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Human ageing and its discontents: rethinking health, disease and intervention

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Abstract

Human ageing is a complex biological process characterized by age-related functional decline, resulting in increased vulnerability to illness, disease and death. Although advances in molecular gerontology have elucidated the cellular and molecular underpinnings of ageing, translating these insights into effective strategies that extend both health span and lifespan in humans remains a pressing challenge. A persistent obstacle is the absence of a coherent and operational definition of health within the field. Traditional models define health as the absence of disease or functional impairment, but this conception becomes increasingly inadequate in the context of ageing, where multimorbidity, subclinical dysfunction and frailty often occur without overt pathology. Ageing can be conceptualized as a contraction of the homeodynamic space, reflecting diminished resilience, adaptability and repair capacity. From a philosophical perspective, health may be understood as a sustained pattern of adaptive traits over time. In this review, we explore conceptual distinctions between health, illness, disease and related terms, with particular attention to clinically significant yet non-pathological states. We argue that biogerontology should adopt resilience-based and systems-level frameworks to capture the complexity of ageing and to guide the development of interventions that support functioning and quality of life across the lifespan. We also propose an integrative model that links personalized geroscience approaches with lifespan-related, behavioural and social factors to promote healthy ageing.

Running title: Human ageing and its discontents

Keywords: ageing, age-related disease, biogerontology, health span, lifestyle interventions, molecular mechanisms

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Introduction

Human ageing is a complex and emergent biological process influenced by mechanisms such as genomic instability, telomere attrition, cellular senescence, epigenetic alterations and loss of proteostasis, among others, which are collectively described in conceptual frameworks as the 'hallmarks' or 'pillars' of ageing [1–7]. While these frameworks have guided research and therapeutic exploration, their causal roles and translational relevance continue to be critically evaluated [8–11].

Key questions in biogerontology include whether ageing can be effectively delayed in humans, whether age-related diseases (ARDs) can be prevented by targeting the hallmarks or pillars of ageing and how 'health' should be defined and measured in this context [10]. The interventionist perspective regards ageing as a modifiable biological process amenable to genetic, pharmacological and nutritional manipulation [2,3,5]. Compounds such as geroprotectors (e.g. metformin, rapamycin) and senolytics (e.g. dasatinib, quercetin) have shown promise in preclinical models [12–16], suggesting that certain aspects of ageing are malleable. Nevertheless, the absence of a coherent and operational definition of health complicates the evaluation and comparison of such interventions.

In this review, we explore the conceptual foundations of health, illness and related states, drawing from biomedical, philosophical and anthropological perspectives. We also propose an integrative model that links personalized geroscience approaches with lifespan-related, behavioural and social factors to promote healthy ageing.

Defining health and its opposites

In the context of ageing, establishing a clear and operational definition of 'health' and related concepts remains a central theoretical challenge in anthropology and medicine. Health is often described as a state of physical, psychological and social wellbeing, encompassing both the subjective experience of feeling well, commonly termed 'wellness', and the objective capacity to function effectively, often referred to as 'wellbeing'. Despite its clinical importance, the concept of health, alongside related terms such as 'illness', 'disease', 'disorder', 'pathology' and 'sickness', continues to provoke debate within the philosophy of medicine, medical anthropology and biogerontology.

Philosophers and clinicians alike have long sought a general theory of health that can inform both medical practice and ageing research [17,18]. One challenge lies in the inherently multidimensional nature of health, which involves not only the absence of disease but also the presence of physiological integrity, adaptability and resilience in response to stressors. Definitions generally fall into two categories: (1) negative, defining health as the absence of dysfunction or pathology; and (2) positive, viewing health as a state of optimal functioning characterized by structural and functional integrity, repair capacity and homeodynamic regulation.

Terminology related to adverse health states includes overlapping but distinct concepts. 'Illness' denotes the subjective experience of unwellness or functional impairment, regardless of whether a diagnosable disease is present (**Fig. 1**). By contrast, 'disease' and 'disorder' refer to clinically identifiable medical conditions marked by deviations from normal biological functioning. 'Pathology' describes the underlying structural, functional or biochemical abnormalities of disease, whereas 'sickness' denotes the social role associated with illness or disease, including the expectations, responsibilities and entitlements, such as access to care, afforded to a person recognized as sick.

In typical clinical scenarios, an individual experiences illness, receives a disease diagnosis and is recognized as sick, which entitles them to care (Case 1, **Fig. 1**). Examples include overt cancers, coronary heart disease, myocardial infarction and stroke, where symptoms are apparent and diagnostic criteria are well established. However, some conditions cause both illness and disease without the individual being recognized as sick (Case 2). For instance, the common cold, migraine and pain produce symptoms that may require treatment, although affected individuals are not generally considered sick in the sociomedical sense.

Conversely, illness may occur without diagnosable disease (Case 3). Persistent grief, sadness, chronic fatigue that does not meet formal syndrome criteria, or chronic insomnia lacking clear pathology can substantially impair quality of life despite the absence of objective biomarkers or definitive diagnostic criteria. Moreover, traits such as emotional hypersensitivity blur the line between normal variation and dysfunction (Cases 4 and 5), and may warrant therapeutic attention even in the absence of clinical disease. Other scenarios involve diagnosed disease and possible recognition as sick, yet without subjective illness (Cases 6 and 7), which is an increasingly common situation owing to advances in diagnostics. Examples include asymptomatic hypertension, early diabetes or preclinical dementia. These conditions may require intervention, underscoring the importance of preventive medicine, particularly in ageing populations. Some diseases remain asymptomatic and undetected without screening, such as ductal carcinoma *in situ* or early infections including HIV, hepatitis B and hepatitis C.

Finally, numerous medically significant conditions and risk factors are not classified as diseases, yet demand clinical attention. These include physical inactivity, overweight, unhealthy diets, tobacco and alcohol use, polypharmacy, physical weakness, fatigue and frailty. Obesity is increasingly recog-

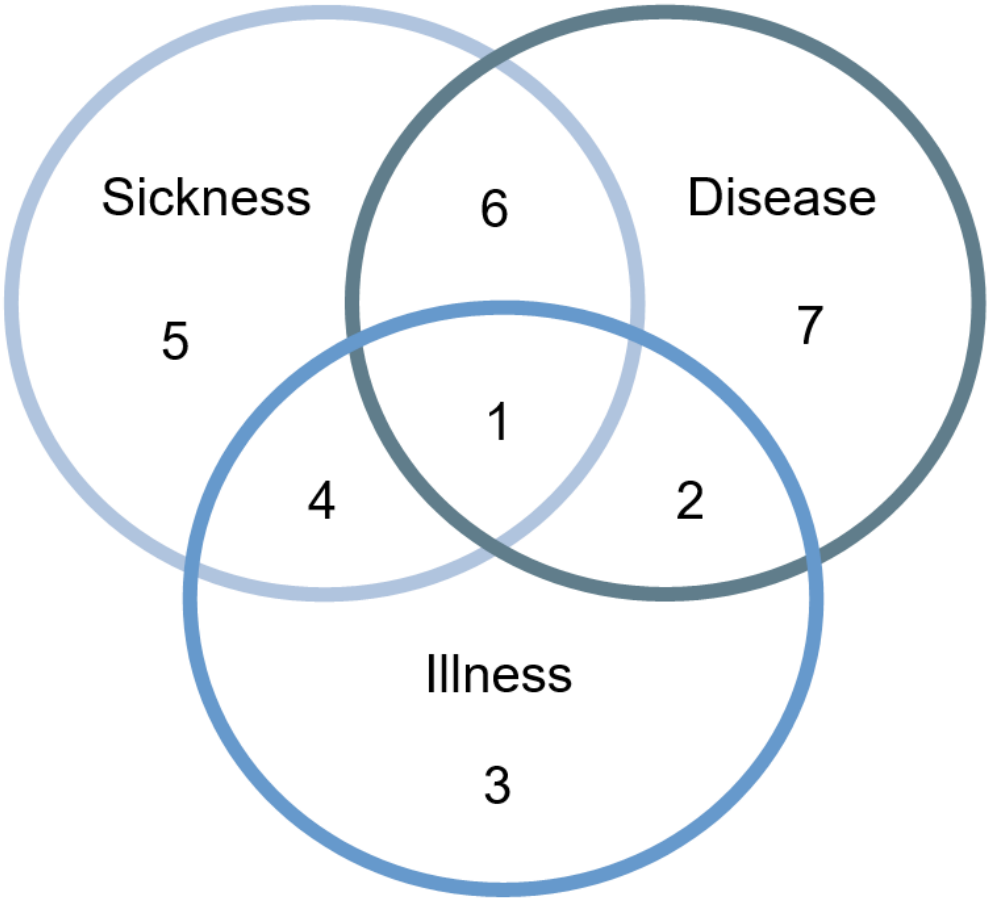

FIGURE 1 Configurations illustrating the conceptual distinctions and overlaps among illness, disease and sickness

nized as a chronic disease that adversely affects multiple organ systems through inflammatory and hormonal pathways [20–23]. Smoking and alcohol use, while behavioural risks, are also linked to diagnosable substance use disorders. Polypharmacy increases the risk of adverse drug reactions and functional decline. Fatigue and frailty, reflecting diminished physiological reserve, are key geriatric indicators despite lacking traditional disease classification.

These examples highlight the limitations of narrow definitions of health and disease in ageing and emphasise the need for integrated frameworks that encompass subjective experience, objective function, social context and preventive care.

Rethinking the health–illness continuum

In both clinical and public health contexts, health is frequently defined in negative terms, as the absence of disease or infirmity. While operationally convenient, this definition becomes increasingly inadequate in ageing populations, where subclinical dysfunction, multimorbidity and diminished physiological resilience often occur in the absence of overt pathology. A more appropriate conceptualisation of health in this context is one that emphasises resilience, robustness and adaptive capacity.

Suresh Rattan has put forward a compelling alternative with his concept of the homeodynamic space, which characterizes an organism's intrinsic biological resilience and its capacity to maintain structural and functional integrity under stress [24,25]. Within this framework, ageing is not considered a 'disease' but a progressive contraction of the homeodynamic space. This contraction reflects a gradual decline in buffering capacity and adaptive potential over time. Rattan conceptualizes ageing as an emergent and dynamic phenomenon resulting from the cumulative burden of lifelong biological activity, even in the presence of somatic maintenance, repair and defence mechanisms. The homeodynamic space comprises three interdependent components: (1) damage repair systems, such as DNA repair and proteostasis, which preserve molecular integrity; (2) stress response pathways, including antioxidant networks and heat shock proteins, which mitigate internal and environmental challenges; and (3) ongoing remodelling and adaptation, including immune and metabolic plasticity, which sustain systemic responsiveness.

A cornerstone of Rattan's model is the principle of hormesis, including mitohormesis, which refers to the activation of protective and longevity-promoting pathways in response to mild biological

stressors [3,25]. Agents that induce these adaptive responses, known as hormetins, encompass physical stimuli such as exercise, thermal exposures like heat or cold, nutritional compounds including polyphenols and flavonoids, as well as cognitive or psychological challenges. These non-pharmacological interventions do not directly treat disease but rather enhance the homeodynamic space and improve resilience. Consequently, Rattan advocates shifting away from narrowly disease-focused models towards health-oriented and systems-based strategies that prioritize the preservation of function and independence across the lifespan [10,25]. Central to this approach is the development of personalized assessments based on objective biomarkers of resilience, such as repair efficiency, stress responsiveness and adaptive flexibility [24,25]. This framework not only promotes individual well-being but also holds potential to mitigate the societal and economic burdens associated with chronic disease and functional decline in later life.

In parallel, Jonathan Sholl highlights a foundational gap in biogerontology: the lack of a coherent definition of health [17,18]. Although ageing research routinely seeks to prevent disease and extend health span, its conceptual basis often remains fragmented. Without a clearly articulated theoretical framework, scientific efforts risk inconsistency in both methodology and interpretation. Sholl proposes that health be understood as a temporally sustained pattern of traits that reflect resilience and adaptability. He calls for sustained collaboration between philosophers and biomedical scientists to develop and critically assess competing conceptions of health. This interdisciplinary effort, he argues, is essential for advancing the science of ageing with conceptual clarity and theoretical robustness.

Clarifying the distinction between health and its opposites also requires careful attention to terminology. Terms such as 'illness', 'disease', 'disorder' and 'pathology' are often used interchangeably, yet each conveys a distinct clinical and conceptual meaning. Conditions such as frailty, sarcopenia, and polypharmacy frequently inhabit a grey zone. They are clinically significant and associated with poor outcomes, even though they may not meet conventional criteria for pathology. Frailty, for instance, can be described as a state of increased vulnerability to stressors due to reduced physiological reserve. Although not a disease in the strict sense, much like ageing itself, frailty represents a critical risk factor and remains an important target for preventive and therapeutic strategies.

Pharmacological interventions and the limits of reductionism

Caloric restriction (CR) attenuates ageing in multiple species [26,27], primarily by modulating nutrient-sensing pathways such as the mechanistic target of rapamycin (mTOR) and sirtuins. However, its long-term feasibility and efficacy in humans remain uncertain [10,28,29]. This has spurred interest in CR mimetics and other pharmacological strategies, including senolytics and senomorphics [30–43]. These interventions aim to extend health span and, potentially, lifespan, either by selectively eliminating senescent cells (senolytics) or by suppressing their pro-inflammatory secretory phenotype (senomorphics).

Despite their promise, these strategies raise critical questions. Do they target the fundamental biology of ageing, or merely its downstream manifestations? Can they meaningfully extend health span, which is arguably the more desirable outcome, or only lifespan, which may not correspond to improved quality of life? In the absence of a robust conceptual framework for health in the context of ageing, defining appropriate endpoints and interpreting clinical outcomes remains especially challenging.

Moreover, there is a need to critically assess the implications of medicalizing normal ageing [10,24,25]. Not all age-related changes are pathological, and not all warrant intervention. For example, certain cancers may progress more slowly in biologically older individuals than in younger ones, although the underlying mechanisms of these associations are not fully understood. Therapies aimed at resetting biological age, such as genetic modifications or epigenetic reprogramming, need to address our still-incomplete understanding of the physiological foundations of ageing and health. It is unlikely that all mechanistically plausible interventions will extend health span and lifespan alike. In addition, an overly reductionist biomedical model risks neglecting the social, psychological and functional dimensions of ageing.

Six pillars of health: lifestyle and molecular strategies

The concept of 'health span' refers to the period of life spent in good health, free from chronic disease and significant functional decline. While pharmacological interventions hold promise, lifestyle and environmental factors remain central to shaping health trajectories in later life. Six interrelated domains underpin healthy functioning across the lifespan: (1) diet and nutrition, (2) social and emotional support, (3) sleep hygiene, (4) stress management, (5) regular physical exercise alongside cognitive engagement, as well as (6) modulation of the biological mechanisms of ageing. Together, these pillars provide a foundation for enhancing physiological resilience and reducing the burden of ARDs (**Fig. 2**).

Dietary patterns with low caloric content, anti-inflammatory potential and high concentrations of natural antioxidants, polyphenols and other bioactive compounds (e.g. omega−3 fatty acids), together

FIGURE 2 Six pillars supporting healthy functioning by enhancing resilience and mitigating functional decline across the lifespan

with adequate intake of essential nutrients including vitamins (e.g. C and D) and micronutrients, as well as the inclusion of probiotics, play a critical role in maintaining metabolic integrity and have been associated with a reduced risk of developing several ARDs [44,45]. Diets rich in fresh fruits, vegetables and whole grains, such as the Mediterranean diet, are associated with lower all-cause mortality and reduced risks of insulin resistance, type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), stroke and cancer. Advances in personalized nutrition, incorporating genetic, metabolic and microbiome data, are shifting the field towards precision strategies tailored to individual biological and lifestyle profiles.

Social and emotional support is a vital determinant of health in later life. Increasing evidence links loneliness and social isolation to higher risks of depression, cognitive impairment and premature mortality in older people [46,47]. Strong social networks, whether familial, communal or virtual, can buffer stress responses, promote adaptive behaviour and enhance overall resilience. Supportive relationships have been shown to modulate stress biomarkers, including cortisol and inflammatory mediators. Structured interventions such as community-based programmes or digital platforms that promote engagement are crucial to public health strategies targeting older populations.

Sleep quality declines with age, with significant consequences for cognitive performance, immune function and metabolic health. Sleep loss from various causes, including irregular sleep patterns, prolonged screen exposure, physical inactivity, sedentarism and untreated sleep disorders such as insomnia or obstructive sleep apnoea, can negatively impact overall health. There are strong links between sleep loss and serious medical conditions such as insulin resistance, T2DM, high blood pressure, depression and anxiety. These health conditions increase the risk of cardiovascular and cerebrovascular events, including stroke and myocardial infarction. Other adverse effects of sleep loss include increased morbidity and mortality [48]. Deep sleep facilitates glymphatic clearance of neurotoxic waste products, a process that deteriorates with age. Evidence-based strategies to support sleep include maintaining consistent routines, limiting blue light exposure and addressing underlying disorders. Interventions targeting circadian rhythms, such as

light therapy or chrononutrition, are emerging as effective methods to strengthen sleep architecture in older adults.

Psychological stress is a potent but frequently underestimated contributor to both physical and mental morbidity. Chronic stress activates the hypothalamic–pituitary–adrenal (HPA) axis, increasing cortisol levels and promoting oxidative stress, inflammation and immune dysfunction [49]. These effects are implicated in the pathogenesis of hypertension, hyperlipidaemia, CVD, gastrointestinal disorders and mood disturbances. Multimodal stress reduction strategies include mindfulness-based approaches, cognitive behavioural therapy, meditative practices and somatic techniques such as yoga. Creative and emotionally fulfilling activities, including art, music, nature exposure and animal-assisted therapies, also support emotional resilience. Complementary practices such as aromatherapy, humour-based interventions and relationship enrichment may further enhance well-being [49].

Physical and cognitive activity is strongly associated with improved outcomes in ageing. Regular exercise, such as aerobic, resistance, flexibility and balance training, improves muscular strength, cardiovascular efficiency, metabolic control and fall prevention [49]. It also supports neurogenesis, mitochondrial health and proteostasis [43]. Cognitive training, particularly tasks that challenge memory, attention and executive function, enhances neuroplasticity and may delay cognitive decline. Activities that combine physical and cognitive demands, such as dance or martial arts, have demonstrated benefits across multiple domains of function and well-being. Interventions should be personalized to support adherence over the long term.

Beyond lifestyle, molecular insights deepen our understanding of the biology of ageing and offer novel targets. At the molecular level, the hallmarks of ageing, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication, provide a conceptual framework for understanding and modulating ageing [1–7, 30–44]. Targeting these mechanisms offers a plausible route to slow functional decline and extend both lifespan and health span. Pharmacological agents that target ageing pathways are now under active investigation. Senolytics such as dasatinib and quercetin reduce the burden of senescent cells and improve tissue function. Metformin and rapamycin, both of which modulate nutrient-sensing pathways, are undergoing trials to assess their capacity to delay multiple ARDs, including the Targeting Ageing with Metformin (TAME) trial [12,50]. Similarly, nicotinamide adenine dinucleotide (NAD^+) precursors, such as nicotinamide mononucleotide (NMN), show potential in supporting mitochondrial function and DNA repair in preclinical models [51,52]. Although the integration of pharmacological and lifestyle interventions may produce additive or synergistic benefits, clinical translation will require carefully designed human studies to determine safety, efficacy and long-term impact.

Conclusions

Human ageing, both at the individual and population level as exemplified by the global increase in older populations, represents one of the most formidable challenges in contemporary medicine, raising fundamental questions about health, disease and the very nature of human life. Although recent advances show considerable promise, they must be understood within the broader context of ageing as a natural and emergent biological process. The complexity of ageing demands interdisciplinary collaboration and recognition of its multifactorial determinants, including genetic, environmental and lifestyle factors.

Ethical approval

This was a descriptive study. No animal or human subjects were involved in this research

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Conflict of interest

The authors declare no conflict of interest.

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