Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Air Pollution – risk and avoidance

Evidence Summary

Even low levels of exposure can be harmful, certainly to aging & lifespan, and probably also to dementia risk. Actions can be taken to reduce exposure.

Neuroprotective Benefit: Limited but consistent epidemiology and preclinical research for risk from air pollution, particularly traffic-related exhaust.

Aging and related health concerns: Strong evidence indicates increased risk of premature non-accidental mortality even at low levels of exposure.

Safety: Air pollution avoidance is definitely safe.

What is it? Air pollution has many components including particulates, gases, metals, and organic compounds. Harmful components may include sulfur dioxide, nitrogen oxides, acid aerosols, carbon monoxide, and ozone (O_3). Particulate matter has been heavily implicated in cardiovascular and respiratory premature mortality, especially the fine particulate matter (PM) below 2.5 um in diameter (PM2.5) that deeply penetrate and lodge within the lungs (up to 50% are retained in the lung parenchyma). Ultrafine particles (<100nm) are also a concern. Major components of PM include "transition metals, ions (sulfate, nitrate), organic compound, quinoid stable radicals of carbonaceous material, minerals, reactive gases, and materials of biologic origin." (Valavandis 2008). In urban areas, vehicle exhaust is the primary source of PM ambient air pollution, but it can also be generated by indoor cooking, smoke, industry, and natural causes of pollution.

Air pollution exposure in utero and in children has been associated with cognitive deficits, autism-spectrum disorders, schizophrenia, and low birth weight (Woodward 2015, Clifford 2016, Calderón-Garcidueñas 2016). However, this report does not evaluate the strength of that research. Similarly, indoor air pollution, primarily from burning wood and other solid fuel, is estimated to be a major health risk factor (WHO Fact Sheet). This report focuses primarily on ambient (outdoor) air pollution effects in older adults.

Risks to cognition and dementia: Limited but consistent epidemiology and preclinical studies support potential risk from air pollution, particularly traffic-related exhaust

Types of evidence:

- *3 systematic reviews based on 12-18 observational studies*
- *2 observational studies published too recently to include in the systematic review*
- *1 clinical trial on acute cognitive dysfunction in young adults*
- *3 pathology studies*
- *Numerous laboratory studies*

Human research on dementia risk, cognitive decline, and cognition

No clinical trial data are available. Epidemiological evidence, while limited, is rapidly emerging. In Ontario, residential proximity to a major roadway was associated with a higher risk of dementia (adjusted Hazard ratio (HR) was 1.07, 95% Confidence Interval (CI) 1.06-1.08 for <50 meters) with a clear dose-dependent relationship. While the HR is modest, the narrow confidence intervals, dose-dependent relationship, and numerous sensitivity analyses raise confidence in the results. The HR also likely underestimates the total effect of air pollution exposure, which is not limited to people who live

within 50 meters of a major roadway. The association was stronger in urban residents of major cities (~1.12, 95% CI 1.10-1.14) and for those who had never moved. Indirectly controlling for socioeconomic status did not change the results. No association was seen with Parkinson's disease or multiple sclerosis, suggesting that confounders like access to neurologists are unlikely to be involved (Chen 2017).

These results add to a small number of somewhat consistent reports that air pollution exposure correlates with increased dementia risk or related hospitalization (e.g. Wu 2015, Oudin 2016, Jun 2015, Kioumourtzoglou 2016). Most of the reports on dementia risk have relied on health care records of dubious quality (Power 2016) but the more recent Ontario study used a relatively validated database with information gathered from hospitalization discharge, physician claims, and prescription use (Chen 2017). A correlation with poorer cognitive function has been more extensively reported, although few of those studies looked at within-person cognitive decline (Power 2016).

Residual confounding is possible, as with all epidemiologic studies. Most epidemiologic studies did control for socioeconomic status, however, and a sensitivity analysis from a 2016 systematic review concluded that socioeconomic differences are unlikely to be sufficient to account for the observed correlations (Power 2016).

Evidence is limited on which type of pollutant is particularly harmful. Most studies on cognition have focused on PM2.5 but nitrogen dioxide (NO_2), ultrafine PM, and ozone have been investigated in preclinical studies. The recent Ontario study on dementia incidence focused on proximity to major roadways, with similar associations seen for NO_2 and PM2.5 levels. Exposure to air pollution could also correlate with exposure to other forms of pollutants but, to date, no plausible alternative has been identified (Power 2016).

Human research on progression in patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research: Given the many components of air pollution, and even PM2.5, it is not surprising that many mechanisms of action have been suggested. Damage to the cerebrovascular system is likely given the relationship between cardiovascular disease and air pollution, including a temporal link with stroke incidents (Levy 2012, Shah 2015). Damage to the blood-brain barrier and endothelial cells have been reported in animal models and some human pathology (e.g. Block 2009, Calderon-Garciduenas 2015). Respiratory and gastrointestinal tract exposure leading to chronic systemic inflammation may also exacerbate neurodegeneration.

Direct effects on the brain are also proposed. *In vivo* rodent studies have reported that exposure to air pollutants can cause changes consistent with Alzheimer's disease, such as an increase in Aβ42, tau hyperphosphorylation, neurofibrillary tangles, neuroinflammation and microglial activation, oxidative stress, DNA damage, and neurodegeneration (Weuve 2014, Fougere 2015, Yan 2016, Cheng 2016). For example, just 3 hours of exposure to air pollution led to 129% increases in Aβ40 & Aβ42 levels in wildtype mice (Kim 2012). PM2.5 or ultrafine particles are thought to reach the brain via olfactory and cranial nerves and possibly via transfer from circulation to brain endothelial cells or trafficking of macrophage-like cells from the lung capillary bed to systemic circulation (Calderon-Garciduenas 2013, Genc 2012). In autopsy studies, PM has been found in olfactory bulb neurons (Calderon-Garciduenas 2008) and magnetite nanoparticles have been broadly detected in the CNS (Maher 2016).

Studies in humans on neurodegenerative pathology have been limited. A long series of papers from Lilian Calderón-Garcidueñas at the University of Montana indicate that children and young adults in Mexico City, exposed to high air pollution levels, exhibit unusually early pathological signs of Alzheimer's and Parkinson's disease (e.g. Calderon-Garciduenas 2016 & 2013). These signs have included cognitive impairment, prefrontal white matter lesions, proinflammatory cytokine and COX2 expression in the CNS, frontal tau hyperphosphorylation, beta-amyloid diffuse plaques, reduced cerebrospinal fluid levels of Aβ42 & brain derived neurotrophic factor, and aggregated hyperphosphorylated alpha-synuclein in the brainstem and olfactory nerves. Despite these alarming results, studies from other laboratories or on older adults are limited. Smaller brain volumes or white matter hyperintensities have reported in some cohorts (Chen 2015, Casanova 2016, Wilker 2015) but not all (Wilker 2016), with air pollution measured by proximity to major roads or PM2.5 exposure.

APOE4 interactions: APOE4 status did not influence the relationship between dementia and air pollution in one case-control study (Wu 2015) but APOE4 carriers were more likely to show a negative correlation with air pollution and cognitive function in another study (Schikowski 2015). A series of studies from young people exposed to pollution in Mexico City report that APOE4 exacerbates sensitivity to air pollution, resulting in worsened cognitive deficits and more extensive Aβ42 immunoreactivity (e.g. Calderon-Garciduenas 2016, 2008).

Aging and related health concerns: Strong evidence indicates increased risk of premature non-accidental mortality even at low levels of exposure

Types of evidence:

- *World Health Organization reports*

- *3 meta-analyses and 3 cohorts selected as representative of a large literature*
- *1 review on mechanisms of action and frailty*

An estimated 2.6 million premature deaths worldwide are estimated to be caused by ambient air pollution, largely due to exposure to PM below 10 microns (PM10). Of these deaths, 72% are related to ischemic heart disease and stroke, 14% to lung cancer, and 14% to respiratory illness (WHO Fact Sheet). The list of diseases includes atherosclerotic cardiovascular disease, COPD, lung cancer and lung infection, myocardial infarction, stroke, and others under investigation (Laumbach 2015).

There is no lower threshold for risk to PM2.5. In European countries where many cities have air quality levels within WHO recommended guidelines, exposure to human-generated PM has been estimated to shorten average life expectancy by 8.6 months (WHO Fact Sheet). Similarly, in Canadian regions with low average exposure to PM2.5, the risk of non-accidental mortality increases by 26% with each 10ug/m^3 increase in exposure (HR 1.26, 95% CI 1.26-1.84) (Pinault 2016). Short-term changes in exposure have been temporally linked to cardiovascular and stroke-related hospital admissions and mortality (Levy 2012, Shah 2015).

Susceptibility to health risks from air pollution can vary. The elderly and those with asthma, COPD, diabetes, and cardiovascular diseases are thought to be vulnerable. Children and the developing fetus may be particularly susceptible as well. Children and young adults appear susceptible to subclinical effects like inflammation and deposits of PM2.5 in the lung during exercise. In one study, people who have never smoked were particularly harmed by air pollution (mortality HR 1.76, 95% CI 1.15-2.69) although the difference from smokers was not significant (Pinault 2016). The same study also reported a non-significant trend for increased harm in obese individuals. Elderly people may be particularly sensitive. It has been proposed to exacerbate pathological aging and frailty through chronic inflammation (e.g. increased c-reactive protein), systemic oxidation from polycyclic aromatic hydrocarbons (PAHs) and transition metals, metabolic disorders caused by PM2.5 and dioxin, DNA damage from PM and other toxins, and epigenetic effects such as DNA methylation and increased histone acetyl transferase activity (Fougere 2015).

Which toxins are most harmful for air pollution? Ozone or smog is less likely to contribute to mortality rates according to a meta-analysis of data from 8 cohorts (Atkinson 2016). PM2.5 and sulfate exposure share similar associations with increased mortality from all-cause, lung cancer, or cardiopulmonary causes (Pope 1994). For stroke-related mortality or hospitalizations, the associations appear to be similar for carbon monoxide, nitrogen dioxide, sulfur dioxide, and PM2.5 (Shah 2015). PM2.5 itself is a complex and varied mixture of molecules but evidence is very limited on which types are most harmful

(Levy 2012). PM has been specifically categorized as carcinogenic (IARC), particularly for lung cancer. The organic components of PM have been suggested to be involved with atherosclerotic disease based on preclinical research (Keebaugh 2015).

Actions to reduce exposure:

Some actions can reduce an individual's exposure (Laumbach 2015).

- Air pollution levels vary locally, daily, seasonally, and even by time of day. They can be monitored online, with apps (e.g. PlumeAirReport, BreezoMeter, AirVisual), and even handheld devices. For example, community efforts using the AirCasting platform have been used to record PM2.5 levels across NYC, observing up to 6 fold differences in PM2.5 concentration (e.g. Wired article, TakingSpace.org). Consider staying inside on days with particularly bad air pollution. Shift exercise routes away from polluted areas – even moderate exercise can cause a 5-fold increase in the deposition of ultrafine PM in the lungs. Do not avoid exercise, however. The cardiovascular benefits of exercise are likely to outweigh the risks of air pollution exposure, (for example commuting via bicycle) (Laumbach 2015).
- Breathing through the nose instead of the mouth can somewhat reduce lung penetration of particles (Laumbach 2015).
- For many people, the highest exposure to PM occurs while driving. Exposure may be reduced by closing car windows and vents while in heavy traffic, installing a high efficiency particle filter, avoiding idling and long-warm-ups in enclosed spaces, avoiding smoking in the car, keeping the vehicle tuned and maintained, and buying a low-emitting vehicle such as electric or hybrid. (Laumbach 2015, CA Fact Sheet)
- Indoors, cooking is a major source of PM. The use of exhaust fans that vent outdoors may reduce exposure. Other common indoor sources include smoking, fires in wood stoves or fireplaces, candles, and incense (Fact Sheet).
- Staying indoors and closing the window can reduce but not eliminate outdoor pollution without additional efforts. PM2.5, ozone, and sulfate toxins penetrate into buildings and PM2.5 specifically can remain in circulation. However, effective portable or central air cleaning systems are available such as in-duct HEPA filtration systems (Laumbach 2015).
- Indoor air quality monitors are available, allowing personalized efforts to reduce exposure in the home. No single monitor seems to cover all air pollutants (reviewed here, here, and here). The Foobot can monitor VOCs, PM2.5, and CO_2 levels and can be connected with other devices, for example to turn on air purifiers or send an alert to your phone when levels are

high. The AirPi is a low-cost air monitor with DIY instructions that can monitor CO, NO_2 and smoke.

- Respirators and personal protective equipment are somewhat common in some areas of the world. No single filter is able to remove all types of air pollutants but some, including PM, can be reduced by some filters. Negative pressure air-purifying respirators are also available (Laumbach 2015)

Despite all of these options to reduce personal exposure, air pollution is and will remain largely influenced by societal actions. History has shown that emissions can be successfully reduced. Average PM2.5 levels declined by 37% from 2000-2015 in the USA (EPA). In Los Angeles from 1960 to 2010, maximum ozone levels reduced from 600 to 150 ppbv and VOC concentrations (volatile organic compounds, a source of PM) decreased by a factor of 50 (EOS.org).

Research underway: The evidence for dementia risk is rapidly evolving, with all papers on dementia risk published in the last several years. More is undoubtedly underway. To date, no drugs or supplements have been shown to be effective at protecting against related toxicity, despite some claims for PUFAs and antioxidants.

Technology continues to innovate, lowering emissions from industry and vehicles and enabling individuals to reduce their exposure. PlumeLabs.com is developing a connected mobile accessor to track, monitor, and reduce air pollution exposure. A passive transparent air filter for high efficiency PM2.5 capture was reported in 2015 (Liu 2015). Vegetation in urban planning is another interesting possibility. PM2.5 and NO_2 deposit onto vegetation at much higher rates than on hard non-porous surfaces. While common urban planning with occasional trees has minimal influence, more extensive vegetation planting in street canyons was predicted in one model to reduce street-level concentrations by 40-60% (Pugh 2012, Salmond 2016).

Search terms:

Pubmed: air pollution or particulate with mortality, cognition, dementia, white matter hyperintensities, Alzheimer's

Google: Air pollution + mortality, air pollution monitor, PM2.5 monitor

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