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Environmental Factors in Successful Aging: The Potential Impact of Air Pollution

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Global demographic trends are coalescing around an unprecedented milestone in human history: It is estimated that by 2020, people over age 60 will for the first time outnumber children under the age of 5 years old.[1] Global fertility rates have fallen by half over the last half-century from an average of 5 children per woman in 1960 to 2.5 today.[2] In addition, major advances against what were once the world's top killers—infectious diseases and acute threats to child and maternal health—are allowing more people to live longer than ever before.[3]

This demographic shift has sparked growing interest in *how* people age and, in particular, their capacity for what those in the geriatrics field call "successful aging"—with vitality, resilience, and good health. Seen this way, the number of years lived is not as important as how many of those years can be lived free of disease and disability.[4,5]

Premature declines in cognitive and physical functioning pose threats to successful aging, and mounting evidence indicates that environmental exposures may play a part in such declines.[6,7,8,9] Yet older adults have been long understudied in environmental health.[10] In addition, toxicologists rarely test chemicals in older animals, so mechanistic insights into their effects on aging bodies are limited. That's raising concerns that the world's fastest-growing demographic group may be insufficiently protected from environmental exposures that younger adults more readily tolerate.

"Without hesitation, I can say that the published literature on environmental chemicals and their effects on older people and the aging process is extremely limited," says Wayne Cascio, director of the Environmental Protection Agency's (EPA) National Health and Environmental Effects Laboratory. "If we want to see more people age successfully, then we need to get a better handle on how specific toxicants advance the aging process, either alone or in combination. And we need to understand how the mix of toxicants, underlying clinical conditions, and social aspects of aging contribute[s] to adverse outcomes."

Air Pollution and Dementia

A growing body of evidence suggests that certain air pollutants may cause or accelerate age-related diseases. Exposure to fine particulate matter ($PM_{2.5}$) has been implicated in the incidence of dementia,[11] which is one of the most burdensome age-related chronic conditions confronting society today. Dementia is a

"Successful aging" means retaining vitality, resilience, and good health throughout one's later years. As the global population shifts toward more older people than children, investigators want to understand the environmental and genetic factors that influence how "successfully" an individual ages. Image: © iStockphoto/MindStorm-inc.

syndrome reflecting diminished memory, reasoning, speech, and other cognitive functions. It afflicts an estimated 47 million people globally, a number that is projected to increase to 75 million by 2030.[12]

According to Gali Cohen, a PhD candidate in epidemiology at Tel Aviv University, most research on aging comes from higher-income countries. Yet, by 2050 an estimated 80% of people over age 60 will live in low- and middle-income countries,[1] where air pollutant levels often exceed World Health Organization guidelines.[13] Many of these countries are struggling already with a rise in age-related noncommunicable diseases such as heart and lung disease,[14] some of which are caused or exacerbated by environmental agents.[15]

Linda Fried, dean of Columbia University's Mailman School of Public Health, points out that dementia rates are falling among educated, wealthier people in the developed world—who have benefited from healthier environments and health-promoting resources over their lives—while continuing to rise in the developing world.[16] "That tells me that a significant proportion of dementia is preventable," she says.

Fried suggests that rising dementia rates in poorer countries may result in part from toxic effects of air pollutants, and emerging evidence supports that view. In 2018, for instance, researchers reported an association between declines in scores on word-recognition tests and higher estimated cumulative exposure to air pollution in Chinese cities.[17] The declines were greatest in men in the 65+ age group with the lowest levels of education. Study coauthor Xi Chen, an assistant professor at the Yale School of Public Health in New Haven, Connecticut, says that's possibly because men with the lowest levels of education in China are more likely to work outside and breathe polluted outdoor air for many hours a day.

The evidence on cognitive effects from air pollution is not sex-specific, however. A 2016 study by a different research team drew from the Women's Health Initiative Memory Study, a long-term clinical trial of U.S. women age 65 and older. The researchers estimated that participants had nearly twice the risk of dementia if their average $PM_{2.5}$ exposure levels exceeded the EPA standard of $12\ \mu m/m^3$ in the preceding 3 years.[18] The risk was highest among women with two copies of a gene allele called *APOE* ε4, which is an established inherited risk factor for Alzheimer's disease.[19]

An animal experiment described in the same paper[18] generated complementary findings. In that case, female transgenic mice expressing the *APOE* ε4 allele were exposed to ultrafine airborne particles in the laboratory. After 15 weeks of exposure, their brains had accumulated high levels of the same amyloid proteins found in human Alzheimer's disease patients.

Jiu-Chiuan Chen, an associate professor of preventative medicine and neurology at the University of Southern California, Los Angeles, led the human part of that study. He says the findings are alarming in light of the fact that more and more of the world's elderly are living in cities, where traffic emissions contribute to poor air quality.[20]

However, the underlying toxic mechanisms by which air pollution might accelerate cognitive declines remain unclear. Scientists have for years debated various hypotheses: Some experts blame pollution-induced heart disease and commensurate changes in the

It is estimated that four-fifths of the global over-60 population will live in low- and middle-income countries by 2050. Dementia rates are already on the rise in poorer countries. One reason may be chronic exposure to air pollutant levels in these countries, which often exceed World Health Organization guidelines.[13] Image: © iStockphoto/photojournalis.

brain's vasculature. Others hypothesize that airborne particles enter the brain directly through nerve connections in the olfactory system, and then cause damaging neuroinflammation.[8] "The bottom line is we still do not know," says Jennifer Weuve, an associate professor of epidemiology at Boston University in Boston, Massachusetts.

Air Pollution and Frailty

The evidence connecting air pollution with frailty is even more limited. Studies are complicated by the fact that frailty does not have a widely accepted clinical definition. One study described it as "a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, and social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes."[21] The severity of frailty is assessed with a variety of diagnostic tools which reflect different definitions for the condition.[22]

One of these tools is a frailty phenotype that was proposed and validated in 2001 by Columbia's Fried and colleagues. In this phenotype at least 3 of 5 criteria must be present: unintentional loss of more than 10 pounds, self-reported exhaustion, weak grip strength, slow walking speed, and low physical activity. Another is the 7-point Clinical Frailty Scale published in 2005 by Kenneth Rockwood, a professor of geriatric medicine at Dalhousie University in Halifax, Nova Scotia, Canada.[23] That scale assigns frailty scores according to a person's activity levels, the presence or absence of comorbidities (coexisting chronic diseases), and dependence on others for care. Ursula Staudinger, a professor at the Robert N. Butler Columbia Aging Center at Columbia University in New York explains that the frailty phenotype reflects a specific geriatric syndrome, whereas the Clinical Frailty Scale measures multimorbidity.

Frail people have weakened physical and cognitive reserves, and that puts them at high risk of falls, disability, hospitalization, and disability.[24] A review of frailty studies using a variety of definitions estimated a prevalence of approximately 10% among people over age 60 and up to half of all people over age 85.[25]

One of the few studies that have looked at how outdoor air pollution affects scores on the Clinical Frailty Scale was published in 2013.[26] The analysis looked at 1,120 older individuals who had survived a heart attack 10–13 years earlier. In the years since their heart attack, patients exposed to higher estimated $PM_{2.5}$ levels over a representative 2-year exposure period were more likely to have become frail than their less-exposed counterparts, after adjusting for clinical confounders. In separate papers, the same researchers reported a stronger association between air pollution and mortality during follow-up among frail heart attack patients in comparison with nonfrail patients.[27,28]

The frailty phenotype was used in a 2012 study of air pollution and lung function among nearly 3,400 older Americans.[29] In that study, investigators found a stronger association between exposure to air pollutants and poor lung function in frail older people in comparison with more-robust participants.

Scientists have also linked frailty—as defined by the frailty phenotype—with exposures to lead, with the most pronounced features seen in women with osteoporosis. Lead accumulates in

Up to half of all people over age 85 show symptoms of frailty,[25] but the condition itself does not have a widely accepted clinical definition. One proposed definition is the so-called frailty phenotype, which is characterized by unintentional weight loss, exhaustion, weakness, slow walking speed, and low levels of physical activity. Image: © iStockphoto/Willowpix.

the skeleton and then reenters the blood stream when bones demineralize. In a 2015 report,[30] researchers hypothesized that lead and/or cadmium exposures might contribute to frailty. According to their analysis of data from the third U.S. National Health and Nutrition Examination Survey, adults over the age of 60 with higher blood lead levels were more prone to exhaustion, weakness, and slowness than those with lower levels.

Biological Aging

Dementia and frailty are both clinically obvious age-related conditions. However, researchers say additional insights can be gleaned from how environmental agents affect subclinical markers of biological aging.

Chronological age, or the number of years lived, differs from biological age, which incorporates risk factors for future disease and early death.[31] Being at risk of a fatal disease makes someone biologically older than their chronological age would indicate; however, very few studies so far have looked into how environmental exposures act on specific markers of biological age.

A seminal paper published in 2013 enumerated nine such markers, or "hallmarks of aging": genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence,

In 2013 investigators identified nine cellular and molecular changes that characterize the aging process in different organisms, especially in mammals. Identifying these "hallmarks of aging" could inform future studies that improve our understanding of the mechanisms that underlie aging. Image: López-Otín et al. (2013).[32]

stem cell exhaustion, and altered intercellular communication.[32] Each of the markers, the authors wrote, contributes to a "progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death."

Staudinger emphasizes that no single marker has yet been shown to drive biological aging independently, though scientists have tried for years to find one in a hunt that she likens to a search for the Holy Grail. Instead, Staudinger says, multiple markers drive the aging process as part of a larger puzzle.

Among them, telomere length attracted much of the initial research interest. Telomeres are stretches of DNA lining the ends of chromosomes, and their length decreases with each cell division. Excessive telomere shortening has been cited as a cause of genomic instability and is a risk factor for heart disease and other age-related health problems.[33] In a 2016 study of 166 nonsmoking older adults, investigators reported that telomere length was inversely associated with estimated annual residential exposures to $PM_{2.5}$.[34] However, Staudinger says the overall evidence linking telomere shortening with biological aging in humans is inconsistent.

More recently, epigenetic factors that may accelerate aging have begun to gain attention. Epigenetic changes alter gene expression in ways that do not accord with their nucleotide sequences, and they often result from methyl groups accumulating on DNA over time. These methylation patterns correlate with various disease states, and they can be measured in a number of ways. Steve Horvath, a professor of human genetics and biostatistics at the University of California, Los Angeles, developed an "epigenetic aging clock" to calculate a measure called DNA methylation age (DNAm age), also known as epigenetic age, which is in turn based on methylation patterns specific to a set of 353 CpG sites on DNA.[35] These sites selectively gain or lose methyl groups in response to environmental stress.

According to Horvath, DNAm age "predicts life span even after adjusting for chronological age, sex, smoking, and other mortality risk factors." He says the most recent versions of epigenetic clocks, such as DNAm GrimAge, are particularly strong predictors of time to death, time to coronary heart disease, time to cancer, and number of comorbidities.[36]

After demonstrating that DNAm age can also predict frailty and other age-related conditions,[37,38,39] researchers are now beginning to study how the measure varies with environmental exposures among older adults. The first such investigation, led by Jamaji Nwanaji-Enwerem, an MD-PhD candidate at Harvard University in Boston, Massachusetts, measured epigenetic age in a subset of 1,032 older men who were enrolled in the Normative Aging Study conducted by the U.S. Department of Veterans Affairs. The authors concluded that men exposed to the highest percentile of $PM_{2.5}$ exposures were epigenetically older by about half a year than their chronological age, which averaged 74.8 years.[40]

Study coauthor Andrea Baccarelli, chair of the Department of Environmental Health Sciences at the Mailman School of Public Health in New York, says that although half a year may not seem like much, the effects are more consequential when they are extrapolated to larger numbers of people. "The size of the effect is about the same as the estimated impact that air pollution has on

With a better understanding of aging-related processes and influences, it may be possible to design interventions that support successful aging. These interventions might include regulations that protect older adults against environmental exposures that younger people more readily tolerate. However, the heterogeneity of the older population makes it difficult to ascribe specific risks to this age group. Image: © iStockphoto/vgajic.

life expectancy at the population level," he says. "It is a small effect, but one that affects everyone, hence huge numbers of deaths across the world."

Investigators studying a German cohort of 1,799 older men and women reached similar conclusions: In both sexes, higher $PM_{2.5}$ exposures were associated with an average increase in epigenetic age of about a third of a year.[41] Both the U.S. and German studies measured DNAm age in blood samples. However, according to Horvath, additional information could be gained by measuring methylation patterns in other tissues as well. For instance, he speculates, patterns associated with dementia might be more evident in the brain.

Scientists still do not know how—or even whether—$PM_{2.5}$ exposures actually alter methylation patterns. Horvath is now collaborating on rodent studies that could generate mechanistic insights. Led by Amin Haghani, a PhD candidate at the University of Southern California, investigators are exposing mice to ultrafine particles. Horvath says, "Our data are suggestive that particles might enter the brain, but we are not certain about that. Still, he adds that the unpublished results point to widespread DNA methylation changes, neuroinflammation, and neurotoxic effects that resemble some processes of Alzheimer's disease.

Ascribing Risks

Could markers of biological aging factor into new regulatory standards that better protect older adults? Staudinger describes environmental research with biological markers as important, "especially when they are combined with clinical diagnoses and behavioral measures." Horvath, meanwhile, says he's recently been funded by the National Institute on Aging to investigate how epigenetic clocks might be used in clinical trials of interventions to foster successful aging; however, he adds that for now, "We're nowhere near being able to use these tools for setting regulatory standards, although DNA methylation will hopefully be useful for that purpose at some point in the future."

The U.S. EPA's Cascio was a panelist during a workshop on aging and the environment held at the Society of Toxicology 2018 annual meeting. The workshop's premise was that older adults have unique susceptibilities to environmental toxicants that haven't been adequately addressed. Cascio says EPA officials recognize these susceptibilities, but he adds that the agency is also grappling with the challenge of ascribing specific risks to aging populations, which are highly heterogeneous. He says frailty is an especially problematic descriptor for environmental risk assessment, and EPA policy documents likewise state that frail people "should not be considered separately from older, healthier adults," because the term itself is subject to "vague and sometimes conflicting definitions."[42]

Cascio pointed out that the EPA's Sustainable and Healthy Communities Research Program—and its Air and Energy Research Program—are mindful of risk issues among older populations, although the agency does not call out senior citizens specifically. Susceptibilities of older people are "more integrated within our research," he adds, "but as we rewrite our strategic research plan, this demographic change will be a topic of discussion."

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