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Proposition of a new cumulative frailty index

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Abstract

Frailty is one of the greatest challenges for healthcare professionals in aging societies being associated with adverse health outcome, dependency, institutionalization, and mortality.
However, even if frailty is widely recognized as a specific, clinical syndrome there are no universally accepted diagnostic criteria. Several frailty indexes have been described in the literature but few of them seem to be demonstrably valid, reliable and diagnostically accurate. We have created a new, composite frailty index, the My-AHA Frailty Index, that encompasses all the frailties (physical, cognitive, psychological, social) and the main functions (nutrition and sleep) that have been investigated in the My-Active and Healthy Aging study. This new frailty index has been investigated and tested in all the subjects involved in the My-Active and Healthy Aging study.

Disclaimer

[Full project title] MY-AHA – **my A**ctive and **H**ealthy **A**geing

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Executive summary

The purpose of this deliverable is to discuss and suggest a new cumulative frailty index, based on the results of the My-AHA randomized controlled study. At present. there is no universally accepted diagnostic criteria for frailty and a numerous frailty indexes have been suggested. After reviewing the literature on this topic and considering the data provided by the My-AHA RCT study, we propose a new cumulative frailty index (My-AHA FI). This new index includes the measurement of physical, cognitive, psychological and social frailties, as well as nutrition and sleep functions. According to a standardized procedure, this new index has been tested initially in the subjects involved in the My-AHA RCT and, subsequently, will be deployed in population studies.

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List of abbreviations

ADL – Activity of Daily Life
HADS – Hospital Anxiety and Depression Scale
HVLT – Hopkins Verbal Learning Test
IADL – Instrumental Activity of Daily Life
ICT – Information and Communication Technology
LNSR-R - Lubben Social Network Scale, Short form
MCI – Mild Cognitive Impairment
MMSE – Mini Mental State Examination
MoCA – Montreal Cognitive Assessment
RCT – Randomized Controlled Study
Self-MNA – Self-Mini Nutritional Assessment
SPSS.26 – Statistical Package for Social Sciences – ed. 26
WHOQOL-OLD - World Health Organization Quality of Life scale – OLD extension

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1 Introduction

Frailty is one of the greatest challenges for healthcare professionals in aging societies. It is associated with adverse health outcome, dependency, institutionalization, and mortality (1).

However, even if frailty is widely recognized as a specific, clinical syndrome affecting mainly older adults yet there are no universally accepted definitions of this syndrome. Furthermore, frailty lacks specific diagnostic criteria.

At present, there is no universal and accepted definition of frailty. The challenge in developing a consensus definition of frailty is due in large part to the complexity of the syndrome, which involves many different domains, physiological, cognitive, psychological and social. As no single manifestation of frailty can encompass the range of presenting signs or symptoms, defining frailty for clinical practice and research remains paradoxically difficult. A clear clinical definition of frailty is critical in characterizing subsets of vulnerable older people, who are not currently evaluated for disability risk in the clinical health care process. In addition, without an operational definition available in clinical practice, the health practitioner's ability to recognize and provide care for this phenomenon is limited.

Currently, frailty is regarded as a multidimensional syndrome characterized by loss of physiologic reserves that predisposes to the accumulation of deficits and adverse outcome from acute stressors. Frailty develops when age-associated degenerative processes overwhelm reserve capacity and plasticity processes that maintain function of the nervous system and other physiologic systems. Overall, frailty represents the vulnerability of aged population to adverse events as the result of the subtle and progressive metabolic and physical changes.

Over the past two decades, the physical frailty syndrome has been widely investigated. Although there is not a universally accepted operational definition of physical frailty, the most commonly used definition of a physical phenotype of frailty comes from Fried and colleagues (2001) who proposed identifying frailty by using the Fried Frailty Index (2). The Fried Frailty Index is used to assess the presence of physical frailty if three or more symptoms are observed: A. shrinking (i.e., a nutritional/metabolic component assessed by unintentional weight loss), B. weakness (i.e., indicated by muscle strength), C. poor endurance and energy (i.e., self-reported exhaustion), D. slowness (i.e., demonstrated by slow walking speed), and E. low amounts of physical activity. Strong associations have been observed between the physical frailty phenotype, as defined by Fried et al. criteria, and the risk of developing certain health related outcomes. Thus, physical frailty can be partially explained by the occurrence of age-related body composition changes loss of muscle mass, reduced muscle quality, and increased fat mass, which altogether precipitate in the development of frailty syndrome in older adults.

More recently, the term cognitive frailty has emerged in the literature. The term cognitive frailty refers to cognitive impairment occurring as people reach advanced age, as well as to cognitive disturbances or pre-dementia occurring in association with other medical conditions. The current working definition of cognitive frailty, however, provides a foundation for clinical studies aimed at establishing an operational definition of this phenomenon. Motivated by growing awareness that many people with physical frailty are also prone to cognitive difficulties, an international consensus group comprised of investigators from the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics recently established a working definition for cognitive frailty in older adults (3). The consensus group summarized cognitive frailty as a heterogeneous clinical manifestation characterized by the simultaneous presence of physical frailty and cognitive impairment, in the absence of dementia. Unlike physical frailty, the primary criteria for cognitive frailty is the presence of mild cognitive impairment as defined by a clinical dementia rating (CDR) score of 0.5, without Alzheimer's disease or another progressive brain disturbance leading to dementia (e.g.. mild cognitive impairment). The recently proposed definition of cognitive frailty has yet to be empirically tested with previous research focusing on a variety of different phenomena related to the concept of cognitive frailty.

In the last few years, several criticisms have been addressed to the frailty syndrome related only to physical and cognitive deficits. The presence of psychological frailty as well as social frailty has been described in the medical literature (4). These frailties have been less studied and still require operational criteria. Frailty is a dynamic process that involves several physiologic systems and there is a need to incorporate the notion of dysfunction across multiple systems in a common pathway. Finally, there is a need to adopt a holistic approach to frailty, one that encompasses the multidimensional nature of the frailty syndrome in older adults.

The My Active and Healthy Aging (My-AHA) project was designed to support and promote active and healthy aging by enabling early detection and minimization of multidimensional frailty risks. Early risk detection occurred across multiple domains of physical activity, cognitive activity, psychosocial activities, nutrition and sleep. The My-AHA project mapped an individual's frailty risk profile across multiple domains and delivered ICT-based interventions tailored and targeted to identify risk profile for each individual.

After a detailed analysis of all the data collected in the randomized controlled study (RCT) of the My-AHA project, we suggested a new cumulative frailty index that may be used in the measurement of frailty both in observational and intervention studies.

2 Instruments to measure frailty

Two major frailty models have been described in the literature: the frailty **phenotype and the frailty index**.

The frailty phenotype model is characterized by a predefined set of five specific signs and symptoms, used to measure the degree of frailty of an individual. According to previously described Fried et al. criteria (weakness, slowness, low level of physical activity, self-reported exhaustion, and unintentional weight loss), subjects may be classified as pre-frail (one or two criteria present) of frail (three or more criteria present). The Fried criteria have been used in several epidemiological and interventional studies. They are relatively easy to use and allow for rapid assessment of strength and gait speed but are difficult to implement in some clinical settings due to lack of proper equipment, time, and/or space to conduct the assessments. Further, it is not possible to use the Fried model for assessment in the presence of disability or cognitive impairment. With the exception of objectively measured gait speed, which is a strong predictor of poor clinical outcomes in different populations, the added value of the other criteria used in Fried's definition remains unknown. In addition, the heterogeneous constellation of the Fried criteria includes very diverse phenotypes of frailty, making the syndrome difficult for targeting with specific pharmacologic interventions. From an interventional perspective, a more constrained definition of frailty, involving for example, only physical performance, would be of more practical utility. An additional limitation of the Fried model is that it does not account for the role of cognition and other psychosocial factors in determining the frailty status. There is increasing evidence that such factors need to be considered and could improve the ability to predict adverse health outcomes.

Alternatively, frailty has been viewed from the perspective of an accumulation of deficits in the form of a frailty index (FI). A robust frailty index requires a significant number of individual items which are utilised to record deficit accumulation, and which are recorded as a score or index. This can also then be monitored in subsequent assessments to record the effectiveness or otherwise of specific interventions aimed at reducing an individual’s level of frailty.

At present, many FI have been suggested, generally related to the comprehensive geriatric assessment (CGA). A recent systematic review showed that more than 20 frailty instruments have been described in the literature (5). However, only a few frailty measures seem to be demonstrably valid, reliable and diagnostically accurate, and have good predictive ability. In addition, clinometric properties of these instruments as evaluative outcome measures are unclear.

3 Suggestions from the My-AHA RCT

The My-AHA project was a multicenter, multicultural 12-month RCT (ClinicalTrials.gov identifier: NCT03342976) involving centers from Europe, Australia, and Asia. The RCT was conform to Consolidated Standards of Reporting Trials guidelines and was designed to result in the measurement of multidimensional prefrailty (physical, cognitive, social, and psychological) as well as to evaluate the efficacy of an ICT-based platform to monitor tailored interventions to prevent decline into clinical frailty states. A detailed description of the study protocol has been previously published (6). The results of the study have been submitted to a major peer-reviewed medical journal and are currently under evaluation.

To be eligible for participating in the study, individuals were required to be over 60 years old, familiar with use of smartphones and tablets or computers, meet Fried criteria for pre-frail status, able to stand and walk unassisted, free of significant cognitive impairment, free of clinically significant mood disturbances, free of any acute or unstable medical conditions, and able to understand directions and participate in the protocol. Exclusion criteria were related to the presence of mobility problems, concomitant injury or diseases known to impact cognitive, psychological or physical function, presence of deficit that interfere with assessment validity.

Participants have been randomly allocated to one of two study arms: Study Arm 1 (My-AHA intervention group) and Study Arm 2 (standard care control group). Subjects selected for the Study Arm 1 (Intervention Group) were enabled to use and interact with My-AHA platform by using their own smartphone. The My-AHA system is an ecosystem of platforms that integrates both commercials and developed ad-hoc platforms is an ICT network composed of the following: (a) a Middleware able to store data about the user (demographic, health status, habits, and activity) and to connect to third-party application that can be used to monitor data, like physical activity, (b) a decision support system that implements the rules for assessing the risk of frailty-related problems and the interventions addressed to reduce them, (c) a front end ("dashboard") designed for web and mobile applications, and (d) connectors with third-party applications that can be used to register data (e.g., physical activity monitoring through wearable sensors) or support the proposed interventions (e.g., cognitive games).

At baseline, all participants underwent comprehensive assessment of multidomain functions. The assessments included measurements of: Fried criteria, quality of life (Health World Health Organization Quality of Life scale–OLD extension (WHO-QoL-OLD), activities of daily living (Lawton-Brody Instrumental Activities of Daily Living (iADL) scale), physical measures (weight, height, Dual-Task Performance, Timed up and Go test, Short Physical Performance Battery (SPPB)–Balance subtest, Sit-Stand subtest, Activities-specific Balance Confidence (ABC) scale, Physical Activity Enjoyment Scale (PACES), cognitive function (Mini–Mental State Examination (MMSE), Hopkins Verbal Learning Test (HVLT), Spatial Span (SSP) from the Wechsler Memory Scale, 3rd edition, Trail Making Test (TMT), 24 item Victoria version Stroop test, Digit Symbol coding subtest (DSC) from the Wechsler Adult Intelligence Scale), psychological function (Psychological Hospital Anxiety and Depression Scale (HADS), social function (Social Lubben Social Network Scale, Short form (LSNS-R), University of California, Los Angeles Loneliness Scale–Revised), sleep (Pittsburgh Sleep Quality Index) and nutrition (Self-Mini Nutritional Assessment (Self-MNA). These assessments were repeated at six-month intervals across the duration of the RCT (6, and 12-month time points). Data from these three assessment points were used to ascertain the effect of the intervention program on the functional status of each participant in each study arm. Assignment of interventions was based on algorithms developed to match the need for intervention across each domain and participant preference. Recalculation of the intervention package for each participant occurred following each assessment point, with intervention prescriptions having an effective 6-month duration. Intervention packages were developed for physical, cognitive, psychosocial, nutrition, and sleep domains and were reported in detail (6). Between Sep. 2, 2017 and Sep. 30, 2018, 636 individuals were screened and 249 were randomly assigned to the intervention group (n=123) and to the

control group (n=126). 201 (80.7 %) participants completed the 12 months assessment. The intervention was completed in December 2019. The study was completed by 201 subjects (101 in the Active group and 100 in the Control group).

Analysis of the primary outcome variables indicated that there were some select domains of improvement that could be attributed to an intervention effect. A repeated measures ANOVA examining change in quality of life over time, identified a significant phase effect (p. = .003, η2p = .056, power = .873), and a significant group by phase interaction effect (p. = .025, η2p = .037, power = .682). Examination of the interaction effect indicates that the control group displayed a significant decrease in Quality of Life (QOL-OLD -WHO) at the 12-month phase, with no change in QoL evident in the intervention group (Figure 1).

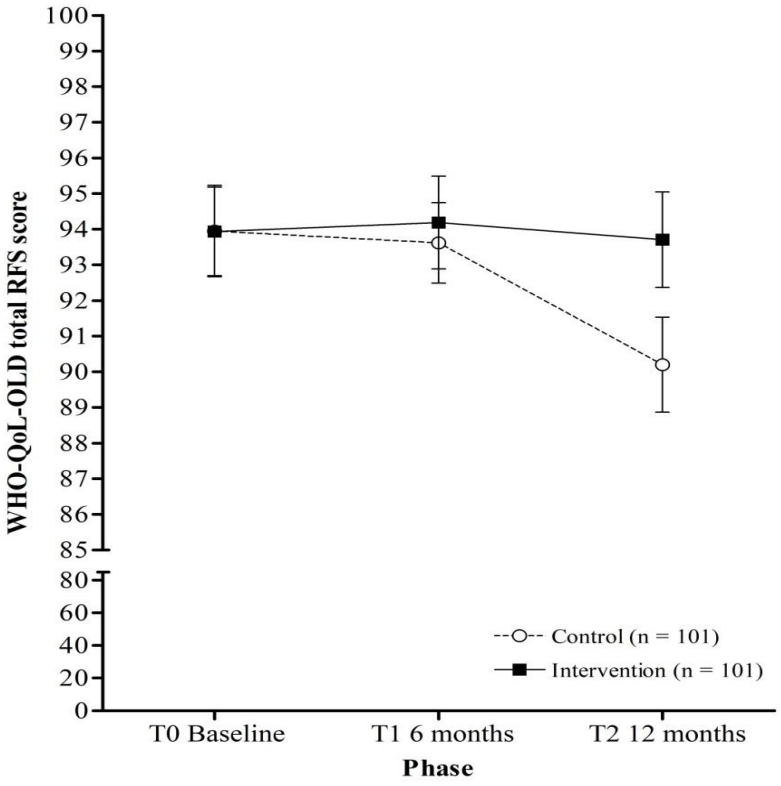

Figure 1: Group differences in QoL score across RCT phases (mean ± SEM)

In addition, repeated measures ANOVA of the HADS-Depression scores identified a significant group by phase effect (*p.* = .048, η^2_p = .015, power = .590). Examination of the interaction effect indicates that the control group displayed a significant decreased in level of depressed mood at the 6 month phase which was maintained at the 12 month phase, with the control group's level of depression mood increasing across 6- and 12-month phases of the RCT (Figure 2).

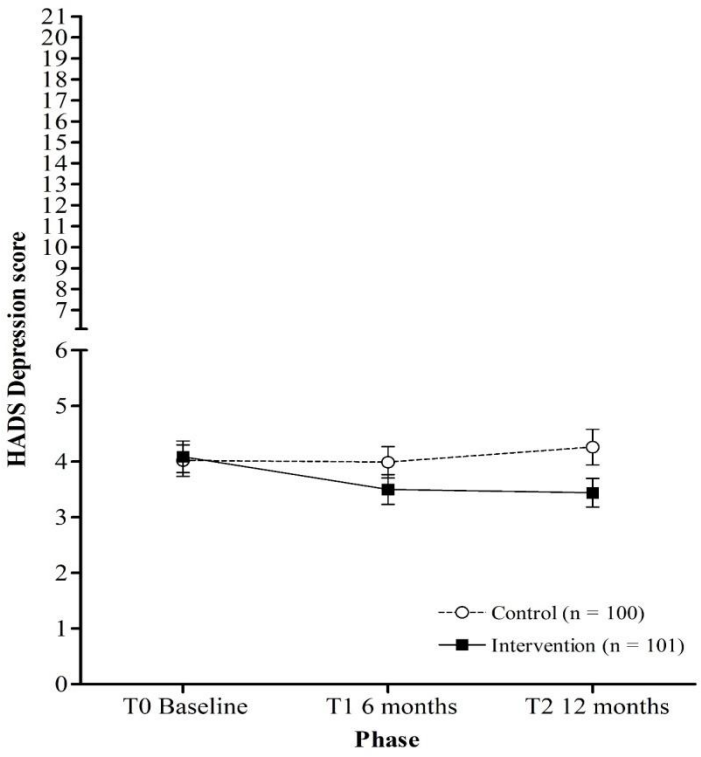

Figure 2: Group differences in HADS-Depression score across RCT phases (mean ± SEM)

Finally, repeated measures ANOVA of the self-MNA score identified a significant phase effect

(*p.* = .004, η^2_p = .027, power = .849), and a significant group by phase effect (*p.* = .047, η^2_p = .015, power = .591).

Therefore, main results of the My-AHA RCT study were that participants in the active group, in comparison with controls, showed **no decline in quality of life** and improved **mood** and **nutritional** functions.

4 Frailty and Quality of life

In the last decade, concurrent with increased research interest in frailty in aging, there has been an increase interest in research investigating quality of life (QoL) in older adults.

According to WHO, QoL is a complex concept which encompasses "An individual's perception of their positions in life, in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standard and concerns" (7).

For older subjects, the WHO developed a specific scale, the WHOQOL-OLD, in order to measure the specific characteristics of quality of life in aging individuals. This scale comprises 24 facets grouped into 4 domains focusing on the physical, the psychological, the social and the environmental respectively. Besides, there were two general items about health conditions which are analyzed independently.

In addition to WHOQOL-OLD, several scales evaluating QoL in the aging population have been validated worldwide and the evaluation of QoL in older adults is becoming an increasingly important outcome measure for planning and delivery of health and social services.

Intriguingly, several studies have identified a link between QoL and frailty, reporting a robust inverse association between frailty/prefrailty and QoL in older adults (8,9). These data suggest a complex relation between quality of life and frailty that is simplified in figure 3. In addition, this relationship suggests that interventions targeted at reducing frailty may have the additional benefit of improving corresponding QoL.

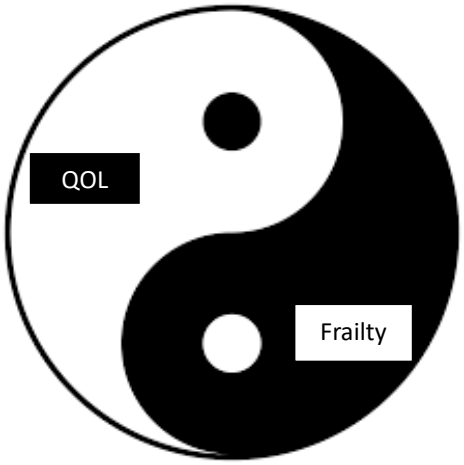

Figure 3: The complex relationship between frailty and quality of life

5 A new cumulative frailty index

According to previous considerations, we propose a new cumulative frailty index derived from the results of the My-AHA protocol (**My-AHA FI**). This index is based on a dynamic and reversible framework of the frailty syndrome and postulates that different frailties may be equally involved in the conversion from a robust condition to a frail condition (Figure 4). This index derives from the evaluation of six different parameters: 1. Physical frailty, 2. Cognitive frailty, 3. Psychological frailty, 4. Social frailty, 5. Nutrition, 6. Sleep.

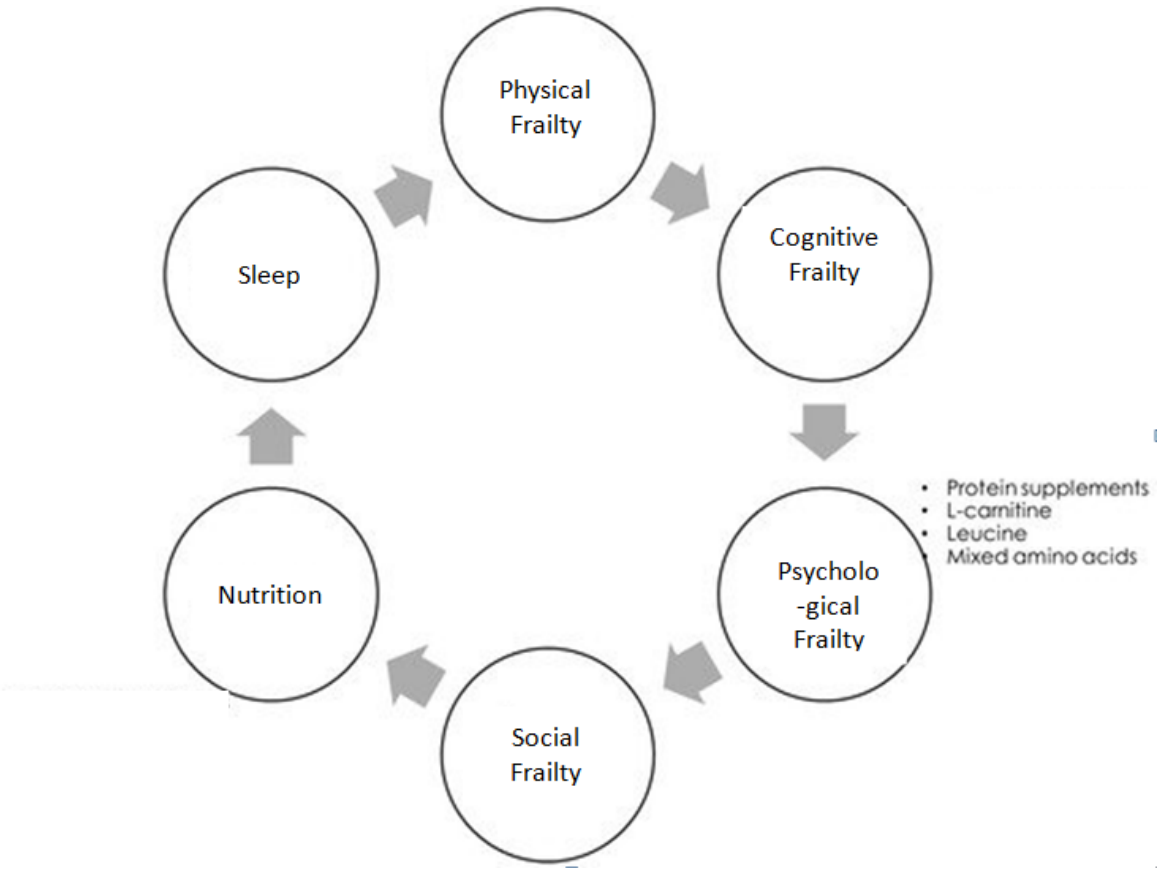

Figure 4: The cycle of different frailties according to the new My-AHA frailty index

The following tests are used in order to define the My-AHA Frailty Index:

1. **Physical frailty:** Grip strength**,** Timed Up and Go test, Short Physical Performance Battery (SPPB)–Balance subtest
2. **Cognitive frailty:** Mini Mental State Examination test (MMSE)
3. **Psychological frailty:** Psychological Hospital Anxiety and Depression Scale (HADS)
4. **Social frailty:** Social Lubben Network Scale, Short form

5. **Nutrition:** Self-Mini Nutritional Assessment (Self-MNA)
6. **Sleep:** Pittsburgh Sleep Quality Index

The thresholds for each test have been already defined and all the tests have been already validated in different languages.

As for the Fried et al criteria, subjects scoring positive at one or two tests, may be considered pre-frail while subjects scoring three of more may be considered frail.

A first attempt to evaluate this new frailty index is under way. We are re-examining the results obtained in the comparison between cases and controls of the My-AHA study looking for significant differences between the baseline and the assessment at six and twelve months. Furthermore, we are trying to relate the scores of the My-AHA FI with those of WHOQOL-OLD, ADL and iADL tests in order to evaluate the potential correlations between these two tests.

6 Procedure for creating and validating a new frailty index

There is a standard procedure for creating and validating a new frailty index that starts from solving the need to operationalize frailty (defined as increased vulnerability to adverse outcomes) and ends with a validation of the new index in a large population study.

A Frailty Index can be created by utilizing health deficits that are routinely collected in health assessments, such as chronic diseases, symptoms and signs, laboratory, imaging and echocardiographic abnormalities, example of cognitive impairment or deficits in activities of daily living. Alternately, individuals may be evaluated according to a standardized protocol for abnormalities in different tests.

Variables can be included in a frailty index if they satisfy the following 5 criteria:

1. Deficits must be associated with health status (for example, not be just age related);
2. A deficit's prevalence must generally increase with age (although there may be exceptions);
3. The chosen deficits must not reach saturation in a population too early (for example presbyopia and age-related lens changes occur nearly universally by age 55 so reach saturation too early);
4. Chosen deficits must cover a range of systems (for example, not just cognitive impairment items);
5. Deficits must be the same from one iteration to the other of the index, if used serially on the same people.

The Frailty Index is defined as the proportion of deficits present in an individual out of the total number of age-related health variables considered. For example, an elderly patient with 20 health deficits out of 50 considered has a FI of 0.4 whilst another elderly patient with 10 health deficits out of 50 considered, has a FI of 0.2. The FI developed by Rockwood et al. (10) has been used both in research and health settings as a proxy measure of aging and as a predictor of risk/vulnerability to poor outcomes. Across several frailty index measures and studies, people were found to accumulate deficits, on average, at about 0.03/year and the frailer the person was (the higher the deficit count) the more vulnerable they were found to adverse outcomes.

Then, results collected in large database need to be analyzed, in a retrospective way, in order to evaluate concordance rates (kappa values) with previous used Frailty Indexes. Finally, a prospective study is necessary in order to evaluate sensitivity and specificity of the new FI towards well defined outcomes, like dependence and death.

7 Conclusions

In this deliverable, after reviewing literature data regarding the available frailty indexes, we suggested the creation of a new frailty index (the My-AHA Frailty Index) that encompasses, in a dynamic and simply way, the physical, cognitive, psychological and social frailties as well the nutrition and the sleep functions. The data obtained in the My-AHA RCT study will be re-analyzed according to this ne FI. In addition, the potential correlation between the My-AHA FOI and the WHOQOL-OLD will be investigated.

This new index on quantifying frailty can aid out understanding of frailty-related health characteristics in older adults.

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