Towards a multidimensional healthy ageing phenotype

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Abstract

Purpose of Review: There is great interest in developing tools to measure healthy ageing and to identify early stages of health impairment which may guide the implementation of interventions to prevent or delay the development of disease, disability and mortality. Here we review the most recent developments directed to operationalise, and test, definitions of healthy ageing.

Recent Findings: There is lack of consensus about how to define healthy ageing and, unsurprisingly, diversity in the instruments for its measurement. However, progress is being made in describing and in devising tools to capture the healthy ageing phenotype. Attempts to measure healthy ageing have relied primarily on cross-sectional data collected in older people. More recent studies have assessed the healthy ageing phenotype using markers of multiple functional domains and have used longitudinal data to model the dynamics and trajectories of healthy ageing.

Summary: Given the complexity of the ageing process, no single measure is able to predict the ageing trajectory. Current attempts to operationalise the healthy ageing phenotype have relied on markers and data from earlier cohort studies and are limited by the tools used to collect data in those studies. Such data are often unsuitable to detect early subtle declines in function and/ or are inappropriate for use in younger old-adults. Future studies employing more objective and novel markers of healthy ageing are likely to offer opportunities to define and operationalise the healthy ageing phenotype.

Key words: Healthy Ageing Phenotype, Validation, Markers

Introduction

What is ageing? Ageing has been described as the biological changes that occur in an individual that are associated with a gradual decline in function. For most, ageing is experienced as a slow deterioration resulting eventually in frailty, disability, disease and death. However, evidence from model systems and from human studies shows that the ageing process is malleable, the ageing trajectory can be slowed and the link with disease weakened. Given favourable circumstances, individuals can maintain good physical and cognitive function. In part those circumstances are genetic but socioeconomic factors and lifestyle are major determinants. Recent data from the USA illustrate the strong association between higher income (as a surrogate for more favourable circumstances) and longevity (1). This study also showed that whilst those with higher income gained about 0.2 years of life extra per year over the period 2000 – 2014, the poorest had no improvements. In addition, Chetty and colleagues noted that income was associated strongly with higher physical activity and with lower likelihood for smoking and obesity – lifestyle-related factors which are established modulators of ageing and risk of age-related disease (1).

Reaching consensus on how healthy ageing should be defined has proven to be a difficult task. This lack of consensus is a significant impediment not only for research but also for national surveillance programmes, public health interventions and for commercial developments. This difficulty is due partly to the different perspectives, expectations and aims of researchers from different disciplines. While from a scientific perspective the preservation of health and function is a priority, evidence indicates that other more subjective aspects of wellbeing are also important to the individual. Interviews with older people have indicated that wellbeing is produced by having the "capability" to mobilise resources to achieve contextually appropriate goals and to respond effectively to changing personal circumstances (2). Lastly, there is heterogeneity in the terminology used to denote the concept of healthy ageing in the literature. For the purpose of the present review we will adopt the term healthy ageing.

The importance of defining and measuring healthy ageing is underlined by the fact that the global population is ageing; By 2080, 29% of the European population will be aged > 65 years (3). This is due to the combination of reduced birth rate and increased life expectancy. To reduce the risk of economic instabilities and to prevent social collapse as a result of too few people in economically productive work, several countries are raising the retirement age to maintain the workforce and to reduce the pension burden associated with greater longevity. In addition, because ageing is the major driver of most common complex diseases, the chronic disease burden is increasing (4). These pressures emphasise the importance of finding ways to enable people to age better and to maintain good function and high levels of wellbeing. To facilitate the development of targeted interventions which may be more resource efficient, it would be helpful to distinguish those who are ageing well from those who are ageing less well. In other words, we need to be able to identify a healthy ageing phenotype (5). The benefits of maintaining good health into old age include saving health care costs, improving quality of life, and enabling older people to continue to participate productively in society and to offer their stability, heightened capacity for synthetic problem solving, increased ability to manage conflicts, and ability to consider perspectives from other age groups (6).

Models of healthy ageing

Cellular dysfunction is the biological basis for the age-related decline in function and for the increasing risk of frailty, disability and disease, the cardinal features of ageing. The accumulated macromolecular damage in ageing is pervasive affecting virtually every cellular, tissue and whole body function and is remarkably similar in multiple species. This observation underpinned the recent proposal for 9 hallmarks of ageing (7) which help to conceptualise and systematise a highly complex collection of processes. Importantly, the ageing process is plastic and the accumulation of molecular damage and cell dysfunction can be slowed (8). Models of healthy ageing have been based on Rowe and Kahn's 1987 proposal which differentiated between healthy older individuals and those with disease and/or disability (6). More recently there has been emphasis on models which include both subjective e.g. psychosocial wellbeing as well as

objective, i.e. biological, measurements (9). Psychological based models emphasise “how” healthy ageing occurs whereas the biological models emphasise the “what” (6).

The different conceptual frameworks of healthy ageing models have been reviewed. Martinson and Berridge conducted a systematic review of critiques of successful ageing models and the suggestions for improvement from the social gerontology literature (10). More recently Anton et al. provided an overview which focussed on physical function, and the role of interventions that may enhance mobility and physical function and so promote independence among older adults (11).

Healthy ageing phenotypes

Currently most literature focuses on morbidity and mortality as ageing phenotypes. Our group, and others, have emphasised the need to focus on a combination of objective and subjective outcomes including physical capability, cognitive function, physiological and metabolic health, and psychosocial well-being (9), In addition, the importance of assessing sensorial functions has been identified (12). Olfactory function may be an indicator of the integrity of the ageing brain in older people, since smell dysfunction is among the earliest “preclinical” signs of neurodegenerative diseases such as Alzheimer disease and sporadic Parkinson's disease (13).

Frailty vs. Healthy ageing

It could be argued that the development of frailty is an example of failure to age healthily. Frailty indicators have been extensively validated in multiple populations for their ability to predict age-related adverse health outcomes ranging from falls to mortality in elderly populations (14). Measures of frailty have been reviewed recently by Roppolo et al. (2015) who showed that different instruments captured different characteristics of frailty and that whether an individual is classified as frail or not depends on the index of frailty used in the assessment (15). Whilst frailty may be evidence of a failure to age healthily, it is unlikely that assessments which are used to assess frailty would be sufficient to assess healthy ageing. This is because the instruments used in such assessments are designed for individuals experiencing a

substantial degree of disability or illness and are usually applicable only to the oldest segments of the population. Because of floor and ceiling problems, such tools would be insensitive when applied to younger individuals. However, recently, Romero-Ortuno proposed that a simple 5-item index called the Frailty Instrument (FIt) for primary care which is based on the Survey of Health, Ageing and Retirement in Europe (SHARE) may be useful for assessing and monitoring frailty in community dwelling people over the age of 50 (16).

Current evidence on operationalisation of definitions of healthy ageing

To identify recent studies operationalising healthy ageing, a systematic search was performed using PubMed from 01-01-2013 until 01-05-2016. Publications were included if the authors intended to measure the healthy ageing phenotype or employed a multidimensional approach to measure healthy ageing. Using this strategy, twelve studies (17-28) were found (Table 1). All tools which are included in this brief review were multidimensional.

Although evidence is still scarce, we identified several studies that focused on operationalising healthy ageing. Among the papers identified, the very recent paper by Tampubolon (28) is novel in using the concept of the healthy ageing phenotype (9) and in assessing the trajectories of some of the biomarkers proposed in that model among participants of the English Longitudinal Study of Ageing (ELSA). ELSA is a prospective, nationally-representative sample of people aged $\geq$ 50 years. The biomarkers included measures of cardiovascular function, glucose homeostasis, lung function, adiposity, lipid metabolism, and inflammation. This study showed a secular decline in healthy ageing from middle-age, which was sharper among women and differed by socioeconomic position. Those with greater material advantage and higher educational attainment had smaller declines in biomarkers of healthy ageing (28). In addition, the findings were in line with previous studies (e.g. Pruchno et.al.) suggesting that maintenance of healthy ageing at follow up was more common among men, those who were working, the married, and those having better social relationships at baseline (25).

Two other studies proposed different tools to assess healthy ageing (19, 20). Tyrovolas et al. used a composite index of healthy ageing which included 10 elements viz. education, financial status, social activities (subdivided into friends, family and excursions per year), CVD risk, BMI, depression, physical activity and Mediterranean diet. Using data on older adults from Mediterranean countries, these authors reported that a 1-point increase in their 10-point index was associated with one less annual visit to health centres. Using data from the Medical Research Council's Cognitive Function and Aging Study (CFAS), Cosco et al. tested an ageing index based on activities of daily living, cognitive function, and subjective aspects such as personal resources and engagement (19). These authors reported that their index was associated with use of health services, informal care and other services such as meals on wheels.

The Whitehall study, a longitudinal cohort of civil servants in the UK with a long follow-up period (median 16 years) and a large sample size, has been recently used to classify individuals as successfully ageing or not. In this study, healthy ageing has been defined as survival in the follow up period (mean age 60), with no diagnosis of chronic disease or abnormal oral glucose tolerance test, no mental health problems and normal cognitive (Alice Heim 4-I, short-term verbal memory test, 2 tests of verbal fluency, Mill Hill Vocabulary test), cardio metabolic (SBP), respiratory (FEV1/height^2 in L/m^2) and musculoskeletal function (walking speed over a clearly marked 8-foot walking course) (29).

DISCUSSION

To date, few studies have attempted to operationalise healthy ageing using comprehensive and multi-dimensional approaches (such as that proposed by Lara et al. 2013 [12]) and to apply the resulting tools to data from current longitudinal cohorts. Current studies have relied on data with only partial or proxy measures for each of the different domains associated with the healthy ageing phenotype. The available indices focus on different combinations of domains of healthy ageing but commonly focus on cognitive function and measures of physical capability. Decline in cognitive function is a hallmark of ageing and recent data from the Sydney Memory and Ageing Study (an observational population-based cohort study) showed that both baseline cognitive ability and decline in cognitive ability over 2 years predicted

mortality, even in the absence of dementia (30). Cognitive decline also has important financial, personal and societal consequences, and is the cause of 40% of admissions to institutionalised care in the UK. Most of the studies reviewed included at least one measure of global cognitive functioning, commonly the mini mental state examination (MMSE). This tool has been used widely in, and accepted as appropriate for, elderly populations. However its ability to detect subtle deficiencies, namely mild cognitive impairment (31), or cognitive changes at high levels of cognition such as among highly educated people has been questioned. A recent Cochrane review concluded that the MMSE was insufficient as a stand-alone single-administration test in the identification of MCI patients who could develop dementia (31). Subtle changes in cognitive function can be meaningful and the majority of tools ignore this by using tools designed to identify more evident declines in cognitive function and it is likely that "one size does not fit all" in cognitive screening (31).

The reviewed studies have mostly used activities of daily living, with few using more objective measures of gait or walking tests. All but one study focused on older populations, those aged 70+ and often in 85 to 90+ individuals. Puchno et al. found that midlife predictors of healthy ageing differed from those which apply later in life (25). In addition, it appears that some biomarkers of ageing which appear robust in younger old individuals may not be valid in very old people. Indeed, in some cases the reverse may apply e.g. higher BP is a risk factor in younger people but may be a protective factor in very old people (32).Overall, assessment of the utility of markers of healthy ageing is limited by uncertainties and lack of consensus about the appropriate outcome measures to be used in such assessments. Whilst earlier studies have focussed on hard end points such as death or diagnosis of major age-related disease, some recent studies have considered other outcomes such as use of health services (e.g. hospitalisations).

None of the studies identified in the current search have used markers of sensorial functions. Sensory functions are critical for normal function, independence and social interaction and most decline with age (12). Smell dysfunction is one of the earliest indications of preclinical neurodegenerative diseases (13) but the predictive value of sensory function for age-related health outcomes has yet to be validated (12).

Lastly, few tools consider social function in the assessment of the healthy ageing trajectory despite the fact that social interactions and personal support networks are strongly associated with both morbidity and mortality (33).

Conclusion

Healthy ageing is the maintenance of a range of functions including physical capability, cognition, physiology, social, sensory and psychological wellbeing. A suitable approach to measure healthy ageing should include both subjective and objective assessments of as many as possible of these factors since the complex interplay of these factors determines health and wellbeing outcomes (11), However, this must be balanced against the resource requirements for more comprehensive assessments and future research should aim to identify the minimum set of measures which provides reliable prediction of the ageing trajectory and which could be used as outcome measures for interventions [12]. However, current models of healthy ageing remain incomplete; the operationalisation of the healthy ageing phenotype is a work in progress.

Key Points

- The lack of an agreed definition of healthy ageing limits the development of tools for its measurements and, therefore, the ability to predict the ageing trajectory.
- Current models focus on absence of frailty and on functional status including the ability to carry out the activities of daily living.
- Conceptualisation and operationalization of the healthy ageing phenotype offers a potential route to the development of tools for assessing ageing which are age-, sex-and culturally-appropriate.
- Tools for healthy ageing will need to be validated in younger and older populations in a range of settings to determine their generalizability.
- Testing of tools for healthy ageing is limited by uncertainties about the most appropriate outcomes measures to use at different stages in the life-course. Outcome measures such as hospitalisation,

institutionalisation and disability which are sensitive in younger populations need to be developed and validated.

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Conflict of Interest

None.

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Table 1. Characteristics of studies

(Legend to table 1)

Abbreviations: SBP systolic blood pressure, FVC forced vital capacity, FEV-1 forced expiratory volume in one second, MMSE- Mini-mental state examination, sCRT serum creatinine, Glc glucose, ADL Activities of daily living, TChol total cholesterol, HDL High density lipoprotein, ALT Alanine aminotransferase, CRT creatinine, Trigly Triglycerides, IADL instrumental activities of daily living, sMMSE standardised MMSE, PA Physical activity, WC waist circumference, MedDietScore Mediterranean diet, PANAS Positive and Negative affect schedule, HBA1c, FEV1 Forced expiratory volume in one second/height2 in L/m2, CBVD cerebrovascular disease, HGS handgrip strength, CVD cardiovascular disease, COPD chronic obstructive pulmonary disease..