health-related modifiable risk factors, air pollution has recently emerged as a further risk factor worthy of consideration, due to its associations with adverse cardiovascular and systemic inflammatory effects [1].

In recent years, there has been an increasing interest in the adverse effects of air pollution, particularly in regard to cardiovascular disease, with a 2013 systematic review reporting an association between exposure to airborne fine particulate matter and an increased risk of cardiovascular and all-cause mortality [2]. An analysis of 11 European cohorts, published in 2014, also found an association between particulate matter and incident coronary events [3]. In addition to particulate matter (fine particulate matter <2.5 μm ($PM_{2.5}$), UltraFine Particulate Matter <0.1 μm (UFPM) and larger particulates), exposures to gaseous pollutants, such as ozone and nitrogen dioxide, have also been associated with increased cardiovascular and cardiopulmonary mortality [4–6], though the evidence base is less robust than for air borne particulates (reviewed in Review of evidence on health aspects of air pollution—REVIHAAP Project, WHO, 2013) [http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2013/review-of-evidence-on-health-aspects-of-air-pollution-revihaap-project-final-technical-report (11 July 2015, date last accessed)]. It has been hypothesised that inhaled particulates may reach the brain, either via the lungs or directly, via the olfactory bulb [7–11]. Potential mechanisms by which particles or material desorbed from the particle surface could negatively impact on the brain include induction of an inflammatory response, microglial activation, direct production of reactive oxygen species (ROS), as well as by promoting increased production and deposition of Aβ peptides [7–11]. Animal studies have demonstrated ultrafine particle penetration into the olfactory bulb, the frontal cortical and subcortical areas of the brain [8, 9].

In addition, inhalation of ambient air pollution [7, 12, 13] and diesel exhaust has been shown to elicit inflammatory changes within the brain [14, 15] consistent with the stated hypothesis above. The association between exposure to urban air pollution with particulate deposition and inflammation within the brain has also been shown in autopsy samples obtained from children and young adults living in Mexico City [16, 17]. Given the epidemiological links between cognitive impairment/dementia and inflammation and oxidative damage, this implies a potential link between exposure to air pollution and an increased risk of cognitive decline or dementia [18]. Furthermore, there is evidence linking higher cardiovascular risk to an increased risk of cognitive impairment/dementia [19–21], and here too air pollution may play a role.

Given the growth in the 60 plus population worldwide, allied to the increasing proportion of the world's population living in polluted urban environments [22], particularly within developing countries, it is timely to investigate whether there is a link between air pollutant exposure and cognitive decline. This aim is addressed in this systematic review, focusing on the link between air pollution exposure and dementia and/or cognitive function and decline in adults.

Method

Search strategy

The search strategy was based on that used for previous systematic reviews [2, 23] and developed in discussion with experts in relevant fields.

The databases MEDLINE, Embase and *PsychINFO* were searched from inception to the 1 November 2013. Reference lists of all papers identified were screened for other published papers. In addition, searches were carried out for any ongoing relevant trials using the following sources:

- Cochrane Central Register of Controlled Trials (Central) from 1980 to 1 November 2013
- ISRCTN Register—trials registered with a unique identifier
- ClinicalTrials.gov (http://www.ClinicalTrials.gov)

Further details of the methods and search strategies are given in Supplementary data, File A, available in *Age and Ageing* online.

The protocol for this review is registered with Prospero: the International prospective register of systematic reviews CRD42014007582. No funding was received for this work.

Results

Searches identified 2,883 records. One thousand five hundred and fifty-one remained after duplicates were removed, and these were assessed. Ten full-text papers were selected and examined [24–33]. Two papers were excluded at the full-text stage: one because it reported only blood lead levels [33] and the other because it was a review paper [30]. Our initial aim was to focus more closely on studies with a measure of incident cognitive decline/dementia to most robustly examine any causality; however, we identified several articles that only reported on prior/historical exposure to air pollution and subsequent cognitive assessment, that is measuring prevalent cognitive decline/function but with no measure of cognitive change. Six articles reported on historical exposure to air pollution and association with prevalent cognitive function [26–29, 31, 32]. These were from the Veterans Affairs Normative Aging Study (NAS) [26], the Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston (MOBILIZE Boston) study [29], the 3rd National Health and Nutrition Examination Survey (NHANESIII) [32] and Study on the influence of air pollution and lung function, inflammation and Aging (SALIA) [28]. Two articles reported on the third and third and fourth waves, respectively, of the Chinese Longitudinal Health and Longevity Survey (CLHLS) [27, 31]. See Supplementary data, Figure S1 and Table S1 (File B), available in *Age and Ageing* online for details.

The two remaining papers each reported change in cognitive function/incident cognitive decline and were also from well-established longitudinal studies: the Nurses' Health Study [24] and the Reasons for Geographic and Racial Differences in Stroke study (REGARDS) [25]. See Supplementary data, Table S2 (File B), available in *Age and Ageing* online for details.

Study characteristics

Prevalence studies

All studies were observational cohort studies with analysis restricted to those for whom both cognitive testing and historical (prior to cognitive testing) air pollution data were available. For the SALIA study, the sample was further restricted to those who had not moved address in the preceding 20 years [28], and for the MOBILIZE Boston study, participants had to live within 5 miles of the study clinic be able to walk 20 feet without assistance and have a Mini-Mental State Exam (MMSE) score >17 [29].

Three of the studies reporting prevalent cognitive outcomes recruited from the USA [26, 29, 32]: one from across the States [32] and the other two from the Boston area [26, 29]. The SALIA study recruited from the Ruhr region of Germany [28] and the CLHLS from multiple Chinese Provinces [27, 31].

In general, participant mean age was in late mid/late life. The NHANES III cohort were the youngest at baseline with a mean age of 37.4 [standard deviation (SD) 10.9] [32] while the MOBILIZE Boston study recruited only those aged ≥65 years and reported a mean age of 78.1 (SD 5.4) [29] similar to that seen in the NAS [26] and SALIA [28] studies at 71.0 (SD 7.0) and 74.1 (SD 2.6), respectively. Mean age of those in the CLHLS was older at 86.3 (11.4) [27, 31]. NHANES III, the two analytical samples from the CLHLS and the MOBILIZE Boston study recruited men and women with the percentage female ranging from 50 [32], 56.9 [27], 57.3 [31] to 63.9 [29]. The SALIA study recruited only women to

exclude bias from occupational exposure [28] and the NAS recruited only men [26].

Incidence studies

The Nurses' Health Study included only female registered nurses recruited from 11 US states [24]. Results relate to those aged 70 or over in 1995–2000 and with no history of stroke at that point. Average age at baseline for the sample overall can be roughly estimated as ~74, based on the mean age per quintile as published. The REGARDS study recruited both men and women via random mailings within region, sex and race strata [25]. Average age at baseline for the sample can be estimated as ~64 years based on the mean age per quartile as published.

Assessment of cognitive function

Prevalence studies

Assessment of cognitive function was via standard widely used tests. The NAS and CLHLS (third and fourth waves) both used the MMSE screening test, where higher scores indicate better performance, with the former opting for a cut-off of <26 indicating cognitive impairment [26] and the latter reporting results for a cut-off of <18 [31]. Analysis of data from the third wave of data collection in the CLHLS reported outcomes per point increase in the MMSE, where MMSE scoring was such that higher MMSE score was associated with poorer cognitive performance [27].

NHANES III used a small neuropsychological battery via the Neurobehavioral Evaluation System including simple reaction time, serial digit learning and digit symbol substitution tests [32]. The MOBILIZE Boston study in contrast used a wider set of neuropsychological tests including the MMSE (cut point <26) the Hopkins Verbal Learning Test Revised (HVLT-R), trail making, category and letter fluency and a clock drawing test [29]. The SALIA study reported the most detailed testing using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery alongside a Stroop test [28]. They were also unique in reporting the number of individuals completing tests and used in the analyses. In general, detailed data on the number of participants completing assessments and the number of times they completed them were omitted. In two instances, at least it seems likely that participants only completed one set of tests from which cognitive function was assessed [27, 31].

Incidence studies

Both longitudinal studies examined change in cognitive function and used standard assessments of cognitive function, although neither reported incident dementia cases. The Nurses' Health Study carried out cognitive assessments at a mean of 1.9 (SD 0.4) and 4.3 (SD 0.8) years after baseline. The investigators used the Telephone Interview for Cognitive Status (TICS) at the first assessment of cognitive function and added five more cognitive tests as high participation in cognitive testing became apparent. As a consequence, slightly differing numbers were available for analyses at follow-up. Cognitive change was assessed via a *Z*-score composite measure of cognition [24]. The REGARDS study also used a telephone assessment, the Six Item Screening (SIS) test. Testing was annual. Participants were required to score ≥5/6 at baseline to be included in these analyses, and cognitive impairment was defined on the basis of a subsequent score of ≤4/6 [25].

Assessment of exposure to air pollution—see Supplementary data, File C, available in *Age and Ageing* online.

Air pollution and cognitive function

Prevalence studies

In general, studies reported mixed results. Analytical models varied, but all included versions of logistic and linear regression with adjustment for a range of relevant covariates. Some studies reported use of measures to take account of multiple testing and repeat measures [26] or to take account of clustering [27, 31].

In NAS, a doubling of BC exposure over the previous year was associated with an increased risk of an MMSE <26 in a Boston population [odds ratio (OR) 1.3 95% confidence intervals (CI) 1.1–1.6] [26]. A point increase in API in China was associated with an increased risk of MMSE <18 (OR 1.09 95% CI 1.01–1.18) and a worsening of MMSE by 0.52 of an MMSE point (95% CI 0.27–0.75) [27, 31].

In the MOBILIZE Boston study, there was a suggestion of an association between living nearer to a busy road (per 851.2 m) and having an MMSE <26 (OR 1.07 95% CI 0.84–1.36), but only in those with a College education [OR 1.54 (1.10–2.17)] or aged ≤77 years [OR 1.34 (1.01–1.76)]. For BC (for a 0.11 $\mu g/m^3$ greater exposure during the preceding year), the OR for an MMSE <26 was 1.15 (95% CI 0.99–1.34); results by age and College education were not reported [29]. Individual cognitive test scores (HVLT-R, category and letter fluency and clock drawing) showed no pattern of association with BC but were worse in individuals living nearer to busy roads [29]. Traffic and PM_{10} exposure over the preceding 5 years were associated with worse cognitive performance as assessed by the CERAD battery and Stroop test in the SALIA study [28]. There was also the suggestion of a dose–response relationship, such that the closer the residence was to the road the lower the cognitive performance. In NHANES III, greater exposure to PM_{10} (per 10 $\mu g/m^3$) or ozone (per 10 ppb) over the preceding year was associated with poorer cognitive performance on all tests except simple reaction time [32].

Incidence studies

Both longitudinal studies reported some association between exposure to air pollution particulate matter and worsening cognition. The Nurses' Health Study reports a 2-year change in global cognitive score per 10 $\mu m/m^3$ increase over time (preceding month, 1, 2 and 5 years) and per quintile of exposure to $PM_{2.5–10}$ and $PM_{2.5}$ [quintiles of exposure were

calculated based on exposure from 1988 to the month preceding cognitive assessment (1995–2001)]. There was a significant relationship for the highest quintile of $PM_{2.5–10}$ and worsening of cognitive score. This finding persisted when levels of exposure over time were examined with significant relationships for all time periods except the preceding month. Similar patterns were seen for quintiles of $PM_{2.5}$ and for duration of exposure although, for the latter, only exposure since 1988 was significantly associated with worsening cognition [24]. The REGARDS study reports results by 10 $\mu m/m^3$ increase in $PM_{2.5}$. Logistic regression results for incident cognitive impairment were an OR 1.26 (0.97–1.64); however, this was attenuated after multiple adjustment to 0.98 (95% CI 0.72–1.34) $n = 20{,}150$. Further sensitivity analysis in subjects with >12-month exposure data resulted in an OR 1.02 (0.61–1.70), attenuated to 0.71 (0.38:1.32) after adjustment $n = 18{,}180$ [25].

Quality assessment

Prevalence studies

In general, studies reported clearly focused questions, although air pollution and cognitive function were not always the primary focus or analysis (see Supplementary data, Table S3 (File D), available in *Age and Ageing* online). Reporting of methodology was mixed and sometimes insufficient to fully understand methods. Exposure data were gathered prior to cognitive testing, but duration, type, classification and level of exposure to pollutant varied widely. Data on timing and use of cognitive testing were not always clear, and although the stated aim of several studies was to include a representative population, the need to have cognitive and air pollution data and other restrictions made this difficult. Data on those who were excluded are not presented. Finally although adjustment has in general been carried out for a wide variety of potential confounding factors, without a measure of cognitive change, causality cannot be explored.

Incidence studies

Of the two longitudinal studies that reported on cognitive change, both studies asked clearly focused questions and used appropriate cohort study methods. While the quantification of exposure to air pollution is difficult to assess accurately and the resolution of the model used in the Nurse's Health Study was unclear, both studies used standard data and adjusted for multiple factors likely to influence results. Both studies also used standard, albeit brief, cognitive assessments. The REGARDS study aimed to recruit within sex and race strata, although the representativeness of their final population is not reported. The Nurses' Health Study sought to recruit female registered nurses and is therefore representative of a selected population.

Discussion

Although data from studies of prevalent cognitive function outcomes show some association between a variety of pollutants and poorer cognitive function, data from the two studies looking at incident change are mixed. Alongside the existence of plausible physiological mechanisms to underlie this relationship [10–21], this implies a possible relationship between greater exposure to air pollution, at least to particulate matter, and an increased risk of decline in cognitive function.

It is difficult to infer further given the quality of evidence available. Although the majority of studies were well-known established population studies following participants over time, the majority did not measure incident decline. The measurement of outcomes was particularly limited with no studies reporting incident dementia and preferring screening tests rather than more sensitive neuropsychological test batteries or formal assessment for dementia. Studies also tended to use differing assessment of both exposure and outcome. This applies even when using similar measures. For example, measurement of exposure was reported by distance from a roadway of ≤50 m, 50–100 m, >100 m [28] or per 851.2 m [29]. Cognitive impairment as assessed by MMSE score was categorised as an MMSE score of <18 [31], <26 [26, 29] or per point increase, but where higher MMSE score was associated with higher risk [27] (i.e. as opposed to the usual scoring where lower score indicates worse cognitive function). In general, most studies used a single mean or composite score measure of exposure representing less than a 5-year period, and this may mean that any impact may be too subtle to be evaluated without multiple testing with detailed neuropsychological tests. Furthermore, the use of existing monitoring station data or surrogate measures based on distance to roads to examine exposure to pollutants may not be a sufficiently sophisticated measure of individual exposure. Populations also vary, although most were older adults and therefore at some risk of cognitive decline. None of the articles provided clear evidence to show that they had recruited or analysed a representative population; some were clearly not representative.

Strengths of this review include the breadth of the literature searched and the identification of studies that report both prevalent and incident cognitive outcomes to provide a detailed overview of the topic. Limitations include the possibility of missing evidence from the grey literature or non-English language publications. Furthermore, it could be said to be limited by the fact that only two incident outcome studies could be identified; however, reviews are an opportunity to take stock of the evidence base irrespective of maturity. In this sense, our findings should inform future practice, priorities and configuration of research in this area.

In spite of the limited data available with regard to cognitive function, societal awareness of the negative impact of air pollution on cardiovascular outcomes continues to rise [http://www.independent.co.uk/life-style/health-and-families/health-news/air-pollution-reduces-life-expectancy-by-six-months-for-every-briton-9251260.html (11 July 2015, date last accessed), http://www.bbc.co.uk/news/health-26730178 (11 July 2015, date last accessed)]. Dementia and cognitive decline, unlike cardiovascular disease, have no current treatment options and could be considered an even greater risk to the population if this link is shown to be robust. The need to understand any

potential relationship with cognitive decline, the mechanisms and aetiology of cognitive outcomes becomes increasingly important as the population ages. Future research must include assessment of incident change in cognitive function, representative samples from the populations at risk, including adults in mid and late life, and taking account of occupational exposures, as well as indoor pollutant sources, with better overall assessment of individual exposures to air pollutants. This includes a more detailed understanding of the sources of air pollution, the composition of ambient PM and how these change over time, for example exposure to use of home fires, coal fired power stations, vehicular emissions, leaded petrol, etc: all may vary over time and by region. These exposures, alongside changes in individual exposure from an increasingly mobile population, need to be taken into account.

Future studies, or further analyses of existing cohorts, should report sensitive measures of cognitive change and assessment of incident dementia following exposure to a range of air pollutants over several years duration and fully report on details of the participating populations at each assessment/analysis ensuring any loss to follow-up due to unmeasured cognitive impairment is minimised. This would substantially extend the evidence base. From such studies, potential interventions to protect cognitive function may therefore be identified and have a positive impact on the cognitive health of a globally ageing population.

Key points

- Air pollution has been associated with adverse cardiovascular and systemic inflammatory effects.
- Inflammatory processes and increased cardiovascular risk have been associated with increased risk of cognitive decline or dementia.
- There is biological plausibility for a link between air pollution and cognitive decline or dementia.
- This systematic review of available evidence found seven studies: five assessing prevalent cognitive function outcomes and providing some evidence for an association between increased exposure to pollutants and worse cognitive function; two examining incident cognitive decline following exposure to air pollution one of which reported an association.
- Further evidence is needed from new or ongoing longitudinal studies to gain a greater understanding of air pollution as a potential risk factor for cognitive decline/dementia.

Conflicts of interest

None declared.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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