Towards measurement of the Healthy Ageing Phenotype in lifestyle-based intervention studies

This is a pre-copyedited, author-produced PDF of an article accepted for publication in Maturitas following peer review. The final published version of the article Lara et al. (2013) is available online at:

http://dx.doi.org/10.1016/j.maturitas.2013.07.007

Jose Lara1*, Alan Godfrey2, Elizabeth Evans2, Ben Heaven3, Laura J. E. Brown4, Evelyn Barron1, Lynn Rochester2, Thomas D. Meyer5, John C. Mathers1

1 Human Nutrition Research Centre, Institute for Ageing and Health, Newcastle University. Biomedical Research Building, Campus for Ageing and Vitality, Newcastle on Tyne, NE4 5PL, UK

2 Clinical Ageing Research Unit, Institute for Ageing and Health, Newcastle University. Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL

3 Institute of Health and Society, Newcastle University. Baddiley-Clark Building, Richardson Road. Newcastle Upon Tyne, NE2 4AX, UK

4 Department of Psychology, Research Institute for Health and Social Change, Manchester Metropolitan University. Elizabeth Gaskell Campus, Hathersage Road. Manchester, M13 0JA, UK.

5 Institute of Neuroscience, Doctorate in Clinical Psychology, Newcastle University. Ridley Building (4th floor), Newcastle upon Tyne, NE1 7RU, UK.

* Corresponding author:

Dr Jose Lara

Human Nutrition Research Centre

Institute for Ageing and Health

Newcastle University

Biomedical Research Building, Campus for Ageing and Vitality

Newcastle upon Tyne NE4 5PL, UK

Tel: +44 (0) 1912481141

Email: jose.lara@newcastle.ac.uk
Abstract

Introduction Given the biological complexity of the ageing process, there is no single, simple and reliable measure of how healthily someone is ageing. Intervention studies need a panel of measures which capture key features of healthy ageing. To help guide our research in this area, we have adopted the concept of the “Healthy Ageing Phenotype” (HAP) and this study aimed to i) identify the most important features of the HAP and ii) identify/develop tools for measurement of those features.

Methods After a comprehensive assessment of the literature we selected the following domains: physiological and metabolic health, physical capability, cognitive function, social wellbeing, and psychological wellbeing which we hoped would provide a reasonably holistic characterisation of the HAP. We reviewed the literature and identified systematic reviews and/or meta-analysis of cohort studies, and clinical guidelines on outcome measures of these domains relevant to the HAP. Selection criteria for these measures included: frequent use in longitudinal studies of ageing; expected to change with age; evidence for strong association with/prediction of ageing-related phenotypes such as morbidity, mortality and lifespan; whenever possible, focus on studies measuring these outcomes in populations rather than on individuals selected on the basis of a particular disease; (bio)markers that respond to (lifestyle-based) intervention. Proposed markers were exposed to critique in a Workshop held in Newcastle, UK in October 2012.

Results We have selected a tentative panel of (bio)markers of physiological and metabolic health, physical capability, cognitive function, social wellbeing, and psychological wellbeing which we propose may be useful in characterising the HAP and which may have utility as outcome measures in intervention studies. In addition, we have identified a number of tools which could be applied in community-based intervention studies designed to enhance healthy ageing.

Conclusions We have proposed, tentatively, a panel of outcome measures which could be deployed in community-based, lifestyle intervention studies. The evidence base for selection of measurement domains is less well developed in some areas e.g. social wellbeing (where the definition of the concept itself remains elusive) and this has implications for the identification of appropriate tools. Although we have developed this panel as potential outcomes for intervention studies, we recognise that broader agreement on the concept of the HAP and on tools for its measurement could have wider utility and e.g. could facilitate comparisons of healthy ageing across diverse study designs and populations.

Keywords: healthy ageing phenotype, physiological and metabolic health, physical capability, cognitive function, social wellbeing, psychological wellbeing, lifestyle intervention, biomarkers.
1. Introduction

For many people, longer life is associated with more years of poor health. Indeed, much of humankind’s experience of ill-health and expenditure on medical and social care (especially in Western countries) are concentrated in the later years of life [1]. The challenge is to find ways of improving health and maintaining wellbeing throughout the life-course.

There is very good evidence that behavioural factors (notably smoking, diet, alcohol consumption and physical activity) and social factors (including roles, relationships and support) are strongly associated with health and wellbeing in later life [2, 3]. However, there is very little evidence about the long-term efficacy of practical, lifestyle-based interventions to change these factors and thereby promote health and wellbeing in later life. In addition, evaluating the efficacy of such interventions is limited by the lack of appropriate outcome measures. Most of the existing tools for measuring change in health and wellbeing in response to interventions have not been developed or validated for use in older individuals and many are focussed on disease or disability rather than on healthy ageing.

Given the biological complexity, and the heterogeneity, of the ageing process, it is highly unlikely that any single measure will be capable of capturing reliably healthy ageing at the level of the individual. So, in intervention studies, especially lifestyle-based intervention studies such as those that we are developing in the LiveWell Programme¹, we need a panel of measures which capture key features of healthy ageing (Figure 1). To help guide our research in this area, we have adopted the concept of the “Healthy Ageing Phenotype” (HAP) which is intended to encapsulate the ability to be socially engaged, productive and to function independently both at physical and cognitive levels. A Spark Workshop convened by Unilever and the Medical Research Council UK suggested that the HAP may be defined as the condition of being alive, while having highly preserved functioning metabolic, hormonal and neuro-endocrine control systems at the organ, tissue and molecular levels [4]. However, as yet, there is no agreed definition of the HAP and no consensus on how it should be measured [4]. The Workshop on which the present Report is based aimed to address this research gap by i) identifying the most important features of the HAP and ii) identifying or developing tools for measurement of those features specifically in the context of community-based intervention studies. Although we had specific aims for the Workshop in respect of tools for measuring outcomes in intervention studies, the work that we have done on conceptualisation of the HAP and on tools for its measurement may have wider utility. For example, adoption of common measures for “healthy ageing” could facilitate comparisons across diverse studies and populations and with a range of study designs.

This Workshop held in October 2012 in Newcastle, UK involved approximately 50 professionals from complementary disciplines including Physiology, Medicine, Nutrition, Epidemiology, Physical activity, Movement and Rehabilitation, Geriatrics, Gerontology, Psychology, and Social Sciences. Ageing is a complex process with many definitions [5] and, for pragmatic reasons, the Workshop considered five HAP domains: 1) physiological and metabolic health, 2) physical capability, 3) cognitive function, 4) psychological wellbeing, and 5) social wellbeing. After a critical analysis of current evidence on the characterisation of healthy ageing, we decided to focus on specific functional biomarkers (where possible) in each of these 5 domains. Potential measurements in each of the domains were proposed in a presentation by a member of the organising panel and critiqued by an invited “Discussant” before further discussion by the rest of the

¹ LiveWell is a research programme intended to develop interventions to enhance health and wellbeing in later life. LiveWell focuses on the retirement period (defined as 55 to 70 years of age) as a window of opportunity for successful intervention. http://www.livewell.ac.uk
group. We prioritised identification of those features of the particular domain which are associated most strongly with “healthy ageing” and, where possible, identified (validated) tools for measuring those features. In this report we summarise the outcomes of the workshop in each of the areas covered (Figure 2).

Our aim is to establish a minimum set of (bio)markers to assess relevant processes associated with the ageing process which can be used holistically to quantify the HAP. For this purpose, we focused on objectively assessed outcomes and biomarkers commonly used in population studies which are potentially applicable in community-based intervention studies, expected to change with age, capable of predicting ageing-related phenotypes (e.g. morbidity, mortality, Quality of Life (QoL), Health span), and amenable to modification by lifestyle interventions. We recognise that our work is limited by conceptual and practical problems. In particular, we are trying to measure something (healthy ageing) which has yet to be defined adequately and, as a consequence, we have had to use information from studies using (inadequate) surrogates such as mortality or lifespan.

2. Biomarkers of physiological and metabolic health

One of the current theories of ageing proposes that the ageing phenotype results from accumulated molecular damage [6] due to stochastic events and the effects of chronic exposure to stressors (e.g. smoking, obesity, or physical inactivity). A gradual loss of the homeostatic mechanisms necessary to maintain tissue function and physiological capacity is thus a hallmark of ageing [7, 8]. Such loss may translate eventually into metabolic dysregulation leading to the development of early signs and symptoms of disease or pre-disease which, if not identified and managed, will eventually result in functional loss, chronic disease and finally death. Therefore, biomarkers of physiological and metabolic processes are potentially useful measures within the HAP which may be responsive to lifestyle-based interventions.

We searched the literature for systematic reviews and meta-analysis on objectively assessed physiological and metabolic biomarkers in relation to healthy ageing and reviewed evidence from longitudinal studies which investigated their potential to predict surrogates outcomes including mortality and lifespan. We found that mortality was the ageing-related phenotype most commonly evaluated for associations with physiological and metabolic biomarkers and there was good evidence that biomarkers of cardiovascular function, metabolic processes, inflammation, organ (e.g. lung) function, and body mass and composition are associated with ageing phenotypes. For example, of the components of the Metabolic Syndrome, only raised BP and impaired fasting glucose concentration are significant predictors of greater mortality [9]. A difference of 20 mm Hg in Systolic BP (or 10 mmHg in Diastolic BP) is associated with more than a twofold difference in death from several vascular causes [10]. In addition, high BP in midlife is associated with lower cognitive function in later life [11]. Markers of dysregulation of glucose metabolism are important predictors of mortality [12-15] and poorer glycaemic control is associated with cognitive impairment even in non-diabetics [16].

Central adiposity is a risk factor for ageing and for age-related diseases with the lowest all-cause mortality risk for those with waist circumferences (WC) of 94 cm and 77 cm for men and women, respectively, and the relative risk (RR) of mortality is doubled for those with WCs of 132 and 116 cm in men and women, respectively [17]. Overall adiposity may also be important since each 5 kg/m² increase in body mass index (BMI) is associated with 30% higher overall mortality, 40% higher vascular mortality; 60-120% higher
diabetic, renal, and hepatic mortality [18]. High BMI, independent of gender and other confounding factors, is a risk factor for cognitive decline [19].

In addition, individuals with the lowest Forced Expiratory Volume (FEV1) [20], a marker of lung function, have the highest risk of mortality (RR, 1.99; 95% CI, 1.71 to 2.29). This relationship remained significant after adjustment for smoking behaviour suggesting that FEV1 is a general biomarker of mortality risk. The evidence for associations of FEV1 with other ageing-related phenotypes such as cognitive decline is more limited [21].

In summary, the following physiological and metabolic (bio)markers show potential as measures of the HAP (Table 1):

1. Arterial blood pressure as a measure of cardiovascular function [10, 22];
2. Fasting glucose and/or glycated haemoglobin (HbA1C) as a marker of glucose homeostasis [12-15];
4. Waist circumference, waist to hip ratio [17, 23, 24], or body mass index [18, 25] as a measure of adiposity;
5. Plasma concentrations of total cholesterol and cholesterol fractions (LDL and HDL cholesterol) [26, 27] and triglycerides [28] as biomarkers of lipid metabolism.

2.1 Potential future markers of physiological and metabolic health

There is evidence that other biomarkers of cardiovascular function such as Fibrinogen [29] and markers of (chronic) inflammation such as IL-6 [30] and C-reactive protein (CRP) [31] are associated with risk of mortality and of age-related disease. However, their advantages over the better established biomarkers identified above is still debated. There is also emerging evidence of the potential importance of more novel biomarkers including 25-hydroxy cholecalciferol (vitamin D) concentrations [32], Brain Natriuretic Peptide [33], IGF-1 [34], and Cystatin C [35], which deserve further investigation as possible additions to the suite of biomarkers of physiological and metabolic health useful for characterising and quantifying the HAP.

There is growing interest in the use of challenge tests to assess the flexibility of physiological and metabolic systems e.g. the glucose tolerance test is a measure of the individual’s ability to maintain glucose homeostasis which may be an advance on the “static” measurement of fasting glucose concentration. However, the additional complexity involved in and time required for these measurements so far have limited their use to laboratory and clinical settings. In some areas, other surrogate measures might fulfil this role to some extent. For example, glycated haemoglobin it is an integrated measure of the consequences of excursions in blood glucose concentration over longish time periods. Challenge tests targeting important aspects of physiological and metabolic processes (e.g. inflammation and substrate oxidation) which can identify early functional decline preceding age-related disease [36] could lead to more sensitive and/or informative measures of the HAP.

3. Physical capability

Physical capability has been described by Cooper et al. [37, 38] as the physical or functional capacity of an individual to carry out successfully activities of daily life which, in turn, is an indicator of healthy ageing. Capturing physical capability is therefore important to inform measures of the HAP. It encompasses a broad
range of physical functions and a plethora of measurement tools are used to capture its multidimensional nature, ranging from hand grip strength to walking endurance. Evidence to support the use of measures of physical capability as surrogate markers of current and future health status is promising. For example, grip strength, balance, gait speed and chair rise time predict longevity, risk of age-related diseases and/or rates of mortality in observational studies [37, 39, 40].

Although such measures appear simple to use and convenient for implementation in a wide variety of contexts, there is considerable variation in testing protocols [37, 38]. Inconsistent application and reporting have led to efforts to harmonise protocols to facilitate data capture, reliability and multicentre studies and as the basis for possible data pooling across trials. Issues relevant to standardised assessment of motor functioning have been addressed recently by the development of the NIH Toolbox [41]. This Toolbox aims to define a standard set of measures that can be used as a “common currency” across diverse studies [41] and includes 5 domains and associated tests for assessment of motor function (Table 1). Criterion validity was established for all recommended tests along with test-retest reliability.

In the present context, the NIH Toolbox offers guidance on standardising and instrumenting a number of tools within the larger domain of physical capability. Some commonly used measures are notably absent such as the timed up and go (TUG) and timed sit-to-stand tests which are used ubiquitously for assessment of mobility in older adults. Suitable tests are captured in other NIH domains [42] and should be included within a comprehensive assessment of physical capability. While the NIH Toolbox tests have been developed for use across the lifespan (3-85 years), tests such as the TUG have been designed specifically for older adults. In practice the choice of test should take into account the age range of interest and may need to incorporate a broader range, or levels of complexity, of tests. Nevertheless the NIH toolbox is an important start to drive consistency and which will be strengthened by testing within larger longitudinal studies.

3.1 Potential future markers of physical capability

Looking to the future a number of advances are currently being employed, or are in the process of development and validation, which will ultimately complement the approaches summarised in Table 1. Recent developments to evaluate physical capacity include the use of stress tests where protocols are modified to increase their difficulty. Such stress tests may be more sensitive because they invoke compensatory strategies which may be compromised in those ageing less healthily. An example from the NIH toolbox is gait measured at fast walking pace. Other examples include walking or carrying out a balance task while being distracted by concurrent secondary task performance, often a cognitive task. Decrement in performance under dual-task conditions increases with age and is exacerbated in at risk populations [43, 44].

Advances in technology will drive innovation in methods of data collection and contribute novel metrics in two key areas: instrumentation of physical performance testing batteries and measurement of physical performance and function over extended periods in real-world settings [45]. With regard to the former, instrumentation of tests using body worn sensors (e.g. accelerometers and gyroscopes) is now possible due to low cost and increased analytical methods to derive sensitive physical capability outcomes [46-51]. Whilst some current methods remain complex, difficult and time consuming to derive (e.g. patterns), ultimately this approach will bring considerable advantages related to accuracy of recording, extraction of metrics with increased sensitivity and ease of data collection in a wide variety of environments. On the basis of previous work, current developments and future potential, we make the following
recommendation: five subdomains, which are also recommended in the NIH Toolbox tests, should be used to assess physical capability. Further evidence is needed on the predictive power of other tests which at present are relevant to populations over 70 years of age e.g. timed up and go (TUG) and timed sit to stand tests.

4. Cognitive function

Numerous facets of cognitive processing decline over the later stages of adult lifespan [52], and thus offer potential as markers of healthy cognitive ageing that can be targeted in intervention studies. However, psychometric measures of these so-called ‘fluid’ [53] cognitive abilities are often highly correlated with one another [54], indicating that patterns of cognitive change can be explained with reference to a smaller set of more fundamental functions.

One function that accounts for much of the variance seen in other cognitive tasks, and thus offers an efficient measure of overall functioning, is ‘cognitive processing speed’ [54]. Measures of cognitive processing speed, such as visual inspection time or speeded reaction time [55], predict morbidity and mortality [56]; are responsive to physical activity interventions [57]; and correlate with performance-based measures of everyday functioning [58], demonstrating their validity as indices of healthy ageing. Many processing speed tasks also benefit from very simple task instructions, and rely on differences in speed rather than accuracy to judge ability. This can make them more acceptable and less anxiety-provoking for participants compared with tasks in which errors are frequent and more salient.

Other cognitive functions that likely make unique contributions to patterns of overall cognitive change with age, include episodic memory [54] and aspects of executive function [59]. Indices of memory and executive functioning are also of particular significance to cognitive health in later life and deficits in these areas are characteristic of Alzheimer’s disease [60] and other forms of later-life dementia [61]. The addition of such measures to a battery of cognitive tests was therefore considered likely to provide a broader index of overall cognitive health. However, Workshop participants recognised the difficulty of treating ‘executive function’ as a single domain, when it is likely comprised of several subdomains that may be affected differentially by age and health interventions.

4.1 Tools to measure the cognitive function component of the HAP

Opinions vary amongst researchers regarding the most appropriate tools with which to measure these domains of cognitive function over time, and Workshop participants felt that it would be difficult to reach consensus on a single battery suitable for all intervention studies. Nevertheless, several considerations can be used to guide test selection. First, practice effects should be minimised by e.g. using random stimulus generation or alternative equivalent versions of the test. Tests should not show floor or ceiling effects in the population being considered, and should be robust to the effects of different administrators. Where possible, alternative stimulus presentation and response modes (e.g. auditory as well as visual presentation; verbal as well as button press response) should also be available to maximise the inclusion of participants with physical or sensory impairments. Finally, if using computerised assessments rather than traditional ‘pen and paper’ tests, Workshop participants recommended that researchers should select tests that are supported by on-going technical development to increase the likelihood that they will be ‘future-proof’ against advances in operating systems and computer hardware. Some examples of suitable tools for
measuring each of the domains are presented in Table 1. Details of these tools can be found in Lezak et al. 2004 [62].

4.2 Prior cognitive ability

Measures of ‘crystallised’, knowledge-based abilities, such as vocabulary [63], as well as indices of educational achievement correlate with levels of prior cognitive ability [64]. These measures can therefore be useful for determining the extent or rate of cognitive decline that an individual has already experienced before taking part in an intervention. Such measures are particularly important when selecting participants for interventions targeted towards particular stages or levels of cognitive decline, or when investigating the absolute effect of an intervention on overall levels of cognitive ageing.

4.3 Subjective ratings of cognitive ability

Other contextual data regarding cognitive health that are potentially useful include participants’ subjective ratings of their own cognitive ability [65]. We recognise that subjective ratings show relatively weak correlation with objective measures of current or future cognitive ability, and are often influenced by other variables relating to mood, personality, and mental health [66]. However, subjective perceptions of cognitive ability may be particularly important in the context of lifestyle-based intervention studies, in which participants’ goals and motivation for undertaking and adhering to the intervention may be influenced by their own view of how successfully they are ageing, or how effective they perceive the intervention to be.

5. Psychological and subjective wellbeing

Psychological wellbeing (PWB) and subjective wellbeing (SWB) do not decrease significantly over later adulthood, despite increased physiological and cognitive dysregulation. The trajectory of this so-called ‘wellbeing paradox’ is likely underpinned by strategic shifts in individuals’ self-regulation to accommodate the additional challenges of ageing [67]. Phenotypic markers of healthy ageing, therefore, should ideally include both wellbeing outcomes and indices of the optimally-adaptive mechanisms through which they arise.

PWB and SWB comprise complementary but distinct self-reported aspects of what it means to age well. SWB, the personal experience of evaluating life in positive terms, includes elevated positive affect (PoA), low negative affect (NeA) and high levels of life satisfaction. PWB consists of successful engagement with the developmental and existential challenges of later life i.e. challenged thriving [68]. Large-scale population data support the separability of the two overarching domains, whilst qualitative data indicate that older adults afford many of the components of PWB and SWB priority over physiological function in their conceptualisations of healthy ageing [69].

There is strong evidence for the validity of SWB as a marker of healthy ageing. Meta-analyses show that measures of PoA and NeA respond favourably to physical activity interventions in older adults [70]. PoA, NeA and life satisfaction are also associated with self-perceived health in older adults and predict subsequent mortality and morbidity irrespective of initial health status [71]. Several tools which capture the components of SWB can detect change in response to interventions with older adults, and have good psychometric credentials. These include Diener et al. Satisfaction With Life Scale [72] and the Life Satisfaction Index Z [73]. Although single-item measures of global life satisfaction have been included in
numerous population-level surveys, discussants at the Workshop concluded that they lack the sensitivity and conceptual specificity required for use in intervention studies.

The components of PWB, as proposed by Ryff [74], have received considerable research attention as markers of healthy ageing. Autonomy, self-acceptance, environmental mastery, purpose in life, personal growth and positive relations with others all contribute to successful thriving in the face of age-related challenges. Meta-analyses indicate that the Scales of Psychological Wellbeing [74, 75] respond to lifestyle interventions [76] and, like SWB, predict mortality, morbidity and institutionalization [77]. Workshop discussants agreed that Ryff’s scale benefits from an explicit theoretical foundation in social gerontology and sound psychometric credentials, but noted that its length might affect negatively its feasibility and acceptability in large-scale intervention studies, and that its multidimensional factor structure has been questioned [78].

Resilience, the “process of negotiating, managing and adapting to significant sources of stress or trauma”, is a concept closely related to PWB [79]. Resilience appears to provide a roadmap to successful adaptation to developmental challenges in healthily ageing adults; in this respect it may be a distinct marker of healthy ageing. However, measurement of resilience is in its infancy and Workshop discussants concluded that evidence of the responsiveness of resilience measures to public health interventions is suggestive rather than decisive [79]. Currently, Windle, Markland and Woods’ [80] psychological resilience scale appears best suited as an outcome measure for healthy ageing interventions, due to the large, non-clinical sample of adults aged 40-90 years used in its development and its strong conceptual origins. More broadly, the case of resilience also highlights the fact that psychological markers of healthy ageing are often also understood as process variables by which healthy ageing is sustained i.e. causality is not unidirectional.

5.1 Tools to measure the psychological wellbeing component of the HAP

Current knowledge of PWB and SWB in healthy ageing is constrained by the varied and inconsistent ways in which researchers have selected wellbeing tools, some of which bear little or no specified relation to theory. Absence of mental health problems is not synonymous with either PWB or SWB, and Workshop discussants recommended that both domains be captured when assessing intervention efficacy. The four key principles we identify in Section 6 of this paper on ‘Social wellbeing’, provide additional guidance on the process of tool selection. As an extension of these principles, we recommend that investigators using PWB and SWB as markers of healthy ageing be explicit when describing the component(s) of wellbeing that they seek to measure in light of theory, and provide a brief rationale for selecting both this component and their tool of choice. Following a systematic literature review and an iterative mapping exercise to link extant tools with key wellbeing domains, suggestions for measurement are summarised in Table 1. Recent innovations in ecological momentary assessment methods, which involve repeatedly sampling participants’ experiences in real time and in real-world settings, may be used to capture intra-individual variability in psychological wellbeing with maximal ecological validity and minimal recall bias [81].

5.2 Subjective ratings of physical and emotional health

Workshop discussants also noted that, compared with objective functional data, subjective ratings of health are superior predictors of both SWB and subsequent mortality [82]. As a sensitive index of subjectively-rated health, the SF-36 is particularly popular, and has been used widely in intervention studies with healthy older adults. However, the SF-36 does not have its basis in theoretical understandings of either SWB or PWB and so is frequently misrepresented as a measure of wellbeing itself. Despite this limitation, along with measures of perceived cognitive function, the SF-36 might be used to examine the
extent to which declines in participants’ subjective functioning presage the onset of objectively verifiable functional declines, as a potential early indicator of non-healthy ageing.

6. Social wellbeing

Good health and wellbeing in later life extends beyond issues of physiological functioning to include social factors such as engaging in supportive and rewarding relationships and having opportunities to explore personal interests. This conceptualisation of ageing ‘well’ is both intuitive and embedded in the empirical and theoretical research literature [5, 83-85]. ‘Social wellbeing’ - as an umbrella term for social relationships and personal development – is a key component of a number of models of ageing[5, 86-91]. However whilst ‘social wellbeing’ is also widely recognised as an important outcome, a definition remains elusive and the absence of an agreed definition limits the ability to develop tools suitable for its measurement.

Factors that contribute to ‘social wellbeing’ in later life have been defined and measured in numerous ways, for example as social integration [92], social engagement [93-97] social participation [98], social networks [99], social ties [100], social connections [101] and social connectedness [102]. Studies of these concepts, including a meta-analysis of the impact of social relationships defined more broadly, suggest that maintaining active social relations in later life is associated with better health outcomes and reduced mortality [94, 98, 99, 101, 103, 104]. However, the specific aspects of social wellbeing that are conceptually important, and those that are amenable to intervention, remain unclear. In the context of the development of the HAP, this conceptual diversity is a further significant barrier to the identification of appropriate measurement tools.

Within the LiveWell programme we investigated social wellbeing through the pursuit of 3 explicit objectives: (i) to identify an appropriate question for a systematic review of ‘social interventions’ with health and wellbeing outcomes; (ii) to understand how people moving through a retirement transition understood the term ‘wellbeing’, and how they experienced variations in their own wellbeing; (iii) to identify appropriate outcome measures to assess the effectiveness of lifestyle interventions.

To meet the first objective, we scoped the literature to generate a list of key concepts relating to social wellbeing and older people, then - through a series of small workshops - worked with local experts to refine the list and generate an agreed set of ‘core’ conceptual components constituting social wellbeing. The components were refined iteratively and used as a ‘filter’ to help identify gaps in the literature through which we were able to identify a suitable question for systematic review. To meet our second objective, we undertook a qualitative study of the experiences of people in retirement transition. We used early findings from the qualitative study to inform further development of our core set of conceptual components of social wellbeing. In working toward the third objective, we applied the conceptual components of social wellbeing to outcomes reported in studies included in our systematic review [105] and the broader literature previously scoped. We used the concepts as a ‘filter’ to identify relevant measurement tools. We were guided in this task by investigating the intended conceptual target of the tool as reported by its author or by the author of the study reporting its use (as appropriate), in addition to our own judgement. We tabulated the range of conceptual categories, the tools used to measure them (as reported in the literature), and the methods through which we identified the tools (e.g. systematic review or convenience sample). A more detailed explanation of our methods and outcome is being prepared for publication.
The roundtable discussion at the Workshop was divided into two halves. In the first half the group discussed general conceptual issues regarding measurement of social and psychological concepts. The aim of this discussion was to identify the most adequate measures of ‘healthy ageing’ with respect to psychological and social wellbeing. Four key principles for the selection of measures were identified:

1) Identification of a minimal set of scales of mutually exclusive constructs. One suggested approach was to map existing measures onto the results of the completed qualitative work described earlier (publication of the qualitative work is currently in progress) and its evolved concepts.

2) Assessment of the acceptability of the measures by the specific population under study.

3) The most relevant measures will be those with the robustness and sensitivity to measure change in this aspect of the HAP in response to a lifestyle-based intervention.

4) Wellbeing outcome variables should differ conceptually from the core behaviours that an intervention seeks to modify, and from the moderators and mediators from which they are hypothesised to arise.

Two possible development pathways for the social wellbeing component of the HAP were identified. The first was to develop integrated social and psychological wellbeing components through a concept mapping exercise, identifying relevant concepts from: a systematic review of the topic ‘wellbeing’ in our target population, terms identified through the previous card sorting activities, and the qualitative work cited above. Appropriate outcome measures would be identified by applying HAP criteria to the concepts, then matching each concept to suitable measurement instruments. The second approach suggested was to draw on work already conducted in development of the NIH Toolbox [106] where components within the ‘emotion’ domain (specifically: life satisfaction; meaning; social support; companionship; social distress; positive social development; and social network integration) may be compatible with the social wellbeing components of the HAP. However, norms for NIH Toolbox instruments were derived from the general population including children and young adults, and their appropriateness for measuring the wellbeing of people in the peri-retirement life stage has not been established.

The decision to pursue a rigorous concept mapping process in order to identify relevant measurement instruments was taken by the team. Subsequently two hundred and ninety eight terms were printed on individual cards and sorted into loose conceptual categories by three members of the research team across three meetings. Decisions regarding the categories were reached through debate between the team members and all decisions and underpinning rationale were logged. In total this mapping process took eight hours to complete. The work of matching conceptual categories and specific constructs to outcome measures is on-going. Some potentially appropriate measurement tools are presented in Table 1.

7. Concluding remarks

In the context of lifestyle-based intervention studies designed to enhance healthy ageing, there is need for a panel of measurements which captures and quantifies features of the HAP that are objectively important (predict the ageing trajectory) and for which there are tools that are sufficiently sensitive to have utility as outcome measures. Our work on this issue is limited by both conceptual and practical problems. In
particular, we are trying to measure something (healthy ageing) which has yet to be defined adequately and, as a consequence, we have had to use information from studies using (inadequate) surrogates such as mortality or lifespan. Nevertheless, we have suggested, tentatively, 5 domains viz. 1) physiological and metabolic health, 2) physical capability, 3) cognitive function, 4) psychological wellbeing, and 5) social wellbeing which collectively may provide a reasonably holistic assessment of the HAP. We then attempted to identify key sub-domains within each of these 5 main domains and tools for their measurement. In some domains e.g. cognitive function, there was good agreement about the key sub-domains but debate about the appropriate tools for their quantification. In contrast, selection of measurement domains is less well developed in other areas e.g. social wellbeing (where the definition of the concept itself remains elusive) and this has implications for the identification and development of appropriate tools. Our research did not consider all possible components of the HAP and e.g. we did not address the senses (taste, vision, smell, hearing and somato-sensation related domains). It is well-established that acuity of these senses declines with age and that lifestyle-based intervention may modulate this age-related decline see e.g. Richer et al. [107]. However, it remains to be established whether change in sense acuity is an independent predictor of the ageing trajectory (or simply a fellow traveller) and so whether this domain should be included within the HAP. In the event of their inclusion, the NIH Toolbox provides protocols for their assessment [108-113].

Research on conceptualisation of the HAP and on the development of tools for its measurement is in its early stages. We believe that such research is timely and has the potential to benefit from advances in other fields. For example, innovations in the development of body worn sensors (allowing higher sampling frequencies and greater data storage capabilities) together with algorithms for interrogation of the resulting data are likely to provide the basis for much more informative measures of physical capability. Challenge tests offer the promise of more sensitive measures of physiological and metabolic health whilst stress tests may be the basis for better measures of both physical and cognitive function. The priority should be to develop test protocols which i) are acceptable to older participants, ii) can be deployed in community settings, iii) have low costs in terms of skills and resources, iv) are relatively quick to complete (to minimise both researcher and participant burden) and v) are capable of measuring change in response to lifestyle-based intervention.

Although the research summarised in this Workshop report had very utilitarian objectives, it may have some value in helping to conceptualise the HAP. In addition, we hope that these tentative proposals will encourage other researchers to test their utility and to add to, or subtract from, the domains and tools summarised in Table 1.
Contributors and their roles

Contributors of this paper include Jose Lara, Alan Godfrey, Elizabeth Evans, Ben Heaven, Laura J. E. Brown, Evelyn Barron, Lynn Rochester, Thomas D. Meyer and John C. Mathers. Jose Lara and John C. Mathers planned and organised the Workshop and the preparation of this report. All authors contributed to the design of the study; analysis and interpretation of data; and drafting the manuscript or revising it critically for intellectual content.

Competing interest

The authors report no conflicts of interest.

Funding

The Healthy Ageing Phenotype Workshop was organised by members of the LiveWell Programme which is funded by the Lifelong Health and Wellbeing (LLHW) Cross-Council Programme initiative in partnership with the UK Health Departments. JCM’s research through the Centre for Brain Ageing and Vitality is also funded by the LLHW initiative. The LLHW Funding Partners are: Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Medical Research Council, Chief Scientist Office of the Scottish Government Health Directorates, National Institute for Health Research /The Department of Health, The Health and Social Care Research & Development of the Public Health Agency (Northern Ireland), and Wales Office of Research and Development for Health and Social Care, Welsh Assembly Government.

Acknowledgements

The authors thank Mrs Sanchia Coatsworth for help in organising the Workshop. Special thanks to Prof Daan Kromhout, Prof Oscar Franco, Prof Ian Deary and Prof Anne Bowling for their valuable participation in the Workshop as Discussants and to Prof Philip Rowe and Prof Elaine Denison for additional contributions.

List of Workshop Participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof Ashley Adamson</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Miss Lynn Barron</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Laura Brown</td>
<td>Manchester Metropolitan University</td>
</tr>
<tr>
<td>Prof Mike Catt</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Mrs Sanchia Coatsworth</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Mr Teddy Cosco</td>
<td>Cambridge University</td>
</tr>
<tr>
<td>Mrs Karen Davies</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Prof Ian Deary</td>
<td>Edinburgh University, UK</td>
</tr>
<tr>
<td>Prof Elaine Dennison</td>
<td>Southampton University</td>
</tr>
<tr>
<td>Prof Christian Drevon</td>
<td>University of Oslo, Norway</td>
</tr>
<tr>
<td>Prof Jim Edwardson</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Liz Evans</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Janine Felix</td>
<td>Erasmus University, Netherlands</td>
</tr>
<tr>
<td>Prof Oscar Franco</td>
<td>Erasmus University, Netherlands</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Prof Richard Gershon</td>
<td>Northwestern University, USA</td>
</tr>
<tr>
<td>Dr Alan Godfrey</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Antoneta Granic</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Ben Heaven</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Nicki Hobbs</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Louisa Jenkin</td>
<td>BBSRC</td>
</tr>
<tr>
<td>Dr Victoria Keevil</td>
<td>Cambridge University</td>
</tr>
<tr>
<td>Prof Daan Kromhout</td>
<td>Wageningen University, Netherlands</td>
</tr>
<tr>
<td>Dr Jose Lara</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Miss Suzanne MacDonald</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Riccardo Marioni</td>
<td>Cambridge University</td>
</tr>
<tr>
<td>Dr Carmen Martin-Ruiz</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Prof John Mathers</td>
<td>Newcastle University, UK</td>
</tr>
<tr>
<td>Dr Lynn McInnes</td>
<td>Northumbria University</td>
</tr>
<tr>
<td>Dr Thomas Meyer</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Eugene Milne</td>
<td>NHS North East</td>
</tr>
<tr>
<td>Dr Suzanne Moffatt</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Ms Alex Munro</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Prof Mark Pearce</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Prof Louise Robinson</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Prof Lynn Rochester</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Prof Philip Rowe</td>
<td>Strathclyde University</td>
</tr>
<tr>
<td>Miss Caroline Shaw</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Mario Siervo</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Falko Sniehotta</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Sabita Soedamah-Muthu</td>
<td>Wageningen University, Netherlands</td>
</tr>
<tr>
<td>Dr John Starr</td>
<td>Edinburgh University, UK</td>
</tr>
<tr>
<td>Dr Blossom Stephan</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Prof Michael Trenell</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Dr Janet Valentine</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>Prof Joe Verghese</td>
<td>Albert Einstein College of Medicine, USA</td>
</tr>
<tr>
<td>Prof Thomas von Zglinicki</td>
<td>Newcastle University</td>
</tr>
<tr>
<td>Prof Martin White</td>
<td>Newcastle University</td>
</tr>
</tbody>
</table>
References


...


Figure 1. Measuring change in intervention studies

Baseline measures of healthy ageing phenotype → Intervention → Behaviour change → Functional benefit → Outcome measures of healthy ageing phenotype

Lifestyle interventions:
- Drinking in moderation
- No smoking
Figure 2. Proposed measurement domains for the Healthy Ageing Phenotype

Healthy Ageing Phenotype

Psychological wellbeing
- Positive and negative affect
- Life satisfaction
- Quality of life
- Mental health
- Resilience

Social wellbeing
- Social network
- Social functioning
- Perceived emotional/social support
- Sense of purpose

Physiological and metabolic health
- Cardiovascular function
- Lung function
- Glucose metabolism
- Body composition

Physical capability
- Strength
- Locomotion
- Endurance
- Dexterity
- Balance

Cognitive function
- Processing speed
- Episodic memory
- Executive function
Table 1. Tools to measure selected domains and sub-domains of the Healthy Ageing Phenotype

<table>
<thead>
<tr>
<th>Domain</th>
<th>Subdomain</th>
<th>Tool/measure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological and metabolic health</strong></td>
<td>Cardiovascular function</td>
<td>Blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood lipids</td>
</tr>
<tr>
<td>Lung Function</td>
<td>Forced expiratory volume (FEV1)</td>
<td></td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td>Glycated haemoglobin (HbA1C)</td>
<td></td>
</tr>
<tr>
<td>Body composition</td>
<td>Waist circumference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Waist to hip ratio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Body mass index (BMI)</td>
<td></td>
</tr>
<tr>
<td><strong>Physical capability</strong></td>
<td>Strength</td>
<td>Handgrip strength</td>
</tr>
<tr>
<td></td>
<td>Locomotion</td>
<td>Gait speed</td>
</tr>
<tr>
<td>Endurance</td>
<td>Walk endurance test</td>
<td></td>
</tr>
<tr>
<td>Dexterity</td>
<td>Pegboard dexterity test</td>
<td></td>
</tr>
<tr>
<td>Balance</td>
<td>Standing balance test</td>
<td></td>
</tr>
<tr>
<td><strong>Cognitive function</strong></td>
<td>Processing speed</td>
<td>Speed reaction time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symbol digit modalities test</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>Story recall</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Word list recall</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paired associate learning</td>
<td></td>
</tr>
<tr>
<td>Executive function</td>
<td>Stroop</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trail making tests A &amp; B</td>
<td></td>
</tr>
<tr>
<td><strong>Psychological wellbeing</strong></td>
<td>Positive and negative affect</td>
<td>Positive and negative affect schedule</td>
</tr>
<tr>
<td>Life satisfaction</td>
<td>Satisfaction with life scale</td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td>Control, Autonomy, Pleasure and self-realization, quality of life scale (CASP-19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WHO Qulaity of Life-BREF (WHOQoL-BREF)</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>Centre for epidemiological studies depression scale</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warwick-Edinburgh mental wellbeing scale</td>
<td></td>
</tr>
<tr>
<td>Resilience</td>
<td>Psychological resilience scale</td>
<td></td>
</tr>
<tr>
<td><strong>Social wellbeing</strong></td>
<td>Social network</td>
<td>Lubben social network scale</td>
</tr>
<tr>
<td></td>
<td>NIH-Toolbox: Friendship</td>
<td>PROMIS: Companionship</td>
</tr>
<tr>
<td></td>
<td>PROMIS: Social isolation</td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>PROMIS: Satisfaction with social roles and activities</td>
<td></td>
</tr>
<tr>
<td>Perceived emotional/social support</td>
<td>Revised UCLA loneliness scale</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Social support behaviors scale</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NIH-Toolbox: Emotional support</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Instrumental support</td>
<td>Loneliness</td>
</tr>
<tr>
<td></td>
<td>Loneliness</td>
<td>Perceived rejection scale</td>
</tr>
<tr>
<td>Sense of purpose</td>
<td>NIH-Toolbox: Psychological wellbeing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meaning and purpose</td>
<td></td>
</tr>
</tbody>
</table>