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60 years of healthy aging: On definitions, biomarkers, scores and challenges

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ABSTRACT

Background and objective: As the proportion of aging people in our population increases steadily, global strategies accompanied by extensive research are necessary to tackle society and health service challenges. The World Health Organization recently published an action plan: "Decade of healthy aging 2020–2030", which calls for concerted collaboration to prevent poverty of older people to provide quality education, job opportunities, and an age-inclusive infrastructure. However, scientists worldwide still struggle to find definitions and appropriate measurements of aging per se and healthy aging in particular. This literature review aims to compile concepts of healthy aging and provide a condensed overview of the challenges in defining and measuring it, along with suggestions for further research.
Materials and methods: We conducted three independent systematic literature searches covering the main scopes addressed in this review: (1) concepts and definitions of healthy aging, (2) outcomes and measures in (healthy) aging studies and (3) scores and indices of healthy aging. For each scope, the retrieved literature body was screened and subsequently synthesized.
Results: We provide a historical overview of the concepts of healthy aging over the past 60 years. Furthermore, we identifiy current difficulties in identifying healthy agers, including dichotomous measurements, illness-centered views, study populations & designs. Secondly, markers and measures of healthy aging are discussed, including points to consider, like plausibility, consistency, and robustness.
Finally, we present healthy aging scores as measurements, which combine multiple aspects to avoid a dichotomous categorization and display the bio-psycho-social concept of healthy aging.
Discussion and conclusion: When deducting research, scientists need to consider the diverse challenges in defining and measuring healthy aging. Considering that, we recommend scores that combine multiple aspects of healthy aging, such as the Healthy Ageing Index or the ATHLOS score, among others. Further efforts are to be made on a harmonized definition of healthy aging and validated measuring instruments that are modular, easy to apply and provide comparable results in different studies and cohorts to enhance the generalization of results.

1. Introduction

The demographic transition is one of the most challenging developments in our modern world. In 2020, 9% of the world's population was 65 years and older. In Europe, the number of people older than 65 even outnumbered the number of children below 15 years by three percent (Population Reference Bureau, 2021). While in 2019, about one in 11 people worldwide were 65 years and older, by 2050, one in six people in the world will be over the age of 65 (United Nations - Department Of Economic And Social Affairs - Population Division, 2019).

This age distribution requires changes in society, economy, and

Abbreviations: AAI, active aging index; ATHLOS, Aging trajectories of health-longitudinal opportunities and synergies; HA, Healthy aging; (i)ADL, (instrumental) activities of daily living; IC, Intrinsic capacity; ICF, International Classification of Functioning, Disability and Health; QoL, quality of life; WHO, World Health Organization; HAI, Healthy aging index; HAS, Healthy aging score.

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politics since it results from increasing longevity but is not necessarily accompanied by an extended time in good health (Cosco et al., 2017). Indeed, the percentage of people suffering from one or more chronic diseases increases (Fiacco et al., 2019) because aging is the most significant risk factor for most common chronic diseases (Zhang et al., 2020).

Health conditions in older people show increasing variability (Cosco et al., 2017), distinguishing the aging process as heterogeneous and modifiable. This observation immediately leads to healthy or successful aging as expressions describing a good aging process.

The World Health Organization (WHO) recently published an action plan, "Decade of healthy aging 2020–2030 ", which calls for ten years of concerted, catalytic, sustained collaboration (WHO Team Ageing & Health, 2021; WHO Team Demographic Change And Healthy Ageing 2020). Specific goals of the action plan are, e.g., preventing poverty of older people, providing quality education, job opportunities, and age-inclusive infrastructure. It aims to bring together all the involved instances, such as *"governments, the civil society, international agencies, professionals, academia, the media and the private sector to improve the lives of older people* " (WHO Team Demographic Change And Healthy Ageing 2020). This critical literature review aims to provide an overview of the development of the concept of "healthy aging", including bio-psycho-social aspects. Based on that, we highlight the means and difficulties of defining and measuring healthy aging and make suggestions for future research.

1.1. On aging

Most scientists agree that aging is the physiological, universal, but not uniform process of getting older, which every person will experience, albeit at an individual rate (Baltes et al., 1994; Hayflick, 2007). Because of the variability of aging rates, it is essential to distinguish between chronological and biological age. While chronological age only reflects the time since birth, biological age relates to the wide range of physical, physiological, and cognitive functions and their maintenance, both provoked by molecular and cellular processes (World Health Organization, 2015). Beyond that point, the biology of aging is still controversially discussed, and thus, it is challenging to find a universal definition of normal aging (Cohen et al., 2020).

Human cells are continuously exposed to stressors like reactive oxygen species, non-enzymatic protein modifications, environmental substances, UV-radiation and genetic impacts like the activation of oncogenes (Ungewitter and Scrable, 2009). Throughout the lifetime of every molecule and cell, damage caused by these stressors accumulates gradually. Although cells possess protective and repair mechanisms to counteract, the damage is eventually too exhaustive to be repaired.

Consequently, aging occurs from this molecular damage to cellular and organismal consequences. Cells enter replicative senescence, characterized by an altered cell function, secretory phenotype, and inflammation. Senescence, in turn, leads to changes in the microenvironment and the whole tissue (López-Otín et al., 2013). López-Otín and Kennedy proposed models to summarize and interconnect the molecular processes in aging and their reasons and effects. These so-called Pillars and Hallmarks of aging include: macromolecular damage, telomere attrition, mitochondrial dysfunction, cellular senescence, metabolic dysfunction and deregulated nutrient sensing, stem cell exhaustion, changes in proteostasis, adaption to stress and epigenetic and genomic alterations (López-Otín et al., 2013; Kennedy et al., 2014).

Biological, organismal aging could then be understood as the accumulation of senescent cells and molecular damage in an organism and the ongoing molecular aging described by the mentioned models (Fulop and Larbi, 2018).

The increasing knowledge and insight into the biological mechanisms of aging also changed how aging is perceived. Initially, aging was seen as an unavoidable, immutable process determined by genetic programs or accidental events and deemed an ultimately necessary function of life itself (Cumming et al., 1960). Scientists later described that the speed of aging is modifiable and influenceable by interventions. For example, age-associated pathways of inflammation and insulin signaling can be improved by caloric restriction (Zhang et al., 2020). Finally, aging was defined as a modifiable process that can be influenced even on the molecular level: DNA methylation and repair systems play a significant role in maintaining a tolerable level of molecular damage (Bürkle et al., 2015).

This mechanism is exploited in the concept of epigenetic clocks. Initially designed to measure chronological age accurately, epigenetic clocks of the second and third generations can detect biological aging processes and predict age-associated outcomes (Horvath and Raj, 2018; McCrory et al., 2020).

In a review of McCrory, four epigenetic clocks have been compared regarding their association to clinical health outcomes: the two first-generation-clocks Horvath DNAm Age and Hannum DNAm, which are more likely associated with chronological age, and the second-generation-clocks DNAm PhenoAge and DNAm GrimAge, which include correlations of mortality and morbidity. The comparison of the four epigenetic clocks showed no prediction of health for the first-generation clocks. At the same time, PhenoAge was associated with walking speed, frailty, Montreal Cognitive Assessment and Mini-Mental-State-Examination in an unadjusted model. GrimAge showed the best results, as it remained a predictive marker for walking speed, polypharmacy, frailty and mortality in fully adjusted models (McCrory et al., 2020) and seemed, therefore, auspicious for using it as a biomarker of aging and healthy aging alike.

1.2. Healthy aging

With the possibility of differences in individual aging rates and the constantly increasing lifespans, the idea of healthy aging as an optimal biological, sociological and physiological development throughout life arose. If society wants to support healthy aging, researchers need to measure healthy aging, and therefore a definition is needed. However, finding a uniform definition is quite difficult for researchers. Healthy aging looks back on a long historical development with the coexistence of concepts like successful, healthy, productive or active aging.

Thus, only establishing a coherent definition of healthy aging can lead to international comparability of results and population conditions (Daskalopoulou et al., 2017) and the development of standardized measurements and biomarkers (Lara et al., 2013).

2. Materials and methods

2.1. Literature search

Systematic literature reviews were conducted for three specific scopes as parts of this review: (1) concepts and definitions of healthy aging, (2) outcomes and measures in (healthy) aging studies and (3) scores and indices of healthy aging.

A different database search was conducted for each scope on 9th January 2023. For all searches, variations of search terms due to American and non-American spellings were considered, e.g., aging and ageing.

2.1.1. Scope – concepts and definitions

The Pubmed database was queried using the search terms healthy aging, healthy biological aging, successful aging, productive aging, active aging or selective optimization with (or and) compensation or healthy longevity in the title and either definition, defines, concept or particularities in the manuscript title or abstract. The results were filtered for English and German records. In total, 293 unique records were retrieved for screening.

2.1.2. Scope – outcomes and measures

Pubmed and the Cochrane library were queried on 9th January 2023. For Pubmed search, search terms to describe healthy aging were used as before and combined with study, cohort, survey, or outcome in the title. Additionally, results were filtered for clinical study/trial, comparative study, controlled clinical trial, evaluation study, validation study, multicenter study, observational study, randomized controlled trial or twin study and German or English as languages. The Cochrane Library was queried accordingly, searching in titles without any filters.

In total, 303 unique records were retrieved for screening. Additional 135 records were added from parallel searches (concepts and scores), the G2Aging database, and extensive citation searching.

2.1.3. Scope - scores & indices

The Pubmed database was queried using the search terms healthy aging, healthy biological aging, successful aging, productive aging, active aging or selective optimization with (or and) compensation or healthy longevity and either index or scale or score in the manuscript title. The results were filtered for English and German records. In total, 61 unique records were retrieved from database screening, and six records were added from parallel searches, i.e., other scopes and citation searches.

2.2. Screening and inclusion

All resulting records were imported to the Rayyan systematic review software for automated duplicate removal and screening of titles and abstracts (Ouzzani et al., 2016). A second independent researcher validated the screening of manuscripts in a blinded manner for 50% of the records. Conflicting decisions were subsequently discussed among the authors.

Records were excluded if they were not accessible, did not match the topic of the scope (Scope), were duplicates, were background articles, or contained only redundant information (Redundancy). Furthermore, studies that only validated previously described findings were excluded from all scopes (Validation). In the scopes concerning concepts and scores, articles only assessing healthy aging (Assessment) were excluded since such studies did not provide new metrics or concepts. Detailed exclusion criteria are presented in modified prisma flow diagrams in Supplementary Figures 1–3 (Haddaway et al., 2022).

Reports identified in one scope but potentially includable in the others were manually transferred for a second screening.

2.3. Synthesis

The results were synthesized from the reports eligible for each scope to summarize the findings. To synthesize the search for outcomes and accompanying variables, ten categories were defined: Demographics, Social Factors, General Health, Emotional & Psychological Health, Cognitive Functioning, Lifestyle & Risks, Aging, Anthropometry, Performance and Biomarkers. Variables, tests, measures, questionnaires and other items were sorted into those categories, and reports with outcomes in only one category were excluded. Subsequently, the number and percentages of included reports that cover a specific category were determined. Assignment of individual variables, tests, measures and outcomes to the categories mentioned earlier can be found in Suppl. Table 2.

3. Results

3.1. Historical overview of concepts of healthy aging

Throughout the development of a definition of healthy aging, the concepts were mainly shaped by social sciences, which still imprints on the perception of what healthy aging could be.

Until the 1960ies, the prevailing view of aging was negative (Fig. 1). The aging process was considered a progressive, linear decline toward death (Cumming et al., 1960). Research believed in aging as a fixed fate and assigned older people a passive role without any possibility of changing their situation. The disengagement theory, published in 1961 by Cumming & Henry (Cumming and Henry, 1961), emphasized once again this negative focus, defining successful aging as the ability to detach oneself from the activities of mid-life in the sense of a preparation for death (Cumming, 1968; Cumming et al., 1960).

The first step toward a more positive view of aging was Havighurst's Activity Theory in 1961 (Havighurst, 1961; Hicks and Conner, 2014). He defined successful aging as actively staying involved in enjoyable activities and strongly contrasts the idea of a detachment of Cumming & Henry (Cumming and Henry, 1961).

Consecutively multiple theories of successful aging were developed. The concept of "productive aging" of Butler (Butler, 1985) became important in the field of social work and occupational therapy (Hicks and Conner, 2014).

With their article "Human Aging: usual and successful", Rowe & Kahn finally succeeded in 1987 in propelling the focus of successful aging into the mainstream media and popularizing it amongst researchers (Rowe and Kahn, 1987). At a time when most researchers only focused on chronological age to determine individual health, Rowe and Kahn observed the considerable diversity of health conditions within each age group (Rowe and Kahn, 1987; Lu et al., 2019b). They pointed out that the effects of aging were, in fact, effects of diseases (Strawbridge et al., 2002). Aging characteristics were described as age-related rather

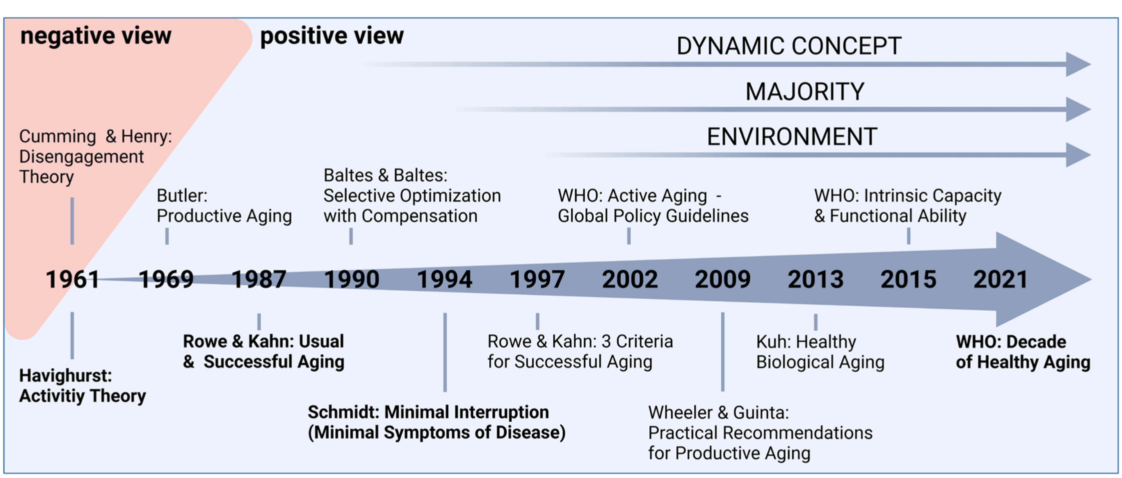

Fig. 1. **:** Overview of the historical development of the definition of healthy aging. WHO: World Health Organization.

than age-dependent (Lu et al., 2019b). Their concept distinguished between "usual" and "successful" aging. Usual aging is age-intrinsic and involves non-pathological but high-risk disease-associated reduction of physiological function with increasing age. Conversely, there is successful aging with little or no age-related decrements in physiological function, being low-risk and high-functioning (Strawbridge et al., 2002; Lu et al., 2019b).

Rowe & Kahn illustrated the importance of intrinsic and extrinsic factors and their influence on maintaining an individual's health within each age group (Lu et al., 2019b). Although their concept of successful aging was revolutionary in offering the possibility of becoming old without significant age-related diseases, it also received much criticism. Since the absence of disease or disability is an almost inaccessible ideal that only a few can reach, this concept focuses on a minority. Furthermore, it was criticized that it overrates the role of individual behavior. The concept of Rowe & Kahn would absolve policy makers' responsibility to offer a health-promoting environment for older people (Masoro, 2001). In the following years, many researchers used modifications of Rowe and Kahn's concept by changing the description of "successful" to "minimal disease and disability" or "high levels of physical functioning" (Strawbridge et al., 2002).

In 1990 Baltes & Baltes came up with a new concept: selective optimization with compensation (Baltes and Baltes, 1990). They describe a process of adaption to changes and losses. An older adult may experience a functional decline in cognitive, emotional, or physical domains (Lu et al., 2019b). In this situation, "selection" can be seen as an adaptive procedure that not only includes a reduction in the number of high-efficacy domains but also involves rearranging life goals, and adjusting to remaining capacities, environmental conditions and motivations (Lu et al., 2019b). Hence, new or transformed domains can be set up (Baltes and Baltes, 1990). "Optimisation", as the second element, considers how older people use their remaining capacities, enrich their available reserves and maximize their chosen life courses quantitatively and qualitatively (Baltes and Baltes, 1990; Lu et al., 2019b). The third element, "compensation", refers to an adjustment for the restrictions of the capacities and can be mental and technological. This concept describes a lifelong dynamic process amplified in old age (Baltes and Baltes, 1990). For the first time, healthy aging was seen as an adapting process instead of a static state.

Schmidt's definition of successful aging, seen as minimal interruption of usual function, even if mild signs and symptoms of chronic disease may be present (Strawbridge et al., 2002), has broadened the focus from a minority to a majority. By allowing chronic diseases for the category "successful aging", the concept makes this category reachable to many older people: about 50% of their study participants could be categorized as "successful agers" (Strawbridge et al., 2002).

In 1997, Rowe & Kahn published an expansion of their definition, proposing three specific criteria for successful aging (Rowe and Kahn, 1997). Even though only a small proportion of older persons could be described as aging successfully, the concept implements some positive aspects. It was recognized that the absence of any disease or disability in old age is barely possible and that social and environmental conditions play an essential role. Most importantly, these conditions can be influenced: Negative factors can be avoided, and favorable conditions can be supported. This idea led to a shift toward protective factors (Strawbridge et al., 2002). As a result of the rising awareness of the variability of the aging process and potential protective factors against unfavorable aging outcomes, calls for interventions became loud. The WHO reacted in 2002, presenting their "global policy guidelines for active ageing ". It demanded efforts for active aging to allow society and older people to appreciate aging as a positive experience. "Active Ageing" was defined as "*the process of optimizing opportunities for health, participation and security to enhance the quality of life as people age*" and requested policymakers to offer these opportunities. In addition, precise suggestions on implementing such actions for each of the three pillars: health, participation and security, were made (World Health Organization, 2002). Again, this concept highlights the importance of the social environment for the process of active aging (Lu et al., 2019b).

Resuming Butler's concept of productive aging (Butler, 1985), Wheeler and Giunta also focused on practical recommendations in 2009. They researched increasing productivity and opportunities for older people in the workplace, increasing the retirement age and decreasing the dependence of older people on society (Wheeler and Giunta, 2009).

In 2013, Kuh and colleagues presented another concept and defined healthy biological aging according to three criteria: 1) optimal physical and cognitive functioning, 2) delay of the onset of chronic diseases and 3) maximally extended lifespan (Kuh et al., 2013). In addition, well-being was outlined as a second component besides healthy biological aging (Bousquet et al., 2015). Furthermore, the importance of developing a dynamic health concept in a life-course approach was highlighted.

Within the "World report on ageing and health", the WHO proposed a public health framework in 2015 with strategies for health services, long-term care and aging-friendly environments. This report also outlines a model of healthy aging with three primary factors: intrinsic capacity, functional ability, and environment. "Intrinsic capacity" is defined as "all the physical and mental capacities that an individual can draw on at any point" (World Health Organization, 2015). An approach to translating this theoretical concept into practical pieces of advice was made in a review by Cesari and colleagues (Cesari et al., 2018). Starting from the International Classification of Functioning, Disability and Health framework, five domains for measurements of IC were developed: locomotion, vitality, cognition, psychological aspects and sensory (Cesari et al., 2018). Besides the IC, the environment with possible resources and obstacles influences decisions and options. Even if a person has a limited capacity, environmental conditions like available assistive devices can balance these restrictions and enable this person to participate successfully. These combinations and interactions of individual capacity and environment define a person's functional ability (Calder et al., 2018). The conclusion of these three interacting factors designs then a definition of healthy aging: "*Healthy ageing is the process of developing and maintaining the functional ability that enables wellbeing in older age.*" (WHO Team Ageing & Health, 2021). Thus, healthy aging should be perceived as an activity-based concept for the majority of older people. Although there were still some knowledge gaps, the report called for immediate action and proposed critical approaches to maximize functional ability.

However, the authors also state that "*focused research, increased data collection and improved measurements are essential to better understand and act on healthy aging.*" Thus, while the presented concept of healthy aging gains acceptance throughout the research community, it will not be the end of the story (WHO Team Ageing & Health, 2021).

3.2. Alternate concepts

3.2.1. Healthspan and optimal longevity

In the last decades, more significance was assigned to biological aspects of healthy aging in terms of a general concept instead of particular measurements. As mentioned in Section 3.1, concepts of healthy biological aging include optimal physical and mental functioning, delayed age-associated disease onset and the extension of the lifespan (Bousquet et al., 2015; World Health Organization, 2015). The timespan devoid of functional limitations was introduced and consequently termed healthspan (Fig. 2) (Kirkland and Peterson, 2009; Seals et al., 2016). Healthy aging in this concept thus equals a maximally extended healthspan as described by physiological and mental functioning. Seals and colleagues even extended this notion, including the compressed period of disease at the end of life and coined the term optimal longevity. Stemming from this conception is a newly named field of aging research, geroscience, which aims to identify and intervene in the biological mechanisms that increase healthspan and thus actively create healthy aging in individuals (Seals et al., 2016).

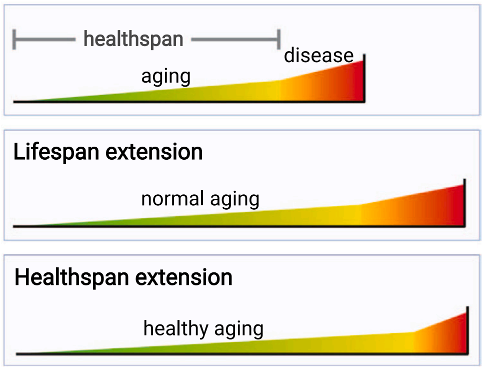

Fig. 2. **:** Lifespan and healthspan extension in healthy aging. Modified from Seals and colleagues (Seals et al., 2016).

3.2.2. *Resilience & hormesis*

Another way to approach healthy, active or successful aging is the concept of resilience. Instead of avoiding or compressing diseases and disabilities like in traditional models of healthy aging or optimal longevity, resilience allows adversity and observes which level of functioning can be maintained. With this addition, healthy aging is made more achievable for more than just a minority of older people (Cosco et al., 2017).

The term resilience originated in developmental psychology: In the first instance, children born into adverse situations managing to avoid psychopathologies were analyzed (Cosco et al., 2017). After studies to differentiate between resilient and non-resilient individuals, researchers began to understand resilience processes, test interventions, and integrate resilience into other frameworks (Hughes et al., 2012). Finally, the term resilience has been opened up to older adults.

The definition of psychological resilience also holds for biological systems. If a cell or organism can timely and fully recover after a set-off from the original state, the system is resilient (Ukraintseva et al., 2021). Biological resilience is defined at multiple levels of the human body. For example, on the molecular level, as tandem duplications (Crespi et al., 2021), at the cellular level as DNA repair, at the tissue level as blood pressure and glucose regulation and at the organ level as wound healing. Furthermore, psychological and biological resilience are linked by the stress axis. Thus, resilience factors like emotion regulation and self-control can influence biological processes: Harvanek and colleagues (Harvanek et al., 2021) described a positive association between cumulative stress and age-related DNA methylation patterns. The epigenetic clock "GrimAge" (Lu et al., 2019a) and adrenal sensitivity and insulin resistance were modulated by resilience. Results like these demonstrate the mutual influence of psychological and biological resilience mechanisms and the importance of understanding resilience as a bio-psycho-social concept and an expansion of healthy aging. Thus it is a valuable concept because whoever faces functional decline cannot be classified as aging healthy but can still be resilient (Pruchno et al., 2015). On top of that, resilience should be considered when thinking about interventions to support healthy aging because it engages hormesis.

Hormesis describes the paradox of a "*biphasic dose-response to an environmental agent characterized by a low dose stimulation or beneficial effect and a high dose inhibitory or toxic effect*" (Mattson, 2008). Studies on hormesis indicated the beneficial effects of low doses of otherwise noxious stressors like food limitation, reactive oxygen species or irradiation (Rattan, 2008) and the importance of the stressor doses, for example, in exercise (Radak et al., 2008). Through such triggered stress pathways, protective and resilience mechanisms are activated and can support the extension of life- and healthspan (Rattan, 2008).

In general, all concepts of healthy aging and alternatives have their justification in describing desirable mechanisms of and adaptions to aging processes. Even if they cover different aspects of healthy aging, they have connections and overlap.

3.3. *Current difficulties in identifying healthy agers*

3.3.1. *Lack of agreement on a definition of aging and healthy aging*

Researchers have not agreed on a standard definition of aging (Cohen et al., 2020) or healthy aging and its operationalization. The scientific community does not fully understand the complexity of aging mechanisms. Furthermore, changes in these mechanisms with age are still not fully decoded. However, it would be advantageous to understand the underlying aging processes to capture "normal aging", before defining "healthy aging".

A study of the prevalence of healthy agers in a population shows the importance of reaching an agreement about a standard definition. Rodriguez-Laso and colleagues showed a 4.5% to 49.2% prevalence of healthy aging when comparing four healthy aging classifications with decreasing stringency (Rodriguez-Laso et al., 2017). Thus, some significant challenges in defining healthy agers should be considered.

A systematic literature search identifying 74 studies and reviews concerning the definition and concepts of healthy aging showed that facilitated by historical development, several parallel concepts are frequently used in research (Suppl. Table 1). Healthy, successful, active and productive aging all describe similar and partly interwoven concepts of operationalizing and measuring the process of aging well.

Cosco and colleagues (Cosco et al., 2014) evaluated operational definitions of successful aging and highlighted five key aspects of healthy aging concepts across 84 studies: physiological constructs, engagement constructs, wellbeing-constructs, personal resources and extrinsic factors. Michel and Sadana (Michel and Sadana, 2017) deal with health outcomes of healthy and active aging and classify them into four domains: health and wellbeing, symptom-oriented measures of illness or morbidity, performing roles, activities and functions, and adaption to or coping with limitations. These results can be used to understand and find a standard for defining healthy aging. However, at the same time, they highlight the diversity in concepts and operationalizations the field is facing.

According to Martinson and colleagues (Martinson and Berridge, 2015), critiques can be divided into four categories. These were named: Add and Stir: dealing with the multidimensional expansion of criteria; Missing Voices: including older adults' subjective perception; Hard Hitting Critiques: using more inclusive frameworks to avoid stigma and intervene in the structural context of aging; and New Frames and Names: presenting alternative ideal models. This categorization also holds for most of the studies screened for this review.

Furthermore, current definitions, concepts and operationalizations are often criticized, but some authors do not necessarily provide new definitions (Suppl. Table 1, category criticism of current concept). This shows that critiques of healthy aging emerge because there are still multiple challenges when trying to find a standard definition of healthy aging.

3.3.2. *Focus on defining illness rather than health*

Researchers are used to identifying illnesses or pathological processes, not health. Most of the current outcomes are illness-centered, such as mortality, morbidity, hospitalization or disability. However, for further research and to make prevention possible, it is necessary to detect healthy aging older adults and examine them and their environment (Bousquet et al., 2015). Therefore, measurements of health need to be established.

The WHO compiled the International Classification of Functioning, Disability and Health (ICF) in 2001 to tackle this gap. It became the international standard for describing and measuring health (World Health Organization, 2001). Nevertheless, the "ICF checklist for health professionals", which only includes the shortlists for body functions, impairment of body structures, activity limitations and environmental factors, already contains more than 120 items. Thus, the ICF impressively reveals the existing complexity when defining the health status of people (World Health Organization, 2001).

3.3.3. Need to define unhealthy aging

Even if healthy aging is defined, the question of how to define the opposite remains. For some, frailty is, to some extent, the inverse of healthy aging (Franco et al., 2009). Frailty is an accumulation of deficits, including symptoms, signs, diseases and disabilities (Rockwood and Mitnitski, 2007; Fried et al., 2001). It is also one modifiable stage within the cascade of functional decline in older adults from a resilient state to disability (Taylor et al., 2023). Frailty scales are valuable instruments to measure a gradual increase in the risks of disability and death (Rockwood et al., 2005). Thus, frailty is a multifactorial and dynamic construct or even a phenotype (Rockwood and Mitnitski, 2007; Fried et al., 2001).

Since most older adults will achieve an average outcome for frailty and healthy aging, strict dichotomous cut-offs will lead to unrepresentative results (Bowling, 2007; Kusumastuti et al., 2016). A categorization on a continuous scale from more to less healthy seems more practicable.

3.3.4. Differences in the prevalences and outcomes depending on the research intention

Whether the goal is to minimize healthcare costs or improve conditions for the well-being of older people will impact the choice of a definition (Friedman et al., 2019; Yang et al., 2019). Concomitant with that, the perspective of the evaluator influences the categorization.

In our literature review, six reports directly contrast self-rated and scientific definition approaches and emphasize the importance of inclusion of subjective aspects to healthy aging concepts (Suppl. Table 1, category comparison self-rated and scientific definition).

Cosco and colleagues showed that perspectives of successful aging posed by researchers did not align with those of older adults (Cosco et al., 2017). The discrepancy was also examined in Strawbridge's study, comparing self-rated categorization to a rating according to Rowe and Kahn: 50% of the participants rated themselves as aging successfully, whereas only 18.8% were defined as successful agers by Rowe and Kahn (Strawbridge et al., 2002). A study by Brown and Bond found a difference between 66,6% to 87,4% by participant-defined successful aging and 11,4% successful agers according to a scientific definition (Brown and Bond, 2016). Furthermore, Phelan, Torres and colleagues explored this contradiction between self-rated and scientific healthy aging aspects and pointed out that multiple aspects, which the participants rated as important for a definition of successful aging, are still missing in current concepts (Phelan et al., 2004; Torres, 2006).

A citation network analysis by Kusumastuti and colleagues also describes this topic by defining two clusters of research approaches. The „Havighurst-Cluster" is based on the point of view of older people themselves. It emphasizes the importance of adaptive processes, participation and cultural influences and warns of ageism as a possible effect of categorization in success and failure. The „Katz-Cluster" focuses more on the perspective of clinicians or researchers, objective measurements of successful aging and identifying risk factors for prevention (Kusumastuti et al., 2016).

3.4. Current difficulties in choosing an appropriate study design, cohort and outcomes

3.4.1. Overall cohort characteristics define results

Besides choosing a suitable definition of healthy agers, choosing the appropriate study population to examine this group is challenging.

External circumstances like wars, crises, prosperity, and environmental influences shape the individual aging process. Furthermore, the economic, social, psychological and medical factors vary between birth cohorts, making different age groups incomparable (Sadana and Thiyagarajan, 2019). Cohort effects (Atingdui, 2011) are present especially in cross-sectional approaches and strongly influence the scientific perception of the aging process and the identification of "normal" (average) and "healthy" (better than the average) aging individuals in a cohort.

Cut-offs for healthy aging can shift with the peculiarities of the cohort used as a normal distribution, if scientists use percentiles. Then healthy agers in one generation or cohort may have been classified unfavorably in another.

One possibility to avoid this effect is to choose individuals of the same chronological age as a comparative cohort and observe possible modifications of the progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death (López-Otín et al., 2013). Generally, the definition of "normal" aging by an appropriate comparative cohort or a fixed scale of healthy aging is paramount.

Centenarians are often chosen as study subjects for an ideal of healthy aging. However, these populations might not be representative (Sanders et al., 2014). Another problem is the lack of an adequate control group for centenarians. Following this assumption that (all) centenarians are ideal healthy agers, the non-healthy aging controls of the same birth cohort cannot be examined because they have already died. However, participants in their 80ies, for example, are unsuitable as a control group because they grew up under different social, environmental and political conditions. Those unique experiences and exposures shape life courses, making a comparison, e.g., of pre- and post-war generations difficult. Among other studies, the Healthy Ageing and Biomarkers Cohort Study (HABCS) tries to circumvent this problem by including new, aged participants in each wave, replacing deceased ones and conducting home interviews to include frail probands (Lv et al., 2019). However, such concepts only mitigate the bias.

3.4.2. Diverse outcomes and associated variables in healthy aging studies

In cohort-based research, the question arises: which outcomes or endpoints might be reasonable for studies on (healthy) aging? Some studies chose hospitalization, functional decline or institutionalization as an outcome (O'Caoimh et al., 2015), but often published research still focuses on morbidity and mortality (Mount et al., 2016). These objective outcomes might be helpful when testing interventions and their effects on aging processes but cannot measure a current state and are highly focused on disease. Furthermore, they neglect the complexity of (healthy) aging (Mount et al., 2016).

That is why aging outcome variables are often expanded to measure an aging phenotype, including objective and subjective factors.

In a screening of 222 studies on (healthy) aging identified in this review (Table 1 and Suppl. Table 2), the variety of variables and outcomes in current research becomes obvious. On average, a single variable, outcome or assessment was utilized in only 10% of the analyzed studies. Even factors like depression, assessed in more than half of all studies, were measured with more than ten different tools.

From 10 defined categories ranging from different aspects of health to biomarkers (Suppl. Table 2), outcomes and variables covered a median of 6 categories. The least frequently assessed categories were aging (29.3%), social factors (37.8%) and biomarkers (38.3%). Even though many healthy aging scores have been constructed until now (see Section 3.6), only 5.9% of studies used a score, scale or index to assess healthy aging. Among them, most scores were only assessed in one single study. Even tools like the NIH Toolbox (FDA-NIH Biomarker Working Group 2016), a set of easy-to-perform tests to assess cognitive, emotional, sensory and motor functions, that have been established thoroughly and are well suited for measuring outcomes in longitudinal studies were only utilized sporadically (3 studies) (Hodes et al., 2013; Lara et al., 2013; Northwestern University, 2022). The most commonly assessed categories were demographics (all studies) and individual aspects of general health (82%). However, apart from gender and age, no variable, outcome or assessment was covered in more than one-third of all studies.

In summary, many categories of interest are not yet comprehensively covered in studies of healthy aging. Since more subjective components

Table 1
Synthesis of the screened outcomes and variables of healthy aging. Studies were allocated to the concepts investigated. Ten categories were devised to summarize the outcomes and associated variables assessed in studies, and the number and percentage of studies measuring the individual categories were determined. QoL: Quality of Life, (i)ADL: (instrumental) activities of daily living.

Concept	n	%
Aging	37	16.7
Healthy Aging	109	49.1
Successful Aging	39	17.6
Active Aging	20	9
Productive Aging	1	0.5
Secondary analyses	27	12.2
Category		
Demographics	222	100
Social Factors	84	37.8
General Health	182	82.0
• Status	140	63.1
• QoL	77	34.7
• Medical information	87	39.2
• Physical activities	56	25.2
• ADL / iADL	81	36.5
• Functioning / Disability	138	62.2
Emotional & Psychological Health	151	68.0
Cognitive Functioning	131	59.0
Lifestyle & Risks	121	54.5
• Lifestyle	108	48.6
• Risks	34	15.3
Aging	65	29.3
• Biological	21	9.5
• Healthy/Successful/Active	41	18.5
• Scores	13	5.9
Anthropometry	115	51.8
Performance (physical, cardiovascular)	129	58.1
Biomarkers	85	38.3

might be more challenging to measure in a standardized way, researchers fall back on more objective biomedical components of healthy aging. Furthermore, sensory functions are rarely included in measurements or assessments (less than 10% of studies), even though they can be early indicators of diseases: a loss of olfactory function is one of the first early symptoms of neurodegenerative diseases (Mount et al., 2016).

Ideally, researchers should choose interdisciplinary outcomes which combine biological and psycho-social aspects, e.g., in a score, instead of one-point outcomes, especially for intervention studies.

Lastly, the cultural context should be considered. In some cultures, longevity might not be desirable but instead viewed as disrespectful (Aldwin and Gilmer, 2017). Also, many assessment tools, especially questionnaires, must be adapted for cultural contexts and are thus not universally applicable.

3.5. *Markers and measures of healthy aging*

When describing measurements of healthy aging, one has to distinguish between the following: measurements of the current state, effects of interventions on aging processes, outcomes of healthy aging, and predictive measures. Generally, tools for measuring these aspects of healthy aging can be divided into three groups: Bio- and performance markers, questionnaires, and scores (Fig. 3).

3.5.1. *Bio- and performance markers as objective measuring instruments*

A common approach is the measurement of biomarkers to detect functional decline early and test interventions for their effects on aging.

According to the „American Federation for Aging Research“ (American Federation For Aging Research, 2011), a biomarker can be defined by the following:

1) It must predict the rate of aging
2) It must monitor a basic process that underlies the aging process, not the effects of disease
3) It must be able to be tested repeatedly without harming the person
4) It must be something that works in humans and laboratory animals, such as mice

These criteria already indicate the functions and advantages of biomarkers as measuring tools: They can detect functional decline early and test interventions and may be applicable for prevention. Moreover, some biomarkers have a predictive potential. As surrogates for healthy aging outcomes, they facilitate the comparability of studies. Furthermore, the ideal biomarker should be: objectively assessed, distinctive between healthy and unhealthy aging or following the trajectory of healthy aging, not limited to use in a laboratory or clinic setting and show evidence of replication in different cohorts and study designs (Lara et al., 2015).

Based on that definition, Lara and colleagues proposed a panel of biomarkers to measure healthy aging, representing five areas of function: physical capability, cognitive, physiological and musculoskeletal, endocrine and immune function. Each domain consists of numerous subdomains: cardiovascular and lung function, glucose metabolism and musculoskeletal function for physiological function; strength, locomotion, balance and dexterity for physical capability; memory, processing speed and executive function as critical subdomains of cognitive function; HPA-axis, sex and growth hormones as biomarkers of endocrine function and inflammatory factors for measurement of immune function (Lara et al., 2015).

When including the concept of resilience, performance measures like stress tests are also attractive. Cardiac function in a stress ECG, the Timed Up and Go test, pulmonary performance in ergo spirometry or the response to vaccination are possibilities to assess the reserve capacity of body functions. Stress tests show which capability can be mobilized if needed and distinguish between individuals with a higher available reserve capacity and those with only a small or no reserve capacity. Involving the fast return to homeostasis, markers like a glucose tolerance test can directly measure biological resilience (Ukraintseva et al., 2021).

Another promising attempt at biomarkers of (healthy) aging is epigenetic clocks. These clocks can be used as age predictors, as the composite methylation status of various genomic loci often correlates with chronological age (Liu et al., 2020). As shown in two *in vitro* experiments (Liu et al., 2020; Levine et al., 2018), epigenetic clocks were associated with cellular senescence and mitochondrial dysfunction (López-Otín et al., 2013), thus fulfilling points 1 and 2 of the requirements for biomarkers.

Additionally, epigenetic clocks might also be markers for healthy aging, provided epigenetic age deviates from chronological age (Horvath and Raj, 2018). The differentiation of epigenetic and chronological age can be used furthermore to predict diverse susceptibility to death or disease (Levine et al., 2018). Other epigenetic clocks were designed to predict all-cause mortality (Zhang et al., 2017) or a clinical aging phenotype (Levine et al., 2018).

However, it is still unclear which pathways are involved in the effects of epigenetic alterations associated with aging. By testing multiple epigenetic clocks of different genomic positions in several tissues and more accessible materials, e.g., cells in body fluids, in further studies, overlapping signals can be detected and form the basis for a clock-biomarker of (healthy) aging (Liu et al., 2020).

As a tool for measuring healthy aging, biomarkers are relatively easy to apply clinically, detecting the decline of different body functions and having a predictive potential. On top of that, they can also be used to test the effects of interventions on (healthy) aging.

Generally, each marker, newly established score or measurement should be evaluated regarding its transferability and suitability in longitudinal studies. Several requirements for suitable markers have been established and must be carefully considered, along with potentially disturbing influences.

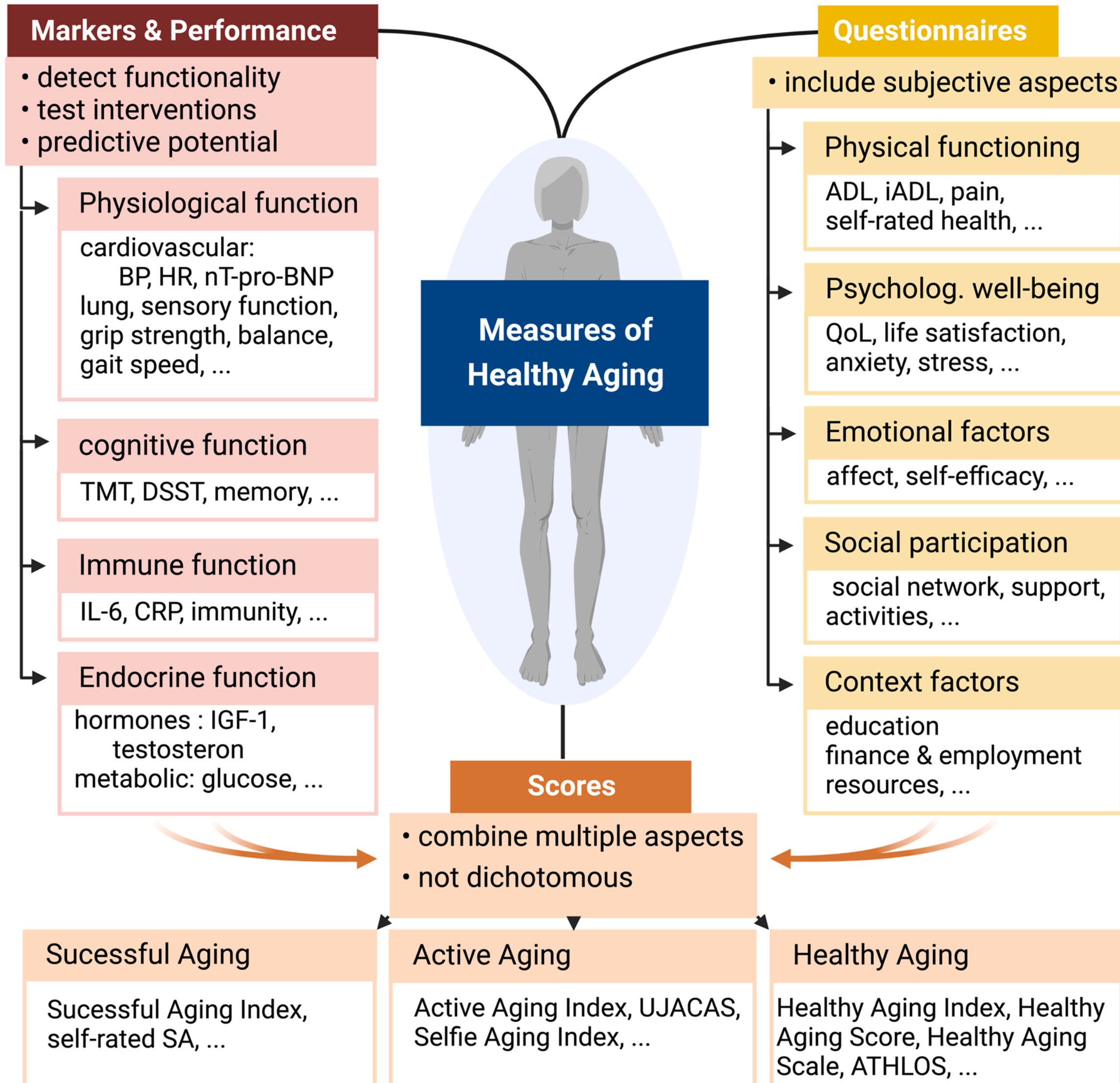

Fig. 3. : Measures of Healthy Aging. BP: blood pressure, HR: heart rate, nT-pro-BNP: N-terminal precursor B-type natriuretic peptide, TMT: trail-making test, DSST: digit symbol substitution test, IL-6: interleukin 6, CRP: c-reactive protein, IGF-1: Insulin-like growth factor 1, (i)ADL: (instrumental) activities of daily living, QoL: quality of life, SA: successful aging.

3.5.2. Factors affecting the consistency, robustness and reproducibility of biomarkers

3.5.2.1. Age, sex and ethnicity. Study results show multiple influencing factors on markers, i.e., the comparability between different groups of people and the time points of measurements. Many biomarkers increase or decline with age and must be measured in an age-related context or described longitudinally. For example, cortisol was elevated in older compared to younger adults, maybe due to a more robust response to challenges in older individuals (Fiacco et al., 2019).

Furthermore, sex significantly influences some biomarkers, mainly due to hormones. On top of that, hormone milieus also change during one person’s lifetime. Additionally, markers and measurements may differ between ethnic groups as recently described, e.g., for cardiovascular risk markers, Alzheimer’s dementia, and health (Gijsberts et al., 2016; Barnes, 2019).

3.5.2.2. Day, night and seasonal oscillations. Circadian and circannual rhythms of production and release result in different levels of biomarkers depending on the daytime or season. A classic example is cortisol, with shows peak levels in the early morning at the beginning of the active phase directly after wake-up and a steady decline to an evening minimum (Manoogian and Panda, 2017). Even blood pressure, a relatively simple measurement, is subject to a circadian influence (Millar-Craig et al., 1978). The circadian system also affects the metabolism to isolate rivaling processes and maintain homeostasis. Hence, the production and release of regulating hormones like insulin and glucagon and even gene expression are controlled by the circadian clock, which must be considered in the measurements of metabolic or genomic markers (Manoogian and Panda, 2017).

Not only day-wise alterations but also seasonal differences are reported for some markers and measurements. For example, values of sunlight-dependent markers like vitamin D are lower from October to April than in summer (Kramer et al., 2014). In work by Dopico and colleagues, more than 4000 protein-coding mRNAs in white blood cells and adipose tissue showed a seasonal expression profile (Dopico et al., 2015).

3.5.2.3. Environmental behavior. The robustness of biomarkers can be defined as the stability of the marker upon changing environmental influences and behavior. Eating patterns and nutrition can influence levels of biomarkers directly or indirectly (Manoogian and Panda, 2017). For example, time-restricted feeding as a nutritional intervention showed the potential to prevent chronic diseases in experimental studies with mice. The intervention furthermore reduced biomarkers of inflammation and supported defense mechanisms against reactive oxygen species (Chaix et al., 2014). Even the hydration status influences biomarkers in the blood, and dehydration is associated with renal disease, diabetes and impaired cognition (Hooper et al., 2016).

Moreover, exercise has more subtle effects than the apparent influence on obesity, diabetes or diseases of immobility like deep vein thrombosis. Kaliman and colleagues showed an association between physical activity and biomarkers of aging: active older people had less telomere shortening than inactive ones (Kaliman et al., 2011).

These examples exemplify the extensive influence of environmental factors and behavior on the robustness of biomarkers, which should be considered in choosing covariables and can be used in interventions on aging.

3.5.2.4. Methodologies and protocols. Researchers should optimally deduct every suitable marker or measurement's validity and biological plausibility (FDA-NIH Biomarker Working Group 2016). In reality, the biological backgrounds and effects of potential markers are often not fully understood. That makes it challenging to gauge influences on measurements and possible confounders of markers.

Furthermore, many factors contribute to the replicability and reproducibility of biomarkers and measurements, e.g., pre-analytical factors like cohort design, operation procedures and post-analytical ones. Additionally, a publication bias, leading to negligence of negative results and non-associations, contributes to the irreproducibility of data (Scherer, 2017).

In healthy-aging studies, especially cohort characteristics, e.g., recruitment, inclusion and exclusion criteria, and cohort size need to be considered. Furthermore, results should be validated in an independent cohort after the initial study. It is essential to mention that independence, in this case, aims for the smallest possible overlap of biases in the discovery and validation cohort (Mattsson-Carlgren et al., 2020). Although cohort studies are less prone to different types of biases than other study types, they can be further minimized by careful study design (Muriel, 2018).

3.5.3. Questionnaires as a valuable tool for measuring subjective aspects of healthy aging

Questionnaires are valuable tools for measuring subjective aspects of aging and healthy aging, often not examined with traditional biomarkers. Besides physical functioning and self-rated health, physical and psychological wellbeing can be studied by assessing the quality of life and (instrumental) activities of daily living (i)ADL. Also, satisfaction with life and resilience can be easily interrogated by questionnaires. Many psychological and emotional health aspects are also frequently described by various questions on anxiety, stress, depression, loneliness, self-efficacy and regulation, affect, effort and rewards, mood, emotions, coping, expectations and many more.

Another vital component of healthy aging is social wellbeing, which can be investigated by questions about participation, social networks, support, activities and a sense of purpose.

Lifestyle factors like smoking, alcohol, nutrition and exercise, as well as risks and health-promoting behaviors, are also only assessable by the self-reports of study participants.

Additionally, context factors significantly impact aging processes and might confound healthy aging. Therefore, questionnaires about education, financial situation, employment, and resources can collect essential data for a comprehensive picture of an aging person. Although questionnaires are easy to apply and can be used in clinical settings and at home, the answers are influenced by psychological effects, such as social desirability and error of central tendency (Braun et al., 2001).

3.6. Healthy aging scores

Often scores, scales or indices measure multiple aspects of a research topic. The merit of those instruments is the multidimensional classification of healthy aging in contrast to single data points or dichotomous categorizations. Multiple measurements of different aspects of aging also capture the complexity of aging and its influence on several areas of life.

3.6.1. Measuring adverse health outcomes

In aging studies, frailty and morbidity are frequently used to describe older people at risk for adverse health outcomes and with diverse prevalent diseases. According to Fried and colleagues, frailty can be understood as a physiological syndrome or phenotype including at least three listed criteria: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity. This categorization showed a predictive validity for hospitalization, incident falls, worsening mobility, disability in ADL, and death. Disability can be seen as an outcome of frailty, while comorbidity is more of an etiologic factor for frailty (Fried et al., 2001).

Charlson and colleagues created the widely-used weighted comorbidity-index. This index considers the number and the seriousness of the comorbid disease and has a predictive potential for death from comorbid disease (Charlson et al., 2022). The frailty and comorbidity indices are used in (healthy) aging studies, albeit at low percentages of 5.8% and 3.6% of studies in our outcome-search. In general, frailty and morbidity measures only cover a limited number of factors determined to be important for characterizing healthy aging (Table 2).

3.6.2. Measuring multiple dimensions of healthy aging

In contrast, scores and scales designed to determine healthy aging measure positive aspects of aging phenotypes. According to the definition of the WHO (World Health Organization, 2015), healthy aging includes intrinsic capacity, consisting of locomotion, vitality, cognition, psychological and sensory aspects (Cesari et al., 2018) and functional ability, which compromises basic needs, learning and decision making, mobility, relationships and contribution to society (WHO Team Ageing & Health, 2020); as well as the environment, that consists of factors like policies, society and services (World Health Organization, 2015). In Table 2, exemplary scores using different concepts are contrasted regarding their capability to measure IC, functional ability and environmental influences. All 21 genuine analyzed scores and their validation are listed in Suppl. Table 3.

One of the first "healthy aging scores" was the Physiologic Index of Comorbidity (PIoC). It measures five parameters of physiological functioning. Only if the person reaches average results in all five examinations, the criteria for healthy aging are met, which was valid only for 1.7% of the discovery cohort. However, this score also aims to detect older adults at risk of suffering from a chronic disease and covers only few dimensions of IC (Newman et al., 2008). In addition, the assessment of the PIoC is time-consuming and needs blood work, ultrasound and MRI imaging.

Based on the PIoC, the Healthy Ageing Index (HAI) was built (McCabe et al., 2016). It includes cardiovascular, pulmonary and kidney function measures and an additional cognitive assessment and was used, modified and validated most often in the studies identified in the literature search. The modified versions of the HAI utilize slightly different parameters for assessing the domains, but the overall scoring remains the same. Both versions convert the measurements based on the discovery-cohort tertiles (0–2 points) and sum the results creating a scale from 0 to 10. In this frame, 0–2 points indicate healthy, and 9–10 points indicate unhealthy aging (Sanders et al., 2014).

A scale, picking up all criteria of IC, was conceived by the ATHLOS consortium (Aging trajectories of health-longitudinal opportunities and

Table 2
Exemplary selection of frailty, comorbidity and healthy aging scores and their assessed components classified according to domains of intrinsic capacity, functional ability and environment.

	Comorbidity Index (Charlson et al., 2022)	Frailty (Fried et al., 2001)	Physiologic Index of Comorbidity (Newman et al., 2008)	(modified) Healthy Ageing Index (McCabe et al., 2016, Wu et al., 2017)	ATHLOS (Sanchez-Niubo et al., 2021)	Active Ageing Index (European Centre Vienna, 2013)	Selfie Aging Index (Gonçalves et al., 2017)
Intrinsic capacity acc. to Cesari (Cesari et al., 2018)							
Locomotion		X			X		
Vitality	X	X	X	X	X		X
Cognition			(X)	X	X	X	X
Psychological					X		X
Sensory					X		
Functional ability & environment acc. to WHO (WHO Team Ageing & Health, 2020)							
Basic needs					X		X
Learn, grow, make decisions							
Mobility		X			X	X	X
Relationships						X	X
Contribute to society						X	X
Environment						X	X
Characteristics							
Level P: population I: individual	I	I	I	I	I	P	I
Assessment P: professional S: self	P	P & S	P	P	P & S	P	S
Blood/ imaging Y: yes, N: no	(Y)	N	Y	Y	N	N	N

synergies). Using data from 16 international cohorts, this project aimed to develop a novel measuring scale of healthy aging that can be used worldwide. The designed scale consists of 41 items covering IC and additionally functional ability with the components iADL and mobility (Sanchez-Niubo et al., 2021).

The “Active Ageing Index“ (AAI) of the UNECE refers to social factors and influences of our society on aging and is a population-based rather than an individual measure. It assesses 22 healthy aging indicators in 4 domains: employment, participation in society, independent, healthy, secure living and the capacity and enabling environment for active aging (European Centre Vienna, 2013).

The “Selfie Aging Index” stands out by solely reflecting the perspective of older adults. It is based on the four domains of the “Active Aging Index” but transforms them towards an individual score based on self-assessment. The test includes questions about ADL, limitations, psychological status and context factors like education or employment (Gonçalves et al., 2017). Because of the self-assessment, the data of this score are easy to collect without any medical equipment, and it would even be possible to transform it into an app for individual monitoring of older people.

It is noticeable that most of the scores of our scope only focus on IC and measure body functions, i.e., vitality and cognition (Li et al., 2021; McCabe et al., 2016; Newman et al., 2008; Sanders et al., 2012; Wu et al., 2017, 2018). Aspects of IC rarely used are locomotion and sensory function. A score taking up locomotion is the “Healthy Aging Score” of Assmann (Assmann et al., 2015), including the short physical performance battery; sensory is included in the “Healthy Aging Scale” of Gao (Gao et al., 2022) with the component sensory capacity. A score that includes both rare elements is the “Healthy Aging Index in Latin American countries”, which measures walking, hearing and eye problems (Daskalopoulou et al., 2019).

In the category functional ability, (i)ADL is the most used assessment: nine of the fifteen scores measure (i)ADLs. Furthermore, social aspects are frequently assessed. The criteria “learn, grow and make decisions” is taken up rarely in measuring instruments: it is only represented in four scores (Daskalopoulou et al., 2019; Thanakwang et al., 2014; Haque and Afrin, 2022; Pham et al., 2020). All components of functional ability are covered in the scores of Pham and colleagues and Haque and Afrin (Pham et al., 2020; Haque and Afrin, 2022), who designed adaptions of the” Active Aging Index” for Bangladesh and Vietnam.

According to the WHO definition, the environment is the third factor of healthy aging. Environmental aspects of healthy aging are often retrieved via questions about social participation among those scores found in the literature. Depending on the political situation of the study population, security or access to health care services are environmental criteria added to scores.

Taken together, the analysis of healthy aging scores found that most scores primarily focused on physiological functions and aspects of intrinsic capacity. However, more and more scores are starting to broaden the view on multiple dimensions of healthy aging and include the other two pillars of healthy aging according to the WHO with measurements of psychological well-being, subjective aspects and environmental factors.

4. Discussion

4.1. Complexity of concepts of aging and healthy aging

In summary, the route to a definition of healthy aging includes the continuous development and diversification of concepts over the last 60 years. The notions broadened over time, starting from a rather pessimistic view of aging and an exclusive definition for a minority of older people. Since Rowe and Kahn set the standards for research in the 1980ies, many modifications of the term healthy aging have occurred. Those widened the understanding, finally leading to a more positive conception and inclusion of most older people, but at the same time, also to fundamental challenges for the research field.

The first uncertainty to be considered is the definition of aging itself. It is generally difficult to distinguish between the normal, physiological processes of aging, the beginning pathological processes of diseases, and healthy aging. Those notions overlap, and there is a gradual transition between them. Indeed, aging is not a disease but increases vulnerability and is the most significant risk factor (Hayflick, 2007).

However, if there is only either successful aging or failure, chronically ill elders cannot achieve positive aging (Hicks and Conner, 2014).

Thus, the questions remain how to avoid strict cut-offs, this misleading results and how to define the opposite of healthy aging.

A further problem with the dichotomy and the dependence of the categorization of healthy or unhealthy aging on diseases is that subclinical diseases cannot be detected, leading to a healthy rating, even if there might already be a functional restriction. Thus, resilience (introduced in Subsection 3.2.2) might be valuable to avoid a healthy vs. failure classification (Pruchno et al., 2015).

Additionally, if aging is understood as a multidimensional, bio-psycho-social, modifiable process, older people should be empowered to influence their aging processes by promoting health mechanisms. Some researchers even go as far as to suggest lifestyle interventions based on the life of centenarians living in so-called blue zones, regions of the world where people get consistently older than in other areas (Buettner and Skemp, 2016). In light of these suggestions, it would be essential to understand what older people see as healthy aging. These views are, however, often seen as mutually exclusive and create a paradox between measured and perceived success in healthy aging.

Furthermore, it should be pointed out that self-assessment is psychologically influenced. The participants always tend to declare socially acceptable data, so subjective assessments are generally more favorable than objective ones. Additionally, personal expectations and experiences influence self-rated health status (Whitley et al., 2016). The disparity's effects on the results show why it might be reasonable to allocate different concepts and measurements of healthy aging into clusters, as Kusumastuti did (Section 3.3.4).

For Michel and Sadana (Michel and Sadana, 2017), the life course approach of the WHO concept of active aging combines both perspectives of older people and researchers to support intrinsic capacity in the first part of life and the maintenance of functional ability in the second part of life.

Currently, the research field struggles to include all those aspects and minorities and disadvantaged groups in the concepts and definitions. Unfortunately, this development does not lead to unified descriptions but rather an additional diversification. Now, researchers are faced with multiple concepts like successful, healthy, productive or active aging that all have slightly different emphases but, at the same time, are extensively interwoven. Additionally, the uncertainties in definitions and existing concepts pose a problem in operationalizing healthy aging for use in studies. Researchers often choose assessments, variables and outcomes that are of primary interest for their own, sometimes narrow, research topics or are easy to implement because the involved scientists and study personnel are familiar with the particular tool. However, this kind of understandable selection leads to a need for extensive cross-validation of tools and considerable efforts in harmonization only realizable through consortia like the G2Aging-platform (https://g2aging.org/), the International HundredK+ Cohorts Consortium (IHCC) or ATHLOS (Sanchez-Niubo et al., 2021). These consortia might be the best opportunity to catalog the existing cohorts, studies and assessed parameters and extract harmonized results to develop unified definitions further and describe healthy aging worldwide. If tools and measures used in cohorts are well standardized, then data from relatively small cohorts can be pooled and used for replication and validation (Hassan et al., 2022).

In their baseline report of the decade of healthy aging, the WHO delineates feasible and meaningful assessments, variables and outcomes to determine healthy aging based on the domains of intrinsic capacity and functional ability (WHO Team Ageing & Health, 2021). These lists of items contribute to a unified operationalization and comparable results worldwide in future studies and longitudinal set-ups.

In summary, we recommend understanding healthy aging as a complex, multidimensional concept that combines aspects of biology, functionality, living and psychosocial components. Thus, various disciplines must work together to understand the mechanisms, influences and possible interventions and define healthy aging for setting public health strategies.

4.2. Measurements of healthy aging

4.2.1. Objective but influenceable biomarkers

The choice of adequate instruments to measure healthy aging comes with multiple challenges. All of the influencing factors described in the results section need to be considered for biomarkers. However, this might be challenging since some markers, e.g., ferritin, is influenced by many factors and must undergo multiple adjustments to reach a general predictive value (Tahmasebi et al., 2020). As a large-scale integrated project, the European MARK-AGE study tried to tackle the problem of the wide variability of biomarkers in cross-sectional studies and attempted to define a set of biomarkers that could, in their combination, depict biological aging. Thereby, consistent DNA-based, immunological and oxidative stress markers, clinical chemistry, hormones, metabolism markers and markers based on proteins and their modifications were identified (Bürkle et al., 2015; Capri et al., 2015). Epigenetic clocks are also promising for creating a compound biomarker of healthy aging. However, they need to find their way into studies on healthy aging to validate the initial results and verify the independence from discovery cohorts and certain ethnicities. Additionally, efforts need to be made to minimize the panels of epigenetic marks that need to be assessed to allow for a worldwide affordable utilization of those clocks.

On top of biological and statistical considerations, practical aspects must be considered while choosing useful biomarkers: Is it easy to measure? Is it possible to examine it non-invasively? Is it stable over time? Are there standard measurements and a reference sample to enhance comparable results?

Moreover, the influenceability of biomarkers harbors the possibility of unexpected, unrepresentative results. Thus, turning away from one-time measurements and carrying out validation in independent cohorts is recommended.

4.2.2. Bias in subjective questionnaires

Questionnaires should be wisely constructed and suitable as an addition to objective measurements to make aging people tangible. However, it is essential to use only validated questionnaires, for example, the „Short Form 36“ (SF 36) or the (i)ADL questionnaires, among others. Generally, analyzing the existing research body in the field before choosing questionnaires and using existing, well-validated items whenever possible is advised.

In addition, when using a questionnaire, researchers should consider which target group they want to study and for which group the questionnaire was designed initially. If it is a geriatric tool, a cohort of younger participants will underlie a ceiling effect which means mostly achieving the optimal results. The other way around, floor effects can also be observed. Both effects diminish the validity of the assessment.

4.2.3. Weighting scores for comprehensive insights

The major advantage of scores, in general, is the avoidance of single measurements or data points in only one area. Instead, participants' scores reflect a direction of health conditions or behavior in multiple dimensions. Nevertheless, summing scores like the HAI or HAS do not allow for the weighting of the different domains. However, some may significantly influence aging processes more than others.

Additionally, scores bring some inherent challenges with them. Depending on the assessments used, some scores require imaging, vital sign measurements, and blood work, limiting their use in some clinical contexts, especially in population-based assessments and prevention tools. Furthermore, when constructing scores, some researchers use a percentile approach, which links the score to the characteristics of the cohort utilized. This approach is not feasible for all cohorts; additionally, the measurement scales and cut-offs change over time. Additional efforts are then needed to validate the score in each new cohort, leading to modified versions of the score, as seen in the HAI. Compared to frailty and comorbidity scales, many constructed healthy aging scores are not thoroughly validated because they are only used in a few studies. Lastly, scores or scales harbor the danger of oversimplification. If multiple measures are dichotomized and summed to build a quantitative score instead of using the multidimensional underlying data, the score's reliability might diminish.

However, in light of the presented considerations, a score, scale or index that is easy to assess, weights domains of intrinsic capacity, functional ability and environment and allows for interchangeable standardized items within each domain would be close to an ideal solution to measure healthy aging. However, choosing a good score always depends on the intention of the research and its designated use. Specific questions, fast results and easy implementation might demand less elaborate measuring tools.

5. Conclusion, future prospects and challenges

Starting from an inconsistent definition of healthy aging, researchers use multiple, often insufficiently validated instruments to assess healthy aging. A standard definition of healthy aging should be health-centered, not dichotomous and include multiple interdisciplinary viewpoints and subjective aspects. If a unified definition is not feasible, single concepts like active, successful and productive aging would need to be separated from each other and defined in detail to establish independent parallel concepts for more specific aspects.

Biomarkers and functional tests can provide a basis for measuring healthy aging and for prevention. Older people at risk of unfavorable aging could be detected and cared for before developing a disease or syndrome. At this point, biological concepts like life- and healthspan and their extension by geroscience come into play leading to optimal longevity. Biomarkers, in turn, can be used to test interventions for healthy aging and offer a basis for international comparability, as they are objective tools.

To get a comprehensive idea of healthy aging, the biological or functional base measurements should be complemented by several other subdomains of healthy aging. Firstly, self-rated health should be evaluated to capture the perception of older people of their health state. As described in several passages, these assessments can differ markedly from the results of biomedical or functional tests. Secondly, psychosocial factors, such as wellbeing or depression, should be included. Data about these aspects can be collected via questionnaires, and depending on the results, education about healthy behavior can be implemented to support older people in optimizing their health status.

Thirdly, contextual factors should be observed because they influence aging and disease processes. For example, socio-economic conditions, education and environmental factors have a significant impact and should be considered.

Furthermore, healthy aging should be understood as a dynamic and integrative concept, including resilience mechanisms and time as influencing factors. Therefore, measurements should, fourthly, include stress tests and homeostasis regulation and be repeated multiple times.

In general, suitable biomarkers and measurements for healthy aging, known and new, will need to be investigated in light of their validity, robustness and reproducibility to yield unified definitions and markers for healthy aging.

Scores combine base measurements of objective biomarkers with more subjective and self-rated aspects of healthy aging. On these grounds, scores appear to be the best tool currently available to measure healthy aging in terms of a complex process that affects multiple life areas. However, they might be too complicated to apply in some settings.

Above all, considerable funding and workforce should be allocated not to creating the next score, scale or test or planning additional cohorts and studies but to the consolidation, harmonization, detailed evaluation and validation of existing results from previous studies, cohorts and frameworks. Only validated scores, measures, concepts and operationalizations will help advance the understanding and definition of healthy aging. The WHO called for a "decade of healthy ageing", for ten years of working together in international collaborations. The task of the scientific community will be to discover the underlying mechanism of aging not yet understood and the influences on these processes and, at the same time, harmonize, evaluate and exploit results of existing data sets, studies and cohorts in great detail. Therefore, a universal definition that includes all the complex subdomains of healthy aging, consistent operationalizations, outcomes, and validated, harmonized measuring methods and items is necessary to enable the international comparability of future research results. Only then can researchers develop proper instructions for politics and the economy on supporting healthy aging and enabling a positive aging experience for older people.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data used is attached as Supplementary Material.

Acknowledgments

All figures were created with BioRender.com.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2023.101934.

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