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Invited Opinion

Environmental influences on brain aging

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1. Introduction

In this commentary I argue that current evidence demonstrates a greater influence of the environment as opposed to genetic factors on human aging and longevity. Even though a few genetic factors have been highlighted as influencing the aging process, including APOE and FOXO3A, as yet, the list is sparse. Statistics on longevity and aging are based on life-expectancy and healthy-life expectancy. However, those born in the 1930s were not exposed to the massive increases in chemical pollution to which recent generations were exposed. A recent research focus is how epigenetic processes linking the environment to gene expression are implicated. Key discoveries are being made on how methylation patterns during development are linked to brain aging and cognitive processes. Similarly, life-style is increasingly recognized as a modulator of healthy longevity and cognitive agility or degeneration. Numerous environmental factors have been demonstrated to be involved, but diet, exercise and social context are currently seen to be of overriding importance.

2. Healthy life expectancy versus life expectancy

Statistics on longevity and aging are based on life expectancy and healthy life expectancy. The World Bank data base[1] reports that the current life expectancy at birth in Japanese women is 87 and that for Japanese men 81 years. In the US it is for women 81 and only 76 for men, whereas in South Africa it is under 60 years. What accounts for the difference in countries and gender? Here I focus on environmental factors that modulate the aging process.

Of the many hypotheses that can be put forward I will focus on chemical pollution and particularly, air pollution and endocrine disrupting chemicals (EDCs). Many aspects of EDCs make them difficult to regulate as they display non-monotonic dose-responses and low dose responses [1]. That chemical contamination adversely affects healthy life expectancy as well as overall life expectancy is established, especially through increasing incidence of non-communicable disorders (NCD). As a result, even though life expectancy was still increasing at the end of the 20th century, the gap between healthy life expectancy was widening [2]. This is explained in large part as being due to an increase in non-infectious diseases that deteriorate healthy life expectancy. For instance, metabolic disorders such as obesity and diabetes [3], are linked to inflammatory disorders including arthritis [4]. All of these diseases have been shown to have environmental contributions involving EDCs [1].

By definition, the actual figures on which the current life expectancy statistics are based were those born at the beginning of the last century (1930s or before). As a result they were spared the massive increase in chemical production that was seen from the 1950s on. The UN produces data sets on chemical production. Their registers show that there has been a 300-fold increase in chemical production since 1970 [5].

Yet eight years previously, Rachel Carson had written *Silent Spring* [5]. The book galvanised the public's attention on pesticides, but clearly did little to staunch the expansion of the chemical industries. Carson's focus was on excessive use of dichlorodiphenyltrichloroethane (DDT), as a major cause of loss of bird and fish life. The population losses were not only due to reductions in food sources, insects, but also to accumulation in the bird's organs, affecting reproductive capacity. Since then, the excessive use of DDT has been shown to reduce oestrogen levels in birds [6], so acting as an EDC. Carson also presciently realized that humans would be contaminated too and that

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[1] https://data.worldbank.org/indicator/SP.DYN.LE00.IN Consulted 1st November 2020

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ultimately effects would be seen on human health. This was unfortunately shown to be the case. Fifty years after widespread applications, Barbara Cohn reported that female foetuses that had been exposed to high levels of DDT *in utero* during the 1960s had an increased risk of breast cancer [7].

However, chemical production goes far beyond pesticides, now including molecules and mixtures that cover a multitude of consumer products such as plastics, food additives, food contact materials and packaging, building materials, personal care products and cosmetics. The result is that chemical pollution (both legacy products that are now banned and the new substitutes that replace them) are found not only in the serum and urine of pregnant women [8], but also in amniotic fluid [9] and the foetal/placental compartments [10].

3. The developmental origins of adult health and disease (DOHaD) as a driver of aging

The Developmental Origins of Adult Health and Disease (DOHaD) hypothesis is based on the concept that prenatal exposure to different stressors, whether chemical, psychological or infectious, determines later health and disease. Many examples have been described, from butterflies to mammals including humans.

In 1989, David Barker published in a commentary in *Nature* [11], correctly foreseeing, that in developed countries, death from infectious disease would decrease and that an increased incidence of non-infectious, NCDs would grow in industrialised and emerging economies. This rapid increase of NCDs exceeds all predictions that could have been made when Barker first published his thoughts. We know that industrialization is linked to the increased incidence of NCDs, such as metabolic disorders (including obesity and diabetes, cardiovascular disease), cancers of the reproductive system, reduced fertility and neurodevelopmental diseases Even though, they are all multifactorial, the incidence of these conditions is rising inexorably, with documented evidence that their origins can be traced to chemical pollution and EDCs [12]. An example is diabetes, with around 422 million people suffering from diabetes type 2 (T2D) that reduces life expectancy by 10 years or more, with incalculable costs in terms of suffering, care and medication as well as productivity. Various EDCs have been implicated in T2D risk, especially the ubiquitous plasticiser bisphenol-A and its substitutes [13]. The World Health Organisation (WHO) classed T2D as a pandemic in 2016.

Subsequent work by Barker and colleagues emphasized the first trimester of foetal life, the first 100 days, others have insisted that the window of time in which healthspan (and, ultimately lifespan) are determined should be widened to include the first 1000 days of life when nutrition in infant- and early childhood is a critical factor [14]. At the same time, we know that vulnerability to multiple stressors continues throughout life, i.e. from early gestation through to early childhood, adolescence and adulthood, although the adverse programming by the environment, including atmospheric pollution [15], seems to be most pronounced at younger life stages. Adverse programming by environmental factors involve a multiplicity of mechanisms (often cascading and amplifying), including inflammation, oxidative phosphorylation and epigenetic modulation of transcription at the levels of cellular and physiological metabolic responses.

4. Cognition and aging is linked to general health and metabolism

The concept of a healthy, active mind in a healthy body is even more apt today, particularly in the context of aging. In 2001, Whalley and Deary had concluded that 'Childhood mental ability is a significant factor among the variables that predict age at death' [16], at a time when cognitive epidemiology was just emerging. Later, in 2008, Ian Deary asked 'Why do intelligent people live longer?' [17]. Deary cites data from Sweden that shows that military conscripts with higher IQ scores had reduced risk of mortality and morbidity.

He puts forward a series of arguments and plausible mechanisms that could account for the differences in mortality. These range from the more obvious, such as better education and therefore better employment and, as a consequence, higher standards of living. For instance, those with more free-time could, for instance, take account of advice about healthy lifestyles and exercise. The final concept Deary refers to is 'systems integrity', where the basic idea is that, during prenatal life, if the mechanisms ensuring proper body and brain function proceed unperturbed by stress, then both will be more robust and resilient. Dreary has consolidated his theory with the idea of 'optimal bodily functioning'. The result would be that those with higher intelligence and hence higher socio-economic conditions have reduced risk of disease such as cardiovascular disease, stroke, cancers (particularly, smoking related cancers), but also dementia. The principle argument has a number of parallels with the DOHaD theory and epigenetic changes during development (see previous section and the next).

However, given the increase in chemical and air pollution, even those that are gifted with greater intelligence might not continue to enjoy healthy lives, especially given the increase in neurodevelopmental disease that can be associated with decreased IQ [18]. The final point here is that all of these concepts linking aging of the brain and body are also intimately linked to questions of social justice. The important factors here include access to healthy diet, especially during pregnancy, education, medical care and where you live and how far you need to commute to work.

5. Air pollution and the epigenetic link: Programming through methylation

Numerous studies have linked epigenetic changes through methylation of DNA in blood samples as a predictive factor for all-cause mortality and hence the aging process, see for example, [19]. The authors examined the methylation status of the genome for the addition of methyl groups to the DNA. They then calculated the difference between DNA methylation-predicted age minus

chronological age of the persons in the cohort. One of the cohorts showed a clear survival advantage for those with the lowest quartile of DNA methylation acceleration rates. Multiple other publications have confirmed these findings.

Most focus on the detrimental effects of air pollution in general have concentrated on the prenatal, perinatal and adolescent phases, with far less emphasis on the long-term consequences as these indivduals enter adulthood and old age. However, a number of publications provide links to DOHaD hypothesis and epigenetic changes. For instance, placental changes in leptin epigenetic markers were lower in those with higher particulate matter (PM) exposure [20]. As leptin is related to growth and development it will affect metabolic capacity not only in fetal life but also in later life.

That mortality is linked to air quality has been emphasized by the World Health Organisation (WHO) and the Organisation for Economic Cooperation and Development (OECD). Air and chemical pollution interact to affect not only one's general health, notably the link to respiratory diseases such as asthma, but also, at all ages, behaviour and cognition. Many components of air pollution are detrimental to health including PM, heavy metals, Polycyclic Aromatic Hydrocarbons (PAHs), dioxins and volatile organic compounds (VOCs). The major sources of health-endangering air pollution are emissions from power stations (especially coal-powered stations), refineries, petrochemical industries including fertilizer production plants, municipal incinerators, domestic cleaning and traffic.

Two sources of degradation of air quality are well known: traffic-related pollution and agricultural sources. Air pollution is classed according to the size of the PM formed <10 μm and <2.5 μm. Traffic-related pollution is mostly associated with combustion products discharged through exhaust pipes. However, friction of tires on tarmac and brake linings contribute equally, even reaching 90% of vehicle emissions in Northern Europe, where more severe winters are found [21]. Air quality is known to be degraded by particulate matter from traffic, but less well known is the reaction between fertilisers applied in the surrounding countryside on air pollution in cities [22]. Here, the link is that the two interact to produce PM that contains ammonium sulphate and ammonium nitrate. To this one can add the VOCs that form aerosol pollution derived from a plethora of products including pesticides, printing inks in packaging, household cleaning agents and personal care products [23]. Ironically, the authors note that this form of air (and chemical) pollution has increased in the US simultaneously with decreased transport and traffic. More specifically, it has been demonstrated that the risk of developing dementia increases as a function of proximity to major roads [24]. Similarly, traffic-related pollution decreases cognitive function in older men [25], but less is known about agricultural fertilizer use and cognitive performance during aging.

So, here again we have a vicious circle: increased air pollution from whatever source whether traffic or agriculture, increases risk of brain aging. Air pollution also incites those working in offices in large cities to prefer prepackaged food deliveries. This situation is aggravated during COVID-19 lockdowns when restaurants are closed. In turn, increased food deliveries by motorized transport increases air pollution and the disposal of the packages also impacts air pollution whether they are disposed of by incineration or burying in landfills.

To date, most COVID-19 deaths were those with multiple risk factors including being overweight or diabetic, smoking, gender (men having higher death rates) and lower socio- economic status [26]. Those with lower economic classes have poorer nutrition and exposures to endocrine disruptors a fact that will exacerbate mortality if infected with COVID-19, again emphasising problems of social injustice.

6. Taking advantage of the natural environment improves brain health

There is a clear, positive, association between physical health during aging and natural environments. This holds true whether our horizons allow us to see blue seascapes, clear skies or green landscapes. The inverse is also true,

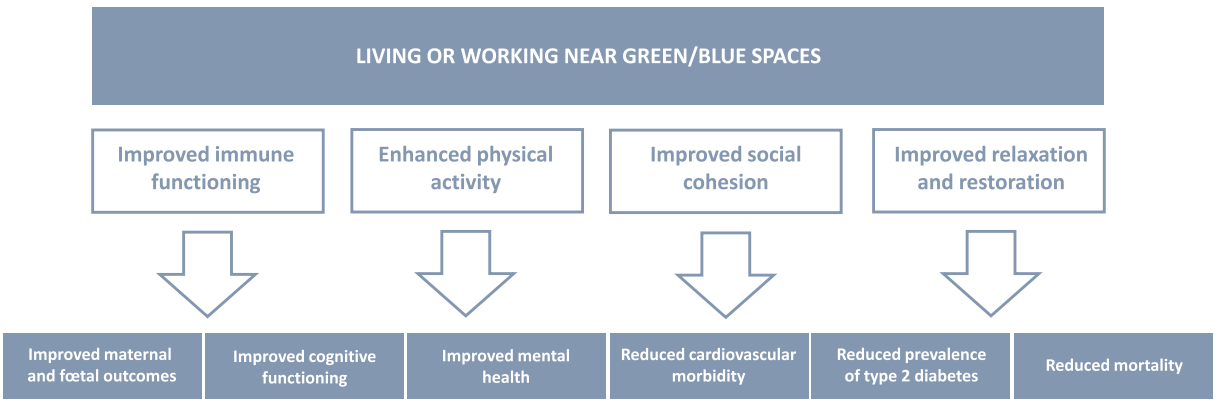

Fig. 1. Interactions of environmental factors with brain health. Schema of the numerous environmental factors that impinge on health and ultimately mortality placed in the context of the DOHaD hypothesis. Reducing environmental stressors during pregnancy and early childhood diminishes ill-health in childhood, adolescence and aging. At all stages taking advantage of green/blue environments improves cognitive function and mental health. Similarly, exercise improves immune function and thereby reduces incidence of non-communicable disease risk. Adapted from https://www.eea.europa.eu/publications/healthy-environment-healthy-lives [27].

with excess mortality being linked to environmental stressors that range from ambient air pollution, especially PAHs, to indoor air pollution, personal care products, VOCs and noise.

As per usual this will also depend on the individual's socio-economic conditions, the quality of the environments that they experience on a daily basis and whether within them the individuals are able to maintain dynamic social relationships [27]. Oddly enough, urban living is associated with better cognitive health in aging [28]. Thus, there is a nexus between well-being, health and the environment that engenders resilience to the entropy that the aging process inevitably entails. Unfortunately, few today can achieve the optimal conditions required for health brain aging (Fig. 1).

7. Future directions and research

That the EU has invested €52 million in eight projects on adverse effects on human development caused by EDCs is certainly a step forward in understanding how environmental stressors affect health. The projects financed range from women's reproductive health to developmental neurotoxicity and thyroid endpoints (including brain effects). However, the investment is somewhat limited when compared to the costs of neurodevelopmental and neurodegenerative diseases. In 2015 Bellinger et al. estimated the yearly costs of neurodevelopmental disease due to EDCs in the EU over €157 billion [29]. Global neurodegenerative disease costs are increasing exponentially too. In 2010 costs in Europe were at least €105 billion, [30]. The fear is that the neurodevelopmental costs could morph into neurodegenerative costs, with the increasingly top heavy age pyramid. Even though certain genetic factors have been identified as common to both forms of neuronal dysfunction, there is a need to invest greater research efforts into the how the environment modifies neuronal processes. A focus could be mechanistic studies on how epigenetic factors modulate physiological and cellular processes, both acutely as well as during development and aging.

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