How does the environment affect human ageing? An interdisciplinary review

Barbara Plagg^{1,2,3}, Stefan Zerbe¹

¹ Faculty of Science and Technology, Free University of Bozen-Bolzano, Italy; ² Faculty of Education, Free University of Bozen-Bolzano, Italy; ³ Institute of General Medicine, Claudiana, College of Health Care Professions, Bozen-Bolzano, Italy

The multifactorial process of ageing is one of the biggest biological and medical challenges of the 21st century with age-related conditions such as cardiovascular diseases, neurodegeneration and cancer being among the leading causes of death among industrialized countries. Rather than one single causative factor, a range of environmental, demographic, biological, behavioral and social factors determine the development and onset of age-related diseases (ARDs). While it remains a challenge to assess the cumulative effect of environmental influences on human ageing, growing evidence indicates that both ARDs and non-pathological ageing processes are driven by environmental influences. The present review takes a closer look at the different environmental factors including air, climate, water, soil, urban green, social and individual environments and their influence on common ARDs and other life-limiting pathologies. It is of major public health relevance, to understand the interactions between these factors to develop preventive strategies both at individual and societal level to support healthy ageing.

Key words: environmental influences, ageing, human-environment-interaction, exogenous influences, healthy environments, senescence

Received: December 20, 2019
Accepted: May 12, 2020

Correspondence

Institute of General Medicine, Claudiana, College of Health Care Professions, Via Lorenz Böhler 13, 39100, Bozen-Bolzano and Free University of Bozen-Bolzano, piazza Università 1, 39100 Bozen-Bolzano, Italy
E-mail: barbara.plagg@unibz.it

Conflict of interest

The Authors declare no conflict of interest

How to cite this article: Plagg B, Zerbe S. How does the environment affect human ageing? An interdisciplinary review. Journal of Gerontology and Geriatrics 2021;69:53-67. <https://doi.org/10.36150/2499-6564-420>

© Copyright by Società Italiana di Gerontologia e Geriatria (SIGG)

OPEN ACCESS

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: <https://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>

INTRODUCTION

Ageing is a unidirectional, intrinsic process occurring in all cells and characterized by functional decline related to an increased risk of morbidity and mortality. Both genetic and environmental factors have an impact on cellular senescence ^{1,2}. People age at different rates and this diversity is the result of the cumulative impact of advantage and disadvantage within the physical and social environments they live in. The environment itself is a complex and manifold combination of different dimensions such as physical, psychological, social and cultural ³. As estimated by the World Health Organization, only as less as approximately 25% of the diversity in longevity is explained by genetic factors, while the other 75% is largely the result of the impact of our interactions with environments and exposures ⁴. The degree to which environmental factors exert a profound effect on these processes is currently investigated in multiple studies and to date not fully understood, yet some risk factors have been identified. It is a major challenge to link environmental factors to specific cellular processes due to the complexity of the interaction, the long-term efficacy, the multifaceted interactions and the interference of several confounding factors. In light of the demographic change and considering that environmental

exposure is potentially one of the modifiable risk factors for different diseases, the identification of such factors is a major strategy in lowering the burden of disease in elderly people ⁵.

We here critically review the most appealing findings regarding environmental factors influencing and accelerating the ageing process and supporting the development of life-limiting ARDs such as cancer, dementia and cardiovascular disease because they represent the leading causes of death in industrialized countries and pathologies deriving from specific environmental influences (air, climate, water, soil, built and social environments) and associated with intrinsic mortality leading to premature death.

Given the complexity of this extensive topic, the present review can only provide a basic overview.

AGE-RELATED DISEASES

ARDs are generally viewed as being triggered by and evolve around the physiologic deterioration that occurs with advancing age. Thus, ARDs, which may manifest with both chronic and acute symptoms, are usually the results of long-term processes ⁶. It remains however of debate, whether ARDs are an integral part of the physiologic aging process or rather a pathophysiologic process. The trans-National Institutes of Health

Geroscience Interest Group (GSIG) has identified a set of seven highly intertwined processes at the core of ARDs: i) adaptation to stress; ii) loss of proteostasis; iii) stem cell exhaustion; iv) metabolism derangement; v) macromolecular damage; vi) epigenetic modifications, and vii) inflammation ^{7,8}. In regard of the fact that both “normal” ageing and ARDs share these common mechanisms, it has been hypothesized that ARDs and geriatric syndromes are to be understood as acceleration of the ageing process and therefore part of one continuum ⁶. This acceleration, however, is dependent on molecular and cellular processes that are influenced by both genetic and environmental factors (Fig. 1).

The most common examples of severe ARDs leading to premature death are dementia, cardiovascular diseases and cancer. Other age-related conditions, such as type 2 diabetes, hypertension, osteoporosis or arthritis may act as modulating risk factors. Several ARDs are among the leading causes of morbidity and mortality ⁹ and pose an enormous emotional, physical and financial burden on affected patients, caregivers and societies. Recent findings and a broader knowledge of the underpinning mechanisms of ageing and age-related diseases have led to the consensus that human health span is potentially to be prolonged ⁸.

Figure 1. Normal ageing and ARDs, boundaries, interactions, and possible environmental factors.

METHODS

Within an in-depth PubMed-search we considered studies (including meta-analyses and reviews) published in the past 15 years (2004-2019). For each of the environmental and socioeconomic factors (e.g. “air”) and the keyword “ageing” (e.g. “air AND ageing”) and the most frequent ARDs, a literature search was performed (Fig. 2). In case of less than five or fragmentary results, an additional search within google scholar was performed. References from selected papers were manually reviewed for additional studies and other age-related pathologies outside the three disease clusters.

ENVIRONMENT AND HUMAN AGEING

The human environment with its abiotic and biotic compartments is complex and encompasses different dimensions on multiple layers all of which are constantly interacting. As described by Dahlgren and Whitehead (1991) and others, an individual with his inherent constitutional factors finds himself at the center of different interacting layers, framed by socioeconomic, cultural and environmental conditions ¹⁰. All of these dimensions interact such as the conditions of one level determine

those of another (e.g. lower socioeconomic status is more likely to be associated with a lower education level, poorer living environment).

NATURAL ENVIRONMENT

The ecological environment comprises abiotic (soil, water, air) and biotic factors (organisms) ¹¹. These factors determine human evolution and are the most basic framework to any social and cultural development since people need to interact with the environment to obtain basic needs such as food, shelter and to create social and cultural networks. However, the natural environment does not only promote evolution and longevity, but triggers pathologies, mutations and tissue aberrations. With increasing civilization (i.e. invention of antibiotics, hygienic conditions, biomedical understanding) acute threats coming from the natural environment have been minimized. Within the Anthropocene with significant human impact on natural environments, a shift from acute to chronic and ARDs is observed ¹².

Air

The interaction, manipulation and exploitation of the environment for human purpose leads within a modern Western perception towards improved living standards but introduced also environmental damage such as air

Figure 2. Key words used for the literature research. For the search, one age-related disease keyword plus one environmental factor keyword was entered into the search engine.

pollution. Air pollution is a major global health problem with severe effects on human health¹³. While the health-associated risks have been identified for decades and policies towards a less polluted air have been initiated, many middle and high-income countries have failed to decrease urban pollution levels¹⁴. The World Health Organization estimates that 7 million premature deaths per year are linked to global air pollution^{14,15}. While in Asian developing countries residential energy use (e.g. heating and cooking) have the largest impact, in Europe, USA and Russia agricultural emissions make the largest relative contribution to particulate matter (PM) 2.5¹⁶. Overall, 20% of the global burden of air pollution are due to ammonia, which contributes to PM2.5 formation, whereas in much of the USA and in a few other countries also traffic and power generation account for air pollution¹⁶.

Exposure to polluted air was in multiple studies described as a major threat to human health triggering different severe somatic and psychiatric diseases with respiratory diseases, cancer and cardiovascular damage being among the most prominent ones. A broad range of pathophysiological processes are initiated or enhanced after acute short-term exposure to polluted air, i.e. altered inflammatory and oxidative status, reduced heart rate variability, arrhythmias, endothelial dysfunction, promotion of thrombosis, progression of atherosclerotic damage, stroke, atrial fibrillation and heart failure can be associated with acute exposure to air pollution¹⁷. The International Agency for Research on Cancer has defined air pollution as a group I carcinogen^{18,19}. A prospective analysis from the European Study of Cohorts for Air Pollution Effects used within the framework of a longitudinal study the data of 17 cohort studies from nine European countries with over 4 million participants and concluded that PM air pollution contributes to lung cancer incidence²⁰. Importantly, not only lungs and airways are affected, but air pollution can also damage most other organ system of the body as the smallest particles can reach the bloodstream²¹. A recent study underlined, that long-term exposure to PM10 and O3 increases cancer risk but the effect on cancer risk was compounded by obesity, smoking, and physical inactivity among subjects over 50 years old²². Additionally, inhaled or ingested pollutants contribute to vascular morbidity since the heart and vascular system are highly vulnerable and susceptible to environmental agents²³. Most strikingly, air pollutants can trigger a broad range of cardiovascular symptoms, including myocardial infarct and stroke, as they can occur within hours of exposure²⁴. Supporting evidence comes from epidemiological studies linking roadway-proximity to an elevated risk of myocardial infarction, sudden cardiac death, fatal coronary disease, post-stroke mortality and

elevated mortality risk after hospitalization with acute heart failure²⁵.

Alzheimer's (AD) pathology with its well-described amyloid beta plaques and tau tangles as histopathological key components can only account for around 50% of all reported dementia cases in most industrialized countries, while for most other forms such as vascular or mixed dementia environmental determinants may play a major role^{26,27}. The effect of air pollution on cognitive decline is mirrored in epidemiological research pointing towards differences in cognitive performance between individuals of all ages living in more and less polluted areas²⁸⁻³⁰. The Health Retirement Study found a specific memory deficit with increased exposure to PM2.5 that was the equivalent of a 1.7 to 2.8-year age difference³¹. For individuals living close to a major road, Wellenius et al. (2012) found 34% increased odds of having a low score in cognitive testing³². These results were mirrored in other studies, where BC concentrations were associated with 30% increased odds of lower scores³³ and a five-year average PM2.5 and PM10 with changes in memory function³⁴.

Besides, some studies suggest an increased risk of Parkinson's disease, a neurodegenerative disease clinically characterized by motor symptoms such as resting tremor and muscle rigidity^{35,36}. While more research is needed to fully understand the interaction between air and neurodegenerative diseases, a recent meta-analysis of the major published data concluded that long-term exposure to NOx, NO₂, CO, and O₃ was associated with an increased risk of PD³⁷.

Climate

Climate (assessed via temperature, precipitation, humidity, wind, atmospheric pressure etc. on the long term) defines and directly affects public health as exposure to ambient temperature has an immediate and strong impact on people's health and wellbeing. While humans are capable of adapting to small changes in mean ambient temperature, both being exposed to extreme cold or hot temperature is problematic for the human body. Generally, extreme cold and increased heat are associated with higher mortality especially amongst the elderly³⁸. Meanwhile, it is widely consensus that global climate change mainly due to anthropogenic causes will lead to a rise in mean temperatures and frequency of extreme heat waves, in particular in urban settings³⁹. While political controversy regarding causation is ongoing, over the past decades the global average surface temperature has been steadily increasing and the frequency, duration and severity of heat waves have become more frequent. Especially in the elderly, exposure to extreme temperatures causes health problems leading to increased morbidity and

Figure 3. Human environment is multidimensional and different interacting layers including inherent factors and environmental and socioeconomic factors (few examples per layer given) determine the overall health status of an individual (from Dahlgren and Whitehead, 1991, mod.)¹⁰.

mortality during heat waves⁴⁰. Within the thermoregulatory responses to heat stress, the human body increases blood flow trying to redistribute blood volume from the central to peripheral circulations and sweat rate placing therewith a great demand on the ageing cardiovascular system⁴¹. While for humans short-period physiological homeostasis through evaporation of sweat is even in extreme temperatures possible, prolonged moderate heat stress is difficult to outbalance for older individuals, which have, amongst an aged vasculature, also a decreased sweat rate⁴². Consequently, especially in the elderly, the majority of excess deaths during heat waves are due to cardiovascular problems, but an increase in respiratory deaths and cerebrovascular deaths contribute to the increased mortality as well⁴¹. During the 2003 heat wave in Europe, three days after the start and until four days

after the conclusion of the heat wave, 70.000 excess deaths across the entire continent were counted^{43,44}. With rising temperature due to climate change, older adults with a low socioeconomic status – since owning air condition, hydrating, dressing in light clothes and having access to transportation and social contacts are associated with decreased mortality – and poorer health conditions are most at risk to suffer from heat stress⁴⁵. Climate is therefore a tolerance factor relating to longevity with a moderate climate being more conducive to human longevity than extreme climate^{46,47}. With the increasing number of older people on the one hand and the rapidly warming earth's climate on the other, further measurements in order to lower anthropogenic pollution leading to global warming and irreversible changes in ecosystems around the world are therefore much needed to allow human longevity.

Water

The quality of drinking water is closely linked to human health as the consumption and use of water is an essential and everyday part of human life. Lack or excess of certain chemical elements may result not only in acute but also in long-term adverse health effects. Classic contaminants in water such as nitrites leading to gastrointestinal infections are well documented and strictly limited in drinking water regulations. However, also chronic and ARDs may be triggered by the specific composition of water and due to human's needful lifelong consumption of it. Accordingly, several studies suggest a relationship between water hardness, calcium (Ca) and magnesium (Mg) levels in drinking water and cardiovascular diseases: Many but not all studies found a protective association between Mg levels and cardiovascular diseases while for Ca and water hardness little evidence was found regarding these diseases ⁴⁸. However, as Ca is one of the most abundant elements in humans – being a major component of bones and also essential for both muscle and nerve functioning – drinking water rich in Ca may have a positive impact on both bone density and reduce associated diseases such as osteopenia and osteoporosis in elderly population ⁴⁹⁻⁵¹. Additionally, several studies link deficits in both Ca and Mg to an increased mortality regarding oncological diseases).

Recently, a study assessing the entire Slovakian territory found worse health status and lower life expectancy with regard to an increase in oncological, cardiovascular, gastrointestinal and respiratory diseases at low level of both Ca and Mg ⁵². The scientists concluded that drinking water from public supply should be increased at the following concentrations: $\text{Ca} > 50 \text{ mg}\cdot\text{l}^{-1}$, $\text{Mg} > 25 \text{ mg}\cdot\text{l}^{-1}$, and $\text{Ca} + \text{Mg} > 2 \text{ mmol}\cdot\text{l}^{-1}$ ⁵². Additionally, when examining water properties in Southern Chinese regions high total hardness and Mg/Ca ratio was found to be positively associated with a prolonged lifespan ⁵³. Regarding alkaline drinking water, often discussed of having beneficial effects on vessels and prevent cancer, a systematic review suggested lately that to date findings are insufficient to either support or dismiss this hypothesis ⁵⁴.

Often discussed is the effect of lithium (Li^+) in drinking water: Zarse et al. (2011) found that long-term and low-dose intake of Li^+ via drinking water may exert anti-aging capabilities in nematodes and decrease mortality in humans ⁵⁵. In 2014, a systematic review concluded that according to findings thus far, Li^+ in both standard and trace doses appear to have biological benefits for dementia ⁵⁶. Meanwhile, a recent Danish nationwide study found a lower level of lithium exposure to be associated with a lower incidence rate of dementia in a non-linear way while confounding factors can clearly not be excluded ⁵⁷. Chinese regions associated with

longevity seem to have a higher level of Li^+ in their drinking water ⁵⁸. In Texas, trace lithium in water was negatively associated with rising rates of AD, as well as obesity and type 2 diabetes, which are important risk factors for AD ⁵⁹. Previously they found lithium concentrations in tap water negatively associated with all-cause mortality and years of potential life span ⁶⁰. Other substances and above all heavy metals such as lead (Pb) and cadmium (Cd) negatively influence people's health: Cumulative lead exposure may adversely affect cognitive functions ⁶¹. Additionally, high levels of manganese in drinking water in Bangladesh or Myanmar were shown to have neurotoxic effects and may lead to Parkinson's disease ⁶². Long-term exposure to selenium through drinking water has been associated with elevated risk for several cancers and neurodegenerative diseases such as Parkinson's and amyotrophic lateral sclerosis ⁶³. However, results are ambiguous as high soil Se concentrations were also associated with a reduction in Parkinson's disease mortality rates in the USA ⁶⁴. Also for uranium (U), which seems to promote cancers as well ⁶⁵, further investigations are needed. Altogether, while further research is necessary, studies thus far suggests that water consistency may have an impact on ARDs with especially heavy metals being detrimental and moderate doses of Mg, Ca and Li^+ being potentially beneficial for the process of healthy ageing.

Soil

Like water, soil can influence human health as it contains trace elements and may contain other, potentially harmful substances. Anthropogenic activities (industry, agriculture, mining etc.) significantly change the properties of soil. The quality of soil has an impact on human health, as through plants, water and animals it finds its way into the food chain and can directly be ingested by children as part of voluntary or involuntary geophagy. To date, there are only few studies on soil and its impact on ageing. Selenium (Se), a micronutrient of both natural and anthropogenic sources (e.g. fertilizer) was positively correlated with longevity index in China ⁶⁶. Consistently, some studies have demonstrated an anticarcinogenic effect of some organic forms of Se in regard to lung, colorectal and prostate cancer when taken in adequate dose ⁶⁷ while others found a negative impact of Se on human health when taken in high concentrations ⁶⁸. Liu et al. found a negative correlation between barium (Ba) and nickel (Ni) with longevity indexes ⁶⁶. Both Ba and Ni are heavy metals, increased in soil through anthropogenic activities. Other substances, such as organochlorine pesticides, meanwhile banned in most developed countries, act as neurotoxins and have been linked to cognitive decline in elderly ⁶⁹.

Recently, the effects of aluminum were brought into discussion: Aluminum is absorbed through food, water, drugs and the use of cosmetic products on the skin. While some studies pointed out a potential association between aluminum and AD and breast cancer, it remains controversial whether it contributes to the development of these diseases ⁷⁰. A high dose of aluminum as it may occur within dust exposure in specific workplaces may lead to severe critical adverse effects including specific encephalopathy, which is, however, not identical with the pathophysiology of AD ⁷¹. Recently, an increasing trend to consume organic food, which is produced with restricted use of synthetic pesticides, is observable. However, environmental contamination occurs in both, conventional and organic foodstuff since the proximity to traffic, chemical industries etc. determines the occurrence of pollutants ⁷².

Accordingly, a recent review concluded, that organic food might not necessarily be healthier than conventional food when exposed to indirect pollution ⁷².

Altogether, while further research is necessary to shed light on how the different components of soil may interfere with human aging, with regard to the principal of minimizing, exposure to potentially harmful substances should be kept as low as possible.

MAN-MADE SETTINGS: BUILT AND SOCIAL ENVIRONMENTS

The human imprint on the natural environment and its consequences for humankind are manifold, as it not only changes ecological patterns and systems, but also assets, economies, cultures and public health. Social and personal lifestyles arise from culture-mediated interdependencies and take place within natural settings changed by humans. There is, however, no strict dichotomy between natural environments and human constructs, since these dimensions are closely intertwined and influence the respective scenery. Individual health choices always take place within a society, where different policies shape with regulations, legislations and cultural norms the environments and health risk for populations ⁷³. People's health is strongly related to the environment they live in, but as the environment itself is complex and multidimensional rather than a single factor, the interaction of ecological, social, personal and cultural factors promotes the development of ARDs. The different bio-social dimensions are therefore to be understood in their interrelation, as multiple environmental exposures on different levels (e.g. air, lifestyle, socioeconomic background, working situation, nutrition, access to green spaces etc.) play together in the development of age-related phenotypes. Since these complex dimensions are important as they determine the risk of ARDs and longevity, the following section will give a tight overview

about the most important aspects without illustrating them in its entirety.

Urban green

Humans act upon local ecology and create cultural and social identities through settlement into cohesive communities ²⁵. Throughout the process of civilization, humans have built artificial, non-natural environments to protect themselves from natural threats and created new anthropogenic threats to human health such as pollution, noise and crowding. By now, daily life for the majority of the world's population takes place in artificial built environments. While urbanization is clearly one of the leading global trends of the 21st century, humans display innate biophilic preferences ²⁵. There is a large body of evidence, that people prefer viewing natural over urban environments and that walking in nature is associated with increased wellbeing, cognition and fewer mental disorders among older people ⁷⁴⁻⁷⁸. While on the one hand cities tend to be better equipped regarding access to health-care infrastructure and greater educational opportunities, on the other hand they offer less interaction with natural vegetation, animals and sunlight. Residential green has been repeatedly associated with lower levels of cardiovascular diseases such as stroke ²⁵. Additionally, living within the proximity of greenspaces is associated with lower levels of stress, diabetes, with increased physical activity, better general health and social cohesion ^{75,79-81}. Within elderly people, urban green spaces seem to have a restorative effect ⁸² and can thus be considered both a protective factor against accelerated ageing and a therapeutic measure after onset of ARDs. Altogether, frequent exposures to landscapes with natural elements such as neighborhood street trees, small parks, or views of nature out of a window have a salutogenic impact on human health ⁸³.

There are, however, rural-urban disparities regarding ARDs: Dementia appears to be more often diagnosed in rural settings ⁸⁴. It remains to be understood, why rural populations seem more susceptible to dementia and cognitive decline, however, educational opportunities and reduced public health supply may play a role ⁸⁵. For ARDs belonging to the cardiovascular cluster, particulate matter as it occurs in both urban areas and rural environments with intensive agriculture is a known risk factor. Several epidemiological studies examined the incidence rate of different cancer types, however, the results seem ambivalent ⁸⁶. Altogether, while further interdisciplinary research is needed, both rural and urban environments with its diverse environmental conditions poses positive and negative challenges onto human health.

Socioeconomic background

The sociocultural context of a person's life determines

longevity and the individual risk for age-related diseases. The development of ARDs depend on exposure to harmful or protective environments, which in turn are strongly associated with an individual's social status (e.g. working place, living conditions etc.). A well-described and significant socioeconomic gradient in health accounts for large differences in long-term health outcomes between people of different social backgrounds⁸⁷. The higher individuals rise in social hierarchy, the better is their health. Since the "Black report" in 1988, a compelling body of studies from different countries has accumulated showing how social determinants shape health and promote or reduce healthy ageing^{87,88}. By now, multiple studies have consistently shown that each grade of employment in industrialized countries has a higher level of morbidity and mortality than the one above it^{89,90}. The improved health status in higher positions derives from increased human capital, better education, favorable living conditions, better psychosocial resources, higher occupational complexity, healthier lifestyle and better access to health care. Low education level and potentially modifiable risk factors account for almost half of all deaths in the USA⁹¹ – findings, which have been mirrored in multiple European studies. The socioeconomic position defines not only the broader contextual environment with its diverse abiotic and biotic factors an individual lives in, but determines also which lifestyle behaviors are more likely to be adopted. All of these environmental conditions be it natural or social, exert ultimately an influence on cellular level and promote or reduce the outbreak of ARDs.

Social cohesion

Individuals are intertwined through social relationships. Deficits in social relationships such as social isolation or low social support can lead through chronic activation of immune, neuroendocrine, and metabolic systems to ARDs⁹²: a representative longitudinal sample of the US population found that social isolation increases the risk of inflammation and promotes hypertension⁹³. Moreover, social activities and religious involvement are associated with lower levels of allostatic load⁹⁴ and help to preserve cognitive function as people age⁹⁵. Like most ARD-risk-factors, physiological vulnerabilities to social integration may be specific to life stage and seem to set the course early: Individuals who experience social deficits in early life are more prone to diseases in later life and have higher level of C-reactive protein in mid-life⁹⁶. Lack of social connections increases the odds of death by at least 50%, comparable to risk factors such as smoking, alcohol consumption, high blood pressure, physical inactivity and obesity⁹⁷. As people age, the environment plays an increasingly important role and defines whether and to what degree an

individual participates in social interaction, community engagement and physical activity⁹⁸. Accordingly, geriatric depression is triggered by social and economic variables⁹⁹. Research has found a strong correlation between social participation and positive health status in elderly among different communities in North America, Asia and Europe⁹⁶. People, who regularly engage in social, cultural or intellectual activities built up a so-called "cognitive reserve" and are less likely to develop neurodegenerative disorders^{97,98}.

LIFESTYLE: PHYSICAL ACTIVITY AND NUTRITION

People in lower socioeconomic positions seem to adopt more readily and more frequent health-harming behaviors^{88,100,101} such as smoking, sedentary behavior, poorer diets, lower therapeutic compliance¹⁰². The contributing factors are manifold and complex and include besides material factors, differences in knowledge and skills, in living and working conditions and cultural norms^{103,104}. Moreover, people with lower educational status appear to be more pessimistic, put more weight into short-term gratification than into long-term outcomes and have a stronger belief in the influence of chance on health¹⁰². Most of these underlying behaviors do not follow free and individual choices but are rather a form of adaptation to the social, cultural and economic constraints.

Physical activity

The default mode for humans is to be physically active while inactivity is associated with a higher burden of disease in older age. Effectively, sedentary behavior is an independent parameter of mortality¹⁰⁵. Several epidemiological studies have examined the association between physical activity and healthy ageing. The Harvard Alumni Study, the Whitehall Study and the Nurses' Health Study have consistently proved associations between physical activity and exceptional survival¹⁰⁶⁻¹⁰⁸. It is known that physical activity is a key element in predicting a non-disabled 65-year-old man's chances of surviving to age 80 and being non-disabled prior to death¹⁰⁹. Health benefits of physical activity are even seen among individuals who became physically active late in life – suggesting that physical activity has both protective and restorative impact¹¹⁰. The underlying mechanisms are not fully understood, it seems, however, that aerobic exercise improves DNA repair mechanisms, is associated with an upregulation of protective proteins, has a positive impact on mitochondrial function and on telomere length and leads to a downregulation of negative regulator proteins of cell cycle progression¹¹¹. Moreover, physical activity is beneficial for circulating concentrations of insulin, insulin-related pathways and inflammation¹¹². Physical activity

with its many effects on multiple organ systems is inversely associated with different cancer types such as breast ¹¹³, endometrial ^{114,115} and colorectal cancer ¹¹⁶. In terms of prevention, a minimum of 2.5 h per week of moderate-to-vigorous physical activity led to a significant 13% reduction in cancer mortality ¹¹⁷. Moreover, regular physical activity and elimination of sedentary lifestyle has been associated with a reduction of 15–39% of cardiovascular disease and 33% of stroke ¹¹⁸. Additionally, physical activity is associated with a lower incidence of psychiatric conditions in older age such as cognitive impairment and dementia ^{119,120} possibly due to improved mechanisms of neural plasticity triggered by regular physical activity ¹²¹.

However, movement takes place where the physical environment allows it. The environmental influence on physical activity participation is well established: A high proportion of urban green spaces provides a venue for outdoor physical activity; cycling and pedestrian networks contribute positively to movement for those living in proximity ¹²². Environment features such as destinations to walk to, fewer uncontrolled intersections and low traffic density are also associated with increased outdoor activity ¹²³. The concept of “walkability”, as measure of the extent to which built environment allows physical movement and presence of people, is therefore of high public health relevance ¹²⁴. Eventually, socioeconomics define where and how people live. Accordingly, poverty may account for environmental barriers to physical activity. Besides, seasonality – as another strong environmental factor – has an impact on human movement. Both very cold and very hot weather is a barrier to physical activity participation ¹²⁵. In sum, physical activity is a key element for healthy ageing while it depends on a variety of personal, social, economic and environmental factors whether people engage in physical activity or not.

Nutrition

Additionally to physical activity, nutrition plays a major role in healthy ageing and has the potential to reduce the risk of several ARDs. While the debate on the optimal nutrition is ongoing, the Mediterranean diet, characterized by a balanced combination of fruit, vegetables, fish, cereals and polyunsaturated fats and reduced meat and dairy products is considered the optimal combination to preserve health and improve longevity ¹²⁶. This dietary pattern contributes with its anti-cancer, anti-inflammatory and anti-obesity properties due to its antioxidant elements, unsaturated fats and fibers to a risk-reduction of many ARDs ¹²⁷. Moreover, a moderate caloric restriction (i.e. restriction of proteins or other individual nutrients with respects to carbohydrates) positively affects lifespan and cognitive

function ¹²⁸. The quality of people's foods depends, however, on its production. In any urbanized society, the majority of people eat food raised by others, which most often contain non-additional additives that may influence human health. Moreover, the socioeconomic background plays an important role in people's food choices, as higher occupational social classes are significantly associated with greater food expenditure, which in turn is associated with healthier purchasing. Altogether, energy-dense and less nutritious foods are often cheaper sources of calories while higher food quality is often associated with higher cost ¹²⁹.

CONCLUSIONS

GUIDANCE AND NORMS, POLICIES AND LEGISLATION

Environmental health policies can be implemented from local to international levels. Accordingly, policies vary between regions and according to decision-makers. A recent approach at a global level to protect the environment and thus indirectly human health is the so-called “Paris Agreement”, adopted under the United Nations Framework Convention on Climate Change (UNFCCC) in 2015. However, by 2017 a study found that all major industrialized countries were failing to meet the pledges they made ¹³⁰. With regard to healthy ageing, the World Health Organization has adopted a “Global Strategy and Action Plan on Ageing and Health” in 2016, where the development of age-friendly and sustainable environments plays a central role ¹³¹. Moreover, it is pointed out that more research is needed to identify the determinants of a long and healthy life including structural, biological and social determinants ¹³¹. Thus, while the importance of environmental factors for healthy ageing is increasingly recognized, the consistent implementation of protective measures is not yet successful and requires both further scientific research and political efforts.

FURTHER PERSPECTIVES

As humans, we carry out our lives within a complex physical environment characterized by manifold biological and chemical systems that interfere with our health and wellbeing. With humankind constantly manipulating and acting upon the bio-social environment, it is of main public health interest to understand how these dimensions interfere with ageing and longevity. While it remains a challenge to associate environmental influences to specific age-related conditions due to the multifactorial etiology and the impossibility to exclude confounding factors in the chronic development of a disease throughout years and decades,

epidemiological evidence thus far indicates that common ARDs such as cardiovascular and neurodegenerative diseases are driven by diverse environmental influences. Rather than one single causative factor a range of environmental, demographic, biological, behavioral and social factors determine the development and onset of the multifactorial diseases such as dementia and CVD. Exposure to harmful environmental conditions can alter biochemical pathways at the sub-/cellular level and therewith trigger the outbreak of age-related conditions. While further interdisciplinary research needs to be carried out and since the individual has only limited control over the exposure to environmental pollutants, policy intervention to reduce

pollution are both urgent and necessary to allow healthy ageing on a global scale (Tab. I).

Altogether, while preventive strategies often aim at individual interventions, collective actions on the societal level such as restructuring cities regarding green and blue spaces and reducing anthropogenic air pollution, support healthy ageing and the prevention of ARDs. With regard to the complexity of the ageing process and the high emotional and economic burden ARDs pose on human societies, further interdisciplinary research needs to target potentially modifiable factors in order to structurally reduce harmful environmental influences on human health.

Table I. Preventive measurements on societal and individual level.

	Societal	Individual
Air	<ul style="list-style-type: none"> • Reduce emission sources. • Facilitate decision-making and implementation of laws to reduce air pollution • Exert regular control over the quality of air • Provide walkable infrastructures and bike lanes and reserve green spaces in urban and rural planning 	<ul style="list-style-type: none"> • Susceptible individuals (e.g. elderly) should avoid acute and long-term exposure to polluted air • Regular physical activity improves heart and respiratory systems • Reduce outdoor activity on high pollution days • Use public transportation, carpool, and bike or walk
Climate	<ul style="list-style-type: none"> • Lower anthropogenic pollution leading to global warming and irreversible changes to the ecosystems • Improve management during heat waves: Allow transportation and access to cooling rooms for people • Help people with education and information to lower their “carbon footprint” 	<ul style="list-style-type: none"> • Know your individual “carbon footprint” in order to lead towards a more sustainable lifestyle • Reduce, reuse and recycle • Conserve electricity, buy energy-efficient products, unplug electronics, consume consciously • During heat waves: Keep doors and windows closed, use blinds and drapes, drink enough water, wear light clothes, keep social contacts
Water	<ul style="list-style-type: none"> • Provide access to sanitation to prevent drinking water contamination from human waste • Exert regular control over the concentrations of different components in drinking water • Drinking water with high total hardness (TH) and Mg/Ca ratio might be good for the health. Heavy metals in drinking water seem to have health-damaging effects 	<ul style="list-style-type: none"> • Avoid contamination of water with non-degradable products, medications, chemical cleaners or any other product with toxic ingredients • Stay hydrated especially during days with elevated temperatures
Soil	<ul style="list-style-type: none"> • Promote ecological complexity and robustness of soil biodiversity to suppress disease-causing soil organisms and provide healthy food • Avoid poor land-management practices • Control and restrict anthropogenic activities changing the properties of soil and increasing the accumulation of toxins such as heavy metals 	<ul style="list-style-type: none"> • Keep exposure to harmful substances as low as possible • Avoid ingestion of possible contaminated soil • Buy local food from known and safe sources
Urban green	<ul style="list-style-type: none"> • Reserve green spaces in planning to improve physical and social activities of communities, reduce air and noise pollution, heat islands effects and provide refuge to disappearing species to support biodiversity 	<ul style="list-style-type: none"> • Take benefit from the restorative effect of green spaces; visit them regularly for walks, social interactions, sports, relaxing time
Social and individual environment	<ul style="list-style-type: none"> • Close health gaps between higher and lower income classes • Improve and support the consumption of healthy diet • Provide safe spaces for physical activity and community interaction • Provide transport and education 	<ul style="list-style-type: none"> • Mediterranean diet and caloric restriction positively affect lifespan • Regular physical activity decreases chronic inflammation and oxidative stress • Regular social interaction and community engagement improves wellbeing and preserves cognitive function

References

- 1 Geller AM, Zenick H. Aging and the environment: a research framework. *Environ Health Perspect* 2005;113:1257-62. <https://doi.org/10.1289/ehp.7569>
- 2 Troen BR. The biology of aging. *Mt Sinai J Med* 2003;70:3-22.
- 3 Lalonde M. A New perspective on the health of Canadians. Ottawa, Ontario, Canada: Minister of Supply and Services, 1974.
- 4 World Health Organization. Fact file: misconceptions on ageing and health, 2019 (<https://www.who.int/ageing/features/misconceptions/en>).
- 5 World Health Organization. World Report on Ageing and Health, 2015 (https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf).
- 6 Franceschi C, Garagnani P, Morsiani C, et al. The continuum of aging and age-related diseases: common mechanisms but different rates. *Front Med (Lausanne)* 2018;5:61. <https://doi.org/10.3389/fmed.2018.00061>
- 7 Kennedy BK, Berger SL, Brunet A, et al. Geroscience: linking aging to chronic disease. *Cell* 2014;159:709-13. <https://doi.org/10.1016/j.cell.2014.10.039>
- 8 Kennedy BK, Berger SL, Brunet A, et al. Aging: a common driver of chronic diseases and a target for novel interventions. *Cell* 2014;159:709. <https://doi.org/10.1016/j.cell.2014.10.039>
- 9 Niccoli T, Partridge L. Ageing as a risk factor for disease. *Curr Biol* 2012;22:R741-52. <https://doi.org/10.1016/j.cub.2012.07.024>
- 10 Dahlgren G, Whitehead M. Policies and strategies to promote social equity in health. Stockholm, Sweden: Institute for Futures Studies 1991.
- 11 Zerbe S, Plagg B, Polo A. Städtische Ökosysteme und menschliche Gesundheit. Ein interdisziplinärer Brückenschlag zur nachhaltigen Entwicklung und Renaturierung urbaner Lebensräume. In: Fehr R, Hornberg C, Eds. Stadt der Zukunft – Gesund und nachhaltig; Band 1;. Munich: oekom 2018, pp.169-85.
- 12 World Health Organization. The Top 10 causes of death, 2018 (<https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>).
- 13 Chen B, Kan H. Air pollution and population health: a global challenge. *Environ Health Prev Med* 2008;13:94-101. <https://doi.org/10.1007/s12199-007-0018-5>
- 14 World Health Organization. 7 million premature deaths annually linked to air pollution, 2014 (<https://www.who.int/mediacentre/news/releases/2014/air-pollution/en>).
- 15 Kelly FJ, Fussell JC. Air pollution and public health: emerging hazards and improved understanding of risk. *Environ Geochem Health* 2015;37:631-49. <https://doi.org/10.1007/s10653-015-9720-1>
- 16 Lelieveld J, Evans JS, Fnais M, et al. The contribution of outdoor air pollution sources to premature mortality on a global scale. *Nature* 2015;525:367-71. <https://doi.org/10.1038/nature15371>
- 17 Lelieveld J, Klingmüller K, Pozzer A, et al. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. *Eur Heart J* 2019;40:1590-6. <https://doi.org/10.1093/eurheartj/ehz135>
- 18 Loomis D, Grosse Y, Lauby-Secretan B, et al. The carcinogenicity of outdoor air pollution. *Lancet Oncol* 2013;14:1262-3.
- 19 Hamra GB, Guha N, Cohen A, et al. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. *Environ Health Perspect* 2014;122:906-11. <https://doi.org/10.1289/ehp.1408092>. Erratum in: *Environ Health Perspect* 2014;122:A236.
- 20 Raaschou-Nielsen O, Andersen ZJ, Beelen R, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol* 2013;14:813-22. [https://doi.org/10.1016/S1470-2045\(13\)70279-1](https://doi.org/10.1016/S1470-2045(13)70279-1)
- 21 Schraufnagel DE, Balmes JR, Cowl CT, et al. Air pollution and noncommunicable diseases: a review by the Forum of International Respiratory Societies' Environmental Committee, Part 2: air pollution and organ systems. *Chest* 2019;155:417-26. <https://doi.org/10.1016/j.chest.2018.10.041>
- 22 Kim KJ, Shin J, Choi J. Cancer risk from exposure to particulate matter and ozone according to obesity and health-related behaviors: a Nationwide Population-Based Cross-Sectional study. *Cancer Epidemiol Biomarkers Prev* 2019;28:357-62. <https://doi.org/10.1158/1055-9965.EPI-18-0508>
- 23 Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol* 2015;12:627. <https://doi.org/10.1038/nrcardio.2015.152>
- 24 Stafoggia M, Cesaroni G, Peters A, et al. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the ESCAPE project. *Environ Health Perspect* 2014; 122:919-25. <https://doi.org/10.1289/ehp.1307301>
- 25 Bhatnagar A. Environmental determinants of cardiovascular disease. *Circ Res* 2017;121:162-80. <https://doi.org/10.1161/CIRCRESAHA.117.306458>
- 26 Killin LO, Starr JM, Shiue IJ, et al. Environmental risk factors for dementia: a systematic review. *BMC Geriatr* 2016;16:1-28. <https://doi.org/10.1186/s12877-016-0342-y>
- 27 Peters R, Ee N, Peters J, et al. Air pollution and dementia: a systematic review. *J Alzheimers Dis* 2019;70:S145-63. <https://doi.org/10.3233/JAD-180631>
- 28 Zhang X, Chen X, Zhang X. The impact of exposure to air pollution on cognitive performance. *Proc Natl Acad Sci U S A* 2018;115:9193-7. <https://doi.org/10.1073/pnas.1809474115>
- 29 Cipriani G, Danti S, Carlesi C, et al. Danger in the air: air pollution and cognitive dysfunction. *Am J Alzheimers Dis Other Dement* 2018;33:333-41. <https://doi.org/10.1177/1533317518777859>
- 30 Clifford A, Lang L, Chen R, et al. Exposure to air pollution

- and cognitive functioning across the life course – a systematic literature review. *Environ Res* 2016;147:383-98. <https://doi.org/10.1016/j.envres.2016.01.018>
- 31 Ailshire JA, Crimmins EM. Fine particulate matter air pollution and cognitive function among older US adults. *Am J Epidemiol* 2014;180:359-66. <https://doi.org/10.1093/aje/kwu155>
 - 32 Wellenius GA, Boyle LD, Coull BA, et al. Residential proximity to nearest major roadway and cognitive function in community-dwelling seniors: results from the MOBILIZE Boston study. *J Am Geriatr Soc* 2012;60:2075-80. <https://doi.org/10.1111/j.1532-5415.2012.04195.x>
 - 33 Power MC, Weisskopf MG, Alexeeff SE, et al. Traffic-related air pollution and cognitive function in a cohort of older men. *Environ Health Perspect* 2011;119:682-7. <https://doi.org/10.1289/ehp.1002767>
 - 34 Tonne C, Elbaz A, Beevers S, et al. Traffic-related air pollution in relation to cognitive function in older adults. *Epidemiology* 2014;25:674. <https://doi.org/10.1097/EDE.0000000000000144>
 - 35 Lee H, Myung W, Kim DK, et al. Short-term air pollution exposure aggravates Parkinson's disease in a population-based cohort. *Sci Rep* 2017;7:44741. <https://doi.org/10.1038/srep44741>
 - 36 Palacios N. Air pollution and Parkinson's disease – evidence and future directions. *Rev Environ Health* 2017;32:303-13. <https://doi.org/10.1515/reveh-2017-0009>
 - 37 Hu CY, Fang Y, Li FL, et al. Association between ambient air pollution and Parkinson's disease: systematic review and meta-analysis. *Environ Res* 2019;168:448-59. <https://doi.org/10.1016/j.envres.2018.10.008>
 - 38 Mitchell D, Heaviside C, Schaller N, et al. Extreme heat-related mortality avoided under Paris Agreement goals. *Nat Clim Chang* 2018;8:551-3. <https://doi.org/10.1038/s41558-018-0210-1>
 - 39 Meehl GA, Tebaldi C. More intense, more frequent, and longer lasting heat waves in the 21st century. *Science*. 2004; doi:10.1126/science.1098704.
 - 40 Basu R. High ambient temperature and mortality: a review of epidemiologic studies from 2001 to 2008. *Environ Health* 2009;8:40. <https://doi.org/10.1186/1476-069X-8-40>
 - 41 Kenney WL, Craighead DH, Alexander LM. Heat waves, aging, and human cardiovascular health. *Med Sci Sports Exerc* 2014;46:1891. <https://doi.org/10.1249/MSS.0000000000000325>
 - 42 Smith CJ, Alexander LM, Kenney WL. Nonuniform, age-related decrements in regional sweating and skin blood flow. *Am J Physiol Regul Integr Comp Physiol* 2013;305:R877-85. <https://doi.org/10.1152/ajpregu.00290.2013>
 - 43 Robine JM, Cheung SL, Le Roy S, et al. Death toll exceeded 70,000 in Europe during the summer of 2003. *C R Biol* 2008;331:171-8. <https://doi.org/10.1016/j.crvi.2007.12.001>
 - 44 Fouillet A, Rey G, Laurent F, et al. Excess mortality related to the August 2003 heat wave in France. *International Archives of Occupational and Environmental Health*, 2006;80:16-24. <https://doi.org/10.1007/s00420-006-0089-4>
 - 45 Vandentorren S, Bretin P, Zeghnoun A, et al. August 2003 heat wave in France: risk factors for death of elderly people living at home. *Eur J Public Health* 2006;16:583-91. <https://doi.org/10.1093/eurpub/ckl063>
 - 46 Huang Y, Rosenberg M, Wang Y. Is extreme climate or moderate climate more conducive to longevity in China? *Int J Biometeorol* 2018;62:971-7. <https://doi.org/10.1007/s00484-018-1499-1>
 - 47 Huang Y, Rosenberg M, Hou L, et al. Relationships among environment, climate, and longevity in China. *Int J Environ Res Public Health* 2017;14:1195. <https://doi.org/10.3390/ijerph14101195>
 - 48 Monarca S, Donato F, Zerbini I, et al. Review of epidemiological studies on drinking water hardness and cardiovascular diseases. *Eur J Cardiovasc Prev Rehabil* 2006;13:495-506. <https://doi.org/10.1097/01.hjr.0000214608.99113.5c>
 - 49 Wynn E, Raetz E, Burckhardt P. The composition of mineral waters sourced from Europe and North America in respect to bone health: composition of mineral water optimal for bone. *Br J Nutr* 2009;101:1195-9. <https://doi.org/10.1017/S0007114508061515>
 - 50 Meunier PJ, Jenvrin C, Munoz F, et al. Consumption of a high calcium mineral water lowers biochemical indices of bone remodeling in postmenopausal women with low calcium intake. *Osteoporos Int* 2005;16:1203-9. <https://doi.org/10.1007/s00198-004-1828-6>
 - 51 Vannucci L, Fossi C, Quattrini S, et al. Calcium intake in bone health: a focus on calcium-rich mineral waters. *Nutrients* 2018;10:1930. <https://doi.org/10.3390/nu10121930>
 - 52 Rapant S, Cvečková V, Fajčíková K, et al. Chemical composition of groundwater/drinking water and oncological disease mortality in Slovak Republic. *Environ Geochem Health* 2017;39:191-208. <https://doi.org/10.1007/s10653-016-9820-6>
 - 53 Liu YL, Luo KL, Lin XX, et al. Regional distribution of longevity population and chemical characteristics of natural water in Xinjiang, China. *Sci Total Environ* 2014;473:54-62. <https://doi.org/10.1016/j.scitotenv.2013.11.134>
 - 54 Fenton TR, Huang T. Systematic review of the association between dietary acid load, alkaline water and cancer. *BMJ Open* 2016;6. <https://doi.org/10.1136/bmjopen-2015-010438>
 - 55 Zarse K, Terao T, Tian J, et al. Low-dose lithium uptake promotes longevity in humans and metazoans. *Eur J Nutr* 2011;50:387-9. <https://doi.org/10.1007/s00394-011-0171-x>
 - 56 Mauer S, Vergne D, Ghaemi SN. Standard and trace-dose lithium: a systematic review of dementia prevention and other behavioral benefits. *Aust N Z J Psychiatry* 2014;48:809-18. <https://doi.org/10.1177/0004867414536932>
 - 57 Kessing LV, Gerds TA, Knudsen NN, et al. Association of lithium in drinking water with the incidence of dementia. *JAMA Psychiatry* 2017;74:1005-10. <https://doi.org/10.1001/jamapsychiatry.2017.2362>
 - 58 Deng Q, Chen L, Wei Y, et al. Understanding the association between environmental factors and longevity in Hechi, China: a drinking water and soil quality perspective.

- Int J Environ Res Public Health 2018;15:2272. <https://doi.org/10.3390/ijerph15102272>
- 59 Fajardo VA, Fajardo VA, LeBlanc PJ, et al. Examining the relationship between trace lithium in drinking water and the rising rates of age-adjusted Alzheimer's disease mortality in Texas. *J Alzheimers Dis* 2018;61:425-34. <https://doi.org/10.3233/JAD-170744>
 - 60 Fajardo VA, LeBlanc PJ, Fajardo VA. Trace lithium in Texas tap water is negatively associated with all-cause mortality and premature death. *Appl Physiol Nutr Metab* 2018;43:412-4. <https://doi.org/10.1139/ap-nm-2017-0653>
 - 61 Weisskopf MG, Proctor SP, Wright RO, et al. Cumulative lead exposure and cognitive performance among elderly men. *Epidemiology* 2007;1:59-66. <https://doi.org/10.1097/01.ede.0000248237.35363.29>
 - 62 Frisbie SH, Mitchell EJ, Sarkar B. Urgent need to reevaluate the latest World Health Organization guidelines for toxic inorganic substances in drinking water. *Environmental Health* 2015;14:1-5. <https://doi.org/10.1186/s12940-015-0050-7>
 - 63 Vinceti M, Ballotari P, Steinmaus C, et al. Long-term mortality patterns in a residential cohort exposed to inorganic selenium in drinking water. *Environ Res* 2016;150:348-56. <https://doi.org/10.1016/j.envres.2016.06.009>
 - 64 Sun H. Association of soil selenium, strontium, and magnesium concentrations with Parkinson's disease mortality rates in the USA. *Environ Geochem Health* 2018;40:349-57. <https://doi.org/10.1007/s10653-017-9915-8>
 - 65 Banning A, Benfer M. Drinking water uranium and potential health effects in the German Federal State of Bavaria. *Int J Environ Res Public Health* 2017;14:927. <https://doi.org/10.3390/ijerph14080927>
 - 66 Liu Y, Li Y, Jiang Y, Li H, et al. Effects of soil trace elements on longevity population in China. *Biol Trace Elem Res* 2013;153:119-26. <https://doi.org/10.1007/s12011-013-9673-0>
 - 67 Kieliszek M, Błażej S. Current knowledge on the importance of selenium in food for living organisms: a review. *Molecules* 2016;21:609. <https://doi.org/10.3390/molecules21050609>
 - 68 MacFarquhar JK, Broussard DL, Melstrom P, et al. Acute selenium toxicity associated with a dietary supplement. *Arch Intern Med* 2010;170:256-61. <https://doi.org/10.1001/archinternmed.2009.495>
 - 69 Kim SA, Lee YM, Lee HW, et al. Greater cognitive decline with aging among elders with high serum concentrations of organochlorine pesticides. *PLoS One* 2015;10:e0130623. <https://doi.org/10.1371/journal.pone.0130623>
 - 70 Colomina MT, Peris-Sampedro F. Aluminum and Alzheimer's disease. *Adv Neurobiol* 2017;10:978-3. https://doi.org/10.1007/978-3-319-60189-2_9
 - 71 Klotz K, Weistenhöfer W, Neff F, et al. The health effects of aluminum exposure. *Dtsch Arztebl Int* 2017;114:653. <https://doi.org/10.3238/arztebl.2017.0653>
 - 72 González N, Marquès M, Nadal M, et al. Occurrence of environmental pollutants in foodstuffs: a review of organic vs conventional food. *Food Chem Toxicol* 2019;125:370-5. <https://doi.org/10.1016/j.fct.2019.01.021>
 - 73 Mayer JD. The political ecology of disease as one new focus for medical geography. *Progr Hum Geogr* 1996;20:441-56.
 - 74 Kondo MC, Fluehr JM, McKeon T, et al. Urban green space and its impact on human health. *Int J Environ Res Public Health* 2018;15:445. <https://doi.org/10.3390/ijerph15030445>
 - 75 Roe J, Aspinall P. The restorative benefits of walking in urban and rural settings in adults with good and poor mental health. *Health Place* 2011;17:103-13. <https://doi.org/10.1016/j.healthplace.2010.09.003>
 - 76 van den Berg M, van Poppel M, van Kamp I, et al. Visiting green space is associated with mental health and vitality: a cross-sectional study in four European cities. *Health Place* 2016;38:8-15. <https://doi.org/10.1016/j.healthplace.2016.01.003>
 - 77 Cassarino M, Setti A. Environment as 'Brain Training': a review of geographical and physical environmental influences on cognitive ageing. *Ageing Res Rev* 2015;23:167-82. <https://doi.org/10.1016/j.arr.2015.06.003>
 - 78 Wu YT, Prina AM, Jones A, et al. Older people, the natural environment and common mental disorders: cross-sectional results from the Cognitive Function and Ageing study. *BMJ Open* 2015;5. <https://doi.org/10.1136/bmjopen-2015-007936>
 - 79 Gascon M, Triguero-Mas M, Martínez D, et al. Residential green spaces and mortality: a systematic review. *Environ Int* 2016;86:60-7. <https://doi.org/10.1016/j.envint.2015.10.013>
 - 80 Ji JS, Zhu A, Bai C, et al. Residential greenness and mortality in oldest-old women and men in China: a longitudinal cohort study. *Lancet Planet Health* 2019;3:e17-25. [https://doi.org/10.1016/S2542-5196\(18\)30264-X](https://doi.org/10.1016/S2542-5196(18)30264-X)
 - 81 McMorris O, Villeneuve PJ, Su J, et al. Urban greenness and physical activity in a national survey of Canadians. *Environ Res* 2015;137:94-100. <https://doi.org/10.1016/j.envres.2014.11.010>
 - 82 Neale C, Aspinall P, Roe J, et al. Correction to: the ageing urban brain: analyzing outdoor physical activity using the emotiv affectiv suite in older people. *J Urban Health* 2017;94:869-80. <https://doi.org/10.1007/s11524-017-0209-3>
 - 83 Frumkin H, Bratman GN, Breslow SJ, et al. Nature contact and human health: a research agenda. *Environ Health Perspect* 2017;125:075001. <https://doi.org/10.1289/EHP1663>
 - 84 Jia J, Wang F, Wei C, et al. The prevalence of dementia in urban and rural areas of China. *Alzheimers Dement* 2014;10:1-9. <https://doi.org/10.1016/j.jalz.2013.01.012>
 - 85 Harris JK, Beatty K, Leider JP, et al. The double disparity facing rural local health departments. *Annu Rev Public Health* 2016;37:167-84. <https://doi.org/10.1146/annurev-publhealth-031914-122755>
 - 86 Afshar N, English DR, Milne RL. Rural-urban residence and cancer survival in high-income countries: a

- systematic review. *Cancer* 2019;125:2172-84. <https://doi.org/10.1002/cncr.32073>
- 87 Gray AM. Inequalities in health. The Black Report: a summary and comment. *Int J Health Serv* 1982;12:349-80. <https://doi.org/10.2190/XXMM-JMQU-2A7Y-HX1E>
 - 88 Macintyre S. The Black Report and beyond: what are the issues? *Soc Sci Med* 1997;44:723-45.
 - 89 Marmot M, Bobak M. International comparators and poverty and health in Europe. *BMJ* 2000;321:1124. <https://doi.org/10.1136/bmj.321.7269.1124>
 - 90 Marmot M, Brunner E. Cohort Profile: the Whitehall II study. *Int J Epidemiol* 2005;34:251-6. <https://doi.org/10.1093/ije/dyh372>
 - 91 Jemal A, Thun MJ, Ward EE, et al. Mortality from leading causes by education and race in the United States, 2001. *Am J Prev Med* 2008;34:1-8. <https://doi.org/10.1016/j.amepre.2007.09.017>
 - 92 Cacioppo JT, Hawkley LC. Social isolation and health, with an emphasis on underlying mechanisms. *Perspect Biol Med* 2003;46(Suppl 3):S39-52.
 - 93 Yang YC, Schorpp K, Harris KM. Social support, social strain and inflammation: evidence from a national longitudinal study of U.S. adults. *Soc Sci Med* 2014;107:124-35. <https://doi.org/10.1016/j.socscimed.2014.02.013>
 - 94 Seeman T, Gleit D, Goldman N, et al. Social relationships and allostatic load in Taiwanese elderly and near elderly. *Soc Sci Med* 2004;59:2245-57. <https://doi.org/10.1016/j.socscimed.2004.03.027>
 - 95 Gleit DA, Landau DA, Goldman N, et al. Participating in social activities helps preserve cognitive function: an analysis of a longitudinal, population-based study of the elderly. *Int J Epidemiol* 2005;34:864-71. <https://doi.org/10.1093/ije/dyi049>
 - 96 Lacey RE, Kumari M, Bartley M. Social isolation in childhood and adult inflammation: evidence from the National Child Development study. *Psychoneuroendocrinology* 2014;50:85-94. <https://doi.org/10.1016/j.psyneuen.2014.08.007>
 - 97 Holt-Lunstad J. Why social relationships are important for physical health: a systems approach to understanding and modifying risk and protection. *Annu Rev Psychol* 2018;69:437-58. <https://doi.org/10.1146/annurev-psych-122216-011902>
 - 98 Vogelsang EM. Older adult social participation and its relationship with health: rural-urban differences. *Health Place* 2016;42:111-9. <https://doi.org/10.1016/j.healthplace.2016.09.010>
 - 99 Brinda EM, Rajkumar AP, Attermann J, et al. Health, social, and economic variables associated with depression among older people in low and middle income countries: World Health Organization Study on Global AGEing and Adult Health. *Am J Geriatr Psychiatry* 2016;24:1196-208. <https://doi.org/10.1016/j.jagp.2016.07.016>
 - 100 Lynch JW, Kaplan GA, Salonen JT. Why do poor people behave poorly? Variation in adult health behaviours and psychosocial characteristics by stages of the socioeconomic lifecourse. *Soc Sci Med* 1997;44:809-19.
 - 101 Martikainen P, Brunner E, Marmot M. Socioeconomic differences in dietary patterns among middle-aged men and women. *Soc Sci Med* 2003;56:1397-410.
 - 102 Nettle D. Why are there social gradients in preventative health behavior? A perspective from behavioral ecology. *PLoS One* 2010;5:e13371. <https://doi.org/10.1371/journal.pone.0013371>
 - 103 Blaxter M. Whose fault is it? People's own conceptions of the reasons for health inequalities. *Soc Sci Med* 1997;44:747-56.
 - 104 Mansyur CL, Amick BC, Franzini L, et al. Culture and the social context of health inequalities. *Int J Health Serv* 2009;39:85-106. <https://doi.org/10.2190/HS.39.1.d>
 - 105 Bouchard C, Blair SN, Katzmarzyk PT. Less sitting, more physical activity, or higher fitness? *Mayo Clin Proc* 2015;90:1533-40. <https://doi.org/10.1016/j.mayocp.2015.08.005>
 - 106 Yu E, Rimm E, Qi L, et al. Diet, lifestyle, biomarkers, genetic factors, and risk of cardiovascular disease in the Nurses' Health studies. *Am J Public Health* 2016;106:1616-23. <https://doi.org/10.2105/AJPH.2016.303316>
 - 107 Ahmadi-Abhari S, Sabia S, Shipley MJ, et al. Physical activity, sedentary behavior, and long-term changes in aortic stiffness: the Whitehall II study. *J Am Heart Assoc* 2017;6:e005974. <https://doi.org/10.1161/JAHA.117.005974>
 - 108 Lee IM, Paffenbarger RS. Physical activity and stroke incidence: the Harvard Alumni Health Study. *Stroke* 1998;29:2049-54.
 - 109 Leveille SG, Guralnik JM, Ferrucci L, et al. Aging successfully until death in old age: opportunities for increasing active life expectancy. *Am J Epidemiol* 1999;149:654-64. <https://doi.org/10.1093/oxfordjournals.aje.a009866>
 - 110 Hamer M, Lavoie KL, Bacon SL. Taking up physical activity in later life and healthy ageing: the English longitudinal study of ageing. *Br J Sports Med* 2014;48:239-43. <https://doi.org/10.1136/bjsports-2013-092993>
 - 111 Rebelo-Marques A, De Sousa Lages A, Andrade R, et al. Aging Hallmarks: the benefits of physical exercise. *Front Endocrinol (Lausanne)* 2018;9:258. <https://doi.org/10.3389/fendo.2018.00258>
 - 112 Ballard-Barbash R, Friedenreich CM, Courneya KS, et al. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst* 2012;104:815-40. <https://doi.org/10.1093/jnci/djs207>
 - 113 de Boer MC, Wörner EA, Verlaan D, et al. The mechanisms and effects of physical activity on breast cancer. *Clin Breast Cancer* 2017;17:272-8. <https://doi.org/10.1016/j.clbc.2017.01.006>
 - 114 Schmid D, Behrens G, Keimling M, et al. A systematic review and meta-analysis of physical activity and endometrial cancer risk. *Eur J Epidemiol* 2015;397:412. <https://doi.org/10.1007/s10654-015-0017-6>
 - 115 Aune D, Navarro Rosenblatt DA, Chan DS, et al. Anthropometric factors and endometrial cancer risk: a systematic review and dose-response meta-analysis of prospective studies. *Ann Oncol* 2015;26:1635-48. <https://doi.org/10.1093/annonc/mdv142>
 - 116 Van Blarigan EL, Meyerhardt JA. Role of

- physical activity and diet after colorectal cancer diagnosis. *J Clin Oncol* 2015;33:1825. <https://doi.org/10.1200/JCO.2014.59.7799>
- ¹¹⁷ Li T, Wei S, Shi Y, et al. The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. *Br J Sports Med* 2016;50:339-45. <https://doi.org/10.1136/bjsports-2015-094927>
 - ¹¹⁸ Giada F, Biffi A, Agostoni P, et al.; Joint Italian Societies' Task Force on Sports Cardiology. Exercise prescription for the prevention and treatment of cardiovascular diseases: part I. *J Cardiovasc Med (Hagerstown)* 2008;9:529-44. <https://doi.org/10.2459/JCM.0b013e3282f7ca77>
 - ¹¹⁹ Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA* 2008;300:1027-37. Erratum in: *JAMA*. 2009;301:276. <https://doi.org/10.1001/jama.300.9.1027>
 - ¹²⁰ Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med* 2011;269:107-17. <https://doi.org/10.1111/j.1365-2796.2010.02281.x>
 - ¹²¹ Voss MW, Vivar C, Kramer AF, et al. Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn Sci* 2013;17:525-44. <https://doi.org/10.1016/j.tics.2013.08.001>
 - ¹²² Mäki-Opas TE, Borodulin K, Valkeinen H, et al. The contribution of travel-related urban zones, cycling and pedestrian networks and green space to commuting physical activity among adults – a cross-sectional population-based study using geographical information systems. *BMC Public Health* 2016;16:760. <https://doi.org/10.1186/s12889-016-3264-x>
 - ¹²³ Brownson RC, Hoehner CM, Day K, et al. Measuring the built environment for physical activity: state of the science. *Am J Prev Med* 2009;36:S99-123. <https://doi.org/10.1016/j.amepre.2009.01.005>
 - ¹²⁴ Createore MI, Glazier RH, Moineddin R, et al. Association of neighborhood walkability with change in overweight, obesity, and diabetes. *JAMA* 2016;315:2211-20. <https://doi.org/10.1001/jama.2016.5898>
 - ¹²⁵ Chan CB, Ryan DA. Assessing the effects of weather conditions on physical activity participation using objective measures. *Int J Environ Res Public Health* 2009;6:2639-54. <https://doi.org/10.3390/ijerph6102639>
 - ¹²⁶ Merchant AT, Dehghan M, Akhtar-Danesh N. Seasonal variation in leisure-time physical activity among Canadians. *Can J Public Health* 2007;98:203-8.
 - ¹²⁷ Di Daniele N, Noce A, Vidiri MF, et al. Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. *Oncotarget* 2017;8:8947. <https://doi.org/10.18632/oncotarget.13553>
 - ¹²⁸ Picca A, Pesce V, Lezza AMS. Does eating less make you live longer and better? An update on calorie restriction. *Clin Interv Aging* 2017;12:1887. <https://doi.org/10.2147/CIA.S126458>
 - ¹²⁹ Darmon N, Drewnowski A. Contribution of food prices and diet cost to socioeconomic disparities in diet quality and health: a systematic review and analysis. *Nutr Rev* 2015;73:643-60. <https://doi.org/10.1093/nutrit/nuv027>
 - ¹³⁰ Rogelj J, Den Elzen M, Höhne N, et al. Paris Agreement climate proposals need a boost to keep warming well below 2 C. *Nature* 2016;534:631-9.
 - ¹³¹ World Health Organization. The Global strategy and action plan on ageing and health (<https://www.who.int/ageing/WHO-GSAP-2017.pdf?ua=1>).