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Intrinsic capacity and resilience vs frailty: On the way to healthy aging

Edited by
Elena Vladimirovna Frolova, Wee Shiong Lim and Beatrice Arosio

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Intrinsic capacity and resilience vs frailty: On the way to healthy aging

Topic editors

Elena Vladimirovna Frolova — North Western state medical University, Russia
Wee Shiong Lim — Tan Tock Seng Hospital, Singapore
Beatrice Arosio — University of Milan, Italy

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Tzvi Dwolatzky,
Technion Israel Institute of Technology, Israel

*CORRESPONDENCE
Elena Frolova
✉ efrolovamd@yandex.ru

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Editorial: Intrinsic capacity and resilience vs. frailty: On the way to healthy aging

Elena Frolova[1]*, Beatrice Arosio[2] and Wee Shiong Lim[3,4]

[1]The Family Medicine Department, North Western State Medical University, St-Petersburg, Russia, [2]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [3]Department of Geriatric Medicine, Institute of Geriatrics and Active Aging, Tan Tock Seng Hospital, Singapore, Singapore, [4]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore

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Editorial on the Research Topic
Intrinsic capacity and resilience vs. frailty: On the way to healthy aging

One of the most intriguing aspects of aging is the heterogeneity of the older adult population. Some age rapidly and lose their independence, while others remain physically active and cognitively preserved despite their age and number of comorbidities (1). Although geriatricians have long used the concept of frailty as a measure of an individual's risk profile in clinical practice, there is increasing appreciation that the unitary concept of frailty may not adequately address all situations.

The World Health Organization (WHO) advocates moving away from a disease-focused model of aging and frailty, and toward a more positive model of healthy aging (2) that focuses on preserving functional ability through optimizing intrinsic capacity (IC) and the environment. IC is defined as "the composite of all the physical and mental capacities that an individual can draw on" at any point in time (3). IC includes five domains, namely locomotion, vitality, sensory, cognition, and psychological (4–6). These domains influence each other and are, in turn, influenced by environmental factors (7). The related concept of physical resilience has been defined as one's ability to resist decline or recover from functional decline after a significant health stressor (8).

However, to date, the tools that geriatricians can use to measure the contribution of each domain to the IC model, as well as the factors and mechanisms that contribute to sustainability and physical reserve, are not fully understood. This highlights the need for more studies to understand the inter-dependent yet distinct contribution of IC and resilience vis-à-vis frailty toward healthy aging (3, 9). This Research Topic is therefore timely, with the over-arching goal of bridging the knowledge gap about the healthy aging model. We aim to demonstrate the possibility of interventions to return the aging processes from pathological to healthy, describe the difference between frailty and IC, and explicate the mechanisms of resilience and physical and cognitive reserves.

Notwithstanding the consensus regarding the concept of frailty aligning with either the phenotypic or deficit accumulation model, debate persists about the tools for assessing and measuring frailty in clinical practice (10). Of note, it is imperative to consider the national, cultural and organizational context in which screening tools are administered. In this regard, Jung, Baek, Kwon, et al. describe their experience using the Clinical Frailty Scale (CFS) to evaluate patients in the emergency department of a busy Asian hospital. They demonstrated that CFS administered in the emergency department could predict adverse events, such as the development of pressure sores, delirium, falls, repeated hospitalizations, and placement

in long-term care institutions. Thus, the choice of a tool for screening and measuring frailty is determined largely by the clinical purpose of frailty identification. Another article by Jung, Baek, Jang, et al. compared the original classification and culturally modified classification of the CFS by considering the culturally-sensitive items of food preparation and household chores in instrumental activities of daily living (IADL) which may be less applicable to older men in Korea. The main implication is the reclassification of CFS 5 (impairment in IADL) to CFS 4 in the affected men. The results demonstrate that the modified CFS had better construct validity and comparable predictive validity for the composite outcome of institutionalization and death, alluding to the salience of cultural adaptation of selected items for accurate frailty assessment in older persons. In addition, it is important to consider the perception of older persons toward their functional capabilities, especially in the context of concomitant cognitive impairment (11). The paper by Hartle et al. highlights the lack of awareness of ADL in persons with dementia, and the relevance of informant reports and cognitive testing for fluency to complement clinical assessment of ADL performance. Regarding awareness, general cognitive level was a significant predictor of instrumental ADL awareness, and memory was the only predictor of awareness of basic ADL.

In recent years, there is increasing interest within the field to understand the biological basis of IC and its component domains, in particular, the vitality domain (12–15). Four papers in this Research Topic shed further insights into possible mechanisms and pathophysiology which underpins the biological basis of IC. Meng et al. set out to justify not only the assessment of each domain, but also the overall composite assessment of the IC, in association with the functional status. In addition, they tried to ascertain the biological basis of IC and determine the prognostic value of this estimate for 4-year mortality. The results showed that a scoring system considering different weights of individual IC subdomains not only predicts mortality but also suggests different pathophysiologies across the life course of aging, including inflammation, nutrition, stress, and the ApoE4 genotype. The remaining three papers examine the important entity of sarcopenia, which predisposes to adverse outcomes such as reduced mobility, functional decline, falls, institutionalization and mortality, and has been proposed to be the antecedent of physical frailty (16, 17). Lu et al. investigated the association of sarcopenia with the fasting insulin level and other markers of lipid and insulin metabolism in both diabetic and diabetes-free older persons. They reported that sarcopenia is associated with low insulin levels, regardless of diabetic status, and also uncover interesting associations with leptin, C-peptide, and Insulin Growth Factor-1. In their Perspective article, Chew et al. explore the recent experimental and clinical evidence in support of the novel interaction between gut microbiota and muscle function in the gut-muscle crosstalk and discuss potential exercise and pharmacological interventions which may influence the microbiome to provide novel approaches to the treatment of sarcopenia and frailty. Another area of emerging interest is to understand the relationship between chronic diseases with IC and vitality in order to accrue fresh insights for early intervention (18). Loh et al. provided a comprehensive commentary of the cardio-sarcopenia syndrome which refers to the co-occurrence of alterations in myocardial structure in older adults with skeletal muscle sarcopenia. Investigations into this syndrome have spurred a fresh level of interest in the cardiac-skeletal muscle axis and raise the tantalizing possibility of inter-disciplinary interventions aimed at improving the condition of skeletal muscles, such as resistance exercises, aerobic physical activity and dietary protein consumption, to improve myocardial function.

Three articles in the Research Topic touch upon the psychosocial aspects of IC. The cognitive and psycho-emotional domains of IC are determined not only by the individual characteristics of each person, but also by the state of one's social environment (19, 20). Fang et al. evaluated the social support of frail, pre-frail and robust elderly and showed that the frail and pre-frail have a lower level of social support than the robust. Chen et al. reported in their cross-sectional study of 3 cities in China that moderate-to-strong levels of sense of coherence conferred lower odds of being frail and proposed improving sense of coherence as a possible strategy to prevent frailty. Lastly, using latent cluster analysis, Merchant et al. identified three patterns of participation restriction (low/moderate/high) in community dwelling older adults $\geq$60 years with falls or risk of falls. Of note, the presence of 3 out of 6 impaired IC denotes a $>$80% probability of belonging to the low/moderate participation class. The identified IC risk factors of physical functioning, cognitive status, hearing impairment and malnutrition may thus be potential intervention targets to improve participation of older adults with falls or at risk of falls.

The next major theme in our Research Topic revolves around the area of interventions to regress the process of pathological aging and to restore healthy aging. In the area of outcome measures of multidimensional aging, Zhang et al. developed a new composite measure of aging that integrated phenotypic and functional aging with potential for assessment of geroprotective programs. This composite measure better predicted mortality risk compared with each aging measure in isolation, and was responsive to modifiable lifestyle factors including smoking status, body mass index, alcohol consumption, and leisure-time physical activity. Tan et al. demonstrated preliminary evidence of a novel technology-enabled autonomous multi-domain community-based interventions with exercise, nutrition, and polypharmacy components in improving frailty status, physical performance and strength in pre-frail older adults. Using the Senior Technology Acceptance and Adoption Model, the study also explicated user experience insights which can affect the usability and enjoyment of technological interventions for older persons. In their non-randomized controlled study of a multi-domain exercise and nutrition intervention in pre-frail older persons, Tay et al. reported that reversal to robustness at 1-year was similar between intervention and control groups, suggesting that focusing only on the locomotion and vitality domains may not adequately address component domain losses to optimize pre-frailty reversal. Furthermore, the intriguing result that IC rather than intervention exposure influences reversal to robustness suggest that an IC-guided approach to target identified domain declines may be more effective in preventing frailty progression. Lastly, in the systematic review of multi-domain and lifestyle interventions to support IC, Bevilacqua et al. reported that the majority of successful interventions are based on a goal

setting approach whereby older persons are actively and involved in defining the intervention goals. The observation that there were no studies which utilized the IC framework to design the intervention, highlights a significant gap which can inform the future research agenda.

As guest editors, the 14 papers presented in this Research Topic provide a valuable compendium of fresh insights and perspectives in the rapidly-growing field of IC, frailty, and healthy aging. It is our sincere hope that this Research Topic will spur further conversations and explorations to advance this exciting field of research in geroscience and geriatrics.

Author contributions

EF, BA, and WL contributed to conception of the editorial. EF wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Biological Features of the Outcome-Based Intrinsic Capacity Composite Scores From a Population-Based Cohort Study: Pas de Deux of Biological and Functional Aging

*Lin-Chieh Meng[1], Shih-Tsung Huang[1], Li-Ning Peng[2,3], Liang-Kung Chen[2,3,4] and Fei-Yuan Hsiao[1,5,6]**

[1] Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, [2] Aging and Health Research Center, National Yang Ming Chiao Tung University Yangming Campus, Taipei, Taiwan, [3] Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan, [4] Taipei Municipal Gan-Dau Hospital, Taipei, Taiwan, [5] School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, [6] Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan

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Edited by:
Wee Shiong Lim,
Tan Tock Seng Hospital, Singapore

Reviewed by:
Jun Pei Lim,
Tan Tock Seng Hospital, Singapore
Heewon Jung,
University of Ulsan, South Korea

***Correspondence:**
Fei-Yuan Hsiao
fyshsiao@ntu.edu.tw

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Introduction: This study aims to develop and validate an integrative intrinsic capacity (IC) scoring system, to investigate its associations with a wide spectrum of biomarkers and to explore the predictive value of the integrative IC score on 4-year mortality among community dwelling people aged 50 years and older.

Methods: We included 839 adults aged ≥50 years from the Social Environment and Biomarkers of Aging Study (SEBAS) and randomly divided them into derivation and validation cohorts to develop the IC scoring system. The multivariate logistic regression model was used to weight each subdomain (locomotion, sensory, vitality, psychological, and cognition) of IC according to its association with impairments in instrumental activities of daily living (IADL) and to construct the integrative IC score. Age-related biomarkers and genetic markers were compared between IC groups by ordinal logistic regression. A Cox proportional hazard model was used to examine the association between IC and mortality, and subgroup analysis was used to assess the robustness of the results among participants aged 60 years and older.

Results: A 12-score IC scoring system (AUROC = 0.83; Hosmer–Lemeshow goodness-of-fit test $p = 0.17$) was developed, and higher scores indicated better intrinsic capacity. High interleukin (IL)-6, high E-selectin, low serum albumin and low folate were significantly associated with low IC in the whole sample. However, high IL-6, low serum albumin, low folate, high allostatic load, and APOE ε4 genotype were significantly associated with low IC in those aged 60 years old and older. Compared to the high IC group, the low IC group was significantly associated with all-cause mortality (HR: 2.50, 95% CI: 1.22–5.11, $p = 0.01$ for all participants; HR 2.19, 95% CI 1.03–4.64, $p = 0.04$ for participants aged 60 years and older).

Conclusions: The conceptually proposed IC can be easily transformed into a scoring system considering different weights of individual subdomains, which not only predicts mortality but also suggests different pathophysiologies across the life course of aging (inflammation, nutrition, stress, and ApoE4 genotype). An intervention study is needed using the composite IC score to promote healthy aging and determine the underlying pathophysiology.

Keywords: intrinsic capacity, biomarkers, genetic markers, mortality, healthy aging

INTRODUCTION

The World Health Organization (WHO) published the World Report on Aging and Health and highlighted the importance of intrinsic capacity and functional ability to promote healthy aging, which shifted the focus of health care systems from a disease-centric to a function-centric approach. The intrinsic capacity (IC), defined as the composite of all physical and mental capacities of an individual, is therefore proposed to also serve as a potential indicator of functional reserve in the aging process. According to the conceptual proposal, IC consists of five pivotal domains, i.e., locomotion, sensory, vitality, psychological, and cognition (1–4). Through interactions with environmental factors, IC affects different dimensions of functional ability over time. The Integrated Care for Older People (ICOPE) guidelines published by the WHO emphasize the importance of assessment, prevention, and development of personalized intervention strategies for IC declines (5), which is especially critical to promote healthy aging. Although the conceptual framework and dimensions of IC are generally agreed upon, no universally agreed operational definition of IC has been established. A previous study in nursing home residents indicated that certain individual domains of IC (i.e., balance and nutrition) significantly predicted the adverse outcomes of mortality and risk of falling (6). Other studies constructed their own IC scales and reported associations between IC, functional impairments and frailty (7, 8). However, most studies assigned equal weightage to each domain of IC (9, 10) premised on the assumption of equal contribution of each domain to outcomes, which can be problematic when developing a composite IC scale covering all components.

Although IC was conceptualized through a function-centric approach, the underlying biological features of IC remained unclear. Allostatic load, a model of biological aging, effectively captured the risk of adverse outcomes as people age and was inversely associated with IC (11). Moreover, biomarkers of systematic inflammation, e.g., homocysteine and C-reactive protein, have been reported to be associated with muscle weakness, slow gait, reduced physical function, and low IC (12–15). On the other hand, apolipoprotein E (ApoE) genotypes (16) and the serotonin transporter promotor polymorphism (5-HTTLPR) (17) strongly affect mental health and vitality in the construction of IC. Obviously, IC defined by functional phenotypic features may consist of intertwined biological features and their interactions. Until now, little was known about the biological features of IC, and the search for underlying biological features may further facilitate the development of a systematic approach linking age-related biological features and functional phenotypes.

Hence, the aims of this study are to develop and validate a composite IC scoring system that weights each subdomain according to its association with the functional outcome, to explore the underlying biological features of IC and to explore the predictive value of the integrative IC score on 4-year mortality in a nationwide population-based cohort study.

METHODS

Data Source

This retrospective observational study used data from the Social Environment and Biomarkers of Aging Study (SEBAS), a national population-based cohort sample subsampled from the Taiwan Longitudinal Study of Aging (TLSA), to represent all Taiwanese individuals aged 50 years and older. TLSA has been conducted by the Health Promotion Administration (HPA) through face-to-face interviews since 1989 and was a national longitudinal survey designed to gather comprehensive data on demographics, socioeconomic factors, physical capacity, mental status and laboratory tests of study participants. SEBAS was approved by the institutional review board at the National Institute of Family Planning in Taiwan. The details of SEBAS and TLSA are described on the HPA website and in previous studies (18, 19).

Study Population

Among 1,284 participants who joined the 2006 SEBAS survey, 1,036 participants who completed the health examination were retrieved for the present study. To capture the effects of IC during the natural aging process, participants aged 50 years and older were identified. Participants ($n = 197$) without available data on IC development were excluded, so a total of 839 study subjects were included in this study.

Phase 1: Development of Intrinsic Capacity Score

The IC score was constructed according to the definition proposed by the WHO ICOPE (5). All components emerging from the guidelines and available in the SEBAS were selected. Each subdomain was divided into two categories and further weighted by their associations with their impairments in instrumental activities of daily living (IADL) measured in SEBAS 2006 survey, which indicated early loss of functional ability.

Locomotion Domain

The usual gait speed test and repeated chair-stand test were used to assess locomotion capacity. Robust was defined as walking speed or chair stand speed above the lowest quintile, and the slowest 20% of the population was defined as slowness (20).

Sensory Domain

The sensory domain was measured by self-reported hearing loss and visual impairments. Visual screening was performed using Snellen chart and was recorded by the decimal scale (i.e., 1.0 = 20/20). Visual impairment was defined as visual acuity of 6/18 or <6/12 (21).

Vitality Domain

Two variables were used for this domain: body mass index (BMI) and handgrip strength. The study subjects who were underweight, overweight, or obese (e.g., BMI < 18.5 or ≥25.0) were considered potentially malnourished according to the WHO's definition (22, 23). Handgrip strength was measured by the North Coast™ hydraulic hand-dynamometer (NC70142, California, US), and the maximal reading of three trials was recorded. Weakness was defined by the Asian Working Group on Sarcopenia (AWGS) <28 kg for men and <18 kg for women (24), whereas others were recorded as robust.

Psychological Domain

The psychological domain was assessed by the 10-item Center for Epidemiologic Studies Depression (CES-D-10) for depressive symptoms and the 10-item Perceived Stress Scale (PSS-10) for stress. The cut-off point for defined depression was 8 or more on the CES-D-10 (25, 26); participants with a PSS-10 score ≥14 were considered to have higher levels of perceived stress (27, 28).

Cognition Domain

The Short Portable Mental Status Questionnaire (SPMSQ) (29), an easy-to-handle and validated tool, and two subparts of the Mini-Mental State Examination (MMSE) (30) related to language and 3-item recall were used to evaluate the cognitive performance of the study participants. Cognitive impairment was defined as an SPMSQ score ≥3 or lower than 1 standard deviation of the subdomains (language and 3-item recall) of the MMSE in the population.

Instrumental Activities of Daily Living Impairments

The 6-item Instrumental Activities of Daily Living (IADL), including purchasing personal items, managing money, taking bus/train alone, doing physical work at home, making telephone calls, and doing light tasks at home, was measured to assess the functional ability of our study participants. One or more impairments in IADL functions were defined as functional impairments.

Phase 2: The Association Between Biomarkers and Intrinsic Capacity

All participants fasted for 10 h overnight, and then 12-h urine samples and venous blood samples were collected by the research staff. The samples were immediately shipped from the hospital to Union Clinical Laboratory (UCL) in Taipei by noon and were processed according to the standard laboratory protocol.

Biomarkers

As cardiometabolic risk markers, hemoglobin was measured by sodium lauryl sulfate (SLS) hemoglobin, and serum levels of homocysteine were assessed by using a fluorescence polarization immunoassay (FPIA, Abbott IMx). Hyperhomocysteinemia was defined as homocysteine concentrations >15 μmol/L (15). For neuroendocrine biomarkers, dehydroepiandrosterone sulfate (DHEA-S) was determined by electrochemiluminescence immunoassay (ECLIA, Roche Hitachi Elecsys 2010), and insulin-like growth factor-1 (IGF-1) was estimated by enzyme-linked immunosorbent assay (ELISA, Diagnostic System Laboratories).

Biomarkers related to inflammation and endothelial function, such as interleukin-6 (IL-6), soluble intercellular adhesion molecule-1 (s-ICAM-1), E-selectin, and soluble IL-6 receptor, were measured using ELISA (R&D Systems); fibrinogen was assessed by the coagulation method (Sysmex CA-1500; reagent: Dade Behring Company). In addition, serum albumin was measured, and a low serum albumin level (<4.0 g/dL) was defined according to previous research (31). As one of the B vitamins, folate was analyzed by chemiluminescence (Beckman CoulterACCESS® Immunoassay analyser). To explore possible non-linear relationships, each biomarker was categorized into tertiles for analysis (**Supplementary Table 1**).

Allostatic Load

The selected biomarkers and cut-off points for AL construction were based on a previous study (32). In brief, 20 biomarkers related to cardiometabolism, neuroendocrine function, and inflammation were included in this study (**Supplementary Table 2**). For each biomarker, a value below the 10th and higher than the 90th percentile was considered positive for AL estimation, except for DHEA-S, high-density lipoprotein cholesterol (HDL-C), serum albumin, and serum creatinine. For DHEA-S, HDL-C, and serum albumin, a certain proportion of cortisol and epinephrine measurements were undetectable, and these undetectable values were categorized as positive for risk, which was consistent with a previous study (32).

Genetic Markers

To determine ApoE genotypes, DNA was extracted from whole blood and amplified using the polymerase chain reaction amplification refractory mutation system (PCR-ARMS) and polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis. ApoE ε4 carriage was defined as having at least one ε4 allele. To determine the 5-HTTLPR genotype, DNA was extracted from venous blood and then amplified with polymerase chain reaction (PCR). Subjects were classified into four groups based on their genotypes (i.e., S/S, S/L, S/XL, and L/L or L/XL) (33).

Phase 3: Intrinsic Capacity Predicts 4-Year All-Cause Mortality

Mortality

The follow-up status of all participants was obtained from their interview date until 31 December 2010, and the date of death was identified from the National Death Registry held by the Ministry of Health and Welfare, Taiwan, which was linked with the study database.

Other Variables

Demographic characteristics of all participants, including age, sex, and levels of education, were collected in SEBAS 2006 survey. Smoking status was defined as ever tobacco consumption in the past 6 months. A self-rated 10-score ladder scale was used to measure socioeconomic status. The number of comorbidities was documented according to self-reported physician diagnosis, including hypertension, diabetes, heart disease, stroke, cancer, pulmonary disease, gastric disease, liver disease, arthritis, kidney disease, gout, cataract, degenerative joint disease, spinal/vertebrae spur, and hip fracture.

Statistical Analysis

Phase 1

In the first study phase, data from all participants were randomly divided into the derivation cohort (70%) and the validation cohort (30%) by sex and age. In the derivation cohort, univariate logistic regression was used to examine the associations between each IC component and IADL impairments. The significance level in univariate analyses was set at 0.25. Components with statistical significance or clinical importance in univariate analyses were selected for multivariate logistic regression. Although BMI was insignificant in univariate logistic regression, we kept it in the model as a clinical indicator of nutrition status. Subdomains with a p-value < 0.05 in the multivariate logistic regression were considered statistically significant and were weighted for the development of the IC score. For those regression coefficients that reached statistical significance in the model, each component was transformed into a subdomain score by dividing the coefficients by the smallest regression coefficient and then rounding up the absolute values of the coefficients to the nearest integer. Regression coefficients that were not statistically significant in the model were regarded as 1 point. A summary IC score was derived by adding points of all components. The higher the score was, the better the intrinsic capacity became.

For both the derivation and validation cohorts, model performance was evaluated by the area under the receiver operating curve (AUROC) and the Hosmer–Lemeshow goodness-of-fit test.

Phase 2

In the second phase of the study, we divided the study participants into three groups based on IC tertiles. The three groups were (1) High IC (Q3), (2) Medium IC (Q2), and Low IC (Q1). Continuous variables in the text and tables are expressed as the mean ± standard deviation, and categorical variables are expressed as percentages. Comparisons of baseline characteristics across different IC groups were performed by analysis of variance (ANOVA) for continuous variables and chi-square tests or Fisher's exact test for categorical variables. Ordinal logistic regression was used to examine the magnitude of association between biomarkers and IC groups, from low to high. Level of education, smoking status, socioeconomic status, and number of comorbidities were included as covariates in the adjusted model. Subgroup analysis was conducted in participants aged ≥60 years to evaluate whether the biological features of IC were different across age groups. The odds ratio (OR) and 95% confidential interval (95% CI) were reported.

Phase 3

In the last phase of the study, Kaplan–Meier survival analysis with the log-rank test was used to compare mortality risk between different IC groups. Cox proportional hazard models were used to explore the associations of IC score and 4-year all-cause mortality after adjustment for age, sex, levels of education, smoking status, socioeconomic status, number of comorbidities, and biomarkers. Kolmogorov-Type Supremum test was used to check the proportional hazards assumption for Cox proportional hazard models. We further performed subgroup analysis to assess the robustness of the results, and only participants aged 60 years and older were included. The hazard ratio (HR) and 95% confidential interval (95% CI) were reported.

Statistical significance was evaluated as $p < 0.05$, and all data were analyzed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Characteristics of the Study Subjects

The average age of 839 participants was 65.3 ± 9.4 years, and males accounted for the majority (54.1%) in the study. Among them, 15.9% did not receive any formal education (no schooling). The average number of comorbidities was 2.2 ± 1.8. The mean socioeconomic status among study subjects was level 4 (4.4 ± 1.8).

Development and Validation of the Scoring System for Intrinsic Capacity

Multivariate logistic regression modeling in phase 1 for IC development involved 590 subjects (70%) in the derivation cohort and 249 subjects (30%) in the validation cohort. The final IC derivation model contained ten variables, five of which were statistically significantly associated with IADL impairments ($p < 0.01$). The significant regression coefficients of the variables in the IC model were transformed into integer subdomain scores, and the insignificant variables were counted as 1 point, as displayed in **Table 1**. Participants with robust chair stand speed and wellbeing had more capacity in terms of functional ability, weighted by two points; other subdomains were scored with one point. The summed IC score ranged from 0 to 12.

The constructed IC model achieved AUROCs of 0.83 and 0.86 in the derivation and validation cohorts, respectively, confirming its good clinical performance in association with functional ability. The p-value for the Hosmer-Lemeshow test was 0.17 for

TABLE 1 | Development and validation of scoring system for intrinsic capacity using multivariate logistic regression model.

Intrinsic capacity (IC), 0–12	OR	95% CI	*P*-value	Regression coefficient	Weight
Locomotion					
Gait speed					
Slowness (Q1)	–	–	–	–	0
Robust (Q2–Q5)	0.42	0.23–0.76	<0.01	−0.87	1
Chair stand					
Slowness (Q1)	–	–	–	–	0
Robust (Q2–Q5)	0.19	0.11–0.35	<0.01	−1.64	2
Sensory					
Visual acuity					
With visual impairment	–	–	–	–	0
Without visual impairment	0.79	0.48–1.32	0.37	−0.23	1
Hearing					
With hearing loss	–	–	–	–	0
Without hearing loss	0.77	0.26–2.32	0.65	−0.26	1
Vitality					
Body mass index					
Malnutrition	–	–	–	–	0
Normal BMI	0.70	0.42–1.07	0.09	−0.40	1
Grip strength					
Weakness (male < 28 kg, female < 18 kg)	–	–	–	–	0
Robust (male ≧ 28 kg, female ≧ 18 kg)	0.32	0.19–0.53	<0.01	−1.15	1
Psychological					
CES-D-10					
Depression (>8)	–	–	–	–	0
Wellbeing (≦8)	0.22	0.12–0.39	<0.01	−1.52	2
PSS-10					
Higher level of stress (≧14)	–	–	–	–	0
Lower level of stress (<14)	0.61	0.36–1.03	0.06	−0.50	1
Cognition					
SPMSQ					
Cognitive impairment (≧3)	–	–	–	–	0
Cognitive health (<3)	0.33	0.15–0.71	<0.01	−1.11	1
MMSE (language and recall)					
Cognitive impairment (≦5)	–	–	–	–	0
Cognitive health (>5)	0.32	0.10–1.01	0.05	−1.13	1

OR, Odds ratio; CI, confidence interval; BMI, Body mass index; CES-D-10, 10-item Center for Epidemiologic Studies Depression; PSS-10, 10-item Perceived Stress Scale; SPMSQ, Short Portable Mental State Questionnaire; MMSE, Mini-Mental State Examination.
AUROC: Derivation = 0.831, Validation = 0.858.
Hosmer-Lemeshow test: Derivation p = 0.173, Validation p = 0.143.

the derivation cohort and 0.14 for the validation cohort, which was marginally calibrated but acceptable.

Biomarkers

In the phase 2 study, participants were classified into a high IC group (11–12, $n = 367$), a medium IC group (9–10, $n = 257$), and a low IC group (0–8, $n = 215$) based on IC tertiles. **Table 2** summarizes the baseline characteristics and biomarkers of the different IC groups. People in the low IC group were older, more likely to be women, have lower levels of education and had more comorbidities than those in the high and medium IC groups ($p < 0.01$). In addition, the low IC group had higher systolic blood pressure ($p < 0.01$) and serum levels of homocysteine ($p < 0.01$), IL-6 ($p < 0.01$), creatinine ($p < 0.01$), sICAM-1 ($p < 0.01$), hs-CRP ($p < 0.01$), urine epinephrine ($p < 0.01$), and allostatic load ($p < 0.01$) at baseline.

The results of the ordinal logistic regression are presented in **Figure 1** and **Supplementary Table 1**. After adjusting for age, sex, level of education, smoking status, socioeconomic status, and number of comorbidities, the associations between IC and numerous biomarkers remained significant. For people in the 1st (≤1.75 pg/ml) and 2nd tertiles (2.00–3.00 pg/ml) of serum IL-6 concentrations, the odds of being in the higher IC groups (i.e., high IC group or medium IC group vs. low IC group)

TABLE 2 | Comparison of characteristics and biomarkers according to intrinsic capacity tertiles.

Data values show M ± SD, or number (%)	Intrinsic capacity (IC) groups (n = 839)			P-value
	High IC (11–12)	Medium IC (9–10)	Low IC (0–8)	
Number	367	257	215	
Sex (female)	140 (38.2%)	120 (46.7%)	120 (55.8%)	<0.01
Age (year)	61.7 ± 7.5	64.6 ± 8.9	72.2 ± 9.0	<0.01
<60	191 (52.0%)	106 (41.2%)	30 (14.0%)	
60–64	70 (19.1%)	35 (13.6%)	13 (6.0%)	
65–74	72 (19.6%)	66 (25.7%)	73 (34.0%)	
75–84	30 (8.2%)	45 (17.5%)	79 (36.7%)	
≧85	4 (1.1%)	5 (2.0%)	20 (9.3%)	
The level of education				<0.01
No schooling	24 (6.5%)	41 (16.0%)	68 (31.6%)	
Elementary	161 (43.9%)	114 (44.3%)	92 (42.8%)	
Junior/senior high	114 (31.1%)	66 (25.7%)	45 (20.9%)	
College/graduate school	68 (18.5%)	36 (14.0%)	10 (4.7%)	
Smoking status				0.33
No	300 (81.7%)	201 (78.2%)	183 (85.1%)	
Sometimes	7 (1.9%)	5 (2.0%)	5 (2.3%)	
Frequently	60 (16.4%)	51 (19.8%)	27 (12.6%)	
Comorbidities* (number)	1.6 ± 1.6	2.0 ± 1.8	3.2 ± 2.0	<0.01
Socioeconomic status	4.7 ± 1.7	4.3 ± 1.8	4.1 ± 1.8	<0.01
INTRINSIC CAPACITY				
Locomotion				
Gait speed (m/s)	0.9 ± 0.2	0.8 ± 0.2	0.6 ± 0.2	<0.01
Chair stand (s/5 stands)	8.7 ± 2.2	10.5 ± 4.1	15.3 ± 5.3	<0.01
Sensory				
Visual acuity	0.8 ± 0.3	0.6 ± 0.4	0.5 ±0.3	<0.01
Hearing loss	1 (0.3%)	5 (2.0%)	17 (7.9%)	<0.01
Vitality				
Body mass index (kg/m^2)	24.4 ± 2.9	25.2 ± 3.5	25.4 ± 4.0	<0.01
Grip strength (kg) Male	37.2 ± 7.2	33.1 ± 7.7	26.4 ± 8.3	<0.01
Female	22.8 ± 5.3	22.1 ± 12.5	15.7 ± 5.9	<0.01
Psychological				
CES-D-10 (0–30)	2.2 ± 2.5	4.4 ± 4.8	8.1 ± 6.7	<0.01
PSS-10 (0–40)	7.8 ± 5.1	10.7 ± 6.5	11.4 ±7.2	<0.01
Cognition				
SPMSQ (0–10)	1.2 ± 0.4	1.4 ± 0.7	1.9 ± 1.1	<0.01
MMSE (language and recall, 0–6)	6.0 ± 0.0	6.0 ± 0.2	5.8 ± 0.6	<0.01
BIOMARKERS (N = 836)				
Cardiometabolic				
Systolic blood pressure (mm Hg) (n = 838)	125.1 ± 18.8	129.0 ± 19.0	136.2 ± 21.6	<0.01
Diastolic blood pressure (mm Hg) (n = 838)	74.2 ± 10.1	72.9 ± 10.5	72.5 ± 11.1	0.13
Total cholesterol (mg/dL)	200.1 ± 38.5	200.5± 38.1	198.1 ± 37.9	0.77
HDL cholesterol (mg/dL)	47.7 ± 14.1	48.9 ± 13.4	47.7 ± 13.9	0.49
Triglycerides (mg/dL)	111.5 ± 67.4	112.1 ± 72.5	119.5 ± 71.6	0.37
Glycosylated hemoglobin (%)	6.0 ± 1.1	6.2 ± 1.2	6.3 ± 1.3	0.02
Fasting glucose (mg/dL)	103.9 ± 25.9	108.4 ± 32.0	110.5 ± 35.3	0.03
Waist-to-hip ratio (n = 838)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	<0.01
Homocysteine (μmol/L) (n = 828)	11.2 ± 4.7	11.3 ± 4.6	13.2 ± 5.6	<0.01
Neuroendocrine				
DHEA-S (μg/dL)	122.1 ± 75.9	114.6 ± 71.3	83.6 ± 60.0	<0.01

(Continued)

TABLE 2 | Continued

Data values show M ± SD, or number (%)	Intrinsic capacity (IC) groups (n = 839)			*P*-value
	High IC (11–12)	Medium IC (9–10)	Low IC (0–8)	
IGF-1 (nmol/L)	162.6 ± 64.9	147.6 ± 60.0	133.9 ± 56.8	0.04
Urine Cortisol (μg/g creatinine) (n = 813)	17.9 ± 27.9	18.7 ± 20.1	23.0 ± 45.5	0.15
Urine Epinephrine (μg/g creatinine) (n = 822)	3.9 ± 2.6	3.9 ± 2.3	4.6 ± 2.9	<0.01
Urine Norepinephrine (μg/g creatinine) (n = 822)	25.9 ± 12.2	27.5 ± 13.1	29.0 ± 16.4	0.03
Urine Dopamine (μg/g creatinine) (n = 822)	176.8 ± 66.0	184.1 ± 69.0	216.5 ± 623.6	0.34
Inflammation and disease progression				
White blood cell count (109 /L) (n = 826)	6.0 ± 1.7	6.1 ± 1.7	6.3 ± 1.8	0.04
Neutrophils (%) (n = 827)	57.0 ± 10.1	58.5 ± 9.3	58.9 ± 10.1	0.04
Interleukin-6 (pg/mL)	3.3 ± 6.8	3.3 ± 4.4	4.9 ± 7.6	<0.01
Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.3	1.1 ± 0.6	<0.01
sICAM-1(ng/ml)	254.2 ± 80.5	264.7 ± 84.9	291.6 ± 105.1	<0.01
Fibrinogen (mg/dL)	323.5 ± 61.5	330.0 ± 70.0	344.8 ± 70.3	0.01
hsCRP (mg/dl)	0.2 ± 0.3	0.3 ± 0.7	0.3 ± 0.7	<0.01
E-selectin (ng/mL)	38.3 ± 26.4	43.2 ± 30.7	44.2 ± 27.0	0.02
sIL-6R (ng/mL)	41.1 ± 11.4	43.1 ± 12.4	43.4 ± 13.0	0.04
Albumin (g/dL)	4.5 ± 0.3	4.5 ± 0.3	4.4 ± 0.3	<0.01
Folate (ng/mL)	9.4 ± 6.1	9.2 ± 5.5	10.1 ± 9.8	0.30
Allostatic load (0–12) (n= 797)	3.6 ± 2.1	3.7 ± 2.2	4.5 ± 2.3	<0.01
GENETIC MARKERS				
APOE ε4 carrier (n = 835)	49 (13.4%)	37 (14.6%)	38 (17.7%)	0.37
5-HTTLPR (n = 826)				0.63
S/S	167 (45.9%)	116 (46.2%)	93 (44.1%)	
S/L	128 (35.2%)	94 (37.5%)	86 (40.8%)	
S/XL	21 (5.8%)	17 (6.8%)	13 (6.2%)	
L/L or L/XL	48 (13.2%)	24 (9.6%)	19 (9.0%)	

CES-D-10, 10-item Center for Epidemiologic Studies Depression; PSS-10, 10-item Perceived Stress Scale; SPMSQ, Short Portable Mental State Questionnaire; MMSE, Mini-Mental State Examination; DHEA-S, Dehydroepiandrosterone sulfate; IGF-1, Insulin-like growth factor-1; sICAM-1, Soluble intercellular adhesion molecule-1; hsCRP, high sensitivity C- reactive protein; sIL-6R, Soluble IL-6 receptor; APOE, Apolipoprotein E; 5-HTTLPR, The Serotonin Transporter Polymorphism.

[*] *Comorbidities = self-report physician diagnosed chronic conditions, including hypertension, diabetes, heart disease, stroke, cancer, pulmonary disease, gastric disease, liver disease, arthritis, kidney disease, gout, cataract, degenerative joint disease, spinal/vertebrae spur, and hip fracture.*

were 62% (OR = 1.62; 95% CI, 1.15–2.29; $p < 0.01$) and 57% (OR = 1.57; 95% CI, 1.11–2.20; $p < 0.01$) higher than those of people in the 3rd tertile (3.50–64.00 pg/ml). For people in the lower tertiles of serum E-selectin concentration, the odds of being in higher IC groups were 70% (7.0–27.5 ng/ml: OR = 1.70; 95% CI, 1.21–2.39; $p < 0.01$) and 49% (28.0–43.5 ng/ml: OR = 1.49; 95% CI, 1.07–2.09; $p = 0.01$) higher than that of people in highest tertile of E-selectin concentration (44.0–232.5 ng/ml). Moreover, the odds of being in the higher IC group was 54% lower (OR = 0.46; 95% CI, 0.24–0.90; $p = 0.01$) in the low serum albumin level group (<4 g/dL) as compared with the higher albumin level group (4–5 g/dL) and 42% lower (2.0–6.0 ng/ml: OR = 0.58; 95% CI, 0.41–0.83; $p < 0.01$) in the lowest tertile of folate concentration compared to the highest tertile group (10.5–58.0 ng/ml) (**Figure 1A**).

In the subgroup analysis (**Figure 1B**), the associations between IL-6, albumin, folate and IC were similar to the main findings for all participants. In addition, compared to the reference group of AL (4–12 abnormal biomarkers), the odds of being in a higher IC group was 54% (OR = 1.54; 95% CI, 1.01–2.45; $p = 0.04$) higher for those with 0–2 abnormal biomarkers of AL. Notably, the presence of the APOE ε4 allele (OR = 0.48; 95% CI, 0.29–0.80; $p < 0.01$) was associated with being in a lower IC group only among people aged 60 years and older.

Mortality

Kaplan–Meier analysis showed significantly lower survival probability among the low IC group than the others ($p < 0.01$) (**Figure 2**). **Table 3** shows the associations between IC groups and 4-year mortality. After adjustment for age, sex, level of education, smoking status, socioeconomic status, and the number of comorbidities, participants in the low IC group had a significantly higher mortality risk than people in the high IC group (HR = 3.02; 95% CI, 1.52–6.00; $p < 0.01$), whereas there was no statistical significance in the medium IC group (HR = 0.92; 95% CI, 0.42–2.03; $p = 0.83$). The results with additional adjustment for biomarkers persisted in the low IC group (HR = 2.50; 95% CI, 1.22–5.11; $p = 0.01$), as well as in the subgroup analysis (HR = 2.19; 95% CI, 1.03–4.64; $p = 0.04$).

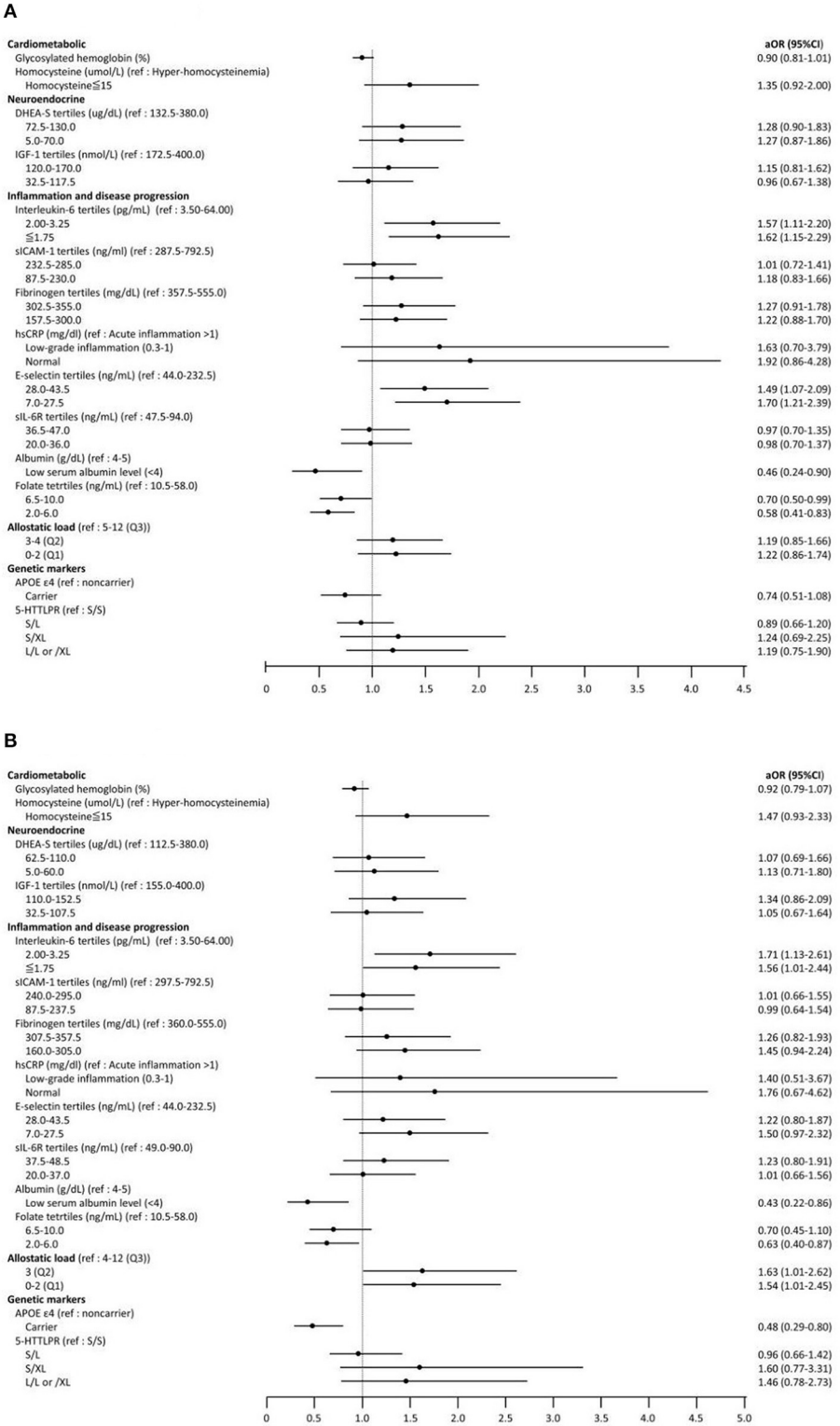

FIGURE 1 | Forest plot for ordinary logistic regression examining the association between biomarkers and intrinsic capacity (IC) groups (from low IC to high IC). Adjust for age, sex, level of education, smoking status, socioeconomic status, and number of comorbidities. **(A)** Total study subjects (aged ≧ 50). **(B)** Subgroup analysis (aged ≧ 60). OR, Odds ratio; CI, Confidence interval; DHEA-S, Dehydroepiandrosterone sulfate; IGF-1, Insulin-like growth factor-1; sICAM-1, Soluble intercellular adhesion molecule-1; hsCRP, high sensitivity C- reactive protein; sIL-6R, Soluble IL-6 receptor; APOE, Apoliprotein E; 5-HTTLPR, The Serotonin Transporter Polymorphism.

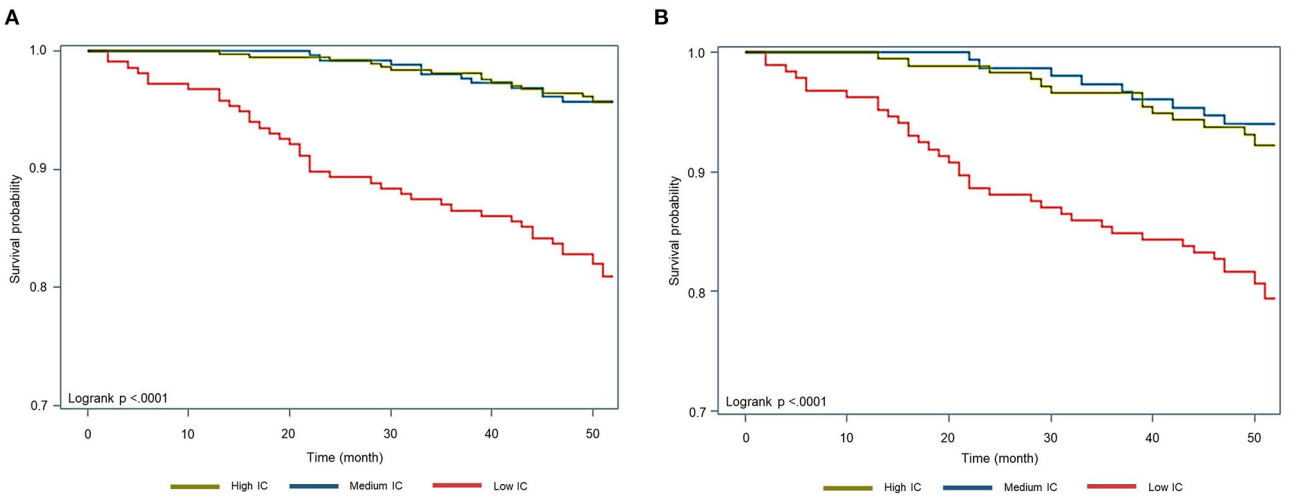

FIGURE 2 | Kaplan-Meier survival curve by tertiles of intrinsic capacity. **(A)** Total study subjects (aged ≧ 50). **(B)** Subgroup analysis (aged ≧ 60).

TABLE 3 | Tertiles of intrinsic capacity (IC) and 4-year mortality.

	Unadjusted model			Model 1			Model 2		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Total study subjects (aged ≧ 50)									
High IC	*ref*	–	–	*Ref*	–	–	*ref*	–	–
Medium IC	1.05	0.48–2.28	0.91	0.92	0.42–2.03	0.83	0.84	0.38–1.88	0.67
Low IC	4.88	2.69–8.85	<0.01	3.02	1.52–6.00	<0.01	2.50	1.22–5.11	0.01
Subgroup analysis (aged ≧ 60)									
High IC	*ref*	–	–	*ref*	–	–	*ref*	–	–
Medium IC	0.80	0.34–1.87	0.60	0.81	0.34–1.93	0.64	0.73	0.30–1.76	0.52
Low IC	2.89	1.53–5.45	<0.01	2.63	1.30–5.36	<0.01	2.19	1.03–4.64	0.04

HR, Hazard ratio; CI, Confidence interval.
Model 1: adjust for age, sex, level of education, smoking status, socioeconomic status, and number of comorbidities.
Model 2: adjust for age, sex, level of education, smoking status, socioeconomic status, number of comorbidities and biomarkers (e.g., IL-6, E-selectin, albumin and folate for total study subjects; IL-6, albumin, folate and APOE gene for subgroup analysis).

DISCUSSION

To the best of our knowledge, this is the first study to develop an outcome-based IC scoring system and to examine its association with mortality. Moreover, this study also aimed to capture the biological features of IC to explore its potential underlying pathoaetiology and intervention strategies. In the present study, we found that serum levels of IL-6, E-selectin, serum albumin and folate were significantly associated with IC and that IC status substantially predicted 4-year mortality risk. However, among those aged 60 years and older, serum levels of IL-6, albumin, folate, allostatic load, and ApoE ε4 carriage were associated with IC status. Biomarkers associated with IC were more closely related to systemic inflammation, such as albumin, IL-6, and E-selectin, stress responses (allostatic load), and the ApoE ε4 genotype, which suggested potential mechanisms of aging across the lifespan.

In the context of healthy aging, this study used IADL impairments as the early loss of functional ability to weight each domain and develop an integrative IC score. The good performance of the ROAUC in both the derivation cohort and validation cohort indicates that the IC score is not only an empirically rigorous but also a useful assessment tool. In our scoring system, we found that the chair stand test (locomotion domain) and CES-D (psychological domain) accounted for higher weights (2 points), which implied the prognostic impacts of mobility and depression on overall functional ability. The results were compatible with previous studies in which the chair stand test was significantly associated with functional decline in a pooled analysis (34). In addition, poor mental health negatively affects the daily living of older people and increases the risk of ADL and IADL difficulties (35). Kondo et al. reported that old age depressive symptoms accelerated the deterioration of functional ability, particularly among old-old people (35). Therefore, more

aggressive intervention programs focused on mobility and mental health are of critical importance to preserve intrinsic capacity, prevent loss of functional ability and promote healthy aging. In contrast to the frailty index developed by the cumulative deficit theory, the IC composite score in this study builds upon the construct of IC based on the WHO expert consensus and supporting evidence that shifted the focus from disease-centric to function-centric, and from reactive to preventive approaches. Although this study adopted incident IADL impairment as the outcome indicator to construct the IC composite score, the IC composite score was different from frailty index because the constructing domain of IC carried its own hypothesis in healthy aging and carried potentials for reversibility and improvement. The frailty index was constructed using various and sufficiently abundant amount of health data that substantially predicted adverse health outcomes, but the reversibility of frailty index was limited (36). Hence, the nature of IC composite score in this study was different from frailty index although both models were constructed to predict adverse outcomes.

Examining the associations between IC and biomarkers enabled us to justify the construction of the IC scoring system. Previous studies have demonstrated several promising biomarkers to predict frailty and other age-related syndromes (37–40). Frailty and IC are two constructs stemming from the same need to overcome traditional medical paradigms (41), and they may share common biological mechanisms and pathoaetiological processes. It has been reported that malnutrition and inflammation play critical roles in the pathophysiology of frailty (37–39). SEBAS examined multiple inflammatory biomarkers, such as c-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), soluble intercellular cell adhesion molecule-1 (ICAM-1), and E-selectin. Our previous study revealed that ICAM-1 was independent of all other inflammatory biomarkers in predicting frailty using the same SEBAS dataset (42). However, in this study, based on the conceptual framework of IC, associations of inflammatory markers other than sICAM-1 were shown. Interestingly, the statistical significance of E-selectin disappeared when we focused on the older population (aged 60 years and older), but allostatic load and ApoE4 carriage became important factors. Compared to other inflammatory biomarkers, E-selectin was more strongly associated with endothelial dysfunction and subclinical atherosclerosis (43, 44), which may suggest that endothelial dysfunction started earlier in the aging process and was then followed by more systemic inflammatory responses. A recent study reported different roles of E-selectin and ICAM-1 in cardiac function over the life course of decades (45), so more in-depth studies are needed to clarify the different pathological roles of different inflammatory markers in the aging process. Recently, the roles of folate in aging and age-related diseases have attracted research attention because folate is an important dietary resource required to maintain and modulate DNA methylation (46).

Interestingly, this study only identified the associations between the ApoE4 allele and IC but not 5-HTTLPR. In the construct of the IC scoring system, only mobility and depressive symptoms were highly associated with IADL impairments. The discrepancy suggested potentially undiscovered confounding factors linking IC phenotypic presentation and genetic predisposition. Most likely, SPMSQ was not sensitive enough to identify early cognitive impairment, or ApoE4 was associated with multiple physiological functions in the aging process (47). Allostatic load, representing the dysregulated homeostasis of multiple organ systems from the accumulation of repeated or chronic stress (11, 40), was significantly associated with IC in this study, which indicated the roles of stress and related chronic systemic inflammation in the aging process.

Despite all of the efforts made in this study, there were still some limitations. First, the study sample size was relatively small, and therefore, the power of the study may be decreased. Second, we conducted a cross-sectional design to construct the IC scoring system based on the IADL impairments, which may not be able to establish causality between IC and functional impairments. Further longitudinal research may be warranted. In addition, we could only investigate potential biomarkers relevant to IC because of the lack of repeated measurements in follow-up studies. Third, the model performance on calibration in the current study was relatively marginal but acceptable. Future studies consider other variables that may be associated with the IC scoring system should be conducted to improve the model performance. Fourth, IC aims to capture early physiological changes in aging, so a longer follow-up period may be necessary to identify the long-term impacts of IC declines over time. Last but not the least, similar to most community aging cohort studies, the questionnaire and assessment tools aimed to capture "impairments" to predict adverse outcomes. However, this study used "not impaired" as the reference to describe the robustness of IC would underestimate the IC itself. Future research with different designs is needed to better capture the construct of IC.

In conclusion, the integrated IC scoring system, developed from the concept proposed by the WHO, substantially captured the mortality risk of people aged 50 years and older. The associations between IC and E-selectin, allostatic load and ApoE ε4 genotype suggested the underlying biological features of IC, indicating that mental health issues and endothelial dysfunction may be of greater impact in the biology of IC. Further investigations with a larger sample size and longer follow-up period are important to explore the longitudinal changes and impacts of IC in healthy aging.

DATA AVAILABILITY STATEMENT

The data analyzed in this study was obtained from the Social Environment and Biomarkers of Aging Study (SEBAS), the following licenses/restrictions apply: legal restrictions imposed by the government of Taiwan in relation to the Personal Information Protection Act. The public-use version is available to access (http://doi.org/10.3886/ICPSR03792.v7). Requests to access these datasets should be directed to ICPSR http://www.icpsr.umich.edu/icpsrweb/ICPSR/.

ETHICS STATEMENT

The Institutional Review Board of Taiwan approved the study protocol, and written informed consents were obtained from all of the participants. The design and procedures of the study were carried out in accordance with the principles of the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

L-CM, S-TH, F-YH, and L-KC designed the research. L-CM, S-TH, L-NP, L-KC, and F-YH wrote the paper. L-CM analyzed data. F-YH and L-KC provided critical methodological inputs. L-CM, S-TH, and F-YH provided methodological and statistical inputs. L-NP and L-KC contributed to the clinical interpretation. All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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SUPPLEMENTARY MATERIAL

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Association Between Sense of Coherence and Frailty: A Cross-Sectional Study in China

*Hao Chen[1], Hua Fu[1], Bo Ye[2], Yi Wang[1], Huihui Yan[1], Yingwei Chen[1], Jixiang Xu[1], Xin Nie[1] and Junling Gao[1]**

[1] Department of Preventive Medicine and Health Education, School of Public Health, Fudan University, Shanghai, China,
[2] Department of Geriatric Medicine, Huadong Hospital Affiliated to Fudan University, Shanghai, China

Purpose: Frailty is an emerging global public health burden. Most existing studies have focused on risk factors for frailty, focusing less on protective factors against frailty. This study aims to examine the association between the sense of coherence (SOC), the most common construct of salutogenesis and frailty status among community-dwelling old adults.

Method: A cross-sectional study was conducted among 7,970 old adults aged ≥65 years in three cities in China from June 2019 to October 2020. Frailty was operationalised as the sum of self-reported fatigue, resistance, ambulation, illness, and loss of weight (FRAIL scale). The χ^2 test was used to analyse the distribution difference of frailty in demographic, behavioural, and SOC levels. Confounder-adjusted multinomial logistic regression was used to examine the association between SOC and frailty.

Results: The prevalence of pre-frailty and frailty was 43.1 and 8.0%, respectively. The results of the confounder-adjusted regression showed that older adults with moderate-level SOC (odds ratio, OR: 0.61, 95% CI: 0.54–0.69) and strong-level SOC (OR: 0.55, 0.48–0.64) had lower odds of being pre-frail compared to those with weak SOC. It also showed that older adults with moderate-level SOC (OR: 0.32, 95% CI: 0.27–0.40) and strong-level SOC (OR: 0.22, 95% CI: 0.16–0.29) had lower odds of being frail compared to those with weak SOC.

Conclusion: SOC may be a protective factor against frailty. Improving SOC may be a strategy to prevent frailty among Chinese community-dwelling older adults.

Keywords: frailty, sense of coherence, healthy ageing, older adults, community

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Jean-Marie Degryse, KU Leuven, Belgium

****Correspondence:***
Junling Gao
jlgao@fudan.edu.cn

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INTRODUCTION

Frailty is a geriatric syndrome characterised by non-specific vulnerability to adverse events (e.g., mortality, institutionalisation, falls, hospitalisation), which is attributed to the deregulation of multiple and complex physiological system factors associated with advancing age (1–3). The biological basis of frailty is multifactorial, involving multiple etiologic dysregulations across many physiological systems, cumulative cellular damage, inflammation, malnutrition, and sarcopenia (4). The cycle of frailty described by Fried et al. also considers the effects of behaviours and environmental determinants on deteriorated frailty states, including inadequate nutrition intake, physical inactivity, and stressful life events (5).

Research has found that frailty heterogeneity exists among older adults of the same age group with the same risk factors (6, 7). To determine whether health heterogeneity was the initial purpose of *salutogenesis*, a theory proposed by Aron Antonovsky in the late 1970s, raises the question of which salutary factors actively maintain or promote health and which risk factors cause disease (8, 9). *Salutogenisis* argued that the human system is inherently flawed, subject to unavoidable entropic processes and unavoidable final death, which follows a continuum health model of ease/dis-ease movement rather than dichotomous classification (health and illness) (6). Sense of coherence (SOC), the most important construct of *salutogenesis*, refers to an orientation toward life that characterises the extent to which an individual appraises internal and external environments as comprehensible, manageable, and meaningful (10). This would influence the dynamically continuous movement between ease (robust) and dis-ease (frail). The three components of SOC are comprehensibility, manageability, and meaningfulness, which reflect their respective (1) perception of internal and external stimuli as structured, predictable and explicable; (2) conviction that one has the available resources to meet the demands of these stimuli; and (3) belief that all of these demands have a reason and are worth challenging (8). SOC is a critical salutary health factor. Studies found that strong SOC has a protective effect against negative health outcomes in terms of depression, (11) low quality of life, (12) disability, (13) and mortality (14, 15) as well as toward an ease status. In addition, SOC is malleable and can be enhanced by appropriate interventions in the older adult population (16). Although some studies found that older adults with strong SOC had less physical functional decline (17) and more cognitive functional reserve, (18) few studies have examined the relationship between SOC and frailty. Therefore, the present study aimed to examine whether SOC was associated with frailty status among community dwelling older adults aged $\geq$65 years.

MATERIALS AND METHODS

Participants and Study Design

This cross-sectional study was conducted in three cities in China: Shanghai (Southern China), Tianjin (Northern China), and Ordos (Northern China) from June 2019 to October 2020. A total of 8,590 community-dwelling older adults were randomly recruited from 31 districts using a multistage stratified sampling method, among which 16 communities were in Shanghai, 6 in Tianjin, and 9 in Ordos. The minimum sample size of each selected community was required to have no less than 200 participants. The general practitioners from each selected community visited participants in their homes or invited them to community healthcare centres by using uniform questionnaires after obtaining informed consent. Inclusion criteria were as follows: (1) residing in the community for more than 6 months and (2) aged 65 or older. Exclusion criteria were as follows: (1) severe psychological disorders and (2) an inability to answer questions. We ultimately included 7,970 (92.8%) participants in the present study after excluding incomplete data. The Ethics Committee for Medical Research at the School of Public Health, Fudan University, approved this study (IRB00002408 and FWA00002399).

Measurements

Frailty

The Chinese version of the FRAIL scale was used to measure Frailty. The scale consists of five "yes/no" items assessing five different functional ability domains (Fatigue, Resistance, Ambulation, Illness, and Loss of weight), (19) which is a validated and widely used screening tool to identify frail or prefrail individuals in over 15 countries, including China (20). Frailty scores range from zero to five (i.e., one point for each component; 0 = *best* to 5 = *worst*) and represent robust (0), pre-frail (1–2), and frail (3–5).

Sense of Coherence

The Chinese version of the SOC scale (C-SOC-13) with acceptable reliability and validity consists of three dimensions: comprehensibility (five items), manageability (four items), and meaningfulness (four items), and was used to measure the level of SOC (21). Each item is scored on a seven-point Likert scale, ranging from 1 (*very often*) to 7 (*never or very seldom*). The total SOC score is obtained by summing the corresponding item scores after revising the five negatively worded items, with a higher SOC score indicating a preferable sense of coherence level (22). In the present study, Cronbach's alpha coefficient for the internal consistency of the C-SOC-13 was 0.88, and the SOC score was categorized into tertiles for weak, moderate, and strong levels (14).

Covariates

Based on the literature, (23–25) covariates in this study included age (5-year categories), sex (male and female), marital status (married or cohabiting vs. other), educational attainment (illiteracy, primary, junior high school, and above), location (Southern and Northern China), and health-related behaviours including smoking, drinking, physical activity, vegetable intake, and fruit intake.

Smoking status was assessed using two questions: "Q1. Have you ever smoked over 100 cigarettes? (yes/no); Q2. Have you smoked in the past 30 days? (yes/no)." Participants who answered "yes" to both questions were classified as smokers; otherwise, they were classified as non-smokers.

Drinking status was derived from frequency responses (never/once per month or less/2–4 times per month/2–3 times per week/over four times per week) to the question "How often do you drink alcohol?" Participants who answered "never" were classified as non-drinkers; otherwise, they were classified as drinkers.

Physical activity was assessed using two questions: "Q1. How many times did you participate in moderate-intensity physical activity (heart rate and breathing rate increase and slight perspiration) per week? (None, 1–2 times, 3–4 times, 5–6 times, seven times or more); Q2. For how long did you participate each time? (less than 20 min, 20–30 min, 30–40 min, 40–50 min, or more than 50 min)" (26). In accordance with

the current recommendations for the practising of physical activity, this study classified participants with at least 150 min of moderate physical activity per week as physically active, while other participants were physically inactive (27).

Vegetable intake was derived from weight responses (0–200 g, 200–300 g, 300–400 g, 400–500 g, and over 500 g) to the question "On average, how much fruit do you eat per day?" (28). Fruit intake was also derived from weight responses (0–100, 100–200, 200–350, 350–500, and over 500 g) to the question "On average, how much fruit do you eat per day?" (28). In accordance with the current recommendations for the Chinese Dietary Guidelines, the present study defined at least 300 g of vegetable intake and 200 g of fruit intake as adequate intake (29).

Statistical Analysis

Firstly, we used descriptive analysis to show the characteristics frailty states and SOC of participants, and then ANOVA test and multiple-comparisons (Bonferroni method) were used to examine the difference distribution of SOC according to frailty states (robust, pre-frail, and frail). Secondly, χ^2 tests were used to examine the distribution of frailty states according to demographic characteristics, health-related behaviours, and ranked SOC (weak, moderate, and strong). Furthermore, multinomial logistic regression models were used to examine the associations between SOC and pre-frailty (Model a1) and frailty (Model a2) after adjusting for age, sex, marital status, educational attainment, and location. Then, health-related behaviours were added to Models a1 and a2 in order to examine the associations between SOC and pre-frailty (Model b1) and frailty (Model b2). The estimates of SOC and health-related behaviours for frailty were summarized using odds ratios (Ors) and their 95% confidence intervals (Cis). Statistical analyses were performed using the R software (version 4.1.1) (25).

RESULTS

Descriptive Results of Demographic Characteristics, Frailty, and Sense of Coherence

As shown in **Table 1**, the average age of 7,970 participants was 72.33 years (SD: 6.00, Range: 65–101); 52.7% of them were female, and nearly half of the participants were illiterate (43.5%). The majority of the participants (81.6%) were married or co-inhabited. The prevalence of smoking and drinking was 24.0 and 12.8%, respectively. Over half of the participants (60.1%) reported that they were physically inactive. Inadequate vegetable and fruit intake was reported by 47.2 and 74.9% of participants, respectively.

As for the frailty states, 48.9% of participants were robust, 43.1% were pre-frail, and 8.0% were frail. The mean score of SOC was 60.80 (SD: 11.00, Range: 13–91), and its distribution among different frailty states examined by using ANOVA test and multiple-comparisons is shown in **Figure 1**. The mean score of SOC among frail participants (mean: 54.99; SD: 11.52) was lower than pre-frail participants (mean: 59.38; SD: 10.75) and robust participants (mean: 63.00; SD: 10.56), $p < 0.001$.

Univariate Analysis for Frailty Distribution

As shown in **Table 1**, the univariate analysis results indicated that the distribution of frailty showed statistical differences in age, sex, education attainment, marital status, SOC, smoking, drinking, physical activity, vegetable intake, and fruit intake (all $P < 0.001$). The prevalence of frailty significantly decreased with decreasing age (5-year categories) and with increased SOC levels (strong to moderate to weak). The prevalence of frailty among those who were unmarried (12.9%) and females (9.4%) was

TABLE 1 | The frailty stage distribution in demographic characteristic, SOC, and behaviours (n = 7,970).

Variable	Total [n(%)]	Frailty stage [n(%)]			*P*-value
		Robust	Pre-frail	Frail	
Age (years)					**<0.001**
65–69	3159(39.6)	1739(55.0)	1263(40.0)	157(5.0)	
70–74	2362(29.6)	1214(51.4)	987(41.8)	161(6.8)	
75–79	1401(17.6)	597(42.6)	648(46.3)	156(11.1)	
>80	1048(13.2)	350(33.4)	535(51.0)	163(15.6)	
Sex					**<0.001**
Male	3766(47.3)	1983(52.7)	1542(40.9)	241(6.4)	
Female	4204(52.7)	1917(45.6)	1891(45.0)	396(9.4)	
Education level					**<0.001**
Illiteracy	3470(43.5)	1457(42.0)	1673(48.2)	340(9.8)	
Primary school	2515(31.6)	1381(54.9)	978(38.9)	156(6.2)	
≥Junior-senior high school	1985(24.9)	1062(53.5)	782(39.4)	141(7.1)	
Marital status					**< 0.001**
Married	6502(81.6)	3317(51.0)	2738(42.1)	447(6.9)	
Not married	1468(18.4)	583(39.7)	695(47.3)	190(12.9)	
SOC					**<0.001**
Weak	1864(23.4)	645(34.6)	932(50.0)	287(15.4)	
Moderate	4280(53.7)	2200(51.4)	1804(42.1)	276(6.4)	
Strong	1826(22.9)	1055(57.8)	697(38.2)	74(4.1)	
Smoke					**<0.001**
Non-smoker	6061(76.0)	2851(47.0)	2686(44.3)	524(8.6)	
Smoker	1909(24.0)	1049(55.0)	747(39.1)	113(5.9)	
Drink					**<0.001**
Non-drinker	6946(87.2)	3280(47.2)	3072(44.2)	592(8.7)	
Drinker	1024(12.8)	620(60.5)	361(35.3)	43(4.2)	
Physical activity					**<0.001**
Physical inactivity	4792(60.1)	2016(42.1)	2261(47.2)	515(10.7)	
Physically active	3178(39.9)	1884(59.3)	1172(36.9)	122(3.8)	
Vegetable intake					**<0.001**
Inadequate	3764 (47.2)	1537(40.8)	1796(47.7)	431(11.5)	
Adequate	4204 (52.8)	2363(56.2)	1637(38.9)	206(4.9)	
Fruit intake					**<0.001**
Inadequate	5967(74.9)	2664(44.6)	2761(46.3)	542(9.1)	
Adequate	2003(25.1)	1236(61.7)	672(33.5)	95(4.7)	

Bold values are statistical difference were significant (p < 0.05).

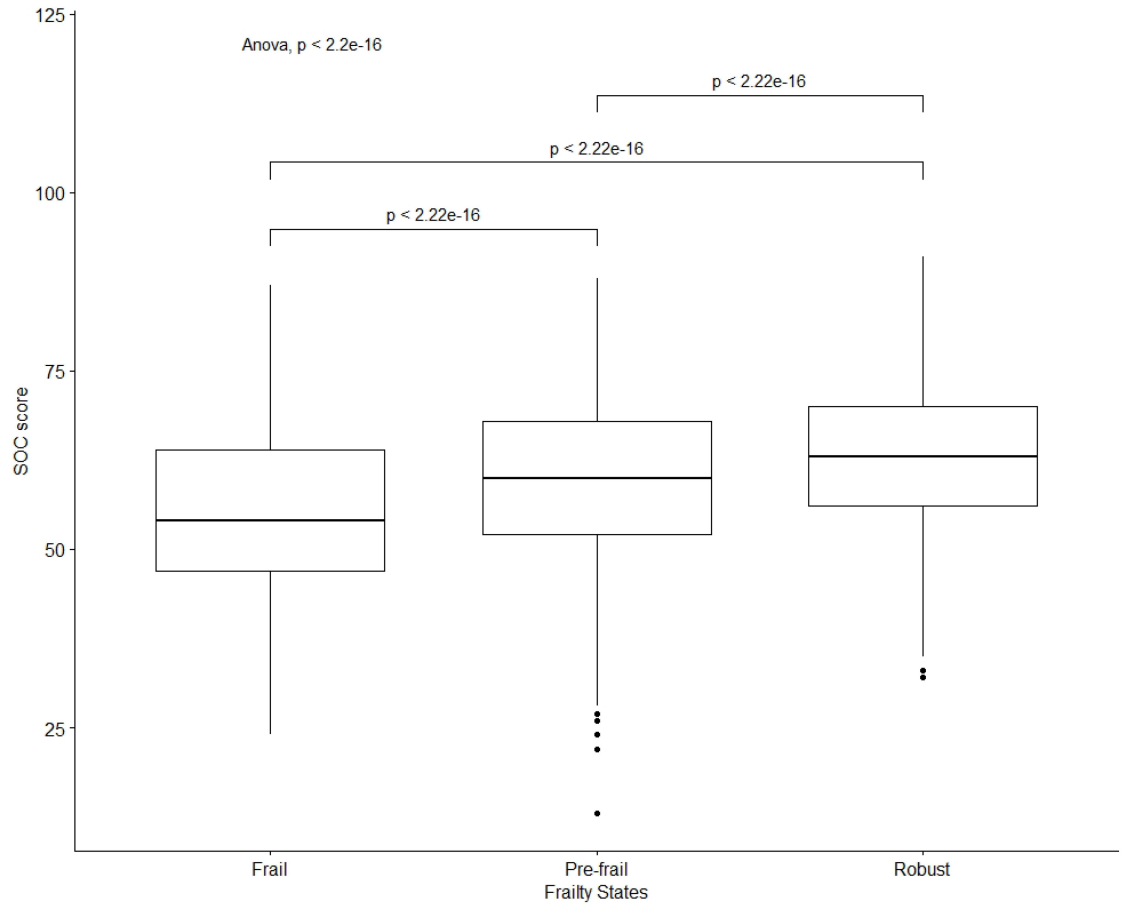

FIGURE 1 | A boxplot of the distribution of SOC score among frail, pre-frail, and robust participants.

higher than among married (6.9%) and male (6.4%) older adults. Compared with illiteracy elders (9.8%), the frailty prevalence was lower among elders who received primary (6.2%) and junior-senior high school and above (7.1%). Frailty prevalence was lower among smokers (5.9%) and drinkers (4.2%) than among non-smokers (8.6%) and non-drinkers (8.7%). The prevalence of frailty was higher among the physically inactive (10.7%), those with inadequate vegetable intake (11.5%), and those with inadequate fruit intake (9.1%) than among those who were physically active (3.8%), had adequate vegetable intake (4.9%), and those with adequate fruit intake (4.7%). The prevalence of pre-frailty among participants with weak SOC was 50.0%, while that among participants with moderate and strong SOC was 42.1 and 38.2%, respectively. The prevalence of frailty among participants with weak SOC was 15.4%, while that among moderate and strong SOC participants was 6.4 and 4.1%, respectively.

Multivariate Analysis for Associations Between Sense of Coherence and Frailty

The results of the confounder-adjusted multinomial logistic regression models for associations of SOC with the odds of being pre-frail and frail are shown in **Table 2**. In the adjusted Model 2, older adults with moderate SOC (odds ratio, OR: 0.61, 95% CI: 0.54–0.69) and strong SOC (OR: 0.55, 95% CI: 0.48–0.64) levels had lower odds of being pre-frail compared to those with weak SOC, respectively, $P < 0.001$; older adults who had moderate SOC (OR: 0.32, 95% CI: 0.27–0.40) and strong SOC (OR: 0.22, 95% CI: 0.16–0.29) levels had lower odds of being frail compared to those with weak SOC, respectively, $P < 0.001$.

Furthermore, older adults who were drinkers (OR: 0.81, 95% CI: 0.69–0.95; $P = 0.010$) or physically active (OR: 0.63, 95% CI: 0.57–0.70; $P < 0.001$), had adequate vegetable intake (OR: 0.77, 95% CI: 0.70–0.86; $P < 0.001$), or adequate fruit intake (OR: 0.63, 95% CI: 0.56–0.71; $P < 0.001$) had lower odds of being pre-frail compared to those who were physically inactive or had inadequate fruit intake, respectively. Similar results were shown in the association between health-related behaviours and frailty (robust vs. frail). Older adults who were drinkers (OR: 0.69, 95% CI: 0.47–0.99; $P = 0.041$) or were physically active (OR: 0.35, 95% CI: 0.28–0.44; $P < 0.001$), had adequate vegetable intake (OR: 0.48, 95% CI: 0.39–0.58; $P < 0.001$), or had adequate fruit intake (OR: 0.62, 95% CI: 0.48–0.80; $P < 0.001$) had lower odds of being frail.

DISCUSSION

Preventing and even reversing frailty is crucial to achieving healthy ageing which emphasises positive processes for strengthening older adults to adapt and compensate for the negative consequences of ageing (30–32). On the one hand, *salutogenesis* focuses on searching for these positive determinants or factors that strengthen the ability to cope with intrinsic capacity decline, (32) while the main goal of healthy ageing is to maintain intrinsic capacity and delay its loss (30). On the other hand, intrinsic capacity and frailty might represent the two faces of the same coin among the elderly (31). Furthermore, some resilience factors (e.g., psychology resilience and SOC) were regarded as potential reserves of functional ability in the face of adversity (7). Therefore, it is justified to apply the theory of *salutogenesis* to frailty. The present study found a decreased prevalence of pre-frailty and frailty with advanced SOC levels. In all confounder-adjusted multivariate analysis models, it was also found that high and moderate SOC were negatively associated with the OR of frailty. From the perspective of frailty, SOC may directly affect the physiological response through an allostatic load process to stress triggered by frailty (33, 34). Besides this intermediate way to the frailty process directly, there are some explanations for why SOC may protect robust older adults from frail deterioration by reducing the risk of frailty-related psychological and physical diseases. Previous studies have reported that the protective effect of high SOC could reduce the risk of depression and anxiety, (35, 36) which are recognised as crucial indicators of frailty (37, 38). SOC was also found to be negatively associated with comorbidity, (39) which is an important component of frailty constructs (40). In addition, the SOC score tended to show a relationship with the inflammatory mediators (serum C-reactive protein and IL-6) in older adults, (41) both of which were significantly higher in pre-frailty and frail older adults than in robust older adults (42). A systematic review concluded Saultogenic-based interventions among older adults, which aimed to enhance SOC level by empowering self-management and strengthening utilisation of resource, were found to be beneficial to promotion of quality of life (43). A resistance training intervention in older adults, where resistance moving was a component of the FRAIL scale, found that participants with weak SOC before intervention may not benefit as much from training as those with strong SOC (44). Besides resistance, strong SOC was associated with decreased risks of fatigue and comorbidity (illness) which also are components of FRAIL scale in two longitudinal studies among Swedish older adults (45, 46).

TABLE 2 | The associations between SOC and frailty by using multinomial logistic regressions.

Variable	Model 1 (Robust as ref.)		Model 2 (Robust as ref.)	
	Pre-frail	Frail	Pre-frail	Frail
SOC				
Weak	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Moderate	0.59(0.53–0.67)***	0.29(0.24–0.36)***	0.61(0.54–0.69)***	0.32(0.27–0.40)***
Strong	0.52(0.45–0.60)***	0.18(0.14–0.24)***	0.55(0.48–0.64)***	0.22(0.16–0.29)***
Smoke				
Non-smoker			1 (ref.)	1 (ref.)
Smoker			0.88(0.78–1.01)	0.84(0.63–1.07)
Drink				
Non-drinker			1 (ref.)	1 (ref.)
Drinker			0.81(0.69–0.95)**	0.69(0.48–0.99)*
Physical activity				
Physical inactivity			1 (ref.)	1 (ref.)
Physically active			0.63(0.57–0.70)***	0.35(0.28–0.44)***
Vegetable intake				
Inadequate			1 (ref.)	1 (ref.)
Adequate			0.77(0.70–0.86)***	0.48(0.39–0.58)***
Fruit intake				
Inadequate			1 (ref.)	1 (ref.)
Adequate			0.63(0.56–0.71)***	0.62(0.48–0.80)***

*ref., reference; *, P < 0.05; **, P < 0.01; ***, P < 0.001. Model 1 include SOC and age, sex, education level, and marital status; Model 2 adds smoking, drinking, physical activity, vegetable intake, and fruit intake based on Model 1.*

The three domains of SOC (comprehensibility, manageability, and meaningfulness) may play different but reciprocal roles in frailty progression. As the vicissitudes of growing old independently strike seniors, the ageing-related process becomes unpredictable and uncontrollable for them (47). Older adults with higher comprehensibility may be more inclined to accept internal or external environmental changes as natural processes, attributing them to fate, such as poor mobility or the shrinking of social nets (48). In a salutogenic model of health, this process is a type of mechanism that promotes health status by "defining stimuli as non-stressors"(49). Seniors with strong manageability believe that they can confront stressors successfully and know how to mobilise resources to deal with risk factors for health (49). It has been reported that older adults need to engage in pursuits that are worthwhile and desirable to achieve a general view of healthy ageing to maintain a healthy status and delay deterioration (50). Furthermore, the three components are dynamically dependent, which refers to comprehensibility as a cognitive component, manageability as an instrumental/behavioural component, and meaningfulness as a motivational component (51). For example, manageability in adopting protective behaviours for frailty (e.g., physical activity and nutrition intake) can be supported by supplementing this knowledge with comprehensibility and meaningfulness, which provides older adults with the motivation to adopt frailty prevention behaviours.

There are some limitations in our study. First, the cross-sectional study design could not calculate the causal relationship between SOC and frailty. Moreover, although we controlled for demographic characteristics and behavioural covariates, we cannot exclude the possibility of residual confounding caused by unmeasured factors.

CONCLUSION

This cross-sectional study elucidated a negative association between the sense of coherence and frailty. Much more research needs to be done to examine the causal relationship between the sense of coherence and frailty and how to enhance the sense of coherence among older adults.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Research Ethics Committee of the Medical Research at the School of Public Health, Fudan University, approved the study protocol (IRB00002408 and FWA00002399). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JG and HF designed the study and obtained the data. HC undertook the analysis supervised by JG and wrote the manuscript. JG organized the manuscript. BY helped HC in data topic selection. HC, BY, YW, HY, YC, JX, and XN performed the survey. All authors read the final manuscript and agreed with the text.

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Predictive Utility of Mortality by Aging Measures at Different Hierarchical Levels and the Response to Modifiable Life Style Factors: Implications for Geroprotective Programs

Jingyun Zhang[1†], Xingqi Cao[1†], Chen Chen[2], Liu He[1], Ziyang Ren[1], Junhua Xiao[3], Liyuan Han[4,5], Xifeng Wu[1] and Zuyun Liu[1*]*

[1] Center for Clinical Big Data and Analytics of the Second Affiliated Hospital and Department of Big Data in Health Science School of Public Health, Zhejiang University School of Medicine, Hangzhou, China, [2] National Institute of Environmental and Health, Chinese Center for Disease Control and Prevention, Beijing, China, [3] College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai, China, [4] Department of Global Health, Ningbo Institute of Life and Health Industry, University of Chinese Academy of Sciences, Ningbo, China, [5] Hwa Mei Hospital, University of Chinese Academy of Sciences, Ningbo, China

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Tzvi Dwolatzky,
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***Correspondence:**
Zuyun Liu
Zuyun.liu@outlook.com;
zuyunliu@zju.edu.cn
Xifeng Wu
xifengw@zju.edu.cn

[†] These authors have contributed equally to this work

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Background: Aging, as a multi-dimensional process, can be measured at different hierarchical levels including biological, phenotypic, and functional levels. The aims of this study were to: (1) compare the predictive utility of mortality by three aging measures at three hierarchical levels; (2) develop a composite aging measure that integrated aging measures at different hierarchical levels; and (3) evaluate the response of these aging measures to modifiable life style factors.

Methods: Data from National Health and Nutrition Examination Survey 1999–2002 were used. Three aging measures included telomere length (TL, biological level), Phenotypic Age (PA, phenotypic level), and frailty index (FI, functional level). Mortality information was collected until December 2015. Cox proportional hazards regression and multiple linear regression models were performed.

Results: A total of 3,249 participants (20–84 years) were included. Both accelerations (accounting for chronological age) of PA and FI were significantly associated with mortality, with HRs of 1.67 [95% confidence interval (CI) = 1.41–1.98] and 1.59 (95% CI = 1.35–1.87), respectively, while that of TL showed non-significant associations. We thus developed a new composite aging measure (named PC1) integrating the accelerations of PA and FI, and demonstrated its better predictive utility relative to each single aging measure. PC1, as well as the accelerations of PA and FI, were responsive to several life style factors including smoking status, body mass index, alcohol consumption, and leisure-time physical activity.

Conclusion: This study demonstrates that both phenotypic (i.e., PA) and functional (i.e., FI) aging measures can capture mortality risk and respond to modifiable life style factors, despite their inherent differences. Furthermore, the PC1 that integrated phenotypic and functional aging measures outperforms in predicting mortality risk in comparison with each single aging measure, and strongly responds to modifiable life style factors. The findings suggest the complementary of aging measures at different hierarchical levels and highlight the potential of life style-targeted interventions as geroprotective programs.

Keywords: aging, frailty, telomere shortening, mortality, life style

INTRODUCTION

Aging is a critical risk factor for many chronic diseases. As a comprehensive and multi-dimensional process, aging could be measured at different hierarchical levels, including biological, phenotypic and functional levels (1). Biological aging measures focus on changes at the molecular, cellar, and intracellular levels, such as telomere length (TL) and DNA methylation clocks (1–3). Phenotypic aging measures include composite indexes derived from multi-system clinical chemistry biomarkers, such as Phenotypic Age (PA) (4), reflecting changes in body composition, homeostatic mechanisms, energetics, and brain health over time. Functional aging measures include composite indexes derived from different functional aspects (e.g., cognitive and physical function). Frailty index (FI) is a widely used functional aging measure that integrates deficits across multiple functional domains (5–7). These aging measures are conceptually different; however, direct comparative analyses of their predictive utility of mortality risk are limited. To the best of our knowledge, only one study based on adults $>$ 50 years in Sweden compared aging measures at three hierarchical levels (8). Since aging starts early in life (9), it remains unclear how these aging measures behaves in terms of mortality prediction among a general population with younger, middle-aged, and older adults. It is also of interest to examine whether integrating two or more aging measures at different hierarchical levels would provide a more informative one, which is valuable in geroprotective programs where these aging measures serve as endpoints to help with assessing the effectiveness of interventions.

One important feature of qualifying aging measures includes effective responsiveness to interventions (10). This feature has been rarely emphasized in previous work whereas it is the key to the application of aging measures in clinical settings. Life styles such as smoking and physical activity are modifiable factors and have been demonstrated to be associated with individual aging measures such as TL (11) and FI (12, 13). However, few studies have simultaneously evaluated the response of aging measures at different hierarchical levels to modifiable life style factors in the same population.

Using data from the National Health and Nutrition Examination Survey (NHANES) 1999–2002, including three aging measures at three hierarchical levels (i.e., TL, PA, and FI), this study aimed to (1) compare the predictive utility of mortality risk by three aging measures at three hierarchical levels; (2) develop a new composite aging measure that integrated aging measures at different hierarchical levels; and (3) evaluate the response of these aging measures to modifiable life style factors.

MATERIALS AND METHODS

Study Population

NHANES is an ongoing program conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention in the United States. NHANES began in the early 1960s and focuses on the health and nutritional status of adults and children in the United States. Since 1999, NHANES has become a continuous program that collects a wide range of health-related data via interview, examination, and laboratory tests in counties across the country biennially (4). NHANES is approved by the National Center for Health Statistics Research Ethics Review Board (Protocol #98-12), and all participants provided informed consent. In this study, we included participants with TL data and complete information to calculate PA and FI. In total, 3,249 of 9,882 participants aged from 20 to 84 years in NHANES 1999–2002 were included. NHANES data are publicly available (https://www.cdc.gov/nchs/nhanes/index.htm). The analytic roadmap of this study is shown in **Supplementary Figure 1**.

Measurements

TL and Acceleration of TL (TL.Accel)

In NHANES, TL assay was performed in the laboratory of Dr. Elizabeth Blackburn at the University of California, San Francisco, using the quantitative polymerase chain reaction (PCR) method to measure TL relative to standard reference DNA (T/S ratio) based on blood samples (14, 15). Each sample was assayed three times on three different days. The mean of the T/S ratio was used to represent TL and details of laboratory methods are described at the official website of NHANES (https://wwwn.cdc.gov/Nchs/Nhanes/1999-2000/TELO_A.htm). To eliminate the effect of chronological age (CA) on TL, we calculated a new index, TL.Accel, defined as residual from a linear model when regressing TL on CA. TL.Accel was classified into normal (TL.Accel $\geq$ 0, indicating that a participant's TL is equal or longer than expected based on his/her CA) or shorter (TL.Accel $<$ 0, indicating that a participant's TL is shorter than expected based on his/her CA).

PA and Acceleration of PA (PA.Accel)

PA was first developed based on NHANES III (4, 16). In brief, PA was derived from CA and 9 biomarkers including albumin, creatinine, glucose, (log) C-reactive protein, lymphocyte percent, mean cell volume, red cell distribution width, alkaline phosphatase, and white blood cell count. As done to TL, we calculated PA.Accel, defined as residual from a linear model when regressing PA on CA. PA.Accel represents phenotypic aging after accounting for CA, i.e., a participant is phenotypically older (younger) if his/her PA.Accel > 0 (< 0) than expected based on his/her CA (4, 16).

FI and Acceleration of FI (FI.Accel)

FI integrates 36-item deficits (**Supplementary Table 1**) including comorbidities, activities of daily living, physical tasks, cognition, and performance testing (17). FI was calculated as a ratio of the number of deficits in a participant out of the total possible deficits considered, with a range of 0–1, and the higher score indicates the frailer a participant was. FI.Accel was defined as residual from a linear model when regressing FI on CA. FI.Accel was used as a categorical variable, and divided into frail (FI.Accel > 0) or robust (FI.Accel ≤ 0).

Mortality

Mortality follow-up was based on linked data from records taken from the National Death Index (NDI) through December 31, 2015, provided by the Centers for Disease Control and Prevention (18). Survival time was calculated as months from the date of interview to the date of death or the end of follow-up, whichever came first.

Covariates

Demographic factors (CA, gender, ethnicity, and education level), body mass index (BMI), and life style factors [i.e., smoking status, binge drinking status, alcohol consumption, leisure-time physical activity level (PAQ), and health eating index-2010 (HEI-2010) (19)] were included as covariates. Ethnicity was grouped as non-Hispanic white, non-Hispanic black, Hispanic, and others. Education level was grouped as less than high school (<HS), HS/general educational development (HS/GED), having attended college but not receiving at least a bachelor's degree (some college), and having a bachelor's degree or higher (college). BMI was grouped as underweight (BMI < 18.5 kg/m^2), normal (18.5 kg/m^2 $\leq$ BMI < 25 kg/m^2), overweight (25 kg/m^2 $\leq$ BMI < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). Smoking status was grouped as never smoker, former smoker, and current smoker. Alcohol consumption was grouped as never drinker (never drinking or didn't drink in the past year), low to moderate drinker (drinks <3 times per month), and heavy drinker (drinks at least one time per week). PAQ was grouped as low (<one time per week), moderate (1–2 times per week), and heavy ($\geq$3 times per week). HEI-2010 was grouped by tertiles (Tertile 1, 2, and 3).

Statistical Analyses

The basic characteristics are presented as mean $\pm$ standard deviation (SD) and number (percentage) for continuous and categorical variables, respectively.

TABLE 1 | Characteristics of the study participants, NHANES 1999–2002.

Characteristics	No. (%) or mean ± SD
All	3,249
Chronological age, y	48.4 ± 17.8
Young- and middle-aged adults (20–59 years)	2,206 (67.9)
Older adults (60–84 years)	1,043 (32.1)
Gender	
Female	1,649 (50.8)
Male	1,600 (49.2)
Ethnicity	
Non-Hispanic white	1,653 (50.9)
Non-Hispanic black	510 (15.7)
Hispanic	995 (30.6)
Others	91 (2.8)
Education[a]	
<HS	1,056 (32.5)
HS/GED	742 (22.9)
Some college	858 (26.4)
College	589 (18.2)
Smoking status	
Never smoker	1,635 (50.4)
Former smoker	882 (27.2)
Current smoker	727 (22.4)
BMI[b]	
Normal	990 (30.9)
Underweight	40 (1.2)
Overweight	1,177 (36.7)
Obese	998 (31.1)
Alcohol consumption[c]	
Never drinker	1,042 (33.2)
Low to moderate drinker	1,096 (34.9)
Heavy drinker	1,002(31.9)
Binge drinking status	
Yes	415 (12.8)
No	2,834 (87.2)
PAQ	
< 1 time/week	1,857 (57.2)
1–2 times/week	1,099 (33.9)
≥3 times/week	289 (8.9)
HEI-2010	
Tertile 1	31.5 ± 5.4
Tertile 2	45.7 ± 3.8
Tertile 3	62.3 ± 8.0
Three aging measures	
Frailty index	0.11 ± 0.09
Phenotypic age, y	41.56 ± 19.45
Telomere length	1.02 ± 0.26

NHANES, the National Health and Nutrition Examination Survey; SD, standard deviation; HS, high school; GED, general educational development; BMI, body mass index; PAQ, leisure time physical activity level; HEI, health eating index.

Percentages may not sum to 100 because of rounding. There were missing data on education (n = 4), smoking status (n = 5), drinking status (n = 109), BMI (n = 44), PAQ (n = 4), and HEI-2010 (n = 40).

[a] *Education levels included less than HS (<HS), HS/GED, having attended college but not receiving at least a bachelor's degree (some college), and having a bachelor's degree or higher (college).*

[b] *Underweight was defined as BMI < 18.5 kg/m^2; normal was defined as $18.5 \leq$ BMI < 25.0 kg/m^2; overweight was defined as $25.0 \leq$ BMI < 30.0 kg/m^2; and obese was defined as BMI ≥ 30.0 kg/m^2.*

[c] *Alcohol consumption was defined as never drinker (never drinking or didn't drink in past year), low to moderate drinker (drinks <3 times per month), and heavy drinker (drinks at least one time per week).*

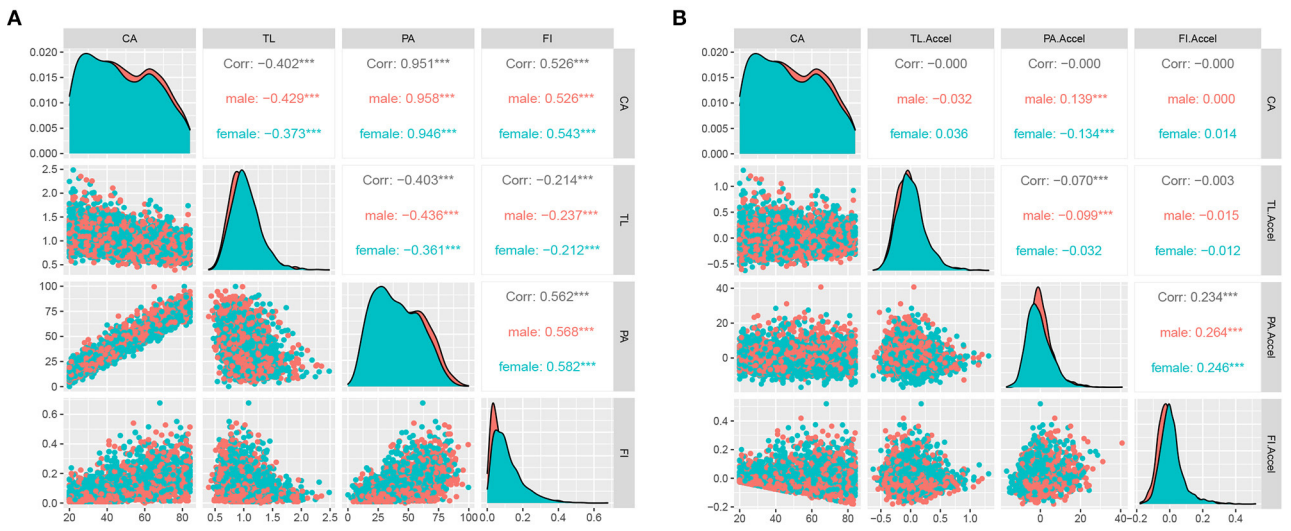


FIGURE 1 | Correlations between three aging measures and chronological age. CA, chronological age; TL, telomere length; PA, Phenotypic age; FI, frailty index; TL.Accel, PA.Accel and FI.Accel represent residuals from linear models when regressing TL, PA, and FI on CA, respectively. ***$p < 0.001$. **(A,B)** represent correlations before and after adjustments of chronological age, respectively.

To assess the predictive utilities for all-cause mortality of three aging measures, survival analysis was conducted. Kaplan–Meier (K-M) curves were plotted and log-rank tests were conducted. Meanwhile, Cox proportional hazards regression was performed based on three models: model 1 was a crude model; model 2 adjusted for CA and gender; and model 3 additionally adjusted for ethnicity, education level, smoking status, alcohol consumption, binge drinking status, BMI, PAQ, and HEI-2010 based on model 2. Hazard ratio (HR) and 95% confidence intervals (95% CI) were documented. Next, time-dependent receiver operating characteristic (ROC) curves (20) were applied to evaluate the predictive utility of different aging measures using model 2 and model 3. Three indices of predictive utility [i.e., area under the curve (AUC), integrated discrimination improvement (IDI), and continuous net reclassification improvement (NRI) (21)] for each of three aging measures were calculated, in comparison to those of the basic model with CA and gender only.

Since two of the three aging measures (PA.Accel and FI.Accel) outperformed relative to TL.Accel, we next tried to develop a new composite aging measure with better predictive utility by integrating aging measures at different hierarchical levels. Principal component analysis (PCA) was applied to PA.Accel and FI.Accel, and the first principal component (PC1) was defined as a new composite aging measure. We then performed the same analyses (i.e., K-M curves and Cox proportional hazards regression) to assess the predictive utility for all-cause mortality of PC1.

We applied linear regression to examine the responses to the life style factors (i.e., smoking status, BMI, alcohol consumption, binge drinking status, PAQ, and HEI-2010) of PA.Accel, FI.Accel, and PC1, the three showing significant predictive utilities of mortality in the previous analysis. Because PC1 was scaled, PA.Accel and FI.Accel were also scaled for comparability. We adjusted for CA and gender, and documented regression coefficients and 95% CI in these associations.

We performed several sensitivity analyses. Due to the wide age range of study population, we tested whether the associations of three aging measures and the new composite age measure with mortality differed by age groups. Moreover, we also estimated whether the responses of PA.Accel, FI.Accel, and PC1 to the life style factors differed by age groups. Additionally, the durations of the exposition to life style risk factors may have potential impact on aging; thus, we estimated the association of smoking duration (the only available variable in NHANES) with PA.Accel, FI.Accel, and PC1, for previous and current smokers.

All analyses were conducted via R (version 4.0.3, 2020-10-10) and a two-sided $p < 0.05$ was considered to be statistically significant.

RESULTS

Basic Characteristics of Study Participants

The basic characteristics of 3,249 participants are shown in **Table 1**. The mean CA of 3,249 participants was 48.4 ± 17.8 years and around a third of them were old adults (≥60 years). Around half of the participants were females (50.8%). The proportions of non-Hispanic white, non-Hispanic black, and Hispanic were 50.9, 15.7, and 30.6%, respectively. More than half of the participants didn't go to college and only 18.2% received a bachelor's degree or over. Half of the participants were never smokers, and 22.4% were current smokers. The proportions of participants at different alcohol consumption levels were similar. Around 13% of the participants reported being binge drinkers. Only 1.2% of participants were underweight and around 31% had normal weight. More than half reported performing physical activity < 1 time per week. The mean

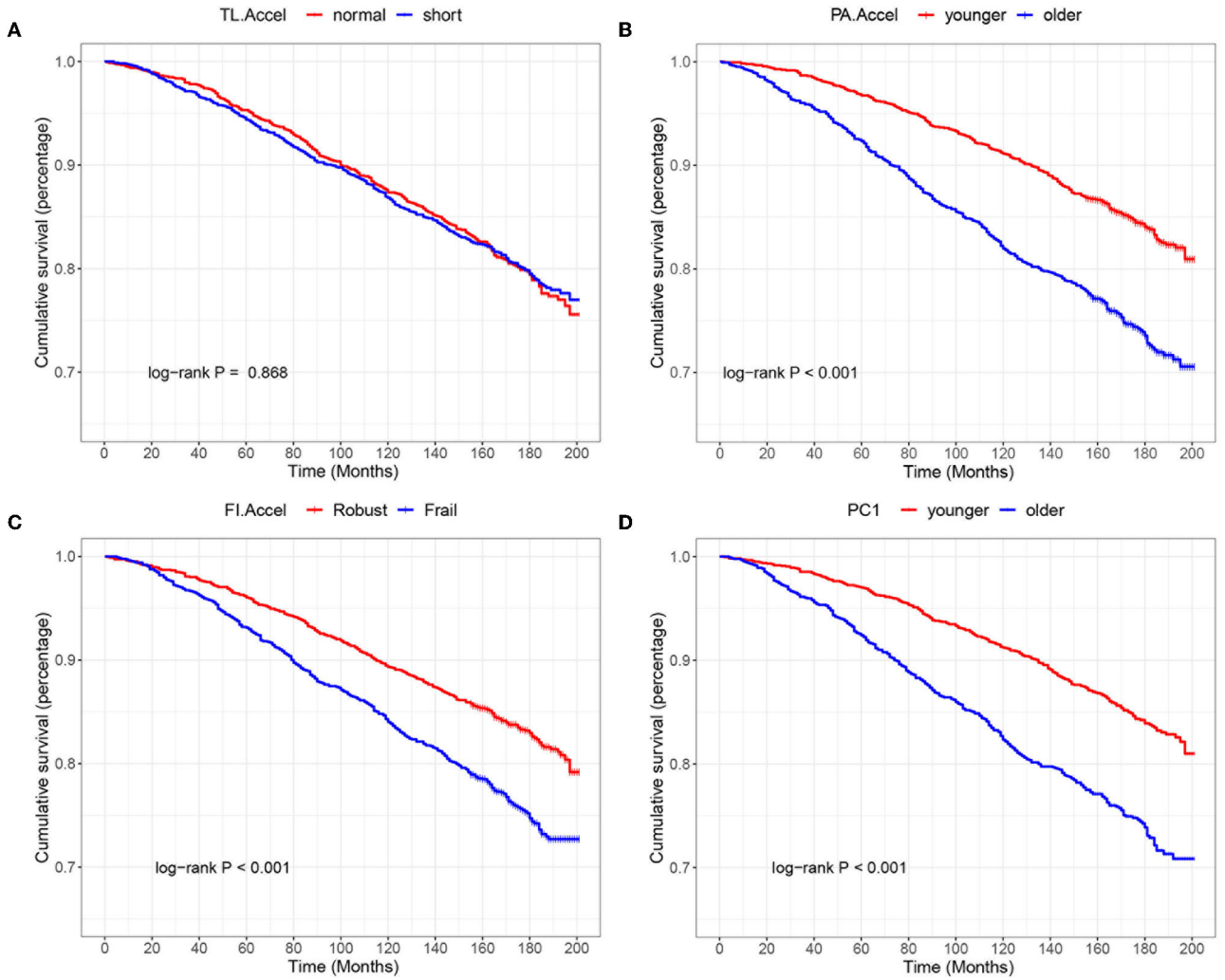


FIGURE 2 | K-M curves of different aging measures for predicting all-cause mortality. TL.Accel, PA.Accel and FI.Accel represent residuals from linear models when regressing telomere length, Phenotypic age, and frailty index on chronological age, respectively. PC1 is the first principal component of PA.Accel and FI.Accel through the principal component analysis. **(A–D)** represent K-M curves of TL.Accel, PA.Accel, FI.Accel and PC1 for predicting all-cause mortality, respectively.

HEI-2010 of the three tertiles group were 31.5, 45.7, and 62.3, respectively.

Were Three Aging Measures Correlated to CA?

As shown in **Figure 1A**, all three aging measures significantly were correlated to CA. Among them, shorter TL was correlated to older CA with a Pearson correlation coefficient of −0.40, while the other two aging measures were positively correlated to CA. **Figure 1B** illustrates the correlations after eliminating the effects of CA on aging measures by linear regression.

Did Three Aging Measures Predict All-Cause Mortality?

Figures 2A–C presents the associations of the three aging measures with mortality. We found that PA.Accel (log-rank $p < 0.001$) and FI.Accel (log-rank $p < 0.001$), but not TL.Accel (log-rank $p = 0.868$), could identify participants at different risks of death. The similar results implied by Cox regression are shown in **Table 2**. According to the crude model (model 1), compared to phenotypically younger participants (PA.Accel < 0), phenotypically older participants (PA.Accel ≥ 0) had a 79% increase in mortality risk (HR = 1.79, 95% CI = 1.54–2.09). Similarly, compared to robust participants (FI.Accel ≥ 0), frail ones (FI.Accel < 0) had a 52% increase in mortality risk (HR = 1.52, 95% CI = 1.31–1.77). However, TL.Accel was found not to be significantly associated with mortality risk based on Cox regression ($p = 0.868$). After adjusting for covariates, these associations did not change substantially (models 2 and 3).

Did Aging Measures Show Additional Predictive Utilities Than CA and Gender?

Figures 3A,B exhibits the ROC curves for predicting mortality by different aging measures.

TABLE 2 | Associations of three aging measures with mortality.

	No. of death (%)	Model 1		Model 2		Model 3	
		HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
TL.Accel							
Short	301 (20.46)	Ref	–	Ref	–	Ref	–
Normal	362 (20.36)	0.99 (0.85–1.15)	0.868	1.00 (0.86–1.17)	0.992	0.97 (0.82–1.14)	0.711
PA.Accel							
Younger	291 (16.04)	Ref	–	Ref	–	Ref	–
Older	372 (25.92)	1.79 (1.54–2.09)	**<0.001**	1.85 (1.58–2.16)	**<0.001**	1.67 (1.41–1.98)	**<0.001**
FI.Accel							
Robust	321 (17.19)	Ref	–	Ref	–	Ref	–
Frail	342 (24.75)	1.52 (1.31–1.77)	**<0.001**	1.62 (1.38–1.88)	**<0.001**	1.59 (1.35–1.87)	**<0.001**
PC1							
Younger	313 (16.60)	Ref	–	Ref	–	Ref	–
Older	350 (25.68)	1.80 (1.54–2.11)	**<0.001**	1.85 (1.58–2.17)	**<0.001**	1.79 (1.51–2.12)	**<0.001**

HR, hazard ratio; TL.Accel, PA.Accel, and FI.Accel represent residuals from linear models when regressing telomere length, Phenotypic age, and frailty index on chronological age, respectively; PC1, the first principal component of PA.Accel and FI.Accel through the principal component analysis.
Model 1 was a crude model; model 2 adjusted for chronological age and gender; model 3 further adjusted for ethnicity, education level, body mass index, smoking status, binge drinking status, alcohol consumption, leisure time physical activity level, and health eating index based on model 2. The bold values represent that the tests were statistically significant with two-tailed $p < 0.05$.

Compared to the basic model (only CA and gender were included, AUC = 0.816), the model with PA.Accel or FI.Accel had higher predictive utility, evidenced by significantly increased AUC (PA.Accel: 0.829, $p < 0.001$; FI.Accel: 0.820, $p = 0.067$ in model 2), IDI (PA.Accel: 0.019, $p < 0.001$; FI.Accel: 0.010, $p < 0.001$ in model 2), and continuous NRI (PA.Accel: 0.193, $p < 0.001$; FI.Accel: 0.105, $p < 0.001$ in model 2). We did not observe that TL.Accel added significantly predictive utility. When adjusting for more covariates in the models (i.e., model 3), we observed similar patterns.

Can We Develop a New Composite Aging Measure?

Due to the inherent difference shared by aging measures at different hierarchical levels and the better predictive utility of PA.Accel and FI.Accel (relative to TL.Accel), we asked that whether we could develop a new composite aging measure with a better predictive utility by integrating aging measures at different hierarchical levels. Thus, PCA was applied to PA.Accel and FI.Accel and the scatter plot of PCA is shown in **Supplementary Figure 2**. We found that PC1 accounted for 61.70% of the total variance and can be calculated as follows:

$$PC1 = 0.707 \times PA.Accel + 0.707 \times FI.Accel \quad (1)$$

We then calculated PC1 for each participant. As shown in **Figure 2D,** PC1 could identify participants at different risks of death (log-rank $p < 0.001$). Moreover, we found that PC1 outperformed each single aging measure (**Figure 3C**) with larger AUC (0.829, $p < 0.001$, model 2), and greater increases of IDI (0.020, $p < 0.001$, model 2) and NRI (0.194, $p < 0.001$, model 2) compared to the basic model, and the pattern was more obvious in model 3.

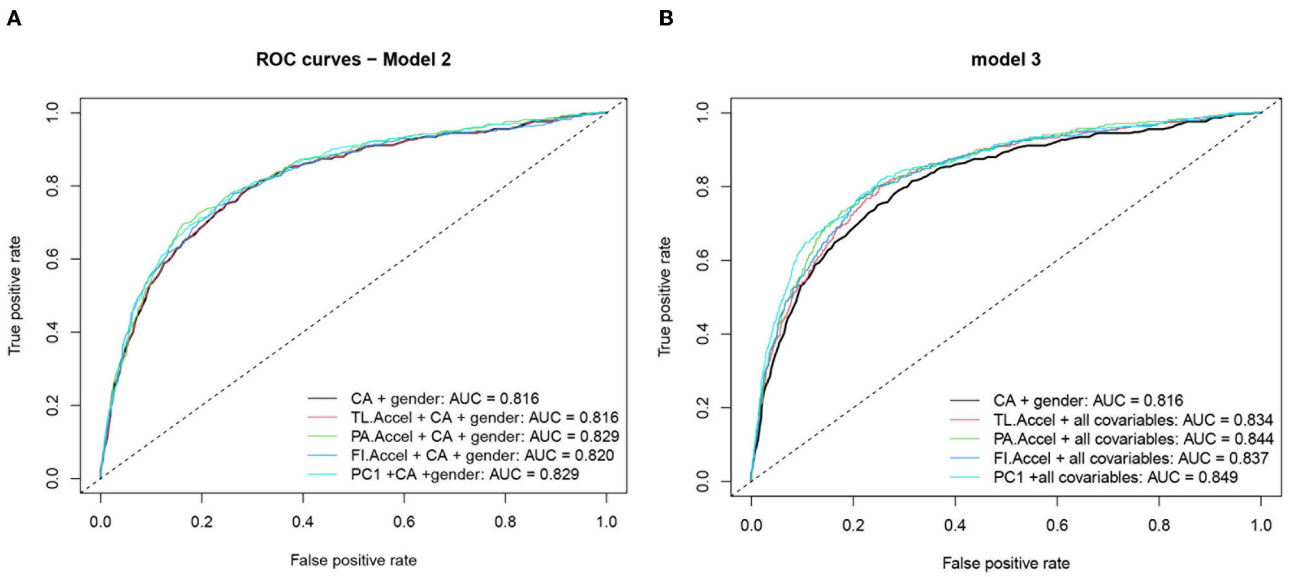
Are These Aging Measures Responsive to Modifiable Life Style Factors?

Figure 4 presents results from linear regression to examine the association of modifiable life style factors (i.e., smoking status, BMI, binge drinking status, alcohol consumption, PAQ, and HEI-2010) of PA.Accel, FI.Accel and PC1, the three showing significant predictive utilities of mortality in the previous analysis. Overall, PA.Accel, FI.Accel, and PC1 were responsive to smoking status, BMI, alcohol consumption, and PAQ. For instance, compared to never smokers, current smokers had a significantly higher level of PA.Accel ($\beta = 0.36$, $p < 0.001$) and FI.Accel ($\beta = 0.23$, $p < 0.001$). Interestingly, relative to PA.Accel and FI.Accel, PC1 showed stronger responses to almost all modifiable life style factors (except for HEI-2010), with the largest absolute values of regression coefficients in these associations (**Supplementary Table 2**), indicating that the new composite aging measure might be more sensitive to modifiable life style factors.

Sensitivity Analysis

Supplementary Table 3 shows the associations of the three aging measures and PC1 with mortality by age groups. After adjusting for all covariates (model 3), both single aging measure (i.e., PA.Accel and FI.Accle) and the new composited aging measure (i.e., PC1) showed predictive utilities of mortality risk in different age groups. However, compared to short TL, normal TL (HR = 0.70, 95% CI = 0.51–0.97) was a protective factor of mortality among young- and middle-aged adults (20–59 years).

Supplementary Table 4 shows the responses of different aging measures to modifiable life style factors by age groups. Among young- and middle-aged adults (20–59 years), aging measures responded to modifiable life style factors,



C

Model	Predictive variable	AUC	P value	IDI		Continuous NRI	
				Point est. (95% CI)	p	Point est. (95% CI)	p
Reference Model	CA + gender	0.816	-	Ref	-	Ref	-
Model 2	TL.Accel	0.816	0.922	0.000 (-0.001, 0.003)	0.631	0.017 (-0.030, 0.074)	0.452
	PA.Accel	0.829	<0.001	0.019 (0.009, 0.032)	<0.001	0.193 (0.143, 0.240)	<0.001
	FI.Accel	0.820	0.067	0.010 (0.004, 0.022)	<0.001	0.105 (0.056, 0.162)	<0.001
	PC1	0.829	<0.001	0.020 (0.011, 0.031)	<0.001	0.194 (0.137, 0.242)	<0.001
Model 3	TL.Accel	0.834	<0.001	0.022 (0.012, 0.039)	<0.001	0.161 (0.124, 0.238)	<0.001
	PA.Accel	0.844	<0.001	0.039 (0.026, 0.051)	<0.001	0.238 (0.187, 0.306)	<0.001
	FI.Accel	0.837	<0.001	0.032 (0.020, 0.051)	<0.001	0.212 (0.159, 0.286)	<0.001
	PC1	0.849	<0.001	0.041 (0.027, 0.059)	<0.001	0.244 (0.182, 0.300)	<0.001

FIGURE 3 | The predictive performance of different aging measures. CA, chronological age; TL, telomere length; PA, phenotypic age; FI, Frailty index; TL.Accel, PA.Accel and FI.Accel represent residuals from linear models when regressing telomere length, Phenotypic age and frailty index on CA, respectively; PC1, the first principal component of PA.Accel and FI.Accel through the principal component analysis; AUC, area under the curve; IDI, integrated discrimination improvement; NRI, net reclassification improvement; est., estimation. Model 2 adjusted for CA and gender; Model 3 further adjusted for ethnicity, body mass index, education level, smoking status, alcohol consumption, binge drinking status, leisure time physical activity level, and health eating index based on Model 2. **(A)** and **(B)** represent the ROC curves of different aging measures based on model 2 and 3, respectively. **(C)** shows the AUC, IDI and NRI of each aging measure and the comparison to reference model.

as observed in the total population. However, among older adults (60–84 years), fewer significant associations were observed. For instance, FI.Accel and PC1 didn't respond to diet quality (HEI-2010) anymore, but they were both responsive to HEI-2010 among young- and middle-aged adults. Furthermore, PA.Accel didn't respond to smoking status anymore, but PC1 remained a significant response to smoking status.

Supplementary Table 5 shows that for previous smokers, longer durations of smoking were associated with higher level of PA.Accel and PC1. No above associations were observed for current smokers.

DISCUSSION

Based on the unique data from US NHANES, this study demonstrated that both PA and FI, but not TL, was significantly predictive of all-cause mortality. Building on the better performance of PA and FI, we integrated them to develop a new composite aging measure, which has been demonstrated to be predictive of mortality risk as well, even better than each single aging measure. Finally, we demonstrated that PA and FI, as well as the new composite aging measure, were responsive to some modifiable life style factors, including smoking status, alcohol consumption, and PAQ. The findings, for the first time,

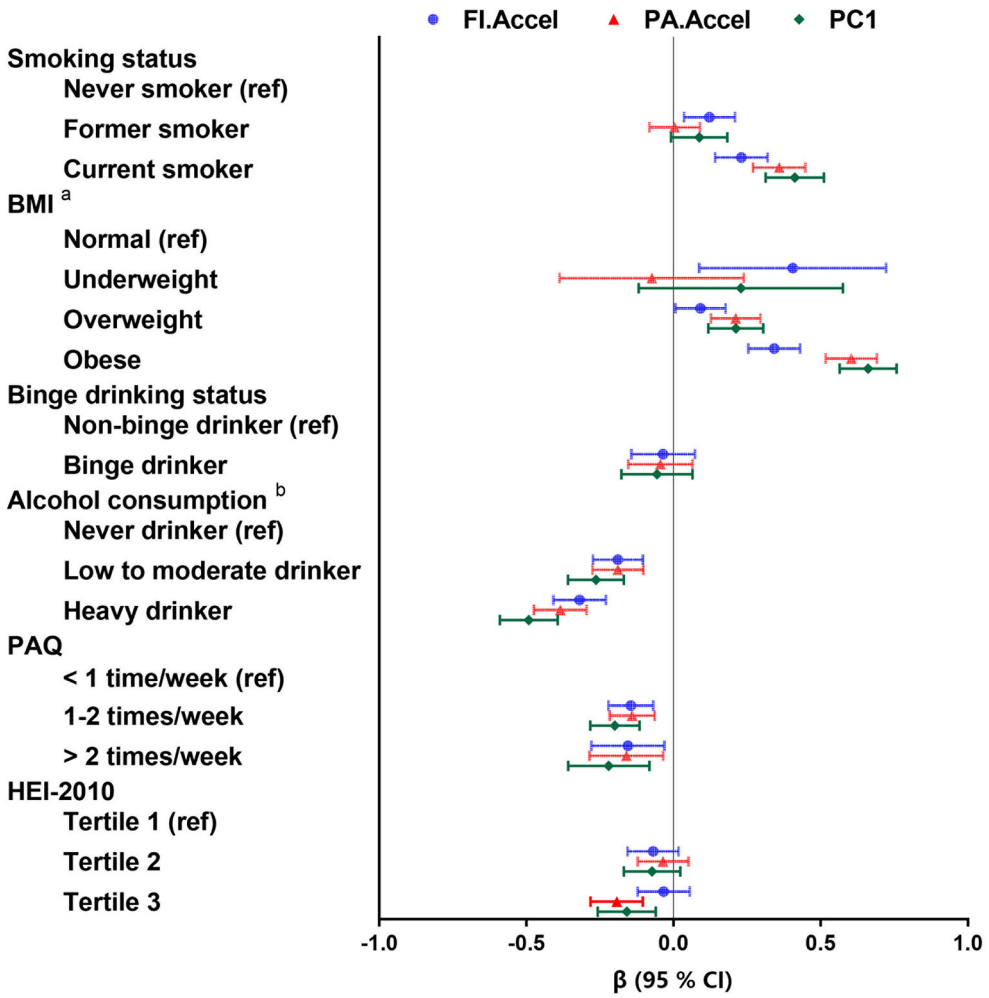


FIGURE 4 | The responses of different aging measures to modifiable life style factors. Coefficients (β) and 95% confidence intervals (CI) were calculated via linear regression adjusted for chronological age and gender. PA.Accel and FI.Accel represent residuals from linear models when regressing telomere length, Phenotypic age and frailty index on chronological age, respectively. PC1, the first principal component of PA.Accel and FI.Accel through the principal component analysis; BMI, body mass index; PAQ, leisure time physical activity level; HEI, health eating index. [a]Alcohol consumption was defined as never drinker (never drinking or didn't drink in past year), low to moderate drinker (drinks <3 times per month), and heavy drinker (drinks at least one time per week). [b]Underweight was defined as BMI < 18.5 kg/m^2; normal was defined as $18.5 \leq$ BMI < 25.0 kg/m^2; overweight was defined as $25.0 \leq$ BMI < 30.0 kg/m^2; and obese was defined as BMI ≥ 30.0 kg/m^2.

provide a full picture of the predictive utility of mortality risk by three aging measures at three hierarchical levels and the response to modifiable life style factors, with important implications for geroprotective programs.

The findings of the positive associations of PA and FI with all-cause mortality risk are consistent with previous studies (4, 22–25). To date, the association of TL and mortality remains less conclusive in epidemiological studies (25–28), and the discrepancy may be partly explained by the differences among the study populations, and methods to measure TL (29). Two studies based on the Dunedin birth cohort (25) and the National Health and Nutrition Examination Survey (NHANES) (27), respectively, considered TL and PA, and reported that TL was not consistently associated with multiple health span-related characteristics as compared to PA. However, FI was not considered in these two studies. The current study fills this knowledge gap by simultaneously evaluating the predictive utility of mortality risk by three aging measures at three hierarchical levels. The differences observed confirm that these aging measures did not necessarily reflect the same aging processes, as originally proposed by Ferrucci et al. (1).

The increased predictive utility by PC1 relative to each single aging measure further demonstrated the differences shared by PA and FI. A similar finding was reported in a Canadian study in which FI-combined (the sum of the deficits in blood biomarkers and functional items) shows greater addition in the predictive utility of mortality relative to each single FI measure based on either blood biomarkers or functional terms (30). PCA is

a simple dimensionality reduction technique that transforms the columns of an original dataset into a new set of features called PCs. By doing this, a large amount of the information across the original dataset is effectively compressed in fewer feature columns (i.e., the variance). Here, partially due to that PC1 captures the characteristics/information across hierarchical levels, our analysis (**Table 2**, **Figures 2D**, **3**, **4**) confirms that PC1 outperformed each single aging measure in terms of mortality prediction and associations with lifestyle factors. The findings suggest that aging measures at phenotypic and functional levels might be complementary (8). This indicates that integrating information across hierarchical levels may have the potential to develop better aging measures.

In addition to helping identify persons at risk, aging measures also serve as a potential endpoint for geroprotective programs. That being said, ideal aging measures should be responsive to risk factors (10). In this study, PA and FI were found to meet this criterion since they were responsive to some modifiable life style factors such as smoking status, BMI, alcohol consumption, and PAQ, which are largely consistent with previous studies (31–33). More interestingly, the new composite aging measure we developed, PC1, was strongly responsive to the same set of modifiable life style factors, highlighting its qualification as an aging measure.

Our findings have important implications in both large-scale epidemiological studies and clinical settings. First, the predictive utility of mortality risk by these aging measures (PA, FI, and PC1) suggests that we could identify vulnerable persons at risk of premature death. Together with the fact that they were responsive to modifiable life style factors, it seems that life style-targeted interventions may have the potential to slow aging and further reduce the burden of premature death. Finally, one can also apply these aging measures to examine the roles of various factors in healthy aging. Furthermore, it is promising to use these aging measures (particularly PC1) to test the effectiveness of antiaging interventions and therapies in human beings, where these aging measures serves as surrogate markers of life span. Application of aging measures is more practical and feasible in comparison to previous approaches using endpoints such as death, and the occurrence of chronic diseases, the latter requiring a long time of follow-up and high expenditures.

The present study has several strengths. First, we compared aging measures at three hierarchical levels in the same population, which is scarce in the literature. Second, the three aging measures we adopted in this study are widely recognized in the literature. We also acknowledge limitations in this study. First, the findings were based on the US population and thus may not be generalizable to other populations from different countries. Second, due to the unavailability of repeated measurements of these aging measures, we were unable to evaluate the associations between the rate of changes in aging measures and mortality risk. Third, NHANES did not collect information on exposure duration (except for smoking), which might have an impact on the results. Finally, only one aging measure at each hierarchical level was considered, in particular, only TL at the biological level. In recent years, DNA methylation age has been widely demonstrated as a promising aging measure (34–38); however, it was not available in the NHANES data. In moving forward, with more aging measures available, a more comprehensive picture of aging would be forthcoming.

CONCLUSIONS

Our study demonstrates that both phenotypic (i.e., PA) and functional (i.e., FI) aging measures can capture mortality risk and respond to modifiable life style factors, despite their inherent differences. Furthermore, the PC1 that integrated phenotypic and functional aging measures outperforms in predicting mortality risk in comparison with each single aging measure, and strongly responds to modifiable life style factors. The findings suggest the complementary of aging measures at different hierarchical levels and underscore the need to involve multi-level information when quantifying aging. The findings also highlight the potential of life style-targeted interventions as geroprotective programs.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. The data can be found at the National Health and Nutrition Examination Survey website: https://www.cdc.gov/nchs/nhanes/index.htm.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Center for Health Statistics Research Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization was proposed by XW and ZL. The methodological design and data analyses were conducted by JZ and ZL. Data collection and preparation were performed by XC, CC, and ZL. The results were interpreted by JX and LHa. The first draft of the manuscript was written by JZ, XC, LHe, and ZR. XW and ZL provided overall supervision. All authors reviewed and edited the manuscript. All authors contributed to the article, reviewed, edited the manuscript, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Operationalization of the Clinical Frailty Scale in Korean Community-Dwelling Older People

Hee-Won Jung†, Ji Yeon Baek†, Il-Young Jang* and Eunju Lee*

Division of Geriatrics, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: The Clinical Frailty Scale (CFS) is a simple measure of global fitness validated in various populations in real-world settings. In this study, we aimed to assess the characteristics and validities of the CFS in community-dwelling older people in Korea, with the original classification tree (oCFS) and a culturally modified tree (mCFS).

Methods: The comprehensive geriatric assessment records of 1,064 individuals of the Aging Study of the Pyeongchang Rural Area were used for this study. For mCFS, we considered the dependency of the food preparations and household chores not to be deficits in the male population. The frailty index was used as a reference for construct validity. We used a composite outcome of death and institutionalization for outcome validity.

Results: The correlation coefficients with frailty index were higher in mCFS (.535) than in oCFS (.468). The mean frailty index was lower in individuals reclassified by mCFS (5 to 4) than people who stayed in mCFS 5. The classification coefficient of mCFS was significantly higher than that of oCFS (p <0.001) in determining people with frailty (frailty index.25 or higher). Trends of a higher incidence of the composite outcome were observed in both higher oCFS and mCFS, in which oCFS and mCFS did not differ significantly in predicting the risk of the outcome.

Conclusion: The classification tree of CFS could be culturally adopted in a community-dwelling population of Korea and considered valid in detecting the vulnerable population.

Keywords: clinical frailty scale, culture, classification, Asian, older adults

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Jean-Marie Degryse, K.U. Leuven, Belgium

***Correspondence:**
Hee-Won Jung
dr.ecsta@gmail.com
Il-Young Jang
onezero2@gmail.com

†*These authors share first authorship*

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INTRODUCTION

Korea is experiencing the fastest pace of transformation in the population structure among developed countries and facing social and economic challenges from its aging population (1). Accompanied by a rapid shift in social structure, including the decreasing family size and urbanization, Korea is expecting decades of a super-aged society. Meanwhile, even Western countries with better resources and a slow rate of population aging have been struggling to maintain high-quality services for their older populations (1, 2). The long-term care system in Korea is expected to be overwhelmed in the near future by soaring care demands from older adults with disabilities (3). Hence, there is an urgent need to develop sustainable care models to address the spectrum of individual care demands while optimizing available resources.

Growing knowledge on the importance of the frailty spectrum might be one of the most remarkable achievements in geriatric medicine in this century in person-centered risk assessment and care provision for older adults (4–6). Measured by either the phenotype or the index, the spectrum of frailty has shown high prediction ability for adverse health outcomes encompassing healthcare use and incidence of geriatric syndromes, such as fall and delirium, as well as disability and death (7, 8). These features of frailty have led to a growing research interest in incorporating frailty as a risk measure in many specialized fields of medicine outside geriatrics (9). Translation studies have shown content validity of the frailty spectrum as a measure of human biological age (10, 11). It has been reported that frailty was a dynamic and malleable feature, which responded to appropriately designed multicomponent intervention targeting geriatric functional domains (12, 13). Consequently, addressing the frailty spectrum might be a potential cornerstone in designing tailored care models for the older population, encompassing areas of health promotion, disease treatment, prevention of disabilities, and even long-term caregiving.

Despite its importance, assessing and interpreting frailty has long been regarded as a barrier in incorporating this condition into real-world clinical practice (14). However, the Clinical Frailty scale (CFS), a simplified measure including pictographs and brief descriptions on global fitness and functional capabilities, has been suggested as a viable approach (15, 16). After being initially developed to trace the frailty index, validity of the CFS has been shown in diverse spectrums of care situations, including intensive care units, long-term care facilities, and sometimes in a large population (15, 17). In the Korean population, studies have shown validities of the CFS in geriatric outpatients and inpatients in a hospitalist unit and an intensive care unit (18–20). However, to the authors' knowledge, its utility and validity in community-dwelling older people in Korea are yet to be proven, even though the CFS has potential advantages as an efficient measure of the frailty in community-based public health programs. Furthermore, in previous attempts adopting CFS in the present authors' institution, we faced questions on interpreting and classifying capabilities on instrumental activities of daily living (IADL) of male patients.

Recognizing this knowledge gap, we aimed to assess the characteristics and validities of the CFS in community-dwelling older people in Korea. We measured the CFS by adopting the decision tree, which was recently developed and validated by Theou et al. (21), and assessed its characteristics with the generally well-accepted measures of frailty phenotype and frailty index. In this adoption, we compared the original classification and culturally modified classification considering controversial IADL items of older male population in Korea. We then evaluated whether the CFS could predict a composite outcome of institutionalization and death.

METHODS

Study Design and Population

We used the records of the Aging Study of the Pyeongchang Rural Area (ASPRA), a population-based prospective cohort study on frailty, sarcopenia, and geriatric syndromes in community-dwelling older Korean adults. Details of the study characteristics, evolutions in the designs, and summary of study findings have been described previously (22). Briefly, the ASPRA was established in 2014 in Pyeongchang county, Gangwon Province, Korea, using the Community Health Post network of the National Healthcare Service (NHS), a health system operated by the Korean government. It started with 382 individuals in three small villages and gradually expanded to the surrounding regions, eventually including 1,529 participants who underwent at least one examination before December 2018.

In the study, we used the records of the 1,064 participants who were recruited and underwent baseline examination from July 2015 to June 2018, including the Comprehensive Geriatric Assessments (CGA) assessing frailty, disability, and were assessed for a composite outcome as described below. As the International Physical Activity Questionnaire Short Form (IPAQ) included an item on the "participation of strenuous activity" used in the classification tree for CFS, which was introduced in 2015, we excluded 382 participants who had assessments from October 2014 to June 2015 without IPAQ.

The eligible participants in the ASPRA were individuals aged 65 years or older, living at home, able to walk with or without assistive devices, able to provide informed consent by themselves or their legal proxy, and registered in the NHS. Persons living in nursing homes, chronic care hospitals, or receiving nursing-home level care at home due to disabilities were excluded. Also, individuals apparently approaching their end-of-life were not considered to be eligible. The protocol of this study was approved by the Institutional Review Board of Asan Medical Center. Written informed consent was obtained from all participants or their legal proxy.

Classification of the CFS

The original classification of the CFS (oCFS) was scored using the classification tree (**Supplementary Figure 1**) adapted to be compatible with variables of the ASPRA from previous work by Theou et al. that showed good agreement with an expert rated CFS (21). The classification tree was developed based on the descriptions of individual CFS levels and included basic activities of daily living (ADL) and IADL, chronic conditions, self-rated health, energy level, and physical activity.

We used parameters from the baseline CGA in the study to capture variables in the classification tree. For ADL, we used items on dressing, bathing, eating, walking, and transferring from the Korean ADL (23). The IADL included items such as using a phone, shopping, food preparation, household chores, managing medications, and handling own money from the Korean IADL (23). Chronic conditions included 11 physician-diagnosed illnesses, such as angina, arthritis, asthma, cancer, chronic lung disease, congestive heart failure, diabetes, heart

attack, hypertension, kidney disease, and stroke. Self-rated health was measured as excellent, good, or poor. Poor endurance and energy (everything is an effort) were assessed by the exhaustion item used in the Cardiovascular Health Study (CHS) frailty phenotype described below (24). Engagement in strenuous sport or recreational activities was captured using the IPAQ questionnaire (25).

The cultural characteristic of the Korean older family has long been considered an issue in assessing disability in IADL items with the presence of gender-specific differences in household-related items (26). For the culturally modified classification of the CFS (mCFS), we excluded male participants with dependencies in IADL only for items on preparing meals and doing housework from the determination of CFS 5.

Frailty Index and Phenotype

We used a 34-item frailty index as a standard measure of frailty in this study (**Supplementary Table 2**). The frailty index ranging from 0 to 1 using the deficit accumulation approach was established from 34 health-related items encompassing the domains of chronic conditions, physical performance, cognitive function, and daily functions (7, 27, 28). We established cut-off values for the frailty index adopting definitions and observations of previous studies (7, 29), and a frailty index of 0.25 or higher as frail.

As a measure of the physical frailty, CHS frailty phenotype comprised the following items: (1) exhaustion ("moderate or most of the time during the past week" for either of "I felt that everything I did was an effort" or "I could not get going"); (2) low activity (lowest 20 percentile in physical activity using the IPAQ); (3) slowness (usual gait speed <0.8 m/s in the 4-m walk); (4) weakness (dominant hand grip strength <26 kg for men and <17 kg for women); and (5) weight loss (unintentional weight loss >3 kg during the previous 6 months). We considered a CHS frailty phenotype score of 3 or higher as indicating frailty (24).

Co-variables

Basic demographic, anthropometric, and social information, including the education level, were recorded by the interviewers. Geriatric functional parameters were assessed from the CGA performed by the trained nurses. We considered the disability in ADL as the presence of dependency in at least one in seven items, such as bathing, continence, dressing, eating, toileting, transferring, and washing the face and hands, in the Korean ADL (23). Similarly, the disability in IADL was determined as the presence of at least one dependency in 10 items: food preparation, household chores, going out a short distance, grooming, handling finances, doing laundry, managing medications, shopping, transportation, and using a phone, in the Korean IADL (23). Cognitive dysfunction was determined with the Korean version of the Mini-Mental State Examination (K-MMSE) score cut-off of <24 (30). From the medication history, we defined polypharmacy as the use of five or more prescription medications. History of fall in the previous 12 months was recorded.

Outcome Assessment

We used a composite endpoint of death and long-term institutionalization due to functional impairment as an outcome. This information was acquired by telephone interviews with the participants or their family members, performed every 3 months. Death was additionally captured from records of the Community Health Post network system. For this analysis, we used composite outcome data captured until August 2020.

Statistical Analysis

Descriptive characteristics according to oCFS and mCFS were calculated. Spearman's correlation coefficients between oCFS, mCFS, and frailty index, and CHS frailty phenotype score were calculated. Boxplots were used to display distributions of frailty index upon each score of oCFS and mCFS. The receiver operating characteristics (ROC) analysis, net classification improvement (NRI), and integrated discrimination improvement (IDI) were used to compare the classification ability of oCFS and mCFS for frailty index 0.25 or higher. Kaplan–Meier and Cox regression analysis were used to evaluate the impact of oCFS and mCFS on the composite outcome. Before performing the Cox regression, the proportional-hazards assumption was checked using the log-log plots. In Cox regression analyses, age and sex were introduced as covariables in Model 2, and the number of chronic conditions was further included in Model 3, in which the CFS 1 was considered a reference. The discriminatory ability was assessed using the Harrell's C index (31), and compared using linear comparison. Two-sided p-values of <0.05 were considered significant. Statistical analyses were performed using the Stata 15.0 (StataCorp, College Station, TX, USA).

RESULTS

Descriptive Characteristics

To compare basic demographic and clinical parameters, we grouped participants into two groups: CFS 1–3 ($n = 398$, 37.4%); and CFS 4–7 ($n = 666$, 62.6%), according to our previous observation suggesting that CFS 4 or higher as a cut-off for the frailty in the geriatric outpatients in Korea. Parameters between the two groups are shown in **Table 1**. The population in the higher CFS group were older, less educated, had more chronic conditions, and were living with a high frailty index and CHS frailty phenotype score. Individuals in the higher CFS group had a high number of impaired ADL and IADL items, a low MMSE score, and was more likely to experience a fall in the previous year.

Comparisons Between oCFS and mCFS as Frailty Constructs

By oCFS, 89 (8.4%), 171 (16.1%), 138 (13.0%), 193 (18.1%), 403 (37.9%), 51 (4.8%), and 19 (1.8%) individuals had an oCFS score of 1–7, respectively. Among the male population, 98 persons who were initially considered to have an oCFS of 5 had impairments in IADL only for items on preparing meals and doing housework care needs. Hence, 291 (27.4%) and 305 (28.7%) persons were considered to be mCFS 4 and 5. The mean (SD) frailty index was 0.10 (0.06), 0.09 (0.07), 0.14 (0.07), 0.23 (0.09), 0.19 (0.12), 0.43

TABLE 1 | Basic demographic and clinical characteristics.

	CFS 1-3	% or SD	CFS 4-7	% or SD	*p*-value
Sample size (*n*, %)	398	37.4	666	62.6	
Age (mean, SD)	73.6	5.5	77.4	7.1	<0.001
Women (*n*, %)	203	51.0	380	57.1	0.055
Years of education (mean, SD)	7.4	4.1	5.3	3.2	<0.001
Number of chronic conditions (mean, SD)	1.1	1.0	1.5	1.1	<0.001
CHS frailty score (range: 0–5) (mean, SD)	1.0	1.0	1.8	1.2	<0.001
Frailty index (range: 0–1) (mean, SD)	0.11	0.07	0.23	0.14	<0.001
Number of impaired ADL items (mean, SD)	0.07	0.25	0.46	1.64	<0.001
Number of impaired IADL items (mean, SD)	0.02	0.15	2.08	3.82	<0.001
MMSE score (mean, SD)	26.9	3.2	24.4	4.9	<0.001
Number of daily medications (mean, SD)	2.3	2.4	3.3	3.1	<0.001
Falls in the previous 1 year (*n*, %)	33	8.3	104	15.6	0.001

ADL, activities of daily livings; CFS, Clinical Frailty Scale; CHS, Cardiovascular Health Study; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; SD, standard deviation.

(0.10), and 0.58 (0.09) for the oCFS scores of 1–7, respectively (p-value for the trend of the frailty index by oCFS, <0.001). By mCFS, the mean (SD) frailty index was 0.19 (0.10) and 0.22 (0.12) for mCFS 4 and 5 (p-value for the trend of frailty index by mCFS <0.001). Distributions of the frailty index and CHS frailty phenotype categories by groups of oCFS and mCFS are shown in **Figure 1**.

The correlation coefficients for oCFS and mCFS with frailty index were 0.468 ($p < 0.001$) and 0.535 ($p < 0.001$), respectively. Those for oCFS and mCFS with CHS frailty phenotype score were 0.277 ($p < 0.001$) and 0.320 ($p < 0.001$), respectively. In summary, the correlation coefficients with two frailty measures were higher in mCFS than in oCFS.

We compared the frailty index among male participants in CFS 4–5 to assess the potential impact of reclassification from oCFS to mCFS. The mean (SD) frailty indexes of reclassified individuals were 0.12 (0.08), which was significantly lower ($p = 0.014$ by t-test) than those who remained in mCFS 5, of 0.15 (0.11).

To compare the explanation abilities of oCFS and mCFS, we performed an ROC analysis with frailty index as an anchor. The area under the curve of mCFS [0.812, 95% confidence interval (CI): 0.787–0.837] was significantly higher ($p < 0.001$) than that of oCFS (0.776, 95% CI: 0.749–0.803), to classify the frailty that was determined by the frailty index 0.25 or higher. For the accurate comparison of oCFS with mCFS, we additionally calculated the value of NRI and IDI using frailty index (cutoff 0.25) as reference. NRI was 0.193 [standard error (SE) 0.043] ($p < 0.001$), and IDI was 0.071 (SE 0.006) ($p < 0.001$), which means the new model (mCFS) classifies frailty status better than the original model (oCFS) significantly.

Outcome Relevance of oCFS and mCFS

To assess the outcome validity of oCFS and mCFS, we performed survival analysis using the data of the composite outcome in the study population. The Kaplan–Meier curves for oCFS and mCFS scores are shown in **Figures 2A,B**, respectively. Hazard ratio (HR) and 95% CI using univariate for oCFS and mCFS scores are displayed in **Figures 2C,D**, respectively. The increasing burden of the frailty either by oCFS or mCFS were associated with a higher risk of composite outcome incidence, and statistical significances were maintained after adjusting for age, sex, and the number of chronic conditions (**Table 2**). The crude incidence rate of composite outcome and HR of each CFS score is shown in **Supplementary Table 1**.

Prediction performances for the composite outcome of oCFS and mCFS were compared with the frailty index. The Harrell's C statistics were 0.771 (95% CI: 0.727–0.815), 0.721 (95% CI: 0.675–0.768), 0.719 (95% CI: 0.671–0.766) for the frailty index, oCFS, and mCFS, respectively. There was no significant difference between the C statistics of oCFS and mCFS ($p = 0.719$). However, the C statistics of both oCFS ($p = 0.016$) and mCFS ($p = 0.004$) were significantly lower when compared with that of the frailty index.

DISCUSSION

In this study, we evaluated the validities of oCFS and mCFS in community-dwelling Korean older adults, using the classification tree of CFS that was previously validated in a population from the United Kingdom. When the frailty index was used as a standard, mCFS was better than oCFS in construct validity. On the other hand, mCFS and oCFS were comparable in predicting the composite outcome. To the authors' knowledge, this is the first study adopting the classification tree of CFS in an Asian population evaluating construct and criterion validity.

The growing consensus support that frailty is a core clinical feature of the complex system of aging physiology (5), and both the phenotype model and the deficit-accumulation model converge with each other (7), even though controversies still exist to date on the biological and clinical construct of frailty. The CFS was conceptualized from a theoretical model of fitness and frailty (32), encompassing the functional spectrum as a measure of global fitness (16). In the original study, the CFS highly correlated

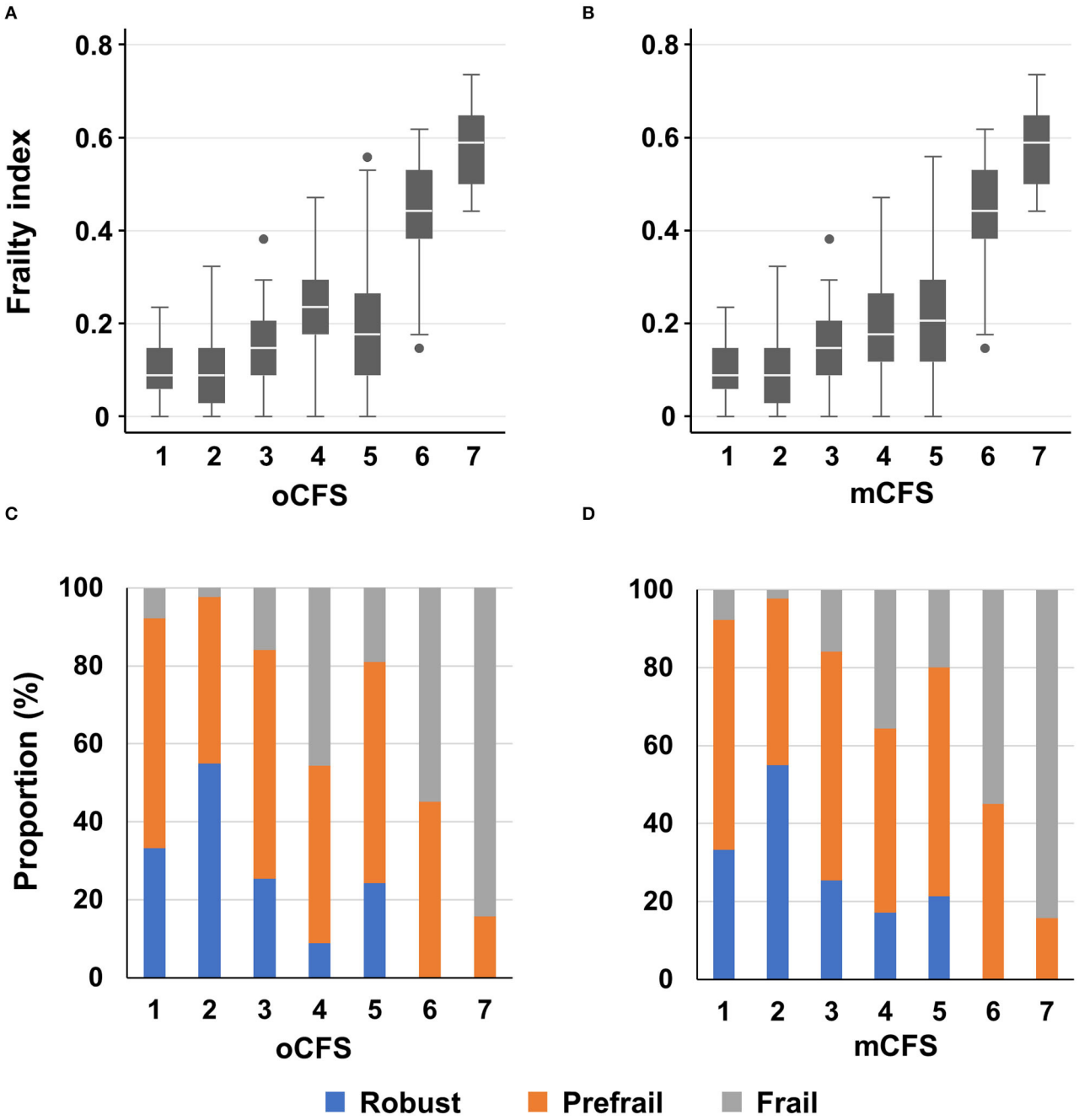

FIGURE 1 | Boxplots for frailty index according to clinical frailty scale scores, by original classification tree [oCFS, **(A)**] and culturally modified classification tree [mCFS, **(B)]**, and bar plots showing the prevalence of the Cardiovascular Health Study frailty phenotype categories according to oCFS **(C)** and mCFS **(D)**; In the box plot, the upper, mid, and lower lines denote 75th, 50th, and 25th percentiles and upper and lower margin of whiskers denote ± 1.5 interquartile range from the 50th percentile. Data outside the ± 1.5 interquartile range from the 50th percentile are shown as outliers.

with the frailty index and had comparable prediction ability for outcomes of mortality and institutionalization (16). Hence, the validity of the CFS from the classification tree is predictable because of its high agreement with the CFS by the geriatricians (21). Even though the CFS directly measured by the geriatricians were unavailable, the CFSs determined from the CGA records correlated with both the frailty index and CHS frailty phenotype, supporting convergent validity of the classification tree.

For mCFS, we did not consider the presence of dependency in IADL items of household chores and preparing meals as sufficient to classify as CFS 5 in men. Controversies existed in interpreting care needs in IADL items in the older Asian populations in

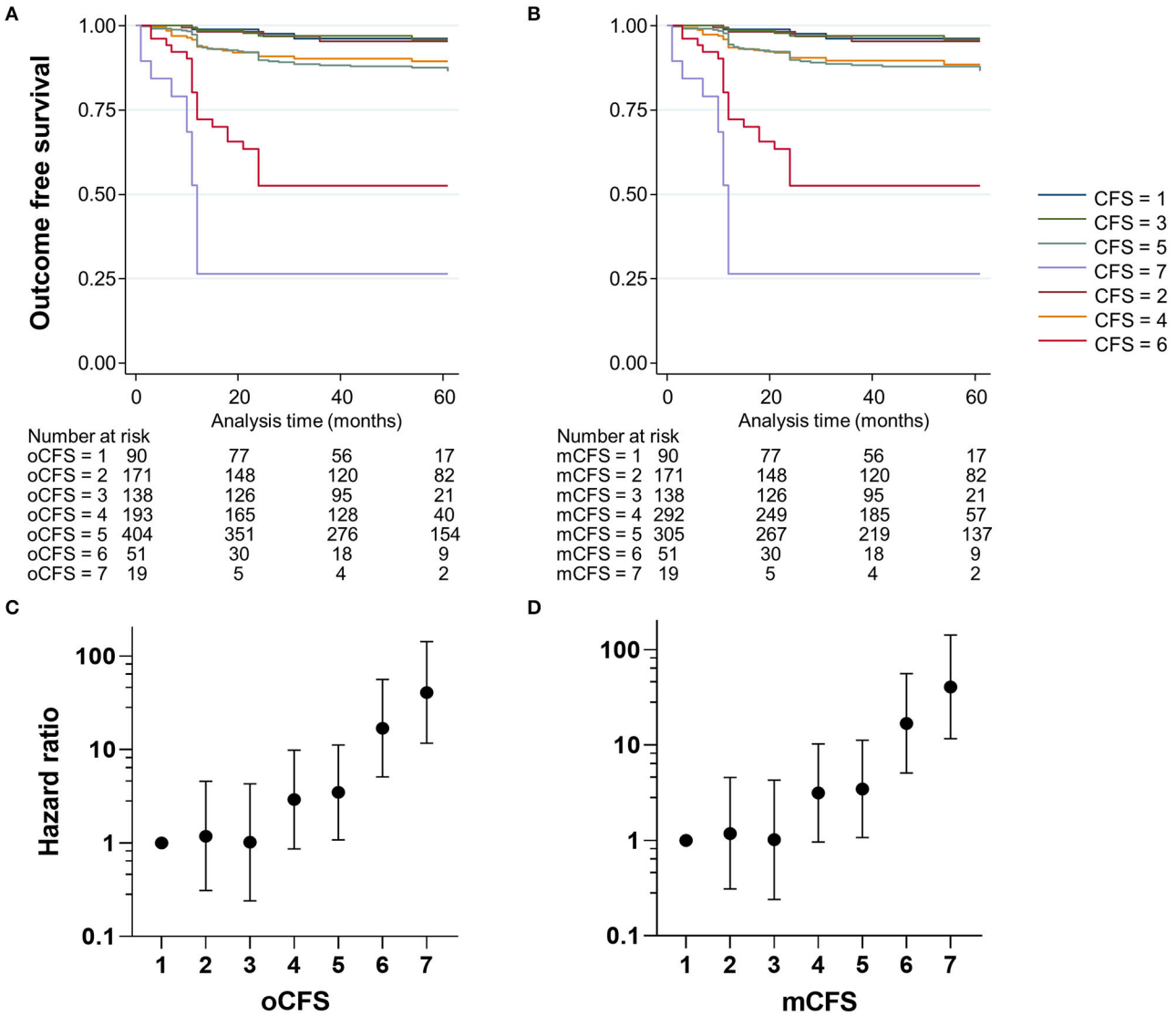

FIGURE 2 | Kaplan–Meier plots showing the incidence of the composite outcome according to clinical frailty scale scores, by original classification tree [oCFS, **(A)**] and culturally modified classification tree [mCFS, **(B)**], and plots showing hazard ratios (dots) and 95% confidence ratio (whiskers) of the composite outcome by oCFS **(C)** and mCFS **(D)**.

geriatrics and gerontology research (26, 33), as traditionally, household work was largely performed by women in the region. In a Korean study on gender differences of ADL and IADL items, men were more likely to rate themselves as dependent in household activities, such as preparing meals and doing laundry (26). A similar gender bias was noted in a Singaporean study, reporting high dependency in preparing meals, doing laundry, and taking medication in men (34). Despite the relevance of these items in the clinical construct of IADL disability being difficult to conclude, we observed that the convergent validity of the CFS was better when dependencies in household items were interpreted leniently (mCFS) than strictly (oCFS) in men. Furthermore, the frailty index of men reclassified from CFS 5 to CFS 4 by the 'cultural modification' was lower than the population who remained at CFS 5. These findings support the potential cultural impact has on defining the construct of disability and frailty, calling for research on this topic as many Asian countries are experiencing rapid population aging and the need to establish social support systems for their aging population (2).

There was no significant difference between mCFS and oCFA in predicting the composite outcome of death and institutionalization. As HRs of CFS 4 and CFS 5 for both classifications were relatively similar, the effect of the reclassification would be minimal in prediction ability for the outcome. As we merged the two outcomes of death and institutionalization into a composite outcome in this analysis, given limitations in sample size and observation period, we could not dissect the impact of IADL interpretation on mortality and

TABLE 2 | Increased risk of composite outcome according to Clinical Frailty Scale scores, by original classification tree (oCFS) and culturally modified classification tree (mCFS).

	Model 1		Model 2		Model 3	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
oCFS (by 1 increment)	2.08	1.75–2.47	1.64	1.38–1.95	1.59	1.34–1.90
Age (by 1-year increment)			1.11	1.08–1.14	1.11	1.09–1.14
Sex (ref, male)			0.63	0.44–0.91	0.57	0.39–0.83
Number of chronic conditions (by 1 increment)					1.19	1.01–1.40
mCFS (by 1 increment)	2.04	1.74–2.41	1.63	1.37–1.93	1.58	1.33–1.87
Age (by 1-year increment)			1.11	1.08–1.14	1.11	1.08–1.14
Sex (ref, male)			0.58	0.41–0.84	0.53	0.36–0.77
Number of chronic conditions (by 1 increment)					1.20	1.02–1.41

Model 1: crude model; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, and number of chronic conditions.
CI, confidence interval; HR, hazard ratio.

functional decline. The minimal outcome differences between CFS 4 and CFS 5 might be due to availability of long-term care insurance that provides at-home assistance for community-dwelling older adults with disabilities in IADL items. Yet, the impact of this service on preventing institutionalization of people living with IADL impairment cannot be proven under the current study design (3). However, with survival analysis showing a discrete and decisive increment in outcome risk from CFS 4, the CFS could be used to screen community-dwelling older adults at risk of adverse health outcomes.

Evidence supports well-designed multicomponent intervention programs that effectively prevent adverse health outcomes in community-dwelling older adults (12, 35, 36). A recent paper published from Korea, analyzing the long-term outcomes of a 6-month program with a propensity-score-matched control group, showed that both the frailty status and physical performance was better in the intervention group, and the benefit in physical performance remained significant for 2 years after the end of the program (12). Furthermore, the 30-month mean institutionalization-free survival time was longer by 5.2 months in the intervention group than in the comparison group. To scale up these programs with multiple domains in the public health scale for a more extended period, selecting the target population that might benefit maximally from such interventions is necessary. In this regard, early programs may start by focusing on the population of CFS 4–5, considering its prediction ability for institutionalization-free survival. Given the brief nature of the CFS, the burden of finding mass-scale cases might be minimal.

There are several limitations to this study. We used recorded data of the CGA to estimate oCFS and mCFS, rather than prospectively measuring CFS by geriatricians. Nevertheless, as we constructed the CFS from individual items of the CGA, we were able to tag individuals from IADL items; however, recording all relevant IADL items and frailty index parameters might be less feasible in real-world CFS examinations by geriatricians. Generalizability is limited, as we were only able to assess cultural impact in determining the CFS in a community-dwelling population in a rural area in Korea. As noted in the literature, cultural characteristics are rapidly changing with alterations in family and social structures in Asian countries, including China (37). Our data were acquired from a rural area in the mid-2010s, and the results might differ if performed using individuals in an urban area. Also, baseline characteristics of participants with or without IPAQ differed considerably in terms of age, frailty, and other geriatric parameters (**Supplementary Table 3**), which might act as a limitation for generalizability. As the current analysis was from the observational cohort, we could not assess the potential effect of interventions on the CFS, as studies showing the frailty spectrum could be altered by interventions (12). As the ASPRA primarily comprised of community-dwelling, ambulatory participants, we had no CFS 8–9 individuals.

In conclusion, the classification tree of CFS could be culturally adopted in a community-dwelling population in Korea and considered valid in detecting vulnerable population. As such, further studies are warranted to assess the feasibilities and benefits of CFS when performed in the public health scale to screen vulnerable population who might benefit from community-based programs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Asan Medical Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

H-WJ, JB, I-YJ, and EL conceptualized the study and reviewed and edited the manuscript. H-WJ did the formal data analysis.

H-WJ, JB, and I-YJ did the investigation. H-WJ and JB wrote the first draft of the manuscript. H-WJ and I-YJ supervised the study and acquired study funding.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.880511/full#supplementary-material

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Conflict of Interest: H-WJ cofounded Dyphi Inc., a startup company based on sensor technology.

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ORIGINAL RESEARCH
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At-Point Clinical Frailty Scale as a Universal Risk Tool for Older Inpatients in Acute Hospital: A Cohort Study

Hee-Won Jung[1†], Ji Yeon Baek[1†], Young hye Kwon[2], Il-Young Jang[1], Dae Yul Kim[3], Hyouk-Soo Kwon[4], Sun hee Lee[2], Hyun jin Oh[2], Eunju Lee[1] and Younsuck Koh[5*] for the Asan Multidisciplinary Committee for Seniors (AMCS)[‡]*

[1] Division of Geriatrics, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea, [2] Department of Nursing, Asan Medical Center, Seoul, South Korea, [3] Department of Rehabilitation Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea, [4] Department of Internal Medicine, Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea, [5] Department of Pulmonary and Critical Care Medicine, Health Screening and Promotion Center, Asan Medical Center, Seoul, South Korea

Background: While the Clinical Frailty Scale (CFS) has been extensively validated for predicting health outcomes in older adults, the role of the at-point CFS at the time of examination is unclear. We aimed to examine the ability of the at-point CFS for predicting clinical outcomes of older inpatients.

Methods: As a single-center and prospective cohort study, we enrolled 1,016 older adults who were 65 years or older and were admitted to one of 9 medical or surgical units from May 2021 to September 2021. The associations of the at-point CFS with outcomes of falls, delirium, pressure ulcers, 30-day unplanned readmission and/or emergency department (ED) visits, institutionalization, and a composite outcome were analyzed.

Results: In the study population (n = 1,016), 26 patients had incident pressure ulcers, 6 patients had falls, 50 patients experienced delirium, and 13 patients died during hospitalization. Also, 37 patients experienced an ED visit and 22 patients had an unplanned readmission within 30 days after discharge. The composite outcome was 1.7% among patients with the CFS $<$ 5 and 28.5% among patients with the CFS $\geq$ 5. The higher CFS was associated with an increased risk of a fall [odds ratio (OR) 1.74 (1.01–3.01)], pressure ulcers [OR 3.02 (2.15–4.23)], delirium [OR 2.72 (2.13–3.46)], 30-day readmission [OR 1.94 (1.44–2.62)], ED visit [OR 1.81 (1.47–2.23)], death [OR 3.27 (2.02–5.29)], and institutionalization after discharge [OR 1.88 (1.62–2.18)].

Conclusion: The at-point CFS assessed in older inpatients can screen high-risk individuals who might experience adverse geriatric conditions and in-hospital outcomes.

Keywords: Clinical Frailty Scale, adverse health outcomes, in-hospital outcomes, screening tool, older adults

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***Correspondence:**
Hee-Won Jung
dr.ecsta@gmail.com
Younsuck Koh
yskoh@amc.seoul.kr

†These authors have contributed equally to this work and share first authorship
‡List of AMCS members is shown in the Supplementary Material

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INTRODUCTION

Frailty is an age-related condition that is defined as a state of decreased physiological reserve and increased vulnerability to adverse outcomes due to the accumulation of biological aging processes (1, 2). While initially discovered and studied as a clinical construct (3), subsequent research has validated frailty as a biologically relevant measure of aging in humans and animal models, such as mice, rats, and nonhuman primates (4–6). Clinical studies have shown the outcome relevance of frailty in diverse medical or surgical conditions (7, 8) and the clinical consequences of frailty, namely, immobility, functional decline, falls, and cognitive impairment, could be managed and alleviated by appropriately designed interventions (9). There have been numerous frailty assessment tools; however, two types of frailty measurements are dominant: frailty phenotype and frailty index (4). Frailty phenotype emphasizes the importance of physical decline, including five clinical parameters: unintended weight loss, weakness, low physical activity, slow walking speed, and exhaustion. The total counted number of applicable parameters, ranging from 0 to 5, is determined as a frailty score (3). The other concept of defining frailty is the frailty index, which calculates the proportion of deficits among more than 30 age-related parameters having an association with adverse health outcomes (10).

Many older individuals experience hospitalizations as their burden of clinical diseases and subclinical pathologies accumulate with aging. In acute clinical situations, older patients with frailty are more likely to suffer from geriatric syndromes such as delirium and adverse health outcomes after discharge as compared with individuals without frailty (11–13). To minimize adverse clinical outcomes while preserving the functional status of older patients, models of geriatric acute care have been developed and shown to have clinical benefits (14). Also, screening measures of frailty have been studied to identify vulnerable populations who might benefit from person-centered, geriatric-focused care provisions (15–17).

Among many tools for measuring frailty, the Clinical Frailty Scale (CFS) (18), a scale ranging from 1 to 9 with descriptions and pictograms, has been widely used in various clinical settings from the emergency department (ED) to chronic care facilities as a measure of the degree of frailty (13, 18, 19). As the tool summarizes key functional features of a Comprehensive Geriatric Assessment, numerous studies support its construct validity and the clinical relevance of the CFS in aged populations (13). With its simplicity and strong prediction ability for health outcomes, the CFS has been even advocated as a potential triage tool to make decisions such as allocating scarce healthcare resources in case surges of the COVID-19 pandemic in some countries (20), and a prognostic indicator *per se* (21, 22).

In acute medical situations, the functional status may change significantly in a short time. Hence, the CFS is supposed to be applied to assessing the baseline functional status by asking how the person performed 2 weeks ago, before the person became acutely ill (20, 23). In prognosticating patients, a recent article by Rockwood and Theou suggested that the CFS could be used to assess acute severity (20). Given at-point the CFS includes not only baseline functional status, but also an acute decline of inpatients, it is expected to evaluate the health status of patients at the time of presentation. However, the clinical implications of the at-point CFS have not been reported. In acute hospitalization, we hypothesized that the CFS at admission may serve as a measure of the vital sign of older adults and have role in identifying high-risk patients who may experience adverse health outcomes during and after the index hospitalization.

TABLE 1 | Clinical characteristics of the study population.

	CFS < 5 (n = 637)	CFS ≥ 5 (n = 379)	p-value
Age (yr)	71.8 ± 5.1	75.0 ± 7.2	<0.001
Women	215 (33.8%)	200 (52.8%)	<0.001
Admitted through ED	20 (3.1%)	128 (33.8%)	<0.001
Surgical departments	404 (63.4%)	180 (47.5%)	<0.001
BMI (kg/m^2)	24.6 ± 5.6	23.1 ± 3.9	<0.001
Hypertension	301 (47.3%)	223 (58.8%)	<0.001
Diabetes	154 (24.2%)	127 (33.5%)	0.001
Cancer	230 (36.1%)	135 (35.6%)	0.88
Hemoglobin (g/dL)	12.8 ± 1.6	11.4 ± 2.2	<0.001
Albumin (g/dL)	3.9 ± 3.0	3.2 ± 0.7	<0.001
Fall in previous year	48 (7.5%)	109 (28.8%)	<0.001
Incident delirium	1 (0.2%)	49 (13.0%)	<0.001
Incident sore	0 (0.0%)	26 (6.9%)	<0.001
Incident fall	1 (0.2%)	5 (1.3%)	0.03[a]
Length of stay	6.2 ± 4.5	10.4 ± 8.9	<0.001
ED visit in 30 days	9 (1.4%)	38 (10.1%)	<0.001
Unplanned readmission in 30 days	2 (0.3%)	20 (5.3%)	<0.001
In-hospital mortality	1 (0.2%)	12 (3.2%)	<0.001
Composite outcome	11 (1.7%)	108 (28.5%)	<0.001
Discharge to chronic care facilities	39 (6.2%)[b]	75 (20.7%)[b]	<0.001

[a] *Fisher's exact test.*
[b] *Data available in 632 individuals with CFS <5 and 363 with CFS ≥5.*
BMI, body mass index; ED, emergency department.

METHODS

Study Design, Setting, and Population

This study was a prospective cohort study from Asan Medical Center, a tertiary teaching hospital in Seoul, Korea. From May 2021, a multidisciplinary team started to measure the CFS in 9 acute inpatient units encompassing 24 medical and surgical specialties/subspecialties, as one part of our activities to develop an age-friendly health system, which was proposed by The

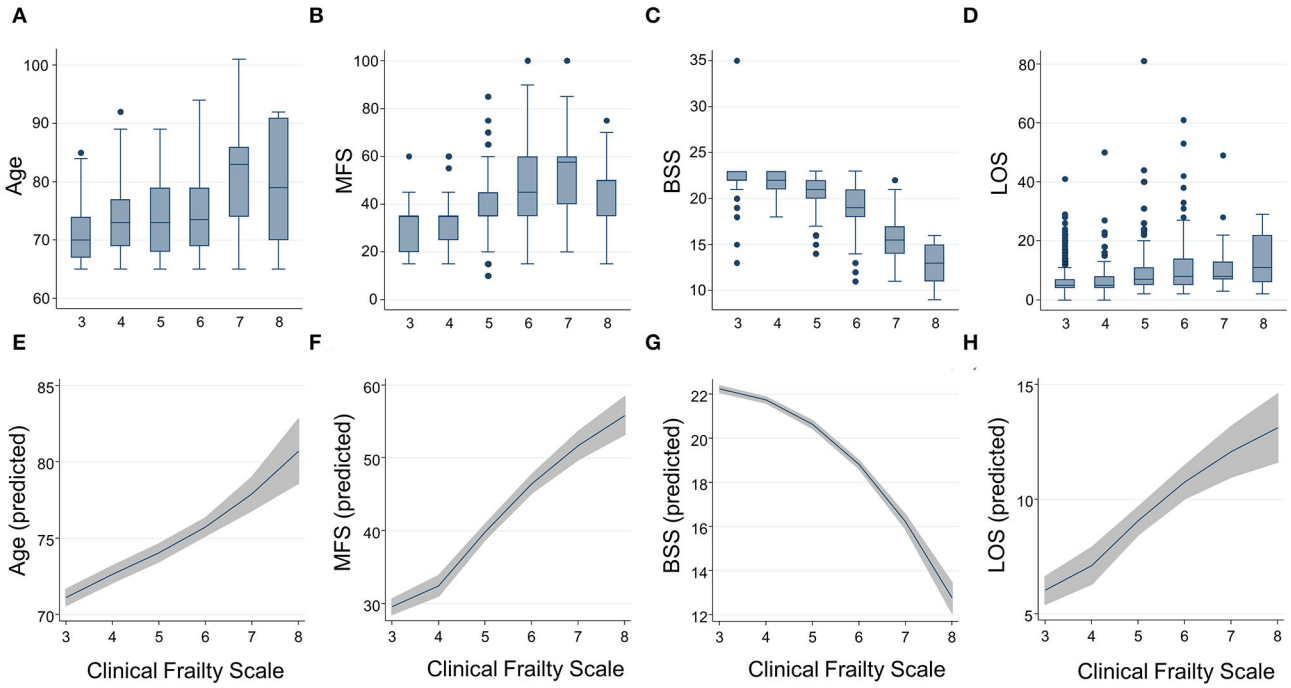

FIGURE 1 | Distributions by box and whisker plots and predicted means by fractional polynomial plots with 95% CIs for age **(A,E)**, the Morse Fall Scale **(B,F)**, the Braden Sore Scale **(C,G)**, and length of stay **(D,H)** according to the Clinical Frailty Scale. BSS, Braden Sore Scale; LOS, length of stay; MFS, Morse Fall Scale.

John A Hartford Foundation and the Institute for Healthcare Improvement (IHI) for establishing evidence-based high-quality care for older adults throughout the hospital. All the older inpatients aged 65 years or older in these 9 units were screened by a geriatric nurse specialist. A geriatric nurse visited these units and measured the CFS and patient-specific needs in domains of "What matters," "Medication," "Mentation," and "Mobility," as part of a process of developing care pathways to link these needs with resources from Monday to Friday (8 a.m. to 6 p.m.). For these assessments, we included patients admitted through both the outpatient clinic and the ED and the geriatric nurse specialist visited patients on the morning of the day after admission. We included patients 65 years or older admitted to these units from May to September 2021 for this study. The exclusion criteria were patients who needed to be quarantined because of infection issues, received radiation therapy within 24 h, and went through discharge within 24 h. As all the measures were conducted by a single nurse, patients admitted on Saturday were also excluded. The average number of enrolled inpatients in a day was about 15–20. This study protocol was reviewed and approved by the Institutional Review Board of Asan Medical Center (Approval Number: 2021-1523). The written informed consent was waived, as evaluating the general health status of patients at admission is a routine procedure, and no additional harm was expected. To best reflect the real-world settings embracing a wide range of clinical circumstances, as we are aiming to develop an acute electronic frailty pathway, including the entire hospital, there were no exclusion criteria for applying the CFS.

At-Point the Clinical Frailty Scale

The CFS was measured once on the day afterward admission by a trained geriatric nurse specialist who had completed a 2-year geriatric nurse specialist course and >10 years of experience in clinical units of rehabilitation medicine, neurology, and geriatrics, participated in the process of Korean translation, and adoption of the CFS 2.0 in the institution. We used the Korean-translated version of the CFS 2.0 that has had its construct validity established in Korean geriatric outpatients (24) and its accuracy for predicting adverse outcomes in hospitalized older medical patients was demonstrated (12). For consistent scoring of the CFS, we measured the CFS by using the classification tree (25). Patients' activity of daily living, the instrumental activity of daily living, and self-rated health status were investigated by a geriatric nurse. While the original CFS was intended to be used to assess the baseline functional status before acute medical deterioration, we used the at-point CFS, which combines both the baseline functional status and acute deterioration and presents the current functional state of the persons in this study. From prior observations, we considered the CFS scores $\geq$ 5 to indicate frailty (12, 13). For patients who are unable to communicate due to altered mental status or cognitive problems, functional status was assessed by interviewing their direct caregivers in person or over the phone.

Clinical Parameters

Demographic factors and the pathway of admission (ED vs. outpatient clinics) were recorded. Vital signs on the

TABLE 2 | Associations between an increasing burden (1 point higher) of frailty by the Clinical Frailty Scale and the risk of geriatric conditions and hospital outcomes by the logistic regression analyses.

	OR (unadjusted)	OR (age, sex-adjusted)
Risk of geriatric conditions		
Fall risk by MFS (MFS ≥45)	3.58 (3.03–4.24)	3.36 (2.83–4.00)
Fall incidence	1.74 (1.01–3.01)	**1.39 (0.74–2.60)**
Pressure ulcer risk by BSS (BSS ≤18)	5.14 (3.96–6.68)	4.88 (3.74–6.37)
Pressure ulcer incidence	3.02 (2.15–4.23)	2.77 (1.94–3.96)
Delirium incidence	2.72 (2.13–3.46)	2.56 (1.98–3.31)
Hospital outcomes		
Length of stay 14 days or longer	1.77 (1.54–2.03)	1.87 (1.61–2.18)
ED visit in 30 days	1.81 (1.47–2.23)	1.96 (1.56–2.45)
Unplanned readmission in 30 days	1.94 (1.44–2.62)	1.99 (1.44–2.76)
In-hospital mortality	3.27 (2.02–5.29)	3.20 (1.94–5.30)
Composite outcome	2.63 (2.22–3.12)	2.54 (2.12–3.03)
Discharge to chronic care facilities	1.88 (1.62–2.18)	1.91 (1.63–2.24)

BSS, Braden Sore Scale; MFS, Morse Fall Scale; OR, Odds ratio.
Statistically insignificant result is highlighted in bold font.

morning of the day of the assessments were recorded. From the medical records, clinical diagnoses of angina, arthritis, asthma, cancer, chronic lung disease, congestive heart failure, dementia, depression, diabetes, myocardial infarction, hypertension, chronic kidney disease, spine problems, and stroke were reviewed. The risk of falls and pressure ulcers were assessed by the Morse Fall Scale (MFS) and the Braden Sore Scale (BSS) that were applied by the nursing staff on the day of examination (26, 27). For clinical laboratory parameters, we used hemoglobin and serum albumin levels taken at the admission date.

Outcome Measures

By medical record review, we assessed the incidence of new pressure ulcers, delirium, and in-hospital death. Delirium was detected by medical review, as the presence of either clinical remark, nursing diagnosis, or consultation to psychiatry or geriatrics due to clinical suspicion of delirium. Fall incidence was acquired from the fall reports that are mandatory for every fall event throughout the hospital. Length of stay (LOS) was recorded. We defined a long hospital stay as a LOS of 14 days or longer. Unplanned ED visits and readmission within 30 days after discharge were reviewed. The location of discharge was assessed by medical review. We defined a composite outcome, including events of new bed sores, delirium, falls, in-hospital death, 30-day unplanned readmission, or an ED visit.

Statistical Analysis

For sample size, we used a previous report using the CFS in older inpatients of a Korean acute medical unit (12) that reported in-hospital mortality of 1.3 and 4.6% in patients with the CFS $<$ 5 (54.9% of total population) and the CFS $\geq$ 5 (45.1% of total population), respectively. With alpha of 0.05 and beta of 0.80, the total sample size of 814 was required. We aimed to collect records of 1,016 patients, with a safe margin of 20%. We used the *t*-tests for continuous variables and the chi-square tests or the Fisher's exact test for categorical variables to compare clinical characteristics between individuals with the CFS $<$ 5 and the CFS $\geq$ 5. To assess the correlation of the CFS with the MFS and the BSS, we used a 95% CI fractional polynomial plot for visualization and linear regression analysis with the calculation of the standardized beta (B). The association between the CFS and dichotomized outcomes, namely, falls, new pressure ulcers, delirium, death, length of stay 14 days or longer, 30-day ED visit, readmission, the composite outcome (falls, new pressure ulcers, delirium, death, 30-day ED visit, and readmission), and discharge to a chronic care facility, was assessed by logistic analyses (unadjusted and adjusted models with covariables of age and sex). To evaluate the prediction ability for falls and new pressure ulcers, we performed the receiver operating characteristic (ROC) analyses with the CFS as a classifier and these outcomes as references. Sensitivities and specificities for each CFS score and C-statistics predicting the outcomes were calculated. We considered two-sided *p*-values $<$ 0.05 as statistically significant. Stata version 15.0 was used for the analysis (Stata Corporation, College Station, Texas, USA).

RESULTS

Clinical Characteristics

Among 1,016 patients with a mean age of 73.0 years (SD 6.2) and 415 (40.9%) women, 329 (37.3%) patients had the CFS of 5 or higher. Specifically, 461 (45.4), 176 (17.3), 170 (16.7), 154 (15.2), 44 (4.3), and 11 (1.1%) individuals had the CFS score of 3–8, respectively. The clinical characteristics of patients with the CFS $<$ 5 or $\geq$ 5 are shown in **Table 1**. Individuals with the CFS $\geq$ 5 were older, more likely to be women, admitted through the ED, and had a higher burden of comorbidities such as hypertension or diabetes. Their hemoglobin and albumin levels were lower and experiences of falls in the previous year were higher in the frail population. During the hospitalized period, the probabilities of delirium, pressure ulcers, and falls were all higher in the frail group. Also, the length of stay for the index admission, the likelihood of experiencing an unplanned ED visit, readmission within 30 days after discharge, and in-hospital mortality were higher in the frail group. The CFS correlated with chronological age ($B = 0.342$, $R^2 = 0.117$, $p < 0.001$, **Figures 1A,E**) and was higher ($p < 0.001$ by *t*-tests) in women (mean $\pm$ 4.48, SD $\pm$ 1.34) than that in men (mean $\pm$ 3.99, SD $\pm$ 1.27).

At-Point the Clinical Frailty Scale as a Geriatric Risk Indicator

The CFS correlated with the MFS ($B = 0.538$, $R^2 = 0.289$, $p < 0.001$) and the BSS ($B = 0.572$, $R^2 = 0.328$, $p <$

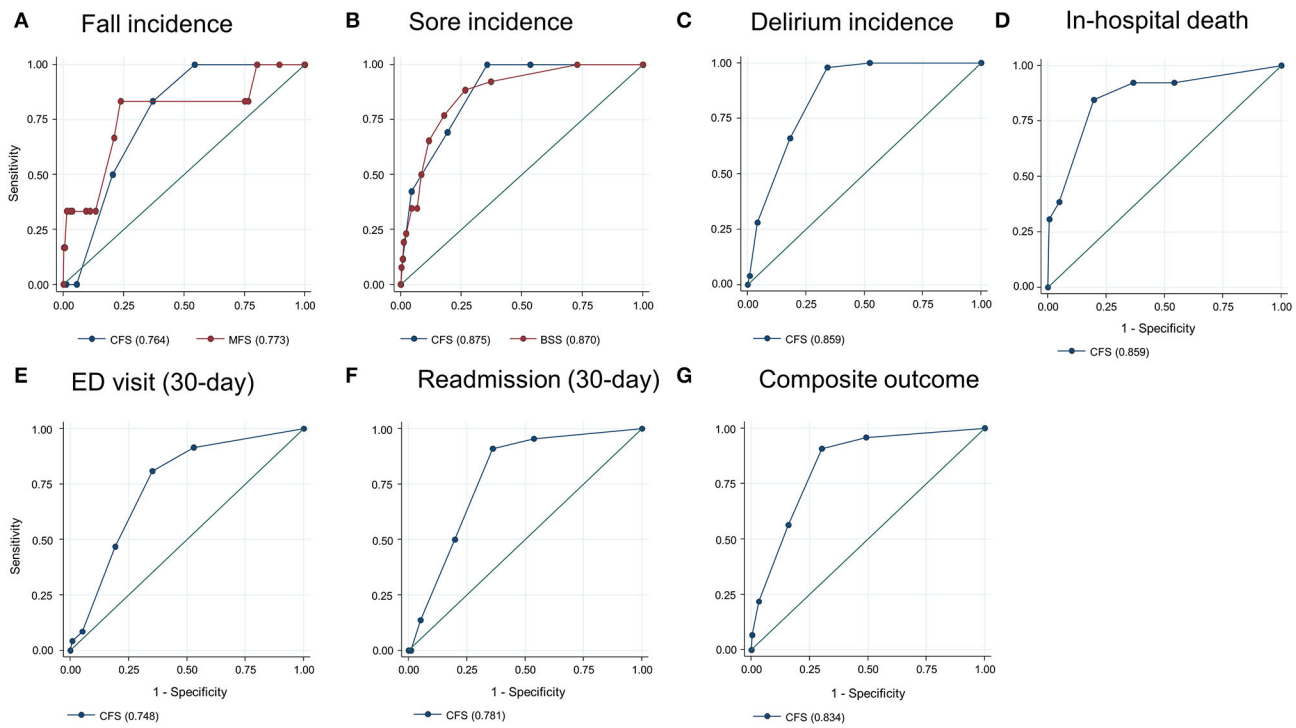

FIGURE 2 | Prediction ability of the Clinical Frailty Scale (CFS) for fall incidence [**(A)**, compared with the Morse Fall Scale (MFS)], sore incidence [**(B)**, compared with the Braden Sore Scale (BSS)], delirium incidence **(C)**, in-hospital mortality **(D)**, 30-day emergency department (ED) visit **(E)**, unplanned 30-day readmission **(F)**, and composite outcome **(G)**. Numbers in parentheses denote the area under the curve.

0.001), as the trends shown in **Figures 1B,C,F,G**. A higher frailty burden estimated by the CFS was associated with increased odds for risks of falls and pressure ulcers as determined by the MFS and BSS (**Table 2**). C-statistics of the CFS to classify the fall risk (MFS $\geq$ 45) and pressure ulcer risk (BSS $\leq$ 18) were 0.884 (95% CI 0.863–0.905) and 0.907 (95% CI 0.880–0.934). A cutoff of the CFS $\geq$ 5 maximized the sensitivity + specificity of classifying the fall risk (sensitivity 88.9% and specificity 76.6%) and pressure ulcer risk (sensitivity 95.5% and specificity 71.4%). Sensitivities and specificities for the individual CFS scores are shown in **Supplementary Table 1**.

The total observation time for the incidence of falls and pressure ulcers in this study was 7,885 patients × day. There were 26 incident pressure ulcers, 6 falls (including 1 injurious fall), and 50 patients who experienced delirium during the index hospitalization. A higher frailty burden by the CFS was associated with an increased risk of the incidences of falls, pressure ulcers, and delirium during hospitalization (**Table 2**), even though the significant association between the CFS and fall incidence was attenuated after adjusting for age and sex. Only 1 patient (CFS 4) below the CFS 5 experienced a fall, which was noninjurious. The prediction ability of the CFS for falls (C-statistic 0.764, 95% CI 0.655–0.872) did not significantly differ from that of the MFS (C-statistic 0.773, 95% CI 0.543–1.000) (**Figure 2A**). The CFS predicted pressure ulcers incidence (C-statistic 0.885, 95% CI 0.831–0.919) was similar to that of the BSS (C-statistic 0.870, 95% CI 0.811–0.928) (**Figure 2B**). The CFS was able to predict the incidence of delirium (C-statistic 0.859, 95% CI 0.827–0.892) (**Figure 2C**). The sensitivities and specificities for the individual CFS scores predicting these outcomes are also shown in **Supplementary Table 1**.

Hospital Outcomes

In the study population, 13 patients died during hospitalization, 37 patients experienced an ED visit, and 22 patients had an unplanned readmission within 30 days after discharge. The mean LOS was 7.8 (SD 6.8) days. Patients with the higher CFS tend to stay longer during the index hospitalization (**Figures 1D,H**), as the CFS was correlated with the LOS ($B = 0.295$, $R^2 = 0.087$, $p < 0.001$). The higher CFS was associated with a longer hospital stay, 30-day ED visit, unplanned readmission, and in-hospital death either by unadjusted or age- and sex-adjusted logistic regression analyses (**Table 2**). The CFS was able to predict in-hospital mortality (C-statistic 0.859, 95% CI 0.747–0.972), 30-day ED visit (C-statistic 0.748, 95% CI 0.689–0.806), and unplanned readmission (C-statistic 0.781, 95% CI 0.710–0.852) (**Figures 2D–F**). As shown in **Table 2**, the CFS was associated with the composite outcome (falls, new pressure ulcers, delirium, readmission in 30 days, death, and 30-day ED visits) and the C-statistic was 0.834 (95% CI 0.801–0.866) (**Figure 2G**). Sensitivities and specificities for the individual CFS scores predicting these outcomes are shown in **Supplementary Table 2**. After excluding

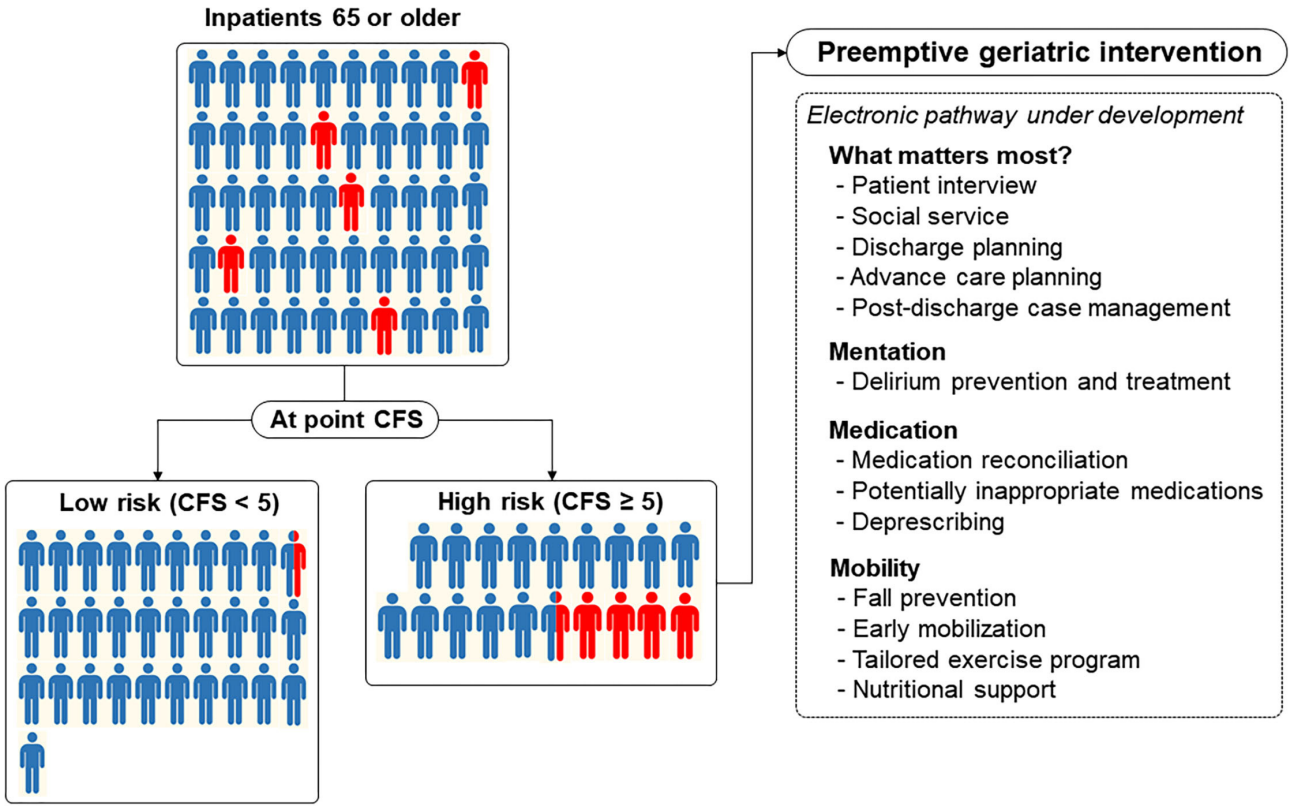

FIGURE 3 | Acute electronic frailty pathway under development using the Clinical Frailty Scale (CFS) as a universal risk indicator for older inpatients to provide a preemptive geriatric intervention encompassing domains of an age-friendly health system. In this figure, a red-colored human denotes a person (1 person denotes 2% incidence) who developed the composite outcome and is shown to reflect the distribution of the CFS and prevalence of the composite outcome in our study.

individuals deceased or transferred to other acute facilities, 881 individuals were discharged to homes and 114 individuals were discharged to chronic care facilities. The higher CFS scores were associated with institutionalization in chronic care facilities after discharge (**Table 2**).

DISCUSSION

In this study, we found that the at-point CFS, capturing the functional state of patients at the time of examination within 24 h after acute admission, could predict both the geriatric outcomes (falls, pressure ulcers, and delirium) and hospital outcomes (death, 30-day ED visit, and 30-day readmission). Also, the prediction ability of the CFS for falls and pressure ulcers was similar to existing scales such as the MFS and the BSS. To the authors' knowledge, this study is the first study to show the potential role of the CFS in acute hospitalization as a measure of geriatric conditions, especially for falls. In contrast to the widespread perception that the CFS should be assessed by evaluating the patient's functional status before the acute deterioration, we observed that the at-point CFS was valid as a risk indicator.

The at-point CFS may detect different clinical constructs of older inpatients than the baseline CFS, which measures global fitness as a reflection of functional deficits accumulated due to aging. In the at-point CFS, baseline functional status and acute deterioration are combined and this measure is sensitive to the rapidly changing clinical course of inpatients in an acute care setting; hence, it is more like a functional vital sign rather than a stable indicator of baseline frailty. Our observation of the good performance of the at-point CFS in predicting various outcomes might be due to this characteristic, as this tool encompasses both the baseline frailty and disease severity. Indeed, our study was in accordance with prior observation with the baseline CFS for inpatients, albeit with a trend of the higher area under the curve value in predicting adverse outcomes even though the direct comparison is not possible considering population characteristics (28). As geriatric conditions such as delirium, falls, and pressure ulcers are consequences of a combination of frailty and disease severity, the at-point CFS might be especially useful as a universal predictor of these outcomes.

Traditionally, the risks of geriatric conditions such as falls, pressure ulcers, and delirium in hospitalized patients have been assessed using tools for the separate conditions (26, 27, 29–31). However, in this prospective population of a large acute hospital, we observed that the at-point CFS could predict various geriatric conditions with no statistically significant differences in prediction ability compared to

condition-specific measures such as the MFS or the BSS. Furthermore, the at-point CFS showed construct validity, including convergence validity and criterion validity, for classifying high-risk patients when directly compared with the MFS and the BSS. Based on this evidence and the obvious simplicity of using the CFS when compared to using a combination of the MFS and the BFS, the at-point CFS might be used as a universal measure to screen high-risk populations who may experience an adverse clinical course, including geriatric syndromes.

In large hospitals, performing full geriatric assessment on all the older patients is less feasible. This advantage of the at-point CFS might be leveraged as a case-finding solution for a vulnerable older adult who needs more geriatric attention to prevent adverse outcomes. From this approach, we may maximize both the efficiency and efficacy of adopting the concept of geriatric intervention in a large, acute hospital. One example is our hospital, which is in the process of establishing an acute pathway for older adults by adopting the 4M framework of matter, mentation, medication, and mobility with the Plan-Do-Study-Act (PDSA) cycles (32). As the largest tertiary hospital in Korea with 2,715 beds, one of the most challenging steps in developing a clinical pathway in the hospital would be expanding a standardized way of case finding and care provision while achieving maximal efficiency. In the first step of scaling up with limited resources, screening geriatric risks with separate tools for each condition in all the older inpatients would be less feasible. Based on our findings, we are planning to focus on older adults with the CFS $\geq$ 5 to provide preemptive, person-centered geriatric interventions on 4M domains through an electronic frailty pathway (**Figure 3**). To enhance the scalability and efficiency of coordination, pathways embedded in the electronic health records using the CFS measured daily and a 4M framework aiming to provide geriatric care similar to the Acute Care for Elders (ACE) model throughout the hospital are under development (14).

Even though the at-point CFS showed validity in predicting the fall risk in this population, an association between the CFS and fall incidence was attenuated when adjusted for age and sex. This might be potentially affected by the type II error due to the low actual number of fall incidences (6 falls in 7,885 patients $\times$ day). Underreporting falls is unlikely, since we use the mandatory hospital administration data that monitors every falls throughout the hospital. The incidence of falls in our data is consistent with prior reports from large hospitals in Korea (33).

There are several limitations to this study. As we did not measure the baseline CFS of patients before their acute clinical conditions, we could not dissect the "acute factor" from the at-point CFS that we measured. Also, as we measured the CFS only once at the baseline, the dynamic nature of the at-point CFS during the clinical course could not be evaluated in this study. Statistical uncertainty might exist as the incidence of delirium that was collected from medical record review and, hence, might be affected by underreporting of hypoactive or mixed delirium. Generalizability is limited, since our study was performed in a prospective cohort in a single institution and some patients admitted on Saturday were excluded due to our shortage of manpower. The performance of the at-point CFS as a universal risk indicator in acute inpatients should be confirmed in different populations or settings.

In conclusion, the at-point CFS assessed in older inpatients can screen high-risk individuals who may experience adverse geriatric conditions and hospital outcomes during their clinical course. This measure may serve as a universal risk indicator with the characteristics of a functional vital sign and it can be used to select an eligible population who may benefit from person-centered geriatric interventions in acute hospitals.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Asan Medical Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

H-WJ, JB, I-YJ, EL, and YK conceptualized the study and reviewed and edited the manuscript. H-WJ conducted the formal data analysis. H-WJ, JB, YhK, DK, H-SK, SL, HO, EL, and YK conducted the investigation. H-WJ and JB wrote the first draft of the manuscript. H-WJ, I-YJ, and YK supervised the study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.929555/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Perceived Social Support and Associated Factors Among Community-Dwelling Older Adults With Frailty and Pre-frailty in Hangzhou, China

Juan Fang†, Jianping Ren†, Lixian Ren, Xiantao Qiu, Shuang Yuan, Wenting Wang and Jinjing Wang*

Department of Health Management, School of Public Health, Hangzhou Normal University, Hangzhou, China

Objectives: The present study aimed to explore the social support among community-dwelling older adults with frailty and pre-frailty and to ascertain associated factors.

Methods: The frailty status of the participant was assessed *via* the Chinese FRAIL Scale. The dependent variable, level of social support, was evaluated using the Social Support Rating Scale (range: 12–66). This study explored the influencing factors from three aspects containing sociodemographic characteristics, family environment, and community environment. Independent-sample *t*-test, Analysis of Variance, and multiple linear regression analyses were conducted to examine determinants of social support.

Results: There were significant differences in overall social support between non-frail, pre-frail, and frail participants [38.01 (SD = 6.48) vs. 33.62 (SD = 6.25) vs. 30.50 (SD = 6.68), $F = 62.157$, $p < 0.001$]. Older adults with frailty and pre-frailty who were single would have lower levels of overall social support. In the pre-frail group, living alone was associated with lower overall social support. In contrast, the relationship with children and the availability of recreational activities were associated factors for the frail group.

Conclusions: The level of social support among frail and pre-frail community-dwelling older adults was lower than the robust older adults and influenced by different factors according to the frailty category, which suggests taking targeted measures for social support improvement.

Keywords: aged, frailty, pre-frailty, social, support

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Tan Tock Seng Hospital, Singapore

Reviewed by:
Elena Vladimirovna Frolova,
North Western State Medical University, Russia
Jun Pei Lim,
Tan Tock Seng Hospital, Singapore

***Correspondence:**
Jianping Ren
jpren2016@163.com

†These authors have contributed equally to this work

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INTRODUCTION

Frailty, a significant public health issue (1), is a multisystem age-related syndrome with an individual's increased vulnerability to adverse health outcomes when exposed to stressors due to declined physiological reserve (2–4). Pre-frailty is a dynamic syndrome, a transitional and potentially reversible risk state before the onset of frailty, including four subtypes: physical, social, cognitive, and nutritional (5). Physical frailty, described as pre-disability (6), is mainly characterized by three or more of five components: weakness, slowness, shrinking, exhaustion, and low physical activity, according to Fried et al. (2). Physical pre-frailty is linked with alterations in physiology

and pathophysiology (5) and is also commonly identified by the Fried Frailty Phenotype with one or two of the above components (2). Community-dwelling older adults are prone to developing frailty, and the incidence of frailty was significantly higher in pre-frail individuals than in robust individuals (7). Frail and pre-frail older adults frequently use primary and hospital care (8). Improving prognosis and preventing deterioration from a pre-frail to frail status is vital to promote healthier aging and reduce the burden on health systems (9).

Social support is the perception and actuality that one is cared for by others, which is meaningful and will provide care for frail people (10). Previous studies have demonstrated associations between social support and frailty (11–13). A study from the USA found that, for older adults who were already frail, increased social support was related to less-steep increases in frailty (13). Social isolation accompanying aging accelerates frailty and worsens chronic health issues (14). Lack of social support is one of the various pathophysiologic mechanisms for the development of frailty (12). Several underlying pathways of social support on frailty have been explored (15, 16). One is the physiological pathway, in which social support could prevent the worsening of frailty by reducing the disease burden. Another study elucidated the psychological and behavioral health pathway (16). On one hand, social support could delay the deterioration of frailty by decreasing depressive symptoms (16). On the other hand, older adults with higher-level social support may be more motivated to participate in physical activity (17), which is a cornerstone for preventing and even reversing frailty (16, 18). Correspondingly, according to the socio-ecological theory, we speculated that many older persons might be frailer without enough individual-, family- and community-level support.

Social support is a protective factor for both frailty and pre-frailty (19), which was also elucidated in a previous study conducted in China (16). All persons with frailty should receive social support to address unmet needs and encourage adherence to a Comprehensive Management Plan (6). Given that there has been a worldwide increase in the frail population (20–22), it is necessary to explore possible associated factors related to social support in older adults with frailty, and it is urgent to establish and implement social support strategies among older people. Based on previous studies (23, 24), social support was associated with older adults' sociodemographic characteristics, including city, age, living conditions, marital status, and self-rated health. In the present research, we hypothesize it would also be related to family and community environments, which have been underexplored. The purpose of this study was to explore such associations among the community-dwelling older adults in Hangzhou of Zhejiang Province, China, and to provide scientific evidence for policymakers to improve the level of social support for older people with frailty and pre-frailty.

METHODS

Participants and Procedure

A community-based cross-sectional survey was undertaken from July 2021 to September 2021 in Hangzhou City, Zhejiang Province, China. Participants were recruited *via* the method of multi-stage typical sampling. Firstly, three administrative districts (Xihu District, Gongshu District, Shangcheng District) were selected among 10 districts in Hangzhou according to geographical locations and economic development. Secondly, three community healthcare centers of sub-districts were chosen from each district, with nine community healthcare centers chosen eventually.

All adults aged 60 years and over who were in the community healthcare center and could communicate in Chinese were invited to participate in the investigation. Respondents were excluded if they met one of the following criteria: (1) with cognitive impairment; (2) with hearing or visual impairment that might hinder communication; (3) with aphasia; or (4) being unwilling to complete the investigation owing to various reasons.

The sample size was estimated by the calculation formula of the single sample mean, with social support assessed by the same measure was 32.76 ± 6.06 among older adults in Anhui Province (10), with a margin of error of 1. The rejection rate of 30% was also considered. We aimed to recruit a minimum of 202 participants. Finally, 600 older adults who visited the community healthcare centers were invited to participate, and 57 declined. Hence, 543 older adults were investigated face-to-face by four trained investigators. During the survey, investigators highlighted the nature of the study and ensured the anonymity of data collection. For the participants who completed the questionnaire by themselves, investigators explained the use of the questionnaire and answered questions about the ambiguous items if necessary. For the others, researchers filled in questionnaires based on their responses. There were no missing data due to investigators checking questionnaires on the spot.

Measures

Frailty

The frailty status of the older adults was assessed *via* the FRAIL (Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight) Scale, which contains five self-report indicators with dichotomous responses: fatigue, resistance, ambulation, illness, and loss of weight (25). It is a purely self-report physical dimensional scale and has been culturally adapted and validated in China (26). The scores range from 0 to 5, with a score of 0 representing robust, 1–2 for pre-frail, and 3–5 for frail in the original version (25), while a score of 1 representing pre-frailty and 2–5 for frailty in Chinese version (26). The Chinese FRAIL scale had high reliability and validity in Chinese community-dwelling older adults (26).

Social Support

Social support was measured by the Social Support Rating Scale (SSRS) (27), which was developed and used mostly in China with excellent reliability and validity among the older adults (28). It contains ten items with three dimensions: subjective support (4 items and ranges from 8 to 32), objective support (3 items and ranges from 1 to 22), and support utilization (3 items and ranges from 3 to 12). The scale's total score ranges from 12 to 66, with higher scores signifying greater social support. Subjective support refers to an individual's emotional experience and satisfaction degree of being respected, supported, and understood in society.

Objective support refers to visible or practical support, including direct material assistance and the presence and participation of social networks and group relationships. Support utilization refers to the degree of involvement in social activities, as well as the frequency and extent of seeking social support when encountering adverse events.

Sociodemographic Characteristics

The sociodemographic characteristics included gender, age, marital status (married/single), educational level (uneducated/ elementary school/ junior high school/senior high school/college or above), monthly income [Q1 (<$300), Q2 ($ 300–600), Q3 ($ 601–1051), Q4 (≥$1052)].

The Environment of Family and Community

The factors regarding the family situation are as follows: the number of children (≤1/≥2), living alone (yes/no), financial support from children (yes/no), moral support from children (yes/no), relationship with children (poor/fair/good), company of children (rarely/sometimes/often).

The second part is about the community environment, containing medical institutions accessible in 15 min (yes/no), sports fields accessible in 15 min (yes/no), nursing homes accessible in 15 min (yes/no), the management of community (bad/fair/good), availability of recreational activities (sports, music, arts, et al.) and health education (yes/no).

All the measures for sociodemographic characteristics, the environment of family, and the environment of the community were selected and modified according to a previous study in China (29) and expert consultation. A pilot test with 30 older adults—half male, half female- at one community healthcare center by convenience sampling in June 2021, including 10 in the age group of 60–69, 10 in the age group of 70–79, and 10 in the age group of 80–89. Some adjustments were made to respondents' unclear items during the pilot test.

Ethical Considerations

This study was approved by the Ethics Committee of the School of Public Health, Hangzhou Normal University (Number: 20210012). All the participants signed an informed consent statement before participation and were notified that they were free to accept or reject the invitation to participate in the investigation.

Data Analysis

This study used the Statistical Package for the Social Sciences version 22.0 for data analysis. Independent-samples *t*-test or Analysis of Variance (ANOVA) was performed to preliminarily examine the associations between study variables and social support, including three dimensions and the overall social support. To further identify contributing factors of social support, multiple linear regression analyses with social support regarded as the dependent variable and statistically significant variables as independent ones were performed according to the frailty category (non-frailty, pre-frailty, and frailty). The significance level for all analyses was set at 0.05, two-tailed.

RESULTS

Sociodemographic Characteristics

In this study, 239 (44.0%) were non-frail, 169 (31.1%) were pre-frail, and 135 (24.9%) were frail among 543 respondents using the cut-point of the Chinese FRAIL Scale, and more than half (58.6%) were female. Their age ranged from 60 to 94 years, with an average of (70.99 ± 8.26) years. 21.9% of the participants were single (unmarried, divorced, or widowed). Only 15.8% of participants had not been educated. More than three-quarters (76.3%) of the participants have a monthly income ranging from $300 to $1,051. The detailed sociodemographic characteristics are shown in **Table 1**.

Social Support

As shown in **Table 2**, the mean SSRS score for all respondents was 34.78 (SD = 7.15, range = 12–66). Specifically, the overall score of SSRS for non-frail respondents was 38.01 ± 6.48, with the objective support 9.39 ± 2.47, subjective support 20.93 ± 4.06, support utilization 7.69 ± 2.26; for pre-frail ones was 33.62 ± 6.25 (objective support 8.35 ± 2.17, subjective support 19.18 ± 3.94, support utilization 6.09 ± 1.93); and for frail ones, the total score of this scale was 30.50 ± 6.68 (objective support 7.54 ± 2.40, subjective support 17.58 ± 4.15, support utilization 5.39 ± 1.70). There was a statistically significant difference in social support between different frailty statuses ($F = 62.157$, $p < 0.001$).

Factors Associated With Social Support: Results of Bivariate Analysis

As shown in **Table 3**, *t*-tests or ANOVA showed that the total social support score differed by age and marital status for all frailty categories ($p < 0.05$). We also found a statistically significant association between social support and educational level for both robust participants and older adults with frailty ($p < 0.05$). Additionally, monthly income was the potential factor only for non-frail older persons ($p = 0.006$). The influence of demographic characteristics on objective support, subjective support, and support utilization according to the frailty category was shown in **Supplementary Table 1**. In the non-frail group, age and educational level were associated with three dimensions; marital status was associated with objective and subjective support; monthly income was associated with objective support and support utilization. Among the pre-frail participants, marital status was an associated factor for objective support; marital status and monthly income were for subjective support; gender and age were for support utilization. For frail older adults, age was associated with subjective support and support utilization; marital status was associated with objective and subjective support; the educational level was associated with subjective support and support utilization.

In terms of family environment (**Table 4**), living alone or not ($p = 0.001$), and relationship with children ($p < 0.05$) might be the impact factors of social support for three groups. Besides, getting moral support from children or not would have significant differences in social support perceived by pre-frail and frail older adults in the community ($p < 0.05$). For non-frail ones, the number of children was also associated with the level of

TABLE 1 | Demographic characteristics of community-dwelling older adults.

Variable	Total		Frailty category	
	(*N* = 543)	Non-frail (*N* = 239)	Pre-frail (*N* = 169)	Frail (*N* = 135)
Gender				
Male	225 (41.4)	100 (41.8)	72 (42.6)	53 (39.3)
Female	318 (58.6)	139 (58.2)	97 (57.4)	82 (60.7)
Age (years)				
60–69	259 (47.7)	155 (64.9)	74 (43.8)	30 (22.2)
70–79	185 (34.1)	71 (29.7)	62 (36.7)	52 (38.5)
≥80	99 (18.2)	13 (5.4)	33 (19.5)	53 (39.3)
Marital status				
Married	424 (78.1)	203 (84.9)	139 (82.2)	82 (60.7)
Single*	119 (21.9)	36 (15.1)	30 (17.8)	53 (39.3)
Educational level				
Uneducated	86 (15.8)	36 (15.1)	16 (9.5)	34 (25.2)
Elementary school	164 (30.2)	63 (26.4)	58 (34.3)	43 (31.9)
Junior high school	146 (26.9)	73 (30.5)	45 (26.6)	28 (20.7)
Senior high school	90 (16.6)	40 (16.7)	31 (18.3)	19 (14.1)
College or above	57 (10.5)	27 (11.3)	19 (11.2)	11 (8.1)
Monthly income ($)				
<300	90 (16.6)	50 (20.9)	23 (13.6)	17 (12.6)
300–600	212 (39.0)	99 (41.4)	53 (31.4)	60 (44.4)
601–1,051	189 (34.8)	70 (29.3)	71 (42.0)	48 (35.6)
≥1,052	52 (9.6)	20 (8.4)	22 (13.0)	10 (7.4)

**Single: including unmarried, divorced, or widowed.*

TABLE 2 | Social support of community-dwelling older adults according to the frailty category.

Dimension	Total (*N* =543)	Non-frail (*N* =239)	Pre-frail (*N* =169)	Frail (*N* =135)	*F*	*P*
Objective support	8.61 ± 2.48	9.39 ± 2.47	8.35 ± 2.17	7.54 ± 2.40	27.828	<0.001
Subjective support	19.55 ± 4.26	20.93 ± 4.06	19.18 ± 3.94	17.58 ± 4.15	30.608	<0.001
Support utilization	6.62 ± 2.26	7.69 ± 2.26	6.09 ± 1.93	5.39 ± 1.70	63.622	<0.001
Overall	34.78 ± 7.15	38.01 ± 6.48	33.62 ± 6.25	30.50 ± 6.68	62.157	<0.001

social support ($p = 0.000$). The impact of family environment on objective support, subjective support, and support utilization (see **Supplementary Table 2**) according to the frailty category were also explored. In the non-frail group, the number of children, living alone or not, and relationship with children were associated with objective and subjective support. In addition, getting moral support from children or not would be an associated factor for subjective support. In the pre-frail group, living alone or not and getting financial support from children or not were associated with objective support and support utilization, respectively. The associated factors for subjective were living alone or not, getting moral support from children or not, relationship with children, and children's company. For frail respondents, relationship with children was an associated factor for three dimensions; living alone or not and getting moral support from children or not were potential factors for objective and subjective support; children's company was only an impact factor for objective support.

The results of analyses in the aspect of community situation in **Table 5** indicated that the level of social support might be related to community management for pre-frail respondents ($p = 0.004$). Differently, for frail ones, accessibility to medical institutions within 15 min ($p = 0.008$) and utilization of recreational activities ($p = 0.001$) might be associated factors for perceived social support. Supplementary materials also present the association between the community environment and three dimensions (see **Supplementary Table 3**). For non-frail older adults, community management might be related to objective support; accessibility to medical institutions, sports fields, and nursing homes within 15 min might be related to subjective support; availability of health education was a potential factor for support utilization. Community management was the only associated factor for subjective support for pre-frail older adults. In the frail group, the availability of recreational activity was related to three dimensions. Community management

TABLE 3 | The impact of demographic characteristics on social support according to the frailty category.

Variable	Non-frail		Pre-frail		Frail	
	Social support (*N* =239)	*P*	Social support (*N* =169)	*P*	Social support (*N* =135)	*P*
Gender		0.321		0.337		0.266
Male	38.50 ± 6.53		33.08 ± 6.15		31.30 ± 7.32	
Female	37.65 ± 6.45		34.02 ± 6.33		29.99 ± 6.22	
Age (years)		0.000		0.047		0.011
60–69	39.12 ± 6.03		34.95 ± 5.94		32.70 ± 5.90	
70–79	35.20 ± 6.06		32.79 ± 5.79		31.29 ± 6.67	
≥80	40.08 ± 9.16		32.21 ± 7.30		28.49 ± 6.65	
Marital status		0.000		0.000		0.000
Married	39.00 ± 6.03		34.81 ± 5.55		33.15 ± 5.92	
Single*	32.39 ± 6.13		28.10 ± 6.46		26.42 ± 5.67	
Educational level		0.000		0.195		0.011
Uneducated	33.86 ± 5.79		32.06 ± 7.76		29.38 ± 5.63	
Elementary school	36.70 ± 6.46		33.86 ± 5.93		29.05 ± 7.07	
Junior high school	38.44 ± 5.93		33.42 ± 5.90		31.54 ± 6.32	
Senior high school	39.83 ± 5.93		32.52 ± 6.88		30.79 ± 7.29	
College or above	42.74 ± 5.73		36.47 ± 5.09		36.55 ± 4.74	
Monthly income ($)		0.006		0.054		0.133
<300	36.36 ± 5.32		35.17 ± 6.21		30.53 ± 4.24	
300–600	37.71 ± 6.42		32.32 ± 6.30		29.47 ± 6.79	
601–1,051	38.40 ± 7.05		33.30 ± 6.10		30.92 ± 7.28	
≥1,052	42.25 ± 5.71		36.18 ± 5.97		34.70 ± 5.01	

Single: including unmarried, divorced, or widowed.

was associated with objective support. Accessibility to medical institutions and nursing homes within 15 min would significantly differ in subjective support.

Factors Associated With Social Support: Results of Multivariate Analysis

For robust older adults, compared with the 60–69 years age group, participants in the 70–79 years age group reported a lower level of social support ($\beta = -0.151$, $p = 0.011$), objective support ($\beta = -0.227$, $p = 0.000$), and subjective support ($\beta = -0.138$, $p = 0.022$), while participants in the ≥80 years age group reported higher level of social support ($\beta = 0.157$, $p = 0.008$) and support utilization ($\beta = 0.177$, $p = 0.007$). Single ones, including unmarried, divorced, and widowed ones, tend to report lower scores in social support ($\beta = -0.202$, $p = 0.001$) and subjective support ($\beta = -0.253$, $p = 0.000$). It was found that illiterate participants perceived lower scores on social support than those who were educated. Compared with the uneducated respondents, respondents with educational level of junior high school and senior high school reported higher scores in subjective support ($\beta = 0.234$, $p = 0.005$; $\beta = 0.245$, $p = 0.001$), and respondents with educational level of college or above reported higher scores in three dimensions ($\beta = 0.330$, $p = 0.000$; $\beta = 0.174$, $p = 0.015$; $\beta = 0.268$, $p = 0.010$). The older adults who lived alone perceived lower level of objective support ($\beta = -0.233$, $p = 0.000$) than those who did not live alone. Older adults with one or no children had higher social support scores than those with two or more children ($\beta = -0.149$, $p = 0.021$). Respondents with poor relationships with children were more prone to poor social support ($\beta = 0.368$, $p = 0.001$) and subjective support ($\beta = 0.331$, $p = 0.005$). Among the three dimensions, the number of potential associated factors on support utilization was the least. Older adults who lived in the community with fair ($\beta = 0.235$, $p = 0.025$) and good ($\beta = 0.234$, $p = 0.028$) management tend to report higher scores in objective support than those lived in community with bad management. All results are displayed in **Supplementary Table 4**.

The associated factors of social support among pre-frail and frail participants are presented in **Supplementary Tables 5, 6**. Lower perceived social support level was observed among both the aged pre-frail and frail people who were single ($\beta = -0.289$, $p = 0.000$; $\beta = -0.292$, $p = 0.002$). Specifically, single pre-frail older adults reported lower scores in objective and subjective support than married ones ($\beta = -0.295$, $p = 0.000$; $\beta = -0.314$, $p = 0.000$), so as the frail ones ($\beta = -0.302$, $p = 0.000$; $\beta = -0.232$, $p = 0.022$). Living alone negatively affected social support ($\beta = -0.203$, $p = 0.012$) among pre-frail older adults and objective support ($\beta = -0.388$, $p = 0.000$; $\beta = -0.310$, $p = 0.000$) in pre-frail and frail group. Frail participants, who were in fair and good relationships with children were more likely to perceive a higher level of social support ($\beta = 0.240$, $p = 0.042$; $\beta = 0.383$, $p = 0.003$), objective support ($\beta = 0.314$, $p = 0.006$; $\beta = 0.315$, $p = 0.012$), and subjective support ($\beta = 0.143$, $p = 0.248$; $\beta = 0.317$, $p = 0.019$). Frail older adults who were offered opportunities to participate in recreational activities showed greater social support, objective support, and

TABLE 4 | The impact of family environment on social support according to the frailty category.

Variable	Non-frail		Pre-frail		Frail	
	Social support (*N* =239)	*P*	Social support (*N* =169)	*P*	Social support (*N* =135)	*P*
The number of children		0.000		0.678		0.527
≤1	39.61 ± 6.24		33.41 ± 6.19		30.98 ± 7.39	
≥2	36.45 ± 6.35		33.82 ± 6.33		30.22 ± 6.24	
Living alone		0.000		0.000		0.000
No	38.49 ± 6.17		34.43 ± 5.56		31.84 ± 6.22	
Yes	31.25 ± 7.09		25.88 ± 7.32		25.62 ± 6.06	
Financial support from children		0.902		0.102		0.297
No	37.98 ± 6.35		33.20 ± 6.13		30.25 ± 6.80	
Yes	38.12 ± 7.15		35.11 ± 6.54		31.90 ± 5.91	
Moral support from children		0.167		0.007		0.001
No	32.00 ± 7.35		31.72 ± 5.57		28.54 ± 6.81	
Yes	35.94 ± 6.11		34.49 ± 6.38		32.22 ± 6.10	
Relationship with children		0.000		0.017		0.000
Poor	30.57 ± 6.19		28.60 ± 9.86		22.55 ± 7.05	
Fair	33.15 ± 6.13		31.21 ± 6.55		28.08 ± 5.43	
Good	38.90 ± 6.10		34.21 ± 5.92		31.96 ± 6.15	
Children's company		0.861		0.101		0.116
Rarely	37.75 ± 7.33		31.52 ± 6.87		28.10 ± 8.27	
Sometime	37.60 ± 7.44		32.57 ± 6.44		29.19 ± 6.68	
Often	38.17 ± 6.02		34.23 ± 6.02		31.20 ± 6.24	

support utilization than those who had no opportunities (β = 0.197, $p = 0.014$; β = 0.156, $p = 0.015$; β = 0.384, $p = 0.000$).

In addition, in the pre-frail group, older adults with a monthly income of $300-600 reported lower scores in subjective support than those with <$300 (β = −0.239, $p = 0.024$). Participants who were often companied with adult children reported a higher level of subjective support (β = 0.208, $p = 0.032$). Getting financial support from children positively affected support utilization (β = 0.238, $p = 0.002$). In the frail group, the educational level of college or above and living in a community with good management positively influenced subjective support (β = 0.199, $p = 0.029$) and objective support (β = 0.259, $p = 0.025$), respectively. For the pre-frail older persons, the factors affecting subjective support were the most, but for the frail older persons, the factors affecting objective support were the most.

DISCUSSION

The level of social support (34.78 ± 7.15) among participants in this study was similar to the social support level of community-dwelling older adults in Fuzhou, Fujian Province (34.99 ± 5.94) (23), as well as the results of a meta-analysis about social support among Chinese older adults aged 60 years (34.047) (30). For pre-frail and frail older adults, our results were nearly consistent with a previous study conducted in Anhui Province, which reported that the total social support score was 33.43 ± 5.80 and 30.96 ± 5.99 among older adults with pre-frailty in 60–76 years and ≥77 years age group, respectively (10). Furthermore, the total score was 31.57 ± 6.56 and 29.06 ± 6.32 among older adults with frailty in both age groups (10). Though the level of social support among the older adults in Zhejiang Province and Anhui Province was similar, this should be presented cautiously, as the frailty status was assessed by the FRAIL Scale and Frailty Index (10), respectively. Additionally, we recruited the target participants from the community healthcare centers, and they selected the individuals from rural villages (10). Importantly, the more severe the frailty, the lower the level of social support. Interventions should be taken to enhance social support as early as possible, especially for pre-frail persons.

We found the same results as previous studies (23) that the older adults who were unmarried, divorced, and widowed might perceive less social support, mainly subjective and objective support, than those who had spouses. Spouses might offer physical and emotional companionship. With a healthier marital status, older people may be prone to perceive more available social support, and they may enlarger their social networks more easily (31). Therefore, frailty management, especially social support, is called for older pre-frail and frail adults who are unmarried, divorced, and widowed. The effect of marital status on social support among the older adults is not uniformly positive, neutral, or negative (32). Hence, more longitudinal studies are needed. The present study also showed that monthly income was only associated with subjective support among pre-frail participants. Surprisingly, older adults with a monthly income of $300–600, compared with older adults having a monthly income of <$300, perceived less subjective support in our investigation. This phenomenon could be because the older

TABLE 5 | The impact of community environment on social support according to the frailty category.

Variable	Non-frail		Pre-frail		Frail	
	Social support (*N* =239)	*P*	Social support (*N* =169)	*P*	Social support (*N* =135)	*P*
Medical institutions accessible		0.180		0.296		0.008
No	36.94 ± 6.51		32.32 ± 7.61		28.32 ± 6.91	
Yes	38.30 ± 6.46		33.82 ± 6.03		31.56 ± 6.33	
Sports fields accessible		0.096		0.523		0.070
No	36.78 ± 6.60		34.24 ± 7.03		28.78 ± 6.46	
Yes	38.40 ± 6.41		33.47 ± 6.06		31.13 ± 6.68	
Nursing homes accessible		0.175		0.638		0.067
No	37.08 ± 6.21		33.27 ± 6.65		29.06 ± 6.58	
Yes	38.36 ± 6.56		33.77 ± 6.11		31.27 ± 6.64	
Management of community		0.462		0.004		0.365
Bad	36.53 ± 7.54		35.21 ± 5.37		28.33 ± 6.68	
Fair	38.78 ± 6.27		31.81 ± 6.51		30.26 ± 6.41	
Good	37.91 ± 6.46		35.00 ± 5.77		31.22 ± 6.96	
Availability of recreational activity		0.587		0.705		0.001
No	37.88 ± 6.17		33.53 ± 6.26		29.65 ± 6.47	
Yes	38.56 ± 7.74		34.00 ± 6.30		34.46 ± 6.31	
Availability of health education		0.059		0.221		0.149
No	37.71 ± 6.39		33.27 ± 6.12		30.12 ± 6.60	
Yes	40.14 ± 6.82		34.60 ± 6.55		32.29 ± 6.86	

adults with a monthly income of $300–600 might have more subjective needs for social support than those with lower monthly incomes. In addition, the linear regression showed that the educational level of college or above actively impacted subjective support among the frail older adults. Education is beneficial for older adults to acquire better socioeconomic status and job that determines wider social network and more social resources (30). Thus, the illiterate frail older adults in the community should be the target of the intervention programs on social support, especially subjective support.

There were also some factors regarding the family of the older adults contributing to the level of social support. Firstly, it was indicated that pre-frail and frail responders living alone might tend to perceive less social support, especially objective support, which is consistent with the previous results (33). A possible explanation might be that those living alone need more support with, for example, household chores, local transportation, or someone to talk to about their worries and ask for advice (33). Moreover, older adults living alone reported poorer health, more comorbid medical conditions, and more physical limitations, which increases the need for caregivers (33). Cohabiting with adult children could provide greater financial, instrumental, emotional, and physical support (34). Notably, some single (unmarried, divorced, and widowed) respondents lived alone, so the results should be presented cautiously. Secondly, the quality of relationships with adult children was positively associated with overall social support, objective support, and subjective support perceived by the frail older adults. The quality of relationships with children played an important for elders, especially for widowhood ones (34). A stable family may be one reason for a higher objective support score (35). The fact that 89.1% of older adults perceived their children as the primary source of subjective support might explain the above phenomenon partly (23). Besides, the fact in the previous could also explain why the more children accompanied, the higher the score of subjective support among the pre-frail older persons (23). Finally, the pre-frail older adults who had received financial support from adult children, compared to those who had not, perceived higher scores in support utilization. One reason might be that they were more confident and active in seeking social support through various social networks. It might also be due to the significance of intergenerational financial support to subjective wellbeing among older adults (36).

Furthermore, the frequent opportunities provided by the community to participate in recreational activities, such as singing, dancing, painting, and walking, positively impact overall social support, objective support, and support utilization among frail older adults. There are two possible reasons for this result. One is that recreational activity can enhance social confidence, communication, reciprocal relationship, and other interpersonal skills (37). Besides socialization benefits, recreational activities are encouraged for older people as they could increase their smiles and raise their joy (38). The results also indicated that the great management of the community was a positive factor for objective support among frail older adults. The reason perhaps was that a well-managed community is more likely to provide an excellent physical and social environment. It was recognized that a community should be dynamic to support changes in the older citizenry (39), and a community's perceived age-friendliness is associated with the quality of life among older adults (40).

It is worth mentioning that social support decreased with aging in the older persons (24), which was only found in our study among the robust older persons. It was indicated that the association between social support and frailty was negative in the ≥77 years age group, compared to the 60–76 years age group among the Chinese (10). The relationships between age, social support, and progression of frailty need further research on mediating effects and more longitudinal study. An interesting phenomenon that the number of children only works in the robust population but not in the pre-frail and frail population needs further exploration to understand the impact factors and the interaction better.

To our knowledge, this study is the first to explore the comprehensive associated factors of social support among frail and pre-frail older adults in Chinese community centers. However, some limitations should be acknowledged. First, given the cross-sectional research design of our study, causality cannot be ascertained. Second, the scarcity of previous studies aimed at a comprehensive understanding of the contributing factors for social support among community-dwelling older adults with pre-frailty and frailty limited the comparability of our findings. Third, the data were only collected from Hangzhou City, China, limiting the findings' generalization to other regions.

CONCLUSION

The level of social support among the frail and pre-frail older adults in Hangzhou, China, needs improvement. Older adults affected with frailty and pre-frailty may present different levels of social support based on sociodemographic characteristics, family environment, and the community. Social support improvement should be integrated into frailty management.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the School of Public Health, Hangzhou Normal University (Number: 20210012). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JF, JR, and LR conceived and designed the study. JF, LR, XQ, and SY participated in the acquisition of data. JF and LR analyzed the data and drafted the manuscript. JR and WW gave advice on methodology. JR and JW revised the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.944293/full#supplementary-material

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EDITED BY
Marios Kyriazis,
National Gerontology Center, Cyprus

REVIEWED BY
Fahadul Islam,
Daffodil International University, Bangladesh
Sandra Oliveira,
Fiocruz Mato Grosso do Sul, Brazil

*CORRESPONDENCE
Roberta Bevilacqua
r.bevilacqua@inrca.it

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A systematic review of multidomain and lifestyle interventions to support the intrinsic capacity of the older population

Roberta Bevilacqua[1]*, Luca Soraci[2], Vera Stara[1], Giovanni Renato Riccardi[3], Andrea Corsonello[2,4], Giuseppe Pelliccioni[5], Fabrizia Lattanzio[1], Sara Casaccia[6], Johanna Möller[7], Rainer Wieching[8], Toshimi Ogawa[9], Suichiro Watanabe[9], Keisuke Kokobun[9], Izumi Kondo[10], Eiko Takano[10] and Elvira Maranesi[1]

[1]Scientific Direction, IRCCS INRCA, Ancona, Italy, [2]Unit of Geriatric Medicine, IRCCS INRCA, Cosenza, Italy, [3]Clinical Unit of Physical Rehabilitation, IRCCS INRCA, Ancona, Italy, [4]Unit of Geriatric Pharmacoepidemiology and Biostatistics, IRCCS INRCA, Cosenza, Italy, [5]Unit of Neurology, IRCCS INRCA, Ancona, Italy, [6]Department of Industrial Engineering and Mathematical Sciences, Polytechnic University of Marche, Ancona, Italy, [7]Department Elderly Care, Diocesan Caritas Association for the Archdiocese of Cologne, Cologne, Germany, [8]Universität Siegen, Wirtschaftsinformatik und Neue Medien, Siegen, Germany, [9]Smart-Aging Research Center, Tohoku University, Sendai, Japan, [10]Department of Rehabilitation Medicine, National Center for Geriatrics and Gerontology, Obu, Japan

Introduction: The focus on intrinsic capacity (IC) could help clinicians to design interventions to improve the health of the older population. This review aims to map the current state of the art in the field of multi-domain interventions based on the IC framework, to allow health professionals in identifying personalized clinical interventions, oriented to empower the older people with a holistic and positive approach.

Methods: A systematic review of the literature was conducted in July 2021 analyzing manuscripts and articles of the last 10.5 years from PubMed, Scopus, Embase, Google Scholar and Elsevier databases. A total of 12 papers were included.

Results: The majority of successful interventions are based on a goal setting approach where the older people are involved in the definition of the strategy to follow to remain active and independent. None of the study have used the IC as a framework to design a clinical intervention.

Conclusion: To the best of our knowledge, no other reviews are reported in the literature regarding the IC. Our study offers several research directions, which may take the existing debates to the next level.

KEYWORDS

intrinsic capacity, active and healthy aging, functional ability, geriatrics, cognitive support, psychological support, multidomain, multicomponent intervention

Introduction

Intrinsic capacity (IC) was defined as "the composite of all the physical and mental capacities of an individual" (1), including ability to walk, think, see, hear and re-member. Although older age is often characterized by a decline in baseline IC, the rate of decline widely varies among individuals and baseline IC reflects multiple setbacks and potential recoveries (2, 3). If some older adults are able to maintain functional independence up to very advanced ages, other one's experience early onset of severe functional disability which substantially affects their quality of life. According to WHO, such biological diversity can arise from inequity, understood as the differential influences of several factors including genetics, sex, ethnicity, and environment on aging itself (4). Anyway, progressive decline in IC may be more or less tolerated up to a critical point when individuals require care and support. IC is only one of many factors that determine biological age, but it can be an important focus for intervention to reduce the biological and functional age of older adults. Therefore, evaluation of bio-logical age through IC can enhance understanding of the functional trajectories and vulnerabilities of individuals and populations and guide individualized preventive measures and interventions that are tailored to the persons' age, abilities and comorbidities (5).

Assessment of biological age through IC is of extreme importance for the future; losses of IC during the aging process may significantly affect quality of life and become manifested as common problems, such as hearing and vision impairments, memory loss, walking problems, urinary incontinence and loss of positive affect. For such impairments, older people often misbelief that there is no treatment available, and may then disengage from services, lack treatment adherence, with subsequent devastating effects on their quality of life. Recent studies have also shown that loss of IC may decrease quality of life and worsen prognosis in older adults (6). Moreover, IC decline was significantly associated with increased risk of frailty, disability, falls, fractures and death (7).

Regarding frailty and its connection with IC, Belloni et al. (8) assume that the two concepts can be seen as distinct but correlated points on a continuum in which IC represents the reserves of the individual on one side, while frailty is associated with the deficits accumulated with aging on the other. For this reason, it is essential to include also the concept of frailty in the assessment and analysis of the IC-driven interventions.

Due to the heterogeneity of the aging population, characterized by different levels of intrinsic capacity, personalized multicomponent health interventions may represent an effective way to promote health and subjective well-being achievements (9). However, to date, no systematic review focused on evidence about appropriate interventions to preserve intrinsic capacity and daily functioning in older individuals; for this reason, the aim of this systematic review is to map current state of the art in the field of multi-domain interventions based on the IC framework. The availability of evidence on multi-domain interventions that include the IC framework is essential to allow health professionals in identifying personalized clinical interventions, oriented to empower the older people with a holistic and positive approach.

Materials and methods

Literature search and study selection

The methodology of this systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with the main aim of mapping the state of art of multi-domain interventions for older people, grounded on the IC framework. A systematic review of the literature was conducted in July 2021. The data were collected from PubMed, Scopus, Embase, Google Scholar and Elsevier databases, analyzing manuscripts and articles of the last 10.5 years (from January 2011 to June 2021), in order to obtain the latest evidence in the field. The PICOS format (P = population, I = interventions, C = comparator, O = outcome, S = study design) was adopted to formulate inclusion criteria. The inclusion criteria are as follows: (1) randomized controlled trials, quasi-experimental studies, or prospective or retrospective cohort studies, pre-post study with or without control groups; (2) testing of a multi-domain intervention to prevent or treat frailty in people aged $\geq$ 65 years; (3) classification in terms of (pre) frailty status according to an operationalized definition. Systematic and narrative reviews were excluded. A multi-domain intervention was defined as an intervention that intervenes in at least two different domains, including exercise therapy, nutritional intervention, hormone, cognitive or psychosocial interventions (10). As we refer to Intrinsic Capacity, we have included papers on multi-domain interventions on at least three areas within locomotion, cognitive, psychological, vitality and sensory.

Based on consultation with the multidisciplinary research team, multi-modal intervention studies were searched using the following search terms, and the combination thereof: olde*, elde*, intrinsic capacit*, functional ability*/functional status/functional trajectory*, healthy aging/successful aging, prefrail, virtual agent, coaching, self-management, multi-domain intervention, robotic*. The full search string is provided in **Table 1**.

After the preliminary search, 327,563 articles resulted from PubMed, 40,250 from Scopus, 40,098 from Embase, 91,898 from Google Scholar and 492,403 from Elsevier.

The findings were analyzed and screened by four experts of the team, a bioengineer, a clinical neuropsychologist, a statistician and a geriatrician. In particular, three review authors independently reviewed titles and abstract retrieved from the

TABLE 1 Search strategy.

Order of search	Terms
1	Olde* OR elde* AND "intrinsic capacit*"
2	Multicomponent OR multi-component OR multidimension* or multi-dimension*
3	1 AND 2
4	Olde* OR elde* AND "functional abilit*" OR "functional capacity" OR "functional status" OR "functional trajector*"
5	4 AND 2
6	Olde* OR elde* AND "Healthy aging"
7	6 AND 2
8	Olde* OR elde* AND "successful aging"
9	8 AND 2
10	Olde* OR elde* AND "active aging" OR "healthy aging" OR "successful aging"
11	10 AND 2
12	1 AND pre-frail
13	12 AND 2
14	1 AND virtual agent AND 2
15	1 AND coaching AND 2
16	1 AND self-management AND 2
17	1 AND multi-domain intervention AND 2
18	1 AND robotic* AND 2
19	Limit to English AND yr = 2011 -Current

yr, year. *Allows all words with the same root but different ending to be included.

search in order to determine if they met the predefined inclusion criteria. The full text articles were subsequently analyzed.

The first screening was based on the analysis of the title of the findings. After the first step, 61 articles resulted from PubMed, 23 from Scopus, 16 from Embase, 33 from Google Scholar and 55 from Elsevier. A second screening was based on abstract analysis and deduplication of the findings. After this step 41 papers included from Pubmed, 18 from Scopus, 0 from Embase, 11 from Google Scholar and 33 from Elsevier. Another researcher (a statistician) confirmed the accuracy of the papers selection and screened for any possible omission.

Data collection

After the screening based on the inclusion/exclusion criteria, conducted on the full text articles, the studies were selected as follows: 9 from PubMed, 3 from Scopus, 0 from Embase, 0 from Google Scholar, 0 from Elsevier database. **Figure 1** shows the flowchart search strategy applied.

Results

A total of 12 papers were included (11–22). The results could not be pooled into a meta-analysis due to clinical heterogeneity clearly observed in the participants' involvement, in the type of intervention conducted, and in the outcome measures of the included studies.

Study quality evaluation

Quality evaluation of 12 population-based studies was performed based on the PEDro scale, suggested for evidence-based reviews (23). The final score was settled when 3 authors reached agreement after repeated review and analysis. Of the twelve studies considered, the PEDro score ranged from 4 (12) to a maximum of 10 (11) (**Table 2**). In particular, 10 studies were rated as having a high (11, 13–22), 2 studies (12, 19) as having fair methodological quality.

General characteristics of the study population

All the studies were focused on older people with a mean age of 72.9 (± 5.5) years for the multi-domain intervention group and 73.2 (± 5.5) years in the control group. The number of participants involved in all the studies is 8,319, ranging from 46 to 1,827. There were 3,925 males and 4,394 females.

Descriptive analysis and outcome measures

Table 3 shows the characteristics of the included studies. All studies evaluated the impact of multidimensional interventions on some domains of IC, but no one specifically focused on the IC framework as a whole entity. As regards evaluated domains, cognitive functioning was assessed by 7 studies (11, 13–15, 17, 19, 22), physical functioning by 6 studies (13–15, 18, 20, 21), vitality by 5 studies (13–16, 18), and psychosocial well-being by 6 studies (12–16, 18); none of the included studies has instead evaluated the sensory functioning.

Intervention effects

Below is a brief description of the main results reported in the 12 population-based studies categorized according to domains of intervention.

Cognitive functioning

Seven out of twelve studies assessed the effects of interventions on cognitive functioning (11, 13–15, 17, 19, 22). In six studies (11, 14, 15, 17, 19, 22) the intervention was represented by a multidomain training addressing some or all IC domains and made of several components, such as physical activity, cognitive training and social activity, nutritional advice,

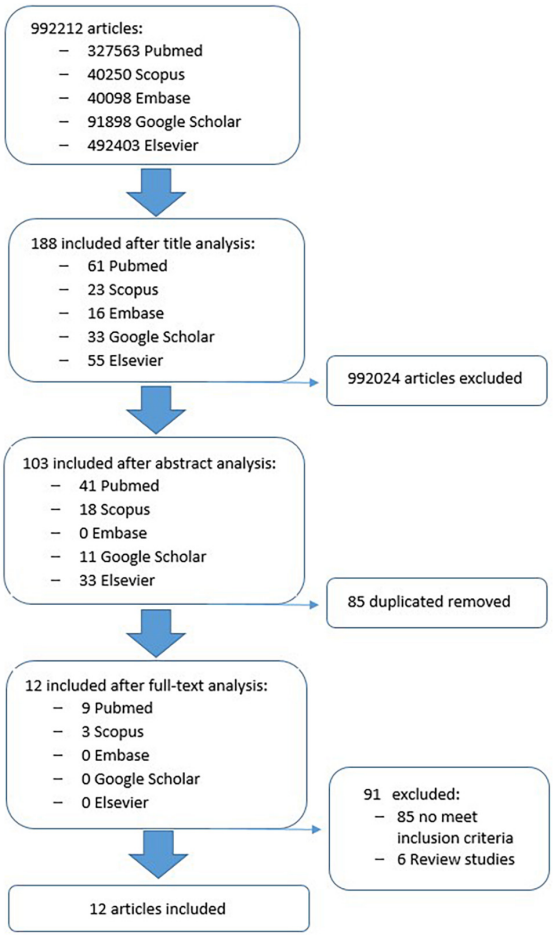

FIGURE 1
The flowchart search strategy.

monitoring and management of risk factors; in one study (13), the multidimensional intervention was designed through a goal-setting approach, asking patients to set up to five goals they wished to accomplish within the coming year.

Four (11, 17, 19, 22) out of the six studies using multidomain intervention training (11, 14, 15, 17, 19, 22) showed a significant benefit on individual cognitive function over time. In particular, in the study by Ngandu et al. (11), individuals in the intervention group (IG) underwent a significant improvement of cognitive scores, executive function and processing speed, even after 2 years; similarly, Moon et al. (11) showed benefits of a 24-week multidomain training on cognitive scores; in the study by Tabue-Tego et al. (19), despite cognitive tests were not significantly different between the control group (CG) and the IG after 36 months of follow-up, a significant trend toward improvement in Trail Making test part A (TMT-A) performance was found in the IG; finally, Lehtisalo et al. (22) showed how adherence to nutritional guidelines in the context of a multidimensional intervention led to benefits in terms of global cognition and executive functioning; only one study (13) assessed the usefulness of a goal-setting approach; individuals in the IG were asked to set up to five goals to accomplish within the coming year; individuals following the goal-setting approach were divided in two groups according to the presence of bi-monthly telephone mentoring. The two goal-setting groups increased their level of cognitive activity relative to controls and achieved additional benefits compared to control in memory and executive function. Adding follow-up mentoring produced further benefits compared to goal-setting alone in global cognition and memory.

Finally, two studies (14, 15) showed no significant effects of multidomain interventions on cognitive scores during follow-up.

Physical activity

Six out of twelve studies assessed the effects of interventions on physical functioning (13–15, 18, 20, 21). In five studies (13–15, 18, 20, 21), the intervention was represented by a multidimensional training program, while in the study by Clare et al. (13) a goal-setting approach was used. Most of the studies

TABLE 2 Scores of methodological quality assessment of the included studies.

PEDro	Ngandu et al., (11)	Scult et al. (12)	Clare et al. (13)	Ng et al. (14)	de Souto Barreto et al. (15)	Rainero et al. (16)	Moon et al. (17)	Huguet et al. (18)	Tabue-Teguo et al. (19)	de Souto Barreto et al. (20)	Kulmala et al. (21)	Lehtisalo et al. (22)
Eligibility	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Randomized allocation	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Concealed allocation	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Baseline comparability	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Blinded subject	Y	N	Y	Y	N	Y	N	N	N	N	N	N
Blinded therapists	N	N	N	N	N	N	N	N	N	N	N	N
Blinded raters	Y	N	Y	Y	Y	N	Y	N	N	N	N	N
Key outcomes	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Intention to treat	Y	N	N	N	Y	N	Y	N	N	Y	N	Y
Comparison between groups	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Precision and variability	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	10/11	4/11	9/11	9/11	9/11	8/11	9/11	7/11	5/11	8/11	7/11	8/11

Y, yes; N, no.

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TABLE 3 Descriptive analysis of the included clinical studies.

	Population		Intervention Type of Study	Measurements	Results
	Participants in multi-domain intervention group (MIG)	Participants in control group (CG)			
Ngandu et al., (11)	*n* = 591 older adults, 267 F/324 M Age: 69.5 ± 4.6 years	*n* = 599 older adults, 284 F/315 M Age: 69.2 ± 4.7 years	CG received regular health advice MIG group additionally received four intervention components: (1) nutritional guidance; (2) physical exercise; (3) cognitive training and social activity; and (4) intensive monitoring and management of metabolic and vascular risk factors Type of study: RCT	Primary outcome: Change in cognition as measured through comprehensive NTB Z score.	Estimated mean change in NTB total Z score at 2 years was 0· · · 20 (SE 0· · · 02, SD 0· · · 51) in the MIG and 0· · · 16 (0· · · 01, 0· · · 51) in the CG. Between-group difference in the change of NTB total score per year was 0· · · 022 (95% CI 0· · · 002–0· · · 042, p = 0· · · 030).
Scult et al. (12)	*n* = 46 older adults, 35 F/8 M Age: 75.5 ± 6.7 years	Not applicable	The intervention consisted of weekly, 90-min sessions for 9 consecutive weeks, directed by a psychologist. The program included sessions that taught participants: (1) a variety of methods to elicit the relaxation response, (2) the practice of adaptive coping and cognitions, (3) behaviors necessary to create a healthy lifestyle, and (4) methods of building social support. Type of study: pre- post- intervention analysis	Primary outcomes: Morale, measured through the PGCMS, CSES, a measure that addresses the multiple dimensions of self-efficacy.	The scores on both the PGCMS and the CSES increased significantly among completers of the intervention; i.e., the pre- to post intervention change was: (1) PGCMS, 1.68 ± 2.94, p = 0.001; (2) CSES, 33.90 ± 36. 30, $p < 0.001$. After the sensitivity analysis, the CSES pre-post change was still significant ($p < 0.001$), and the PGCMS trended toward statistical significance (p = 0.064)
Clare et al. (13)	Goal-setting group *n* = 24 older adults, 23 F/1 M Age = 67.50 ± 7.66 years Goal-setting with mentoring group *n* = 24 older adults, 19 F/5 M Age = 68.21 ± 7.92 years	*n* = 27 older adults, 23 F/4 M Age = 70.22 ± 7.77 years	In both the multi-domain intervention groups, participants engaged in a structured goal-setting process to identify up to five goals they wished to work on over the coming year relating to physical activity, cognitive activity, physical health and diet, and social engagement. Type of study: RCT	Primary outcomes: physical activity, assessed with the PASE, and cognitive activity, assessed with the FCAS. Secondary outcomes: psychosocial well-being, cognition, and physical health, fitness and diet.	Both the goal-setting and goal-setting with mentoring conditions increased their engagement in cognitive and physical activity. Changes in self-efficacy were negligible. Depression mean scores reduced in the control and goal-setting conditions, but increased in the goal-setting with mentoring condition. All three conditions improved in general cognitive ability assessed with the MoCA screening instrument. All three conditions reduced body fat percentage.
Ng et al. (14)	*n* = 96 older adults, 83 F/13 M Age: 75.61 ± 9.01 years	*n* = 98 older adults, 83 F/15 M Age: 77.90 ± 8.84 years	A bi-weekly program comprising cognitive training, physical-cognitive dual-task exercises and nutritional guidance was implemented. The program comprised 48 sessions (31% physical-cognitive dual-task exercises and 69% cognitive sessions) of which 19% were based on small group activities and 50% were computerized cognitive training. Nutritional guidance was intended to be on-going *via* the application throughout the length of the intervention. Type of study: RCT	Primary outcome: RBANS Secondary outcomes: EuroQol EQ-5D-5L, VAS, blood lipid panel and physical assessments.	There were no between-group differences in total RBANS score and domain scores after 6 months. There were also no between-group differences in quality of life measures and all blood parameters. here were no significant changes in total RBANS scores and immediate memory, visuospatial/constructional, language, and delayed memory scores in both the MIG and CG from baseline to follow-up. The MIG improved significantly in physical assessments.

(Continued)

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TABLE 3 (Continued)

	Population		Intervention Type of Study	Measurements	Results
	Participants in multi-domain intervention group (MIG)	Participants in control group (CG)			
Barreto et al. (15)	*n* = 60 older adults, 29 F/31 M Age: 75.2 ± 5.7 years	*n* = 60 older adults, 38 F/22 M Age: 73.2 ± 5.3 years	The web multi-domain platform focused on three lifestyles: nutritional advice, and exercise and cognitive training. The platform was equipped with a chat, to facilitate communication of participants with the research team, a personalized agenda showing the day-by-day activities (i.e., exercise and cognitive training to be done, nutritional advices), a library area where the content of the interventions and educational material on lifestyles were available Type of study: RCT	Primary outcomes: Feasibility and acceptability of study procedures and tools. Secondary outcomes: Cognitive function; physical function; depressive symptoms; nutritional status; HRQOL; Physical Activity; Leisure-time cognitive activities; Food intake	Regarding feasibility, 58 (out of 60) participants in MIG connected to the multi-domain platform at least once during the 6-month trial. Regarding acceptability, 7.5% said the platform was not ready to be used and needed major changes; 5.7% indicated it required minor changes; 34% said it was ready to be used, but minor modifications; and 52.8% indicated the platform was ready to be used without any change. No statistically significant effects were found, except for the two variables of HRQOL, showing MIG had an improved HRQOL compared to CG.
Rainero et al. (16)	*n* = 101 older adults, 71 F/30 M Age: 70.37 ± 6.15 years	*n* = 100 older adults, 77 F/23 M Age: 73.40 ± 6.57 years	Intervention packages were developed for physical, cognitive, psychosocial, nutrition and sleep domains. Type of study: RCT	Primary outcomes: QoL; mood and nutrition function.	CG displayed a significant decrease in QoL at the 12-month phase, with no change in QoL evident in MIG. MIG displayed a significant increase in nutrition score at the 12-month phase relative to the 6-month phase
Moon et al. (17)	Facility-based MI (FMI) *n* = 48 older adults, 35 F/13 M Age = 71.6 ± 4.8 years Home-based MI (HMI) *n* = 50 older adults, 36 F/14 M Age = 70.9 ± 5.0 years	*n* = 42 older adults, 33 F/9 M Age = 70.1 ± 4.6 years	The 24- week intervention comprised vascular risk management, cognitive training, social activity, physical exercise, nutrition guidance, and motivational enhancement. The FMI participants performed all intervention programs at a facility three times a week. The HMI participants performed some programs at a facility once every 1–2 weeks and performed others at home. Type of study: RCT	Primary outcomes: Feasibility measured through retention, adherence, and at least no differences from the CG in the RBANS	The retention rates were 88.2% and 96.1%, and adherence to the intervention was 94.5% and 96.8%, respectively. The RBANS total scale index score improved significantly in the FMI (5.46 ± 7.50, $P = 0.004$) and HMI (5.50 ± 8.14, $P = 0.004$) groups compared to the control group (−0.74 ± 11.51).
Huguet et al. (18)	*n* = 100 older adults, 68 F/32 M Age: 84.5 ± 3.4 years	*n* = 100 older adults, 61 F/39 M Age: 84.5 ± 3.7 years	6-month multifactorial intervention was based on four axes: (1) Assessment of inadequate prescription in polypharmacy patients. (2) Group session, led by an expert on the Mediterranean diet. (3) Physical exercise program. (4) Review of personal and environmental conditions and social support. Type of study: RCT	Primary outcomes: Frailty, Functional and nutritional status, adherence to Mediterranean diet, quality of life, and functional mobility.	Frailty was lower in the intervention group (RR 2.90; 95%CI 1.45–8.69). Functional and nutritional status, adherence to Mediterranean diet, quality of life, and functional mobility were improved in MIG ($p \leq 0.001$).

(Continued)

TABLE 3 (Continued)

	Population		Intervention Type of Study	Measurements	Results
	Participants in multi-domain intervention group (MIG)	Participants in control group (CG)			
Barreto et al. (20)	*n* = 816 older adults, 534 F/282 M Age: 75.3 ± 4.3 years	*n* = 821 older adults, 525 F/296 M Age: 75.3 ± 4.5 years	The MAPT intervention was composed of 3 main components: cognitive training (memory and reasoning), nutrition counseling, and advice on physical activity. Twelve 2-h sessions (1 h of cognitive training, 45 min of advice on physical activity, and 15 min of nutrition counseling) were provided in the first 2 months of the study, followed by a 1-h session each month until the end of the 3-year study. Type of study: RCT	Primary outcomes: severity of frailty (continuous FI score), incident frailty, incidence of persistent frailty (frailty at 2 consecutive time points), and reversibility of frailty (from frailty to non-frailty)	MIG had a decreased risk of developing both frailty (hazard ratio 0.72; 95% confidence interval, 0.55–0.93) and persistent frailty (hazard ratio 0.53; 95% confidence interval, 0.33–0.85).
Kulmala et al. (21)	*n* = 631 older adults, 286 F/345 M Age: 69.7 ± 4.6 years	*n* = 629 older adults, 303 F/326 M Age: 69.4 ± 4.7 years	The FINGER multi-domain intervention included simultaneous physical activity intervention, nutritional counseling, vascular risk monitoring and management, and cognitive training and social activity. Type of study: RCT	Primary outcomes: The ability to perform daily activities (ADLs and instrumental ADLs) and physical performance (Short Physical Performance Battery).	The difference in the change between MIG and CG was −0.95 (95% CI = −1.61 to −0.28) after 1 year and −1.20 (95% CI = −2.02 to −0.38) after 2 years. MIG had a slightly higher probability improvement (from score 3 to score 4; $P = 0.041$) and a lower probability of decline (from score 3 to scores 0–2; $P = 0.043$) for physical activity compared to CG.
Lehtisalo et al. (22)	*n* = 571 older adults, 263 F/308 M Age: 69.5 ± 4.6 years	*n* = 584 older adults, 278 F/306 M Age: 69.1 ± 4.7 years	The FINGER multi-domain intervention included simultaneous physical activity intervention, nutritional counseling, vascular risk monitoring and management, and cognitive training and social activity. Dietary intervention was combination of individual counseling (3 sessions) and group meetings (6 sessions), mainly during the first year Type of study: RCT	Primary outcome: Cognitive performance Secondary outcomes: cognitive domain Z scores for executive function; processing speed; and memory domain.	Adherence to healthy diet at baseline predicted improvement in global cognition, regardless of MIG ($P = 0.003$). Dietary improvement was associated with beneficial changes in executive function, especially in MIG ($P = 0.008$; $P = 0.051$ for groups combined).
Tabue-Teguo et al. (19)	No Frailty group: *n* = 799 older adults, 509 F/290 M Age = 74.41 ± 4.00 years Frailty group: *n* = 665 older adults, 431 F/234 M Age = 76.32 ± 4.62 years	Not applicable	The MAPT intervention consisted of 2 h' group sessions focusing on three domains (cognitive stimulation, physical activity, and nutrition) and a preventive consultation (at baseline, 12 months, and 24 months). For Omega-3 Polyunsaturated Fatty Acids supplementation, participants took two capsules of either placebo or polyunsaturated fatty acids daily. Type of study: comparison between groups	Primary outcomes: Change in cognitive tests over 36 months	No differences in the change in cognitive tests over 36 months. A trend toward significance difference in TMT-A ($P = 0.031$) were found for the effect of the multi-domain intervention between the two groups.

n, number of subjects; F, female; M, male; MIG, Multidomain Intervention Group; CG, Control Group; RCT, Randomized Controlled Trial; NTB, Neuropsychological Test Battery; PGCMS, Philadelphia Geriatric Center Morale Scale; CSES, Self-efficacy the Coping Self-Efficacy Scale; PASE, Physical Activities Scale for the Elderly; FCAS, Florida Cognitive Activities Scale; MoCA, Montreal Cognitive Assessment; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; VAS, Visual Analog Scale; HRQOL, health-related quality of life; QoL, Quality of Life; ADLs, activities of daily living; CI, confidence interval.

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reported beneficial effects of multidomain interventions on physical function over time (13, 14, 18, 20, 21), whereas one study (15) showed no significant effect.

In the pilot study by Clare et al. (13), the goal-setting approach with or without mentoring was associated with improved engagement in physical activity, as well as flexibility, grip strength, balance, and agility; furthermore, the goal-setting approach with mentoring improved physical fitness compared to goal-setting approach without mentoring.

In the study by Ng et al. (14), a 24-week multi-domain intervention for older adults at risk of cognitive impairment at neighborhood senior centers was implemented. The program comprised dual-task exercises, cognitive training, and mobile application-based nutritional guidance. Patients in the IG underwent an improvement in Chair Stand Test and grip strength after 24 weeks. Similarly, in the study by Huguet et al. (18), potential benefits of a multidimensional training program were evaluated among 200 community-dwelling pre-frail older patients; at 12 months, individuals in the IG were characterized by lower prevalence of frailty and improved function mobility, with better performance in both the Timed Up and Go (TUG) and Five Time Sit to Stand (FTSST) tests. In the secondary analysis of the MAPT study by de Souto Barreto et al. (20), the effects of a long-term (3-years) multi-domain lifestyle intervention on the severity and incidence of frailty in older adults was investigated. Compared with controls, subjects in the multi-domain group had a decreased risk of developing both frailty and persistent frailty.

Another important study aimed to investigate the effect of multi-domain lifestyle intervention on daily functioning of older people was the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) conducted by Kulmala et al. In their first publication (21) they analyzed, for 2 years, a total of 1,260 older adults who were at risk of cognitive decline. The multi-domain intervention included simultaneous physical activity intervention, nutritional counseling, vascular risk monitoring and management, and cognitive training and social activity. During the 2-year intervention, the activity of daily living (ADL) disability score slightly increased in the control group, while in the intervention group, it remained relatively stable. In terms of physical performance, the intervention group had a slightly higher probability of improvement and a lower probability of decline for chair rise compared to the control group.

As previously reported, only one study (15) showed no benefit of multidomain intervention on physical activity. In this 6-month eMIND project by Barreto et al. (15), researchers evaluated the effects of a multi-domain lifestyle intervention composed of cognitive training, exercise training, and nutritional advices among community-dwelling older adults. One hundred-twenty participants were enrolled and randomized in the multi-domain intervention group and control group. Compared to controls, the intervention had a positive effect on health-related quality of life; no significant effects were observed across the other clinical and lifestyle outcomes.

Vitality

Five out of twelve studies assessed the effects of multi-intervention training on vitality (13–16, 18). Explored aspects of this domain included physical health (13–15, 18, 21), nutritional status (13, 15, 16, 18), and laboratory parameters (13, 14). In four studies (14, 15, 18, 21), the intervention was represented by a multidimensional training program, while in the study by Clare et al. (13) a goal-setting approach was used. Most of the studies reported beneficial effects of multidomain interventions on vitality at follow-up (13, 14, 18, 21), whereas one study (15) showed no significant effect.

The goal-setting approach (13) was associated with increased physical health, as measured in terms of aerobic capacity, flexibility, balance, agility, and hand grip strength; such approach was also associated with decreased serum cholesterol levels and decreased body fat percentage. Similarly, several multidomain trainings resulted to add some benefit in the IG; observed benefits included increased hand grip strength (14), preservation of daily functioning assessed *via* ADL (21), and increased nutrition and adherence to healthy diet habits (16, 18).

Psychosocial well being

Six out of twelve studies assessed the effects of multi-intervention training on psychosocial well-being (12–16, 18). Several aspects of this domain were investigated: self-efficacy and morale (12), mood (12, 13, 15), quality of life perception (14–16, 18), engagement in social and leisure activities (15). Most of the studies reported beneficial effects of multidomain interventions on psychosocial well-being (12, 13, 15, 16, 18), whereas only one study (14) showed no significant benefits.

In the study by Scult et al. (11), the researchers evaluated the effect of a healthy aging program for older adults on self-efficacy and morale. The Mind Body Intervention consisted of weekly, 90-min sessions for 9 consecutive weeks, directed by a psychologist. The program included sessions that taught participants: (1) a variety of methods to elicit the relaxation response, (2) the practice of adaptive coping and cognitions, (3) behaviors necessary to create a healthy lifestyle, and (4) methods of building social support. Significant increases in self-efficacy and morale were observed for program completers. In the study by Clare et al. (13), the goal-setting approach was associated with decreased depression scores, whilst changes in self-efficacy among groups were negligible.

Effects of multidimensional interventions on quality-of-life improvement were largely confirmed; in the study by Barreto et al. (14), HRQoL was the only dimension to improve in patients belonging to IG compared to CG; similarly, Rainero et al. (16) showed the effects of multidimensional interventions in preserving quality of life of pre-frail older adults after 12 months of follow-up; additionally, active participants showed

an increase in mood during the follow-up period; furthermore, Huguet et al. (18) demonstrated a net improvement in quality of life perception among participants undergoing a 6-month four-dimensional intervention.

The secondary analysis of the MAPT study was conducted by de Souto Barreto et al. (20) to investigate whether a long-term (3-years) multi-domain lifestyle intervention was associated with the severity and incidence of frailty in older adults. Authors recruited 1,637 older people divided in 821 controls and 816 who received a multi-domain lifestyle intervention (cognitive training, nutrition counseling, and advice on physical activity). The intervention involved 12 2-h sessions (in the first 2 months) followed by a 1-h session each month until the study end. Controls received the usual care but did not receive any personalized lifestyle intervention. The 4 outcomes were severity of frailty (continuous FI score), incident frailty, incidence of persistent frailty (frailty at 2 consecutive time points), and reversibility of frailty (from frailty to no-frailty). Compared with controls, subjects in the multi-domain group had a decreased risk of developing both frailty and persistent frailty.

Another important study aimed to investigate the effect of multi-domain lifestyle intervention on daily functioning of older people is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) conducted by Kulmala et al. In their first publication (21) they analyzed, for 2 years, a total of 1,260 older adults who were at risk of cognitive decline. The multi-domain intervention included simultaneous physical activity intervention, nutritional counseling, vascular risk monitoring and management, and cognitive training and social activity. During the 2-year intervention, the activity of daily living disability score slightly increased in the control group, while in the intervention group, it remained relatively stable. In terms of physical performance, the intervention group had a slightly higher probability of improvement and a lower probability of decline for chair rise compared to the control group.

The same data have been used by Lehtisalo et al. (22) to evaluate the effect of dietary changes adopted in older age. Adherence to healthy diet at baseline predicted improvement in global cognition, regardless of intervention allocation. Dietary improvement was associated with beneficial changes in executive function, especially in the intervention group.

Discussion

In the past, the study of aging process was strongly focused on health deficits (8), such as diseases, disabilities, and limitations; this view was supported by the strong relationship between increase in socio-economic burden on healthcare systems world-wide and the increase in prevalence of multimorbidity and disability among populations with high life expectancy. Despite the relevance of this model, aging should be investigated more broadly, since absence of diseases does not always go hand-in-hand with aging well. Rather than considering healthy aging from the disease-based perspective, the functioning-based approach promoted by WHO is oriented around building and maintaining the ability of older people to be and to do the things they have reason to value (4).

The availability of evidence on multi-domain interventions that include the IC framework is of paramount relevance for the health professionals, as they may provide them useful personalized strategies, to support the older patients' resilience and autonomy in daily life, and can be easily integrated with more traditional therapies and treatments. From the analysis of the selected multi-domain interventions, there are important considerations that can be taken into account.

First of all, the majority of successful interventions are based on a goal setting approach (24, 25): the older people are involved in the definition of the strategies to follow to remain active and independent. The wellbeing of the elderly does not necessarily fit the intervention goals derived from the prevention perspective of the researcher. It is very important to include the elderly themselves in the goal-setting process, as they prefer to set goals to achieve well-being that are more focused on the process of adaptation to any functional loss (26). However, a balance between personalization and clinical effectiveness should be reached in agreement with the participants, before the testing phase, in order to find a minimum core of standardized strategies to complement the personalized approach. This may allow the comparability and replicability of the intervention, in addition to assure the adherence and the compliance of the older people.

Despite the undeniable wealth of the IC framework, none of the study have used this to design the intervention, but only to assess the improvement in IC domains. From the analysis of the studies, Physical Activity is the domain that has been received the most of the attention, including specific multicomponent interventions to improve different functional capabilities such as aerobics, muscle strength, balance and gait, while Psychological support has been addressed mostly as counseling activity through pre-selected contents instead of a more patient-centered approach. How to include sensory domain still represents an open topic for the studies in the field. Within the clinical outcomes, moreover, self-efficacy and goal attainment should be considered as important psychosocial determinants to be assessed after any multi-domain intervention previous studies have shown that self-efficacy and social support in older women enhances adherence to strength-training programs (27). In the meta-analysis, barrier self-efficacy was involved in the maintenance of exercise behavior (28). Those competences, in fact, are drivers for the improvement of the health status, as well as for IC and functional ability maintenance (29). They also constitute the basis for the adoption of healthy lifestyles, assuring the sustainability of positive behaviors in the long-term (30). Nevertheless, an assessment tool to identify improvement of Intrinsic Capacity as a whole, not only as sum of domains, is still missing.

In order to be effective, any intervention should be adapted to the older people, easily accessible and integrated into the everyday life (31). At this purpose, the field of coaching through technology is receiving more and more interest, as effective strategies to provide patient-centered multicomponent healthcare interventions integrated with technology to foster self-management, prevention, adherence to treatments, positive health outcomes, and resilience, all factors that improve the IC (32). Therefore, the relevance of this study stands also in the way to identify the existing research trends and possible gaps that need to be applied in the near future when designing technology-based interventions. Indeed, all the aforementioned key strategies (i.e., the goal set-ting approach, the involvement of older adults in the definition of the strategy to follow to remain active and independent, etc.), could be seen as interconnectors between the field of technologies and the IC.

Despite this positive aspect, there are some limitations to this review. Firstly, data sources were drawn from specific databases (i.e., PubMed, Scopus, Embase, Google Scholar and Elsevier). The choice of using specific search terms could have omitted some results from the search. Moreover, we collected a relatively small sample of studies and excluded non-English language studies. It could be possible that other literary sources were available in other unselected databases or in other languages. Another possible limitation is the average age of the patients included in the studies analyzed, which is rather low and refers to an audience of young old people. Therefore, the conclusions we reached cannot be transferred to the entire elderly population. Moreover, results obtained should be interpreted with caution because some studies included in the review were reported as being built with low methodological quality. Despite these limitations, our study offers several research directions, which may take the existing debates to the next level.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

Author contributions

EM and RB: study concept and design. EM, RB, SC, and ET: acquisition of data (literature search and study selection). EM, RB, LS, and ET: analysis and interpretation of data (literature). EM, RB, LS, and VS: writing—original draft preparation. FL, GR, AC, and GP: critical revision of the manuscript for important intellectual content. JM, RW, TO, SW, KK, and IK: supervision. JM and TO: writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Serena Sabatini,
University of Italian Switzerland, Switzerland

REVIEWED BY
Daniel Blackburn,
Sheffield Teaching Hospitals NHS Foundation Trust, United Kingdom
Gabriela Cabett Cipolli,
State University of Campinas, Brazil

*CORRESPONDENCE
Daniel C. Mograbi
daniel.mograbi@kcl.ac.uk

†These authors have contributed equally to this work and share first authorship

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Predictors of functional impairment and awareness in people with dementia, mild cognitive impairment and healthy older adults from a middle-income country

Larissa Hartle[1†], Daniel C. Mograbi[1,2*†], Helenice Charchat Fichman[1], Camila Assis Faria[1], Maria Angélica Sanchez[3], Pricila C. C. Ribeiro[4] and Roberto Alves Lourenço[3,5]

[1]Department of Psychology, Pontifícia Universidade Católica, Rio de Janeiro, Brazil, [2]Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [3]Department of Internal Medicine, Faculty of Medical Sciences, Rio de Janeiro State University, Rio de Janeiro, Brazil, [4]Department of Psychology, Faculty of Philosophy and Humanities, Federal University of Minas Gerais, Belo Horizonte, Brazil, [5]Department of Medicine, Pontifícia Universidade Católica, Rio de Janeiro, Brazil

Objective: To investigate the demographic, clinical and cognitive correlates of functional capacity and its awareness in people with dementia (PwD; *n* = 104), mild cognitive impairment (PwMCI; *n* = 45) and controls (healthy older adults; *n* = 94) in a sample from a middle-income country.

Methods: Dementia and MCI were diagnosed, respectively, with DSM-IV and Petersen criteria. Performance in activities of daily living (ADL) at three different levels [basic (The Katz Index of Independence), instrumental (Lawton instrumental ADL scale) and advanced (Reuben's advanced ADL scale)], measured through self- and informant-report, as well as awareness (discrepancy between self- and informant-report), were compared between groups. Stepwise regression models explored predictors of ADL and their awareness.

Results: PwD showed impairment in all ADL levels, particularly when measured through informant-report. No differences were seen between controls and PwMCI regardless of measurement type. PwD differed in awareness of instrumental and basic, but not of advanced ADL, compared to controls. Age, gender, education and fluency were the most consistent predictors for ADL. Diagnosis was a significant predictor only for instrumental ADL. Awareness of basic ADL was predicted by memory, and awareness of instrumental ADL was predicted by general cognitive status, educational level, and diagnosis.

Conclusion: Results reinforce the presence of lack of awareness of ADL in PwD. Use of informant-reports and cognitive testing for fluency are suggested for the clinical assessment of ADL performance. Finally, assessment of instrumental ADL may be crucial for diagnostic purposes.

KEYWORDS

dementia, MCI, ADL, cognition, awareness, dependence, functional impairment

Introduction

Functional capacity, i.e., the ability to perform activities of daily living (ADL), is an important variable in the context of aging, being affected by a variety of chronic conditions linked to older age. Loss of functional ability is commonly associated with cognitive decline in older adults (1), and can be the distinguishing diagnostic criterion between dementia and mild cognitive impairment (2) (MCI), both being characterized by cognitive decline. It is known that there is a progressive loss of functional capacity in the course of dementia, with deficits in cognition and other abilities affecting the capacity to perform daily activities (3–5). Nevertheless, previous studies provided conflicting results in relation to the extent to which functional capacity is affected at each moment of the condition, probably due to the heterogeneity of patients under the same diagnosis but on different stages of the illness and with different degrees of cognitive impairment (6–9).

One important issue when considering the relationship between ADL performance and cognitive impairment is the existence of different levels of functional capacity according to the complexity of the activity (10). Typically, three levels are suggested: basic ADL, including simple self-care duties such as bathing and eating; instrumental activities, involving more complex tasks such as handling money and preparing meals; and advanced activities, including social life and hobbies. Advanced activities are the first to be impaired with the appearance of cognitive impairment (11, 12), but functional decline progresses until it affects even basic activities (1, 3). Any level of impairment can cause disability and, without the development of compensatory strategies to offset these difficulties, lead to dependence and decreases in the quality of life of people affected and their caregivers (13).

The notion of a hierarchy of ADL is particularly important for the diagnosis of MCI. Initially, it was believed that all levels of ADL would be preserved in this condition (2). However, studies have found that it may be possible to see subtle changes (12, 14), especially in more complex advanced activities (3, 11). It is possible that some measures are not sensitive enough to capture these subtle changes, especially when the activity can still be completed even when the subject makes mistakes (15, 16). Few studies have explored these small variations, but the ones that do suggest that performance accuracy will decrease with the escalation of cognitive impairment until the ability to live independently becomes fully compromised (15).

Studies that analyze the cognitive processes related to loss of functional capacity vary in their conclusions. In general, some evidence suggests that executive functioning is the best predictor of functional capacity (3, 8), but there is also evidence that deterioration in the ability to perform everyday tasks could be related to a general cognitive impairment (17). It is also useful to differentiate between commission errors (performing a step incorrectly—using salt instead of sugar to make a cake) and omission errors (not performing a step—not using sugar at all), with only the latter error being related to a deficit in general cognitive resources (17). Other studies found that omission errors seem to be also linked to memory impairment (14, 15). Generally, studies that search for cognitive correlates of functional capacity focus on one function, one diagnosis or one ADL level at a time, instead of combining all of them. Advanced ADL are the least studied (3).

One potential issue leading to heterogeneity of results may be that cognitively impaired patients do not fully acknowledge the extent to which they have functional impairments. This lack of awareness about the diagnosis and its consequences has been termed anosognosia. Although findings are mixed, it has been shown that people with MCI (PwMCI) may have limited awareness about their abilities (18). A recent meta-analysis, for example, suggested that there already is mild anosognosia of cognitive abilities in PwMCI, and that it becomes more severe in dementia (19), despite the relationship between awareness and dementia severity not being linear (20, 21). Lack of awareness was mainly measured by comparing informant- and self-reports in identified studies (19) and results suggest that the use of informant-based measures assessing functional abilities may be relevant not only to PwD, but also to PwMCI.

A better understanding of the association between cognitive impairment, ADL performance and its awareness is critical to aid the development of better interventions, rehabilitation programs and compensatory strategies. These studies are especially relevant for low- and middle-income countries (LMIC), considering the scarcity of data from these world regions in comparison to developed countries (22). Studies in LMIC may also shed light on the specific contribution

of sociodemographic variables to ADL. For example, lower educational level, and consequently poorer executive functions performance, may impact functional capacity.

Accordingly, the current study aimed to investigate functional capacity and awareness in dementia and MCI with a sample from a LMIC. Specifically, three levels of ADL were explored (advanced, instrumental and basic), measured both by self- and informant-report. In addition to exploring differences between patient groups, sociodemographic and cognitive correlates for each type of ADL and awareness of functional ability were also investigated.

Materials and methods

Participants and setting

The sample for this study was obtained from the Frailty in Brazilian Older People—Rio de Janeiro Section (FIBRA Study) stage II database (23, 24). FIBRA study was organized in two stages: screening for cognitive impairment (I) and diagnostic evaluation (II). A flowchart can be seen in **Figure 1**. During stage I, a gender and age-stratified sample from a Brazilian private healthcare plan received home visits by trained research assistants and had their cognitive performance and functional capacity assessed, respectively, by the Mini-Mental State Examination (25, 26) (MMSE) and the Functional Activities Questionnaire (27, 28) (FAQ). The criteria for inclusion in the FIBRA study were having been a client of the health care plan for at least 12 months, being at least 65 years old, and a resident in one of the districts of the North Zone of Rio de Janeiro City.

During stage I, the sample was divided into two groups based on MMSE and FAQ performances. The first one—250 subjects with MMSE $\geq$ 28, and 215 with MMSE $<$ 28, but without loss of functional capacity (FAQ $<$ 5)—were regarded as cognitively unimpaired and thus negative for dementia syndrome and MCI. From this group, a sample (n = 44) was drawn randomly for evaluation in Stage II, to check for the presence of false negatives (none of them were diagnosed as having dementia). The second group—271 subjects with MMSE scores $<$ 28 and FAQ $\geq$ 5—were considered suspected of having dementia or MCI and were invited to be assessed by clinical and neuropsychological evaluations (stage II). The assessment was carried out by a multidisciplinary team led by a geriatrician.

The eligibility criteria defined for inclusion of participants in Stage II—diagnostic evaluation, in addition to their MMSE score as described above, were their score on the FAQ. They were contacted by telephone and referred for a comprehensive geriatric assessment, which included cognitive and functional evaluation. The diagnosis of dementia syndrome and MCI was established by consensus among geriatricians and neuropsychologists according to the Diagnostic and Statistical Manual of Mental Disorder-Fourth Edition (29) and Petersen (30) criteria, respectively. The diagnosis also relied on laboratory tests and neuroimaging and neuropsychological tests (instruments section below) (23).

In order to take part in the current study, all participants needed to have an informant living or being in close contact with them for at least 10 years and being at least 23 years old [such that informants would have been at least adolescents (13 + years) when their contact initiated]. Some participants had missing informant or self-report measures of ADL and were also excluded.

The present study analyzed data from 243 participants who fulfilled all these criteria. Based on these assessments, the sample was split into the following subgroups: 104 participants diagnosed with dementia; 45 diagnosed with MCI and 94 healthy older adults (hereafter, control participants). Although information about dementia subtype was not fully available for the dementia group, most had a diagnosis of Alzheimer's Disease.

Instruments

Cognitive abilities

General cognitive level was measured through the MMSE (25, 26), with scores ranging from 0 to 30. Episodic memory was assessed through the Rey Auditory Verbal Learning Test (31), focusing on immediate (A1) and delayed recall (A7). Working memory was measured with the digit span test from the Wechsler Adult Intelligence Scale (32), with total scores calculated as the sum of the direct and reverse digit span. Finally, fluency was assessed through the semantic (total number of animals named) and phonemic fluency (total number of words named with the letters FAS) tasks (33, 34). As an informant measure of cognitive decline, the IQCODE (35, 36) was used. The questionnaire contains 26 items and seeks to retrospectively verify change in an elderly everyday cognitive function.

Activities of daily living

Activities of daily living (ADL) were assessed through three different instruments. For all instruments, self-report and informant report were obtained. Informants were people in close contact with the participants (see previous section), typically relatives (partners and children).

Advanced activities of daily living

Were measured with Reuben's advanced ADL scale (37). This 12-item questionnaire assesses independent functioning and participation in activities such as traveling and taking part in cultural events, clubs, political events and religious institutions. Activities that were lost or never tried were scored as 0, and preserved activities were scored as 1. Total scores ranged from 0 to 10.

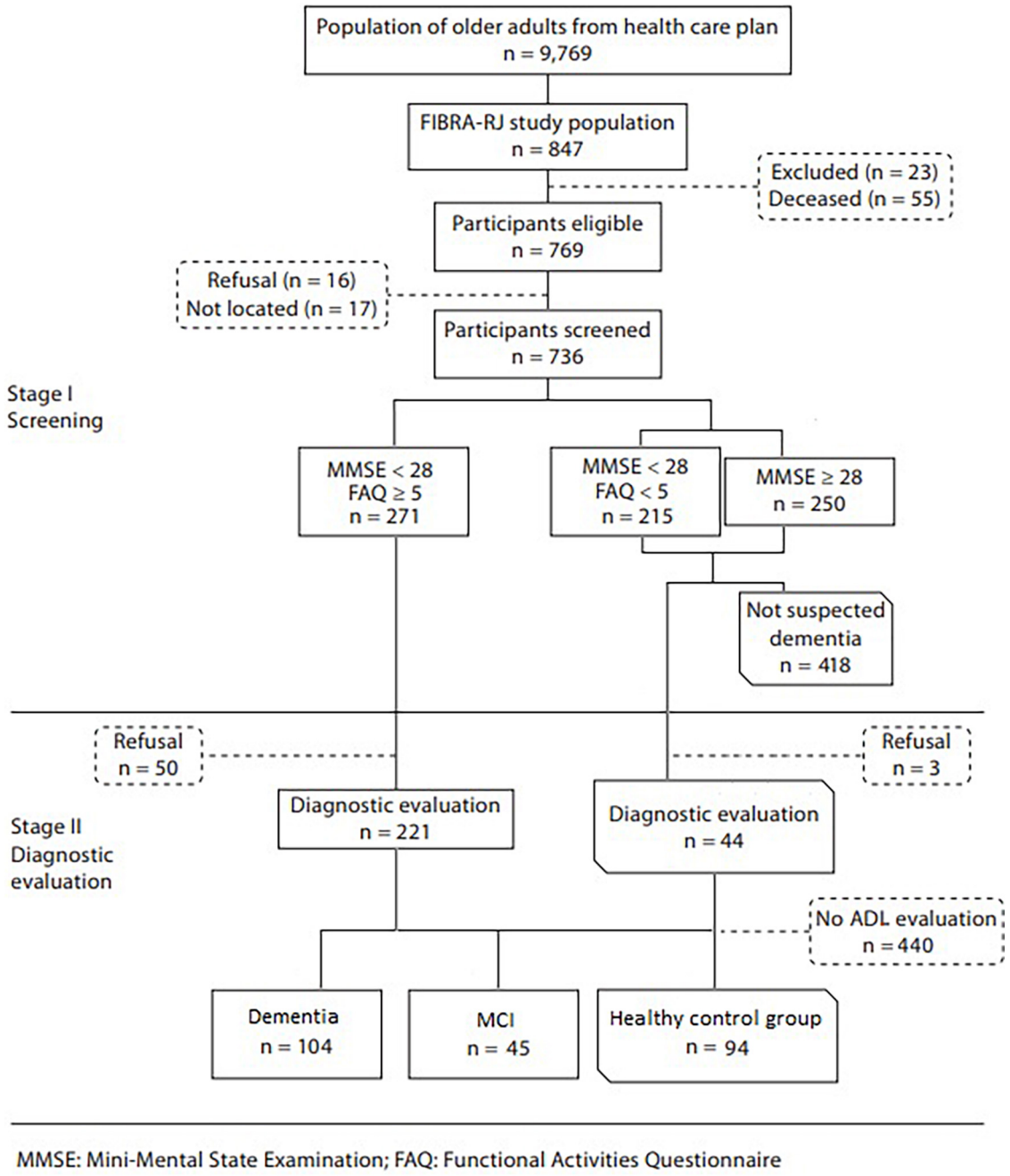

FIGURE 1
Flowchart of the FIBRA study.

Instrumental activities of daily living

Were measured with the Lawton instrumental ADL scale (38, 39). The scale assesses the ability to use the phone, shop, travel alone, prepare meals, do housework and handle finances and medication. Total scores ranged from 8 to 21, with higher scores indicating more preserved abilities.

Basic activities of daily living

Were measured with The Katz Index of Independence in ADL. The scale has six items assessing bathing, dressing, personal hygiene, feeding, mobility and continence (40, 41). To keep consistency with the other ADL measurements, the scale was reverse scored, such that higher scores indicate more preserved abilities. Total scores ranged from 6 to 18.

Awareness of functional ability

Awareness was assessed through the discrepancy between self-report and informant-report, a method widely used in the literature (42). For each ADL questionnaire (advanced, instrumental and basic), informant-report was subtracted from self-reported, such that positive scores indicate overestimation of ability.

Statistical analysis

Data analysis was carried out using SPSS software (version 20.0). Descriptive statistics were used to illustrate the sample characteristics, with differences between groups being tested with one-way ANOVAs, followed by *post hoc t*-tests, or a chi-square test in the case of gender.

For each ADL type (advanced, instrumental and basic), differences between groups (PwD, MCI and controls) were calculated with one-way ANOVAs, followed by pairwise comparisons adjusted with Bonferroni corrections. This was done for self-report, informant-report and discrepancy scores (awareness variables).

Finally, stepwise regression models were calculated to explore predictors of functional capacity and awareness. Predictors included demographic (educational level, gender and age), clinical (diagnostic group) and cognitive variables (MMSE score, digit span, phonemic fluency, categorical fluency, RAVLT immediate memory and delayed recall). Models were run separately for each type of ADL (advanced, instrumental or basic) and variable [self-, informant-report, discrepancy score (awareness)]. In all models, to avoid inflation of type II error and exclusion of predictors involved in suppressor effects, we used a backward regression method. The best models were selected on the basis of a trade-off between highest explained variance (R^2), highest cross-validity (adjusted R^2) and Akaike's Information Criterion (AIC).

Results

Sample characteristics

The demographic characteristics and clinical profile of the sample are described in **Table 1**. There were significant differences in age between groups [$F(2, 240) = 27.94$, $p < 0.001$], with PwD being older than controls and MCI group ($p < 0.001$). Educational level was also significantly different between groups, [$F(2, 239) = 8.72$, $p < 0.001$], with fewer years of education in the PwD group in relation to controls. There were no differences in terms of gender distribution between groups [$\chi^2(2) = 3.14$, $p = 0.214$].

Regarding clinical and cognitive variables, as expected there were significant differences between groups ($p < 0.001$ for all ANOVAs). For the memory variables (RAVLT immediate and delayed recall and digit span), PwD performed worse than MCI and control participants, and MCI participants performed worse than controls (p-values from < 0.001 to < 0.05). For the MMSE, IQCODE, digit to symbol and fluency tasks, PwD performed worse than controls and participants with MCI (p-values from < 0.001 to < 0.05), but there were no significant differences between these two groups.

Differences in activities of daily living

Self-report

ANOVA results indicated significant differences between groups for advanced [$F(2, 211) = 9.77$, $p < 0.001$], instrumental [$F(2, 215) = 27.60$, $p < 0.001$] and basic ADL [$F(2, 216) = 3.70$, $p = 0.026$]. Means can be seen in **Table 2**. *Post hoc* tests indicated that for advanced ADL PwD reported less preserved abilities than controls ($p < 0.001$), but there were no significant differences between participants with MCI and controls ($p = 0.495$) or PwD ($p = 0.070$). Pairwise comparisons of instrumental ADL indicated less preserved abilities for PwD in relation to both MCI and control participants ($p < 0.001$ in both cases), but no significant differences between these two groups ($p = 0.999$). For basic ADL, there were no differences between controls and PwD ($p = 0.135$) or MCI participants ($p = 0.999$), but a significant difference between the latter group and PwD ($p = 0.036$).

Informant report

ANOVA results indicated significant differences between groups for advanced [$F(2, 229) = 18.92$, $p < 0.001$], instrumental [$F(2, 234) = 98.76$, $p < 0.001$] and basic ADL [$F(2, 232) = 26.72$, $p < 0.001$]. Means can be seen in **Table 2**. *Post hoc* tests indicated a similar pattern for all types of ADL, with no significant differences between controls and PwMCI ($p > 0.05$), but PwD having less preserved abilities than controls and PwMCI ($p < 0.001$ in all cases).

Awareness

ANOVA results indicated significant differences between groups for basic [$F(2, 206) = 10.57$, $p < 0.001$] and instrumental [$F(2, 209) = 33.68$, $p < 0.001$], but not for advanced ADL awareness [$F(2, 200) = 0.421$, $p = 0.657$]. Means can be seen in **Table 2**. *Post hoc* tests indicated significant differences in awareness of basic ADL abilities between controls and PwD ($p < 0.001$), and between PwMCI and PwD ($p = 0.002$), but not between controls and MCI ($p = 0.999$). Differences in instrumental ADL awareness were significant only between controls and PwD ($p < 0.001$).

TABLE 1 Sociodemographic and clinical characteristics of participants.

Variable	Dementia (n = 104) Mean (SD), range	MCI (n = 45) Mean (SD), range	Control group (n = 94) Mean (SD), range
Age (mv = 0)	85.1 (7.4), 67–101	79.2 (6.9), 67–92	77.9 (7.5), 67–98
Education (mv = 2)	7.1 (5.3), 0–20	8.7 (4.8), 0–18	10.2 (5.2), 0–22
Gender*(mv = 0)	81/23	30/15	64/30
MMSE (mv = 12)	18.0 (6.5), 0–28	25.6 (3.5), 14–30	27.2 (2.4), 18–30
IQCODE (mv = 65)	4.0 (0.6), 3.0–5.0	3.4 (0.2), 3.0–4.0	3.2 (0.2), 2.8–4.0
RAVLT			
Immediate recall (mv = 49) Delayed recall (mv = 51)	23.2 (7.6), 10–45 2.1 (2.3), 0–10	32.0 (9.1), 9–49 4.7 (2.5) 0–9	38.9 (9.5), 15–60 6.8 (3.0), 0–14
Digit Span (mv = 45)	8.9 (2.9), 2–16	10.7 (3.3), 3–17	12.4 (3.3), 5–23
Digit to symbol (mv = 71)	11.8 (9.0), 0–35	27.4 (13.4), 5–72	28.7 (14.6), 1–69
CAMCOG (mv = 61)	57.7 (15.9), 18–93	78.7 (11.0), 42–100	82.9 (10.4), 44–101
Verbal fluency			
Categorical (mv = 48) Phonemic (mv = 49)	18.8 (4.3), 3–52 8.2 (3.3), 1–15	25.3 (11.2), 9–56 10.9 (3.3), 4–19	29.8 (11.5), 2–67 12.0 (3.4), 1–20

*Number of female/male; Analysis of differences in the gender variable using chi-square test; other analyses using t-test.
mv, missing value.

TABLE 2 Activities of daily living performance and awareness divided by group.

Variable	Dementia (n = 104) mean (SD), range	MCI (n = 45) mean (SD), range	control group (n = 94) mean (SD), range	Differences
Self-report				
Advanced ADL[a] (mv = 29, 0, 0)	3.5 (2.1), 0–8	4.5 (2.7), 1–10	5.1 (2.6), 0–10	PwD = MCI; PwD < CG; MCI = CG
Instrumental ADL[b] (mv = 25, 0, 0)	15.2 (3.8), 8–21	18.7 (2.1), 13–21	18.5 (3.2), 8–21	PwD < MCI = CG
Basic ADL[c] (mv = 25, 1, 0)	16.1 (2.5), 6–18	17.2 (1.3), 11–18	16.8 (2.2), 6–18	PwD < MCI; PwD = CG; MCI = CG
Informant-report				
Advanced ADL (mv = 1, 3, 7)	2.9 (2.3), 0–8	4.5 (2.5), 1–9	5.1 (2.6), 1–10	PwD < MCI = CG
Instrumental ADL (mv = 0, 0, 6)	11.9 (3.9), 7–21	18.3 (2.4), 13–21	18.2 (3.3), 7–21	PwD < MCI = CG
Basic ADL (mv = 1, 0, 7)	13.8 (4.2), 6–18	17.1 (1.5), 10–18	16.7 (2.3), 6–18	PwD < MCI = CG
Awareness				
Advanced ADL (mv = 29, 3, 7)	0.1 (1.6), −5–5	−0.2 (1.6), −6–3	0.0 (1.1), −5–4	PwD = MCI = CG
Instrumental ADL (mv = 25, 0, 6)	2.2 (2.4), −2–9	0.4 (1.1), −1–4	0.2 (1.0), −4–4	PwD = MCI; PwD > CG; MCI = CG
Basic ADL (mv = 25, 0, 7)	0.9 (2.0), −4–8	0.1 (0.5), −1–2	0.1 (0.5), −1–2	PwD > MCI = CG

[a]Reuben's advanced ADL scale.
[b]Lawton instrumental ADL scale.
[c]The Katz Index of Independence.
mv, missing values.

Regression models

There was no evidence of collinearity in the data, with VIF and tolerance values within the recommended range (43). Significant predictors can be seen in **Tables 3–5**.

Self-report

All regression models significantly predicted advanced, instrumental and basic ADLs ($p < 0.01$ in all models). For advanced ADL, the model with the best trade-off between AIC score, explained variance ($R^2 = 0.28$) and highest cross-validity (adjusted $R^2 = 0.27$) included phonemic fluency (standardized $\beta = 0.32$, $p < 0.001$), age (standardized $\beta = -0.24$, $p < 0.001$), and categorical fluency, but the latter variable did not give a significant contribution to the model ($p = 0.181$).

For instrumental ADL, the model with the best (lowest) AIC score, highest explained variance ($R^2 = 0.39$) and highest cross-validity (adjusted $R^2 = 0.37$) included female gender (standardized $\beta = 0.13$, $p = 0.034$), age (standardized $\beta = -0.31$, $p < 0.001$), categorical fluency (standardized

β = 0.23, p = 0.005), immediate recall (standardized β = 0.24, p = 0.029), and variables which did not give a significant contribution to the model, such as phonemic fluency (p = 0.194), delayed recall (p = 0.371) and educational level (p = 0.182).

For basic ADL, the model with the best (lowest) AIC score, highest explained variance (R^2 = 0.13) and highest cross-validity (adjusted R^2 = 0.10) included educational level (standardized β = –0.21, p = 0.008), phonemic fluency (standardized β = 0.30, p = 0.003) and variables which did not give a significant contribution, such as age (p = 0.051), diagnosis (p = 0.387), categorical fluency (p = 0.563) and delayed recall (p = 0.064).

Informant-report

All regression models significantly predicted advanced, instrumental and basic ADLs ($p \leq 0.001$ in all models). For advanced ADL, the model with the best (lowest) AIC score, highest explained variance (R^2 = 0.30) and highest cross-validity (adjusted R^2 = 0.28) included phonemic fluency (standardized β = 0.32, $p < 0.001$), female gender (standardized β = 0.14, p = 0.036), age (standardized β = –0.25, $p < 0.001$), and variables which did not give a significant contribution to the model, such as categorical fluency (p = 0.297) and educational level (p = 0.514).

For instrumental ADL, the model with the best trade-off between AIC score, highest explained variance (R^2 = 0.54) and highest cross-validity (adjusted R^2 = 0.52) included all variables, except delayed recall, with significant contributions of diagnosis (standardized β = –0.18, p = 0.016), female gender (standardized β = 0.15, p = 0.009), age (standardized β = –0.25, $p < 0.001$), educational level (standardized β = –0.15, p = 0.011), categorical fluency (standardized β = 0.18, p = 0.011), MMSE (standardized β = 0.16, p = 0.023), immediate recall (standardized β = 0.17, p = 0.025), but not of phonemic fluency (p = 0.056) or digit span (p = 0.199).

For basic ADL, the model with the best trade-off between AIC score, highest explained variance (R^2 = 0.15) and highest cross-validity (adjusted R^2 = 0.12) included educational level (standardized β = –0.25, p = 0.002), phonemic fluency (standardized β = 0.26, p = 0.007) and variables which did not give a significant contribution, such as age (p = 0.060), categorical fluency (p = 0.391), MMSE (p = 0.360) and delayed recall (p = 0.708).

Awareness

The regression models significantly predicted instrumental and basic ADL awareness ($p \leq 0.01$ in all models), but not advanced ADL awareness. For instrumental ADL awareness, the model with the best trade-off between AIC score, highest explained variance (R^2 = 0.27) and highest cross-validity (adjusted R^2 = 0.24) included diagnosis (standardized β = 0.31, p = 0.001), educational level (standardized β = 0.16, p = 0.036), MMSE (standardized β = –0.20, p = 0.035) and variables which did not give a significant contribution, such as digit span (p = 0.120), phonemic fluency (p = 0.306), and delayed recall (p = 0.082).

For basic ADL, the model with the best trade-off between AIC score, highest explained variance (R^2 = 0.09) and highest cross-validity (adjusted R^2 = 0.07) included only delayed recall as a significant predictor (standardized β = –0.20, p = 0.018), and variables which did not give a significant contribution, such as educational level (p = 0.095), categorical fluency (p = 0.318), and MMSE (p = 0.276).

Discussion

Results have shown more impairments in all ADL levels for PwD. Considering self-reported ability, PwD were more impaired than controls in advanced and instrumental activities

TABLE 3 Regression models with predictors for ADL self-report scales scores.

	Basic ADL[a]		Instrumental ADL[b]		Advanced ADL[c]	
Variable	**β**	***P*-value**	**β**	***P*-value**	**β**	***P*-value**
Educational level	–0.21	0.008				
Phonemic fluency	0.30	0.003			0.32	<0.001
Age			–0.31	<0.001	–0.24	<0.001
Female gender			0.13	0.034		
Categorical fluency			0.23	0.005		
Immediate recall			0.24	0.029		
Model p-value	<0.01		<0.01		<0.01	
R^2	0.13		0.39		0.28	
Adjusted R^2	0.10		0.37		0.27	

ADL, Activities of Daily Living; Basic ADL, The Katz Index of Independence; Instrumental ADL, Lawton. instrumental ADL scale; Advanced ADL, Reuben's advanced ADL scale.
[a] The Katz Index of Independence.
[b] Lawton instrumental ADL scale.
[c] Reuben's advanced ADL scale.

TABLE 4 Regression models with predictors for ADL informant-report scales scores.

	Basic ADL[a]		Instrumental ADL[b]		Advanced ADL[c]	
Variable	**β**	***P*-value**	**β**	***P*-value**	**β**	***P*-value**
Educational level	−0.25	0.002	−0.15	0.011		
Phonemic fluency	0.26	0.007			0.32	<0.001
Diagnostic group			−0.18	0.016		
MMSE score			0.16	0.023		
Categorical fluency			0.18	0.011		
Immediate recall			0.17	0.025		
Female gender			0.15	0.009	0.14	0.036
Age			−0.25	<0.001	−0.25	<0.001
Model *p*-value		<0.001		<0.001		<0.001
R^2		0.15		0.54		0.30
Adjusted R^2		0.12		0.52		0.28

ADL, Activities of Daily Living; Basic ADL, The Katz Index of Independence; Instrumental ADL, Lawton instrumental ADL scale; Advanced ADL, Reuben's advanced ADL scale; MMSE, Mini-Mental State Examination.
[a] The Katz Index of Independence.
[b] Lawton instrumental ADL scale.
[c] Reuben's advanced ADL scale.

and more impaired than PwMCI in instrumental and basic activities. In the informant-reported measures, PwD were more impaired than both groups in all types of ADL. No differences were seen between controls and PwMCI regardless of type of measure. Age, gender, education and fluency were the most consistent predictors for ADL performance, across measurement types and level of complexity. Regarding awareness, for advanced ADL there were no differences between groups and no significant regression model. By contrast, PwD showed decreased awareness relative to controls for instrumental and basic, and relative to MCI for basic ADL. Memory was the only predictor for basic ADL awareness, while diagnosis, general cognitive status and educational level were significant predictors for instrumental ADL awareness.

Significant differences found between controls and PwD are in line with standard findings (22). ADL performance gradually decreases with progression of dementia, eventually affecting even basic activities (1, 3). Although all levels of ADL performance were significantly different concerning informant-report, it is important to highlight that the differences in self-reported measures between PwD and controls did not include basic activities. A possible explanation is related to unawareness within the PwD group, also found in other studies [e.g., (44)]. Because basic activities are the last to be impaired in the course of dementia, cognitive deficits may have already affected the subjects' awareness by then (4). In this case, informants perceive the deficit, but not PwD, who overestimate their performance, attenuating group differences. This notion is supported by PwD showing poorer awareness of ability relative to controls for both instrumental and basic ADL in the current study.

Regarding advanced ADL, in the self-report measures PwD are impaired only in relation to controls, whilst for informant-report PwD have lower ability in relation to both controls and PwMCI. Again, this suggests that informant-report may be more reliable to ascertain functional change. Direct comparison of awareness of advanced ADL between groups did not show significant differences, but it is possible this was caused by generally low scoring in the variable (i.e., a floor effect).

Lack of significant differences in ADL between control participants and PwMCI is consistent with the definition of this condition, with MCI being characterized by cognitive impairment in the absence of functional deficits (2). Nevertheless, this has been recently questioned in the literature (12, 17). It is possible that the measures used may not be sensitive enough to detect subtle functional changes (45), with impairments at this level affecting the processes more than their results, making difficulties less noticeable (15, 16). Results indicate that PwMCI show good awareness of their functional abilities, with consistent scores regardless of type of report, something that has been reported previously (46). PwMCI also did not show significant differences in relation to controls in any of the awareness variables, with mean values very close to zero, suggesting accurate assessment of ability.

Cognitive and demographic predictors of functional ability were generally consistent across measurement type and ADL level. Higher phonemic fluency and lower age predicted better advanced ADL for both measurement types; in the informant variable, women showed better functional capacity. Older age may lead to decreases in advanced ADL since it is the greatest risk factor for cognitive decline (13). By its turn, cognitive decline causes loss of functional capacity (1), which starts with advanced activities (11).

The presence of phonemic fluency in the models may suggest cognitive processes that are at some level linked to advanced ADL performance. This statement, however, should be considered with three caveats. First, fluency tests are

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TABLE 5 Regression models with predictors for ADL awareness.

	Basic ADL[a]		Instrumental ADL[b]	
Variable	**β**	***P*-value**	**β**	***P*-value**
Delayed recall	−0.20	0.018		
Educational level			0.16	0.036
Diagnostic group			0.31	0.001
MMSE score			−0.20	0.035
Model *p*-value		<0.01		<0.01
R^2		0.09		0.27
Adjusted R^2		0.07		0.24

ADL, Activities of Daily Living; Basic ADL, The Katz Index of Independence; Instrumental ADL, Lawton instrumental ADL scale; MMSE, Mini-Mental State Examination.
[a]The Katz Index of Independence.
[b]Lawton instrumental ADL scale.

influenced by a variety of different cognitive processes (47, 48), and also, potentially, demographic variables [e.g., age and educational level; (45), lacking in specificity]. Second, the absence of other cognitive variable suggests that other processes, not cognitive in nature, may be involved [e.g., mood disorder (4)]. Third, in a similar sense, phonemic fluency is a test highly sensitive to conditions that affect the frontal lobes (49) and processing speed (47), which can be linked to mood changes, for instance (50, 51).

In the informant report, gender was also a predictor, with women showing better functional ability. Although biological hypotheses could be made, this finding may be more readily explained by differences in perception due to psychosocial and cultural roles. Men usually engage more in work-life (52) and less in hobbies, groups and social activities in life, continuing with this pattern in older age (53). Diminished activities can be seen as normal by men themselves, being reported differently by caregivers.

Instrumental activities abilities were, in both models, also predicted by age and gender, as well as by categorical fluency, immediate recall and education. Diagnosis and MMSE were present in the informant-report model as well. Age and gender are present in this model probably for the same reasons they were present as predictors for advanced activities. The presence of gender for both informant and self-report may be explained by the fact that men are commonly and consciously less involved in housework than women (52), with instrumental activities measures focusing precisely on this type of activity.

Instrumental ADL models included more cognitive variables than for advanced and basic ADL. Both self- and informant-report models included categorical fluency and immediate recall. This is consistent with previous findings that relate instrumental abilities primarily to executive functioning and memory (3, 45). Categorical fluency is also related to other cognitive functions (47, 48) and demographic variables such as age and education (54). Regarding this and that informant-report model includes also the variables MMSE and diagnosis, a possible conclusion is that instrumental activities performance depends highly on global cognitive status, as has already been indicated in the literature (7, 14, 15, 45, 55). It is worth highlighting the fact that diagnosis was a predictor only for instrumental ADL, which suggests the diagnostic value of this variable when identifying PwD from those with MCI and healthy older adults. This also suggests that although dementia diagnosis contributes to disability across activities type, other factors, such as age, are stronger predictors of functional capacity.

Education is a variable that may often be undetected as a predictor of functional capacity because most studies about the theme have been conducted in developed countries, characterized by higher educational homogeneity. In this study, the variable appeared in instrumental and basic ADL models, both in self- and informant- report. Higher education is one of the factors known to provide higher cognitive reserve (56), a protection against cognitive impairment (56, 57) and consequently against its consequences such as functional loss (1).

In addition to education, both basic ADL prediction models included also phonemic fluency. First, it is important to highlight that phonemic fluency is associated with education (54). It has also been shown to be associated with diverse cognitive processes, such as language, executive functions and processing speed (47, 48). Current findings highlight the fact that cognitive impairment can be linked to poorer basic ADL performance (1), despite lower complexity to perform these activities.

Regarding awareness, general cognitive level was a significant predictor of instrumental ADL awareness, and memory was the only predictor of awareness of basic ADL, although explained variance was low for the latter. Altogether these findings suggest that awareness in can be considered a neurocognitive ability, as proposed by theoretical models (58). Additionally, awareness of instrumental ADL was also predicted by diagnosis and educational level. This reinforces the notion of lack of awareness as a marker of dementia (19), also suggesting that wider social awareness, including access to educational resources and general knowledge about the condition, may impact on self-perception of ability (59). In agreement with

the current study, associations between awareness in dementia and educational level have been reported before [e.g., (56)]. There were no significant models for awareness of advanced ADL, which can be explained either by variables not included in the model, such as mood and personality playing a role in perception of advanced ADL, or by lack of variance for this variable in the current study.

One limitation of the current study refers to the measurement of the main variables explored. The neuropsychological test battery could have been more diverse, exploring also cognitive abilities such as inhibitory control and planning. Nevertheless, a briefer battery was chosen considering application time and the populational approach used in the current study. Questionnaire measurements of ADL also may be criticized for reduced ecological validity, and, ideally, observational measures should be applied. Nevertheless, in the current setting, such measures were not possible, so future community-based work should consider the applicability of ADL outcomes with increased ecological validity. Another limitation is the lack of information regarding specific diagnosis for all participants within the dementia group. Different types of dementia could have led to distinct profiles in terms of ADL and awareness impairment. Nevertheless, where information is available, most participants had Alzheimer's disease, the most common form of dementia in older adults. Future studies could explore ADL performance and awareness, as well as their predictors, in different types of dementia.

Conclusion

In conclusion, the results imply lack of awareness of ADL ability, as well as poorer performance, in PwD, with a subtle decrease in performance in PwMCI in advanced activities. As informant-report consistently showed differences between PwD and both other diagnostic groups in all ADL levels, using informant measures may be crucial for clinical assessment of functional capacity. Using ADL screening may be especially important to LMIC countries, where more expensive methods are not available (60). Regarding cognition, testing fluency can also have an important role as it appeared as a predictor of all ADL types of performance. Even though cognition may play a smaller role in advanced ADL abilities, instrumental abilities are the most consistently affected within each diagnostic group. This finding suggests that the latter level may be the one most directly and purely affected by global cognitive impairment, which is reinforced by the inclusion of diagnosis as a significant predictor. Finally, it is worth highlighting the finding about the relationship between educational level and ADL, considering that this factor may be often overlooked in more developed regions. This suggest that educational achievement, as well as improving cognitive reserve, may, potentially, have a direct impact in functional capacity, warranting further studies in developing countries.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

Ethics statement

Stage I of the FIBRA study was approved by the Pedro Ernesto University Hospital Ethics Committee (1850-CEP HUPE/2007), with subsequent approval for stage II (0163.2008-COEP UERJ 027/2008). All participants and their caregivers provided informed consent.

Author contributions

RL was responsible for the conception and design of the study. CF and PR were responsible for data acquisition and the database organization. LH was responsible for the writing. DM and LH were responsible for data analysis. DM, LH, HF, MS, and RL contributed to the interpretation. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Beatrice Arosio,
University of Milan, Italy

REVIEWED BY
Yanxia Lu,
Shandong University, China
Heewon Jung,
University of Ulsan, South Korea

*CORRESPONDENCE
Laura Tay
laura.tay.b.g@singhealth.com.sg

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Intrinsic capacity rather than intervention exposure influences reversal to robustness among prefrail community-dwelling older adults: A non-randomized controlled study of a multidomain exercise and nutrition intervention

Laura Tay[1,2]*, Ee-Ling Tay[3], Shi Min Mah[3], Aisyah Latib[4] and Yee-Sien Ng[2,5]

[1]Geriatric Medicine, Department of General Medicine, Sengkang General Hospital, Singapore, Singapore, [2]Geriatric Education and Research Institute, Singapore, Singapore, [3]Department of Physiotherapy, Sengkang General Hospital, Singapore, Singapore, [4]Centre for Population Health Research and Implementation, SingHealth, Singapore, Singapore, [5]Department of Rehabilitation Medicine, Singapore General Hospital, Singapore, Singapore

Background: The differential risk profiles associated with prefrailty may be attributable to underlying intrinsic capacity (IC).

Objectives: We examine (i) effect of a multi-domain physical exercise and nutrition intervention on pre-frailty reversal in community-dwelling older adults at 1-year, and (ii) whether IC contributes to pre-frailty reversal.

Methods: Prefrail participants in this non-randomized study were invited to attend a 4-month exercise and nutritional intervention following a frailty screen in the community. Prefrailty was operationalized as (i) FRAIL score 1–2 or (ii) 0 positive response on FRAIL but with weak grip strength or slow gait speed based on the Asian Working Group for Sarcopenia cut-offs. Participants who fulfilled operational criteria for prefrailty but declined enrolment in the intervention programme served as the control group. All participants completed baseline IC assessment: locomotion (Short Physical Performance Battery, 6-minute walk test), vitality (nutritional status, muscle mass), sensory (self-reported hearing and vision), cognition (self-reported memory, age- and education adjusted cognitive performance), psychological (Geriatric Depression Scale-15, self-reported anxiety/ depression). Reversal of prefrailty was defined as achieving a FRAIL score of 0, with unimpaired grip strength and gait speed at 1-year follow-up.

Results: Of 81 participants (70.0 ± 6.6 years, 79.0% female), 52 participants (64.2%) were enrolled in the multi-domain intervention, and 29 participants (35.8%) who declined intervention constituted the control group. There was no difference in age, gender and baseline composite IC between groups. Reversal

to robustness at 1-year was similar between intervention and control groups (30.8% vs. 44.8% respectively, $p = 0.206$). Reduced prevalence of depression was observed among participants in the intervention group at 1-year relative to baseline (7.8% vs. 23.1%, $p = 0.022$). In multiple logistic regression, intervention had no effect on prefrailty reversal, while higher composite IC exhibited reduced likelihood of remaining prefrail at 1-year (OR = 0.67, 95% CI 0.45–1.00, $p = 0.049$).

Conclusion: Focusing only on the locomotion and vitality domains through a combined exercise and nutritional intervention may not adequately address component domain losses to optimize prefrailty reversal. Future studies should examine whether an IC-guided approach to target identified domain declines may be more effective in preventing frailty progression.

KEYWORDS

intrinsic capacity, frailty, prefrailty, exercise, nutrition, elderly

Introduction

Healthy aging has been presented by the World Health Organization (WHO) as the process of developing and maintaining the functional ability to enable well-being in older age (1). Intrinsic capacity (IC), represented by the composite of physical and mental reserves, is central to functional ability through its interaction with the environment (2). Underpinned by the International Classification of Functioning, Disability and Health framework, the construct of IC is supported by five health-related domains: locomotion, vitality, sensory function, cognition and psychological function (3). Pathways addressing these five domains have been developed in the Integrated Care for Older People as an evidence-based strategy for optimizing IC and maintaining functional ability (4).

Since its inception, cumulative evidence has supported declining IC as being representative of the diminished homeostatic reserves underpinning the excess vulnerability typical of frailty (5–7). Accordingly, IC and frailty should thus be considered complementary in their common goal of advancing disability prevention through the maintenance of functionality (8). It is also notable that both frailty and IC are multi-dimensional and dynamic. Domains of IC have been included as key characteristics in both phenotypic and cumulative deficit models of frailty (9, 10). Interventions seeking to reverse frailty or improve health outcomes for frail older adults have largely focused on exercise, nutritional intervention or multicomponent strategies such as the combination of exercise, nutrition and cognition training (11–13). In parallel, a recent review of multidomain lifestyle interventions suggested heterogeneous outcomes for the different IC domains, with benefits on locomotion and, to a lesser extent, cognition and vitality (14).

Prefrailty has been recognized as a prodromal state along the frailty continuum. While the consensus established that prefrailty is reversible, the process is likely non-linear with dynamic transitions and trajectories between robust, prefrail and frail states (15). Further, prefrailty may not be a homogenous biological syndrome, evident by varying outcomes among people identified as prefrail (16). The variable risk profiles of prefrail older adults for frailty development may be attributable to underlying IC, as suggested by a recent cluster analysis in which prefrail older adults could be associated with either intermediate or low IC, with the latter exhibiting greatest risk for decline in physical and functional performance at 1-year (17). This stratification of prefrail older adults by IC with differential risk profiles further underscores the complex health needs of prefrailty. However, the extent by which IC may impact on the outcomes of prefrail older adults exposed to interventions designed to prevent frailty progression has yet been evaluated.

We aim to examine (i) effect of a multi-domain physical exercise and nutrition intervention on pre-frailty reversal in community-dwelling older adults at 1-year, and (ii) whether IC contributes to pre-frailty reversal.

Methods

Study design and participants

For this non-randomized controlled trial of a multi-domain physical exercise and nutritional intervention, potential prefrail participants were identified through our ongoing community frailty screening "Individual Physical Proficiency Test for Seniors (IPPT-S)," which had been previously described (18). In brief, the mobile screening platform is based at the void decks of public housing blocks, senior activity centers, and community clubs in the Northeastern region of Singapore served by a regional healthcare facility, and participants in the programme return for yearly follow-ups. Any individual who is aged $\geq$55 years, community-dwelling and able to ambulate independently (with or without walking aid) is eligible.

Residents of sheltered or nursing homes, and persons who are unable to ambulate for at least four meters independently are excluded. Participants meeting operational criteria for prefrailty were invited to attend the 4-month multidomain intervention programme. Ethics approval was obtained from Singhealth Institutional Review Board and all participants provided written informed consent. The study is registered with ClinicalTrials.gov (Identifier: NCT04656938).

Clinical assessment

All participants completed a multi-domain geriatric screen and physical fitness assessment administered by trained study team members at baseline and 1-year follow-up. The multi-domain geriatric screen included risk factors for frailty—mood (Geriatric Depression Scale-15, GDS-15), cognition (locally validated version of the Chinese Mini Mental State Examination, CMMSE), and nutrition (Mini Nutritional Assessment- Short Form, MNA-SF) (19–21). Functional performance was assessed using Barthel Index (BI) for activities of daily living (ADLs) and Lawton and Brody's scale for instrumental ADLs (22, 23). The University of Alabama Life Space Assessment (LSA) was adopted as a measure of functional mobility (24), while Physical Activity Vital Sign (PAVS) was used to quantify engagement in moderate to vigorous-intensity physical activity (walking, cycling, jogging, swimming, Tai Chi, golf, and housework), documenting the time spent on each activity in the preceding 7 days (25). We assessed social vulnerability based on socio-economic status (self-reported adequacy of expenses) and social support (living alone, availability of a confidant and maintaining social contact with friends or relatives). Medical comorbidities were recorded based on self-reported physician diagnoses of hypertension, diabetes mellitus, malignancy, chronic lung disease, heart disease (myocardial infarction, angina), congestive heart failure, chronic kidney disease, stroke, asthma, and arthritis.

The physical fitness test battery was modified from the Senior Fitness Test (26), and participants who reported feeling unwell on pre-assessment screening were exempted. Measures of physical fitness included (i) gait speed (10 m-walk at usual pace), (ii) grip strength (JAMAR hand dynamometer, with 2 trials for each hand and maximal value used for analysis), (iii) upper and lower limb flexibility (Back Scratch and Chair Sit-and-Reach tests) (27), (iv) upper limb dexterity (Box-and-Block test) (28), (iv) lower limb strength and power (30-second chair stand test) (29), (v) balance (Timed-Up-and-Go test) (30) and (vi) cardiorespiratory endurance (6-minute walk test) (31). Additionally, all participants were scored on the Short Physical Performance Battery (SPPB) (32).

Body composition was measured using multi-frequency segmental Bioelectrical Impedance Analysis (BIA, MC-780 M, TANITA, Tokyo, Japan), with appendicular skeletal mass index (SMI) calculated as the sum of fat-free lean mass of all 4 limbs divided by height-squared (ASM/ht^2). Low muscle mass was defined using Asian Working Group for Sarcopenia 2019 (AWGS2019) cut-off values of $<$7.0 kg/m^2 for men and $<$5.7 kg/m^2 for women (33).

Deriving an intrinsic capacity score

Measures representative of the 5 domains of IC—locomotion, vitality, sensory, cognitive, and psychological—were derived from the multi-domain geriatric screen and physical fitness assessment (7). Each domain was scored on a 3-point scale (0–2), and all 5 domains summated to yield a composite IC score (range 0–10). Locomotion was based on the Short Physical Performance Battery (SPPB, range 0–12) consisting of chair-stand, gait speed and standing balance, and the 6-minute walk test (6 MWT) (31, 32). A score of $\leq$9 on SPPB, and total distance walked of $<$400 m in 6MWT were considered impaired performance for the respective tests. Locomotion domain was scored as 0 (impaired performance in both SPPB and 6 MWT), 1 (impaired performance in either SPPB or 6MWT) or 2 (both SPPB and 6 MWT unimpaired). Vitality was represented by nutritional status and appendicular skeletal muscle mass (ASM). In the Mini Nutritional Assessment-Short Form questionnaire (MNA-SF, range 0–14), a score of 8–11 indicates being at-risk of malnutrition, while $<$8 indicates being malnourished (21). Low muscle mass was defined using AWGS2019 cut-off values (33). The vitality domain was scored as 0 to 2, with a score of 0 assigned for participants who were both at-risk of malnutrition/ malnourished and had low muscle mass, 1 when either at-risk of malnutrition/malnourished or demonstrating low muscle mass, and 2 with normal nutritional status and normal muscle mass. Sensory domain was assessed using self-reported responses to the questions "problems due to poor hearing" and "problems due to poor vision." Participants with a positive response to both hearing and visual problems scored 0, those reporting either hearing or visual problems scored 1, while those with neither hearing nor visual problems scored 2 in the sensory domain. Cognitive domain was evaluated using both subjective report and performance on the modified Chinese version of the Mini Mental State Examination (CMMSE, range 0–28). Participants responded with yes or no to the question "Do you feel you have more problems with memory than most?". We used locally validated age- and education-thresholds to define impaired cognitive performance on the CMMSE (21 and 24 for participants $<$75 years with 0–6 and $\geq$6 years of education; 19 and 23 for participants $\geq$75 years with 0–6 and $\geq$6 years of education) (20). The cognition domain was scored as 0 for participants with CMMSE performance below threshold values for their age and education, 1 for participants with subjective memory problems but unimpaired CMMSE performance, and 0 for participants reporting no memory problem and unimpaired

CMMSE. Psychological domain was assessed using the 15-item Geriatric Depression Scale (GDS-15, range 0–15), and a single question from the EuroQol-5 Dimensions (EQ-5D) question on anxiety/depression. GDS-15 score $\geq$5 suggests depression (19), while the EQ-5D question was assigned scores from 0 (not anxious/depressed) to 4 (extremely anxious/depressed) (34). The psychological domain was scored as 0 for participants with GDS-15 $\geq$5, 1 when EQ-5D anxiety/depression $\geq$1 but GDS-15 <5, and 2 for participants with GDS-15 <5 and EQ-5D anxiety/depression = 0.

Operationalizing prefrailty for intervention

All participants completed the FRAIL scale (35), with 1 point assigned for each positive response—Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight. The identification of prefrailty for intervention was based on (i) 1 or 2 positive responses on the FRAIL questionnaire or (ii) 0 positive response on FRAIL but with weak grip strength (<26 kg for males; <18 kg for females) or slow gait speed (<0.8 m/s) based on the Asian Working Group for Sarcopenia (36).

Participants were considered as having reversed to non-frail state at 12-month if FRAIL score was zero AND grip strength as well as gait speed were unimpaired based on AWGS cut-offs (36).

Intervention

Eligible pre-frail participants were invited to enroll in a 4-month multi-disciplinary intervention programme comprising (i) once-weekly group-based exercise classes lasting 1 h each session (total of 16 sessions) with individually prescribed home exercises for maintenance between sessions and (ii) group-based nutritional education (6 sessions). Group size was maintained at 8–10 participants to ensure that each participant received adequate attention. While the intensity of exercise was not measured, the target was to achieve at least moderate intensity as tolerated by the seniors. The exercises focused on strength, balance and endurance training, with a warm-up and cool-down routine. TheraBands and step boards were used for resistance and balance training, respectively. The exercise sessions were designed for progressive intensity (such as increasing number of repetitions, increased resistance of the TheraBands, height of step boards) based on the group's progress, while catering for individual variability, with group sessions conducted under the supervision of a physiotherapist or an exercise physiologist. Each session commenced with 5 min of dynamic warm-up e.g., slow marching with small to big arm circles, followed by 45 min of exercises focusing on: (a) balance, coordination and speed e.g., heel to toe walks; (b) strength e.g., rising from a chair and Theraband exercises for lower and upper limbs, respectively; and (c) endurance e.g., fast walking. All sessions ended with 5 min of static cool down e.g., stretching muscles of the thigh and arms with slow breathing. Individually prescribed structured home exercise folders comprising pictorials and written explanations were provided at the end of each session, to encourage participants to maintain regular physical exercise between the group classes. Compliance with home exercise was tracked using a weekly diary, and participants were instructed to achieve a target of performing the prescribed home exercises at least 3 days each week. The nutritional intervention was delivered with the aim of facilitating healthy eating habits to achieve adequate protein, energy, calcium and Vitamin D through regular food and beverages that are more specific to the Asian palate. There were 6 sessions over the 4-month intervention period with 2 sessions per month in the first and second months and 1 session per month in the third and fourth months. Each session lasted 1.5 h and was delivered by a trained nutritionist, incorporating a combined modality of teaching methods that included didactics, food-based games and grocery-shopping trips with sponsored vouchers to provide guidance on choosing quality foods within budget.

Control

Participants who fulfilled operational criteria for prefrailty but declined enrolment in the intervention programme following IPPT-S screening served as the controls. As part of the IPPT-S screening, these participants (as well as those in intervention group) would have received an individual counseling session with a member of the study team, providing feedback on the results of their screening, along with advice on physical activity and nutrition for frailty prevention reinforced in a personal frailty booklet. They were also invited to attend 4 group-based education classes on frailty that were conducted within the senior activity centers after each screening cycle.

Outcomes

Reversal of prefrailty was defined as achieving a FRAIL score of 0, with unimpaired grip strength and gait speed at 1-year follow-up. Hospitalization and falls during the 1-year period were captured based on self-report.

Statistical analysis

Descriptive data are presented as means (±SD) or median (interquartile range, IQR) for quantitative variables and as absolute and relative frequencies for categorical variables. Chi-squared and *t*-tests or Wilcoxon rank-rum tests were used

for univariate analyses comparing intervention and control groups in baseline characteristics and outcomes. Within-group changes in functional performance and prevalence of frailty risk factors between baseline and 1-year follow-up was examined using Wilcoxon signed-rank or paired sample *t*-tests and Mc Nemar's tests. Multiple logistic regression was performed to examine the independent effect of intervention and IC on prefrailty reversal, adjusted for age, gender and any significant univariate variables. Two separate models were compared—the first model included individual IC domains and the second model included composite IC score. Statistical analysis was performed using STATA SE 15.0 (Stata Corp., College Station, TX). All statistical tests were two-tailed, with p-value ≤ 0.05 considered statistically significant.

Results

Among 209 participants with complete IC data and meeting operational criteria for prefrailty, only 81 were available for 1-year follow-up owing to restrictions imposed by the COVID-19 pandemic. Fifty two participants (64.2%) were enrolled in the multi-domain exercise and nutritional intervention programme, and 29 participants (35.8%) who declined intervention constituted the control group. There was no difference in age and composite IC score between participants who attended 1-year review compared with those who were excluded, although male participants were more likely to have been excluded albeit not statistically significant (21.0% vs. 32.8%, $p = 0.064$).

Median attendance at group-based exercise and nutritional sessions was 72.7% (interquartile range: 18.2–81.8). Weekly exercise target was achieved only for 5 (interquartile range: 1–9) weeks over the intervention period.

Baseline characteristics

Intervention and control group participants were similar in age, gender, education level and comorbidity burden. Enrolment criteria based on FRAIL responses and measures of gait speed and grip strength were similar between groups. There was no difference in functional performance, life space mobility, and physical activity level at baseline between groups. Among measures representative of social vulnerability, participants in the intervention group were significantly more likely to report having insufficient expenses (38.5% vs. 17.2%, $p = 0.047$), and less likely to be in active employment (11.5% vs. 34.5%, $p = 0.014$). Impaired performance on the CMMSE was significantly more prevalent in the intervention group, contributing to significant decline in the cognition domain compared with control (17.3% vs. 0% with cognition domain score 0, $p = 0.038$). The intervention group also exhibited greater decline in the sensory domain (9.6% vs. 0% with sensory domain score 0, $p = 0.032$). Locomotion, psychological and vitality domains were similar between intervention and control groups, with both groups having similar composite IC scores (Table 1).

Outcomes

Sixteen (30.8%) participants in the intervention group no longer fulfilled operational criteria for prefrailty at 1-year, and reversal to robustness was also observed in 13 (44.8%) of control participants ($p = 0.206$). Individual frailty criteria by FRAIL items were similar between intervention and control groups, although the intervention group had significantly more participants with slow gait speed at follow-up. There was no difference between intervention and control groups in 1-year prevalence of cognitive impairment, depression and malnutrition (Table 2). However, within-group comparisons demonstrated significantly reduced prevalence of depression among participants in the intervention group at 1-year relative to baseline (7.8% vs. 23.1%, $p = 0.022$). Functional performance, life space mobility and physical activity level were similar between intervention and control groups at follow-up, and the measures were stable relative to baseline in both groups. While BMI was similar between groups at follow-up, control group participants registered a significant gain in BMI at 12-month relative to baseline (paired sample t-test $p = 0.002$). Both intervention and control groups exhibited significant improvement in grip strength at follow-up, with weak grip observed in 48.3% of intervention and 51.9% of control group participants at follow-up, relative to 71.2 and 79.3%, respectively at baseline (Mc Nemar's $p = 0.004$; $p = 0.021$). 1-year incidence of hospitalization was similar between groups, with a trend for lower falls incidence in the control group ($p = 0.065$).

Multiple logistic regression for prefrailty reversal, hospitalization and incident falls at 1-year

In Model 1 including age, gender, active employment status, baseline prefrailty enrolment criteria, and the cognition and sensory domains in isolation, receipt of multidomain exercise and nutrition intervention was not associated with prefrailty reversal. Older participants were significantly more likely to remain prefrail (OR = 1.14 95% CI 1.01–1.29, $p = 0.034$). Prefrail participants who were both FRAIL score positive and exhibited slow gait and/or weak grip strength at baseline were most likely to remain prefrail compared with those who were asymptomatic on FRAIL but enrolled due to slow gait speed and/or weak grip strength (OR = 6.89 95% CI 1.19–39.91, $p = 0.031$).

TABLE 1 Baseline characteristics.

	Intervention ($N = 52$)	No intervention ($N = 29$)	p-value
Demographics			
Age	69.8 (6.2)	69.8 (7.0)	0.954
Gender (Female)	40 (76.9%)	24 (82.8%)	0.536
Education (≤6 years)	25 (49.0%)	17 (58.6%)	0.408
Social			
Lives alone	9 (17.3%)	5 (17.2%)	0.994
Lack confidant	8 (15.4%)	9 (31.0%)	0.097
No social contact	1 (7.7%)	0	0.291
No community activities	3 (10.3%)	5 (9.8%)	1.00
Inadequate expenses	20 (38.5%)	5 (17.2%)	0.047
Help others	13 (25.0%)	7 (24.1%)	0.931
Active employment	6 (11.5%)	10 (34.5%)	0.013
Number of comorbidities	2 (1–2.5)	1 (0–2)	0.101
Smoking (ex/current)	4 (7.7%)	5 (17.2%)	0.403
Alcohol	8 (15.4%)	3 (10.3%)	0.738
Clinical characteristics			
CMMSE impaired	9 (17.3%)	0	0.017
Depression	12 (23.1%)	5 (17.2%)	0.536
At-risk/malnourished	13 (25.0%)	5 (17.2%)	0.421
BMI (kg/m^2)	24.7 (4.5)	23.2 (3.3)	0.117
Any fall past 1-year	15 (28.5%)	6 (20.7%)	0.422
Functional performance			
Barthel index	20 (20–20)	20 (20–20)	0.598
Lawton's IADL	23 (22–23)	23 (20–23)	0.863
Life space assessment	77.6 (25.0)	85.5 (17.7)	0.143
Physical activity (hours/week)	19.3 (17.6)	20.9 (18.0)	0.738
Locomotion domain score			0.758
0	13 (25.0%)	8 (27.6%)	
1	8 (15.4%)	6 (20.7%)	
2	31 (59.6%)	15 (51.7%)	
Cognition domain score			0.038
0	9 (17.3%)	0	
1	16 (30.8%)	14 (48.3%)	
2	27 (51.9%)	15 (51.7%)	
Psychological domain score			0.329
0	12 (23.1%)	5 (17.2%)	
1	4 (7.7%)	0	
2	36 (69.2%)	24 (82.8%)	
Sensory domain score			0.032
0	5 (9.6%)	0	
1	11 (21.2%)	13 (44.8%)	
2	36 (69.2%)	16 (55.2%)	
Vitality domain score			0.780
0	9 (17.3%)	4 (13.8%)	
1	11 (21.2%)	8 (27.6%)	
2	32 (61.5%)	17 (58.6%)	
Composite IC	7 (6–9)	8 (6–9)	0.719
Number domains impaired	2 (1–3)	2 (1–3)	0.600
Enrolment criteria			0.24
FRAIL –, weak and/or slow	23 (44.2%)	18 (62.1%)	
FRAIL +, unimpaired grip/ gait	12 (23.1%)	6 (20.7%)	
FRAIL +, weak and/or slow	17 (32.7%)	5 (17.2%)	
Slow gait speed	9 (17.3%)	3 (10.3%)	0.398
Weak grip strength	37 (71.2%)	23 (79.3%)	0.422

CMMSE, modified Chinese Mini Mental State Examination; IADL, instrumental activities of daily living.

Neither cognition nor sensory domain was associated with prefrailty reversal.

Model 2 included age, gender, active employment status, baseline prefrailty enrolment criteria and composite IC score. Older age was associated with remaining prefrail although not statistically significant (OR = 1.12, 95% CI 1.00–1.27, $p = 0.057$). Higher composite IC at baseline was associated with reduced likelihood of remaining prefrail (OR = 0.67, 95% CI 0.45–1.00, $p = 0.049$). Again, intervention had no effect on prefrailty reversal (Table 3A).

In multiple logistic regression including age and gender, hospitalization was not associated with either intervention or composite IC. However, higher composite IC reduced risk of incident falls (OR = 0.72, 95% CI 0.51–1.00, $p = 0.051$), independent of intervention exposure (Table 3B).

Discussion

In this first study to examine the role of intrinsic capacity in contributing to the outcomes of a prefrailty intervention programme, prefrailty reversal and falls incidence were independent of intervention exposure but influenced by

TABLE 2 Frailty and clinical outcomes at 1-year.

	Intervention ($N = 52$)	No intervention ($N = 29$)	p-value
Reversal to robustness	16 (30.8%)	13 (44.8%)	0.206
Prefrailty characteristics			0.603
FRAIL −, weak and/or slow	18 (34.6%)	7 (24.1%)	
FRAIL +, unimpaired grip/ gait	5 (9.6%)	2 (6.9%)	
FRAIL +, weak and/or slow	13 (25.0%)	7 (24.1%)	
Slow gait speed	7 (13.5%)	0	0.039
Weak grip strength	27 (51.9%)*	14 (48.3%)*	0.753
FRAIL item responses			
$Fatigue_{baseline}$	5 (9.6%)	3 (10.3%)	0.916
$Fatigue_{12-mth}$	3 (5.8%)	1 (3.5%)	0.644
$Resistance_{baseline}$	20 (38.5%)	6 (20.7%)	0.100
$Resistance_{12-mth}$	18 (34.6%)	7 (24.1%)	0.328
$Ambulation_{baseline}$	7 (13.5%)	3 (10.3%)	0.683
$Ambulation_{12-mth}$	10 (19.2%)	2 (6.9%)	0.134
$Loss\ of\ weight_{baseline}$	4 (8.0%)	4 (13.8%)	0.411
$Loss\ of\ weight_{12-mth}$	1 (1.9%)	1 (3.5%)	0.693
$Illnesses_{baseline}$	0	1 (3.5%)	0.178
$Illnesses_{12-mth}$	0	0	–
Clinical characteristics			
CMMSE impaired	11 (21.6%)	4 (13.8%)	0.392
CMMSE score change	0.48 (2.22)	−0.28 (1.79)	0.120
Depression	4 (7.8%)*	3 (10.3%)	0.703
GDS score change	0.52 (1.91)	0.24 (0.31)	0.473
At-risk/malnourished	12 (23.1%)	7 (24.1%)	0.914
MNA-SF score change	0.006 (1.39)	0.03 (1.61)	0.946
BMI (kg/m^2)	25.0 (4.8)	23.7 (3.5)*	0.231
BMI change	0.28 (1.24)	0.57 (0.91)	0.258
Functional performance			
Barthel index	20 (20–20)	20 (20–20)	0.408
Barthel index score change	0.13 (0.60)	0.17 (0.76)	0.805
Lawton's IADL	23 (22–23)	23 (22–23)	0.588
Lawton's score change	0.37 (2.31)	0.24 (2.23)	0.815
Life Space Assessment (LSA)	75.7 (21.8)	82.9 (16.1)	0.124
LSA score change	−1.82 (20.2)	−2.2 (21.4)	0.933
Physical activity (hours/week)	20.9 (15.2)	25.5 (19.9)	0.280
Physical activity change	1.66 (17.27)	6.37 (24.64)	0.375
Health-related outcomes			
Hospitalization	9 (17.3%)	4 (13.8%)	0.680
Falls	12 (23.1%)	2 (6.9%)	0.065

CMMSE, modified Chinese Mini Mental State Examination; IADL, instrumental activities of daily living.
* McNemar's $p < 0.05$ for within group comparison between baseline and 12-month follow-up.

TABLE 3A Multiple logistic regression for prefrailty at 12-month.

	Model 1	Model 2
Intervention	2.23 (0.67–7.44), $p = 0.191$	1.90 (0.56–6.42), $p = 0.304$
Decline in cognition	0.47 (0.14–1.56), $p = 0.551$	
Decline in sensory	2.78 (0.72–10.68), $p = 0.137$	
Composite IC		0.67 (0.45–1.00), $p = 0.049$

Model 1 ($R^2 = 26.5\%$): adjusted for age, gender, employment status, baseline prefrailty enrolment criteria.
Model 2 ($R^2 = 27.2\%$): adjusted for age, gender, employment status, baseline prefrailty enrolment criteria.

TABLE 3B Multiple logistic regression for incident falls.

	Model 1	Model 2
Intervention	3.86 (0.78–18.88), $p = 0.097$	3.59 (0.72–17.96), $p = 0.120$
Decline in cognition	1.44 (0.42–4.95), $p = 0.562$	
Decline in sensory	1.11 (0.40–3.06), $p = 0.841$	
Composite IC		0.72 (0.51–1.00), $p = 0.051$

Model 1 ($R^2 = 8.5\%$): adjusted for age, gender.
Model 2 ($R^2 = 13.4\%$): adjusted for age, gender.

baseline composite IC score. Reversal to a state of robustness, represented by a FRAIL score of 0 with unimpaired grip strength and gait speed, was observed in 30–40% of prefrail older adults from both intervention and control groups. Prefrailty reversal was driven by improvement in grip strength in both groups. The multi-domain exercise and nutritional intervention was associated with significant improvement in mood.

Natural transitions in frailty states have been well-explored, demonstrating the dynamic and bi-directional nature of the frailty syndrome (37). Our observed reversal rate of 30–45% over 1-year was higher than the reported spontaneous regression involving approximately 25% of prefrail older adults in recent meta-analyses with average follow-up of 3 to 4 years (38). However, prefrail participants of a combined exercise and nutritional intervention were not more likely to revert to robustness compared with their control group counterparts, contradicting available evidence supporting additive effects of multi-domain interventions in improving frailty characteristics and physical function, albeit in mixed prefrail and frail populations (12). Intervention trials for frailty commonly include both prefrail and frail older adults, but the delineation between prefrailty and frailty will be necessary as the extent of frailty may act as an effect modifier of interventions on frailty status (39). Our study adds to the limited literature focused specifically on prefrail older adults. With prefrailty defined using the Fried phenotype, Serra-Prat and colleagues reported that an intervention addressing nutrition and physical activity was effective in preventing frailty progression, but there was no significant difference in achieving reversal from being prefrail to robust at 1-year follow-up. Similar to our

observations, there was no difference in individual frailty criteria between the intervention and control groups at follow-up (40). Although not subject to active exercise and nutritional intervention, participants in the control group had received individual counseling based on their screening results and group-based education focusing on exercise and nutrition for frailty prevention that was open to all participants post-screening. The potential effect of the counseling and education in the control group cannot be dismissed, considering the higher reversal rate compared with historical natural regression. Components of multi-domain interventions are highly variable across studies. In one multicomponent frailty prevention programme incorporating exercise, cognitive training and board game activities for prefrail older adults, the intervention group was significantly more likely to revert from being prefrail to robust by 12 weeks (41). Another multi-factorial, interdisciplinary intervention focused on physical exercise, dietary advice, review of polypharmacy and social assessment was significantly associated with reversal to robustness in prefrail elderly (42). The general consensus for prefrailty as an intermediate multidimensional risk state associated with physical impairment, cognitive deficits, malnutrition and social vulnerability (15) further support the utility of complex and targeted management strategies beyond a conventional exercise and nutrition approach to optimize its reversal.

Decline in IC was highly prevalent in our cohort of prefrail older adults, affecting 90.1% of the cohort at baseline. Both intervention and control group participants averaged losses in 2 domains. This observation reinforces earlier findings suggesting the significant public health problem of IC impairment (5, 43). The present study builds on the emerging evidence for the relationship between IC and frailty, as composite IC rather than intervention exposure dictated reversal from being prefrail to robust. Interestingly, composite IC score, but not the individual domains, was predictive of prefrailty reversal. This may be attributed to the integrative nature of the IC construct, such that a global score may better reflect the physical and mental capacities, and being more informative in identifying at-risk older adults for tailored preventative care. A recent study suggested that IC trajectories were more likely to parallel frailty transitions among robust and prefrail older adults, while significant losses that have already culminated in a frail individual render it more challenging to seek IC improvement for frailty reversal (44). With declining IC anticipated with age, the monitoring of IC among non-frail older adults can provide opportunities for intervention to reverse the trend and prevent or delay frailty onset.

The multidomain exercise and nutritional intervention had a positive impact on mood, evident by the 15% reduction in prevalence of depression at 1-year among participants in the intervention group. Our results are consistent with reported benefits of physical activity on depressive symptomatology in older adults (45). With social support being a strong predictor of depressed mood among community-dwelling older adults (46), the contacts established through the group-based intervention may have contributed to improvement in mental health. Beyond the psychosocial effects, exercise may influence mood through biological mechanisms including increased neurotrophic factors in circulation, anti-inflammatory effects, reduced oxidative stress and neuroendocrine regulation (47). Despite the focus on nutrition, nutritional status remained unchanged, with approximately one-quarter of participants in intervention and control groups, respectively, being assessed to be at-risk of malnutrition or malnourished at follow-up. Our nutritional intervention emphasized dietary habit change without provision of supplementation, which may be inadequate in the setting of malnutrition. This is consistent with the findings from the Prefrail 80 study, in which a group session on the Mediterranean diet as part of a multifactorial intervention failed to impact on nutritional status, and worsening nutritional status over time was observed among those who progressed to frailty (41). It should be cautioned that the findings do not imply routine use of oral nutritional supplements, which should be considered only for frail older adults presenting with weight loss or malnutrition (48). Thus, the assessment of IC may better guide a targeted approach toward prefrailty/frailty, based on the identified domain losses. For example, ICOPE recommends oral nutritional supplementation with increased protein intake for older adults who are malnourished (4). The reliance on BMI for monitoring intervention should also be cautioned as we observed significant gain in BMI among control group participants even as nutritional status remained unchanged.

Contrary to the extant literature supporting exercise for falls prevention in older adults, we observed a non-significant trend for increased falls risk in the intervention group. There was no change to physical activity level or life space to account for the increased exposure to risk. However, participants in the intervention group were more likely to exhibit significant declines in the cognition and sensory domains, both of which constitute intrinsic risk factors for falls (49). This was supported in the multiple logistic regression, whereby composite IC rather than intervention predicted fall risk during follow-up.

We acknowledge several limitations. Among studies restricted to a prefrail cohort, rates of prefrailty reversal were variable, influenced by follow-up duration, intervention intensity and definition of prefrailty (40, 41). Even with conservative estimates from these studies, an overall sample of at least 164 prefrail participants would be needed assuming a difference of 50% in prefrailty reversal between groups using two-sided sample size calculation with type II error of 0.80. Thus, our sample size of 81 prefrail older adults was statistically underpowered for the reversal of prefrailty status as a primary outcome. This was a pragmatic trial with a convenient control group of participants who declined intervention. The reasons for declining intervention were not tracked, although we noted that participants who declined and constituted the control

group were more likely to be actively employed, and social and physical activities associated with employment status might not have been comprehensively captured by the social questionnaire and PAVS. However, even after adjusting for employment status, intervention exposure was not associated with prefrailty reversal. The suboptimal adherence at 70% to the overall programme could have contributed to the lack of intervention effect. Further, compliance with individually prescribed home exercises was generally poor, with an average of 6 weeks in the 4-month intervention period fulfilling the weekly exercise target of 3 days per week. The observed compliance was consistent with a recent review of interventions for frailty, with adherence varying between 47.5 and 90.4%, and poorer for home-based interventions (50). Additionally, sustainability of exercise and nutritional habits of the intervention group participants beyond the 4-month intervention period was not monitored. The COVID-19 pandemic yielded substantial disruption, such that only 40% were available for 1-year follow-up, although age and composite IC were similar between cohorts included and excluded from this analysis. While validated and objective measures for the assessment of IC were employed for the locomotion, cognition, psychological and vitality domains, both hearing and vision relied on subjective reports.

In conclusion, IC decline is highly prevalent among prefrail older adults. The multidomain exercise and nutritional intervention focuses on the locomotion and vitality domains, and may not adequately address component domain losses to optimize prefrailty reversal. Future studies should consider investigating the effect of multidomain interventions on global IC measure, and the impact that addressing IC may have on frailty transitions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by SingHealth Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LT contributed to overall study design, conducting the study, and analysis and main manuscript writing. E-LT, SM, and AL contributed to intervention design, data collection, and conducting the study. Y-SN contributed to study design and manuscript writing. All authors reviewed the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Wook Song,
Seoul National University, South Korea

REVIEWED BY
Luca Soraci,
Unit of Geriatric Medicine, IRCCS INRCA, Italy
Hyo-Bum Kwak,
Inha University, South Korea

*CORRESPONDENCE
Angela S. Koh
angela.koh.s.m@singhealth.com.sg

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Cardio-sarcopenia: A syndrome of concern in aging

De Rong Loh[1], Ru-San Tan[1,2], Wee Shiong Lim[3,4] and Angela S. Koh[1,2]*

[1]Duke-National University of Singapore (NUS) Medical School, Singapore, Singapore, [2]National Heart Centre Singapore, Singapore, Singapore, [3]Department of Geriatric Medicine, Institute of Geriatrics and Active Ageing, Tan Tock Seng Hospital, Singapore, Singapore, [4]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore

Cardiac alterations in structure and function, namely, the left ventricle, have been intensely studied for decades, in association with aging. In recent times, there has been keen interest in describing myocardial changes that accompany skeletal muscle changes in older adults. Initially described as a cardio-sarcopenia syndrome where alterations in myocardial structure were observed particularly among older adults with skeletal muscle sarcopenia, investigations into this syndrome have spurred a fresh level of interest in the cardiac-skeletal muscle axis. The purpose of this perspective is to summarize the background for this "syndrome of concern," review the body of work generated by various human aging cohorts, and to explore future directions and opportunities for understanding this syndrome.

KEYWORDS

aging, cardiovascular disease, myocardium, sarcopenia, frailty, prevention

Introduction

The traditional view of cardiovascular aging is that of age-related adaptations in the heart characterized by increased left ventricular (LV) mass (LVM) and LV hypertrophy (LVH), which are often secondary to increased systolic blood pressure mainly mediated by arterial stiffening (1, 2). These changes accumulate throughout the lifetime of an individual, increasing the risk of developing cardiovascular disease (CVD), such as heart failure (HF) and coronary artery disease (2). The incidence of CVD increases with age, rising from ∼78% among adults aged 60–79 years to ∼90% in those aged above 80 years (3). CVD is the leading cause of disease burden in the world, with global prevalence doubling from 271 million to 523 million between 1990 and 2019 (4). Incident CVD mortality increased from 12.1 million to 18.6 million in the same period (4), and accounted for 32% of all deaths. With rapidly aging national populations, these numbers are expected to increase. Despite the known association between cardiovascular aging and CVD, this knowledge has not translated into actionable changes that can specifically

target aging-related CVD (2). This underscores the urgent need for in-depth study into the pathophysiology of cardiovascular aging and its prevention, and also highlights the unmet need for specific markers of cardiovascular aging that is "modifiable." Emerging interests surrounding and research into a novel entity of "cardio-sarcopenia" have provided an added dimension to mainstream understanding of cardiovascular aging, and by extension, opened up new avenues for interventional strategies. This term was coined based on observations of associations between LVM and skeletal muscle mass and function that were independent of systemic risk factors such as hypertension and diabetes mellitus, as well as smaller left heart sizes in older adults with skeletal muscle sarcopenia (5). Observed among community older adults without clinical CVD, these distinctive patterns are hypothesis-generating for a possible syndrome of cardiac aging (5). Data from other cohorts have emerged that support relationships between markers of LV and skeletal muscle structure and function across the sarcopenia spectrum (6, 7).

Cardio-sarcopenia: A possible upstream marker of the heart failure spectrum

Skeletal muscle sarcopenia occurs with aging but may be accelerated in heart failure states (8). In advanced stages of heart failure, skeletal muscle wasting accompanied by severe exercise intolerance have long been observed in various cohorts (9–11). Several systemic and humoral mechanisms have been invoked as biological interactions (i.e., cross-talk) between the skeletal muscle system and the heart (12–15).

To date, observations pertaining to the cardiac muscle-skeletal muscle axis among non-heart failure cohorts have provided useful insights (**Table 1**). In a population-based cohort of older Asian subjects without clinical cardiovascular disease, skeletal muscle mass was associated with left ventricular mass, independent of age, diabetes mellitus status, and body size (5). In a selected cohort of frail sarcopenic older European subjects without severe cardiovascular disease (some had mild cardiovascular disease), appendicular lean mass was strongly associated with LVM and cardiac output (6). Although advanced age was associated with loss of skeletal muscle mass, the relationship between LVM and skeletal muscle mass appears to be independent of age (5, 7). Among 228 community adults aged 65–91 years, individuals with low skeletal muscle mass had lower LVM than those without low skeletal mass, without significant interaction between age and LVM (7). These observations are hypothesis-generating for possible *age-related yet age-independent* processes that mediate the cardiac and skeletal muscle systems in older persons.

Cardiac muscle: So, is it big or not big with aging?

The observations seem to run counter to the dogma of aging-associated LVH, especially in the context of hypertension which dominates aging. Traditionally, cardiac aging has been associated with increased LV wall thickness, with or without myocyte hypertrophy (16, 17). High LVM, and not low LVM, has been deemed to be clinically unfavorable (18). Among 3,220 subjects enrolled in the Framingham Heart Study who were 40 years of age or older and free of CVD who were followed up over 4 years, increments in LVM (corrected for height) predicted higher incidence of clinical events, including death, attributable to CVD (18). Interestingly, an earlier report from Framingham had also observed associations between subscapular skinfold thickness (and body mass index, among other variables) and LVM, in multivariable analyses, which may suggest that markers of lean body mass are indeed correlated with LVM (19). These historical considerations appropriately place most of the clinical emphasis on the significance of a large LVM.

In contrast, data from sarcopenic subjects suggest that the spotlight on "LVM" could be widened to include the "lower" end of the LVM spectrum. The observed correlates between LVM and specific measurements of skeletal muscle mass/function, emphasize a need to consider the skeletal muscle system as a possible variable in the evaluation of LVM, in addition to body surface area which is routinely calculated in indexed LVM measurements. This may be particularly important in clinical studies where older adults are the focus. Among older adults, there may be interactions between skeletal muscle sarcopenia and LVM. Aging appears to be associated with lower LVM among sarcopenic subjects (5, 7), suggesting that low LVM may be a phenotype of concern in older adults. Future longitudinal studies are needed to observe how subjects with low LVM evolve over time. However, concentric remodeling and LVH appear to occur when higher levels of physical frailty and sarcopenia are reached, albeit cross-sectionally (20). More understanding of events that occur between low LVM at lower levels of sarcopenia and LVH at higher levels of sarcopenia, would be critical. It is plausible that in the presence of sarcopenia, physiological adaptative responses are exceeded such that the development of LVH becomes pathologically significant. This hypothesis would have implications for the intensity and urgency of skeletal muscle management, in addition to routine hypertension management, in sarcopenic older adults.

The mechanism through which low LVM occurs in the setting of sarcopenia is unknown but potentially intriguing. Studies from autopsy specimens reveal that aging is associated with progressive attrition of myocyte numbers, in addition to hypertrophy of the remaining myocytes (21). While much of

TABLE 1 Summary selection of community cohorts on skeletal muscle and cardiac function/muscle.

Cohort studies, publication year	Study population	Results	Inferences	Details/limitations
Keng et al. (5)	CAS study *N* = 378 Mean age 72 ± 4.4 years No self-reported history of physician diagnosed CVD, stroke or cancer.	Skeletal muscle mass was associated with LV diameter, LVM. Participants with sarcopenia had smaller LV size and lower LVM. LVM was linearly associated with handgrip strength.	Sarcopenic patients had smaller LV and LA sizes with gross preservations in LV function, as well as reduced general skeletal mass and handgrip strength. This suggests a possible syndrome of cardio-sarcopenia.	Cross-sectional study; Asian ethnicity; low risk community cohort.
Pelà et al. (6)	Ancillary study of the Sarcopenia and Physical Frailty In Older People: Multicomponent Treatment Strategies (SPRINT-T) project *N* = 100 selected subjects enrolled from Parma site. Mean age 79 ± 5 years	Appendicular lean mass was strongly and positively correlated with LVM, as well as cardiac output.	Confirmed the concept of cardio-sarcopenia syndrome in a European population of older individuals.	Comorbidities such as heart disease and chronic conditions may account for at least 40% of the study sample. Smaller sample size; cross-sectional study; cohort focused on frail older adults.
Pelà et al. (20)	As above. Additional analyses for blood pressure, physical activity, and medications, etc.	60% showed LVH (assessed by LVM/BSA) with a tendency toward concentric geometry, as assessed by RWT. The main determinants of LVM were BSA and SBP, while RWT was primary correlated with age.	SBP as the main determinant of LVM highlights a key role that hemodynamic condition plays in determining LV geometry in an older population of sarcopenic and physically frail patients. Levels of physical activity did not influence LVM or RWT.	Smaller sample size; cross-sectional study; Ambulatory blood pressure was obtained in only 52% of participants.
Tinti et al. (7)	*N* = 288 Free living individuals Mean age 75.61 ± 6.28 years 50% of the participants had diabetes.	Individuals with low SMM had lower LVM. LVM was significantly correlated with fat and lean mass, as well as with SMM and bone mass.	Confirmed that individuals with low skeletal muscle mass had lower LVM than those without low SMM, as found by Keng et al. (5) Ventricular mass in older adults was significantly correlated with fat and skeletal muscle and bone mass, which persisted even after adjusting for body mass index. Diabetes mellitus exerted a negative interacting influence on the association between age and ventricular mass.	Relatively high proportion of diabetes mellitus in the sample. Prevalence of CVD in the sample was not reported.
Ko et al. (89)	*N* = 67,106 Mean age 40.6 ± 8.1 years Participants with heart conditions, such as CVD, systolic heart failure, hypertrophic, or dilated cardiomyopathy, were excluded.	In 67,106 participants, 19,232 subjects (28.7%) and 1,553 subjects (2.3%) had LVDD and LVH, respectively. SMI was positively associated with E/A ratio and septal E', whereas E/E' ratio and LV mass index were negatively associated with SMI. Lower SMI was associated with increased presence of LVDD.	Suggests a role of skeletal muscle mass in the pathogenesis of LVDD (but not LVM).	Studied young and middle-aged adults (not older adults). High prevalence of obesity in LVDD group.

Limited to original articles that have directly imaged skeletal and cardiac organ systems in older adults. CVD, cardiovascular disease; LA, left atrial; LV, left ventricular; LVM, LV mass; LVH, LV hypertrophy; LVDD, LV diastolic dysfunction; BSA, body surface area; RWT, relative wall thickness; SBP, systolic blood pressure; SMM, skeletal muscle mass; SMI, skeletal muscle mass index.

the developed literature have focused on myocyte hypertrophy, there is far less understanding about myocyte attrition, as a possible upstream phenomenon that occurs prior to adaptive hypertrophy. Cardiac muscle atrophy can occur in response to chronically reduced cardiac workload or to inflammatory disease states such as cancer (22). Interestingly, the failing heart can shrink and yet become stronger (23). In the studied cohorts of sarcopenic older patients with alterations in LVM, this phenomenon could be interpreted as pathologically adaptive with initial preservation of ejection fraction. Hence, there is value in targeting cardio-sarcopenia as an upstream phenotypic syndrome of concern in aging.

Skeletal muscle sarcopenia and cardiac aging: Which one came first, or does it matter?

Recent literature has shown that patients with HF have worse muscle function and atrophy, because of pathological alterations including altered metabolism, energetics, and decreased oxidative capacity (24–27). Possible metabolic pathways linking physical activity, cardiovascular health, and musculoskeletal function with aging have also been described and summarized using insights from metabolomics (28). Of note, genes involved in fatty acid oxidation and glucose metabolism are upregulated by physical activity, whereas these changes are absent or reversed in HF (29). These differences in metabolic gene expression demonstrate that maladaptive cardiac hypertrophy elicited by pathological stimuli should be differentiated from adaptive exercise-induced hypertrophy.

Most of the literature that are involved with dysregulated skeletal muscles in clinical HF have provided us with some understanding of possibly shared pathways. It is therefore reasonable to suggest that a cross-talk may in fact pre-exist even before clinical CVD. Conjecturally, the cardio-sarcopenia syndrome likely results from a framework of partially shared pathways leading to the loss of functional mass involving more than one organ system, with a predilection for HF development. As there is a dearth of longitudinal studies tracking skeletal muscle mass and cardiac function prospectively, any suggestion of a causal link between the two remains speculative. Nevertheless, the co-occurrence of skeletal muscle sarcopenia and myocardial perturbations in older adults without and with co-morbidities observed by us and others may be consistent with common upstream pathological pathway (or pathways) associated with aging.

Recently, a chronic low-grade inflammatory state known as "inflammaging" has been described in older adults (30) that is characterized by elevations in blood inflammatory markers related to aging-related immune dysregulation, high circulating levels of proinflammatory markers such as interleukins, C-reactive protein (CRP), transforming growth factor-beta, tumor necrosis factor (TNF) and TNF receptors, including in those free of active disease (31–33). Observed in association with multi-systemic geriatric conditions, it has been postulated as a mechanism contributing to conditions ranging from sarcopenia to frailty and CVD (34–37). Interleukin (IL)-6 is a promising translational frailty biomarker in humans and mice (38). In a prospective, population-based study of 986 old men and women, high levels of serum IL-6 and CRP were associated with risks of muscle mass and strength loss (39). In another prospective cohort study of 620 old women, high serum IL-6 levels were associated with accelerated declines in muscle strength and physical function (40). IL-6 is a powerful independent predictor of HF (41, 42) and has been associated with impaired coronary flow and cardiac function, and worsening HF (43). Upregulated IL-6 activates gp130/STAT3 signaling, induces reactive oxygen species (ROS) production, leading to mitochondrial dysfunction and increased expression of mitophagy-related proteins, which results in cardiac hypertrophy in HF (44). Excessive ROS appears to aggravate ongoing inflammation, feeding a proinflammatory microenvironmental vicious cycle that exacerbates maladaptive myocardial remodeling and consequent HF manifestation (45, 46).

Insulin resistance features heavily in the biochemical cross-talk between the musculoskeletal and cardiovascular systems. Decreased mitochondrial function and increased inflammatory and oxidative stresses that are observed with skeletal muscle aging induce muscle atrophy and insulin resistance (47). The latter is central to an entity known as sarcopenic obesity (48), which is interestingly also associated with concentric LV remodeling independent of age-adjusted indexed body mass (49). From the metabolic perspective, it is plausible that insulin resistance mediates the cardiac remodeling associated with sarcopenic obesity, along with contributions by fat and inflammation. Further research chronicling the development of insulin resistance, sarcopenia, and cardiac remodeling (and HF) in aging human subjects is urgently needed to confirm this mechanistic link. If true, age-associated sarcopenia might be a pre-disease state that is amenable to upstream preventive strategies, e.g., exercise training, to avert clinical CVD.

Given the increased incidence of HF among older adults with increased risk of sarcopenia, these additional insights would support early preventative and/or therapeutic strategies that target specific aspects of skeletal muscles, potentially benefitting frail older adults who have yet to develop heart disease. For one, it highlights the potential of using screening tools such as SARC-F to identify older population with sarcopenia as an approach to detect early cardiac dysfunction in the community (50). The cardio-sarcopenic phenotype could also be targeted as a modifiable risk factor that may be ameliorated by interventions.

Current detection tools

When considering the potential for scalability for case detection of older adults with cardio-sarcopenia syndrome in the geriatric population, detection tools should be easily accessible, safe with minimal radiation, non-invasive and robust. Currently, muscle mass can be estimated using bioelectrical impedance analysis (BIA) or dual-energy X-ray absorptiometry (DEXA) (5, 51), while myocardial structure and function can be assessed using echocardiography or cardiovascular magnetic resonance imaging, with newer variants including handheld echocardiography and the combined use of artificial intelligence tools (52, 53).

Importantly, some of these tools such as DEXA for body composition can be tagged onto existing imaging procedures for osteoporosis assessment of bone mineral density. Where available, the use of validated multi-frequency BIA facilitates access to measurement of muscle mass in the community setting, Lastly, as per the diagnostic algorithms of recent consensus statements for sarcopenia, the assessment of handgrip strength using a handheld dynamometer allows detection of "possible sarcopenia" defined by low muscle strength, circumventing the need for muscle mass measurement (54). Taken together, this allows clinicians to make more comprehensive risk assessment which combines inputs about the skeletal muscle in conjunction with more objective measurements of patients' cardiac state (e.g., LVM).

Potential to improve human health

Changing the focus from disease management to prevention is a paradigm shift that calls attention to the need for a systems approach to tackling cardiac aging and its complexities. While current HF guidelines recognizes the intimate link between sarcopenia and heart failure, more granular upstream preventative actions before the onset of clinical heart disease can potentially avert joint deteriorations in both organ systems. It is therefore timely to advocate stronger population-based preventative efforts for improving the health of older adults.

Exercise is important for maintaining and promoting skeletal and cardiac muscle health. Resistance training is effective for inducing skeletal muscle growth in older adults (55–57). In addition, there is growing evidence that aerobic exercise favorably affects various mechanisms that collectively stimulate skeletal muscle hypertrophy, and should therefore be considered as a viable exercise prescription in populations prone to muscle loss (58).

Dietary protein constitutes a primary nutrient for maintenance and growth of skeletal muscles (59). To combat sarcopenia, dietary guidelines recommend high protein intake for older adults, who are prone to low energy intake and muscle loss (60, 61). Individual nutrient effects on age-related skeletal muscle preservation (and cardioprotection) are less clear. To date, many studies on dietary fat and diverse micronutrients like whey, casein, Vitamin D, and antioxidants have yielded few definitive conclusions (62, 63).

Angiotensin-converting enzyme inhibitors (ACE-I) are routinely prescribed to patients with hypertension, HF and diabetes due to their beneficial effects on the vasculature and cardiovascular outcomes. At the molecular level, ACE-I promotes glucose uptake (64) and suppresses proinflammatory cytokines (especially IL-6) in skeletal muscles (65). In older adults without HF, ACE-I therapy has been shown to retard loss in muscle strength (66) and increase both muscle strength (67) and exercise capacity (68). Therefore, ACE-I or related pathways constitute promising therapeutic targets for sarcopenia.

On the other hand, sodium-glucose cotransporter-2 (SGLT2) inhibitors have recently been shown to confer renal and cardiometabolic benefits in diabetic and non-diabetic subjects (69–73) but may be associated with myopathy (74) and sarcopenia (75, 76) which will be of concern to aged adults with low baseline pre-treatment skeletal muscle mass. There is potential for SGLT2 inhibitors to be studied as a candidate drug targeting aging-related CVD, although the totality of clinical effectiveness for this class of therapeutics may depend on the needs of specific patient cohorts.

Cardio-sarcopenia—Next steps

Firstly, there is a need for mechanistic understanding of the cross-talk between the various components of body composition and the cardiac muscles. Earlier research has revolved around obesity and its association with cardiovascular structure and function (77, 78). With emerging interest in skeletal muscles, sarcopenia enters the equation for the consideration of LVM. Notwithstanding the relative degree of involvement by adipose tissues or skeletal muscles, there is now greater awareness and scientific acknowledgment that there are close relationships between body composition and heart structure and function. This is in line with the opinion that the observed degenerative bodily changes in older adults is the result of the complex interplay between body composition, the cardiovascular system and aging process (79), far more granular than the body mass index metric (78).

In this regard, several studies have already demonstrated increased Framingham score or CVD risk in sarcopenic and/or obese older adults (80–82). In a large epidemiological study among the Korean population, it was observed that visceral obesity and low muscle mass may be pathophysiologically related, possibly through insulin resistance and inflammation, leading to subclinical LV changes independently and synergistically (83). Further elucidation of biological mechanisms that underlie these cardiometabolic alterations may require animal models.

Secondly, the cohort of older sarcopenic population should be followed up longitudinally with clear documentation of the changes in their skeletal and cardiac muscles as well as their cardiovascular status. This would provide clarity about the development of the cardio-sarcopenia syndrome in relation to the cardiac structure and function over time, which cannot be accomplished by cross-sectional studies that can only make associations at a single point in time. Concurrent biomarker annotation would provide additional mechanistic insights into the development of cardiac aging (84), useful for future clinical translation.

Thirdly, appropriate clinical trials should be conducted to evaluate the amount of change that is necessary to impact clinical outcomes. For example, in patients with clinically stable

chronic HF (predominantly New York Heart Association class II or III), resistance exercise training can improve muscle strength (85, 86). More variability such as intensity and type of exercise should be trialed to determine the optimal level and type of physical exercise intervention for these patients. In addition to monitoring changes in the skeletal muscles, the cardiac structure and function can be concurrently assessed for any improvement over the course of the intervention. These features are not only therapeutic targets, but also markers requiring periodic surveillance, like blood pressure and low-density lipoprotein. The conduct of these interventional studies should additionally evaluate the impact of multi-component interventions such as nutrition, psychosocial support, and strategies personalized to individual needs (87).

Conclusion

In conclusion, the concept of cardio-sarcopenia has evolved from a syndrome which describes the coexistence of alterations in myocardial structure with skeletal muscle sarcopenia in older adults to portend pathophysiologic derangements in the cardiac-skeletal muscle axis. Emerging evidence implicating the involvement of adipose tissue, such as sarcopenic obesity (88), highlights the need to examine deeper into the muscle-, fat- and myocardium triad. From the preventative standpoint, the cardio-sarcopenic phenotype constitutes a potentially modifiable risk factor in older persons that may be amenable to early multi-modal intervention involving physical activity, resistance exercise, and nutrition. This raises the clarion call for greater inter-disciplinary collaboration between cardiologists, geriatricians, bio-scientists, exercise therapists, and nutrition specialists to push the frontiers in both research and clinical practice against this syndrome of concern in aging.

Author contributions

DRL, WSL, and ASK contributed to the conception and design of the manuscript. RST, DRL, WSL, and ASK performed literature critiques and contributed to the writing of the manuscript. All authors critically reviewed previous drafts and approved the final draft for submission.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Robbert Gobbens,
Inholland University of Applied Sciences, Netherlands

REVIEWED BY
Siti Setiati,
University of Indonesia, Indonesia
Giancarlo Logroscino,
University of Bari Aldo Moro, Italy

*CORRESPONDENCE
Wee Shiong Lim
Wee_Shiong_Lim@ttsh.com.sg

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Effectiveness and usability of the system for assessment and intervention of frailty for community-dwelling pre-frail older adults: A pilot study

Ren Siang Tan[1], Eileen Fabia Goh[1], Di Wang[2], Robin Chung Leung Chan[2], Zhiwei Zeng[2], Audrey Yeo[1], Kalene Pek[1], Joanne Kua[1,3], Wei Chin Wong[1,3,4], Zhiqi Shen[2,5] and Wee Shiong Lim[1,3,4]*

[1]Institute of Geriatrics and Active Ageing, Tan Tock Seng Hospital, Singapore, Singapore, [2]Joint NTU-UBC Research Centre of Excellence in Active Living for the Elderly, Nanyang Technological University, Singapore, Singapore, [3]Department of Geriatric Medicine, Tan Tock Seng Hospital, Singapore, Singapore, [4]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore, [5]School of Computer Science and Engineering, Nanyang Technological University, Singapore, Singapore

Background: Effective multicomponent interventions in the community targeted at preventing frailty in at-risk older adults can promote healthy ageing. However, there is a lack of studies exploring the effectiveness of technology-enabled autonomous multi-domain community-based interventions for frailty. We developed a novel end-to-end System for Assessment and Intervention of Frailty (SAIF) with exercise, nutrition, and polypharmacy components. This pilot study aimed to explore SAIF's effectiveness in improving frailty status, physical performance and strength, and its usability in pre-frail older adults.

Materials and methods: This is a single arm 8-week pilot study in 20 community-dwelling older adults who were pre-frail, defined using the Clinical Frailty Scale (CFS) as CFS 3 + (CFS 3 and FRAIL positive) or CFS 4. For outcomes, we assessed frailty status using the modified Fried Frailty Phenotype (FFP) and CFS; physical performance using Short Physical Performance Battery (SPPB); and Hand Grip Strength (HGS) at baseline and 8-week. User experience was explored using the System Usability Scale (SUS), interest-enjoyment subscale of the Intrinsic Motivation Inventory and open-ended questions. We analyzed effectiveness using repeated-measures tests on pre-post scores, and usability using a convergent mixed-method approach *via* thematic analysis of open-ended responses and descriptive statistics of usability/interest-enjoyment scales.

Results: Sixteen participants (71.8 ± 5.5 years) completed the 8-week study. There was a significant improvement in FFP score (−0.5, $p < 0.05$, effect size, $r = 0.43$), but not CFS (−1.0, $p = 0.10$, $r = 0.29$). Five (31.3%) improved in frailty

status for both FFP and CFS. SPPB (+1.0, $p < 0.05$, $r = 0.42$) and HGS (+3.5, $p < 0.05$, $r = 0.45$) showed significant improvements. Three themes were identified: "Difficulty in module navigation" (barriers for SAIF interaction); "User engagement by gamification" (facilitators that encourage participation); and "Perceived benefits to physical health" (subjective improvements in physical well-being), which corroborated with SUS (68/100) and interest-enjoyment (3.9/5.0) scores. Taken together, user experience results cohere with the Senior Technology Acceptance and Adoption Model.

Conclusion: Our pilot study provides preliminary evidence of the effectiveness of SAIF in improving frailty status, physical performance and strength of pre-frail older adults, and offers user experience insights to plan the follow-up large-scale randomized controlled trial.

KEYWORDS

frailty, pre-frail, older adults, community research, health technology, intervention, usability

Introduction

Frailty is an aging-related syndrome characterized by diminished physiological reserves and an increased vulnerability to adverse health outcomes (1). According to the physical phenotype model of Fried et al., frailty may be identified by the presence of at least three of the following components: weakness, unintentional weight loss, slowness, exhaustion, and low physical activity (1). Research has shown that frailty is associated with an increased risk of falls, disability and mortality (1, 2). Frailty is also associated with a greater utilization of healthcare resources such as hospitalization (3) and emergency department visits (4). Healthcare professionals and authorities increasingly recognized frailty as a pressing public health priority due to its significant negative impact on the health of older adults and burden on healthcare systems (5, 6). Longitudinal studies show that the risk of transitioning to greater states of frailty increases with age (7, 8). However, as frailty is potentially reversible, there is increasing interest in shifting the focus toward early identification and timely intervention in the intermediate pre-frail stages (9, 10).

In recent years, emerging technological innovations have transformed the healthcare landscape by providing new opportunities to improve the management of chronic diseases for seniors (11, 12). Similarly, in the context of frailty, there is emerging evidence from small-scale studies supporting the benefit of technology-related intervention studies in pre-frail older adults. Recent studies reported that interventions leveraging sensor-based technology (e.g., video consoles or wearables) for exergaming (13–15) or walking programs (16) can improve frailty status and walking speed, and reduce falls risk in pre-frail seniors. In addition, exercise programs tapping upon telecommunications technology (*via* web or mobile applications) to provide remote instructional guides (17) or weekly telephone coaching (18) reported improvement in quality of life and functional performance in pre-frail older adults. Another trend is the rise in the exploration of Artificial Intelligence (AI) enabled technologies to track frailty progression and provide personalized interventions (19, 20). However, technological interventions tend to exist as isolated, single-domain solutions which do not harness a multi-component approach for interventions.

As a multi-dimensional syndrome with many etiological factors, a multi-domain approach is required to effectively manage the early stages of frailty in the community (6, 21). The Asia-Pacific Clinical Guidelines (21) for the management of frailty have outlined four evidence-based interventions: (i) physical exercise; (ii) polypharmacy reduction; (iii) caloric, protein and Vitamin D supplementation; and (iv) screening for reversible causes of fatigue. Using a combination of physical exercise, nutritional supplementation and cognitive training in a 6-month intervention for pre-frail and frail older persons, Ng et al. found significant improvements in frailty score and status in the multi-domain intervention group which persisted up to 12 months (10). Similarly, a primary-care based multi-component intervention in pre-frail and frail older persons was effective in reversing frailty measures at 18 months (22). Of note, a recent 12-week multi-component frailty prevention program for prefrail community-dwelling older persons reduced frailty and improved physical and cognitive functions and self-rated health (23). While the multi-component intervention studies demonstrated effectiveness in frailty outcomes, they are often resource-intensive with reliance on trained personnel to run

the programs, which may affect the scalability and sustainability of these programs.

Against this backdrop, AI-enabled technology-based innovations provide a viable solution to render multi-component interventions in a scalable manner to alleviate the resource burden. Yet, the effective use of technology to deliver multi-component frailty interventions has hitherto been understudied. Older adults have greater variability in digital literacy as compared to their younger counterparts (24), and past studies have highlighted that some older adults may face barriers to digital adoption due to low perceived ease of use (25–27). Thus, we propose a multi-domain, end-to-end System for Assessment and Intervention of Frailty (SAIF), which aims deliver a holistic user-friendly intervention for frailty in the community. SAIF leverages data-driven AI technologies to provide individualized polypharmacy management, nutritional recommendation, and physical exercises. In this pilot study, we aim to explore the effectiveness of SAIF in improving frailty status, physical performance and strength in community-dwelling pre-frail older adults who are at risk of frailty progression. We also aim to explore the usability of SAIF in terms of adherence, safety and user experience.

Materials and methods

Study design and participants

The study design was an 8-week single arm, pre-post pilot trial. Data was collected at baseline and the end of the 8-week SAIF intervention. Participants were recruited from Peace-Connect Cluster Operator (PeCCO), a senior activity center in Singapore. SAIF intervention sessions and study visits were conducted at PeCCO. Participants were screened using the eligibility criteria stated in the next section and eligible participants were enrolled into the study. Written informed consent was obtained from all participants before their participation in this study. Ethics approval of the study was obtained from the Domain Specific Review Board of the National Healthcare Group (Ref: 2019/01217). This pilot study has not been registered. However, the main study for "An End-to-end System for Assessment and Intervention of Frailty (SAIF)" is registered under clinicaltrials.gov (NCT05371210).

Eligibility criteria

Participants fulfilling all of the following inclusion criteria were eligible for the study: (1) aged 60 years old and above; (2) speak English and/or Mandarin; (3) able to ambulate more than 10 m without walking aid; and (4) pre-frail, defined using the Clinical Frailty Scale (CFS) (28, 29) as either: (i) CFS 3 + [CFS 3 with positive item(s) endorsed on FRAIL scale (30)], or (ii) CFS 4. Participants exhibiting at least one of the following criteria were excluded from the study: (1) Has Dementia/Parkinson's Disease/Arthritis; (2) hip surgery within the last 6 months; (3) hospitalized within the last 1 month; (4) presence of end-stage organ failure/symptomatic heart conditions/Chronic Obstructive Pulmonary Disease; and (5) modified Chinese Mini-Mental State Examination (CMMSE) < 19 (31).

System for assessment and intervention of frailty intervention

The technical aspects of SAIF have been described in detail elsewhere (32; **Figure 1**). In the design phase of the system, clinical inputs were sought from healthcare professionals to develop the interventional modules. Human factors such as familiarity and elderly-friendly human-machine interaction techniques were adopted to ensure that SAIF was simple and intuitive for use by older adults. Designed as an autonomous interventional system, older adults may utilize SAIF with minimal supervision or assistance from caregivers. Before the start of SAIF interaction, the system developers engaged participants one-to-one and demonstrated its usage before allowing the older adults to try on their own. Automated instructions, available in both Chinese and English, are embedded in the system together with a voice-over to help guide the older adult user for subsequent sessions. Additionally, the system development team stationed staff members in the first couple of weeks of the study to ensure that the older adults were able to interact with SAIF independently and correctly and provided remote support afterward whenever technical issues arose. Instructional manuals were also provided to community center staff members to help assist subjects whenever necessary.

Three interconnected elements form the SAIF architecture: (1) interface modules (Virtual Nurse and Caregiver Dashboard) which act as the medium for users to interact with the system; (2) assessment modules to collect subjective questionnaire responses and objective physical measurements and feed the input into a predictive analytics model for frailty status prediction, and (3) intervention modules aimed at managing frailty through a multi-domain approach. For the purpose of this paper, we focus on the intervention modules in SAIF. In line with the Asia-Pacific Clinical Practice Guidelines for frailty management (21), SAIF interventional modules include polypharmacy management, nutritional recommendations and physical exercises (**Figure 2**).

Polypharmacy management module

The polypharmacy management module aims to help users track and improve medication adherence. Prior to the start of SAIF interaction, participants' medication regimen was recorded by research assistants. Pictures of their medications (packaging box and/or pills) were also included to aid

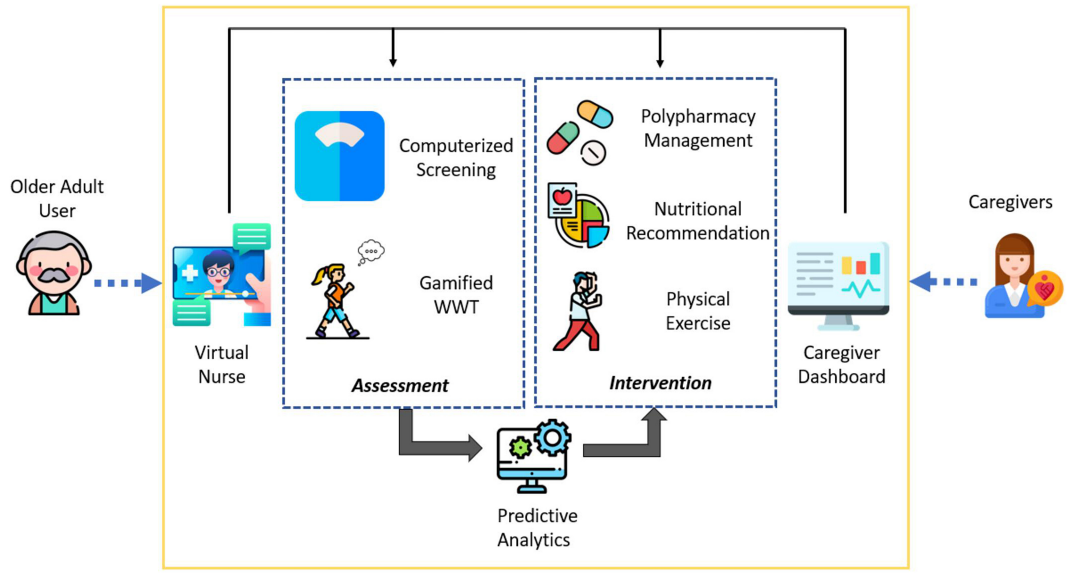

FIGURE 1
Conceptual diagram of system for assessment and intervention of frailty (SAIF) depicting the integrated elements of interface, assessment, and intervention components.

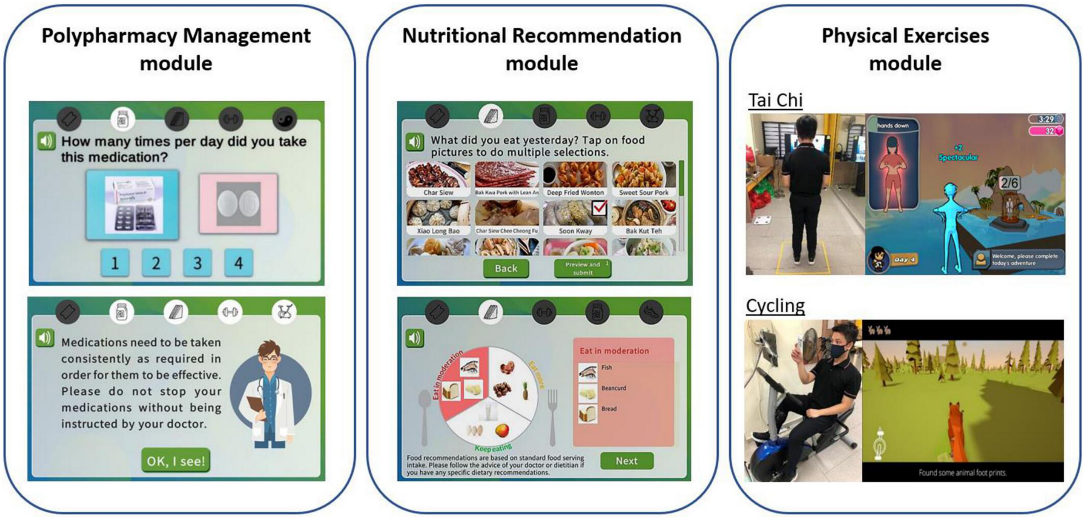

FIGURE 2
Illustration of system for assessment and intervention of frailty (SAIF) intervention modules which consist of polypharmacy management, nutritional recommendation, and physical exercises modules.

in questionnaire selection. Responses regarding medication adherence were collected through self-reported questionnaires administered on the tablet, where the Virtual Nurse resides. SAIF acted as an electronic monitoring system to display the correct frequency and dosing for participants who did not comply with their medication regimen. Remote reminders have been shown to be effective in improving medication adherence (33, 34). Information on medication effects were also delivered by the Virtual Nurse to encourage users to stay on track with their health goals. For users who stopped their medications, the system provided prompts to seek advice from their healthcare provider about the medications.

Nutritional recommendation module

The nutritional recommendation module aims to provide personalized dietary suggestions based on the analysis of the food intake information provided by the participants. Remote dietary assessment and tailored nutritional feedback has gained

traction in the past few years for their potential in health promotion (35–37). Users selected their diet intake from a variety of food categories displayed on the tablet. Pictures of local food cuisines were included to aid the older adult users in food selection. Based on the calculated nutritional values of the selected foods, dietary modeling tools generated food recommendations to supplement nutritional needs. SAIF also harnessed data from the regular dietary inputs from users to identify individual preferences to personalize food recommendations.

To elaborate, the dietary intake upload module does not take into consideration personal information such as height, weight, and activity level. However, it considers other personal information which is provided by the participants, such as tabooed food items due to religious reasons, food allergy or personal preference. For instance, for a Muslim participant, all food items with pork or lard ingredients are filtered out in the food selection to input their diet intakes. Participants are prompted to upload all the food items consumed in the previous day whenever they logged into SAIF.

The food items are organized in a two-level manner which first selects the broad category (such as drink, fruit, type of meat, type of cuisine, etc.) and then the exact food item (such as apple, steak, spicy tofu, etc.). In this 2-month study, the order of both the higher-level categories and the lower-level food items were set by our team members based on heuristics.

Physical exercise module

Tai Chi and Cycling modules are exercise kiosks for training upper and lower limbs, respectively. Each exercise session lasted for 15 min, and on each day during the study period, each participant was randomly assigned by the Virtual Nurse to conduct one of the two exercises. Game elements were incorporated for the Tai Chi and Cycling programs as gamification (i.e., the usage of game elements in a non-game context) can improve the interest and engagement in physical activities for older adults (38) and motivate users to maintain their adherence to the program (39, 40).

Tai Chi is a prominent exercise derived from martial arts, and is popular with Chinese older adults (41). This form of exercise has been shown to improve the balance capacity of seniors (42). The SAIF Tai Chi exercise module is conducted *via* a large-screen TV mounted with Kinect-based motion sensors. Users were instructed to follow a series of upper-body Tai Chi moves demonstrated by a virtual coach as well as to perform a set of stretching exercises with resistance bands for warm-up, and a coin-catching mini game for warming down (32). The Kinect-based motion sensors detect body movements of participants and game points were awarded for accurate replication of the Tai Chi moves by participants.

Stationary cycling is a form of endurance training that can promote physical health in older adults and is relatively safe (43). The SAIF Cycling module consists of a stationary exercise bike with motion sensors mounted onto the pedals. A tablet is mounted onto a stand in front of the exercise bike for the game display. Users were represented by a virtual avatar in a hunting game where the avatar will move according to the pedal speed detected (32). Participants were tasked to race forward and track their prey to earn game points upon capturing the prey.

In line with the self-determination theory, features were incorporated to motivate and sustain user participation (44, 45). For instance, successful completion of the instructional tasks within the games elicited positive messages to commend and reinforce their behaviors. Points were accumulated as participants cleared different levels of the game. A game points ranking system within each game was also incorporated to create extrinsic motivation through competition between the participants.

Procedure

Prior to the start of the intervention, all participants were guided through one complete cycle of SAIF interaction (**Figure 3**). Participants accessed the Virtual Nurse interface using a personalized QR code. Upon login, they were asked to provide responses related to diet intake, medication adherence and subjective measures of frailty. Thereafter, they would be randomly directed to either the Tai Chi or Cycling exercise module. Successful completion of the questionnaires and assigned physical exercise were recorded as one interaction count. Each interaction session took approximately 20 min (5 min for questionnaires and 15 min for Physical Exercise module).

Community staff was trained to provide on-site technical assistance to users when they encountered difficulties. To ensure that effectiveness of the intervention was not undermined by inadequate adherence, participants were advised to complete at least 10 SAIF interactions in a month. Attendance was tracked electronically and authorized community staffs and study members monitored participants' adherence *via* a web-based Caregiver Dashboard.

Measurements

Demographics and clinical assessments

Participants' age, gender, race, education level, housing type, chronic conditions and number of medications were recorded. Standing height and body weight were measured to derive the body mass index (BMI). Cognitive performance was evaluated using the modified Chinese Mini-Mental State Examination (CMMSE) (31). Functional status was assessed using the modified Barthel Index for Basic Activities of Daily Living

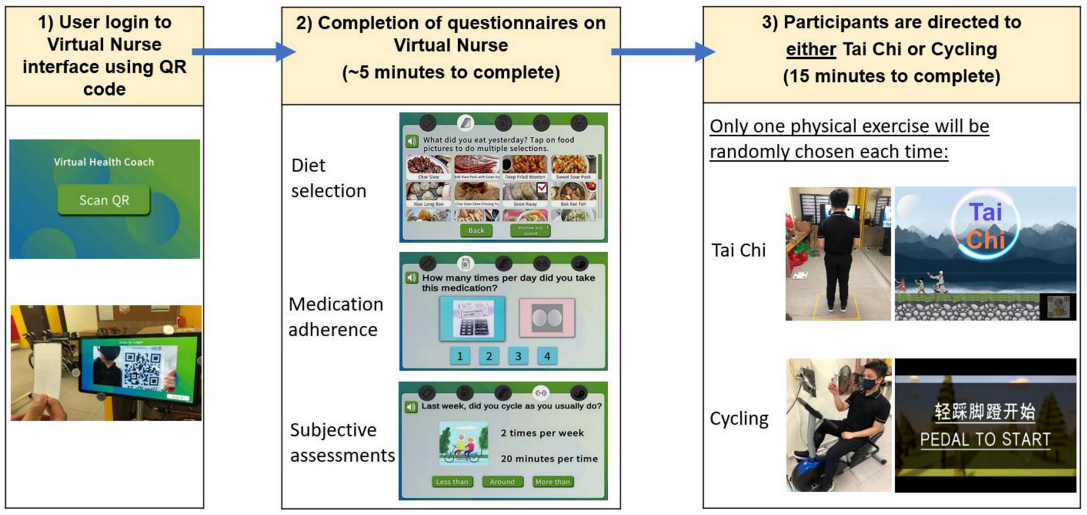

FIGURE 3
Overview of user interaction for system for assessment and intervention of frailty (SAIF) session: login to Virtual Nurse interface, followed by completion of diet, medication, and subjective assessment questionnaires, and then being directed to exercise module (either Tai Chi or cycling).

(BADL) (46) and Lawton's scale for Instrumental Activities of Daily Living (IADL) (47).

Outcome measures

Effectiveness

Physical performance and frailty status of participants were evaluated at baseline and 8-week. Physical performance was assessed using the Short Physical Performance Battery (SPPB) (48) and Hand Grip Strength (HGS). The SPPB is an objective measure of lower extremity functions (static balance, gait speed, and chair-stand) in older adults (48). The highest reading for HGS as measured twice on each hand using the North Coast^{TM} Hydraulic Hand Dynamometer (North Coast Medical Inc., Morgan Hill, CA, USA) was recorded (49).

Frailty status was assessed using two measures: modified Fried Frailty Phenotype (FFP) and CFS. The modified FFP was calculated based on established values for Asian older adults (50) and operationalized using the following components: (1) Handgrip strength of < 28 kg for men and < 18 kg for women; (2) body mass index < 18.5; (3) usual gait speed < 1.0 m/s over the 3-meter walk test; (4) fatigue based on endorsement of either of two questions ("I felt that everything I did was an effort" and "I could not get "going""") from the Center for Epidemiologic Studies-Depression Scale (CES-D); and (5) low physical activity measured using the International Physical Activity Questionnaire – Elderly (IPAQ-E) and defined using cut-off of < 2,826 Metabolic Equivalent Task (MET) minutes per week (51). The CFS is a 9-point global rating scale which allows classification across the frailty continuum ranging from 1 (very fit) to 9 (terminally ill) (29). CFS 3 corresponds to non-frail individuals who are not regularly active beyond routine walking, while CFS 4 refers to the "vulnerable" group with symptoms of slowing or fatigue which limit activities (28). Frailty is diagnosed when individuals are categorized as CFS 5–8.

Usability

Adherence to the SAIF program was measured by the number of SAIF interventions completed. The criterion for success related to intervention adherence was for participants to comply with the instruction to attend a minimum of 10 sessions in a month. We also investigated the user safety of the system, as operationalized by the number of reported incidents out of the total interaction count.

User experience data was measured at the end of the 8-week intervention. For quantitative data, we utilized the System Usability Scale (SUS) which assesses the perceived usability of technological systems and includes 10 items scored on a 5-point Likert scale (0 = "strongly disagree" to 4 = "strongly agree") (52). Item scores were added up and multiplied by 2.5 to obtain a score ranging between 0 and 100 (52). The SUS has been extensively used in previous user research studies and demonstrated good psychometric properties (52). Better usability was indicated by higher SUS scores (53). Interest-enjoyment subscale of the Intrinsic Motivation Inventory (54) was used as a self-report measure of interest and enjoyment of the intervention. The interest-enjoyment subscale comprised of seven items that were measured on a 5-point Likert scale (1 = "strongly disagree" to 5 = "strongly agree") (54). The interest-enjoyment scores were calculated by averaging across the total number of items in the subscale.

Qualitative feedback was gathered using open-ended questions regarding the modules which participants liked the most/least and the reasons for their responses.

Statistical analyses

Analyses were conducted on IBM SPSS version 26.0 (IBM Corporation, Armonk, NY, USA) with a two-tailed significance level of $p < 0.05$ considered as statistically significant. Continuous variables were expressed as means (standard deviation) or as medians (interquartile range). Categorical variables were expressed as counts (percentages).

Effectiveness was analyzed using Wilcoxon signed rank test on pre-and post-intervention scores for continuous variables. As we utilized a non-parametric analysis, correlational effect sizes (r) were computed (55) and interpreted according to Cohen's guidelines (56): Small effect ($r = 0.10$), medium effect ($r = 0.30$), large effect ($r = 0.50$). The change in categorical frailty status between pre-and post-intervention time points was investigated using the McNemar's test.

For user experience, we analyzed the quantitative and qualitative data separately using a convergent mixed-method approach (57) and the results were integrated *via* a joint display through visual means (58). Descriptive univariate analyses were performed on the SUS and interest-enjoyment scales. The qualitative responses collected were analyzed for themes using the thematic analysis framework by Braun and Clarke (59). Most Chinese participants had a good command of Mandarin and understood simple English. To ensure that they were able to answer to the best of their abilities, questions were asked in Chinese. The research assistant, who has proficiency in both English and Mandarin, transcribed the responses into written English. For Malay participants, both questions and responses collected were in English. For analysis, we followed the methods described by Bree and Gallagher (60) in using Microsoft Excel to aid in the generation of themes. Open codes were color-coded, categorized and grouped to form meaningful themes (61).

Results

Amongst 34 participants assessed for eligibility, we excluded 14 to yield a final sample of 20 participants (**Figure 4**). The mean age of participants was (70.9 ± 5.6 years). They were predominantly female (70%), of Chinese ethnicity (75%), and had either primary or secondary education (55 and 30% respectively) (**Table 1**). In terms of frailty status, most had a CFS score of 4 (70%) and the remaining (30%) were CFS 3 and pre-frail on the FRAIL scale. Correspondingly, the median BADL and IADL scores were 100 and 23 respectively (maximum scores), which attested to the relatively good health of the cohort. Out of the 20 recruited participants, 16 participants (71.8 ± 5.5 years) completed the 8-week intervention period. There was no significant difference in baseline characteristics such as age, gender, education, housing type, past medical

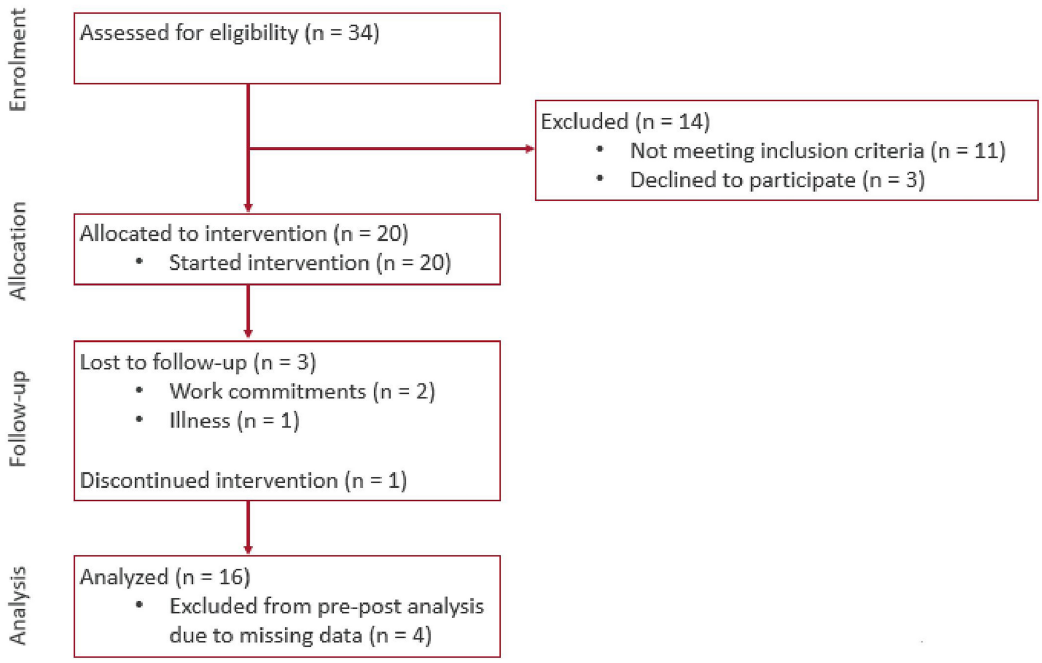

FIGURE 4
Consort flow diagram of progress through the phases of enrolment, allocation, follow-up, and data analysis.

history, CMMSE and functional status between dropouts and the remaining participants (Supplementary Table 1). Amongst the 4 participants who dropped out, 3 reported reasons unrelated to the intervention (2 had work commitments and 1 had illness). The last participant discontinued intervention due to difficulty navigating the Virtual Nurse module despite assistance being rendered to use the system.

Effectiveness

There was a significant improvement in modified FFP scores (Difference: −0.5, $p < 0.05$, $r = 0.43$) of moderate effect size, after the 8-week SAIF intervention. In terms of change in FFP frailty categories, five (31.3%) participants showed improvement ($p = 0.063$), with one improving from pre-frail to robust and four from frail to pre-frail. For CFS, there was a non-significant improvement (Difference: −1.0, $p = 0.10$, $r = 0.29$), and five participants improved from CFS 4 (pre-frail) to CFS 3 (non-frail sedentary) ($p = 0.18$). For physical performance, there was a significant improvement of moderate effect size in SPPB (+1.0, $p < 0.05$, $r = 0.42$); similarly, HGS showed a significantly improvement of moderate effect size (+3.5, $p < 0.05$, $r = 0.45$) (Table 2).

Usability

The mean SUS score was 68.0 out of 100 ($SD = 9.9$), and the interest-enjoyment score was 3.9 out of 5.0 ($SD = 0.4$). The mean interaction count was 11.3 (81% attended 10 times or more) in the first month and 10.1 (63% attended 10 times or more) in the second month. Based on participants' completion records over the period of 2 months, there was good adherence to the SAIF intervention as most participants were able to attend at least 10 sessions in a month. Out of the total participant interaction count of 363, there was 1 reported incident of participant feeling unwell during the course of SAIF interaction (0.3%).

Themes

Three key themes emerged from thematic analysis of participant comments. They allude to the perceived benefits of the intervention to physical health, user engagement by gamification and difficulties encountered in navigating the modules.

Perceived benefits to physical health

Participants enjoyed the physical interventions as they noticed an improvement in their perceived physical health after the SAIF interaction. For instance, one participant noted that it "helped to improve leg strength" (P7). Similarly, another user shared that her "leg has become less painful, (and) can walk faster. . ." (P17).

TABLE 1 Baseline characteristics of study cohort.

Variables	Total ($n = 20$)
Demographics	
Age, years	70.9 ± 5.60
Gender, n (%)	
Female	14 (70.0)
Male	6 (30.0)
Race, n (%)	
Chinese	15 (75.0)
Malay	5 (25.0)
Level of education, n (%)	
No formal education	3 (15.0)
Primary	11 (55.0)
Secondary	6 (30.0)
Education, years	6.40 ± 3.58
Housing, n (%)	
1–2 room	19 (95.0)
3 room	1 (5.0)
Medical history	
Hypertension, n (%)	15 (75.0)
Hyperlipidemia, n (%)	17 (85.0)
Diabetes, n (%)	6 (30.0)
Asthma, n (%)	1 (5.0)
Cancer, n (%)	3 (15.0)
Current medications	4.30 ± 2.74
Anthropometry	
Weight, kg	61.38 ± 9.63
BMI, kg/m^2	25.10 ± 4.02
Cognitive performance	
CMMSE, max 28	23.50 ± 2.37
Functional status	
BADL score*	100.00 (95.00–100.00)
IADL score*	23 (22–23)
Frailty status	
FRAIL, n (%)	
Robust	13 (65.0)
Pre-frail	7 (35.0)
Score*, max 5	0 (0–1.00)
CFS, n (%)	
CFS 3	6 (30.0)
CFS 4	14 (70.0)
Score*, (range 3–5)	4.00 (3.00–4.00)
Physical performance	
SPPB*, max 12	10.00 (8.00–11.00)
HGS, kg	16.35 ± 5.66

Mean ± SD unless otherwise indicated; *median (IQR); BADL, basic activities of daily living; BMI, body mass index; CFS, clinical frailty scale; CMMSE, Chinese mini-mental state examination; EQ–5D–5L, EuroQOL 5-dimension 5–level questionnaire; EQ-VAS, EuroQOL visual analogue scale; FFP, Fried frailty phenotype; HGS, hand-grip strength; IADL, instrumental activities of daily living; SPPB, short physical performance battery.

User engagement by gamification

Gaming aspects utilized in the Tai Chi and Cycling modules motivated and engaged users. For instance, one user shared that

TABLE 2 Effectiveness outcome results (n = 16).

	Pre (baseline)	Post (8 weeks)	*P-value*	Effect size (r)
Physical performance				
SPPB, max 12	10.00 (7.25–11.75)	11.00 (10.00–12.00)	0.02[a]	0.42
Hand grip strength	16.50 (12.00–22.00)	20.00 (16.00–22.75)	0.01[a]	0.45
Frailty status				
FFP, max 5	2.50 (2.00–3.75)	2.00 (1.00–2.75)	0.02[a]	0.43
Robust	0 (0.0)	1 (6.3)	0.06[b]	
Pre-frail	8 (50.0)	11 (68.8)		
Frail	8 (50.0)	4 (25.0)		
CFS	4.00 (3.00–4.00)	3.00 (3.00–4.00)	0.10[a]	0.29
CFS 3	6 (37.5)	11 (68.8)	0.18[b]	
CFS 4	10 (62.5)	5 (31.3)		

[a]Wilcoxon signed rank test.
[b]McNemar's test; two-tailed significance set at $p < 0.05$.

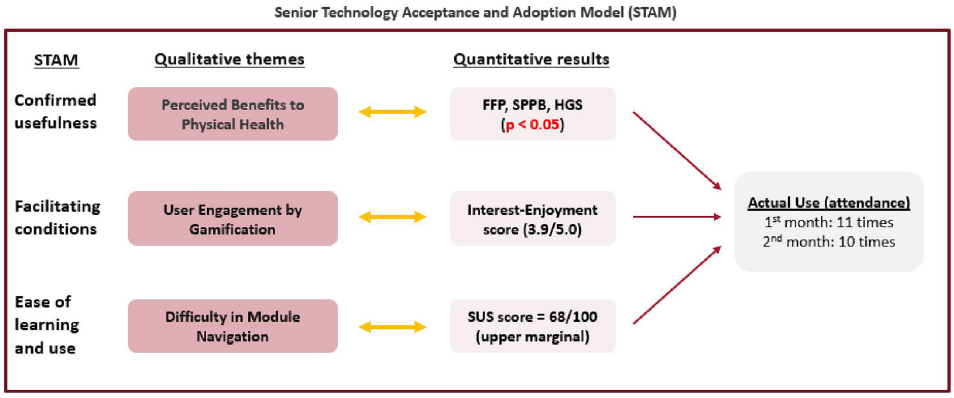

FIGURE 5
Joint-display of qualitative themes and quantitative results using the senior technology acceptance and adoption model (STAM).

she felt "motivated by the points" gained across the different levels of the games (P3). For another participant, the "money-catching segment (of the warm-down exercise for Tai Chi game) is fun... game scores also make it more fun and exciting" (P8). Other participants also commented that the games were interesting to them.

Difficulty in module navigation

Participants highlighted the barriers faced during interaction with SAIF. Some expressed difficulties with using the Virtual Nurse interface module. For example, participants highlighted difficulties in selecting the food options for the nutritional module. One participant found it "troublesome" that there were "too many things to press at food section" (P1) while another commented that she was "not sure how to use this function properly" (P3). For the Tai Chi physical exercise module, some participants noted that the Kinect may not be sensitive enough to detect user movements. To circumvent this, one participant shared how she "... needs to do bigger movements to score points" (P4).

Mixed-methods integration

The Senior Technology Acceptance and Adoption Model (STAM) (62) was adapted to integrate the quantitative and qualitative results. STAM has been used in studies to explain the uptake and utilization of new technologies by older adults (63, 64) by alluding to procedural phases which older adults undergo during the process of technology uptake. In the incorporation phase, the older adult user explores and forms a perception about the technological system. Through this experimentation, positive experiences coupled with a perception of ease of use play an important role in the acceptance of technology for older adults (62).

The themes from our qualitative user feedback cohere with the incorporation phase as described in the STAM (Figure 5). Participants showed good adherence to SAIF system, as evidenced by the complementarity between the qualitative themes with the results of quantitative analysis. According to the STAM, confirmed usefulness and facilitating conditions are

factors that can influence the actual use of the technological system. Through interaction with SAIF, older adult users perceived benefits to their physical health (Theme 1), which was corroborated by the significant improvements ($p < 0.05$) in their frailty status and physical performance. Gamification was a facilitating condition for participants (Theme 2), as they were engaged by the games, and this was reflected in the high interest-enjoyment score of 3.9 out of 5.0. Some participants faced difficulty during the module navigation (Theme 3), which may have contributed to the SUS score of 68 out of 100. Nonetheless, the perceived usefulness of SAIF and engagement from game elements facilitated good adoption from our participants, as reflected in the high usage of the system.

Discussion

The World Health Organization proposed reframing the concept of healthy ageing to emphasize intrinsic capacity, which is a key determinant of an individual's functional abilities (65). Intrinsic capacity and frailty are complementary concepts such that community-based multi-component interventions targeted at the prevention of frailty can inform strategies for healthy aging at the population level (66). Our pilot study contributes to the growing body of evidence which supports early intervention for frailty by investigating the effectiveness and usability of the 8-week SAIF program in community-dwelling pre-frail older adults. Results support the effectiveness of SAIF in improving frailty status, physical performance and strength. The participants also found SAIF to be interesting and enjoyable with fairly good usability. Taken together, our results support the notion of pushing the boundaries of frailty interventions to include the at-risk groups of CFS 3 to 4 before the onset of established frailty. Our pilot study has notable strengths. To the best of our knowledge, this is the first study to demonstrate the effectiveness and usability of a community-based unsupervised multi-domain technology-based intervention consisting of medication management, nutritional recommendation and physical exercises. The novelty of SAIF lies in the use of AI-driven technological applications to deliver an autonomous multi-domain frailty intervention.

The demonstration of effectiveness in terms of frailty status, physical performance and strength corroborates the results of recent intervention studies in cohorts consisting entirely of pre-frail older adults. Notable differences are worth highlighting. Firstly, the criteria to define frailty in prior studies included FFP (67) and FRAIL (23, 68); in contrast, we primarily based our inclusion criteria on CFS, which was supplemented with FRAIL in the CFS 3 (non-frail) group to select an enriched at-risk population. The strength of CFS resides in its simplicity as a measure of global frailty which has been validated in various populations in real-world settings (69). Secondly, approaches to frailty interventions in prior studies comprised either multi-component exercises (67) or interventions (23, 68) in multiple domains of exercise, nutrition, cognition and/or social. Our study likewise employed an evidence-based multicomponent approach premised on the Asia-Pacific Clinical Practice Guidelines for frailty management (21) which addressed the domains of exercise, nutrition and polypharmacy. Lastly, frailty outcome measures in prior studies comprise single measure of FFP or FRAIL. In comparison, the combination of FFP and CFS outcome measures in our study yielded complementary insights respectively about physical frailty (premised on the phenotypic approach) (1) and global frailty (premised on the deficit accumulation approach) (29, 70). The significant benefit in physical frailty is likely mediated *via* the positive intermediary effects on SPPB and grip strength, which in turn may be related to our physical exercise modules with both upper-(Tai Chi) and lower-(Cycling) body exercises. Tai Chi has been found to improve the balance of older adults (42), and aerobic exercises like stationary cycling were beneficial in improving seniors' gait speed and chair-stand tests (71). These improvements in physical components, coupled with nutritional advice and medication management, may have led to the improvement in overall frailty, as demonstrated by the improvement in CFS status of some participants from pre-frail to non-frail, albeit with a larger sample size needed to demonstrate statistical significance with CFS.

User experience with SAIF demonstrated that older adults do not need complex digital skills to use the system as they were able to successfully complete the sessions independently. However, some participants found the food selection of the nutritional module to be complex and troublesome. The Kinect-motion sensors may also not be sensitive enough to detect some user movements. Our study thus highlights the importance of a comprehensive program evaluation in the pilot phase that also includes usability aspects of technological innovations such that insights from user experiences can inform improvements for the subsequent validation study (72). Future developments of the SAIF system can explore the usage of voice inputs, which showed good usability, accuracy and time efficiency for diet reporting amongst older adult users (73). Food categories and items could also be re-ordered according to their frequency of being uploaded by the participants (i.e., the display order following their popularity). Kinect sensitivity may also be improved with identification of optimal placement relative to participants' standing distance (74). The low reported incident count (0.3%) highlighted that the system can be safely deployed in a community setting as an autonomous intervention for pre-frail older adults. Nonetheless, remote monitoring tools may be used to enhance the safety of users during physical exercises (75). Consequently, trigger mechanisms may be incorporated to activate immediate assistance for older adults (76).

We acknowledge several limitations. Firstly, the pragmatic single-group pre-post design in our exploratory study precludes definitive conclusions about causality. Specifically, the lack of

a control group, the small sample size and multiple outcome measures being analyzed raise the possibility that the significant improvement in frailty, physical performance and strength could be the result of a Type-I error; conversely, the lack of significance for CFS outcomes could represent a Type-II error from an inadequately powered study. Secondly, we also did not specifically assess for the effects of mitigating factors such as boredom and mood on user compliance and the usability and interest-enjoyment scores. To study the effects of these factors, the user experience questionnaires may be collected at two time points (e.g., at the 1-month and 2-month follow-up respectively) along with in-depth qualitative interviews to better ascertain the impact of factors affecting motivation/compliance on the participant's perceived levels of interest and enjoyment toward the intervention. Next, the lack of randomization and recruitment from a single center also meant that individuals who joined the research may not be representative of the older adult population in Singapore. Although the baseline CMMSE mean score of our participants is comparable to those reported in an earlier study of community dwelling older adults of normal cognition around the same age group (31), previous studies have highlighted the importance of considering demographic factors such as age, gender, ethnicity and educational level which can influence the level of technological literacy and adherence to health-related technological interventions (77, 78). As such, caution must be exercised in generalizing the effectiveness and usability of SAIF to other groups of older adults. Also, the multi-domain intervention of SAIF focuses on the 3 domains of nutrition, physical exercise and polypharmacy, and did not consider other domains such as sleep, psychological well-being and social interactions. Lastly, as SAIF is a multi-component intervention, it is difficult to gauge the independent contributions of the modules toward improving the physical health of our participants. However, it is also plausible that the modules may create a synergistic effect in improving the frailty status of our older adult subjects.

The current pilot study is preliminary and it sets the stage for a multi-centered, adequately powered, and randomized controlled study which incorporates an adequate duration of post-intervention follow-up assessments to ascertain the sustainability of the benefits in reducing frailty and improving physical performance and strength over time. Importantly, insights from usability data in the pilot study can inform improvements in the implementation and user experience of the SAIF system for the validation study.

Conclusion

Frailty is a syndrome that may be prevented or reversed through appropriate interventions. Effective multi-component interventions in the community targeted at the prevention of frailty can inform strategies to promote healthy ageing at the population level. Our pilot study provides preliminary results to support the use of SAIF as an autonomous interventional system to reduce frailty and improve physical performance and strength in pre-frail older adults. SAIF's novelty lies in the use of technology to deliver a data-driven, community-based, multi-component intervention to improve outcomes in pre-frail older adults. The implementation of a follow-up large-scale randomized controlled trial is warranted.

Data availability statement

The datasets presented in this article are not readily available because, subject to institutional rules for data sharing. Requests to access the datasets should be directed to WL, Wee_Shiong_Lim@ttsh.com.sg.

Ethics statement

The studies involving human participants were reviewed and approved by National Healthcare Group IRB. Written informed consent to participate in this study was obtained from study participants. In addition, written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

RT was responsible for data analysis and writing the manuscript. WL was involved in study design, supervised the data analysis, and the critical appraisal of the manuscript. Rest of co-authors was involved in study design and critical appraisal of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.955785/full#supplementary-material

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EDITED BY
Tzvi Dwolatzky,
Technion - Israel Institute of Technology, Israel

REVIEWED BY
Siti Setiati,
University of Indonesia, Indonesia
Guilherme Eustaquio Furtado,
Instituto Politécnico da Guarda, Portugal

*CORRESPONDENCE
Tze Pin Ng
pcmngtp@nus.edu.sg

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Lower insulin level is associated with sarcopenia in community-dwelling frail and non-frail older adults

Yanxia Lu[1], Wee Shiong Lim[2,3], Xia Jin[4], Ma Schwe Zin Nyunt[5], Tamas Fulop[6], Qi Gao[5], Su Chi Lim[7], Anis Larbi[6,8] and Tze Pin Ng[5]*

[1]Department of Medical Psychology and Ethics, School of Basic Medical Sciences, Cheeloo College of Medicine, Shandong University, Jinan, China, [2]Department of Geriatric Medicine, Tan Tock Seng Hospital, Singapore, Singapore, [3]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore, [4]The Third Hospital of Jinan, Jinan, China, [5]Gerontology Research Programme, Department of Psychological Medicine, National University Health System, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [6]Department of Medicine, Research Center on Aging, University of Sherbrooke, Sherbrooke, QC, Canada, [7]Department of Endocrinology, Khoo Teck Puat Hospital, Singapore, Singapore, [8]Biology of Ageing Laboratory, Singapore Immunology Network (SIgN), Agency for Science Technology and Research (A*STAR), Biopolis, Singapore, Singapore

Background: Sarcopenia is common among older individuals with and without type 2 diabetes mellitus (T2DM). There are conflicting evidence in support of the role of insulin in the development of age-related and T2DM-related sarcopenia. We investigated the relationships between the levels of fasting insulin and other blood biomarkers related to insulin or lipid metabolism with the presence of sarcopenia in two independent studies.

Materials and methods: In 246 pre-frail frail older individuals with (n = 41) and without T2DM (n = 205) in the Singapore Frailty Interventional Trial, sarcopenia was defined by low appendicular lean mass (ALM) relative to total body mass (skeletal muscle index, SMI = ALM/height^2) and low lower limb strength or gait speed according to the Asian Working Group for Sarcopenia (AWGS) criteria released in 2019, and related to levels of fasting insulin and glucose, C-peptide, IGF-1, leptin, and active ghrelin. This investigation was validated in another independent study sample of 189 robust and pre-frail frail elderly in the Singapore Longitudinal Aging Study Wave 2 (SLAS-2).

Results: Compared to non-sarcopenic individuals, those with sarcopenia and possible sarcopenia showed significantly lower fasting insulin ($p < 0.05$) in pre-frail/frail and non-frail older individuals. Consistent trends of relationships were observed for serum levels of C-peptide, IGF-1, leptin, and active ghrelin. In multivariable logistic regression models, sarcopenia was independently associated with low insulin ($p < 0.05$). Levels of fasting insulin, C-peptide, and leptin were also significantly associated with BMI, SMI, knee extension strength, gait speed, and physical activity score.

Conclusion: Dysregulated insulin secretion in diabetic and non-diabetic older individuals may play an important role in age-related and diabetes-related sarcopenia.

KEYWORDS

sarcopenia, diabetes, frailty, insulin, aging

Introduction

Sarcopenia is an incipient manifestation of aging characterized by progressive loss of skeletal muscle mass and function. It is reported that sarcopenia predicts physical frailty, late-life disability, and mortality (1, 2). In a world with an accelerated population aging, the rapidly growing number of older individuals with sarcopenia and physical frailty makes it an important geriatric syndrome in clinical care. The prevalence of sarcopenia is 8–36% worldwide in individuals below 60 years and 10–27% in those equal to or above 60 years. Population-based prevalence of frailty varies by age, gender, and frailty classification, with 12% using physical frailty and 24% using the deficit accumulation model among those aged ≥50 years across 62 countries (3, 4). The underlying pathophysiology of sarcopenia is complex and far from being fully understood, involving nutritional deficiency, reduced physical activity, insulin resistance, atherosclerosis, and changes in inflammatory and endocrine functions (5, 6).

Disordered β cell functioning and insulin resistance are hallmarks of the development of type 2 diabetes mellitus (T2DM), which is prominently associated with sarcopenia (7). The association of insulin level and muscle mass and function decline in old age and those with T2DM is complex. Based on the classical view that insulin resistance is central to the development of T2DM, there are contrary hypotheses that insulin resistance facilitates the development of sarcopenia (8) and conversely that sarcopenia is a risk factor for insulin resistance and T2DM (9). Increasing evidence strongly points to disordered insulin secretion rather than insulin resistance playing a central role in driving the development of T2DM (10–12). Patients with diabetes may be vulnerable to sarcopenia due to primary changes in insulin level and activity (9, 13, 14). As an anabolic hormone, insulin stimulates protein synthesis *via* the uptake of amino acids into muscle tissues. Reduced insulin signaling in aging and diabetes hinders muscle protein synthesis (MPS) and promotes muscle protein degradation, leading to loss of muscle mass and eventually sarcopenia. Sarcopenia in turn further decreases the targeting mass of insulin action, reduces insulin sensitivity, and induces glucose dysregulation (15, 16).

Empirical evidence suggests the critical role of sufficient insulin in promoting protein synthesis, maintaining muscle function, and preventing muscle mass loss and sarcopenia (17, 18). Insulin exerts its anabolic action on skeletal muscles *via* stimulating glucose disposal (19) and inhibiting protein catabolism (20). A meta-analysis of human studies demonstrates that insulin has a permissive role in MPS in the presence of elevated amino acids and a major anti-catabolic effect in alleviating muscle protein breakdown (MPB) (21). In an interventional study, insulin treatmentattenuated annual decline of skeletal muscle index (SMI), especially in the lower extremities in Japanese patients with T2DM (22). There is an age-related decrease in insulin-mediated peripheral glucose utilization (23) and suppression of proteolysis (24) that are associated with sarcopenia. However, few studies have yet investigated the association of insulin and sarcopenia in older individuals with T2DM and those without (25, 26), with conflicting results generated. In the Baltimore Longitudinal Study of Aging, higher fasting and oral glucose tolerance test (OGTT) levels of insulin were associated with lower muscle mass in non-diabetic older individuals (27). On the other hand, Tanaka et al. (28), in a study of 191 male elderly with T2DM, suggested that endogenous insulin reduction is an independent risk factor of sarcopenia. Furthermore, supraphysiological hyperinsulinemia was reported to play an important role in the stimulation of MPS and anabolic signaling in the elderly (29). A possible explanation of the divergences may be related to the different ways of lean mass measurement (30). In individuals with sarcopenia, appendicular muscle mass index defined as muscle mass relative to height is mostly found positively associated with insulin resistance, while this correlation is negative in terms of muscle mass relative to body weight (31). Thus it is imperative to the standardized criteria to classify sarcopenia, in order to draw clear conclusion.

The present study aimed to ascertain whether sarcopenia is associated with the level of fasting insulin and other biomarkers related to insulin or lipid metabolism in diabetic and non-diabetic older individuals. Sarcopenia and physical frailty share core features such as impaired physical function, especially mobility, high prevalence, and intimate association with adverse health-related outcomes including disability and mortality in the elderly, and potential reversibility, and thus have been studied in parallel since the beginning (32, 33). We therefore studied the relationship of sarcopenia and fasting insulin level in a group of community-living pre-frail frail older persons. Furthermore, we validated and extended the results derived from this group to another independent study of elderly consisting of both robust and pre-frail frail elderly. We hypothesized that older

individuals with sarcopenia may have lower levels of fasting insulin than those without sarcopenia, considering the anabolic role of insulin in maintaining muscle mass and function. The present study investigated for the first time, to the best of our knowledge, the association of sarcopenia and fasting insulin level in elderly with and without T2DM, and thus extend the findings from previous research through its broader relevance to community-living elderly without T2DM.

Materials and methods

Study design and participants

Participant recruitment

The subjects in the exploratory study were participants in the Singapore Frailty Interventional Trial, a randomized controlled trial of nutritional, physical, and cognitive interventions among community-living pre-frail frail older persons (clinicaltrial.gov identifier NCT00973258) (34). We used the baseline data from the participants who were 246 pre-frail or frail older individuals (aged 65 years and above) as determined from the Fried criteria for frailty syndrome (35) comprising of 5 components (unintentional weight loss, slowness, weakness, exhaustion, and physical inactivity). We validated the study in an independent validation sample of 189 robust and pre-frail frail elderly from Singapore Longitudinal Aging Study Wave 2 (SLAS-2) (36). The difference between the exploratory study and the validation study lies in that the exploratory study emphasizes 246 pre-frail or frail older individuals, and the validation study covers the full spectrum of 189 robust and pre-frail frail elderly. The participants from both studies were from the same Chinese Singaporean population.

Study design

In both studies, sarcopenia was determined from measures of muscle mass, strength, and function using dual-energy x-ray absorptiometry (DXA) whole body scan, Physiological Profile Assessment (PPA) (37), and the 6-meter fast gait speed test. Serum (in the exploratory study) or plasma (in the validation study) was isolated from blood samples and stored in −80°C until measurements. The studies were approved by National Health Group (NHG) Domain Specific Review Board (DSRB) of Singapore, and all participants provided written informed consent. All methods were performed in accordance with the approved protocol and relevant guidelines and regulations.

Settings

Community-living Singaporean Chinese.

Participant inclusion/exclusion criteria

Inclusion criteria for both studies: (1) community residents in the southwest region of Singapore; (2) aged 65 years and above; (3) able to ambulate without personal assistance; (4) living at home. Exclusion criteria: (1) significant cognitive impairment (Mini Mental State Examination score $\leq$ 23); (2) major depression; (3) severe audiovisual impairment; (4) any progressive, degenerative neurologic disease; (5) terminal illness with life expectancy $<$ 12 months. Additional inclusion criteria for the exploratory study: (1) prefrail and frail older adults identified based on Fried criteria defining physical frailty. Additional exclusion criteria for the exploratory study: (1) simultaneous participation in other interventional studies; (2) unavailable to participate for the full duration of the study. The recruitment procedures are summarized in **Figures 1**, **2**, respectively, for the exploratory study and the validation study.

Frailty measurements

Frailty was assessed by the presence of: (1) Involuntary or unintentional weight loss: body mass index (BMI) $<$ 18.5 kg/m^2 and/or unintentional weight loss $>$ 10 pounds (4.5 kg) in the past 6 months; (2) Slowness: sex and height stratified lowest quintile values from the average of two measurements of the 6 m fast gait speed test; (3) Weakness: dominant knee extension strength measured from the average value from three trials using Lord's strap and strain gauge assembly component of the PPA, falling within the lowest sex and BMI standardized quintile; (4) Exhaustion: exhaustion score was generated from the vitality domain in the SF-12 and those falling within the lowest quintile of energy score [below 10 out of 15, derived in a previous population-based study of frailty (38)] were classified as having exhaustion; (5) Physical inactivity: Physical activity was assessed by the Longitudinal Ageing Physical Activity Questionnaire (LAPAQ) which measured the frequency and duration (in minutes) of six different activities (walking outside, bicycling, gardening, light and heavy household activities, and sports activities) during the past 2 weeks. A participant was considered physically inactive if his/her overall average daily time spent on physical activities fell within the sex-specific lowest quintile. A participant with three and more components was determined to be frail, one or two components as pre-frail, and none of the components as robust.

Dual-energy x-ray absorptiometry scans of body composition

Total and regional lean body mass and body fat was measured by dual energy X-ray absorptiometry (DXA) with the use of Hologic® densitometer. Tests were performed by operators in accordance with the manufacturer's protocol in Department of Diagnostic Radiology, National University Hospital of Singapore. The participant was instructed to lay in a supine position on the DXA table with limbs close to the

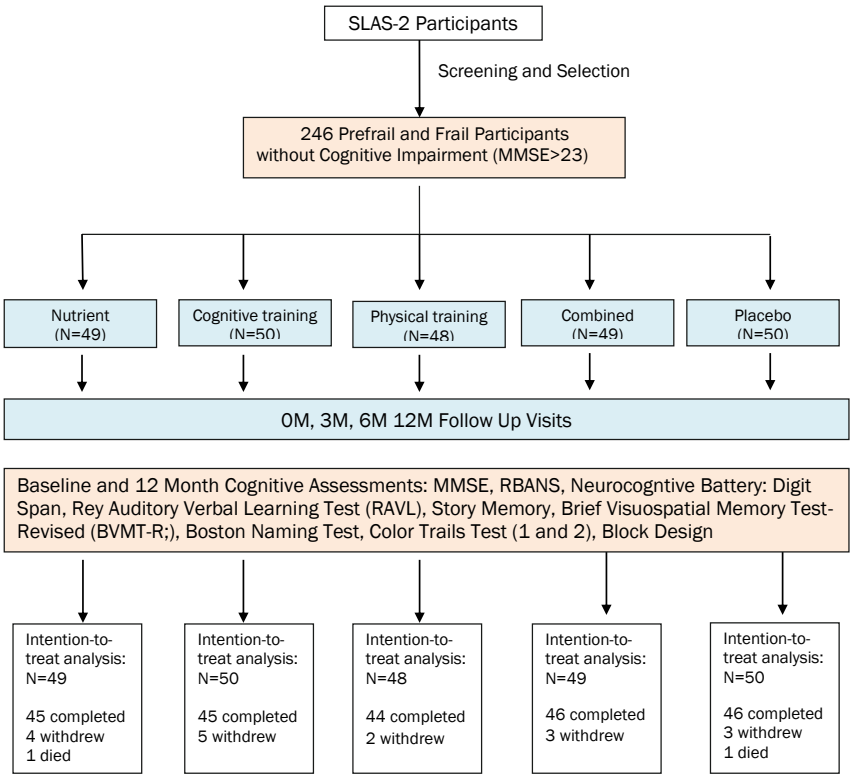

FIGURE 1
Participant recruitment flowchart in the exploratory study.

body. The whole-body lean soft tissue mass was divided into the regions of arms, legs, and the trunk. Appendicular lean mass (ALM) was calculated by summing lean mass (kg) of the two upper limbs and two lower limbs, with the adjustment of limb cut lines according to specific anatomical landmarks as described by Heymsfield et al. (39).

Measurement of lower limb strength

Lower limb strength was assessed by knee extension strength using the strap and strain gauge assembly component of the PPA described by Lord et al. (37), and a mean value from three trials (standardized by sex and BMI) was calculated. Low lower limb strength was classified as less than or equal to 18 kg for men and less than or equal to 16 kg for women.

Gait speed test

The 6 m fast gait speed test was performed following standardized procedures described by Nelson et al. (40). Briefly, participants were instructed to stand with their toes touching the taped start line, and complete the 6 m walking as fast as possible. Total course time was recorded using a second watch from the moment their foot crossed the start line until the moment their foot crossed the stop line. The average speed of two trials was calculated and presented as meters/second (m/s).

Definition of sarcopenia

Sarcopenia was identified in accordance with the recommendations from the Asian Working Group for Sarcopenia (AWGS) criteria released in 2019 (41). SMI was calculated as the ratio of ALM assessed by DXA scan over height squared. Participants were considered to have low SMI if the ratio was <7.0 kg/m^2 in men or <5.4 kg/m^2 in women. Low gait speed was defined as the average speed of two trials < 1.0 m/s. Participants were categorized as having sarcopenia if they had both low SMI and low lower limb strength or gait speed, possible sarcopenia if they had either low lower limb strength or gait speed but not low SMI, and non-sarcopenia if they had neither low SMI nor low lower limb strength or gait speed.

Diabetes status

The presence of diabetes was ascertained by the subjects' self-reports of a doctor's diagnosis and treatment, with

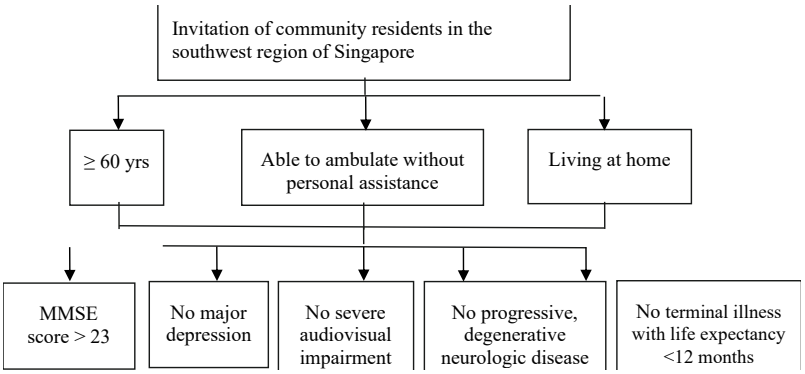

FIGURE 2
Participant recruitment flowchart in the validation study.

additional examination of their medication packages. Participants were determined as having diabetes when the use of appropriate diabetes medications was verified by the interviewer. The cross tables of number of participants with different status of sarcopenia and diabetes are summarized below:

Exploratory study:

	No diabetes	Diabetes
Non-sarcopenia	25	3
Possible sarcopenia	98	21
Sarcopenia	82	17

Validation study:

	No diabetes	Diabetes
Non-sarcopenia	28	4
Possible sarcopenia	49	15
Sarcopenia	79	14

Blood biomarkers

Venous blood was drawn from overnight fasting participants and serum (in the exploratory study) or plasma (in the validation study) was isolated and stored in −80°C freezer until measurements. The levels of fasting insulin, C-peptide, leptin, and active ghrelin were tested using high throughput Luminex technology (Cat no.: HMHEMAG-34K-04 and HIGFMAG-52K-01; Millipore Corp., Billerica, MA, United States) following the manufacturers' instructions. Experiments were performed by the platform operators. After an overnight incubation, the plates were read on a Flexmap 3D instrument (Luminex Corporation, Austin, TX, United States) and data were analyzed using Bioplex Manager 6.0 software (Bio-Rad Laboratories, Hercules, CA, United States). The concentration of IGF-1 was measured using Milliplex Map Human IGFI-II Magnetic Bead Panel (Cat no.: HIGFMAG-52K-01) in the exploratory sample and an enzyme-linked immunosorbent assay (ELISA) kit from Raybiotech Inc. (Norcross, GA, USA; Cat no.: ELH-IGF1) in the validation sample. The level of fasting glucose was measured by Department of Laboratory Medicine, National University Hospital of Singapore.

Statistical analysis

Data analysis was performed using IBM SPSS 22 software (IBM, New York, NY, USA). We compared the differences in demographics, physical and functional status, and biomarkers among the sarcopenia, possible sarcopenia, and non-sarcopenia study participants using chi-squared test or one-way analysis of variance (ANOVA) with *post-hoc* Bonferroni correction for multiple comparisons as appropriate, in the whole group and among non-diabetic and diabetic participants separately. Logistic regressions were performed on each blood biomarker to estimate odds ratio of association with the presence of sarcopenia. Blood biomarkers were analyzed as continuous variables as well as in tertiles, with adjustment for age, sex, diabetes status, and percentage of whole body fat mass to control for potential confounding. *P* for trends across tertiles were calculated by assigning ordinal scores to the tertiles and repeating the logistic regressions. Linear regression models were used to examine the relations of each blood biomarker concentration to clinical and functional measures of sarcopenia and frailty (BMI, SMI, lower limb strength, exhaustion score, gait speed, and physical activity score) in the whole and stratified samples of non-diabetic and diabetic participants after adjusting for potential confounders. The level of statistical significance was set at $p < 0.05$ with a two-sided distribution.

Results

The 246 pre-frail frail study participants in the exploratory study and the 189 robust and pre-frail frail elderly in the validation study were all Chinese and had average ages of 70.0 years (SD: 4.7 years) and 73.2 years (SD: 5.3 years), respectively. The exploratory and validatory samples had similar sex proportions, with 151 (61.4%) and 119 (63.0%) females, respectively. In the exploratory study, there were 41 (16.7%) elderly who had diabetes and 205 (83.3%) who did not have diabetes. The validatory study sample had a similar proportion of participants who had diabetes [33 (17.5%)]. Participants with diabetes had a mean disease history of 10 and 12 years, respectively, in the exploratory and validation studies, respectively, with all but five and four, respectively, taking anti-diabetic medications regularly. The commonest medication used was simvastatin and metformin, respectively. None of them were on insulin sensitizer drugs or treated with insulin.

In both studies, participants with sarcopenia had significantly lower BMI, SMI, knee extension strength, and gait speed in the whole sample and among subgroups of non-diabetic and diabetic individuals. Sarcopenia was associated with significantly higher exhaustion in the validation sample in the whole sample and among the subgroups (Table 1).

As shown in Table 2, sarcopenia was associated with lower fasting insulin ($p < 0.05$) in comparison to non-sarcopenia and possible sarcopenia in the whole exploratory sample of pre-frail/frail elderly. Among participants without diabetes, there was a positive trend of association between sarcopenia with lower fasting insulin, but this did not reach statistical significance, possibly due to the relatively large standard deviation ($p = 0.055$). In the validation study sample of robust and pre-frail/frail elderly, sarcopenic elderly had significantly lower insulin level than the non-sarcopenia and possible sarcopenia elderly in the whole sample and the non-diabetic group ($p < 0.001$). There was no difference in insulin levels among the sarcopenia subgroups of diabetic elderly, given the small sample size of the sarcopenic group. Lower C-peptide was observed in the sarcopenia group than in the non-sarcopenia and possible sarcopenia groups in the whole sample and the non-diabetic group. Sarcopenia was associated with lower leptin level than the non-sarcopenia group. No difference was observed in serum or plasma levels of fasting glucose, IGF-1 or active ghrelin among the sarcopenic subgroups (Supplementary Tables 1, 2).

TABLE 1 Demographic, physical, and functional status of sarcopenia groups in all subjects.

		Sarcopenic subgroups			
		Sarcopenia	Possible sarcopenia	Non-sarcopenia	*P*
Exploratory study					
Sex (female)	151 (61.38)	60 (60.61)	82 (68.91)	9 (32.14)	0.002
Age (years)	70.03 ± 4.69	70.01 ± 4.66	70.08 ± 4.91	69.86 ± 3.97	0.973
Secondary and above education	75 (30.49)	34 (34.34)	30 (25.21)	11 (39.29)	0.194
BMI (kg/m^2)	23.72 ± 3.48	21.47 ± 2.69^{**+++}	25.60 ± 3.10**	23.72 ± 2.76	< 0.001
Skeletal muscle index (kg/m^2)	6.11 ± 1.07	5.41 ± 0.86^{***+++}	6.55 ± 0.87	6.79 ± 1.11	< 0.001
Knee extension strength (kg)	14.17 ± 4.98	13.02 ± 4.56^{***+++}	13.05 ± 3.12***	22.92 ± 4.09	< 0.001
Gait speed (m/s)	0.95 ± 0.23	0.93 ± 0.23***	0.90 ± 0.21***	1.20 ± 1.82	< 0.001
Exhaustion score	10.63 ± 1.30	10.60 ± 1.38	10.63 ± 1.27	10.75 ± 1.14	0.858
Physical activity score	168.70 ± 112.20	162.40 ± 112.75	170.54 ± 103.50	183.19 ± 144.51	0.668
Fat mass (%, whole body)	32.88 ± 7.66	32.34 ± 8.01	34.39 ± 7.19***	28.59 ± 6.51	< 0.001
Validation study					
Sex (female)	119 (62.96)	59 (63.44)	49 (76.56)	11 (34.38)	< 0.001
Age (years)	73.16 ± 5.29	73.83 ± 5.32	72.31 ± 4.89	72.94 ± 5.84	0.204
Secondary and above education	50 (26.46)	24 (25.81)	12 (18.75)	14 (43.75)	0.032
BMI (kg/m^2)	23.59 ± 3.61	21.35 ± 2.67^{***+++}	26.14 ± 2.96	25.00 ± 3.12	< 0.001
Skeletal muscle index (kg/m^2)	5.86 ± 1.04	5.26 ± 0.86^{***+++}	6.39 ± 0.78	6.57 ± 0.97	< 0.001
Knee extension strength (kg)	13.89 ± 5.23	12.27 ± 3.99***	12.52 ± 4.37***	21.34 ± 3.28	< 0.001
Gait speed (m/s)	1.08 ± 0.30	1.07 ± 0.28***	0.98 ± 0.29***	1.32 ± 0.23	< 0.001
Exhaustion score	10.63 ± 2.09	10.40 ± 2.14***	10.27 ± 1.73***	12.06 ± 2.09	< 0.001
Physical activity score	243.84 ± 206.04	249.05 ± 188.05	209.26 ± 147.81	297.85 ± 320.23	0.131
Fat mass (%, whole body)	35.87 ± 6.33	34.90 ± 6.19^{++}	38.19 ± 6.24**	34.04 ± 5.75	0.001

Data are presented as mean ± SD or number (percentage).
*** P <0.001, ** $P < 0.01$ vs. the non-sarcopenia group; $^{+++}$ $P < 0.001$, $^{++}$ $P < 0.01$ vs. the possible sarcopenia group.

Table 3 shows the results of logistic regression analyses of the association of blood biomarkers with the presence of sarcopenia that were adjusted for age, sex, and diabetes status. The levels of insulin were borderlinely or significantly inversely associated with the presence of sarcopenia in the exploratory sample and the validation sample. The top tertile of fasting insulin was associated with lower risk of sarcopenia relative to the bottom tertile, with an OR of 0.297. A similar trend was observed in the validation study sample.

In linear regression models (Table 4), we found significant independent associations of blood biomarker concentrations with clinical and functional measures of sarcopenia and frailty. In the whole sample, the levels of fasting insulin and C-peptide were positively associated with BMI, SMI, and knee extension strength. IGF-1 was positively associated with knee extension strength. We also found that the level of leptin was positively associated with BMI, SMI, and physical activity score. Similar trends were observed in both non-diabetic and diabetic subgroups as shown in Supplementary Tables 3, 4, respectively.

Discussion

This study shows for the first time that the association of sarcopenia with low fasting insulin in the elderly is independent of whether the subjects have diabetes or not. Furthermore, fasting insulin, C-peptide, and leptin were significantly associated with one or more clinical and functional measures of sarcopenia and frailty including total body mass, muscle mass, knee extension strength, gait speed, and physical activity. The results are consistent with studies which showed that measures of endogenous insulin secretion were inversely associated with the presence of sarcopenia in individuals with type 2 diabetes (28) and that insulin treatment attenuates skeletal muscle mass loss (21, 22). Our results suggest that insulin is clearly involved in the biological process of sarcopenia (18, 42) in the elderly.

The mechanisms underlying low insulin in sarcopenia in diabetic and non-diabetic older individuals is not completely understood. The hypothesis that age-related changes in the number and size of Type I versus Type 2 muscle fibers favoring a tendency for altered insulin sensitivity may explain the observed association in this study (9). In diabetes, the pathogenetic role and mechanisms of insulin is highly complex, and a large volume of literature now strongly favor the view that β cell dysfunction but not insulin resistance may be the central defect responsible for the development of Type 2 diabetes (11). Disordered insulin secretion contributes to the development of insulin resistance and may be an initiating factor in the progression to T2DM (43, 44). The loss of β cell function is progressive throughout the course of diabetes, beginning with defect in first-phase insulin secretion, followed by a decreasing maximal capacity of insulin secretion, before a reduction of steady-state and basal insulin secretion and complete β cell failure requiring insulin treatment (45). Reduction of insulin level and dysregulated insulin signaling activity both in diabetic or non-diabetic older individuals diminishes the anabolic capacity of insulin to alleviate MPB in skeletal muscles and may possibly be a primary mechanism shared by age-related sarcopenia and diabetes.

Taken together, a reduced level of endogenous insulin secretion may thus be a risk factor for sarcopenia development in both Japanese and Chinese diabetic elderly. This is particularly so given that it is widely recognized that T2DM in East Asians is characterized primarily by β cell dysfunction (12). As diabetes is a highly heterogeneous condition across different populations, whether this may explain the contrary findings from Western population studies of non-diabetic older persons (27, 46), showing hyperinsulinemia to be associated with lower muscle mass and strength, should be investigated in further studies.

IGF-1 has been shown to have an anabolic effect on muscle tissues. In line with report from previous studies (28, 47), our study found that the level of IGF-1 was associated with increased muscle strength. The serum level of IGF-1 decreases during aging, together with decreased tissue responsiveness and intracellular signaling (48). Previous studies also reported IGF-1 to be associated with various physical performance and mobility tasks, and all-cause mortality in the elderly (49, 50). In mouse models, exogenous systemic administration of IGF-1 improves contractile function, facilitates the functional recovery of injured skeletal muscle, and enhances muscle oxidative enzymes (51, 52). This may be explained by the mediating role of IGF-1 in muscle growth and subsequent regeneration: IGF-1 promotes the stimulation of muscle cell proliferation and differentiation, and MPS while inhibiting its degradation (53). The levels of c-peptide are found lower in participants with sarcopenia and positively associated with BMI, SMI, and knee extension strength in the whole sample and those without diabetes. C-peptide level is not affected by insulin injections or liver metabolization and are thus considered a better measure of portal insulin secretion than insulin itself (54, 55). Leptin is an adipokine secreted by white adipose tissue. Leptin acts on hypothalamic neurons to regulate food consumption and body fat (56). Moreover, leptin impacts on pancreatic beta cells, immune cells and muscle cells and modulate glucose metabolism, inflammatory processes and insulin resistance (57, 58). Considering the proinflammatory properties of leptin, previous studies have investigated the relationship between serum/plasma leptin level and sarcopenia, with generation of conflicting results. Our results of lower leptin level in sarcopenic older individuals corroborate the findings of previous studies which demonstrated an inverse association between serum leptin level and sarcopenia in hemodialysis patients (59). Consistently, frail hospitalized patients with a lower mid-arm muscle area were found to have lower leptin levels than their

healthy counterparts (60). The discrepancies in these studies may be caused by disparate effects of leptin on different populations such as obese individuals, hemodialysis subjects, and individuals with different ethnicities. These findings taken together thus also support the direct and indirect role of insulin in increasing muscle mass and function, regardless of diabetes status.

The present study defined sarcopenia according to the latest population-specific standardized criteria for Asian elderly: AWGS 2019. Furthermore, we validated our results derived from pre-frail frail older individuals in another independent study sample of robust and pre-frail frail older individuals, thus supporting the robustness of these findings. However, there are limitations in the cross-sectional study design and future studies employing longitudinal measurements should be undertaken to elucidate its temporal causal relationship. There is also limited sample size in this study. Insulin secretion and impaired insulin signaling may be a primary defect in sarcopenia associated with their prognosis and quality of life in

TABLE 2 Blood biomarker concentrations of sarcopenia groups in frailty intervention trial (FIT) study subjects and Singapore longitudinal ageing studies (SLAS) subjects.

		Sarcopenic subgroups			
		Sarcopenia	Possible sarcopenia	Non-sarcopenia	*P*
Exploratory study					
Fasting insulin (pg/ml)	453.57 ± 318.30	375.90 ± 233.30^{*+}	489.34 ± 328.09	565.32 ± 453.61	0.023
C-peptide (ng/ml)	1.54 ± 0.85	1.35 ± 0.63	1.64 ± 0.81	1.72 ± 1.39	0.067
Fasting glucose (mmol/L)	5.33 ± 1.28	5.35 ± 1.37	5.36 ± 1.29	5.16 ± 0.80	0.755
IGF-1 (ng/ml)	1.02 ± 0.74	1.02 ± 0.72	0.99 ± 0.76	1.12 ± 0.77	0.751
Leptin (ng/ml)	11.07 ± 10.05	8.92 ± 9.49^{+}	13.16 ± 10.72	9.70 ± 7.27	0.029
Active ghrelin (pg/ml)	3.90 ± 4.51	3.47 ± 3.63	3.89 ± 4.72	5.38 ± 6.00	0.255
Validation study					
Fasting insulin (pg/ml)	307.92 ± 251.07	232.87 ± 206.93^{*+}	395.47 ± 251.30	351.33 ± 303.28	< 0.001
C-peptide (ng/ml)	1.03 ± 0.45	0.90 ± 0.36^{*+++}	1.17 ± 0.49	1.14 ± 0.53	< 0.001
Fasting glucose (mmol/L)	6.19 ± 1.57	6.23 ± 1.70	6.27 ± 1.53	5.94 ± 1.18	0.596
IGF-1 (ng/ml)	14.60 ± 7.15	15.36 ± 7.59	13.75 ± 6.97	14.47 ± 6.46	0.514
Leptin (ng/ml)	15.53 ± 16.23	10.96 ± 9.27^{+++}	23.27 ± 21.87**	13.34 ± 13.39	< 0.001
Active ghrelin (pg/ml)	21.57 ± 16.96	22.39 ± 16.95	21.97 ± 16.70	18.42 ± 17.67	0.510

** $P < 0.01$, * $P < 0.05$ vs. the non-sarcopenia group; $^{+++}$ $P < 0.001$, $^{+}$ $P < 0.05$ vs. the possible sarcopenia group.

TABLE 3 Odds ratio of association of blood biomarkers with sarcopenia in whole sample.

	Per unit of Biomarker		Middle tertile vs. bottom tertile		Top tertile vs. bottom tertile		*P* (Trend)
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	
Exploratory study							
Insulin (pg/ml)	0.998 (0.996–1.000)	0.065	1.739 (0.381–7.947)	0.475	0.297 (0.080–1.111)	0.071	0.083
C-peptide (ng/ml)	0.724 (0.402–1.305)	0.283	1.367 (0.404–4.630)	0.615	1.359 (0.320–5.777)	0.678	0.641
Fasting glucose (mmol/L)	1.055 (0.589–1.892)	0.857	1.524 (0.483–4.805)	0.472	0.785 (0.221–2.792)	0.708	0.860
IGF-1 (ng/ml)	0.894 (0.421–1.899)	0.771	0.913 (0.235–3.543)	0.896	0.972 (0.252–3.745)	0.967	0.978
Leptin (ng/ml)	0.977 (0.915–1.043)	0.487	0.670 (0.156–2.878)	0.590	0.377 (0.069–2.044)	0.258	0.255
Active ghrelin (pg/ml)	0.927 (0.827–1.040)	0.199	1.017 (0.267–3.875)	0.980	0.819 (0.233–2.875)	0.756	0.749
Validation study							
Insulin (pg/ml)	0.998 (0.996–1.000)	0.047	0.750 (0.257–2.191)	0.599	0.372 (0.130–1.066)	0.066	0.069
C-peptide (ng/ml)	0.286 (0.099–0.827)	0.021	1.049 (0.340–3.239)	0.934	0.346 (0.118–1.018)	0.054	0.052
Fasting glucose (mmol/L)	1.232 (0.873–1.740)	0.236	1.155 (0.415–3.211)	0.783	1.401 (0.458–4.287)	0.554	0.553
IGF-1 (ng/ml)	1.008 (0.938–1.083)	0.829	0.814 (0.229–2.891)	0.750	0.836 (0.246–2.842)	0.774	0.768
Leptin (ng/ml)	0.952 (0.900–1.007)	0.086	0.572 (0.182–1.799)	0.339	0.291 (0.059–1.429)	0.128	0.131
Active ghrelin (pg/ml)	1.014 (0.984–1.045)	0.370	1.376 (0.514–3.683)	0.526	2.579 (0.815–8.159)	0.107	0.110

Data are adjusted for sex, age, status of diabetes, and percentage of whole body fat mass. *P* for trends across tertiles can be estimated by assigning ordinal scores of 1, 2, and 3 to the lowest, middle, and top tertile and repeating the logistic regressions. OR, odds ratio.

TABLE 4 Relations of blood biomarker concentrations to clinical and functional measures of sarcopenia and frailty.

	BMI (kg/m^2)			Skeletal muscle index (kg/m^2)		
	b ± SE	β	*P*	b ± SE	β	*P*
Exploratory study						
Fasting insulin (pg/ml)	0.004 ± 0.001	0.318	< 0.001	0.572 ± 0.195	0.167	0.004
C-peptide (ng/ml)	1.456 ± 0.315	0.339	< 0.001	203.419 ± 73.133	0.159	0.006
Fasting glucose (mmol/L)	0.421 ± 0.232	0.152	0.071	56.963 ± 54.743	0.067	0.299
IGF-1 (ng/ml)	0.619 ± 0.374	0.127	0.099	117.567 ± 84.276	0.081	0.165
Leptin (ng/ml)	0.183 ± 0.027	0.510	< 0.001	22.689 ± 6.567	0.210	0.001
Active ghrelin (pg/ml)	0.010 ± 0.063	0.012	0.875	13.174 ± 14.102	0.055	0.352
Validation study						
Fasting insulin (pg/ml)	0.005 ± 0.001	0.325	< 0.001	0.001 ± 0.000	0.239	< 0.001
C-peptide (ng/ml)	3.337 ± 0.543	0.418	< 0.001	0.562 ± 0.126	0.245	< 0.001
Fasting glucose (mmol/L)	0.281 ± 0.187	0.122	0.135	0.024 ± 0.042	0.036	0.566
IGF-1 (ng/ml)	−0.043 ± 0.045	−0.086	0.337	−0.008 ± 0.010	−0.060	0.407
Leptin (ng/ml)	0.127 ± 0.015	0.570	< 0.001	0.015 ± 0.004	0.229	< 0.001
Active ghrelin (pg/ml)	−0.020 ± 0.016	−0.094	0.210	−0.005 ± 0.004	−0.076	0.195
	Knee extension strength (kg)			**Exhaustion score**		
Exploratory study						
Fasting insulin (pg/ml)	0.002 ± 0.001	0.142	0.038	0.000 ± 0.000	−0.026	0.742
C-peptide (ng/ml)	1.129 ± 0.422	0.180	0.008	0.042 ± 0.115	0.029	0.715
Fasting glucose (mmol/L)	0.091 ± 0.293	0.023	0.756	0.035 ± 0.083	0.036	0.671
IGF-1 (ng/ml)	1.240 ± 0.477	0.174	0.010	0.008 ± 0.132	0.005	0.953
Leptin (ng/ml)	0.033 ± 0.039	0.063	0.399	0.013 ± 0.010	0.102	0.224
Active ghrelin (pg/ml)	0.052 ± 0.081	0.044	0.521	−0.014 ± 0.022	−0.051	0.517
Validation study						
Fasting insulin (pg/ml)	−0.001 ± 0.001	−0.043	0.534	−0.001 ± 0.001	−0.077	0.291
C-peptide (ng/ml)	0.905 ± 0.799	0.078	0.259	−0.390 ± 0.340	−0.084	0.253
Fasting glucose (mmol/L)	0.042 ± 0.254	0.012	0.870	0.215 ± 0.107	0.161	0.045
IGF-1 (ng/ml)	0.050 ± 0.057	0.072	0.380	−0.005 ± 0.026	−0.016	0.857
Leptin (ng/ml)	0.021 ± 0.023	0.064	0.378	0.003 ± 0.010	0.026	0.736
Active ghrelin (pg/ml)	−0.006 ± 0.022	−0.018	0.795	0.005 ± 0.009	0.044	0.559
	Gait speed (cm/s)			**Physical activity score**		
Exploratory study						
Fasting insulin (pg/ml)	−0.009 ± 0.006	0.125	0.103	−0.048 ± 0.026	−0.143	0.066
C-peptide (ng/ml)	1.831 ± 2.153	0.065	0.396	−15.974 ± 9.735	−0.126	0.103
Fasting glucose (mmol/L)	0.296 ± 1.512	0.016	0.845	−7.635 ± 7.226	−0.088	0.292
IGF-1 (ng/ml)	−1.356 ± 2.441	−0.043	0.579	3.498 ± 11.073	0.024	0.752
Leptin (ng/ml)	−0.107 ± 0.197	−0.045	0.589	−1.944 ± 0.882	−0.182	0.029
Active ghrelin (pg/ml)	−0.511 ± 0.404	−0.097	0.208	1.888 ± 1.841	0.080	0.307
Validation study						
Fasting insulin (pg/ml)	0.003 ± 0.009	0.026	0.726	0.044 ± 0.061	0.053	0.475
C-peptide (ng/ml)	−3.945 ± 4.811	−0.060	0.413	17.962 ± 33.860	0.039	0.596
Fasting glucose (mmol/L)	−1.188 ± 1.522	−0.063	0.436	2.904 ± 10.715	0.022	0.787
IGF-1 (ng/ml)	−0.214 ± 0.373	−0.050	0.567	2.036 ± 2.405	0.074	0.399
Leptin (ng/ml)	−0.144 ± 0.141	−0.079	0.307	−0.856 ± 0.992	−0.067	0.390
Active ghrelin (pg/ml)	0.026 ± 0.125	0.015	0.837	0.398 ± 0.917	0.033	0.665

Data are adjusted for sex, age, and status of diabetes.

both diabetic and non-diabetic individuals. Moderate-intensity exercise-based interventions, in combination with appropriate nutritional supplementation, are recommended to improve both muscle mass and performance and insulin levels in the elderly.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by National Health Group (NHG) Domain Specific Review Board (DSRB) of Singapore. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YL did the statistical analyses and drafted the manuscript. TN designed the study and directed the data collection as the principal investigator of the study. All authors contributed to the study concept and design, interpretation of data, and critical review of the manuscript and approved the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.971622/full#supplementary-material

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EDITED BY
Elena Vladimirovna Frolova,
North Western State Medical University, Russia

REVIEWED BY
Mohammad Muzammil,
Aligarh Muslim University, India
Liang-Yu Chen,
Taipei Veterans General Hospital, Taiwan

*CORRESPONDENCE
Reshma Aziz Merchant
reshmaa@nuhs.edu.sg

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Patterns of participation restriction among older adults at risk of falls and relationship with intrinsic capacity: A latent cluster analysis

Reshma Aziz Merchant[1,2]*, Yiong Huak Chan[3], Ivan Aprahamian[4] and John E. Morley[5]

[1]Division of Geriatric Medicine, Department of Medicine, National University Hospital, Singapore, Singapore, [2]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [3]Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [4]Geriatrics Division, Department of Internal Medicine, Jundiai Medical School, Jundiai, São Paulo, Brazil, [5]Division of Geriatric Medicine, Department of Medicine, Saint Louis University School of Medicine, St. Louis, MO, United States

Introduction: The concept of participation restriction was first described by the World Health Organization in 2001 as a component of The International Classification of Functioning, Disability and Health Framework. Both falls and fear of falling (FOF) are associated with social isolation, depression, anxiety, poor quality of life and cognitive impairment resulting in participation restriction. Life-space mobility (LSM) is an important indicator for participation restriction which depends on multiple inter-related factors. We aimed to determine participation patterns using latent cluster analysis (LCA) in older adults at risk of falls, its relationship with intrinsic capacity (IC) and its risk prediction.

Methods: Cross-sectional study of 154 community dwelling older adults ≥ 60 years with falls or risk of falls was conducted. Questionnaires were administered on demographics, hearing, LSM, frailty (FRAIL scale), anorexia of aging (SNAQ), cognition (Montreal Cognitive Assessment, MoCA), FOF (Falls Efficacy Scale-International), physical function, and assessment for handgrip strength (HGS), gait speed, 5-times sit to stand (STS), vision and times-up-and-go (TUG) were performed. Six IC domains (vision and hearing, cognition, nutrition, mobility and depression) were measured.

Results: Three pattern of participation cluster were identified, high (n = 63, 40.9%), moderate (n = 83, 53.9%) and low (n = 8, 33 5.2%). Individuals in the high participation cluster were significantly younger, had higher LSM scores and lower FES-I scores, more robust, fewer ADL and IADL limitations, lower prevalence of low HGS, higher gait speed and shorter TUG. In the fully adjusted model compared to the high participation cluster, moderate participation was significantly associated with low MoCA scores (OR 4.2, 95% CI 1.7–10.4, p = 0.02), poor STS (OR 7.1, 95% CI 3.0–17.0, p < 0.001) whereas low participation was associated with anorexia of aging (OR 9.9, 95% CI 1.6–60.9, p = 0.014), poor STS (OR 19.1, 95% CI 2.0–187.5, p = 0.011) and hearing impairment (OR 9.8, 95% CI 1.4–70.8, p = 0.024). Participants with 3 out of 6 IC decline had a probability of greater than 80% to belong to the low/moderate participation class.

Discussion: Physical function, cognition, hearing and nutrition were significantly associated with low and/or moderate participation class. Future studies are needed to evaluate improvement in participation of those with falls or at risk for falls through restoration of IC.

KEYWORDS

life-space mobility, participation restriction, latent class analysis, falls, intrinsic capacity

Introduction

The concept of participation restriction was first described by the World Health Organization (WHO) in 2001 as a component of The International Classification of Functioning, Disability and Health (ICF) Framework (1, 2). The ICF is a classification system which describes health status, disability, and functioning in the context of surrounding environment. Participation is defined as the "ability to perform actions, tasks, and activities related to self-care, home management, work, community, and leisure roles in both socio-cultural and environmental contexts" (2). Participation restriction is associated with financial insecurity, malnutrition, increased healthcare cost, poor quality of life, frailty, institutionalization, and mortality (3–5). One of the biggest limitations of the ICF framework is the lack of a standardized tool to measure activity limitation and participation restriction (1, 6). Life-space mobility (LSM) is an important indicator of participation restriction (7–9). It is defined as the geographical area within which a person travels over a specified period in daily life, extent and frequency of movement, and any assistance needed (9). It depends on multiple complex interrelated factors such as physical function, ability to transfer, cognition, transportation, environment accessibility, vision, frailty, depression, nutrition, hearing impairment, falls, and fear of falling (FOF), which are all highly prevalent in an aging population (5, 7, 8, 10–13).

Falls and fear of falling (FOF) amongst older adults are common issues in countries with rapidly aging populations. Up to one-third of older adults ≥65 years fall each year in Canada and the United States, half of whom may experience recurrent falls, and falls accounts for nine in ten of all fractures in older adults (14, 15). FOF on the other hand affects between 20 and 85% of older adults, with significant threat to autonomy and participation (16, 17). Both falls and FOF are associated with social isolation, depression, anxiety, poor quality of life, and cognitive impairment, which result in participation restriction that imposes significant burden on the society and healthcare system at large (15, 18, 19). Risk factors common to both participation restriction, and falls and FOF are older age, low socio-economic status, gender where FOF is more prevalent in females, poor perceived health, frailty, and comorbidities (15, 20, 21).

Functional status is central to falls, healthy aging, and to the ability of individuals to move safely within their homes and across their environment. In 2015, the World Health Organization (WHO) defined "healthy aging" as "the process of developing and maintaining functional ability that enables wellbeing in older age" (22). The ability to function is determined by a complex relation between older adults' intrinsic capacity (IC) and their environment (23). IC is considered as a positive attribute and physiological reserve. Decline in IC with aging can lead to vicious cycle of sedentary behavior, loss of muscle mass, frailty, functional decline, FOF, and falls, all of which can cause participation restriction (24). The Integrated Care for Older People (ICOPE) care pathway by the WHO recommends screening for decline in IC through measurement of vision, hearing, cognition, nutrition, mobility, and mood, followed by person-centered assessment and development of personalized care and a monitoring plan to delay disability and dependency (22, 25). To enable active aging and participation, the WHO has also published a guide to Global Age-Friendly Cities for national stakeholders, emphasizing age-friendly living environments (transportation, housing, outdoor spaces, and buildings), social aspects (participation, respect, and inclusion), employment, community support, and health services (26).

Individual determinants, focusing on single factors such as activities of daily living (ADL), instrumental activities of daily living (IADL), gait speed, frailty, handgrip strength (HGS), falls, and LSM, have been used to assess mobility and/or participation and are associated with adverse outcomes. However, in real life, mobility and participation are dependent on a cluster of multiple independent interacting factors, most of which may be dynamic, such as physical function and frailty. Methodologies such as latent cluster analysis (LCA) profile can be useful to uncover subpopulations sharing similar characteristics or outcomes, and this can assist in designing future multi-domain prevention-intervention measures.

The aim of this study is threefold. First, we used the LCA to determine participation patterns amongst older adults with falls or at risk of falls. Second, we examined the association of participation patterns with the IC domains. Third, we developed a risk prediction model of IC impairments with the different participation groups.

Method

Study design and participants

This was a cross sectional study consisting of 155 community-dwelling older adults with falls or near-falls recruited for a falls prevention intervention study. Inclusion criteria were: (1) community-dwelling ≥60 years of age and (2) history of falls or near-falls in the past 12 months. Participants had to be able to understand, communicate, and provide informed consent. Participants were excluded if they had underlying severe cognitive impairment, were wheelchair bound, bedridden, or nursing-home residents. We restricted our analysis to 154 participants with complete information on all life-space variables. Written consent was obtained from all recruited participants, and protocol was approved by the National Healthcare Group (NHG), Domain Specific Review Board (DSRB), Singapore. The study complies with the Declaration of Helsinki ethical principles.

Intrinsic capacity

The six IC domains were used to predict participation patterns amongst older adults at risk of falls. IC framework was first proposed by the WHO and released as the "Integrated care for older people: guidelines on community-level interventions to manage declines in intrinsic capacity" in 2017 (27), followed by the "Handbook: Guidance on person-centered assessment and pathways in primary care" in 2019 with a digital app for community-level screening and intervention (25). The recommendations include screening for cognition, vitality (nutrition), mobility [five times sit-to-stand (STS)], depression, and hearing and vision impairment (28). The Montreal Cognitive Assessment (MoCA) was used to assess cognitive status, and a cut off score of <26 was used to define cognitive impairment (29). Impaired STS was defined as >14 s. Performance of 6/18 or worse in one or both eyes was classified as vision impairment (30). For vitality, anorexia of aging was measured using the four-item Simplified Nutritional Appetite Questionnaire (SNAQ), where a score ≤14 indicated significant risk of at least 5% weight loss within 6 months (31). Hearing impairment was assessed by asking "Do you or your family think you may have hearing loss?".

Demographic and covariates

The interview questionnaire was administered by trained research assistants on demographics, chronic diseases, education, falls, physical function, physical activity, cognition, frailty, sarcopenia, depression, self-assessed health status, anorexia of aging, fear of falling, Falls Risk for Older People in the Community (FROP-Com), and LSM. The FRAIL (fatigue, resistance, aerobic, number of illnesses, and loss of weight) scale was used to assess frailty with a maximum score of 5. Pre-frail was defined as 1–2, frail 3–5, and robust 0 (32). Sarcopenia was screened using the SARC-F (lifting and carrying 10 pounds, walking across a room, transferring from bed/chair, climbing a flight of ten stairs, and frequency of falls in the past year), with scores ranging from 0 to 10, and ≥4 points was classified as having sarcopenia (33). ADL was assessed using the Katz ADL scale and IADL using Lawton's IADL scale (34, 35). Depression was assessed using the 15-item Geriatric Depression Scale (GDS), and a cut-off of ≥5 was used to define depression (36). Self-assessed health status was rated as excellent, very good, good, fair, or poor (37).

The Rapid Assessment of Physical Activity tool was used to assess physical activity (38). Fear of falling was assessed using the Falls Efficacy Scale-International (FES-I). This is based on self-reported concern of fear of falling while performing 16 ADLs such as getting dressed and going up or down the stairs). Each of the ADLs were scored based on "not concerned at all" to "very concerned", with total scores ranging from 16 to 64 (39). The FROP-Com screening tool is a comprehensive falls risk assessment tool developed by the National Aging Research Institute Australia (40). It includes 13 risk factors with total scores ranging from 0 to 60, where 19–60 is considered high risk, 12-18 moderate risk, and 0–11 low risk (41). Social isolation was measured using the six-item Lubben Social Network Scale (LSNS-6). It measures size, closeness, and frequency of contact with friends and family members with total scale score ranging from 0 to 30 obtained by summing the six items, and a score below 12 was classified as at risk of social isolation (42). Loneliness was measured using the three-item UCLA scale with scores ranging from 3 to 9, where those scoring 3–5 were classified as "not lonely" and 6–9 as "lonely" (43).

Physical performance test included assessment of HGS, gait speed (4 meters), timed up-and-go (TUG), and short physical performance battery test (SPPB). HGS was measured using Jamar hand dynamometer on the dominant arm in the seated position with elbow flexed at 90°, and maximum HGS was recorded. Poor HGS was based on cut-offs of 28 kg for males and 18 kg for female as defined by the 2019 Asian Working Group for Sarcopenia (44). The SPPB included three components (balance, gait speed, and chair stand) with a maximum score of 12 points (4 points per-component).

Life-space mobility

LSM was measured using the validated University of Alabama at Birmingham Life-Space Assessment questionnaire which was developed in 2003. LSM measures the ability of an individual to move within their own home and across the environment or region, and is quantified using the life-space

mobility index (9, 10). The composite score is measured based on movement within home, neighborhood, or across the region, frequency (less than once a week, 1–3 times a week, 4–6 times a week, or daily), and use of assistance (walking aid and/or human) 4 weeks prior to the assessment. The scores range from 0 to 120, where 0 indicates activity may be limited to bedroom and 120 which indicates participant was fully mobile without aid outside his/her city.

Patterns of participation

Patterns of participation of older adults are dependent on a bundle of variables which share similar outcome such as sedentary lifestyle, decline in physical function, institutionalization, and mortality. The participation patterns were modeled on related but independent factors such as ADL, IADL, gait speed, HGS, frailty, falls, FOF, education, and self-assessment of health status.

Statistical analyses

Analyses were performed using STATA 17.0, with statistical significance set at $p < 0.05$. LCA was used to explore the number of participation clusters. The characteristics of individuals in the different participation clusters were compared using chi-square test for categorical variables and *T*-test for continuous variables. Logistic regression analysis was performed to assess the association between each of the IC domain (hearing, vision, cognition, mobility (poor STS) and nutrition (anorexia of aging)) and the participation clusters. Odds ratios with 95% confidence intervals (CI) were reported. Prediction models on participation typology were explored using ROC curve to evaluate their discriminative abilities.

Results

Development of participation patterns using LCA

Variables from previously published studies were used to explore the number of participation clusters, such as frailty, perceived health, falls, ADL, IADL, poor HGS, gait speed, LSM, FES-I, TUG, age, and years of education (4, 9, 13, 45–47). One to four participation clusters were examined and based on the lowest Consistent Akaike Information Criterion (AIC) and Bayesian-Schwarz Information Criterion (BIC) (9); a three-cluster solution was considered to be optimal (Table 1). Lower AIC and BIC values indicate a better model fit.

TABLE 1 Latent class analysis: Akaike's information criterion (AIC) and Bayesian information criterion (BIC).

Number of clusters	AIC	BIC
1	6,750	6,808
2	6,550	6,650
3	**6,430**	**6,567**
4	6,494	6,670

Bold implies statistical significance.

Co-variates, LCA, and participation patterns

One hundred and fifty-four participants were divided into three participation clusters: high ($n = 63$, 40.9%), moderate ($n = 83$, 53.9%) and low ($n = 8$, 5.2%) (Table 2). Mean age was 74.62 ± 7.96 years, 35.7% were male, and average education was 5.57 ± 4.62 years. For functional status, 9.1% were frail and 50.0% pre-frail, 68.2% had poor HGS, 39.0% had ≥ 1 IADL, and 18.2% ≥ 1 ADL impairments. Mean LSM score was 63.60 ± 23.06, gait speed 0.83 ± 0.30 m/s, FES-I 21.73 ± 6.60, and TUG 13.75 ± 8.68 s. The high participation group compared with moderate and low participation groups were significantly younger: 71.19 ± 6.71, 77.00 ± 7.76, and 77.00 ± 10.12 years, respectively. Education level was highest in the low participation (7.75 ± 1.98 years) and high participation group (6.96 ± 4.68), followed by moderate participation group (4.27 ± 4.39). Half of the low participation group were frail, and the remaining half were pre-frail. On the other hand, there were no frail participants in the high participation group, where 41.3% were pre-frail and 58.7% robust. Functionally, three-quarters of the low participation group had at least one ADL and/or IADL limitation. Amongst the high participation group, only 17.5% had at least one ADL limitation and 4.8% at least one IADL limitation. There were no significant gender differences between the groups.

Low HGS prevalence was highest in the low participation group (87.5%), followed by moderate participation (84.3%) and high participation groups (44.4%). High participation group had the highest LSM score (81.41 ± 16.51) compared with moderate participation (52.91 ± 17.74) and low participation groups (34.19 ± 17.94). FOF depicted by FES-I score was significantly higher in the low participation group compared with moderate or high participation groups: 38.50 ± 12.62, 21.70 ± 5.11, and 19.65 ± 3.82, respectively. Gait speed was significantly lower in the low participation group compared with moderate and high participation groups: 0.32 ± 0.13 m/s, 0.69 ± 0.20 m/s, and 1.06 ± 0.22, respectively. TUG was significantly prolonged in the low participation group. Other variables included in the LCA, but non-significant, included general health status and ≥ 1 falls.

TABLE 2 Latent class analysis co-variates by participation group.

Variables	All subjects ($n = 154$)	Participation group			*P*-value
		High ($n = 63$; 40.9%)	Moderate ($n = 83$; 53.9%)	Low ($n = 8$;5.2%)	
Age (years)	74.62 ± 7.96	71.19 ± 6.71	77.00 ± 7.76	77.00 ± 10.12	<0.001
(range)	(60 to 100)	(60 to 87)	(60 to 100)	(64 to 93)	
Education years	5.57 ± 4.62	6.96 ± 4.68	4.27 ± 4.39	7.75 ± 1.98	0.001
(range)	(0 to 19)	(0 to 19)	(0 to 16)	(6 to 10)	
Frailty					<0.001
Robust	63 (40.9)	37 858.7)	26 (31.3)	0 (0.0)	
Pre-frail	77 (50.0)	26 (41.3)	47 (56.6)	4 (50.0)	
Frail	14 (9.1)	0 (0.0)	10 (12.0)	4 (50.0)	
General Health					0.051
Good	110 (71.9)	51 (81.0)	55 (67.1)	4 (50.0)	
Fair/Poor	43 (28.1)	12 (19.0)	27 (32.9)	4 (50.0)	
Falls	99 (64.3)	38 (60.3)	58 (69.9)	3 (37.5)	0.126
≥1 IADL limitation	60 (39.0)	11 (17.5)	45 (51.8)	6 (75.0)	<0.001
≥1 ADL limitation	28 (18.2)	3 (4.8)	19 (22.9)	6 (75.0)	<0.001
Poor handgrip strength	105 (68.2)	28 (44.4)	70 (84.3)	7 (87.5)	<0.001
Gait speed (m/s)	0.83 ± 0.30	1.06 ± 0.22	0.69 ± 0.20	0.32 ± 0.13	<0.001
(range)	(0.14 to 1.72)	(0.65 to 1.72)	(0.15 to 1.23)	(0.14 to 0.49)	
Life-space mobility	63.60 ± 23.06	81.41 ± 16.51	52.91 ± 17.74	34.19 ± 17.94	<0.001
(range)	(6 to 120)	(46 to 120)	(21 to 110)	(6 to 69)	
Falls-efficacy scale	21.73 ± 6.60	19.65 ± 3.82	21.70 ± 5.11	38.50 ± 12.62	<0.001
(range)	(16 to 61)	(16 to 31)	(16 to 37)	(24 to 61)	
Timed up-and-go	13.75 ± 8.68	9.18 ± 2.36	14.68 ± 4.03	43.93 ± 16.76	<0.001
(range)	(3.39 to 75.61)	(8.31 to 30.72)	(3.39 to 75.61)	(26.58 to 75.61)	

Values are *n* (%), mean ± sd. IADL, instrumental activity of daily living; ADL, activity of daily living.

Background characteristics of study participants

Background characteristics of participants are shown in Table 3. Almost three-quarters (73.4%) of the participants were of Chinese ethnicity, and one-third (35.7%) was male. Amongst the participants, 10.4% were still working, 71.9% rated health status as good, and 64.3% had had one or more falls. For self-reported chronic diseases, 40.4% had diabetes, 70.8% hypertension, and 18.2% high cholesterol. The prevalence of sarcopenia based on SARC-F was 16.9%. Mean SPPB was 8.53 ± 2.73 and FROP-COM 10.56 ± 5.35.

There were significant demographic differences between the three participation groups, where 22.2% of the high participation group were still working, 2.4% in the moderate participation and none in the low participation groups. Sarcopenia prevalence was 50% in the low participant group compared with 25.3% in the moderate and 1.6% in the high participation groups. For chronic diseases, hypertension prevalence was highest in the moderate participation group, followed by low participation and high participation groups: 82.1, 66.7, and 60%, respectively. Similarly, diabetes prevalence was highest in the moderate participation group (55.2%) and lowest in the high participation group (22.2%). SPPB scores were highest in the high participation group (10.51 ± 1.49) and lowest in the low participation group (3.38 ± 1.30). The low participation group had significantly higher FROP-Com scores compared with the high participation group (17.38 ± 5.85 vs. 7.78 ± 4.61, respectively).

Relationship between participation groups and intrinsic capacity

Table 4 shows the prevalence of each IC component and its relationship with the latent participation classes. The prevalence of low cognition defined by MoCA<26 was 59.9%, anorexia of aging 29.9%, poor STS 57.2%, hearing loss 21.6%, visual impairment 78.5%, and depression 27.9%. In the unadjusted model with high participation as a reference category, moderate participation was associated with MoCA <26 (OR 8.1, 95% CI 3.8–17.3; $p < 0.001$), poor STS (OR 8.2, 95% CI 3.8–17.3; $p < 0.001$), hearing loss (OR 3.6, 95% CI 1.4–9.4; $p = 0.010$),

TABLE 3 Demographic co-variates by participation group.

Variables	*n*	All	Participation group			*P*-value
			High	Moderate	Low	
Males	154	55 (35.7)	23 (36.5)	29 (34.9)	3 (37.5)	0.975
Ethnicity	154					0.300
Chinese		113 (73.4)	53 (84.1)	55 (66.3)	5 (62.5)	
Malay		18 (11.7)	4 (6.3)	13 (15.7)	1 (12.5)	
Indian		20 (13.0)	5 (7.9)	13 (15.7)	2 (25.0)	
Others		3 (1.9)	1 (1.6)	2 (2.4)	0 (0.0)	
Still married	154	51 (33.1)	19 (30.3)	29 (34.9)	3 (37.5)	0.195
Still working	154	16 (10.4)	14 (22.2)	2 (2.4)	0 (0.0)	<0.001
Lonely	154	30 (19.5)	6 (9.5)	21 (25.3)	3 (37.3)	0.024
Social isolation	154	79 (51.3)	26 (41.3)	50 (60.2)	3 (37.5)	0.050
Sarcopenia	154	26 (16.9)	1 (1.6)	21 (25.3)	4 (50.0)	<0.001
Hypertension	128	92 (70.8)	33 (60.0)	55 (82.1)	4 (66.7)	0.025
High cholesterol	120	85 (18.2)	31 (64.4)	50 (75.8)	4 (66.7)	0.421
Diabetes	109	44 (40.4)	10 (22.2)	32 (55.2)	2 (33.3)	0.003
Stroke	90	13 (14.4)	5 (11.9)	6 (14.0)	2 (40.0)	0.238
BMI (kg/m^2)	151	24.58 ± 4.71	24.02 ± 4.41	25.11 ± 5.04	23.73 ± 3.23	0.344
(range)		(13.77 to 46.83)	(13.77 to 34.52)	(15.40 to 46.83)	(19.38 to 29.95)	
SPBB	154	8.53 ± 2.73	10.51 ± 1.49	7.52 ± 2.32	3.38 ± 1.30	<0.001
(range)		(0 to 12)	(6 to 12)	(0 to 12)	(1 to 5)	
FROP-COM	154	10.56 ± 5.35	7.78 ± 4.61	12.01 ± 4.67	17.38 ± 5.85	0.001
(range)		(1 to 26)	(1 to 26)	(4 to 24)	(7 to 26)	

Values are *n* (%), mean ± sd.
BMI, body mass index; SPPB, short physical performance battery test; FROP-COM, Falls Risk for Older People in the Community.

and depression (OR 4.5, 95% CI 1.9–10.7; $p = 0.001$). In the adjusted model, only low MoCA scores (OR 4.2, 95% CI 1.7–10.4; $p = 0.02$) and poor STS (OR 7.1, 95% CI 3.0–17.0, $p = <0.001$) remained significant. In the unadjusted model with high participation as a reference category, low participation was associated with anorexia of aging (OR 5.3, 95% CI 1.1–25.0; $p < 0.034$), poor STS (OR 17.5, 95% CI 2.0–187.5; $p < 0.011$), and hearing loss (OR 9.3, 95% CI 1.8–47.2; $p = 0.07$). In the adjusted model, low participation was associated with anorexia of aging (OR 9.9, 95% CI 1.6–60.9; $p = 0.014$), poor STS (OR 19.1, 95% CI 2.0–187.5; $p = 0.011$), and hearing loss (OR 9.8, 95% CI 1.4–70.8, $p = 0.024$).

Prediction model for relationship between participation groups and intrinsic capacity

Three prediction models were investigated: model A, using the saved probabilities of the six IC domains from a logistic regression on low participation; model B, using the odds ratios from model A as the weighted scores and a simple model C, using 1 point for each positive IC (Table 5). There was no statistical significance across the three models. For simple clinical usage, Model C (named **MASHED**: ***M***ocA < 26, ***A***norexia of aging, Poor ***S***TS, ***H***earing Loss, ***E***ye, ***D***epression) was used (Table 6A). A participant with a decline in at least three out of the six IC domains had a probability of greater than 80% (72/88) to belong to the low/moderate participation group, with area under the curve (AUC) of 0.828 (95% CI 0.761–0.894, $p < 0.001$) (Table 6B).

Discussion

Using LCA, we were able to classify older adults at risk of falls as belonging to one of the three participation groups—high, moderate, and low. Participants in the high participation group were significantly younger, had less functional limitations, were more robust, and had better LSM and lower fear of falling. Compared to the high participation group, the low participation group was significantly associated with anorexia of aging, poor STS, and hearing loss, whereas the moderate participation group was significantly associated with poor STS and low cognition. Participants with at least three IC-domain impairments had a higher probability of belonging to the moderate or low participation groups.

TABLE 4 Intrinsic capacity and association with participation group.

Variables	All subjects	Participation group									
		High	Moderate					Low				
				Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value		Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
MocA <26	91/142	21/63	65/81	**8.1**	**<0.001**	**4.2**	**0.002**	5/8	3.3	0.122	2.0	0.457
	(59.9)	(33.3)	(80.2)	**(3.8–17.3)**		**(1.7–10.4)**		(62.5)	(0.73–15.3)		(0.32–12.9)	
Anorexia	46/154	15/63	26/83	1.5	0.318	1.7	0.269	5/8	**5.3**	**0.034**	**9.9**	**0.014**
	(29.9)	(23.8)	(31.3)	(0.70–3.1)		(0.65–4.6)		(62.5)	**(1.1–25.0)**		**(1.6–60.9)**	
Poor STS	87/152	18/63	62/81	**8.2**	**<0.001**	**7.1**	**<0.001**	7/8	**17.5**	**0.010**	**19.1**	**0.011**
	(57.2)	(28.6)	(76.5)	**(3.8–17.3)**		**(3.0–17.0)**		(87.5)	**(2.0–152.6)**		**(2.0–187.5)**	
Hearing impairment	33/153	6/62	23/83	**3.6**	**0.010**	2.1	0.215	4/8	**9.3**	**0.007**	**9.8**	**0.024**
	(21.6)	(9.7)	(27.7)	**(1.4–9.4)**		(0.65–7.0)		(50.0)	**(1.8–47.2)**		**(1.4–70.8)**	
Visual impairment	113/144	43 /60	65/76	2.3	0.051	1.7	0.308	5/8	0.66	0.595	0.34	0.262
	(78.5%)	(71.7)	(57.5)	(0.99–5.5)		(0.60–5.1)		(62.5)	(0.14–3.1)		(0.05–2.2)	
Depression	43/154	8/63	33/83	**4.5**	**0.001**	1.8	0.266	2/8	2.3	0.357	1.0	0.998
	(27.9)	(12.7)	(39.8)	**(1.9–10.7)**		(0.63–5.3)		(25.0)	(0.39–13.4)		(0.14–7.4)	

Reference category: high participation.
Bold implies statistical significance.

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Prior studies on participation have focused mainly on LSM with an arbitrary cut off of LSM <60 or ADL and/or IADL limitation to define low participation, which may be associated with a higher false negative rate compared with LCA used in our study (8). LSM is an important indicator for participation restriction and is shown to correlate with physical performance including activity of daily living (ADL), cognition, FOF, falls, quality of life, frailty, healthcare utilization, undernutrition, and mortality (4, 45–47). A recent study published by Watanabe et al. showed an L-shaped relationship between LSM and mortality over 5 years with dose–response relationship up to a score of 60 points (13). In our study, both the moderate and low participation groups had a mean LSM score of below 60. Falls lead to FOF, social isolation, depression, declining physical function, institutionalization, and mortality, all of which are risk factors for participation restrictions. Based on FROP-COM scores, both the low and moderate participation groups were categorized as at a moderate fall risk and would benefit from targeted personalized interventions (48).

LSM is vital for participation in social life and social inclusion, which was evident from our study, where individuals in the low participation group were three times more likely to be lonely compared with high participation group. Although not statistically significant, six in ten of the moderate participation group were at risk of social isolation compared with four in ten of the high participation group. LSM is also associated with poor health-related quality of life which was evident in our study participants, where only half of the low participation group rated their health as good compared with more than three-quarters of the high participation group (49). Frailty is a state of decreased physiological reserve, dynamic, multidimensional, and is associated with negative outcomes including falls, hospitalization, institutionalization, and mortality (50). Similar to other studies, frailty was significantly more prevalent in the low and moderate participation groups (51). Constricted LSM is a risk factor for frailty, and frailty predicts steeper decline in LSM. As frailty is reversible before the onset of disability, upstream screening and intervention is recommended before the onset of disability (46, 49, 51).

The prevalence of at least one IC impairment in our study population was 96.1%. In another study where the participants were mainly those with memory complaints, the prevalence of

TABLE 5 Prediction models.

Model	AUC (95% CI)	*P*-value	
A	0.795 (0.719–0.870)	Compared to A	
B	0.792 (0.717–0.868)	0.484	Compared to B
C	0.781 (0.707–0.855)	0.138	0.165

Model A: Using the saved probabilities of the six intrinsic variables on low participation.
Model B: Using the odds ratios of Model A as weighted scores.
Model C: Adding up the number of positive intrinsic variables.

TABLE 6B Prediction model and participation group.

Cut offs	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Prediction for low participation (AUC = 0.692, 95% CI 0.550–0.834, $p = 0.068$)				
1	100	4.1	5.4	100
2	100	24.7	6.8	100
3 (Youden Index)	87.5	44.5	8.0	98.5
4	50.0	75.3	10.0	96.5
5	12.5	88.4	5.6	94.9
Prediction for moderate/low participation (AUC = 0.828, 95% CI 0.761–0.894, $p < 0.001$)				
1	100	9.5	61.5	100
2	93.4	47.6	72.0	83.3
3 (Youden Index)	79.1	74.6	81.8	71.2
4	40.7	95.2	92.5	52.6
5	17.6	96.8	88.9	44.9

Values are *n* (%).
PPV, Positive Predictive Value; NPV, Negative Predictive value.

TABLE 6A MASHED score (from intrinsic capacity) and participation group.

MASHED Score (no. of intrinsic capacity domains)	All subjects ($n = 154$)	Participation group			
		High ($n = 63$)	Moderate ($n = 83$)	Low ($n = 8$)	*P*-value
0	6 (3.9)	6 (9.5)	0 (0.0)	0 (0.0)	
1	30 (19.5)	24 (38.1)	6 (7.2)	0 (0.0)	
2	30 (19.5)	17 (27.0)	12 (14.5)	1 (12.5)	
3	48 (31.2)	13 (20.6)	32 (38.6)	3 (37.5)	
4	22 (14.3)	1 (1.6)	18 (21.7)	3 (37.5)	
5	17 (11.0)	2 (3.2)	14 (16.9)	1 (12.5)	
6	1 (0.6)	0 (0.0)	1 (1.2)	0 (0.0)	
Mean ± SD	2.68 ± 1.37	1.76 ± 1.13	3.30 ± 1.17	3.50 ± 0.93	$p < 0.001$

one IC impairment was 89.3% (52). The WHO ICOPE pathway recommends screening for IC, which has proven to be both feasible and practical and can be performed within a few minutes by trained community partners and/or healthcare professionals. It serves as a trigger for comprehensive assessment of underlying causes and intervention. ICOPE screening tools have shown to be able to identify older adults at high risk of progressing to frailty, ADL, and/or IADL disability (24, 53).

There is still ongoing debate on the ideal measurement model for intrinsic capacity, and there are no standardized assessment tools or intrinsic capacity composite score, e.g., IC index for clinical or research use (28). A recent scoping review highlighted that published studies use either a "formative" or "reflective" approach to conceptualize IC (54). The authors suggested that IC should be interpreted as a "system, which depends on the quantity and quality of the dynamical interrelations between its elements (capacities)". The different domains could be interpreted as being separate but interacting entities that form an aggregated construct for physical and mental health, as decline in one domain can also affect impact on decline in another domain (54). González-Bautista et al. showed that impairment of each additional domain over 5 years increased risk of incident frailty by 47%, ADL impairment by 23%, and IADL impairment by 27% (53). Our study showed that participants with a decline in at least three out of the six intrinsic capacity domains had a probability of >80% of belonging to the low/moderate participation group. The benefits of prognostic scoring generated in our study can serve as a tool to stratify and prioritize risk interventions based on type and number of IC domains affected, which is relevant in clinical practice. Our study has further added to the literature that interventions to improve IC should target the different domains concurrently through multidomain interventions as suggested by the WHO (55).

Physical performance limitations defined by low gait speed, longer five times STS, and/or longer TUG was more prevalent in the low followed by moderate participation groups. Poor STS was significantly associated with moderate and low participation. The five times STS test is considered as a proxy-tool for physical performance and muscle strength in many international sarcopenia guidelines, although recent studies show that it is a better proxy of gait speed (physical performance) than HGS (muscle strength) (56).

Cognitive impairment was significantly associated with the low and moderate participation groups in our study population. Similar findings were shown in a systematic review, where prevalence of cognitive impairment was much higher in those with lower LSM (5). Cognition and participation share a complex and bidirectional relationship. It is known that participation may help preserve cognitive function and reduce the risk of dementia, and declining cognition is associated with low participation (5). Physical activity, gait speed, and social network are known to alter the trajectory of cognition and are also known risk factors for participation restriction.

Anorexia of aging is defined as decrease in food intake and/or appetite. It is a well-recognized precursor for malnutrition, loss of muscle mass, and frailty. Those who screened positive for anorexia of aging need to be evaluated for depression, loneliness, polypharmacy, access to food or inability to feed, swallowing disorder, or other chronic medical problems, all of which can be the cause or consequence of participation restriction (31). Earlier studies have shown significant association of LSM with nutrition (7, 10). Various recommendations to optimize dietary intake have been suggested in older adults at risk, including vitamin D supplementation, protein supplementation, and/or dietary modification to enhance nutrient density in combination with exercise, with positive impacts on frailty reversal, physical outcomes, and mobility (57).

Hearing impairment is known to affect many aspects of daily functioning and is a risk factor for disability, depression, activity limitation, and participation restriction mainly in those with severe/major hearing loss (58). Hearing impairment is prevalent in almost two-thirds of older adults and often under-reported in the old-old (59, 60). Compared with audiometric classification, 93.2% of participants ≥80 years old under-estimated hearing impairment when self-reporting (59). In our study individuals, prevalence of self-reported hearing loss was 21.6% and shown to be independently associated with low participation. Polku et al. similarly reported lower LSM scores in participants with major hearing difficulties, and those with mild or major hearing loss at baseline had significantly higher odds for restricted LSM at 2 years (61). While more studies are needed on the role of hearing aids in improving participation, the perceived benefit from hearing aids has been shown to be associated with better LSM scores (62). There was no significant difference in prevalence of vision impairment between the groups, possibly explained by the selection of participants with falls and/or near-falls where prevalence of vision impairment is known to be high. (14).

Prevalence of depression was highest in the moderate participation group, but its association was lost in the fully adjusted model suggesting that depression was secondary to other factors. Hill et al. showed that depressive symptoms associated with self-perceptions of memory problems contributed to lower physical and social participation (63). The low prevalence of depression in the low participation group and lack of association with participation group could be due to small sample size. Furthermore, depression is known to be highly prevalent in those with falls and near-falls (14).

Our study includes validated assessment tools for functional measures and targeted older adults with falls and near-falls. Unlike other studies which used LSM as an independent variable, our study used LCA comprising of factors associated

with participation restriction. However, several limitations warrant mention. First and foremost, we acknowledge the small number of participants in the low participation group, which reflects the real-life scenario where they are the "extremes". It is not known if intervention for anorexia of aging or hearing impairment may reduce the prevalence of low participation. For the exploratory analysis and prediction model, the low and moderate participation groups were combined. Other limitations include lack of objective hearing assessment using audiometry tests. Perceived health, demographics, history of falls, and life-space mobility measurement using questionnaire can be subject to recall bias (9). Objective vital parameters such as blood pressure together with self-reporting may be better indicators of perceived health. The study was conducted during the Covid-19 pandemic, which may have had an impact on overall life-space mobility. The cross-sectional study limits the causality association. In addition, our study population involved only those with falls or near-falls, and the findings from our study cannot be generalized to the population. We have no information on impact of environment on overall life-space mobility scores. However, most older adults in Singapore live in high-rise units in well-built neighborhoods. Lastly, there are no validated questionnaires to measure IC domains, and IC in this study was measured using a simple questionnaire which may be subject to recall bias.

Our study suggests that screening for impairments in IC in those with falls or at risk of falls will help identify older adults at risk of participation restriction especially those with poor STS, hearing impairment, cognitive impairment, and anorexia of aging. Although we have no data on interventions to improve participation and outcomes, most of the IC impairments may be reversible with targeted interventions. The recently published World Guidelines for Falls Prevention and Management for Older Adults have recommended multifactorial risk assessment, which includes all the IC domains with targeted interventions (64). Future longitudinal studies are needed at population level and to determine if interventions for IC decline will lead to improved participation and reduction in disability and frailty.

Conclusion

Three distinct participation clusters were identified. The largest group was moderate participation, followed by high and low participation groups. Cognitive impairment and poor STS were significantly associated with moderate participation, while hearing impairment, anorexia of aging, and poor STS were associated with the low participation group. Screening for IC in those at risk of falls is important to develop a person-centered approach to promote increased participation. Future studies are needed at population level to assess the association of IC with participation and the impact of a personalized management plan on overall participation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by National Healthcare Group Domain Specific Review Board, Singapore. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RM and YC contributed to study concept, design, and preparation of manuscript. RM conducted the data acquisition. YC conducted the data analysis and interpretation. RM, YC, IA, and JM were involved in writing and reviewing the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Ming Yang,
West China Hospital, Sichuan University, China

REVIEWED BY
Nazarii Kobyliak,
Bogomolets National Medical University, Ukraine
Liang-Yu Chen,
Taipei Veterans General Hospital, Taiwan
Siti Setiati,
University of Indonesia, Indonesia

*CORRESPONDENCE
Yusuf Ali
✉ yusuf.ali@ntu.edu.sg

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Gut-muscle crosstalk. A perspective on influence of microbes on muscle function

Weixuan Chew[1,2], Yen Peng Lim[3,4], Wee Shiong Lim[1,2,3], Edward S. Chambers[5], Gary Frost[6], Sunny Hei Wong[1,2,7] and Yusuf Ali [1,2,8,9]*

[1]Nutrition, Metabolism and Health Programme, Lee Kong Chian School of Medicine, Nanyang Technological University Singapore, Singapore, Singapore, [2]Centre for Microbiome Medicine, Lee Kong Chian School of Medicine, Nanyang Technological University Singapore, Singapore, Singapore, [3]Institute of Geriatrics and Active Aging, Tan Tock Seng Hospital, Singapore, Singapore, [4]Department of Nutrition and Dietetics, Tan Tock Seng Hospital, National Healthcare Group, Singapore, Singapore, [5]Section for Nutrition Research, Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, London, United Kingdom, [6]Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, Imperial College London, London, United Kingdom, [7]Department of Gastroenterology and Hepatology, Tan Tock Seng Hospital, National Healthcare Group, Singapore, Singapore, [8]Singapore General Hospital, Singapore Eye Research Institute (SERI), Singapore, Singapore, [9]Clinical Research Unit, Khoo Teck Puat Hospital, National Healthcare Group, Singapore, Singapore

Our gastrointestinal system functions to digest and absorb ingested food, but it is also home to trillions of microbes that change across time, nutrition, lifestyle, and disease conditions. Largely commensals, these microbes are gaining prominence with regards to how they collectively affect the function of important metabolic organs, from the adipose tissues to the endocrine pancreas to the skeletal muscle. Muscle, as the biggest utilizer of ingested glucose and an important reservoir of body proteins, is intricately linked with homeostasis, and with important anabolic and catabolic functions, respectively. Herein, we provide a brief overview of how gut microbiota may influence muscle health and how various microbes may in turn be altered during certain muscle disease states. Specifically, we discuss recent experimental and clinical evidence in support for a role of gut-muscle crosstalk and include suggested underpinning molecular mechanisms that facilitate this crosstalk in health and diseased conditions. We end with a brief perspective on how exercise and pharmacological interventions may interface with the gut-muscle axis to improve muscle mass and function.

KEYWORDS

gut microbes, muscle function, metabolites, cytokines, sarcopenia

Introduction

The gut-muscle axis describes how the gut microbiota can impact muscle mass, muscle quality and muscle function. The gut consists of trillions of microbial cells, which plays an important role in many aspects of human health and can influence muscle health through dietary fiber, proteins and metabolic by-products (1). The gut microbiota

ferments non-digestible substrates such as dietary fibers to produce short chain fatty acids (SCFA) which have important regulatory functions. Emerging evidence suggests a relationship between gut microbiota and sarcopenia, which is the age-related loss of skeletal muscle mass and function. The spectrum of parameters implicated in muscle health ranges from muscle quantity which is typically measured *via* the appendicular lean mass using dual energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA); muscle quality which refers to the amount of fat infiltration into muscle; and muscle function which measures the components of strength and physical performance.

Muscle health is important because skeletal muscles are major sites of insulin stimulated glucose uptake, and thus play a key role in glucose homeostasis and whole-body metabolism. Furthermore, low skeletal muscle mass is often associated with frailty in older adults which increases their susceptibility to adverse outcomes and negatively affects their quality of life. It is also associated with many metabolic diseases such as Type 2 Diabetes Mellitus (T2DM). If it turns out that the gut microbiome does indeed strongly influence muscle health *via* the gut-muscle axis, it can create new avenues of treatment to improve muscle health through direct means such as probiotics or indirectly *via* dietary interventions or prebiotic supplementation. In this article, we summarize recent animal and human studies that suggest the role of gut microbiota in influencing muscle health, and on how gut microbes may in turn be altered during certain muscle disease states. Insofar, the aim is not to provide a systematic review but rather to give a perspective based on existing evidence that exercise and pharmacological interventions provide benefit by impinging on the gut-muscle axis.

Associations between gut microbiome and muscle

Animal studies reveal interesting insights about the gut-muscle axis. In a study on mice, it was found that germ free (GF) mice lacking in gut microbiota displayed reduced skeletal muscle weight, as compared to conventional or specific pathogen free (SPF) mice which have an intact gut microbiota and immune system (2). Upon histological examination of the tibialis anterior and gastrocnemius, fewer but larger muscle fibers could be seen. In the muscles of the GF mice, there was reduced expression of the succinate dehydrogenase (*Sdh*) gene and reduced activity of the mitochondrial SDH enzyme. The amount of mitochondrial DNA content also reduced and there was evidence of dysfunctional mitochondrial biogenesis and oxidative capacity of the soleus (oxidative) and extensor digitorium longus (glycolytic). Reduced expression of glycolytic genes was observed in these muscle groups. However, despite a possible reduction in oxidative metabolic capacity, the GF mice performed as well as SPF mice when challenged till exhaustion, suggesting the involvement of other compensatory pathways especially during the endurance phase. Importantly, upon treatment with SCFA, the muscle strength of GF mice increased as compared to the untreated GF mice, suggesting that SCFAs may be an important link between gut microbiota and muscle function. Transplantation of gut microbiota from SPF mice to GF mice helped to restore muscle mass and mitochondrial DNA content in GF mice muscle. This suggests that modulation of microbiota could potentially be used in humans as a way to treat conditions such as sarcopenia. When similar experiments were repeated in piglets, the results were largely similar to what was observed in mice (3). The GF piglets exhibited a lower growth rate as compared to control piglets with normal microbiota. A group of GF piglets was treated with fecal microbiota transplantation (FMT) from healthy adult pigs and the average body weight of piglets receiving FMT increased by ∼1.4-fold compared to that of the GF piglet. Although the FMT did not completely restore growth of the GF piglet, they showed improved body conditioning and physiological traits as compared to the GF piglets. As for underpinning mechanism, the lower proportion of slow twitch muscle fibers of the GF piglets correlated with reduced SCFA contents pointing toward a role of gut microbes, specifically butyrate-producers in influencing slow-twitch muscle fiber development. In addition, the blood concentrations of triglycerides (TG), glucose and growth hormones in the FMT piglet were also significantly higher than that of the GF piglet suggesting that the introduction of gut microbes improved whole-body metabolic homeostasis in GF piglets.

In another study, when three different antibiotic regimens (1. cefoperazone, 2. enrofloxacin/ampicillin, 3. a four-drug regimen of neomycin, vancomycin, metronidazole and ampicillin) were administered to mice, there was a decrease in mass of the gastrocnemius-soleus complex of the mice (4). However, when the antibiotics were administered to GF mice, they did not lose any muscle mass as compared to the control suggesting that the effects of antibiotics on muscle mass is likely modulated through its impact on the microbiome. This could be due to the concurrent alteration of the gut microbiota, the composition of which depended on antibiotics administered. An intact gut microbiome has also been shown to be important for skeletal muscle adaptation to exercise (5). Mice treated with antibiotics to disrupt gut microbiome showed a blunted soleus and plantaris muscle fiber-type specific hypertrophy in response to progressive weighted wheel running as compared to those without antibiotics treatment. Mice which were colonized with gut bacteria through FMT from high functioning human donors had a 5.4% increase grip strength as compared to those which received FMT from low functioning human (6). While animal studies help with mechanistic underpinnings of phenotypic observations, it is also important to assess how much of these findings translate to the human setting.

It is worth noting that there are also studies the suggest negative associations between gut microbiota and whole-body lean mass. In one study when GF mice were colonized by fecal samples from age matched, conventionally raised mice, the whole-body lean mass decreased by 7–9% with a 57% increase in total body fat content. It was also associated with increased plasma leptin, fasting glucose and fasting insulin levels (7).

In another study, mice treated with pulsed antibiotic treatment (PAT) either using amoxicillin or tylosin phosphate developed larger bones with increased lean and fat mass as compared to controls. It trended toward increased bone in amoxicillin-treated mice and increased fat in tylosin-treated mice (8) and this was corroborated in antibiotic treated piglets. In tylosin phosphate-treated piglets, myofiber density and expression of genes related to type I and type IIb myofibers as well as fatty acid uptake in longissimus muscle was observed to be increased, together with gut microbe changes where the ratio of Firmicutes to Bacteroidetes was increased, while *Prevotella* and *Campylobacter* were decreased in the cecum (9).

Given its highly complex and multi-dimensional nature, the microbiota that evolve with different antibiotics and FMT regimens can exert different corresponding phenotypes. While gut microbiota does have affect muscle mass and function, these discrepant findings do suggest the need for more studies to determine the causality, functionality and directionality of the microbiota and its constituent members.

Human studies associate gut microbe changes with metabolic- and age-related muscle loss

Patients with low muscle mass or sarcopenia, in the context of organ failure or cancer, were observed to have alterations in their gut microbiome. It was reported that patients with chronic liver disease who had lower muscle mass possessed a lower *Firmicutes*/ *Bacteroidetes* ratio than those with normal muscle mass (10). The levels of *Coprobacillus*, *Catenibacterium* and *Clostridium* were also lower while *Bacteroides* was higher comparing between muscle sub-groups. There was also a high relative abundance of Gram-negative bacteria and corresponding lipopolysaccharides (LPS) suggesting a possible link between gut microbes, inflammation and changes to muscle mass. There are cross-sectional human association studies that compare patients with cirrhosis-related sarcopenia with control subjects. The principal alteration in age-related sarcopenia and cirrhosis-related sarcopenia was a reduction in SCFA-producing bacteria. *Lachnospiraceae* family, consisting of *Lachnospira*, *Fusicatenibacter, Roseburia*, and *Lachnoclostridium*, significantly decreased in age-related sarcopenia.

Interestingly, in a study involving nursing-home residents aged 65 years or older, with increasing frailty, residents had lower levels of butyrate producing organisms, higher levels of known dysbiotic species, and higher LPS and peptidoglycan (PGN) biosynthesis. Amongst the residents, with increasing age, there was a reduction in mucin-degrading *Akkermansia muciniphila* and butyrate-producing *Ruminococcus bromii* likely due to a change in diet. With increasing malnourishment, there is increased abundance of LPS-producing *Ruminococcus gnavus* and deceased butyrate-producing *Lachnospiracae* and *Ruminococcaceae* (11). In a separate study on stool samples from frail old people, *Lactobacilli, F. prausnitzii,* and *Bacteroides / Prevotella* ratio declined sharply and *Enterobacteriaceae* increased (12). Such changes in gut microbial species may alter the inflammatory tone as *Lactobacilli, F. prausnitzii* are largely anti-inflammatory while *Enterobacteriaceae* induces pro-inflammatory effects. It has been suggested that age dependent changes in gut microbiota may be the initiator of frailty symptoms facilitated by chronic inflammation, since probiotic rescue reduces inflammation and muscle atrophy (13–15).

Admittedly, metabolic dysregulation and aging are complex conditions that encompass differences in nutritional intake, digestion and assimilation, drug use treatments (usually involving multiple drugs) and background physiology and inflammation, all of which may profoundly confound microbiome changes and muscle health. Mechanistic studies are key to elucidating how the microbiome, and its metabolites, influence muscle metabolism and survivability. Furthermore, the gut microbiota diversity may also be affected by protein intake. Briefly, in a study with professional athletes from an international rugby union squad compared against healthy male controls, there was a significant increase in gut microbiota diversity and this association also correlated with protein intake and plasma creatine kinase values (16). Greater microbiota α-diversity has been reported in athletes in associations with dietary patterns and protein consumption (16, 17).

Involvement of gut microbiota in cancer-related muscle loss

In patients with advanced gastric cancer, cachexia was associated with intestinal barrier dysfunction (i.e., greater intestinal permeability) with a higher degree of bacterial translocation, as compared to patients with gastric cancer but without cachexia (18). Levels of Interleukin-6 (IL-6), Tumor Necrosis Factor α (TNF-α), and Interferon γ (IFNγ) correlated with bacterial translocation in patients with cachexia and these inflammatory cytokines may drive myocyte cell death (19).

Mechanistically, there are a number of gut bacteria that have been singled out as gut barrier function disabling and inflammatory promoting. In lung cancer patients with cachexia, while gut α-diversity was not significantly perturbed when compared to patients without cachexia, a few bacteria species were significantly different. For example, a lower abundance of *Prevotella copri* was observed in patients with cachexia and this

correlated with reduced plasma levels of postulated myogenic branched chain amino acids (BCAAs) isoleucine and leucine. Lower levels of *Faecalibacterium prausnitzii*, a gut bacterium with known anti-inflammatory effects (20), was also observed in cancer patients with cachexia and this may tip the balance to a more proinflammatory state in patients with cachexia. Inversely significantly higher levels of *Klebsiella oxytoca,* a bacterium associated with reduced gut barrier function (21), was seen in lung cancer patients with cachexia, and together with reduced gut barrier function, bacterial translocation and inflammatory cytokines may drive cachexia in patients with cancer (22).

Underpinning mechanisms for gut microbiome and muscle crosstalk

Most published mechanistic studies leverage on the pathophysiology of small animals. Altered patterns of microvillus formation and reduced cell renewal were observed in mice depleted of gut microbiota. Since microvilli are involved in absorption of both macro- and micro-nutrients, pathologies affecting the microvilli may impact overall metabolism including muscle mass and function (23, 24). In a study, GF mice had low levels of 25-hydroxyvitamin D (25D), 24,25-dihydroxyvitamin D (24,25D) and 1,25-dihydroxyvitamin D, and were hypocalcaemic. After 8 commensal bacteria were introduced, the levels of 25D and 24,25D increased to the same extent as conventionalisation. Fibroblast growth factor (FGF)23 was initially high in GF mice, but eventually reduced and normalized the vitamin D and calcium levels (25). GF mice also exhibited increased bone mass due to reduced number of osteoclast per bone surface, and it normalized with colonization by normal gut microbiota (26). However, associations between alterations in gut microbiota and changes in muscle function could also be mediated by gut-derived metabolites such as SCFAs, which play an important role in modulating lipid, carbohydrate and protein metabolism in skeletal muscle. Although SCFAs are formed in the gut, effective concentrations can be found circulating in the body (27). SCFAs are formed from the fermentation of fibers such as non-digestible carbohydrates, and they include acetate, propionate, and butyrate. These SCFAs are critical for maintaining the integrity of the epithelial barrier, the loss of which compromises barrier permeability and increases the risk of bacteria or bacterial antigen translocation. This in turn triggers the inflammatory cascade which may underpin chronic inflammation observed in obesity and insulin resistance (28).

Butyrate, of which higher levels are found in older adults with normal compared to low muscle mass, has been shown to promote mitochondria biogenesis (29, 30). When female mice were given a dietary supplement containing butyrate throughout the gestation and lactation phases, mitochondrial biogenesis was correspondingly enhanced in the offspring, evident by increased ATP content, mitochondrial DNA-encoded gene expression and uncoupling protein 3 (UCP3) in the gastrocnemius muscle of the offsprings (30). Separately, high functioning sedentary older adults had higher levels of *Barnesiella* and *Prevotella* genera, including the species *Barnesiella intestinihominis*, as compared to their low functioning sedentary counterparts. Notably, *Barnesiella* and *Prevotellaceae* were shown to be gut producers of SCFA (31, 32). Among older persons with low functional muscle strength, those with higher levels of SCFAs correlated with greater muscle strength, suggesting that SCFAs may contribute to the observed enhanced muscle strength (33).

When circulating SCFAs were significantly reduced in plasma of antibiotic treated mice, exercise endurance in these mice correspondingly dropped, which was again restored with acetate infusion. Caecal acetate, propionate, and butyrate were eliminated in antibiotic treated mice, suggesting that gut microbe derived SCFAs, especially acetate, may be an important energy substrate during endurance exercise (34). Besides its effects on mitochondria, SCFAs also affects muscle health by altering nuclear gene expression.

Administration of dexamethasone to C2C12 myotubes resulted in increased Atrogin-1 expression. This effect on *Atrogin-1* expression was reduced when the C2C12 myotubes were treated with a cocktail of SCFAs, similar to those generated from fermentation of dietary polysaccharides. In addition, treatment of GF mice reduced the expression of *Atrogin-1* in the tibialis anterior and increased the expression of *MyoD* (2).

Diversified effects of microbial biomolecules for the muscle

Indoxyl sulfate is a gut microbiome derived uremic toxin and is known for its pro-inflammatory properties in chronic kidney disease (CKD) patients (35). Administration of indoxyl sulfate was observed to reduce muscle mass in mice. It significantly increased intracellular ROS production in C2C12 myoblast cells, which plays an important role for skeletal muscle atrophy through various mechanisms (36). Also, indoxyl sulfate caused an increase in expression of myostatin (*Mstn*) and *Atrogin-1* mRNA through the arylhydrocarbon receptor (AHR) pathway, inhibiting cell proliferation and myotube formation (37). Another way in which gut microbiome could negatively affect muscle health is through LPS. LPS is potent endotoxin present in the outer membrane of Gram negative bacteria and is known for its pro-inflammatory properties. Disrupted intestinal barrier may cause translocation of these bacterial components into systemic circulation which may in turn result in inflammation, *via* the Toll-like Receptor 4 (TLR4) pathway, resulting in muscle atrophy (38, 39). This is also seen in chronic diseases where pro-inflammatory factors appear to be the unifying factor of muscle atrophy (40). It was found that LPS decreased the formation of multi-nucleated myotubes and

inhibited myogenic differentiation *in vitro* (41) suggesting that changes in gut permeability may allow leakage of bacterial derived glyco-peptides into the circulation which then affects the function of distal tissues such as skeletal muscle.

Muscle function in common gastrointestinal diseases

Diseases of the gastrointestinal tract such as inflammatory bowel diseases (IBD) and celiac disease (CD) are associated with a decline in muscle function and cachexia (42). Studies have shown that the gut microbiota in IBD patients were significantly altered from that of healthy individuals, and that dysbiosis of gut microbiota accompanied by disruption of diet-microbe interactions, results in damage to intestinal microbial barrier. For instance, in Crohn's Disease, over 50% of patients presented with adherent-invasive *E. coli* colonization in intestinal mucosa (43). Dysbiosis, defined as a disease associated imbalance in the gut microbial community, was reported for IBD. Decreased *Firmicutes* and *Bacteroides*, and increased *Enterobacteriaceae*, were observed in IBD. This microbe diversity shift disrupted the intestinal barrier integrity through increased abundance of mucolytic bacteria facilitating increased penetration of pathogens into intestinal tissue (44). Furthermore, it has been reported that more than a third of IBD patients suffer from sarcopenia. Similar to what was observed in the frail population, there was a reduction in *F. prausnitzii*, a SCFA producer with significant anti-inflammatory function (45). This raises the possibility that the decrease in anti-inflammatory gut microbiota with disruption of the epithelial barrier function in IBD may trigger the inflammatory cascade with release of proinflammatory cytokines such as TNF-α and IL-6 affecting muscle mass and function.

Exercise as a potential modulator of intestinal microbiome composition

While physical exercise directly benefits muscle function, either anatomically through maintenance of muscle sarcomere density or metabolically through increase of myocyte energetics, it has also been suggested have indirect benefits on the muscle through for example the modulation of gut commensals. Physical activity performed continuously at low doses can increase the abundance of health promoting gut bacteria such as *Bifidobacterium spp, R. hominis, A. muciniphilia* and *F. parusnitzii* (46). However, the relationship between gut microbiota and muscle health remains complex. In addition to diet, exercise is a positive modulator of gut microbiota biodiversity and this has been reviewed extensively (47, 48). Conversely, frailty, as determined using the Rockwood Frailty Index, had a negative correlation with gut microbiota α-diversity (49). The microbiota, especially those that produce metabolites such as SCFA, are important to endurance athletes, because they can supply around 10% of the energy needed by the host (50). With regular physical activity, muscle fibers release myokines such as IL-6, contributing to an overall systemic anti-inflammatory tone (51, 52). In turn, this may help to protect the microbiota from changes caused by inflammatory conditions such as IBD and T2DM (53). High-fat diet fed (i.e., pre-diabetic) mice which received fecal microbiota transplantation (FMT) from actively exercising mice showed improved metabolic parameters such as insulin sensitivity, suggesting that microbes obtained from a physically active host contributes positively to overall metabolic function (54).

While exercise is associated with numerous health benefits, intense exercise can result in acutely increased gut permeability, and reduced mucus production, allowing pathogens such as LPS in ultra-endurance runners to enter the bloodstream and causing inflammation (55, 56). Exercise-induced gut barrier disruption is observed with an acute rise in inflammatory markers, such as plasma TNF-α (57). These changes were however found to be reversible and thus may not outweigh the benefits of exercise. Separately, in a 6-week intervention study amongst older adult males who participated in twice weekly resistance training, resistance training did not alter much of their gut microbiome composition (58). Although a subsequent *in silico* analysis revealed a paradoxical increase in mucin synthesis, the study stopped short of validating changes to bacterial translocation and systemic inflammation (47). Taken together, more studies with prospective follow-up are required to better understand the longitudinal impact of these cross-sectional associations of exercise and nutrition with gut microbes and systemic inflammation. These studies also point to the judicious use of antibiotics because inappropriate or excessive use of broad-spectrum antibiotics is a major iatrogenic contributor to a deranged gut microbiome.

Other forms of interventions involving the gut microbiome

Besides physical exercise, alterations either through microbiome depletion/ reconstitution, FMT, diet interventions or pre-/probiotics supplementation may offer a new approach to address the problem of frailty by targeting the gut-muscle axis (59). Probiotics refer to defined viable microorganisms, sufficient amounts of which reach the intestine in an active state and thus exert positive health effects. Prebiotics, on the other hand, refer to selectively fermented ingredients that allow specific changes, both in composition and/or activity in the gastrointestinal microflora that confers benefits upon host wellbeing and health, such as non-digestible oligosaccharides (60).

TABLE 1 List of human and animal studies that relate gut microbes to muscle and its related phenotype.

Study context	Muscle and related phenotype	Gut microbiota	References
Human studies			
Loss of community associated microbiota in long stay subjects correlated with increased frailty.	Significant associations with Barthel Index and functional independence measure (FIM).	Long stay care environment subjects had high proportion of *Bacteroidetes*, whereas individuals living in the community dwelling had a high level of *Firmicutes*. Long stay care subjects had significantly less diverse microbiota with less SCFA-producing bacteria compared to community and rehabilitation subjects.	(64)
Gut microbe changes in patients with sarcopenia compared to age-matched healthy cohort.	Grip strength < 28 kg (male) or < 18 kg (female).	Ruminococcus positively correlated with grip strength in sarcopenic cohort.	(65)
Alterations in gut microbiome after weight loss in human subjects	No measure of muscle mass other than correlations of general adiposity.	High levels of *Firmicutes* in obese subjects. Low levels of *Bacteroidetes* in obese individuals partially normalized with weight loss.	(66)
Obese monozygotic and dizygotic twins have reduced phylogenetic diversity.	No measure of muscle mass.	Lower proportion of *Bacteroidetes and i*ncreased abundance of *Actinobacteria* while the levels of *Firmicutes* remained unaltered.	(67)
Type-2 diabetes mellitus	Reduced muscle insulin sensitivity.	Proportions of the *Firmicutes*, and specifically the *Clostridia* class, were reduced, while the *Bacteroidetes* and the class *Betaproteobacteria* were enriched in a group with T2DM compared with controls.	(68)
		Moderate degree of gut dysbiosis, characterized by an increase in certain opportunistic pathogens, such as number of *Clostridium* spp. in addition to important gut microbes including *Akkermansia muciniphilia, Bacteroides* spp. and *Desulfovibrio* spp.	(69)
Frailty in older adults was associated with reduced gut microbiota diversity.	Measures of frailty index (FI) including Rockwood Frailty Index.	*Enterobacteriaceae* were increased, whereas *Bacteroides/Prevotella* and the bacterial species *Faecalibacterium prausnitzii* sharply declined.	(12, 49)
Chronic liver disease patients with low skeletal muscle mass had lower branch chain amino acid (BCAA) synthesis genes, by 16S RNA, compared to chronic liver disease patients with normal skeletal muscle mass.	Skeletal muscle.	Lower Firmicutes/ Bacteroidetes ratio. *Coprobacillus, Catenibacterium and Clostridium* were also lower while the *Bacteroides* was higher. Microbiome characterized by high relative abundance of gram negative bacteria with LPS	(10)
In patients with advanced gastric cancer, cachexic patients had a higher prevalence of bacterial translocation than non-cachexic patients.	Cachexia measured as weight loss of >10% of the pre-illness state.	Bacterial DNA detected from the portal vein indicative of reduced intestinal permeability and increased bacterial translocation in subset of cachexia patients. Higher alteration of intestinal flora was noted in cachexic patients.	(19)
Cachectic lung cancer patients	Loss in overall muscle mass.	*Prevotella copri* showed significantly lower abundance in cachectic patients. *Klebsiella oxytoca* is significantly higher in lung cancer patients with cachexia *Fecalibacterium prausnitzii* is significantly more abundant in non-cachectic patients. Significant enrichment of microbiota LPS biosynthesis pathway.	(22)
Elderly older than 65 years old with low muscle mass	Skeletal muscle (based on body composition, grip strength, gait speed and flexibility).	*Firmicutes/Bacteroidetes* ratio was significantly reduced in the low muscle mass group. *Marvinbryantia* spp. (SCFA producer) was decreased significantly, *Flavonifractor* spp. (flavonoid degrader) was enriched and Fecal butyrate was significantly diminished and correlated with skeletal muscle mass index	(29)

(Continued)

TABLE 1 (Continued)

Study context	Muscle and related phenotype	Gut microbiota	References
Muscle impairment in older adults	Physical frailty, based Short Physical Performance Battery (SPPB), low appendicular muscle mass (aLM), and absence of mobility disability (i.e., ability to complete the 400-m walk test).	Increase in *Oscillospira* and *Ruminococcus* and decrease in *Barnesiellaceae* and *Christensenellaceae* in physically frail subjects.	(70, 71)
	Sedentary women subjected to exercise interventions including aerobic exercise training (brisk-walking).	Relative abundance of Bacteroides significantly increased in sedentary women after 12 weeks of aerobic exercise. Abundance of Bacteroides positively correlated with an increased physical performance assessed by the 6 min walking test	
Chronic alcohol consumption had a loss of muscle strength	Handgrip strength was significantly lower in the alcohol overconsumers group compared to control patient group.	Higher relative abundance of *Proteobacteria, Sutterella, Clostridium* and *Holdemania.* Lower relative abundance of *Faecalibacterium* with reduced fecal SCFAs levels	(72)
Difference in gut microbiota profile between women with active lifestyle and sedentary women.	Sedentary women performed <3 days of exercise per week for 30 min at moderate intensity.	Higher abundance of health promoting bacterial species in active women, including *Faecalibacterium prausnitzii*, *Roseburia hominis* (butyrate producers), Bifidobacterium spp and *Akkermansia muciniphila.*	(46)
	Active women performed at least 3 h of physical exercise per week.	Lower Bacteroidetes in the active group.	
In a 6 week endurance exercise study without dietary changes amongst previously sedentary overweight women, metagenomic analysis revealed taxonomic shifts.	Non-significant increase in *M. vastus lateralis* thickness	Increase in *Dorea, Anaerofilum and Akkermansia*. Decrease in *Porphyromonadaceae, Odoribacter, Desulfovibrionaceae and Enterobacteriaceae*	(73)
Athletes vs. normal individuals	Overall impact of exercise on gut microbiome.	Higher levels of SCFAs (acetate, propionate, butyrate and valerate) in athletes relative to controls. Concentrations of propionate strongly correlated with protein intake. Concentration of butyrate was shown to have a strong association with the intake of dietary fiber.	(74)
In male runners, multistrain probiotic supplementation significantly increased running time to fatigue. In addition, probiotic supplementation lead to small to moderate reduction in intestinal permeability and gastrointestinal discomfort.	Run time to fatigue.	*Probiotic supplementation consisting of Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus fermentum, Bifidobacterium lactis, Bifidobacterium breve, Bifidobacterium bifidum*, and *Streptococcus thermophilus*	(57)
High performing martial arts athletes have significantly different gut microbial richness and diversity as compared to the lower-level martial arts athletes	Elite atheletes.	Genera *Parabacteroides*, *Phascolarctobacterium*, *Oscillibacter* and *Bilophila* were enriched in the higher-level athletes, whereas *Megasphaera* was abundant in the lower-level athletes. The abundance of the genus *Parabacteroides* was positively correlated with the amount of time participants exercised during an average week.	(75)
Athletes had relative increases in pathways (e.g., amino acid and antibiotic biosynthesis and carbohydrate metabolism) and fecal metabolites (e.g., microbial produced SCFAs acetate, propionate and butyrate) associated with enhanced muscle turnover and overall health when compared to control groups.	Althetes vs. control.	Higher levels of microbial derived SCFAs	(17)

(Continued)

TABLE 1 (Continued)

Study context	Muscle and related phenotype	Gut microbiota	References
Frailty associated changes in gut microbiota amongst community dwelling adults.	Confirmed with Fried et al. definition for frailty.	As compared to controls, the frailty groups had higher *Akkermansia, Parabacteroides, Klebsiella* and lower *Faecalibacterium, Prevotella, Roseburia, Megamonas, Blautia.*	(76)
Intensive, prolonged exercise causes gut dysbiosis in female endurance runners	15 female Japanese elite runners with mean monthly running distance of 547 km.	The abundance of Deferribacteres was significantly higher in the endurance runner group. Concentration of succinate (an undesirab gut bacteria metabolite) is significantly higher in female endurance runners.	(55)
6 weeks of resistance training of older adult males	DXA whole and lower body lean mass and leg extensor peak torque increased.	Increase in mucin biosynthesis. No change in microbiome diversity, LPS levels, SCFA, and mucin degradation	(58)
High fiber diet may be involved in mechanisms related to whole body lean mass and physical functioning in older adults	Physical function measured by short physical performance battery and grip strength.	Higher levels of *Ruminococcus, Lachnospira, and Clostridia*, and genes related to butyrate and SCFA production	(77)
Prebiotic 1-ketoase resulted in recovery of muscle atrophy in super elderly patients with sarcopenia	Increased total muscle mass, trunk mass, skeletal muscle index, skeletal muscle mass increased, as measured using multi frequency bioimpedance analysis device.	Increased *Bifidobacterium longum* in intestine after 1-ketose administration for 12 weeks	(62)
Prebiotic administration improved frailty criteria amongst elderly	Improvement in self-reported exhaustion score and better handgrip strength in the dominant hand.	Mixture of inulin and fructoligosaccharide intake over 13 weeks	(78)
Animal studies			
Genetically obese (ob/ob) mice have altered gut microbiome when compared to lean (ob/+) littermates.	High fat to lean mass ratio.	Higher proportions of *Firmicutes* and lower levels of *Bacteroidetes*	(79)
Fewer but larger muscle fibers compared to germ free (GF) mice.	Tibialis anterior (Fast oxidative muscle).	GF mice with conventionalisation.	(2)
Increased expression of FoxO3, *Atrogin-1* and *Murf-1* encoding E3 ubiquitin ligases, which are known to be involved in muscle atrophy in GF mice, reduced with transplantation of gut microbes.	Similar trend also observed in soleus (slow oxidative muscle) and extensor digitorium longus (fast glycolytic muscle).	GF mice with conventionalisation.	(2)
Reduced expression of myosin heavy genes and glycolytic genes, restored with transplantation of gut microbes.	Quadriceps (fast glycolytic) muscle.	GF mice with conventionalisation.	(2)
Slower growth rates and transplant restored growth in later days.	Reduced growth of lean mass.	GF piglet with conventionalisation.	(3)
Lower total SCFAs content in the colon Muscle mass smaller and muscle fibers thinner	Longissimus dorsi muscle	GF piglet with conventionalisation.	(3)
Increased muscle mass, grip strength, and endurance swimming time	Increased overall muscle mass and function.	Long term *lactobacillus plantarum* TWK10 supplementation in mice	(80)
Obese mice treated with prebiotic, oligofructose.	Increase in lean and skeletal muscle mass.	Associated with increases in family-level *Prevotellaceae*, and genus-level *Prevotella and Barnesiella*	(81)

(Continued)

TABLE 1 (Continued)

Study context	Muscle and related phenotype	Gut microbiota	References
Mouse model of leukemia (transplantation of BaF3 cells containing ectopic expression of Bcr-Abl), treated with probiotic supplements.	Decreased muscle atrophy gene expression (i.e., Atrogin-1, MuRF1, LC3, Cathepsin L), and increased muscle mass.	Lactobacillus spp. led gut dysbiosis was treated with *Lactobacillus reuteri* and *Lactobacillus gasseri* supplementation.	(13)
Microbiota from high functioning (HF) older adults transplanted into GF mice led to increased muscle strength.	Forelimb grip strength.	Genus level *Paraprevotella*, *Akkermansia*, *Barnesiella*, *Eubacterium*, *Prevotella* and *Coprobacillus* were higher in the HF-mice compared to LF-mice one-month after transplantation.	(6)
Antibiotic induced dysbiosis of the gut microbiome blunted hypertrophic response of type 1 fibers. It does not impair skeletal muscle fiber type shift in response to training	Soleus muscle.	Antibiotic (metronidazole, neomycin, ampicillin, vancomycin, streptomycin) treated mice had reduced microbiota composition and resulted in enlarged caecum.	(5)
Antibiotics blunted hypertrophy, myonuclei accretion, satellite cell abundance and fiber-type shift to type 2a fibers.	Plantaris muscle.		(5)
Klebsiella oxytoca is increased in tumor bearing mice with cachexia independently of anorexia.	Loss in overall muscle mass.	*Klebsiella oxytoca*	(21)
GF mice has increased bone mass	GF mice have decreased frequency of CD4+ T cells and CD11b+/GR 1 oesteoclast precursor cells in bone marrow.	Conventionalisation of GF mice normalizes bone mass.	(26)
Maternal butyrate supplementation throughout gestation and lactation did not affect offspring weight but Type 1 myosin heavy chain, mitochondria transcription factor A, PPAR-coactivator-1a and uncoupling protein 3 (UCP3) increased in the gastrocnemius muscle of rats.	Gastrocnemius.	Implications on butyrate-producers in maternal gut.	(30)
Low gut-derived acetate leads to reduced exercise endurance.	Overall impact on exercise endurance in mice.	2 weeks antibiotic treatment reduced exercise endurance. In the cecum, acetate, propionate and butyrate became almost undetectable. Antibiotic treatment associated with a larger population of *Firmicutes* and a smaller proportion of *Bacteroidetes*. Exercise capacity was restored by continuous acetate infusion (but not by butyrate infusion), suggesting that plasma acetate may be an important source of substrate during endurance exercise.	(34)
		6 week low microbiome-accessible carbohydrate (LMC) significantly reduced exercise capacity, and fecal and plasma SCFA concentrations. Ratio of Firmicutes: Bacteroidetes was also higher.	(34)
		In LMC-fed group, there were more *Lactococcus* and *Allobaculum* and lower *Prevotella* (which generates SCFA) and S24-7. Low dietary fermentable fiber content alters the composition of the microbiome in favor of bacteria that produces less SCFA	(34)
In hemodialysis patients, serum levels of indoxyl sulfate or p-cresol suphate may be reduced by either pre-biotics or pro-biotics administration.	Indoxyl sulfate inhibits myotube formation and increases factors related to skeletal muscle breakdown. P-cresol negatively affects the vascular endothelium.	Pre-biotics (oligofructose enriched inulin). Pro-biotics (*Bifidobacterium longum*).	(36, 82, 83)
Disruption of intestinal barrier leads to the development of metabolic disease.	Reduced muscle insulin sensitivity.	Bacterial lipopolysaccharides in systemic circulation.	(84)

(Continued)

TABLE 1 (Continued)

Study context	Muscle and related phenotype	Gut microbiota	References
High fat diet induces change in the composition of gut microbiota	Implied alteration to fat: lean mass ratio.	Reduction in *Bifidobacterium* spp. and *Eubacterium rectale–Clostridium coccoides* (Gram-positive bacteria) as well as *Bacteroides* (Gram-negative bacteria).	(85)
		Negative correlation between Bifidobacterium spp. and plasma LPS levels has been observed, and an increase in bifidobacterial induced by prebiotic intake reduces endotoxaemia.	(85)
		Decrease in Bacteroidetes and an increase in Firmicutes	(85)
Colonization of GF mice with fecal samples from age matched conventionally leads to reduction in whole body lean mass by 7–9%, with a 57% increase in total body fat content.	Reduced lean mass.	Conventionalisation results in elevations in liver mRNAs encoding two key enzymes in *de novo* fatty acid synthesis pathway. It also results in microbial suppression of intestinal fasting-induced adiposcyte factor (Fiaf) which promotes adiposity.	(7)
Exercise changes microbiota composition and increases n-butyrate concentration in the rat cecum.	Voluntary wheel running.	Increased n-butyrate, with no change in SCFA concentrations.	(86)
Diet exerted more influence than exercise in shaping the gut microbiota. The beneficial effects of diet and exercise are transmissible *via* FMT. HFD mice receiving FMT from normal diet exercised donor mice had reduced weight and improved whole-body metabolic profiles.	Fat weight.	Transmissible effect of FMT were associated with bacterial genera *Helicobatcer, Odoribacter* and AF12 and overexpression of oxidative phosphorylation and glycolysis genes. FMT has comparable effect to exercise in reducing body and fat weight in mice fed with high fat diet.	(54)
		As *Odoribacter* is a known producer of SCFA, such as acetate, propionate and butyrate, increased *Odoribacter* may contribute to decreased inflammation,	(87)
Differences in gut micriobiota of GF mice after FMT from children donors of different nutritional status	Nutritional status assessed based on weight-for-height Z-Score (WHZ).	*Faecalibacterium prausnitzii* were predominant in higher muscle mass recipient mice donated by healthy infants, while *Clostridium neonatale* were predominant in recipients donated by malnourished and underweight infants.	(88)
Antibiotic administration increased the myofiber density and expression of genes related to type I and type IIb myofibers in longissimus muscle	Longissimus muscle.	Antibiotic treatent, decreased *Ternericutes, Dialister, Asteroleplasma,* Prevotella, Campylobacter, Selenomonas, Misuokella, Acidaminococcus, and increases *Firmicutes, Bacteroidetes, Phascolarctobacterium, Paraprevotella, Oscillibacter, Coprococcus, Blautia, Ruminococcus.*	(9)
Probiotics (*Fecalibacterium prausnitzi*) increased muscle mass in mice	Gastrocnemius muscle harvested and weighed.	Oral *F.* prausnitzii increased muscle mass which could be due to enhanced mitochondrial respiration, improved insulin sensitivity, modified gut microbiota composition with increased abundance of *Lactobacillus* and *Streptococcus,* and improved intestinal integrity.	(89)
Probiotic delays the appearance of senescence and age-related muscle mass deposition in SAMP8 mouse, and age-related decline in muscle strength	Muscle strength evaluated using the four-limb hanging and grip strength tests.	Administration of *Lactobacillus casei* Shirota by oral gavage for 12 weeks.	(61)

(Continued)

TABLE 1 (Continued)

Study context	Muscle and related phenotype	Gut microbiota	References
Pulsed antibiotic treatment (PAT) (either 1. Tylosin or 2. Amoxicillin or 3. Mixed) produced mice with larger bones and higher lean mass than control. It trended toward increased fat in tylosin-treated mice and bone in amoxicillin-treated mice.	Lean mass.	PAT decreased richness and Shannon eveness after one antibiotic pulse. Bacteroidetes in the mixed group and some on tylosin were dramtically reduced. It was relatively unchanged in the amoxicillin mice.	(8)
		On high fat diet (HFD), members of the phylum Firmicutes increased at the expense of Bacteroidetes in untreated mice. Many similar families were changed, but the changes were not significant in amoxycillin-treated mice on HFD. In tylosin mice on HFD, changes were partially in the same direction (Streptococcaceae, Clostridiales other, Firmicutes other and Prevotellaceae) and partially in the opposite direction (Erysipelotrichaceae, Ruminococcaceae, Rikenellaceae, Bacteroidales other and Bacteroidetes other) compared to untreated HFD mice.	(8)

Since increased gut permeability is seen in cachexic mice and patients, supplementation with probiotics may restore gut barrier dysfunction thereby lowering pathogen leakage and systemic inflammation. Supplementation with *Lactobacillus* and *Bifidobacillus* has the potential to reduce age-induced and cancer induced muscle loss, while supplementation with lactobacillus is suggested to ameliorate muscle wasting *via* increasing butyrate production and decreasing gut permeability.

Most recently, two studies have revealed interesting insights. The SAMP8 mouse is commonly used as a pre-aging animal model because it starts to display an aging phenotype from 4 months of age. Probiotic supplementation of *Lactobacillus casei Shirota* (1×10^8 or 1×10^9 CFU/mouse/day by oral gavage) decreased the senescent scores and increased muscle mass in SAMP8 mice. Furthermore, it helped to maintain muscle strength in the aged mice, as seen from the higher grip force. It also reduced age related increases in inflammation by down regulating the proinflammatory cytokine TNF- α and upregulating the anti-inflammatory cytokine IL-10. In contrast to the fall in SCFAs usually seen in aging, *Lactobacillus casei Shirota* helped to maintain the butyrate levels in the aged mice (61). This study involved a small case series of six non-agenarian older adults (mean age: 90.8 $\pm$ 5.4 years) with sarcopenia who were administered the prebiotic 1-kestose (10 g/day for 2 weeks), there was an increase in the intestinal *Bifidobacterium longum* population along with increased skeletal muscle mass index and reduced body fat percentage (62). This study provided proof-of-concept evidence regarding the potential clinical benefit of prebiotic supplementation even in the oldest-old age group. Although treatment with prebiotics and probiotics may be promising in improving the gut microbiota (63), there are too limited studies at the moment to associate, let alone validate, whether its gut microbe effect carries on to muscle health amongst people with frailty syndrome.

Conclusion

In this perspective, we start with a brief overview on how gut microbiota can influence muscle health through various mechanisms and on how various microbes can be altered in certain muscle disease states. We discuss recent experimental and clinical evidence in support of microbiome impacting muscle mass, with an overall consensus that gut microbes impact muscle mass, either positively or negatively, depending on the microbe strain. This is supported by evidence that microbiome manipulation through either FMT or antibiotic administration can reverse phenotypes in GF and SPF mice, respectively. Meanwhile, human studies are beginning to show that microbiome composition is associated with muscle mass and function, paralleling changes in inflammatory markers in patients with frailty and other cachexic conditions. We looked into as many relevant papers as possible without bias or application of any exclusion criteria (i.e., not a systemic review) when gathering evidence for this perspective, but in doing so may have inadvertently missed a few relevant papers. This remains a limitation of this piece. Nevertheless, while much remains unknown about how microbiome interacts with muscle, this emerging field of research holds promise for improving our understanding of sarcopenia and other age-related muscle loss. Information on human, and animal, gut-muscle axis are now compiled into a single table (Table 1). Importantly, clinical studies will be needed to determine whether microbiome modulation *via* diet modification or pre/probiotic supplements can improve muscle health in humans. With continued research,

we may 1 day be able to use microbiome manipulation to combat sarcopenia and other disorders of muscle loss.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

WC, WL, SW, and YA wrote the manuscript. YL, EC, GF, and YA edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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