Review Article

HEALTHY AGING RESEARCH

OPEN

Atmospheric pollution and cognitive decaying in the elderly: A review

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The narrative review focuses on a problem, atmospheric pollution and the elderly mental decay, detailing literature data and evidence on the double aspect of the potential harm derived from outside air and indoor air. Pertinent studies have been reviewed starting from the original works, adding comments to the published outcomes and highlighting considerations regarding the possible relationship between atmospheric pollution and cognitive decay. After reviewing the first laboratory works and the first experimental evidences on the penetration and diffusion of pollutants in the human organism, general epidemiological works have been taken in consideration as well. More recently a few neurophysiological tests have been used to assess pollution effects on the elderly, with the aim of performing better structured studies in terms of methodology and outcomes.

Epidemiology works specifically addressed to the mental impairment of the aged population have been analysed and commented in this review

A few pertinent reviews on these topics have been included as well, documenting the increasing interest in this topic in the latest years. Furthermore some recent contrasting literature, based on hormesis principles, which questions the negative impact of air pollutants, especially at low dose, has been included and discussed.

Notwithstanding the relative growing body of literature on pollution in the elderly, a long and complex path is expected before reaching evidence-based literature data and recommendations about the possible negative influence of pollutants in the cognitive decay and more in general in the pathologic senescence.

Keywords: Air pollution, Aging, Cognitive decay, Hormesis

Outdoor Atmosphere Pollution and Elderly

Epidemiological studies on the effects of atmospheric pollution on the elderly population focus on the commonly monitored air pollutants (above all SO_2, CO, NO_2, O_3 and particulate matter (PM) as primary and secondary particles), but literature data often estimate, according to the case, different pollutants "penetration" on the outcomes [1,2].

An emerging problem is represented by the unregulated pollution of ultrafine particles (UFP), i.e. those with a diameter <100 nm. UFP are ubiquitous and could have higher adverse effects on human health in comparison to their larger counterparts (PM), although long-term exposure studies are warranted before drawing sound conclusions.

Furthermore, the toxic relevance of several so-called transition metals (such as iron, vanadium, nickel, copper and zinc) is to be clarified, due to the specific PM-related components which are capable of triggering oxidative stress and inflammation and the relative biological damage. Even only indicative data of each of these substances on the health of the elderly are not traceable in the literature [2].

In general, for the particulate pollution there is no definite threshold concentration, under which there is no higher incidence of mortality due to cardiovascular and respiratory causes. In other words, the harmful effects on health from air pollution may also exist at low doses of pollutants, and this is due to the interference of other factors, including seasonal climatic variations and temperature [3].

The fact remains, however, that pollutants are a probable public health problem for the elderly even in concentrations below the normally tolerated standards [4].

Air Indoor Pollution and Elderly

Generally it is written in the prologue of many works-people spend 80-90% of their time indoors. The elderly (and especially the very elderly), due to the reduced activity and to the increased disability and loss of physical autonomy or just for lack of stimulation, spend even more time at home. The prolonged time spent at home potentially exposes the very elderly and disabled patients to indoor air pollutants, with higher doses of most noxious substances in comparison to the rest of the population [5-8].

Hence, independently from the kind of indoor pollutant (chemical, physical, biological agents derived from in-house sources), also the presence of low-dose irritating/harmful substances may have a significant biological impact on the aged population.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Healthy Aging Research (2018) 7:11

Received 14 October 2018; Accepted 24 October 2018

Published online 01 November 2018

DOI: 10.12715/har.2018.7.11

Atmospheric Pollution and Cognitive Decaying in the Elderly

Numerous human studies have shown the detrimental effects of exposure to indoor and outdoor air pollutants on the cardiovascular system [2,9,10], and have partly explained the possible pathogenic mechanisms, connected variously to systemic inflammation, hypertension, heart rate variability, endothelial alterations, anatomic-functional alterations of the autonomic nervous system, changes in blood coagulation. An overall association between increased mortality and short-term elevations in PM10 and PM2.5, approximately equal to a 0.4% to 1.0% increase in cardiovascular death, has been reported [2].

Equally numerous, and in some respects conclusive, are the studies on the respiratory system, which are classified according to the type of pollutant, the severity of the disease, exposure times, and which are variously correlated with the comorbidity and the pre-existing respiratory diseases [7,11].

On the other hand, the potential relationship between exposure to environmental toxicities and cognitive abilities in the elderly has, to date, received little consideration with respect to cardiopulmonary diseases and non-environmental risk factors; yet many air pollutants we know are neurotoxic and many environmental exposures would be modifiable [12].

An extensive literature search pertinent to air pollution and cognitive decaying has been performed through different biomedical literature search engines. More specifically pubmed/medline, google scholar, embase were reviewed using the combination of the terms air pollution, cognitive decline, cognitive function impairment, mental impairment/decline, hormesis. As this article was not intended as a systematic review, after screening the resulting abstracts, the full texts of the most relevant articles have been collected, reviewed and discussed in the present text.

Our main aim was to highlight the main concepts and evidences about the possible link between air pollution and cognitive function impairment.

In the nineties the first *in vivo* works on the neurotoxic effects of atmospheric pollutants began [13,14], together with the reports on the importance of the nose-brain barrier (clearance pathways) as a possible direct access to the central nervous system [15-17]; UFP (size <100 nm) may access brain even under conditions of anatomical integrity of the mucosal barriers mentioned above [18].

A direct route of transport, alternative to the hematic one, was demonstrated, as well as the possibility that the epithelial enzymes of phase 1 of the olfactory mucosa realize biotransformation of atmospheric pollutants into products that are more easily penetrating or toxic [19,20].

In fact literature data on humans have shown that PM reaches the brain both directly through olfactory transport and through the blood-brain barrier once circulating in the blood stream. The resulting neuroinflammation involves microglial cells and white matter specifically [21,22].

Some more literature data were collected through dog brain examination and numerous morphological equivalents of human brain alterations secondary to aging and/or senile dementia were highlighted. In view of these findings dog has been considered an excellent animal model of brain aging and dementia following both the laboratory data and the anatomical-pathological findings of their brain [23].

Thanks to the outcomes of those experimental studies Calderòn and Collaborators began to study the early and progressive alterations in the respiratory and olfactory nasal mucosa, in the olfactory bulb, in the cortical and subcortical structures of the brain in healthy dogs exposed daily to high levels of polluting ambient air; furthermore these findings have been compared with the ones derived from dogs living in places with low levels of pollution [24,25]. These studies confirmed that the breaking of the nasal respiratory and olfactory barriers may play a relevant role for the polluting effects on the brain in the same way as the inflammation of the respiratory tract, the production of mediators of inflammation, the diffusion in the systemic circulation of PM.

Extrapolating animal data, the same authors intended to expand and translate their study to young adults [26], assessing the pertinent data in subjects living in places with high atmospheric pollution. The outcomes of their study on humans highlighted increased levels of inflammatory mediators, deposition of β-amyloid and markers of oxidative damage to DNA, together with the breaking of the hemato-encephalic barrier. The conclusions of Calderon and Coll. were that exposure to air pollution causes neuro-inflammation, alteration of the immune response in the brain, accumulation of A42 and a-synuclein in young subjects; finally these study evidenced how pollution should be considered a risk factor for Alzheimer's diseases (and Parkinson's) especially in the carriers of APOE 4, i.e. in the population with higher risk of developing Alzheimer's disease.

In 2008 a first consistent relationship between prolonged exposure to atmospheric pollutants and decay of cognitive functions in humans was highlighted [27]; in fact a prospective study examined the relationship between carbon black (carbon marker, marker for traffic particles) and cognitive areas of children (mean age 9.7 years) including memory, learning ability and intelligence. The authors found a decrease in the vocabulary (-2.2 %), matrices (-4.0%) and composite intelligence quotient (-3.4%) and a similar decrease on the visual subscale and general index of the memory and learning assessment.

The authors were aware of the presence of some limitations proper of the experimentation, among others the high number of lost-to-follow-up subjects throughout the study and the non-analysis of socio-economic factors; equally the possible presence of some confounding factors, such as traffic noise, which can notoriously interfere with children's cognitive abilities, were highlighted. Nevertheless they considered their results very suggestive to continue to explore the association of atmospheric pollutants and cognitive decay.

A subsequent study [28] on the neuro-behavioural adverse effects associated with long-term exposure to environmental PM and ozone in adults (aged 37.5 +/- 10.9 years) followed.

The interest in the cognitive decline from atmospheric pollution of the elderly population was highlighted in two different articles [29,30], but the first epidemiological study specifically directed towards this problem was published in 2009 [31]. In this case a cohort of 399 women, aged 68-79 years, who lived for more than 20 years in the same residential address, were investigated as to the possible pollution-mental health relationship. In these subjects the cognitive abilities were correlated with two markers of atmospheric pollution, PM10 and the home distance from a main road. The outcomes of three validated neuropsychological tests for mild cognitive impairment showed a statistically significant correlation for the second parameter (distance from main road), whereas a lower association was found with PM10 exposure.

Other authors [32] have shown poorer performances on tests regarding cognition, psychomotricity, language and executive functioning in their cohort of community-dwelling seniors who were living in proximity of major roadways. More specifically living in

proximity to trafficked roadways was associated with increased risk of having a mental score <26 among college-educated participants and in participants aged ≤77 years (OR: 1.34), but not among older participants or those with less formal education. The increase in residential black carbon levels (0.11 μg/m^3) was associated with a higher risk of having a <26 mental score as well. This association in MOBILIZE study may not indicate causality, but the correlation was high, especially for those living at less than 100 mt from the main roadways, which seems to reinforce the negative impact of traffic pollution on cognition in the elderly.

In 2011 the carbon black-cognitive decay relationship was studied in elderly men (mean age 71 ± 7) followed for 11 years [12]. The conclusions of the authors were that air pollution from traffic can have a negative effect on cognitive abilities. Furthermore the final negative effect was greater in smokers or in overweight and obese subjects, i.e. in those "pro-inflammatory" conditions. In 2016 the conclusions of a review from the same authors on air pollution as potential contributor to cognitive function decline and dementia [33] represent a reasonable piece of advice: "we identified several common challenges. First, most studies of incident dementia identified cases from health system records. As dementia in the community is underdiagnosed, this could generate either non-differential or differential misclassification bias. Second, almost all studies used recent air pollution exposures as surrogate measures of long-term exposure. Third, comparing the magnitude of associations may not clearly pinpoint which, if any, pollutants are the probable causal agents. Future studies with improved design, analysis and reporting would fill key evidentiary gaps and provide a solid foundation for recommendations and possible interventions."

In 2012 a population-based study on 19409 female nurses aged more than 70 years proved that higher levels of long-term exposure to PM resulted in a significantly faster cognitive decline. The global mental score at two years was 0.020 standard units worse per 10 μg/m^3 increment in PM2.5-10 exposure. The negative effect of a 10 μg/m^3 concentration of long-term PM exposure was considered equivalent to a 2 years older cognition decay process [34].

Of interest, a recent epidemiologic study [35] focused on large city (London) particulate air pollution: in presence of PM 2.5 at higher concentration (1.1 μg/m^3) a more significant association to the worsening of memory and reasoning score were highlighted, but not on verbal fluency. No relevant differences were found between city (traffic-related) and outer city participants, which did not support the traffic-related pollution higher influence on cognitive function.

The pollution-cognitivity relationship, quite well studied in adult-elderly subjects, has been object in recent years of several studies which included other potential polluting substances (O_3, NO_2). Cognitive deficits have been investigated in terms of relationship to specific cognitive domains [36], while scientific data have highlighted the possibility that subclinical atherosclerosis has a mediating function in the pathogenesis of cognitive decay.

In recent years at least four reviews have been published on the subject [37-40]; one of these articles [41] specifically focused on the possible evidence about the relationship between atmospheric pollution and dementia.

Ailshire and Crimmins examined the cross-sectional association between residential concentrations of PM 2.5 and cognitive function in US adults aged more than 50 years. Older adults living in areas with higher PM 2.5 concentrations had worse cognitive (memory namely) function (β=−0.26,95%confidenceinterval:−0.47,−0.05), regardless of social and economic factors [41].

In 2017 one study focused on the PM air pollution and brain aging of older women and of mice. A greater negative impact was found in individuals carrying Apolipoprotein E ε4 allele, which is a gene promoter of Alzheimer Disease or similar dementias. The main encountered neurological findings in the experimental mouse study were an increased cerebral β-amiloid production and selective changes in hippocampal neurons and glutamate receptors [42].

In a recent review by Oudin [43] the correlation between air pollution and cognitive impairment/dementia was explored and several issues were raised with regards to: which subjects are more susceptible, which particles are more harmful, the role of the other possible confounding risk factors (especially for dementia). Due to the importance of cognitive decaying, dementia, Alzheimer disease in our society, the author ultimately underlines the need of intervene on the modifiable risk factors related to pollution.

Interestingly a few contrasting evidences and speculations have been published on the basis of the hormesis concept, which has increasingly spread also in the pollution-related medical literature. Hormesis is a biochemical phenomenon which invariably happens in nature where a great number of potentially negative chemical/physical stressors may induce a beneficial effect on vital organisms [44]. Hormesis has been defined [45] "a process in which exposure to a low dose of a chemical agent or environmental factor that is damaging at higher doses induces an adaptive beneficial effect on the cell or organism'.

The intermittent exposure at low/mild doses of a specific harmful or potentially lethal agent may induce an adaptive response with overcompensation, which is protective towards further higher exposure to the same stressors [44-46]. This form of resilience, of non-linear reaction, has led a few authors to re-assess literature on pollution-related health issues.

Enstrom [47], specifically, analysed the results of a few past studies performed in USA on 292277 and 212370 participants, in which mortality follow-up was correlated to inhalation of PM2.5 measurements. The relative risk of death from all causes and 95% confidence interval adjusted for age, sex, race, education, and smoking status was 1.023-1.025 in the two main studies for a 10 mg/m^3 increase in PM2.5 .The fully adjusted relative risk was basically null in the examined USA areas, including those ones with higher pollution.

Notwithstanding the recognized negative impact of pollutants, it is acknowledged that human exposure to low-dose of chemical/physical toxins in daily life is basically unavoidable. Different authors have questioned the linear increase of the disease risk with an increasing dose of pollutants, conversely recognizing an inverted U-shaped (hormetic) curve with a low/mild dose exposure. This results in a positive/uneventful effect when low-mild dose of (air) pollutants are contemplated [47-50].

This unconventional concept refers to mortality and health in general, more than just to mental decline [51].

Nearly 20 years ago Phalen already highlighted the controversial findings in the early epidemiologic studies concerning particulate air pollution and adverse health outcomes in urban citizens [52]. The probable influence of several confounding factors on the relative risk was clearly shown in his review, where the need for a better discrimination of the population/s really at risk was elicited. Furthermore he highlighted a great variety of interplaying weather, geographic, chemical-physical, statistical calculation issues which clearly influence any outcome of the epidemiologic studies on pollution and human health.

A recently published review on 489 morbidity studies (31 of them on neurological impairment) concerning air-pollution

impact on human health concluded that "statistically significant and non-significant long-term relationships with air pollution were approximately equally likely" and..."the aggregate of these studies supports the existence of nonlethal physiological effects of various pollutants, more so for non-life-threatening endpoints". The author concludes about the need of "further longitudinal studies to investigate the progress of disease incidence in association with air pollution exposure" [53].

Our narrative review has highlighted an association between PM pollution and mental decay, as shown in most studies, though causality relationship and the relative details about dose/exposure time/kind of PM are to be explored furthermore before drawing sound conclusions.

A few issues may be raised on the need to perform proper studies so to accomplish with the aim of demonstrating a cause-effect link between air pollution and impairment of mental health: a) the use of very sensitive tests to detect cognitive changes, b) a reliable follow-up duration of a longitudinal prospective study (more than cross-sectional studies), c) a comprehensive medical investigation aimed at the overall health of the participating subjects before and during the study, d) minimization of the lost-to-follow-up rate, e) clear discrimination of the multiple involved PM/pollutants, f) possible indoor pollution should be assessed as well.

Conclusions

Aging and the related mental decline are rooted in several interplaying factors within body metabolism; dysregulation of homeostatic mechanisms and neurodegenerative processes, as well as environmental factors such as air pollution may play a role. Biological and functional consequences of inner and outer factors on mental activity are to be studied prospectively and more in depth, so to assess the real weight and effect magnitude of the pollutants in mental senescence.

The overall assessment of the available data deriving from the cohort, prospective and retrospective studies and from literature reviews does not permit to draw any definitive conclusion on the possible (though proposed by many authors) relationship between atmospheric pollution and mental decay in the elderly. Several unanswered questions have been raised on the subject, both concerning the methodology used in the works published so far, and the myriad of the possible confounding factors on pollution and cognitive decay. The hormesis concept, which questions the systematic harm derived from air-pollution on human health (especially at low dose), has introduced another contrasting issue in the panorama of the current medical literature on this topic.

The objectively complex methodology to assess both air pollution and its possible effects on mental/cognitive function explains the low-level evidence resulting from many studies published so far. In a recent review on cognitive functioning and air pollution [40] Clifford et al. have reported about the wide variability (and therefore the different sensitivity of the method) in measuring both exposure to pollutants and the derived results. These speculative conclusions and the authors' perplexities are sharable in our opinion and probably further research is warranted to corroborate a statistically significant causative association between pollution and mental decline.

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