frontiers | Research Topics

Novel indicators and strategies for prevention and management of physical and cognitive frailty in aging population

Edited by
Xin Jiang, Jing Liao, Junhong Zhou and Yurun Cai

Published in
Frontiers in Public Health

ISSN 1664-8714
ISBN 978-2-8325-3893-7
DOI 10.3389/978-2-8325-3893-7

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Novel indicators and strategies for prevention and management of physical and cognitive frailty in aging population

Topic editors

Xin Jiang — Shen Zhen People's Hospital, China
Jing Liao — Sun Yat-sen University, China
Junhong Zhou — Harvard Medical School, United States
Yurun Cai — University of Pittsburgh, United States

Citation

Jiang, X., Liao, J., Zhou, J., Cai, Y., eds. (2023). *Novel indicators and strategies for prevention and management of physical and cognitive frailty in aging population*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-3893-7

Table of contents

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 17 November 2022
DOI 10.3389/fpubh.2022.1032666

OPEN ACCESS

EDITED BY
Xin Jiang,
Shen Zhen People's Hospital, China

REVIEWED BY
Yuan Lu,
Tongji University, China
Yurun Cai,
University of Pittsburgh, United States

*CORRESPONDENCE
Xiaobo Cen
xbcen@scu.edu.cn

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

RECEIVED 31 August 2022
ACCEPTED 31 October 2022
PUBLISHED 17 November 2022

CITATION
Qin F, Luo M, Xiong Y, Zhang N, Dai Y, Kuang W and Cen X (2022) Prevalence and associated factors of cognitive impairment among the elderly population: A nationwide cross-sectional study in China. *Front. Public Health* 10:1032666. doi: 10.3389/fpubh.2022.1032666

Prevalence and associated factors of cognitive impairment among the elderly population: A nationwide cross-sectional study in China

Feng Qin[1,2†], Min Luo[2†], Yang Xiong[2], Ni Zhang[3,4], Yanping Dai[1], Weihong Kuang[3,4] and Xiaobo Cen[1*]

[1]National Chengdu Center for Safety Evaluation of Drugs, State Key Laboratory of Biotherapy/Collaborative Innovation Center for Biotherapy, West China Hospital, Sichuan University, Chengdu, China, [2]Department of Urology, West China Hospital, Sichuan University, Chengdu, China, [3]Department of Psychiatry, West China Hospital, Sichuan University, Chengdu, China, [4]Department of Nuclear Medicine, West China Hospital, Sichuan University, Chengdu, China

Background: Cognitive impairments are associated with increased risk for progression to dementia. In China, limited surveys have been conducted to estimate the national prevalence and risk factors associated with cognitive impairment in China. This study aims to assess the national prevalence and modifiable risk factors for cognitive impairments in the Chinese elderly population.

Methods: This cross-sectional study was based on the 2018 China Health and Retirement Longitudinal Study. The Mini Mental State Examination (MMSE) is recommended to test for cognitive impairment. Univariate and multivariate logistic regression models were used in assessing risk factors for cognitive impairments in the Chinese elderly population.

Results: A total of 3768 participants aged 60 years or older were enrolled in this study. The national prevalence of cognitive impairments was 22.24% in China, and the prevalence of cognitive impairment was higher in the south-west region than in the north region (29.94 vs. 16.53%, $p < 0.05$). The risk for cognitive impairments was higher in the following participants: not married or not living with spouse relative to married with spouse present (OR = 1.39, 95% CI, 1.15–1.70; $p = 0.001$), nap duration of ≥ 90 min relative to 30–60 min (OR = 1.54, 95% CI, 1.20–1.98; $p = 0.001$), sleep duration of ≥ 8 h relative to 6–8 h (OR = 1.73, 95% CI, 1.29–2.31; $p < 0.001$), and depression relative to no depression (OR = 1.67, 95% CI, 1.41–1.97; $p < 0.001$). The risk of cognitive impairment was lower in participants living in the urban areas relative to the rural areas (OR = 0.57, 95% CI, 0.47–0.69; $p < 0.001$) and consuming alcohol once a month relative to never consuming alcohol (OR = 0.69, 95% CI, 0.51–0.94; $p = 0.02$).

10.3389/fpubh.2022.1032666

Conclusion: Cognitive impairment prevalence was high in the Chinese elderly population. The potentially modifiable risk factors for cognitive impairment should be further assessed in the development of interventions for the elderly Chinese population.

KEYWORDS

prevalence, risk factors, Chinese elderly population, dementia, cognitive impairment

Background

Dementia is arguably the most feared and devastating disease affecting the elderly population; and is a leading cause of disability and dependence of aged individuals, worldwide (1). According to the World Alzheimer Report, in 2019, more than 50 million individuals suffered from dementia globally, and this number is estimated to surge to 152 million by 2050 (2). Cognitive impairment is associated with increased risk of disability, increased health expenditures, and progression to dementia (3). Problems in memory, language, thoughts, and judgment are more prominent than normal age-related changes in patients with cognitive impairments, although the basic daily activities are not disrupted (4). Cognitive impairment ranges from mild to severe, and is one of the most common and disabling non-motor symptoms in elderly individuals. Mild cognitive impairment (MCI) is also known as cognitive impairment without dementia. It is considered a preclinical transitional stage between healthy aging and dementia, and gradually progresses to dementia in nearly 10–30% of patients with MCI (5). The updated estimated prevalence of MCI is 15.5%, and the prevalence of severe cognitive impairment (dementia) is approximately 6.0% in individuals aged 60 years or older in China (6). Notably, no effective medication is currently available for the treatment of cognitive impairment. Therefore, identifying the etiologies of cognitive impairments and suppressing the incidence are more important than treating them following their onset.

In the past decades, rapid demographic and epidemiological transition, have led to an aging population in China. Thus, the country has a large number of people with cognitive impairments. Many studies have investigated the prevalence and risk factors for cognitive impairments in China's general population (6–10). Older age, being female, rural residence, illiteracy, living without a partner, smoking, hypertension, hyperlipidemia, diabetes, heart disease, and cerebrovascular disease are the main risk factors for dementia and MCI (6–10). However, the prevalence and risk factors are vary among cities or regions of China, and limited surveys have been conducted to estimate the national prevalence and risk factors associated with cognitive impairments. These inconsistencies require further study for a realistic estimate.

In the present study, by conducting a nationwide cross-sectional survey, we aimed to estimate the prevalence of cognitive impairments and its modifiable risk factors in the elderly in China. The findings can help to enhance understanding of cognitive impairments and strategies for protecting the elderly population against cognitive decline.

Abbreviations: CESD-10, Center for Epidemiological Studies Depression Scale-10; CHARLS, China Health and Retirement Longitudinal Study; MCI, Mild cognitive impairment; MMSE, Mini-Mental State Examination.

Methods

Study sample and data cleansing

To investigate the prevalence of cognitive impairments in the elderly, the China Health and Retirement Longitudinal Study (CHARLS) 2018 follow-up dataset was downloaded and analyzed. The CHARLS was hosted by Peking University and approved by the Peking University Ethics Review Committee (IRB00001052-13074). Initiated in 2008, the CHARLS uses probabilities proportional to the size method to sample aging populations aged 45 years and above in the whole of China, with follow-ups in 2011, 2013, 2015, and 2018. The data were obtained from 150 counties and 450 villages in 28 provinces. The dataset from CHARLS are representative and of high quality. Detailed description and specific study design of the CHARLS project can be accessed from previous publications (11, 12) or its official website (http://charls.pku.edu.cn/). In the 2018 survey, the cognitive functions of participants aged 60 years and above were evaluated with the Mini-Mental State Examination (MMSE) questionnaire (13, 14). The flowchart of data cleansing is displayed in Supplementary Figure 1. In the present study, a total of 3,768 participants were analyzed.

Assessment of cognitive function

Cognitive functions were assessed using the MMSE questionnaire, which comprises 30 items with scores ranging from 0 to 30. The questionnaire is widely used in epidemiology for cognitive function assessment. The MMSE consists of seven aspects: orientation to time (five items), orientation to place

(five items), registration (three items), attention and calculation (five items), recall (three items), and language (nine items). Assessment was performed by two well-trained staff through a face-to-face interview with the native dialect. According to previous studies (10, 13–16), the cutoff of MMSE was set at 16/17 for illiterate individuals, 19/20 for individuals with 1–6 years of education, and 23/24 for individuals with at least 7 years of education. An MMSE score lower than the above-described cutoff values indicated cognitive impairment.

Covariates

Covariates, including individual characteristics and medical histories, were investigated. Individual characteristics self-reported by the respondents (17) included age (60–70, 70–80, or >80 years), gender (male or female), marital status (married with spouse present vs. divorced/separated/widowed/married but not living with spouse), educational level (illiterate, elementary school, middle school, high school, or college degree and above), settlement (central of city/town, urban–rural integration zone, or rural), cigarette consumption (yes or no), alcohol consumption (more than once a month, less than once a month, or never); afternoon nap duration ($\leq$30, 30–60, 60–90, and $\geq$90 min) (17, 18) and sleep duration ($\leq$6, 6–8, and $\geq$8 h) (17–19) were used according to previous studies. Medical histories included information on depression (yes/no), hypertension (yes/no), diabetes (yes/no), arthritis (yes/no), digestive diseases excluding cancers (yes/no), kidney diseases excluding cancers (yes/no), liver diseases excluding cancers, and fatty liver (yes/no), and stroke (yes/no).

Depression was assessed using the Center for Epidemiological Studies Depression Scale-10 questionnaire (14, 20). Medical histories were mainly based on the self-reports of the respondents. Given differences in living and cultural habits, the living localities of the participants were categorized into six regions in the same manner as previous studies did (17, 21): north (Shanxi, Hebei, Beijing, Tianjin, and Inner Mongolia), northeast (Jilin, Liaoning, and Heilongjiang), east (Jiangsu, Fujian, Shanghai, Shandong, Zhejiang, Jiangxi, and Anhui), northwest (Qinghai, Shanxi, Xinjiang, and Gansu), southwest (Sichuan, Chongqing, Yunnan, and Guizhou), and south-central (Hunan, Henan, Guangdong, Hubei, and Guangxi).

Statistical analysis

Data of clinical characteristics were summarized as proportions (%) according to data type. Descriptive statistics were used to investigate the prevalence of cognitive impairments in different groups. Moreover, univariate binary logistic regression was used in scanning risk factors for cognitive impairments. Then, correlation coefficients were calculated using Spearman tests to prevent collinearity before multivariate regressions were performed. The correlations among the covariates were low (Pearson correlation coefficients $<$ 0.5, Supplementary Figure 2), and thus no variable was deleted (22). Variables with p of $<$ 0.05 in univariate logistic regression were included in multivariate logistic regression analysis. Therefore, age, marital status, residence, alcohol consumption, afternoon napping, sleep duration, depression and liver disease were included in the multivariable logistic regression model. All the analyses and figures were made using R 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). A p-value of $<$ 0.05 (two-sided) indicated statistical significance.

Results

Baseline characteristics and prevalence in the grouped population

Between July 2018 and March 2019, a total of 19,816 adults ($\geq$ 45 years) were invited to participate in the CHARLS 2018 survey. First, 8,998 participants under 60 years of age were excluded. Then, 7,050 participants were further removed because the respondents refused to receive MMSE examination and their MMSE questionnaires had missing values. Finally, 3,768 ($\geq$ 60 years) were enrolled (Supplementary Figure 1). The descriptive statistics of enrolled participants are listed in Table 1. The overall prevalence of cognitive impairment was 22.24% (95% CI, 20.94–23.60). In total, 3,768 participants comprised 2,451 (65.0%) males and 1,317 (35.0%) females, and 81.05% of the participants were married. About 30.8% of people lived in urban areas, 60.7% in rural areas, and the remaining in the urban-rural integration zone. The participants were divided into groups based on cigarette use, alcohol consumption, nap duration, and sleep duration, as shown in Table 1.

Age- and gender-specific prevalence

As shown in Figure 1, the prevalence of cognitive impairment increased with age. The prevalence rates were 21.04% (95% CI, 19.52–22.64) in people aged 60–69 years, 23.91% (95% CI, 21.34–26.68) in people aged 70–79 years, and 32.65% (95% CI, 25.51–40.70) in people aged over 80 years. No significant difference in prevalence was found between female and male participants aged 60–69 years (20.79% vs. 21.17%). However, the prevalence of cognitive impairments in females was 1.25 and 1.30 times that in males in participants aged 70–79 years (27.46 vs. 21.98%) and in participants aged >80 years (39.47 vs. 30.27%), respectively.

10.3389/fpubh.2022.1032666

TABLE 1 Baseline population characteristics and prevalence in the grouped population.

Characteristics	Total participants (%)	Cognitive impairment	Prevalence (%)	95% CI
Total	3,768 (100%)	838	22.24	20.94–23.60
Age groups				
60–70 years	2,638 (70.0%)	555	21.04	19.52–22.64
70–80 years	983 (26.1%)	235	23.91	21.34–26.68
>80 years	147 (3.9%)	48	32.65	25.51–40.70
Gender				
Male	2,451 (65.0%)	534	21.79	20.20–23.47
Female	1,317 (35.0%)	304	23.08	20.88–25.44
Marital status				
Married with spouse present	3,054 (81.1%)	635	20.79	19.39–22.27
Separated/divorced/ widowed/ never married	714 (18.9%)	203	28.43	25.24–31.86
Residence				
Urban	1,153 (30.8%)	179	15.52	13.55–17.73
Urban-Rural Integration Zone	320 (8.5%)	61	19.06	15.11–23.76
Rural	2,275 (60.7%)	593	26.07	24.30–27.91
Cigarette consumption				
Yes	2,061 (54.7%)	471	22.85	21.09–24.72
No	1,703 (45.3%)	367	21.55	19.66–23.57
Alcohol consumption				
More than Once a Month	1,227 (32.6%)	256	20.86	18.68–23.23
Less than Once a Month	337 (9.0%)	57	16.91	13.27–21.32
None of These	2,200 (58.4%)	525	23.86	22.13–25.69
Nap duration				
≤30 min	1,960 (52.1%)	428	21.84	20.06–23.72
30–60 min	1,067 (28.3%)	205	19.21	16.96–21.69
60–90 min	233 (6.2%)	58	24.89	19.74–30.88
≥ 90 min	504 (13.4%)	147	29.17	25.35–33.30
Sleep duration				
≤6 h	2,087 (55.4%)	459	21.99	20.27–23.82
6–8 h	1,409 (37.4%)	286	20.30	18.28–22.48
≥8 h	268 (7.1%)	93	34.70	29.21–40.62
Depression				
Yes	1,206 (32.0%)	355	29.44	26.93–32.07
No	2,561 (68.0%)	483	18.86	17.39–20.42
Hypertension				
Yes	435 (11.5%)	106	24.37	20.55–28.64
No	3,333 (88.5%)	732	21.96	20.59–23.40
Diabetes				
Yes	214 (6.4%)	51	23.83	18.57–30.03
No	3,135 (93.6%)	713	22.74	21.31–24.24
Arthritis				
Yes	259 (6.9%)	64	24.71	19.82–30.36
No	3,509 (93.1%)	774	22.06	20.72–23.46
Digestive diseases				
Yes	280 (7.4%)	56	20.00	15.70–25.12
No	3,488 (92.6%)	782	22.42	21.07–23.83
Kidney diseases				
Yes	174 (4.6%)	42	24.14	18.32–31.10
No	3,594 (95.4%)	796	22.15	20.82–23.54
Liver diseases				
Yes	150 (4.0%)	23	15.33	10.37–22.08
No	3,618 (96.0%)	815	22.53	21.19–23.92
Stroke				
Yes	233 (6.3%)	53	22.75	17.79–28.60
No	3,441 (93.7%)	767	22.29	20.93–23.71

CI, Confidence Interval.

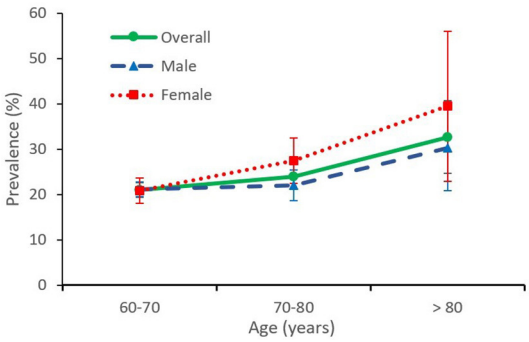


FIGURE 1
Age and gender-specific prevalence of mild cognitive impairment. The prevalences of MCI in females are higher than those in males in the 70–79 years old group and the >80 years old group. Error bars represent 95% CIs.

Gender-specific prevalence across regions

Gender-specific prevalence in different regions is displayed in Figure 2. The highest prevalence of cognitive impairments was found in the southwest region (29.94%); and the lowest, in the north region (16.53%). Difference in prevalence was found between males and females across regions. The prevalence of cognitive impairments in females was 1.68 and 1.38 times that in

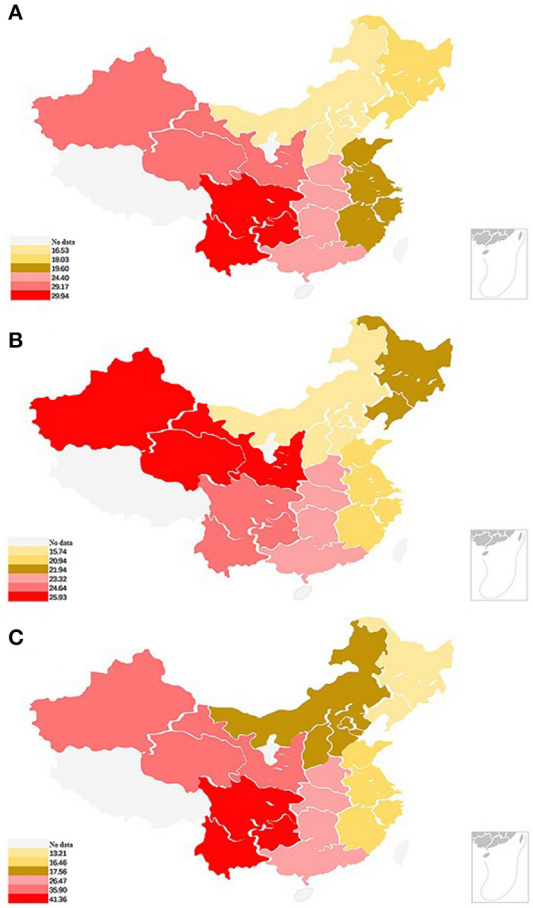


FIGURE 2
Gender-specific prevalence of cognitive impairment in different regions. The prevalence overall **(A)**, in males **(B)** and in females **(C)** of cognitive impairment among the elderly population were calculated, and living localities of the participants were also categorized into six regions. People living in the south-west region have the highest prevalence, while people living in the north region have the lowest prevalence. North region including Shanxi, Hebei, Beijing, Tianjin, and Inner Mongolia. North-East region including Jilin, Liaoning, and Heilongjiang. East region including Jiangsu, Fujian, Shanghai, Shandong, Zhejiang, Jiangxi, and Anhui. North-West region including Qinghai, Shanxi, Xinjiang, and Gansu), South-West region including Sichuan, Chongqing, Yunnan, and Guizhou. and South-Central region including Hunan, Henan, Guangdong, Hubei, and Guangxi.

males in the southwest region (41.36 vs. 24.64%) and northwest region (35.90 vs. 25.93%), respectively.

Associated factors of cognitive impairments

As shown in Table 2, results from univariate logistic regression indicated increased risk of cognitive impairments in participants aged > 80 years compared with participants aged 60–70 years (odds ratio, OR = 1.82, 95% CI, 1.27–2.60; $p < 0.001$), participants that were not married or cohabitating compared with married with spouse present (OR = 1.51, 95% CI, 1.26–1.82; $p < 0.001$), participants with daytime napping of ≥90 min compared those with 30–60 min (OR = 1.73, 95% CI, 1.35–2.21; $p < 0.001$), participants with sleeping duration at night of ≥8 h compared those with 6–8 h (OR = 2.09, 95% CI, 1.57–2.77; $p < 0.001$), and participants with depression compared with those without depression (OR = 1.79, 95% CI, 1.53–2.10; $p < 0.001$). Meanwhile, a lower risk of cognitive impairments were found in participants living in urban areas compared with those living in rural areas (OR = 0.52, 95% CI, 0.43–0.63; $p < 0.001$), participants with less alcohol consumption compared with those who never consumed alcohol (OR = 0.65, 95% CI, 0.48–0.88; $p = 0.005$) or participants with liver diseases than those without liver diseases (OR = 0.62, 95% CI, 0.40–0.98; $p = 0.04$).

Multivariate logistic regression models were used in evaluating risk factors for cognitive impairment. The final multiple logistic regression model included age, marital status, residence, alcohol consumption, nap duration, sleep duration, depression and liver disease. The prevalence of cognitive impairment was higher in participants who were not married or were not living with spouse compared with those married living with their spouses (OR = 1.39, 95% CI, 1.15–1.70; $p = 0.001$) and participants with nap duration of ≥90 min compared with those of nap duration of 30–60 min (OR = 1.54, 95% CI, 1.20–1.98; $p = 0.001$), participants with sleep duration of ≥8 h compared with those with sleep duration of 6–8 h (OR = 1.73, 95% CI, 1.29–2.31; $p < 0.001$), and participants with depression compared with those without depression (OR = 1.67, 95% CI, 1.41–1.97; $p < 0.001$). Notably, a decreased risk of cognitive impairment was observed in participants living in urban areas compared with those living in rural areas (OR = 0.57, 95% CI, 0.47–0.69; $p < 0.001$) and in participants with a low-alcohol consumption (less than once a month) compared with those who never consumed alcohol (OR = 0.69, 95% CI, 0.51–0.94; $p = 0.02$), indicating low risk of cognitive decline.

Discussion

In this nationwide cross-sectional study, we estimated the prevalence and associated risk factors for cognitive impairments in the Chinese elderly population. The highest prevalence of cognitive impairments was found in the southwest region of China, and the lowest was found in the north region, indicating regional differences. Several associated risk factors, including marital status, urban or rural residence, sleep and nap durations, depression, and alcohol consumption, were identified.

With regard to aging, the global elderly population is growing rapidly, especially in mainland China. According to China's Seventh National Population Census in 2020, the

10.3389/fpubh.2022.1032666

TABLE 2 The associated factors and adjusted ORs.

Characteristics	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age groups				
60–70 years	1.00 (reference)	-	1.00 (reference)	-
70–80 years	1.18 (0.99–1.40)	0.063	1.08 (0.90–1.30)	0.398
>80 years	1.82 (1.27–2.60)	<0.001	1.61 (1.11–2.34)	0.013
Gender				
Male	1.00 (reference)	-	-	-
Female	1.08 (1.92–2.60)	0.362	-	-
Marital status				
Married with spouse present	1.00 (reference)	-	1.00 (reference)	-
Others	1.51 (1.26–1.82)	<0.001	1.39 (1.15–1.70)	0.001
Residence				
Central of City/Town	0.52 (0.43–0.63)	<0.001	0.57 (0.47–0.69)	<0.001
Urban-Rural Integration Zone	0.67 (0.50–0.90)	0.007	0.75 (0.56–1.01)	0.061
Rural	1.00 (reference)	-	1.00 (reference)	-
Cigarette consumption				
Yes	1.00 (reference)	-	-	-
No	0.93 (0.79–1.08)	0.339	-	-
Alcohol consumption				
More than Once a Month	0.84 (0.71–0.99)	0.045	0.89 (0.74–1.06)	0.175
Less than Once a Month	0.65 (0.48–0.88)	0.005	0.69 (0.51–0.94)	0.02
Never	1.00 (reference)	-	1.00 (reference)	-
Nap duration				
≤30 min	1.17 (0.98–1.41)	0.09	1.13 (0.93–1.36)	0.225
30–60 min	1.00 (reference)	-	1.00 (reference)	-
60–90 min	1.39 (0.99–1.95)	0.051	1.36 (0.97–1.92)	0.078
≥90 min	1.73 (1.35–2.21)	<0.001	1.54 (1.20–1.98)	0.001
Sleep duration				
≤6 h	1.11 (0.94–1.31)	0.23	1.02 (0.85–1.21)	0.87
6–8 h	1.00 (reference)	-	1.00 (reference)	-
≥8 h	2.09 (1.57–2.77)	<0.001	1.73 (1.29–2.31)	<0.001
Depression				
Yes	1.79 (1.53–2.10)	<0.001	1.67 (1.41–1.97)	<0.001
No	1.00 (reference)	-	1.00 (reference)	-
Self-reported hypertension				
Yes	1.14 (0.91–1.45)	0.257	-	-
No	1.00 (reference)	-	-	-
Diabetes				
Yes	1.06 (0.77–1.47)	0.714	-	-
No	1.00 (reference)	-	-	-
Arthritis				
Yes	1.16 (0.86–1.56)	0.322	-	-
No	1.00 (reference)	-	-	-
Digestive diseases				
Yes	0.87 (0.64–1.17)	0.349	-	-
No	1.00 (reference)	-	-	-
Kidney diseases				
Yes	1.12 (0.78–1.60)	0.538	-	-
No	1.00 (reference)	-	-	-
Liver diseases				
Yes	0.62 (0.40–0.98)	0.04	0.65 (0.41–1.03)	0.064
No	1.00 (reference)	-	1.00 (reference)	-
Stroke				
Yes	0.97 (0.71–1.34)	0.871	-	-
No	1.00 (reference)	-	-	-

Logistic regression was adopted to identify the associated independent factors of cognitive impairment. All plausible variables with P < 0.05 in univariate testing were subjected to further multivariate testing. The crude ORs were calculated in univariate regression, and the adjusted ORs were recorded using multivariate regression. OR, Odds Ratio; CI, Confidence Interval.

number of elderly people over 60 years has reached 264.02 million, accounting for 18.7% of the total population (23). Rapid growth in the elderly population has stimulated interest in elucidating the causes of cognitive impairments and strategies for preventing them. Lu (16) conducted a study in Ji County of Tianjing (a rural area of northern China) and suggested that the prevalence of cognitive impairment is 38.3% (27.8% MCI and 10.5% dementia) in the overall population aged 60 years or older. After studying 96 sites from 12 provinces, Jia (6) suggested that the prevalence of cognitive impairment was 21.5% (15.5% MCI and 6.0% dementia) in the overall population aged 60 years

or older in 2015–2018. A meta-analysis comprising 48 studies with 102,906 participants reported that the overall prevalence of MCI is 14.71% in Chinese people aged 60 years or older (24). A meta-analysis comprising 96 studies reported that the overall prevalence of dementia is 5.3% in Chinese people aged 60 years or older (25). The CHARLS national survey covers 150 counties or districts (a total of 450 villages or resident committees) from 28 provinces from 2018 to 2019. These data were used in estimating the nationwide prevalence of cognitive impairments in the Chinese elderly population. The present study estimated the nationwide prevalence of cognitive impairments (MCI and dementia) at 22.24% in participants aged 60 years and older, revealing prevalence similar to that presented by most reports from other populations in China (6, 24, 25), the United States (16.0%−22.2%) (26), and South Korea (24.1%) (27).

This study found an apparent geographical variation in the prevalence of cognitive impairments in China. As shown in Figure 2, the results of prevalence distribution suggests that the incidence in western China (southwest and northwest regions) was the highest, and the prevalence in the southwest region was 1.81 times that in the north region. A meta-analysis reported that the pooled prevalence of dementia was the highest in western China (9.6%), intermediate in northern China (5.4%), and lowest in central China (3.8%) and south China (3.7%) (25). Another meta-analysis reported that the pooled prevalence of MCI was higher in western China (14.33%) than in eastern China (13.41%) (24). Dietary differences may contribute to this discrepancy. The daily diet of participants living in the north regions contains considerable amounts of milk, dairy products, and flour-based food, whereas participants living in the southwest regions consume more fruits and rice-based diet; dairy products have been confirmed to have a protective effect against cognitive impairment (28). Other differences may be attributed to the uneven economic, educational development, and different living habits across regions in China.

The identification of specific risk factors is crucial for the prevention of cognitive impairments. The prevalence of cognitive impairment was higher among elderly people, females, people who are not married or cohabitating, and people living in rural areas or western China, consistent with the findings of some previous studies (6–8, 10, 24). The present study provides further evidence in support of these risk factors. The results showed that depression is associated with the high prevalence of MCI in the Chinese elderly population, consistent with previous findings (14, 23). Jia et al. (6) showed high prevalence of cognitive impairment in the Chinese elderly population with hypertension (odds ratio: dementia = 1.86; MCI = 1.62), hyperlipidemia (dementia = 1.87; MCI = 1.29), diabetes (dementia = 2.14; MCI = 1.44), heart disease (dementia = 1.98; MCI = 1.17), and cerebrovascular disease (dementia = 5.44; MCI = 1.49), but the above risk factors were not found in the present study. Medical histories were mainly based on the self-reports of the respondents, which may lead to deviation from the present results.

The present study suggested that some other risk factors are modifiable, including nap duration, sleep duration, and alcohol consumption, which are rarely explored. Sleep disturbances are common in the elderly, and approximately 50% of people aged over 65 years reported a chronic sleep complaint (29). Many studies have examined the associations between sleep duration and cognitive impairment. Moreover, The results also suggest that long durations of napping ($\geq$90 min) and long sleeping ($\geq$8 h) are associated with high prevalence of cognitive impairment and an afternoon nap duration of 30–60 min and night sleep of 6–8 h are associated with enhanced cognitive function. The exact biological mechanisms linking excessive sleep nap duration to cognitive impairment remain unclear (30). Further studies are needed to examine whether excessive sleeping or napping is a subtle marker of cognitive impairment in otherwise healthy elderly individuals.

Epidemiological studies have indicated that excessive alcohol consumption can induce cognitive impairments, whereas moderate consumption may reduce the risks for cognitive impairment in the elderly (31, 32). The present study suggested a similar result, that is, consuming alcohol less than once a month is associated with a lower prevalence of cognitive impairment (OR = 0.65, p = 0.005) than that in participant who never consumed alcohol. The potential factors linking low alcohol consumption to cognitive function have been attributed to flavonoids or other antioxidants, which may reduce the risk of cognitive impairment (33).

The present study has some limitations. First, we did not classify MCI and dementia. Clinical diagnosis based on the MMSE, the Montreal Cognitive Assessment, Clinical Dementia Rating score, magnetic resonance imaging, or computed tomography is necessary for MCI and dementia (6). MMSE as a single diagnostic tool is insufficient to diagnose MCI and dementia, and different diagnostic confirmation tools might result in different prevalence rates. Second, gender selection bias was found; more male participants were selected. Third, relying on the participants' self-reporting, the medical histories, nap durations, and sleep durations might not be accurate measures and might generate bias. In the evaluation of covariates, we did not employ objective monitoring devices because collecting data from a large cohort is difficult. Additionally, this cross-sectional study cannot establish causal relationships between the identified associated factors and cognitive impairment, and future longitudinal studies are needed to clarify these associations.

Conclusion

In this nationwide cross-sectional study, the overall prevalence of cognitive impairments was 22.24% in the

participants aged 60 years or over. The prevalence varied among age groups, living areas, regions and between genders. The results revealed that the modifiable risk factors for cognitive impairment were as follows: not married or cohabitating, rural residence, long duration of napping (≥90 min), long duration of sleep (≥8 h), and depression. Thus, preventive strategies for cognitive impairment are needed to improve cognitive function.

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.

Ethics statement

The CHARLS study was approved by Research Ethics Committees of Peking University (IRB00001052-13074). The patients/participants provided their written informed consent to participate in this study.

Author contributions

FQ and ML wrote the manuscript and participated in all aspects of this research. XC edited, reviewed, and supervised this research. YX, NZ, YD, and WK reviewed the final article. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (82071494 and 81871043) and National Key R&D Program of China (2022YFC2009902/2022YFC2009900).

Acknowledgments

The authors express their thanks to the Office of China Health and Retirement Longitudinal Study (CHARLS).

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/fpubh.2022.1032666/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Flowchart of data cleansing. MMSE: Mini-Mental State Examination.

SUPPLEMENTARY FIGURE 2
Matrix of the Spearman's correlation coefficient.

References

1. Calia C, Johnson H, Cristea M. Cross-cultural representations of dementia: an exploratory study. *J Glob Health.* (2019) 9:011001. doi: 10.7189/jogh.09.011001

2. Bhatt J, Comas Herrera A, Amico F, Farina N, Wong J, Orange J. *The World Alzheimer Report 2019: Attitudes to Dementia*. London: Alzheimer's Disease International (2019). p. 1–166.

3. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, et al. Prevalence of cognitive impairment without dementia in the United States. *Ann Intern Med.* (2008) 148:427–34. doi: 10.7326/0003-4819-148-6-200803180-00005

4. van Harten AC, Mielke MM, Swenson-Dravis DM, Hagen CE, Edwards KK, Roberts RO, et al. Subjective cognitive decline and risk of MCI: The Mayo Clinic Study of Aging. *Neurology.* (2018) 91:e300–12. doi: 10.1212/WNL.0000000000005863

5. Espinosa A, Alegret M, Valero S, Vinyes-JunquéG, Hernández I, Mauleón A, et al. A longitudinal follow-up of 550 mild cognitive impairment patients: evidence for large conversion to dementia rates and detection of major risk factors involved. *J Alzheimers Dis.* (2013) 34:769–80. doi: 10.3233/JAD-122002

6. Jia L, Du Y, Chu L, Zhang Z, Li F, Lyu D, et al. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: a cross-sectional study. *Lancet Public Health.* (2020) 5:e661–71. doi: 10.1016/S2468-2667(20)30185-7

7. Ding D, Zhao Q, Guo Q, Meng H, Wang B, Luo J, et al. Prevalence of mild cognitive impairment in an urban community in China: a cross-sectional analysis of the Shanghai Aging Study. *Alzheimers Dement.* (2015) 11:300-9.e2. doi: 10.1016/j.jalz.2013.11.002

8. Li X, Ma C, Zhang J, Liang Y, Chen Y, Chen K, et al. Prevalence of and potential risk factors for mild cognitive impairment in community-dwelling residents of Beijing. *J Am Geriatr Soc.* (2013) 61:2111–9. doi: 10.1111/jgs.12552

9. Li W, Sun L, Xiao S. Prevalence, Incidence, Influence Factors, and Cognitive Characteristics of Amnestic Mild Cognitive Impairment Among Older Adult: A 1-Year Follow-Up Study in China. *Front Psychiatry.* (2020) 11:75. doi: 10.3389/fpsyt.2020.00075

10. Xie F, Xie L. COPD and the risk of mild cognitive impairment and dementia: a cohort study based on the Chinese Longitudinal Health Longevity Survey. *Int J Chron Obstruct Pulmon Dis.* (2019) 14:403–8. doi: 10.2147/COPD.S194277

11. Li W, Liu E, Balezentis T, Jin H, Streimikiene D. Association between socioeconomic welfare and depression among older adults: evidence from the China health and Retirement Longitudinal Study. *Soc Sci Med.* (2021) 275:113814. doi: 10.1016/j.socscimed.2021.113814

12. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). *Int J Epidemiol.* (2014) 43:61–8. doi: 10.1093/ije/dys203

13. Li H, Jia J, Yang Z. Mini-mental state examination in elderly Chinese: a population-based normative study. *J Alzheimers Dis.* (2016) 53:487–96. doi: 10.3233/JAD-160119

14. Zhou L, Ma X, Wang W. Relationship between cognitive performance and depressive symptoms in Chinese older adults: the China health and retirement longitudinal study (CHARLS). *J Affect Disord.* (2021) 281:454–8. doi: 10.1016/j.jad.2020.12.059

15. Yuan M, Qin F, Xu C, Fang Y. Heterogeneous adverse childhood experiences and cognitive function in an elderly Chinese population: a cohort study. *BMJ Open.* (2022) 12:e060477. doi: 10.1136/bmjopen-2021-060477

16. Lu H, Wang XD, Shi Z, Yue W, Zhang Y, Liu S, et al. Comparative analysis of cognitive impairment prevalence and its etiological subtypes in a rural area of northern China between 2010 and 2015. *Sci Rep.* (2019) 9:851. doi: 10.1038/s41598-018-37286-z

17. Xiong Y, Zhang Y, Zhang F, Wu C, Qin F, Yuan J. Prevalence and associated factors of metabolic syndrome in Chinese middle-aged and elderly population: a national cross-sectional study. *Aging Male.* (2021) 24:148–59. doi: 10.1080/13685538.2021.1998432

18. Xie B, Wang J, Li X, Zhang J, Chen M. Association between daytime napping duration and depression in middle-aged and elderly Chinese: evidence from the China Health and Retirement Longitudinal Study (CHARLS): a cross-sectional study in China. *Medicine.* (2020) 99:e22686. doi: 10.1097/MD.0000000000022686

19. Chou YT, Cheng HJ, Wu JS, Yang YC, Chou CY, Chang CJ, et al. The association of sleep duration and sleep quality with non-alcoholic fatty liver disease in a Taiwanese population. *Obes Res Clin Pract.* (2018) 12:500–5. doi: 10.1016/j.orcp.2018.05.002

20. Xiong Y, Zhang YC, Jin T, Qin F, Yuan JH. Depressive males have higher odds of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a retrospective cohort study based on propensity score matching. *Asian J Androl.* (2021) 23:633–9. doi: 10.4103/aja.aja_12_21

21. Zhang W, Zhang X, Li H, Wu F, Wang H, Zhao M, et al. Prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) in China: results from the China Health and Retirement Longitudinal Study. *BMJ Open.* (2019) 9:e022792. doi: 10.1136/bmjopen-2018-022792

22. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Abingdon: Routledge (2013).

23. Xu WQ, Lin LH, Ding KR, Ke YF, Huang JH, Hou CL, et al. The role of depression and anxiety in the relationship between poor sleep quality and subjective cognitive decline in Chinese elderly: Exploring parallel, serial, and moderated mediation. *J Affect Disord.* (2021) 294:464–71. doi: 10.1016/j.jad.2021.07.063

24. Xue J, Li J, Liang J, Chen S. The prevalence of mild cognitive impairment in China: a systematic review. *Aging Dis.* (2018) 9:706–15. doi: 10.14336/AD.2017.0928

25. Wu YT, Ali GC, Guerchet M, Prina AM, Chan KY, Prince M, et al. Prevalence of dementia in mainland China, Hong Kong and Taiwan: an updated systematic review and meta-analysis. *Int J Epidemiol.* (2018) 47:709–19. doi: 10.1093/ije/dyy007

26. Brookmeyer R, Evans DA, Hebert L, Langa KM, Heeringa SG, Plassman BL, et al. National estimates of the prevalence of Alzheimer's disease in the United States. *Alzheimers Dement.* (2011) 7:61–73. doi: 10.1016/j.jalz.2010.11.007

27. Kim YJ, Han JW, So YS, Seo JY, Kim KY, Kim KW. Prevalence and trends of dementia in Korea: a systematic review and meta-analysis. *J Korean Med Sci.* (2014) 29:903–12. doi: 10.3346/jkms.2014.29.7.903

28. Talaei M, Feng L, Yuan JM, Pan A, Koh WP. Dairy, soy, and calcium consumption and risk of cognitive impairment: the Singapore Chinese Health Study. *Eur J Nutr.* (2020) 59:1541–52. doi: 10.1007/s00394-019-02010-8

29. Neikrug AB, Ancoli-Israel S. Sleep disorders in the older adult - a mini-review. *Gerontology.* (2010) 56:181–9. doi: 10.1159/000236900

30. Grandner MA, Sands-Lincoln MR, Pak VM, Garland SN. Sleep duration, cardiovascular disease, and proinflammatory biomarkers. *Nat Sci Sleep.* (2013) 5:93–107. doi: 10.2147/NSS.S31063

31. GBD 2020 Alcohol Collaborators. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. *Lancet.* (2022) 400:185–235. doi: 10.1016/S0140-6736(22)00847-9

32. Ruitenberg A, van Swieten JC, Witteman JC, Mehta KM, van Duijn CM, Hofman A, et al. Alcohol consumption and risk for dementia: the rotterdam study. *Lancet.* (2002) 359:281–6. doi: 10.1016/S0140-6736(02)07493-7

33. Brust JC. Wine, flavonoids, and the 'water of life'. *Neurology.* (2002) 59:1300–1. doi: 10.1212/WNL.59.9.1300

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 09 January 2023
DOI 10.3389/fpubh.2022.1069970

OPEN ACCESS

EDITED BY
Xin Jiang,
Shen Zhen People's Hospital, China

REVIEWED BY
Yijian Yang,
The Chinese University of Hong Kong, China
Irini Patsaki,
University of West Attica, Greece

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

SPECIALTY SECTION
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

RECEIVED 14 October 2022
ACCEPTED 05 December 2022
PUBLISHED 09 January 2023

CITATION
Ho V, Chan YH and Merchant RA (2023) Patterns of improvement in functional ability and predictors of responders to dual-task exercise: A latent class analysis.
Front. Public Health 10:1069970.
doi: 10.3389/fpubh.2022.1069970

Patterns of improvement in functional ability and predictors of responders to dual-task exercise: A latent class analysis

Vanda Ho[1], Yiong Huak Chan[2] and Reshma Aziz Merchant[1,3]*

[1]Division of Geriatric Medicine, Department of Medicine, National University Hospital, Singapore, Singapore, [2]Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [3]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

Background: Exercise is the pillar for healthy aging. "Non-responders" may be due to a mismatch in exercise prescription. A latent cluster analysis (LCA) profile can be useful to uncover subpopulations sharing similar profiles or outcomes. We aim to use the LCA to develop a response prediction model for older adults who would benefit from The Healthy Aging Promotion Program for You, a community-embedded dual-task exercise program.

Methods: A total of 197 participants completed the 3-month follow-up, and the complete data were available for 136 community-dwelling older adults. Inclusion criteria were age ≥60 years, pre-frail or frail and ambulant, mild cognitive impairment, and ability to provide consent. Data collected include demographics, education, falls, physical function (Katz ADL scale and Lawton's IADL scale), physical activity (rapid assessment of physical activity), cognition (Montreal Cognitive Assessment; MoCA), frailty (FRAIL scale), and perceived health, pain, anxiety/depression, fear of falling, and social isolation (Lubben Social Network Scale). The body mass index (BMI), handgrip strength, and short physical performance battery (SPPB) were measured. Those who improved in frailty, anxiety/depression, pain, Lubben, MoCA, SPPB, fear-of-falling, physical activity, falls, and HGS were classified as responders.

Results: The mean age was 74.7 years, BMI 23.5 kg/m^2, 23.5% were male, 96.3% were of Chinese ethnicity, 61% were pre-frail, education level of 4.3 years, and the MoCA score of 23.3 ± 4.8. Two clusters were identified: non-responders (61.8%) and responders (38.2%). Responders had significant improvement in cognition (44.2% *vs.* 0, $p < 0.001$) and SPPB (gait:28.8% *vs.* 0, $p < 0.001$; balance:42.3% *vs.* 15.5%, $p = 0.001$; chair-stand:65.4% *vs.* 4.8%, $p < 0.001$). Responders were significantly older (76.9 *vs.* 73.3 years, $p = 0.005$), had higher BMI (24.8 *vs.* 22.8 kg/m^2, $p = 0.007$), lower education (3.4 *vs.* 4.9 years, $p = 0.021$), lower MoCA scores (21.8 *vs.* 24.3, $p = 0.002$), and lower SPPB scores (8.7 *vs.* 10.6, $p < 0.001$). The predictive variables for the responder cluster were age ≥75 years, BMI ≥23 kg/m^2, robust, no anxiety, pain, fear of falling, MoCA ≤22, Lubben ≤12, SPPB score: chair-stand ≤2, balance ≤2, gait >2, handgrip strength <20 kg, no falls and RAPA >3. With an optimal cut-off of ≥12, this prediction model had

sensitivity of 76.9%, specificity of 70.2%, positive predictive value 61.5%, and negative predictive value of 83.1%.

Conclusion: Response to dual-task exercise was influenced by age, SPPB, BMI, and cognition. Prospective longitudinal studies are needed to validate this LCA model and guide the development of public health strategies.

KEYWORDS

functional ability, dual-task exercises, latent class analysis, responders, physical frailty, cognitive frailty

Introduction

Population aging is a global phenomenon where the number of people aged 80 years and over is projected to triple from 143 million in 2019 to 426 million in 2050 (1). Population aging impacts many sectors including the labor workforce and health and social care cost. In 2015, the World Health Organization proposed the definition of healthy aging as "the process of developing and maintaining the functional ability that enables wellbeing" (2). Functional ability depends on the interaction between intrinsic capacity and the environment. Intrinsic capacity (IC) refers to the sum of physical and cognitive functions and includes the assessment of five domains including cognition, vitality, mobility, psychological, and sensory functions.

Aging is a risk factor for chronic disease and together with a sedentary lifestyle is associated with sarcopenia, frailty, dementia, and disability. Exercise and physical activity have an important role in the prevention of disease and/or treatment for conditions such as frailty or cognitive impairment where no pharmacotherapy is available (3). Exercise influences the trajectory of aging through the release of myokines and exerkines which acts at molecular, cellular, and organ levels (4). Unlike specific pharmacotherapy targeting a single disease or organ, exercise is a therapy directed at the complete physiological system. Like other pharmacotherapies, exercise needs to be prescribed based on intended outcomes and personalized with incremental adjustments similar to other medical treatments (3). Multicomponent exercise programs which include cognitive tasks have been shown to improve both physical and cognitive function (5–9).

The Healthy Aging Promotion Program for You (HAPPY) program adapted from *Cognicise* which originated from the National Center of Geriatrics and Gerontology in Nagoya Japan was started in 2017 to engage older adults with pre-frailty, frailty, and/or cognitive impairment in dual-task exercise in the community (6). The program aimed to improve function and cognition and to reduce frailty prevalence and social isolation among community-dwelling older people. Eighty different dual-task exercise combinations of varying intensities with obstacle navigations were co-created by the health coaches, volunteers, and participants (Figure 1). The exercises are conducted for 60 min two times weekly, and either led by trained health coaches or volunteers. The dual-task components comprised 40 min of the total exercise program. Further details can be found in Merchant et al. (6). The HAPPY program has been found to be effective in reducing pain, and improving quality of life, and physical and cognitive function in older adults (9, 10). Through multisystem collaboration, the program was expanded to more than 70 sites in Singapore prior to the COVID-19 pandemic. There were significant improvements in robustness, cognition, social isolation, and perceived health (6).

The response to exercise in older adults has been heterogeneous and many studies classify them as "responder," "non-responder," or "adverse responder" (3, 11). The most plausible explanation for the "non-responder," or "adverse responder" would be the lack of appropriate type, dose, and intensity of exercise prescription for the intended outcomes (11). A wide variety of exercise prescriptions has been explored in literature, of which one of the more promising ones is dual-task exercise. When incorporated with social activities, dual-task exercise has been shown to reverse cognitive and physical frailty, mild cognitive impairment, and reduce social isolation (9, 12–15). To date, most studies on multicomponent and/or dual-task exercise interventions have focused on the improvement of single factors such as physical function and/or cognitive function. However, the definition of functional ability is broader than that and refers to both physical and cognitive function as well as the interaction with the surrounding environment, which may be affected by the social network, mood, and pain among other factors. Methodologies such as latent cluster analysis (LCA) profile can be useful to uncover subpopulations sharing similar baseline profiles or outcomes, and this can assist in personalizing future prescriptions of type and intensity of exercises depending on the intended outcome. LCA is a type of mixture model, which is increasingly used in behavioral sciences for the identification and understanding of latent subpopulations (16). It has been employed in assessing lifestyle practices of behaviors

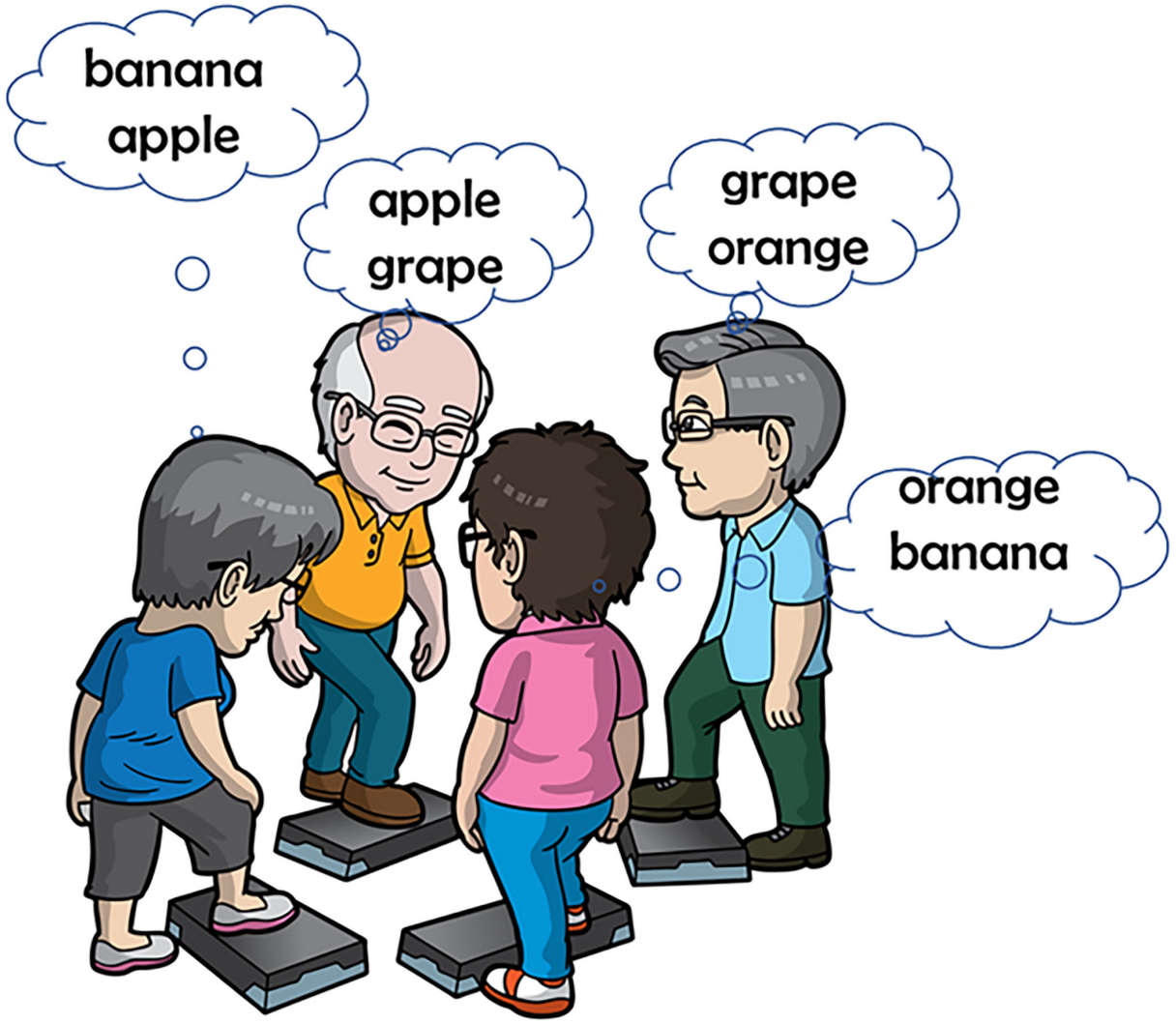


FIGURE 1
Example of a dual task exercise within the HAPPY program. Participants have to remember one and think of name of another fruit while doing stepping exercises.

commonly adopted by adolescents including physical activity (17), and patterns of stages of change for regular exercise over time for participants in a lifestyle intervention (18). Response patterns can be observed on specific characteristics related to a set of latent classes, and this allows focusing on features of individuals who may be heterogeneous (19), as we often see in older adults. Therefore, the aim of the present study is 3-fold. First, we used the LCA to determine patterns of functional ability among older adults who participated in the HAPPY program. Second, we examined the predictors of participants in the cluster with significant improvement in functional ability. Third, we developed a predictive scoring of participants in the cluster with significant improvement in functional ability.

Methods

Out of the 197 participants who completed the 3-month follow-up for the HAPPY program, complete data for the LCA was available for 136 community-dwelling older adults. We conducted a single group pre-post study design, delivered across multiple sites with a standardized program outline. The exercises were conducted for 60 min two times a week on average with a 72% attendance rate. More than 80 different dual-task exercises of different complexity were co-created and led by health coaches and trained volunteers. The dual-task components comprised 40 min of the total exercise program. Participants continued to attend the HAPPY exercise program during the 3-month follow-up. At one of the HAPPY exercise sessions at the

3-month mark, participants are asked to complete the follow-up questionnaire and physical assessments. Written consent was obtained from all recruited participants and the protocol was approved by the National Healthcare Group (NHG), Domain Specific Review Board (DSRB), Singapore.

The inclusion criteria were (1) aged ≥60 years old, (2) pre-frail or frail and ambulant, (3) have mild cognitive impairment defined by the absence of dementia and Chinese Mini-Mental State Examination between 18 and 26, and (4) the ability to provide informed consent. Participants were excluded if they were (1) wheelchair-bound or bedridden, (2) had underlying severe cognitive impairment, or (3) nursing home residents.

An interview questionnaire was administered by trained research assistants at baseline and 3 months on demographics, chronic diseases, education, number of falls, physical function, physical activity, cognition, frailty, anxiety/depression, pain, quality of life (QOL), perceived health, fear of falling and social isolation. Perceived health was assessed using the Euro-QoL Visual Analog Scale (EQ VAS) and QoL using Euro-QoL EQ-5D-5L questionnaire, respectively (20). The EQ-5D-5L consists of five different dimensions of health including mobility, self-care, usual activities, pain, and anxiety/depression. Pain intensity was derived from the EQ-5D-5L and classified into three categories: no pain, mild pain (mild), and moderate (moderate to extreme pain). Anxiety/depression was similarly derived from EQ-5D-5L and classified into three categories: no anxiety/depression, mild (mild anxiety/depression), and moderate (moderate to extreme anxiety/depression).

The Montreal Cognitive Assessment (MoCA) was used to assess cognitive status, and a cut-off score of ≤22 was used to define cognitive impairment (21). The FRAIL scale measuring fatigue, resistance, aerobics, number of illnesses, and loss of weight with a maximum score of 5 was used to assess frailty (22). Pre-frail was defined as 1–2, frail 3–5, and robust 0. ADL was assessed using the Katz ADL scale (23) and IADL using Lawton's IADL scale (24). The Rapid Assessment of Physical Activity tool (RAPA) was used to assess physical activity (25). This tool consists of a nine-item questionnaire assessing strength, flexibility, and level and intensity of physical activity. Fear of falling was assessed using a single question, "Are you afraid of falling?" to which participants had three responses to choose from; "no," "yes" or "yes a lot". "Yes" or "yes a lot" were categorized as fear of falling (26). Social isolation was measured using the 6-item Lubben Social Network Scale (LSNS-6) (27). It measures size, closeness, and frequency of contact with friends and family members with a total scale score ranging from 0 to 30, and a score below 12 was classified as at risk of social isolation.

Physical performance tests included assessment of body mass index (BMI), maximum handgrip strength, and the Short Physical Performance Battery test (SPPB). Handgrip strength was measured using a Jamar hand dynamometer on the dominant arm in the seated position with the elbow flexed at 90° and maximum handgrip strength was recorded. Poor handgrip strength was based on cut-offs of 28 kg for men and 18 kg for women as defined by the 2019 Asian Working Group for Sarcopenia (28). The SPPB includes three components (balance, gait speed, and chair stand) with a maximum score of 12 points (4 points per component) (29).

TABLE 1 Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) of the latent class analysis.

Number of clusters	AIC	BIC	BIC/AIC
2[#]	1,727.79	1,797.69	1.040
3	1,730.18	1,829.21	1.057
4	1,725.16	1,853.32	1.074

[#]Optimal number of clusters with lowest BIC/AIC.

Development of response patterns using LCA

The variables used to explore the number of response clusters were obtained from prior published studies which include frailty (30), anxiety (31), social isolation (32), cognitive impairment (33), pain (10), physical performance (32), and fear of falling (34). Two to four participation clusters were examined and based on the lowest Consistent Akaike Information Criterion (AIC) and the Bayesian–Schwarz Information Criterion (BIC) (9), a two-cluster solution was considered to be optimal (Table 1).

Pattern of responders

An improved response, "responders" to dual-task exercise, was defined by at least 1 category improvement on frailty, anxiety/depression or pain, 1 point improvement in any of the SPPB domains (gait, chair stand or balance), Lubben (≥12), MoCA (≥22), reduction of fear of falling; reduction in the number of falls by at least 1, at least 10% improvement from baseline in handgrip strength and RAPA. If no improvement was seen in any category, participants were considered "non-responders." These variables were selected based on the World Health Organization (WHO) approach to healthy aging white paper (35) and previous publications from the HAPPY program (9, 10, 32).

Sample size

Postulating a moderate Nagelkerke R-sq of 0.7, with a shrinkage factor of 0.9 to account for overfitting, for 25 variables to be used in a logistic regression analysis, the required sample size is 120 (36).

Statistical analysis

Analyses were performed using STATA 17.0 with statistical significance set at $p < 0.05$. LCA was used on cognitive, psychological, and physical characteristics to determine responder clusters. The characteristics of participants in the different responder clusters were compared using the chi-square test for categorical variables and the *t*-test for normally-distributed continuous variables otherwise the Mann–Whitney *U*-test was performed. Predictors for the responder cluster were assessed using multivariate logistic regression, and odds ratios with 95% confidence intervals were presented. A prediction model on cluster membership with odds ratios as the weighted score was developed, and a receiver operating curve (ROC) was constructed to evaluate the discriminative ability of the prediction model.

Results

Background characteristics of study participants

The background characteristics of the participants are shown in Table 2. The mean age was 74.7 ± 7.4 years, with 131 (96.3%) of the participants being of Chinese ethnicity and 32 (23.5%) being male. The mean BMI was 23.5 ± 4.3 kg/m^2. Among the participants, the health rating was 71.4 ± 14.3, with 82 (60.3%) having hypertension, 73 (53.7%) having hyperlipidemia, and 32 (23.5%) having diabetes. Almost a quarter of them (23.5%) lived alone, and 45.6% reported being at risk of social isolation. Functionally, 10 (7.4%) needed help with at least 1 ADL and 20 (14.7%) needed help with IADL, 49 (36%) were robust and 4 (2.9%) were frail. The mean number of falls was 0.48 ± 0.95, and 47 (34.6%) reported being very afraid of falls. Among the participants, 73 (53.7%) reported no pain, 111 (81.6%) had no anxiety or depression and 53 (39.0%) had cognitive impairment with MoCA <22. The mean RAPA score was 3.4 ± 1.0. In terms of physical function, the maximum handgrip strength was 20.8 ± 5.6 kg, the mean gait speed was 1.14 ± 0.28 m/s, the mean SPPB score was 9.9 ± 2.1, and 86 participants (63.2%) scored above 9.

Responders were significantly older (76.9 ± 6.4 *vs.* 73.3 ± 7.7 years, $p = 0.005$), had a higher BMI (24.8 ± 4.6 *vs.* 22.8 ± 3.9 kg/m^2, $p = 0.007$), lower levels of education (3.4 ± 3.3 years *vs.* 4.9 ± 3.8, $p = 0.021$) and correspondingly lower MoCA scores (21.8 ± 4.4 *vs.* 24.3 ± 4.8, $p = 0.002$), and poorer physical performance on SPPB (8.7 ± 2.0 *vs.* 10.6 ± 1.8, $p < 0.001$) which was seen consistently across all categories of balance, gait and chair-stand domains.

Co-variates, LCA, and response patterns

A total of 136 participants were divided into two response clusters: non-responders ($n = 84$, 61.8%) and responders ($n = 52$, 38.2%) (Table 3). Among the study participants, 56 (41.2%) had improvement in the frailty category, and 23 (16.9%) had improvement in MoCA score to above 22. For physical function, on SPPB: 15 (11.0%) had improvement in gait, 35 (25.7%) had improvement in balance, and 38 (27.9%) had improvement

TABLE 2 Variables used in latent class analysis.

Improvement[#]	Total ($n = 136$)	Non-responders ($n = 84$; 61.8%)	Responders ($n = 52$; 38.2%)	*p*-value
Frailty	56 (41.2)	37 (44.0)	19 (36.5)	0.387
Anxiety	14 (10.3)	11 (13.1)	3 (5.8)	0.172
Lubben (cutoff 12)	29 (21.3)	19 (22.6)	10 (19.2)	0.639
MoCA (cutoff 22)	23 (16.9)	0 (0.0)	23 (44.2)	<0.001
Pain	39 (28.7)	21 (25.0)	18 (34.6)	0.228
SPPB gait	15 (11.0)	0 (0.0)	15 (28.8)	<0.001
SPPB balance	35 (25.7)	13 (15.5)	22 (42.3)	0.001
SPPB chair stand	38 (27.9)	4 (4.8)	34 (65.4)	<0.001
Handgrip strength ≥ 10%	29 (21.3)	22 (26.2)	7 (13.5)	0.078
Falls reduced ≥1	36 (26.5)	24 (28.6)	12 (23.1)	0.480
Fear of falling	38 (27.9)	19 (22.6)	19 (36.5)	0.079
RAPA ≥10% improvement	26 (19.1)	18 (21.4)	8 (15.4)	0.384

[#]Defined as improvement by at least 1 category or at least 10% change from baseline.
MoCA, Montreal Cognitive Assessment; SPPB, short physical performance battery; RAPA, rapid assessment of physical activity.

10.3389/fpubh.2022.1069970

TABLE 3 Baseline characteristics of participants by clusters.

Variables	Total ($n = 136$)	Non-responders ($n = 84$; 61.8%)	Responders ($n = 52$; 38.2%)	p-value
Age	74.7 ± 7.4	73.3 ± 7.7	76.9 ± 6.4	0.005
BMI (mean ± SD)	23.5 ± 4.3	22.8 ± 3.9	24.8 ± 4.6	0.007
Education (years)	4.3 ± 3.6	4.9 ± 3.8	3.4 ± 3.3	0.021
Health rating	71.4 ± 14.3	70.5 ± 13.4	72.9 ± 15.6	0.325
Ethnicity				0.322
Chinese	131 (96.3)	81 (96.4)	50 (96.2)	
Malay	3 (2.2)	1 (1.2)	2 (3.8)	
Indian	2 (1.5)	2 (2.4)	0 (0.0)	
Male gender	32 (23.5)	19 (22.6)	13 (25.0)	0.750
Living alone	32 (23.5)	18 (21.4)	14 (26.9)	0.463
Chronic disease				
Hypertension	82 (60.3)	47 (56.0)	35 (67.3)	0.188
Hyperlipidemia	73 (53.7)	44 (52.4)	29 (55.8)	0.700
Diabetes	32 (23.5)	22 (26.2)	10 (19.2)	0.352
ADL ≥ 1	10 (7.4)	5 (6.0)	5 (9.6)	0.426
IADL ≥ 1	20 (14.7)	13 (15.5)	7 (13.5)	0.747
Fear of falls				0.799
Not afraid	38 (27.9)	25 (29.8)	13 (25.0)	
A bit afraid	51 (37.5)	30 (35.7)	21 (40.4)	
Very afraid	47 (34.6)	29 (34.5)	18 (34.6)	
Number of falls	0.48 ± 0.95	0.54 ± 1.0	0.38 ± 0.87	0.370
Frailty				0.169
Robust	49 (36.0)	27 (32.1)	22 (42.3)	
Pre-frail	83 (61.0)	53 (63.1)	30 (57.7)	
Frail	4 (2.9)	4 (4.8)	0 (0.0)	
Pain				0.944
No	73 (53.7)	46 (54.8)	27 (51.9)	
Mild	50 (36.8)	30 (35.7)	20 (38.5)	
Moderate	13 (9.6)	8 (9.5)	5 (9.6)	
Lubben < 12	62 (45.6)	36 (42.9)	26 (50.0)	0.416
RAPA	3.4 ± 1.0	3.4 ± 1.0	3.5 ± 1.1	0.597
Mental health				
Anxiety/depression				0.230
No	111 (81.6)	66 (78.6)	45 (86.5)	
Mild	21 (15.4)	14 (16.7)	7 (13.5)	
Moderate	4 (2.9)	4 (4.8)	0 (0.0)	
Cognition				
MoCA (mean)	23.3 ± 4.8	24.3 ± 4.8	21.8 ± 4.4	0.002
30	9 (6.6)	9 (10.7)	0 (0.0)	0.015

(Continued)

TABLE 3 (Continued)

Variables	Total ($n = 136$)	Non-responders ($n = 84$; 61.8%)	Responders ($n = 52$; 38.2%)	p-value
≤22	53 (39.0)	23 (27.4)	30 (57.7)	<0.001
Physical function				
Handgrip strength	20.8 ± 5.6	21.4 ± 5.5	19.9 ± 5.6	0.134
Gait speed	1.14 ± 0.28	1.18 ± 0.27	1.11 ± 0.30	0.158
SPPB total (mean)	9.9 ± 2.1	10.6 ± 1.8	8.7 ± 2.0	<0.001
Balance	3.4 ± 0.9	3.5 ± 0.8	3.1 ± 1.1	0.005
Gait	3.6 ± 0.7	3.8 ± 0.5	3.4 ± 0.8	0.001
Chair stand	2.9 ± 1.1	3.3 ± 0.98	2.3 ± 1.0	<0.001
SPPB categories				<0.001
4–6	10 (7.4)	4 (4.8)	6 (11.5)	
7–9	40 (29.4)	13 (15.5)	27 (51.9)	
10–12	86 (63.2)	67 (79.8)	19 (36.5)	

Values are n (%) otherwise (mean ± SD).
BMI, body mass index; SD, standard deviation; ADL, activities of daily living; IADL, instrumental activities of daily living; RAPA, rapid assessment of physical activity; MoCA, Montreal Cognitive Assessment; SPPB, short physical performance battery.

in chair-stand timing. For handgrip strength, 29 participants (21.3%) had at least 10% improvement, and 36 participants (26.5%) had one less fall at follow-up, with a corresponding drop in fear of falling in 38 participants (27.9%). For physical activity, 26 (19.1%) had improved by at least 10% on their RAPA score. At 3 months, 29 participants (21.3%) were less socially isolated, 39 participants (28.7%) experienced less pain and 14 participants (10.3%) had less anxiety. The responder cluster had significant improvement to dual-task exercises in domains of cognition [$n = 23$ (44.2%) *vs.* 0, $p < 0.001$] and physical function, seen by improvement in scores for all aspects of SPPB [gait: $n = 15$ (28.8%) *vs.* 0, $p < 0.001$; balance $n = 22$ (42.3%) *vs.* $n = 13$ (15.5%), $p = 0.001$; chair stand: $n = 34$ (65.4%) *vs.* $n = 4$ (4.8%), $p < 0.001$, responder *vs.* non-responder cluster, respectively].

Prediction model for the relationship between response classes and functional ability

Table 4 showed the weighted scores derived from the odds ratios for the prediction of responder membership using the univariate significant variables (age and BMI) and the baseline LCA. Variables found to be significantly associated with response were age ≥75 years, BMI ≥ 23 kg/m^2, being robust, no anxiety, pain, fear of falling, MoCA ≤ 22, Lubben ≤ 12, SPPB chair-stand ≤ 2 (i.e., slow timing), SPPB balance ≤ 2 (i.e., poorer balance), SPPB gait > 2 (i.e., faster gait speed), handgrip strength < 20 kg, no falls and RAPA > 3. The higher the score, the more likely this person will benefit from a dual-task exercise. For example, participants with a score of up to 10 had at most 10% success to be of responder membership with a probability of 12.5% (Table 5). On the other hand, participants with a score of 17 or more had a 70% success to be a responder with a probability of 76.9%.

TABLE 4 Prediction model for responders and weightage scores.

Variable	Weighted score
Age ≥ 75	2
BMI ≥ 23	3
Frail (robust)	2
No anxiety	1
With pain	1
Fear of falling	1
MoCA ≤ 22	2
Lubben ≤ 12	1
SPPB chair-stand ≤ 2	4
SPPB balance ≤ 2	2
SPPB gait > 2	1
Handgrip strength < 20 kg	1
No falls	2
RAPA > 3	1
AUC	0.786 (95% CI 0.709–0.863), $p < 0.001$

BMI, body mass index; MoCA, Montreal Cognitive Assessment; RAPA, rapid assessment of physical activity; SPPB, short physical performance battery; AUC, area-under-curve.

This responder score had an area under the curve (AUC) of 0.786 (95% CI 0.709–0.863, $p < 0.001$) (Figure 2). With an

TABLE 5 Responder prediction model bands.

Band	Responder cluster membership	
	% Success	Probability of success
0–10	Up to 10%	12.5%
11–13	11–30%	42.9%
14–16	31–70%	62.5%
17 and above	>70%	76.9%

optimal (Youden index) cut-off of ≥12, this prediction model has a sensitivity of 76.9% and specificity of 70.2% (Table 5), with a positive predictive value of 61.5% and a negative predictive value of 83.1%.

Discussion

Using LCA, we were able to classify older adults participating in the HAPPY program into two clusters with slightly more than one-third belonging to the responder cluster. Responders showed significant improvement in cognition, SPPB balance, gait, and chair-stand. Responders were significantly older, had higher BMI, lower education, and lower cognitive and SPPB scores. With the increasing number of older adults, the main challenge is to prevent or delay the onset of disability while extending healthspan, the amount of time spent in relatively good health. Currently, on average, the last 10 years of a person's life are spent in poor health. Multicomponent exercise has been recognized as an effective strategy to improve frailty and dementia and delay the onset of disability (9, 12–15). Although there is strong evidence to suggest the role of exercise in primary and secondary prevention, the variability of response to different exercise modalities remains an active area of research (37). As a result, it is important to determine the predictive factors of exercise responders. Our study is one of the first few to develop predictive scoring of those belonging to the responder cluster.

Our study showed that participants who were more likely to respond to dual-task exercises were older. While the heterogeneity in response can be attributable to non-modifiable factors such as age, ethnicity, and gender, this should not be prohibitive as studies have shown proper exercise precision with the tailoring of exercise type, dose, nutrition, and possibly pharmacotherapy can help attenuate the magnitude of heterogeneity and reduce numbers of non-responders (38). Aging is associated with a decline in muscle mass, frailty, decline in cognitive reserve, and neuronal loss, and dual-task exercises may be one of the key interventions to delay the onset of disability. Exercise offers clinical benefits as both a preventive and therapeutic strategy across a wide range of illnesses and disabilities including physical and mental health, quality of life, and reduction of mortality with no age limit (3). Exercises such as Vivifrail, an individualized tailored physical activity program especially for those at risk have been shown to reverse frailty and sarcopenia, and improve SPPB scores and cognition in very elderly hospitalized patients (39). Progressive resistance training is often recommended as a strategy to improve muscle mass, neuromuscular performance, and muscle strength.

An explanation for the possible larger impact of dual-task exercise in older adults lies in the physiological and pathological changes with aging such as decline in cognition, pain, loneliness, falls and gait speed with aging. In older adults, performing other tasks while walking such as negotiating obstacles, talking, or answering the phone has a particularly negative impact on postural stability and gait speed due to difficulties in transferring attention quickly and reacting during task switching. Successful obstacle negotiation and dual tasking require planning, attention, and executive function. Preserved executive function and attention help older adults maintain dynamic balance during dual-task activity (40). With aging, there is increased reliance on cognitive resources to compensate for motor impairments during complex and challenging tasks (40). Executive functions including sustained and selective attention, response inhibition, and memory especially working memory are regulated by the prefrontal cortex and the hippocampus. Volume loss with aging leads to neuronal recruitment and reorganization with increased bilateral activation of the prefrontal cortex and widespread cortical activation including increased functional connectivity between cerebellar, motor, and cognitive regions (40–46). Simultaneous motor and cognitive exercises have shown to improve executive function, attention, baroreflex sensitivity, global cognition, gait, balance and sit-to-stand timing (6, 47).

Our study also showed that those with MoCA ≤22 had greater improvement in functional ability. Almost half of the participants in the responder cluster improved in cognition post-dual-task exercise. This finding is important as the prevalence of dementia is increasing worldwide, and there is no disease-modifying treatment for dementia at present. Kato et al. recently showed that combined physical and cognitive exercises are cost-effective in delaying or preventing dementia (48). The effects are likely synergistic as gait and cognition are closely related *via* the prefrontal cortex, and slower gait is associated with smaller hippocampal volume and prefrontal deactivation (49). In our study population, there is a suggestion of this link as well where almost one-third of the responder cluster improved in the SPPB gait domain and none in the non-responder cluster. Though there was no significant difference in the baseline gait speed between the clusters, the difference was a clinically meaningful one (29). Gait instability can lead to fear of falling and perpetuates a positive feedback cycle, as seen with the higher proportion of responders with fear of falling. Therefore, our study findings further add to the scientific literature on the importance of simultaneous motor and cognitive exercises in improving gait speed and physical function.

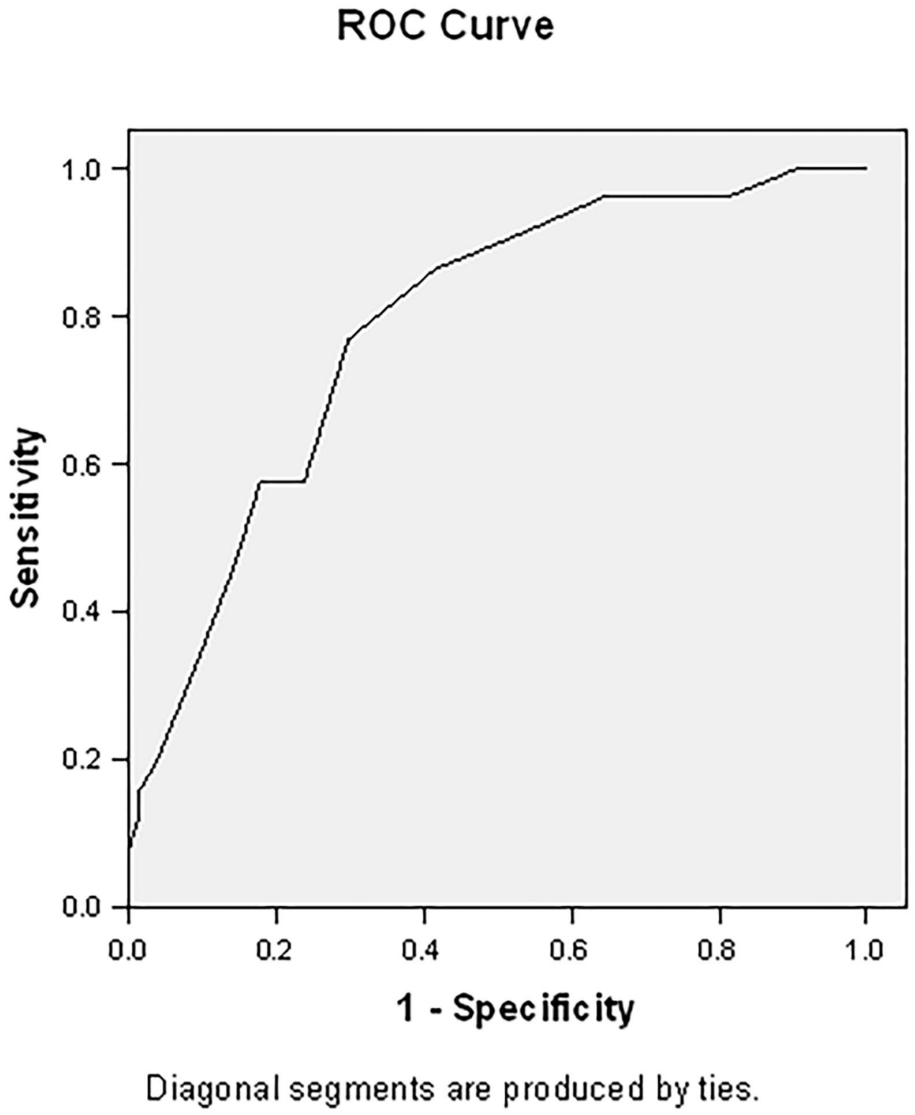


FIGURE 2
Area under the curve for responder score. The responder score has an area under the curve of 0.786 (95% CI 0.709–0.863, $p < 0.001$).

Two-thirds of our responder cluster had an SPPB score below 10 compared to only one-third of the non-responder cluster. This finding is crucial as SPPB scores below 10 are predictive of all-cause mortality (50), and scores of ≤8 for men and ≤7 for women are predictive of physical frailty and geriatric syndromes in community-dwelling older adults (51). Improvement in SPPB scores with dual-task intervention may help avert geriatric syndromes and extend healthspan. Furthermore, almost half of our cohort improved in the SPPB balance and two-thirds in the SPPB chair-stand. Participants in the responder cluster had significant improvement in all the SPPB domains. For SPPB, a change between 0.3 to 0.8 points is considered minimal change and 0.4–1.5 substantial change (29), where study participants were categorized as responded if they improved by 1 point in the relevant domains. The lack of response in the rest could be partially explained by the ceiling effect, as more than three-quarters of the non-responder cluster had SPPB scores of 9–12. Hence with dual-task training, there can be improved balance, postural stability, gait speed, cognition, and fear of falling, all of which can lead to increased functional ability and quality of life (34, 52).

The responder cluster had a higher overall BMI. Findings on high BMI and functional status in older adults have mixed results. Declaire et al. showed a negative effect of high BMI on SPPB improvement, however, most negative studies enrolled participants with BMI ≥ 30 kg/m^2 whereas the mean BMI of our responders was lower at 24.8 ± 4.6 kg/m^2 (53). High BMI may be a protective factor in older adults especially those at risk of

declining functional status and indeed has been associated with improved survivability in older adults (54). Body composition is also an important factor, as men in the high BMI group but without central obesity performed better on the functional and cognitive tests (55).

Our study showed that older adults with poorer function at baseline had better responses to the HAPPY program. This finding correlates with major exercise intervention studies such as the "Sarcopenia and Physical Frailty in Older People: Multicomponent Treatment Strategies" (SPRINTT) trial (56), which recruited participants with SPPB <10, The Lifestyle Interventions and Independence for Elders (LIFE) study (57) and Vivifrail (39), all of which produced positive results. There are multiple reasons to explain this finding. The ceiling effects of commonly used physical performance tests may mask the improvement in those with better baseline function, whereas they would be able to capture the full extent of response in those with poorer function. Additionally, those with poorer function may be more motivated to participate in interventions as they may be more aware of their deficits and feel a more compelling reason to improve and may also be able to see a bigger improvement after each session. Lastly, pre-frailty is a transition phase from robust to frailty with better functional reserves, and studies have shown that multidomain interventions are effective in this group (3).

The biggest strength of our study is that the HAPPY program was embedded in the community and successfully implemented through a multi-sectoral collaborative effort. Participant feedback was constantly sought, and some participants went on to become dual-task exercise trainers as well. Most multicomponent exercise intervention studies are conducted in trial settings with strict inclusion and exclusion criteria. LCA has often been used in the descriptive analysis of types of physical activity and exercise, often with a correlation to metabolic risk factors (16, 19). Our study demonstrates that this powerful technique can also be used in the design and evaluation of exercise programs. With the LCA, we identified often overlooked variables that are important in predicting exercise response, such as pain, fear of falling, and BMI. These factors warrant further research into their relationship with exercise response, both individually and in combination with other factors. With an AUC of 0.786, our model is significantly accurate in predicting response to a dual-task exercise program. Our study included participants from multiple sites across the country within the demographic of pre-frail community-dwelling ambulant older adults who are the vulnerable population and target group for such exercise interventions. Although it needs further validation, our predictive risk scoring holds great potential in screening and identifying vulnerable older adults who are most likely to benefit from improved adherence.

Several other limitations also warrant mention. Exercise response relies on multiple factors such as nutrition, but we lack information on nutrition except for BMI. As the dual-task exercises were tailored by the health coaches, we have no measurable information on the intensity of the physical exercise or the complexity of the cognitive tasks. Exercise intensity is integral to control as overactivation of the prefrontal cortex with failure of compensatory mechanism has shown to be associated with falls, so careful titration of the exercise regime is needed to prevent adverse events. Furthermore, many parameters were from direct interviews and may be subject to recall bias. For non-responders, participants had higher cognitive and physical function scores and poor response may partly be due to the ceiling effect of baseline SPPB and cognitive scores. With our LCA, we are not able to form causal associations, and validation studies are needed for our response prediction model. Lastly, our predictive response scoring is specific to pre-frail demographic and dual-tasking exercise programs, and hence may not be applicable to other age groups, frailer groups of older adults, or different exercise regimes.

Our study is a significant step forward in helping create public health policies at the population level and supports the recommendations by the WHO World Report on the importance of maintaining functional ability, and its role in shortening the gap between lifespan and healthspan. By identifying the factors associated with exercise response, we can better tailor public health exercise policies based on different demographics of older adults, rather than the current model of generic exercise recommendations which may paradoxically lead to injury in some, and lack of effect in others. Prospective longitudinal studies are needed to validate this LCA model, which will enable the scientific and clinical community to prescribe specific personalized targeted exercises to obtain the maximum response based on the intended outcomes.

Conclusion

Our LCA demonstrated that response to dual-task exercise in community-dwelling older adults was influenced by age, baseline SPPB domain scores, BMI, and cognition. Response prediction model may allow personalized exercise prescription with greater precision. Public health strategies targeting improving functional ability should target specific groups at the highest risk of decline and should constitute a more homogenous group to maximize the number of responders.

Data availability statement

The datasets presented in this article are not readily available because dataset will not be released beyond the study team. Requests to access the datasets should be directed to reshmaa@nuhs.edu.sg.

Ethics statement

The studies involving human participants were reviewed and approved by National Healthcare Group Domain Specific Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RM, VH, and YC contributed to the study concept, design, preparation of the manuscript, and were involved in writing and reviewing the manuscript. RM conducted the data acquisition. YC conducted the data analysis and interpretation. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by the Ministry of Health, Singapore.

Acknowledgments

The authors would like to thank Surein Sandrasageran for leading the team of health coaches in the community to conduct the HAPPY exercises.

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

References

1. United Nations. *World Population Ageing* (2019). Available online at: https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Report.pdf (accessed October 24, 2022).

2. World Health Organization. *World Report On Ageing and Health*. Geneva: WHO (2015). Available online at: https://apps.who.int/iris/handle/10665/186463

3. Izquierdo M, Merchant RA, Morley JE, Anker SD, Aprahamian I, Arai H, et al. International exercise recommendations in older adults (ICFSR): expert consensus guidelines. *J Nutr Health Aging*. (2021) 25:824–53. doi: 10.1007/s12603-021-1665-8

4. Chow LS, Gerszten RE, Taylor JM, Pedersen BK, van Praag H, Trappe S, et al. Exerkines in health, resilience and disease. *Nat Rev Endocrinol*. (2022) 18:273–89. doi: 10.1038/s41574-022-00641-2

5. Lundy J, Hayden D, Pyland S, Berg-Weger M, Malmstrom TK, Morley JE. An age-friendly health system. *J Am Geriatr Soc*. (2021) 69:806–12. doi: 10.1111/jgs.16959

6. Merchant RA, Tsoi CT, Tan WM, Lau W, Sandrasageran S, Arai H. Community-based peer-led intervention for healthy ageing and evaluation of the 'HAPPY' program. *J Nutr Health Aging*. (2021) 25:520–7. doi: 10.1007/s12603-021-1606-6

7. Yu R, Tong C, Woo J. Effect of an integrated care model for pre-frail and frail older people living in community. *Age Ageing*. (2020) 49:1048–55. doi: 10.1093/ageing/afaa087

8. Cadore EL, Saez de Asteasu ML, Izquierdo M. Multicomponent exercise and the hallmarks of frailty: considerations on cognitive impairment and acute hospitalization. *Exp Gerontol*. (2019) 122:10–4. doi: 10.1016/j.exger.2019.04.007

9. Merchant RA, Chan YH, Hui RJY, Tsoi CT, Kwek SC, Tan WM, et al. Motoric cognitive risk syndrome, physio-cognitive decline syndrome, cognitive frailty and reversibility with dual-task exercise. *Exp Gerontol*. (2021) 150:111362. doi: 10.1016/j.exger.2021.111362

10. Merchant RA, Au L, Seetharaman S, Ng SE, Nathania J, Lim JY, et al. Association of pain and impact of dual-task exercise on function, cognition and quality of life. *J Nutr Health Aging*. (2021) 25:1053–63. doi: 10.1007/s12603-021-1671-x

11. Gronwald T, Törpel A, Herold F, Budde H. Perspective of dose and response for individualized physical exercise and training prescription. *J Funct Morphol Kinesiol*. (2020) 5:48. doi: 10.3390/jfmk5030048

12. Liang CK, Lee WJ, Hwang AC, Lin CS, Chou MY, Peng LN, et al. Efficacy of multidomain intervention against physio-cognitive decline syndrome: a cluster-randomized trial. *Arch Gerontol Geriatr*. (2021) 95:104392. doi: 10.1016/j.archger.2021.104392

13. Chen LK, Hwang AC, Lee WJ, Peng LN, Lin MH, Neil DL, et al. Efficacy of multidomain interventions to improve physical frailty, depression and cognition: data from cluster-randomized controlled trials. *J Cachexia Sarcopenia Muscle*. (2020) 11:650–62. doi: 10.1002/jcsm.12534

14. Oswald WD, Gunzelmann T, Rupprecht R, Hagen B. Differential effects of single versus combined cognitive and physical training with older adults: the SimA study in a 5-year perspective. *Eur J Ageing*. (2006) 3:179. doi: 10.1007/s10433-006-0035-z

15. Shimada H, Makizako H, Doi T, Park H, Tsutsumimoto K, Verghese J, et al. Effects of combined physical and cognitive exercises on cognition and mobility in patients with mild cognitive impairment: a randomized clinical trial. *J Am Med Dir Assoc*. (2018) 19:584–91. doi: 10.1016/j.jamda.2017.09.019

16. Flynt A, Dean N. A survey of popular r packages for cluster analysis. *J Educ Behav Stat*. (2016) 41:205–25. doi: 10.3102/1076998616631743

17. Miranda VPN, Coimbra DR, Bastos RR, Miranda Júnior MV, Amorim P. Use of latent class analysis as a method of assessing the physical activity level, sedentary behavior and nutritional habit in the adolescents' lifestyle: a scoping review. *PLoS ONE*. (2021) 16:e0256069. doi: 10.1371/journal.pone.0256069

18. Jiang L, Chen S, Zhang B, Beals J, Mitchell CM, Manson SM, et al. Longitudinal patterns of stages of change for exercise and lifestyle intervention outcomes: an application of latent class analysis with distal outcomes. *Prev Sci*. (2016) 17:398–409. doi: 10.1007/s11121-015-0599-y

19. Porcu M, Giambona F. Introduction to latent class analysis with applications. *J Early Adolesc*. (2017) 37:129–58. doi: 10.1177/0272431616648452

20. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. (2011) 20:1727–36. doi: 10.1007/s11136-011-9903-x

21. Dong Y, Lee WY, Basri NA, Collinson SL, Merchant RA, Venketasubramanian N, et al. The montreal cognitive assessment is superior to the mini-mental state examination in detecting patients at higher risk of dementia. *Int Psychogeriatr*. (2012) 24:1749–55. doi: 10.1017/S1041610212001068

22. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging*. (2012) 16:601–8. doi: 10.1007/s12603-012-0084-2

23. Shelkey M, Wallace M. Katz Index of independence in activities of daily living. *J. Gerontol. Nurs.* (2001) 25:8–9. doi: 10.3928/0098-9134-19990301-05

24. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. (1969) 9:179–86. doi: 10.1093/geront/9.3_Part_1.179

25. Topolski TD, LoGerfo J, Patrick DL, Williams B, Walwick J, Patrick MB. The rapid assessment of physical activity (RAPA) among older adults. *Prev Chronic Dis*. (2006) 3:A118.

26. Merchant RA, Chen MZ, Wong BLL, Ng SE, Shirooka H, Lim JY, et al. Relationship between fear of falling, fear-related activity restriction, frailty, and sarcopenia. *J Am Geriatr Soc*. (2020) 68:2602–8. doi: 10.1111/jgs.16719

27. Lubben J, Blozik E, Gillmann G, Iliffe S, von Renteln Kruse W, Beck JC, et al. Performance of an abbreviated version of the Lubben Social Network Scale among three European community-dwelling older adult populations. *Gerontologist*. (2006) 46:503–13. doi: 10.1093/geront/46.4.503

28. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc*. (2020) 21:300–7.e2. doi: 10.1016/j.jamda.2019.12.012

29. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc*. (2006) 54:743–9. doi: 10.1111/j.1532-5415.2006.00701.x

30. Yu R, Tong C, Ho F, Woo J. Effects of a multicomponent frailty prevention program in prefrail community-dwelling older persons: a randomized controlled trial. *J Am Med Dir Assoc*. (2020) 21:294.e1–10. doi: 10.1016/j.jamda.2019.08.024

31. Hejazi-Shirmard M, Lajevardi L, Rassafiani M, Taghizadeh G. The effects of anxiety and dual-task on upper limb motor control of chronic stroke survivors. *Sci Rep*. (2020) 10:15085. doi: 10.1038/s41598-020-71845-7

32. Merchant RA, Chan YH, Hui RJY, Lim JY, Kwek SC, Seetharaman SK, et al. Possible sarcopenia and impact of dual-task exercise on gait speed, handgrip strength, falls, and perceived health. *Front Med*. (2021) 8:660463. doi: 10.3389/fmed.2021.660463

33. Jardim NYV, Bento-Torres NVO, Costa VO, Carvalho JPR, Pontes HTS, Tomás AM, et al. Dual-task exercise to improve cognition and functional capacity of healthy older adults. *Front Aging Neurosci*. (2021) 13:589299. doi: 10.3389/fnagi.2021.589299

34. Wollesen B, Schulz S, Seydell L, Delbaere K. Does dual task training improve walking performance of older adults with concern of falling? *BMC Geriatr*. (2017) 17:213. doi: 10.1186/s12877-017-0610-5

35. Rudnicka E, Napierała P, Podfigurna A, Meczekalski B, Smolarczyk R, Grymowicz M. The World Health Organization (WHO) approach to healthy ageing. *Maturitas*. (2020) 139:6–11. doi: 10.1016/j.maturitas.2020.05.018

36. Riley RD, Snell KI, Ensor J, Burke DL, Harrell FE, Jr., Moons KG, et al. Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes. *Stat Med*. (2019) 38:1276–96. doi: 10.1002/sim.7992

37. Chmelo EA, Crotts CI, Newman JC, Brinkley TE, Lyles MF, Leng X, et al. Heterogeneity of physical function responses to exercise training in older adults. *J Am Geriatr Soc*. (2015) 63:462–9. doi: 10.1111/jgs.13322

38. Lavin KM, Roberts BM, Fry CS, Moro T, Rasmussen BB, Bamman MM. The importance of resistance exercise training to combat neuromuscular aging. *Physiology*. (2019) 34:112–22. doi: 10.1152/physiol.00044.2018

39. Martínez-Velilla N, Casas-Herrero A, Zambom-Ferraresi F, Sáez de Asteasu ML, Lucia A, Galbete A, et al. Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: a randomized clinical trial. *JAMA Intern Med*. (2019) 179:28–36. doi: 10.1001/jamainternmed.2018.4869

40. Mirelman A, Maidan I, Bernad-Elazari H, Shustack S, Giladi N, Hausdorff JM. Effects of aging on prefrontal brain activation during challenging walking conditions. *Brain Cogn*. (2017) 115:41–6. doi: 10.1016/j.bandc.2017.04.002

41. Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, et al. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex*. (2005) 15:1676–89. doi: 10.1093/cercor/bhi044

42. Ross D, Wagshul ME, Izzetoglu M, Holtzer R. Prefrontal cortex activation during dual-task walking in older adults is moderated by thickness of several cortical regions. *Geroscience*. (2021) 43:1959–74. doi: 10.1007/s11357-021-00379-1

43. Kahya M, Moon S, Ranchet M, Vukas RR, Lyons KE, Pahwa R, et al. Brain activity during dual task gait and balance in aging and age-related neurodegenerative conditions: a systematic review. *Exp Gerontol*. (2019) 128:110756. doi: 10.1016/j.exger.2019.110756

44. Wu T, Liu J, Hallett M, Zheng Z, Chan P. Cerebellum and integration of neural networks in dual-task processing. *Neuroimage*. (2013) 65:466–75. doi: 10.1016/j.neuroimage.2012.10.004

45. Watanabe K, Funahashi S. Neural mechanisms of dual-task interference and cognitive capacity limitation in the prefrontal cortex. *Nat Neurosci*. (2014) 17:601–11. doi: 10.1038/nn.3667

46. Doi T, Makizako H, Shimada H, Park H, Tsutsumimoto K, Uemura K, et al. Brain activation during dual-task walking and executive function among older adults with mild cognitive impairment: a fNIRS study. *Aging Clin Exp Res*. (2013) 25:539–44. doi: 10.1007/s40520-013-0119-5

47. Pellegrini-Laplagne M, Dupuy O, Sosner P, Bosquet L. Effect of simultaneous exercise and cognitive training on executive functions, baroreflex sensitivity, and pre-frontal cortex oxygenation in healthy older adults: a pilot study. *Geroscience*. (2022) 1–22. doi: 10.1007/s11357-022-00595-3. [Epub ahead of print].

48. Kato G, Doi T, Arai H, Shimada H. Cost-effectiveness analysis of combined physical and cognitive exercises programs designed for preventing dementia among community-dwelling healthy young-old adults. *Phys Ther Res*. (2022) 25:56–67. doi: 10.1298/ptr.E10153

49. Nosaka S, Imada K, Okamura H. Effects of cognitive dysfunction and dual task on gait speed and prefrontal cortex activation in community-dwelling older adults. *Aging Neuropsychol Cogn*. (2022) 29:284–96. doi: 10.1080/13825585.2020.1866156

50. Pavasini R, Guralnik J, Brown J, Di Bari M, Cesari M, Landi F, et al. Short physical performance battery and all-cause mortality: systematic review and meta-analysis. *BMC Med*. (2016) 14:215. doi: 10.1186/s12916-016-0763-7

51. Ramírez-Vélez R, Sáez de Asteasu LM, Morley J, Cano C, Izquierdo M. Performance of the short physical performance battery in identifying the frailty phenotype and predicting geriatric syndromes in community-dwelling elderly. *J Nutr Health Aging*. (2021) 25:2091. doi: 10.1007/s12603-020-1484-3

52. Silsupadol P, Lugade V, Shumway-Cook A, Van Donkelaar P, Chou L-S, Mayr U, et al. Training-related changes in dual-task walking performance of elderly persons with balance impairment: a double-blind, randomized controlled trial. *Gait Posture*. (2009) 29:634–9. doi: 10.1016/j.gaitpost.2009.01.006

53. Delaire L, Courtay A, Fauvernier M, Humblot J, Bonnefoy M. Integrating a prevention care path into the daily life of older adults with mobility disability risk: introducing a predictive response model to exercise. *Clin Interv Aging*. (2021) 16:1617–29. doi: 10.2147/CIA.S315112

54. Javed AA, Aljied R, Allison DJ, Anderson LN, Ma J, Raina P. Body mass index and all-cause mortality in older adults: a scoping review of observational studies. *Obes Rev*. (2020) 21:e13035. doi: 10.1111/obr.13035

55. Merchant RA, Kit MWW, Lim JY, Morley JE. Association of central obesity and high body mass index with function and cognition in older adults. *Endocr Connect*. (2021) 10:909–17. doi: 10.1530/EC-21-0223

56. Cesari M, Landi F, Calvani R, Cherubini A, Di Bari M, Kortebein P, et al. Rationale for a preliminary operational definition of physical frailty and sarcopenia in the SPRINTT trial. *Aging Clin Exp Res*. (2017) 29:81–8. doi: 10.1007/s40520-016-0716-1

57. Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA*. (2014) 311:2387–96. doi: 10.1001/jama.2014.5616

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 10 January 2023
DOI 10.3389/fpubh.2022.1078304

OPEN ACCESS

EDITED BY
Xin Jiang,
Shen Zhen People's Hospital, China

REVIEWED BY
Liping Huang,
Tianjin University of Sport, China
Xiaolei Liu,
Sichuan University, China
Milan Chang Gudjonsson,
Icelandic Gerontological Research Institute, Iceland

*CORRESPONDENCE
Zengning Li
✉ lizengning@126.com

SPECIALTY SECTION
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

RECEIVED 24 October 2022
ACCEPTED 19 December 2022
PUBLISHED 10 January 2023

CITATION
Du H, Yu M, Xue H, Lu X, Chang Y and Li Z (2023) Association between sarcopenia and cognitive function in older Chinese adults: Evidence from the China health and retirement longitudinal study.
Front. Public Health 10:1078304.
doi: 10.3389/fpubh.2022.1078304

Association between sarcopenia and cognitive function in older Chinese adults: Evidence from the China health and retirement longitudinal study

Hongzhen Du[1,2], Miao Yu[1], Hongmei Xue[1,2], Xuning Lu[1,2], Yaping Chang[1,2] and Zengning Li[1,2]*

[1]Department of Nutrition, The First Hospital of Hebei Medical University, Shijiazhuang, China, [2]Hebei Key Laboratory of Nutrition and Health, Shijiazhuang, Hebei, China

Background: Sarcopenia and cognitive impairment are the most common causes of disability in the aging population. The potential role of sarcopenia in the development of cognitive impairment remains poorly understood. A cross-sectional analysis was performed using nationally representative data to evaluate associations between sarcopenia and cognition in China.

Methods: We included 2,391 participants (35.63% female) who were at least 60 years of age in 2015 from the China Health and Retirement Longitudinal Study (CHARLS). Muscle strength, appendicular skeletal mass (ASM), and physical performance measurements, were measured to diagnose sarcopenia according to the Asian Working Group for Sarcopenia 2019 (AWGS2019). Cognitive function was assessed by 10 items in the Telephone Interview for Cognitive Status (TICS-10), delayed word recall, and graph drawing. Based on cognitive score tertiles, data were divided into three groups. Multiple linear and logistic regression models were used to assess the relationship between sarcopenia and cognition.

Results: The prevalence of possible sarcopenia was 27.16% for men and 27.46% for women. Cognitive decline was significantly associated with sarcopenia status ($\beta = -0.88$, $p < 0.001$) and negatively associated with components of sarcopenia in male group. The results remained consistent in male after further adjusting for creatinine, uric acid, blood sugar, etc. Low cognitive function in female was only associated with low muscle strength ($\beta = -0.85$, $p = 0.02$). In addition, participants with possible sarcopenia had greater risk of cognitive decline than those without sarcopenia (OR = 1.41; 95% CI: 1.06–1.87). However, the same association was not significant in female group.

Conclusion: We suggest that sarcopenia might be associated with cognition function, with possible sarcopenia being significantly associated with higher cognition risk in China population, which providing a further rationale for timely recognition and management of sarcopenia.

KEYWORDS

sarcopenia, possible sarcopenia, cognitive function, muscle mass, older adults

Background

Sarcopenia is a skeletal muscle disease rooted in the lifelong accumulation of adverse muscle changes due to increased protein catabolism or increased anabolic resistance, both common conditions in older adults, and it can increase the incidence of poor clinical outcomes, such as falls, fractures, physical disability, and even mortality (1). Studies have shown that 7–10% of people aged 60–70 years and 30% of people over 80 years have sarcopenia (2). Low cognitive function, a neurodegenerative process due to increasing age, is an impairment of functions in multiple domains, including attention, memory, execution, language, literacy, numeracy, reasoning, planning, and orientation (3). It has been suggested that the prevalence of mild cognitive impairment in people aged 60 and over is 15–20% (4). Aging plays an important role in both skeletal muscle degeneration and low cognitive function. Thus, sarcopenia and cognitive decline share a common pathophysiological pathway. The pathophysiological mechanisms of sarcopenia include aging, reduced activity, neuromuscular damage, insulin resistance, hormonal dysregulation, oxidative stress and chronic inflammation (5). Additionally, these predisposing conditions are also linked to cognitive dysfunction (6). It is unclear how skeletal sarcopenia affects cognitive function, but several studies indicate that several myokines are produced by skeletal muscle and secreted, including those regulating mood, learning, motor activity, and neuronal damage protection, indicating the presence of muscle-brain crosstalk (7). In addition, lifestyle factors, such as physical inactivity, poor diet, obesity and smoking, are common risk factors for both diseases. Moreover, sarcopenia may interact with cognitive function. Advanced sarcopenia and its accompanying frailty and loss of independence are clear causes of depression and low cognitive function. Conversely, low cognitive function leads to reduced physical activity and dietary intake, which in turn accelerates sarcopenia.

At present, accumulating evidence suggests that sarcopenia may be associated with an increased risk of cognitive impairment in older adults, although the findings are inconsistent (8, 9). A meta-analysis confirmed that sarcopenia and cognitive dysfunction were positively associated (10), but these results remained inconsistent in subgroup analyses by study population, study region. China has the largest older population in the world. The total population in China was 1.38 billion, of which adults aged 60 years old or over represented 16.7% as at the end of 2016 (11). A systematic review has pooled the estimate of sarcopenia prevalence in community-dwelling Chinese older adults (male: 12.9%; female: 11.2%) (12), and around 10% of older adults have cognitive impairment (13). However, to our knowledge, relatively few studies based on a large Chinese population have explored the relationship between sarcopenia and its components with cognitive dysfunction in the older population (14, 15). Nationally representative data from the China Health and Retirement Longitudinal Study (CHARLS) was used to conduct a cross-sectional analysis to explore the relationship between sarcopenia status and cognitive function in Chinese communities.

Materials and methods

Study population

The CHARLS is a longitudinal study of people over the age of 45 in China. This study was first established in 2011 and is an ongoing nationally representative longitudinal survey that aims to explore the socioeconomic determinants and consequences of aging (16). Briefly, high quality data from CHARLS was collected through one-on-one interviews using a structured questionnaire. Multilevel stratified probability-proportional-to-size sampling strategy was employed in recruiting the study participants. Sociodemographic, lifestyle, and health data were collected using standardized questionnaires. In 2011, 17,708 participants within 10,257 families were interviewed in 150 counties (districts) and 450 villages in 28 provinces in China. In order to ensure representativeness of the data, these data include weighting variables. Follow-up surveys were conducted every 2 years after the baseline survey (16).

In this study, CHARLS data from 2015 were used. The inclusion criteria for this study were as follows: (a) individuals who were at least 60 years of age at the time of the 2015 CHARLS study and (b) individuals with available data on their sarcopenia status. The exclusion criteria were as follows: individuals with (a) missing sarcopenia status data and cognitive data; (b) missing age data; (c) age <60 years; (d) no physical examination data or blood data. In total, 21,095 participants were interviewed by the CHARLS in 2015. From the CHARLS data booklet we can also derive a blood response rate of only 64%, which may be due to the fact that the collection of blood samples was invasive. In addition, the purpose of the CHARLS data study was to provide high quality data on households and individuals aged 45 years and older in China, so we found 7,222 individuals younger than 60 years of age, and we had to exclude data from these groups as well. During our screening stages, some of the participants were excluded due to a lack of physical examination data (n = 4,689), lack of information on blood tests and health status (n = 3,133), lack of data on sarcopenia status (n = 6,676), lack of information on age or age < 60 (n = 339), missing physical examination and blood test data (n = 53), and missing cognitive data (n = 3,814). Thus, a total of 2,391 participants were included the cross-sectional analysis. The specific screening process is shown in Figure 1. The data were obtained through application from the National School of Development of Peking University (China Economic Research Center). Since this study was a secondary analysis of CHARLS data, we did not require a separate ethical approval.

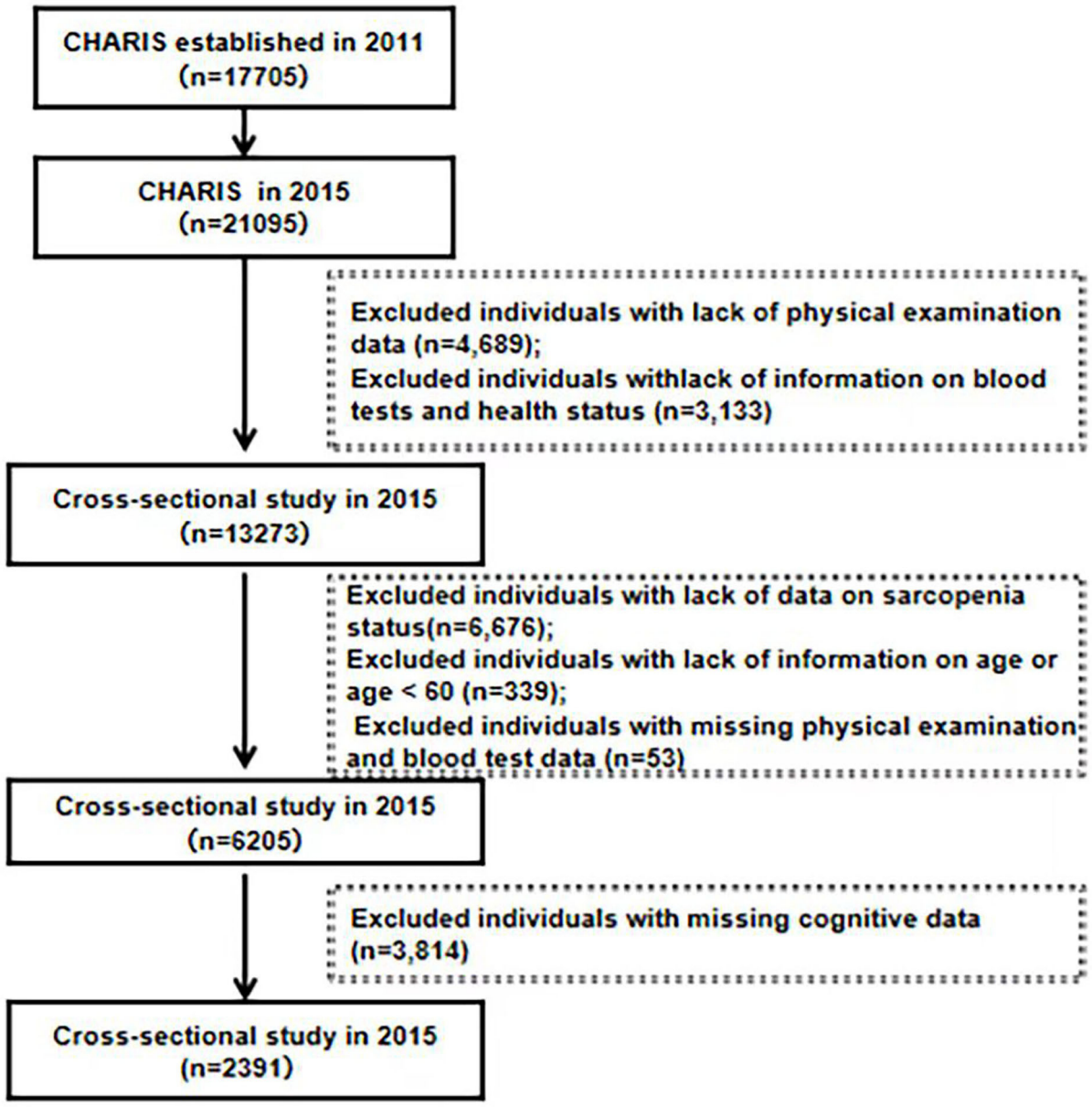


FIGURE 1
Flowchart for the study sample. HS, handgrip strength; GS, gait speed; ASM, appendicular skeletal muscle mass, CST, chair stand text.

Assessment of sarcopenia status

The recommended diagnostic methods of AWGS 2019 were used in the present study (17). The AWGS 2019 guidelines define "possible sarcopenia" as the presence of either low muscle strength or low physical performance. Definition of Sarcopenia is diagnosed when low muscle mass plus low muscle strength, or low physical performance. Severe sarcopenia is considered when low levels of muscle strength, muscle mass and physical performance are detected. Participants without any low muscle strength, low muscle mass, or low physical performance were defined as no sarcopenia.

Muscle strength

Measurements of grip strength were used to determine the overall the strength of muscle. The grip strength of both the dominant and non-dominant hands was measured three times, with the participant was instructed to squeezing a dynamometer

(YuejianTM WL-1000, Nantong Yuejian Physical Measurement Instrument Co., Ltd., Nantong, China) as hard as they could (18). A cut-off point with insufficient grip strength was <18 kg for female and <28 kg for male (17).

Appendicular skeletal mass (ASM)

In our article, we used an anthropometric equation to estimate the muscle mass, which has previously been validated in Chinese individuals (19, 20). The ASM equation model showed a high level of agreement with DXA. (19, 20):

$$\begin{aligned} \text{ASM} = {} & 0.193 * \text{body weight} + 0.107 * \text{height} - 4.157 * \text{sex} \\ & -0.037 * \text{age} - 2.631 \end{aligned} \quad (1)$$

where ASM is in kg, height is in cm, weight is in kg, age is in years, and sex is represented by 1 (male) or 2 (female).

Height-adjusted muscle mass was calculated as $\text{ASM/Ht}^2 = \text{ASM/height (m)}^2$. The cut-off point for low muscle mass was based on the lowest 20% percentile of ASM/Ht^2 in the study population. Since our data are derived from the 2015 CHARLS data, we refer to the criteria of Wu et al. (21). Therefore, the ASM/Ht2 cut-off for female was <5.08 kg/m^2, and the ASM/Ht^2 cut-off for male was <6.88 kg/m^2.

Physical performance measurements (physical fitness)

Chair stand tests and gait speed tests were used to measure physical performance. Gait speed (GS) was used to measure the participant's usual walking speed (m/s) over a 2.5-m distance. Participants walked the 2.5-m distance at normal speed, once back and forth (i.e., twice), timed by a stopwatch; the average of the two recorded values was used (22). Repeated chair stands were used to measure the body strength and endurance (23). Test participants sit on a chair with no armrests to begin the test. In the fifth stand up-sit down cycle, timing came to an end when the patients' buttocks reached the chair. It takes a participant to stand up from a chair five times, keeping their arms folded over their chests to measure the chair stand tests. The criteria for low physical performance were gait speed tests that were calculated to be <1 m/s or 5 chair stands that exceeded 12 s in total (17).

Cognitive function assessment

This study measured four dimensions of cognitive function, including orientation, attention, episodic memory, and visuospatial abilities. Orientation and attention were evaluated by the TICS-10, on a scale of 0 to 10 (9). Attention was assessed using the test in which participants were asked to subtract 7 from 100 five times consecutively. Orientation was assessed by asking the participant the date (month, day, year), day of the week, and season of the year. Episodic memory was measured by immediate and delayed word recall (24). Immediate recall was assessed to asking participants to recall as many words as possible immediately after the interviewer read 10 Chinese nouns. Delayed recall was measured by asking subjects to recall as many original words as possible after 4–10 min. The episodic memory score was calculated by the average number of immediate and delayed word recalls on a scale of 0–10 (25). Visuospatial abilities are assessed through graphic rendering. Respondents were shown a painting and asked to draw a similar figure. Respondents who successfully drew the painting received 1 point, while respondents who failed to draw the painting received 0 points (25). Interviews were conducted face to face to assess the dimensions of cognitive function. The cognitive score including the total score of TICS-10, word recall and graph drawing, ranged from 0–21 (26), with a higher score indicating better cognitive function. Then, the individuals were classified according to tertiles of the cognitive score (Lowest tertile: < 11.5; Middle tertile: 11.5–14; Highest tertile: > 14).

Covariates

Sociodemographic and health-related factors were included as covariates. Sociodemographic variables included age, sex and educational attainment (below elementary school, or primary school and above). Health-related factors consist of body mass index (BMI), smoking (self-reported; yes/no), and blood measurements include blood glucose, total cholesterol (TC), low-density lipoprotein (LDL), creatinine, uric acid, C-reactive protein (CRP) and glycated hemoglobin (GHB).

Statistical analysis

Categorical data are presented as proportions, and continuous data are reported as means ± standard deviations or medians and tertile range for continuous variables and as percentages for categorical variables. First, based on cognitive score tertiles, data were divided into three groups. The baseline characteristics of the cross-sectional samples were summarized and compared between these groups using chi-square tests, Student's *t*-tests, and analyses of variance (ANOVAs). Second, the subjects were divided into two groups according to the diagnostic criteria: those without sarcopenia and those with possible sarcopenia. Additionally, the subjects were divided according to sex and analyzed separately to determine their baseline characteristics and differences in cognitive scores between the two sarcopenia groups. Multiple linear regression models were performed to analyze the relationship between sarcopenia (and its defining components) with the cognitive

10.3389/fpubh.2022.1078304

TABLE 1 Participant characteristics according to sarcopenia status ($n = 2,391$).

Variables	Overall ($n = 2,391$)	Male ($n = 1,539$)			Female ($n = 852$)		
		No possible sarcopenia ($n = 1,121$)	Possible sarcopenia ($n = 418$)	*P*-value	No possible sarcopenia ($n = 618$)	Possible sarcopenia ($n = 234$)	*P*-value
Age	66.00 (7.00)	66.00 (8.00)	69.00 (9.00)	<0.001	65.00 (6.00)	67.00 (9.00)	<0.001
Height (cm)	159.90 (12.00)	164.40 (9.00)	162.50 (9.00)	<0.001	153.00 (8.00)	152.00 (8.00)	0.01
Weight (kg)	60.20 (15.00)	63.00 (15.00)	59.55 (15.00)	<0.001	58.00 (12.00)	55.00 (14.00)	0.01
BMI (kg/m^2)	23.59 (5.00)	23.35 (5.00)	22.41 (5.00)	<0.001	25.00 (4.25)	24.00 (5.25)	0.08
HS (kg)	30.75 (13.00)	37.00 (9.00)	26.95 (10.00)	<0.001	26.00 (7.00)	19.00 (8.00)	<0.001
GS (m/s)	3.03 (1.00)	2.87 (1.00)	3.33 (1.00)	<0.001	3.00 (0.25)	4.00 (1.00)	<0.001
CST (s)	8.81 (4.00)	7.97 (3.00)	12.13 (5.00)	<0.001	9.00 (3.00)	13.00 (4.00)	<0.001
Waist circumference (cm)	87.00 (15.00)	86.20 (14.00)	86.00 (16.00)	0.3	88.00 (14.00)	88.00 (13.25)	0.6
ASM (kg)	18.40 (6.00)	20.52 (3.00)	19.62 (4.00)	<0.001	14.00 (3.00)	13.00 (3.00)	0.001
Cognitive score	13.00 (4.50)	13.00 (4.00)	12.00 (4.00)	<0.001	13.50 (4.00)	12.50 (4.50)	<0.001
Smoking							
Smoking (%)	774 (32.2%)	549 (74.5%)	188 (25.5%)	0.2	21 (56.8%)	16 (43.2%)	0.03
Quit smoking (%)	464 (19.4%)	304 (69.7%)	132 (30.3%)		17 (60.7%)	11 (39.3%)	
Never smoke (%)	1,153 (48.2%)	268 (73.2%)	98 (26.8%)		580 (73.7%)	207 (26.3%)	
Education							
Below elementary school (%)	497 (100%)	207 (66.8%)	103 (33.2%)	0.007	128 (67.4%)	59 (31.6%)	0.2
Primary school and above (%)	1,894 (100%)	914 (74.4%)	315 (25.6%)		490 (73.7%)	175 (26.3%)	

BMI, body mass index; HS, hand strength; GS, gait speed; CST, 5 chair stand tests; ASM, appendicular skeletal mass.

scores. And logistic regression analysis was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs). The covariables models adjusted were as follows: Model 1: adjusted for smoking, education and age; Model 2: as model 1 and additionally adjusted for BMI; Model 3: as Model 2 and additionally adjusted for creatinine, uric acid, blood sugar, LDL, TC, CRP, GHB.

Results

The baseline characteristics of the study subjects according to sex and likelihood of sarcopenia are shown in Table 1. In our study, 652 subjects were included in the possible sarcopenia, 295 in the sarcopenia group, 94 in the severe sarcopenia group. The possible sarcopenia group includes part of the population in the sarcopenia group and the sarcopenia includes part of the population in the severe sarcopenia group. As the three groups are not independent, the subjects only were divided into two groups according to the diagnostic criteria: those without sarcopenia and those with possible sarcopenia. Among the male subjects ($n = 1,539$), 418 (27.16%) had possible sarcopenia, and among the female subjects ($n = 852$), 234 (27.46%) had possible sarcopenia. Regardless of sex, there were significant differences between those with and without possible sarcopenia in terms of age, height, weight, muscle mass, muscle strength, and physical activity ($p < 0.05$). Furthermore, man in the no possible sarcopenia group had higher level of education ($p < 0.001$). The cognitive scores of males with possible sarcopenia (12.00) were significantly lower ($p < 0.001$) than those of males without possible sarcopenia (13.00) in males; the same pattern was observed in females.

Table 2 shows the data separated into three categories based on tertiles of cognitive scores. The group with the highest cognitive scores also performed faster on the 5 chair stands and had a stronger grip and faster gait. Regardless of sex, the group with the highest cognitive scores had a higher ASM ($p < 0.01$). Among male subjects, the percentage of those with the lowest cognitive scores with possible sarcopenia (41.9%) was higher than that of those without possible sarcopenia (32.6%). Comparable results were also observed in females ($p < 0.05$).

Table 3 illustrates the relationships between sarcopenia, its defining components, and cognitive function. Sarcopenia was adversely linked with cognitive scores in the unadjusted

TABLE 2 Characteristics of study participants classified by Cognitive score ($n = 2,391$).

Variables	Overall ($n = 2,391$)	Male ($n = 1,539$)				Female ($n = 852$)			
		Lowest tertile ($n = 541$)	Middle tertile ($n = 511$)	Highest tertile ($n = 487$)	*P*-value	Lowest tertile ($n = 306$)	Middle tertile ($n = 248$)	Highest tertile ($n = 298$)	*P*-value
Age (years)	66.00 (7.00)	67.00 (9.00)	66.00 (8.00)	65.00 (7.00)	<0.001	66.00 (9.00)	65.00 (7.00)	65.00 (7.00)	0.007
Height (cm)	159.90(12.00)	162.30 (9.00)	163.50 (9.00)	165.26 (6.16)	<0.001	152.00 (8.00)	153.00 (7.00)	153.00 (7.00)	<0.001
Weight (kg)	60.20 (15.00)	59.60 (15.00)	62.30 (14.00)	64.90 (15.00)	<0.001	56.64 (9.74)	58.00 (13.00)	58.00 (14.00)	0.06
BMI (kg/m^2)	23.59 (5.00)	22.63 (5.00)	23.08 (4.00)	23.66 (5.00)	<0.001	24.00 (5.00)	24.00 (4.00)	25.00 (5.00)	1.0
HS (kg)	30.75 (13.00)	33.32 (7.46)	35.05 (10.00)	37.40 (10.00)	<0.001	23.00 (8.00)	24.00 (7.75)	25.00 (7.00)	<0.001
GS (m/s)	3.03 (1.00)	3.18 (1.00)	2.94 (1.00)	2.83 (1.00)	<0.001	3.00 (1.00)	3.00 (1.00)	3.00 (1.00)	<0.001
CST (s)	8.81 (4.00)	8.96 (4.00)	8.62 (4.00)	8.25 (3.00)	0.001	9.00 (3.00)	9.00 (4.00)	9.00 (4.00)	0.004
Waist circumference (cm)	87.00 (15.00)	84.20 (16.00)	86.20 (14.00)	88.10 (14.00)	<0.001	88.00 (13.50)	88.00 (14.75)	88.00 (13.00)	0.5
ASM (kg)	18.40 (6.00)	19.61 (2.61)	20.45 (2.66)	20.98 (3.00)	<0.001	14.00 (3.00)	14.00 (3.00)	14.00 (3.00)	0.002
Smoking									
Smoking (%)	774 (32.2%)	272 (36.9%)	237 (32.2%)	228 (30.9%)	0.5	17 (45.9%)	11 (29.7%)	9 (24.3%)	0.02
Quit smoking (%)	464 (19.4%)	149 (34.2%)	154 (35.3%)	133 (30.5%)		11 (39.3%)	14 (50.0%)	3 (10.7%)	
Never smoke (%)	1,153 (48.2%)	120 (32.8%)	120 (32.8%)	126 (34.4%)		278 (35.3%)	223 (28.3%)	286 (36.3%)	
Education									
Below elementary school (%)	497 (20.7%)	109 (35.2%)	119 (38.4%)	82 (26.5%)	0.04	69 (36.9%)	56 (29.9%)	62 (33.2%)	0.8
Primary school and above (%)	1,894 (79.3%)	432 (35.2%)	392 (31.9%)	405 (33.0%)		237 (35.6%)	192 (28.9%)	236 (35.5%)	
Sarcopenia									
No possible sarcopenia (%)	1,739 (72.7%)	366 (32.6%)	360 (32.1%)	395 (35.2%)	<0.001	208 (33.7%)	177 (28.6%)	233 (37.7%)	0.02
Possible sarcopenia (%)	652 (27.3%)	175 (41.9%)	151 (36.1%)	92 (22.0%)		98 (41.9%)	71 (31.3%)	65 (27.8%)	

BMI, body mass index; HS, hand strength; GS, gait speed; CST, 5 chair stand tests; ASM, appendicular skeletal mass.

10.3389/fpubh.2022.1078304

model, with regression coefficients of −0.88 (95% CI: −1.19, −0.58) in males and −0.79 (95% CI: −1.23, −0.36) in females. Components of sarcopenia, such as low muscle mass [males: −1.06 (−1.43, −0.70); females: −0.79 (−1.42, −0.15)], low muscle strength [males: −1.15 (−1.52, −0.79); females: −1.37 (−1.95, −0.79)], and low gait speed [males: −0.75 (−1.07, −0.43); females: −0.78 (−1.28, −0.28)], were negatively correlated with cognitive scores ($p < 0.05$). After adjusted for age, education, smoking, BMI, significant negative correlations (correlation coefficient > 0.5) were observed between cognitive function and sarcopenia, cognitive function and low muscle mass, cognitive function and low GS (Table 3). This effect was attenuated after further adjustment, but remained significant in male after additional adjustment for creatinine, uric acid, blood sugar, etc., (Model 3). Low cognitive function in female was only associated with low muscle strength ($\beta = -0.85$, $p = 0.02$) in the fully adjusted model (Model 3).

Across all study subjects, those with possible sarcopenia were 1.40 (95% CI: 1.05, 1.87) times more likely to have cognitive scores decline than subjects without sarcopenia (Table 4). Subjects with possible sarcopenia were 1.41 (95% CI: 1.06, 1.87) times more likely to have a cognitive score below 11.5 than subjects without sarcopenia, and the difference was statistically significant. Further subgroup analysis by gender provided a similar result in males. Men with possible sarcopenia were 1.46 (95% CI: 1.02, 2.10) times more likely to have a cognitive score between 11.5 and 14 than men without sarcopenia. Individuals with possible sarcopenia were 1.51 (95% CI: 1.05, 2.16) times more likely to have a cognitive score lower than 11.5 points than those without sarcopenia, and the difference was statistically significant ($p = 0.001$). In females, the risk of low cognitive scores in those with possible sarcopenia was 1.69 times (95% CI: 1.17, 2.43) ($p = 0.005$) greater than that in those without sarcopenia. But after adjusting for blood-related variables in females (Model 3), no significant associations were observed.

Discussion

We found that the presence or absence of sarcopenia in an older population may have a differential impact on cognitive performance. According to this cross-sectional study, among the older population in China, those with possible sarcopenia are at high likelihood of having low cognitive function than those without sarcopenia. The present study showed that the prevalence of possible sarcopenia in female subjects was higher than that in male subjects (27.46 vs. 27.16%); this difference may be due to the larger sample size of males than females in this study. The prevalence of sarcopenia was recently found to be 21.7 and 33.3% in females and males, respectively, but the population in that study was aged 80–99 years (27). According to the present study, older Chinese adults with possible sarcopenia are at greater risk of low cognitive function than those without sarcopenia, and sarcopenia and cognitive function are closely related. This finding is consistent with those of other studies (8, 28). However, recent findings regarding the relationship between sarcopenia and cognition are controversial. A study including 3,025 women over the age of 75 found no association between sarcopenia and cognitive impairment, regardless of adjustment for any underlying factors (29). In addition, a US study showed that sarcopenia was not associated with cognitive

TABLE 3 Multivariate linear regression model of sarcopenia and cognitive function.

Models	Sarcopenia ($n = 652$) β (95% CI)	*P*-value	Low muscle mass ($n = 337$) β (95% CI)	*P*-value	Low muscle strength ($n = 366$) β (95% CI)	*P*-value	Low GS ($n = 1,865$) β (95% CI)	*P*-value
Male ($n = 1,539$)								
Unadjusted	−0.88 (−1.19, −0.58)	<0.001	−1.06 (−1.43, −0.70)	<0.001	−1.15 (−1.52, −0.79)	<0.001	−0.75 (−1.07, −0.43)	<0.001
Model 1	−0.64 (−0.95, −0.33)	<0.001	−0.77 (−1.15, −0.39)	<0.001	−0.87 (−1.24, −0.50)	<0.001	−0.61 (−0.93, −0.30)	<0.001
Model 2	−0.63 (−0.95, −0.32)	<0.001	−0.75 (−1.15, −0.35)	<0.001	−0.86 (−1.23, −0.48)	<0.001	−0.61 (−0.93, −0.29)	<0.001
Model 3	−0.56 (−0.93, −0.18)	<0.001	−0.84 (−1.36, −0.32)	<0.001	−0.85 (−1.30, −0.40)	<0.001	−0.61 (−1.00, −0.23)	<0.001
Female ($n = 852$)								
Unadjusted	−0.79 (−1.23, −0.36)	<0.001	−0.79 (−1.42, −0.15)	0.02	−1.37 (−1.95, −0.79)	<0.001	−0.78 (−1.28, −0.28)	0.002
Model 1	−0.59 (−1.04, −0.14)	0.010	−0.53 (−1.17, 0.12)	0.2	−1.20 (−1.78, −0.62)	<0.001	−0.66 (−1.16, −0.16)	0.01
Model 2	−0.59 (−1.04, −0.14)	0.01	−0.55 (−1.19, 0.10)	0.1	−1.20 (−1.78, −0.62)	<0.001	−0.66 (−1.16, −0.16)	0.01
Model 3	−0.39 (−0.94, 0.17)	0.2	−0.49 (−1.40, 0.43)	0.3	−0.85 (−1.57, −0.14)	0.02	−0.44 (−1.09, 0.21)	0.2

Adjusted covariates: Model 1 = smoking + education + age.
Model 2 = Model 1 + body mass index.
Model 3 = Model 2 + (creatinine, uric acid, blood sugar, low-density lipoprotein, total cholesterol, C-reactive protein, Glycated hemoglobin).

10.3389/fpubh.2022.1078304

TABLE 4 Association between Sarcopenia and cognitive function.

Variables	Cognitive function scores						*P-trend*
	Highest tertile		Middle tertile		Lowest tertile		
	N	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	
Overall							
Unadjusted	785	1	759	1.65 (1.31, 2.09)	847	1.90 (1.52, 2.39)	<0.001
Model 1		1		1.52 (1.19, 1.93)		1.60 (1.27, 2.03)	<0.001
Model 2		1		1.51 (1.19, 1.93)		1.59 (1.26, 2.01)	<0.001
Model 3		1		1.40 (1.05, 1.87)		1.41 (1.06, 1.87)	<0.001
Male							
Unadjusted	487	1	511	1.80 (1.34, 2.42)	541	2.05 (1.54, 2.74)	<0.001
Model 1		1		1.59 (1.17, 2.16)		1.67 (1.24, 2.26)	<0.001
Model 2		1		1.59 (1.17, 2.16)		1.66 (1.23, 2.24)	<0.001
Model 3		1		1.46 (1.02, 2.10)		1.51 (1.05, 2.16)	<0.001
Female							
Unadjusted	298	1	248	1.44 (0.97, 2.12)	306	1.69 (1.17, 2.43)	0.02
Model 1		1		1.38 (0.93, 2.06)		1.46 (1.00, 2.13)	0.002
Model 2		1		1.37 (0.92, 2.04)		1.45 (0.99, 2.11)	0.003
Model 3		1		1.25 (0.79, 1.98)		1.30 (0.80, 2.10)	0.1

Adjusted covariates: Model 1= smoking + education + age.
Model 2 = Model 1 + body mass index.
Model 3 = Model 2 + (creatinine, uric acid, blood sugar, low-density lipoprotein, total cholesterol, C-reactive protein, Glycated hemoglobin).

function in adults aged 60–69 but was associated with cognitive function in those over the age of 70 (30). The above discrepancies may be due to different diagnostic criteria for a cognitive decline and sarcopenia. In particular, in regard to assessment of cognitive function, there are many options, such as the Mini-Mental State Examination (MMSE) for the detection of MCI, the Montreal Cognitive Assessment (MoCA) and the Wechsler Adult Intelligence Scale (WAIS). This paper used cognitive scores, rather than grading scales, to understand the relationship between sarcopenia and cognitive function.

This article also examined the relationship between various components of sarcopenia and cognitive scores, finding that low muscle mass, low muscle strength, and slow pace (poor physical fitness) were all negatively correlated with cognitive scores. These results are consistent with those of other studies. For example, studies have shown that in older Chinese men, lower muscle mass was associated with higher depression scores (31). Several possible mechanisms may explain the association between cognitive impairment and sarcopenia. First, cognitive impairment often results in reduced physical activity (e.g., greater bed rest or a more sedentary lifestyle) and inadequate dietary intake, which may contribute to excessive muscle loss in older adults (32). Second, a mechanism shared by sarcopenia and cognitive impairment is inflammation. Age-related chronic low-grade inflammation characterized by elevated interleukin-6 (33) and tumor necrosis factor-α levels is also an important cause of sarcopenia and the development of cognitive impairment (34). Third, excessive oxidative stress associated with chronic diseases may lead to skeletal muscle atrophy (35) as well as muscle loss (36). Excessive oxidative stress also plays a crucial role in neuronal degeneration and cognitive impairment (37). Moreover, sarcopenia is often associated with loss of physical independence, frequent falls, and poor quality of life and results in decreased activity, which may result in reduced blood circulation to the brain, thus impairing cognitive decline (38).

In addition, the present study, which adjusted for sex, found that possible sarcopenia was significantly associated with low cognitive function in men and that participants with possible sarcopenia were at greater risk of having low cognitive function than those without sarcopenia. However, sarcopenia was not associated with low cognitive function in female in fully adjusted model. One possible reason for this difference may be the small sample size in females. In addition, the Partial Androgen Deficiency in Older Men (PADAM) study showed that older men experience a partial, gradual and variable decline in testosterone, manifested by depression, lack of motivation and energy, and lower mental vitality, with age (39). Sex hormone levels decrease with age and play an important role in the pathogenesis of age-related sarcopenia (40, 41). Moreover, the relationship between sarcopenia and depressive symptoms may

be complicated by decreased levels of sex hormones (42). This also suggests that attention should be paid to effect of sex difference on low cognitive function of sarcopenia.

There are some limitations in this study. First, a significant amount of data in CHARLS is missing or incomplete, which could lead to biases. We also did a comparison of basic information between the excluded and included samples, there were still differences in their gender and age. However, we also found the average age of the included participants was 67.04 ± 5.57 years, which was similar to a previous study (68.13 ± 6.46 years) using the 2015 CHARLS data (21). Second, the items in the cognitive questionnaire only assessed cognitive status and could not diagnose the presence of cognitive impairment. Additionally, the cross-sectional design limited the ability to establish causality in the relationship between sarcopenia and cognitive function. Further longitudinal studies are needed to explore the causal relationship between sarcopenia and cognition. The choice of 2.5-m for the pace evaluation method was another limitation of our article. The original data used a 2.5-m walk to test gait speed rather than 6-m walk recommended by the AWGS 2019. Another study concluded that "distance walked during the gait speed test did not influence the recorded gait speed" (43). Thus, 2.5-m walk may be suitable for the walking-pace assessment of older Chinese adults. On the other hand, the present study has many strengths. First, this study analyzed CHARLS data. CHARLS data is nationally representative, and thus our findings reflect the relationship between sarcopenia and cognitive status older Chinese adults. Second, this study analyzed people with possible sarcopenia and provides recommendations for those who do not meet the criteria for sarcopenia diagnosis. Third, as the study used a cross-sectional analysis, there were naturally occurring contemporaneous controls in the sample that were comparable.

The present study found that sarcopenia and low cognitive function were correlated in older individuals and that sarcopenia is a risk factor for low cognitive function in older individuals. Thus, sarcopenia prevention and treatment can be used as a therapeutic measure to prevent or delay low cognitive function in older individuals, to control and manage sarcopenia or reduce the risk of sarcopenia in high-risk groups, and to enable early detection and treatment. Sarcopenia prevention and treatment can reduce low cognitive function in older individuals; prevent cognitive impairment; reduce the burden on individuals, families and society; improve the living standards of older individuals; and provide new methods and ideas for improving the health of older individuals.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics approval for the CHARLS study was obtained from the Institutional Review Board (IRB) at Peking University. The IRB approval number for the main household survey was IRB00001052-11015 and for the biomarker collection was IRB00001052-11014. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HD designed the study and wrote the paper. MY performed the statistical analyses. HX revised the manuscript. XL collected and interpreted data. YC contributed to the interpretation of study results. ZL contributed to acquisition of funding, study design, and provided administrative support. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by the Key Development and Research Program of Hebei Province, China (grant no. 21377728D) and the Young Elite Scientists Sponsorship Program by CAST (grant no. 2022QNRC001).

Acknowledgments

We thank the staff and participants of CHARLS.

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

References

1. Rosenberg IH. Sarcopenia: origins and clinical relevance. *Clin Geriatr Med.* (2011) 27:337–9. doi: 10.1016/j.cger.2011.03.003

2. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences International working group on sarcopenia. *J Am Med Dir Assoc.* (2011) 12:249–56. doi: 10.1016/j.jamda.2011.01.003

3. Ng NF, Osman AM, Kerlan KR, Doraiswamy PM, Schafer RJ. Computerized cognitive training by healthy older and younger adults: age comparisons of overall efficacy and selective effects on cognition. *Front Neurol.* (2020) 11:564317. doi: 10.3389/fneur.2020.564317

4. Sanford AM. Mild cognitive impairment. *Clin Geriatr Med.* (2017) 33:325–37. doi: 10.1016/j.cger.2017.02.005

5. Hollingworth TW, Oke SM, Patel H, Smith TR. Getting to grips with sarcopenia: recent advances and practical management for the gastroenterologist. *Frontline Gastroenterol.* (2021) 12:53–61. doi: 10.1136/flgastro-2019-101348

6. Cruz-Jentoft AJ, Landi F, Topinková E, Michel JP. Understanding sarcopenia as a geriatric syndrome. *Curr Opin Clin Nutr Metab Care.* (2010) 13:1–7. doi: 10.1097/MCO.0b013e328333c1c1

7. Scisciola L, Fontanella RA, Surina, Cataldo V, Paolisso G, Barbieri M. Sarcopenia and cognitive function: role of myokines in muscle brain cross-talk. *Life.* (2021) 11:173. doi: 10.3390/life11020173

8. Lee I, Cho J, Hong H, Jin Y, Kim D, Kang H. Sarcopenia is associated with cognitive impairment and depression in elderly korean women. *Iran J Public Health.* (2018) 47:327–34.

9. Abellan VKG, Cesari M, Gillette-Guyonnet S, Dupuy C, Nourhashémi F, Schott AM, et al. Sarcopenia and cognitive impairment in elderly women: results from the epidos cohort. *Age Ageing.* (2013) 42:196–202. doi: 10.1093/ageing/afs173

10. Peng TC, Chen WL, Wu LW, Chang YW, Kao TW. Sarcopenia and cognitive impairment: a systematic review and meta-analysis. *Clin Nutr.* (2020) 39:2695–701. doi: 10.1016/j.clnu.2019.12.014

11. China, National Bureau of Statistics. *National Data.* (2016). Available online at: http://data.stats.gov.cn/easyquery.htm?cn=C01

12. Chen Z, Li WY, Ho M, Chau PH. The prevalence of sarcopenia in Chinese older adults: meta-analysis and meta-regression. *Nutrients.* (2021) 13:1441. doi: 10.3390/nu13051441

13. Nie H, Xu Y, Liu B, Zhang Y, Lei T, Hui X, et al. The prevalence of mild cognitive impairment about elderly population in China: a meta-analysis. *Int J Geriatr Psychiatry.* (2011) 26:558–63. doi: 10.1002/gps.2579

14. Bai A, Xu W, Sun J, Liu J, Deng X, Wu L, et al. Associations of sarcopenia and its defining components with cognitive function in community-dwelling oldest old. *BMC Geriatr.* (2021) 21:292. doi: 10.1186/s12877-021-02190-1

15. Liu X, Hou L, Xia X, Liu Y, Zuo Z, Zhang Y, et al. Prevalence of sarcopenia in multi ethnics adults and the association with cognitive impairment: findings from west-China health and aging trend study. *BMC Geriatr.* (2020) 20:63. doi: 10.1186/s12877-020-1468-5

16. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China health and retirement longitudinal study (CHARLS). *Int J Epidemiol.* (2014) 43:61–8. doi: 10.1093/ije/dys203

17. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc.* (2020) 21:300–7. doi: 10.1016/j.jamda.2019.12.012

18. Zhang L, Guo L, Wu H, Gong X, Lv J, Yang Y. Role of physical performance measures for identifying functional disability among Chinese older adults: data from the China health and retirement longitudinal study. *PLoS ONE.* (2019) 14:e215693. doi: 10.1371/journal.pone.0215693

19. Yang M, Hu X, Wang H, Zhang L, Hao Q, Dong B. Sarcopenia predicts readmission and mortality in elderly patients in acute care wards: a prospective study. *J Cachexia Sarcopenia Muscle.* (2017) 8:251–8. doi: 10.1002/jcsm.12163

20. Wen X, Wang M, Jiang CM, Zhang YM. Anthropometric equation for estimation of appendicular skeletal muscle mass in Chinese adults. *Asia Pac J Clin Nutr.* (2011) 20:551–6.

21. Wu X, Li X, Xu M, Zhang Z, He L, Li Y. Sarcopenia prevalence and associated factors among older Chinese population: findings from the China health and retirement longitudinal study. *PLoS ONE.* (2021) 16:e247617. doi: 10.1371/journal.pone.0247617

22. Zuo M, Gan C, Liu T, Tang J, Dai J, Hu X. Physical predictors of cognitive function in individuals with hypertension: evidence from the CHARLS basline survey. *West J Nurs Res.* (2019) 41:592–614. doi: 10.1177/0193945918770794

23. Jones SE, Kon SSC, Canavan JL, Patel MS, Clark AL, Nolan CM, et al. The five-repetition sit-to-stand test as a functional outcome measure in copd. *Thorax.* (2013) 68:1015–20. doi: 10.1136/thoraxjnl-2013-203576

24. Lei X, Smith JP, Sun X, Zhao Y. Gender differences in cognition in China and reasons for change over time: evidence from CHARLS. *J Econ Ageing.* (2014) 4:46–55. doi: 10.1016/j.jeoa.2013.11.001

25. Huang W, Zhou Y. Effects of education on cognition at older ages: evidence from China's great famine. *Soc Sci Med.* (2013) 98:54–62. doi: 10.1016/j.socscimed.2013.08.021

26. Fu C, Li Z, Mao Z. Association between social activities and cognitive function among the elderly in China: a cross-sectional study. *Int J Environ Res Public Health.* (2018) 15:231. doi: 10.3390/ijerph15020231

27. Xu W, Chen T, Shan Q, Hu B, Zhao M, Deng X, et al. Sarcopenia is associated with cognitive decline and falls but not hospitalization in community-dwelling oldest old in China: a cross-sectional study. *Med Sci Monit.* (2020) 26:e919894. doi: 10.12659/MSM.919894

28. Chen X, Han P, Yu X, Zhang Y, Song P, Liu Y, et al. Relationships between sarcopenia, depressive symptoms, and mild cognitive impairment in Chinese community-dwelling older adults. *J Affect Disord.* (2021) 286:71–7. doi: 10.1016/j.jad.2021.02.067

29. Abellan VKG, Rolland Y, Gillette-Guyonnet S, Gardette V, Annweiler C, Beauchet O, et al. Gait speed, body composition, and dementia. The epidos-toulouse cohort. *J Gerontol a Biol Sci Med Sci.* (2012) 67:425–32. doi: 10.1093/gerona/glr177

30. Levine ME, Crimmins EM. Sarcopenic obesity and cognitive functioning: the mediating roles of insulin resistance and inflammation? *Curr Gerontol Geriatr Res.* (2012) 2012:826398. doi: 10.1155/2012/826398

31. Lee JS, Auyeung TW, Kwok T, Lau EM, Leung PC, Woo J. Associated factors and health impact of sarcopenia in older Chinese men and women: a cross-sectional study. *Gerontology.* (2007) 53:404–10. doi: 10.1159/000107355

32. Roubenoff R. Exercise, sarcopenia, cognition, and mood. *Nestle Nutr Workshop Ser Clin Perform Programme.* (2002) 6:151–9. doi: 10.1159/000061864

33. Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annu Rev Med.* (2000) 51:245–70. doi: 10.1146/annurev.med.51.1.245

34. Beyer I, Mets T, Bautmans I. Chronic low-grade inflammation and age-related sarcopenia. *Curr Opin Clin Nutr Metab Care.* (2012) 15:12–22. doi: 10.1097/MCO.0b013e32834dd297

35. Siu PM, Pistilli EE, Alway SE. Age-dependent increase in oxidative stress in gastrocnemius muscle with unloading. *J Appl Physiol.* (1985). (2008) 105:1695–705. doi: 10.1152/japplphysiol.90800.2008

36. Meng SJ Yu LJ. Oxidative stress, molecular inflammation and sarcopenia. *Int J Mol Sci.* (2010) 11:1509–26. doi: 10.3390/ijms11041509

37. Mangialasche F, Polidori MC, Monastero R, Ercolani S, Camarda C, Cecchetti R, et al. Biomarkers of oxidative and nitrosative damage in Alzheimer's disease and mild cognitive impairment. *Ageing Res Rev.* (2009) 8:285–305. doi: 10.1016/j.arr.2009.04.002

38. Bunn F, Burn AM, Goodman C, Rait G, Norton S, Robinson L, et al. Comorbidity and dementia: a scoping review of the literature. *BMC Med.* (2014) 12:192. doi: 10.1186/s12916-014-0192-4

39. Zarrouf FA, Artz S, Griffith J, Sirbu C, Kommor M. Testosterone and depression: systematic review and meta-analysis. *J Psychiatr Pract.* (2009) 15:289–305. doi: 10.1097/01.pra.0000358315.88931.fc

40. Maggio M, Lauretani F, Ceda GP. Sex hormones and sarcopenia in older persons. *Curr Opin Clin Nutr Metab Care.* (2013) 16:3–13. doi: 10.1097/MCO.0b013e32835b6044

41. Sakuma K, Yamaguchi A. Sarcopenia and age-related endocrine function. *Int J Endocrinol.* (2012) 2012:127362. doi: 10.1155/2012/127362

42. Hwang AC, Liu LK, Lee WJ, Chen LY, Lin MH, Peng LN, et al. Association of androgen with skeletal muscle mass and muscle function among men and women aged 50 years and older in Taiwan: results from the i-lan longitudinal aging study. *Rejuvenation Res.* (2013) 16:453–9. doi: 10.1089/rej.2013.1442

43. Peel NM, Kuys SS, Klein K. Gait speed as a measure in geriatric assessment in clinical settings: a systematic review. *J Gerontol a Biol Sci Med Sci.* (2013) 68:39–46. doi: 10.1093/gerona/gls174

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 27 January 2023
DOI 10.3389/fpubh.2022.1098609

OPEN ACCESS

EDITED BY
Junhong Zhou,
Harvard Medical School, United States

REVIEWED BY
Su-Ling Yeh,
National Taiwan University, Taiwan
Jiahong Sun,
Shandong University, China
Chuanwei Ma,
Shandong University Jinan, China in collaboration with reviewer JS

*CORRESPONDENCE
Birong Dong
✉ Birongdong123@outlook.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

RECEIVED 15 November 2022
ACCEPTED 28 December 2022
PUBLISHED 27 January 2023

CITATION
Zhang Y, Zhou L, Ge M, Lin X and Dong B (2023) Association between daytime nap duration and risks of frailty: Findings from the China Health and Retirement Longitudinal Study. *Front. Public Health* 10:1098609. doi: 10.3389/fpubh.2022.1098609

Association between daytime nap duration and risks of frailty: Findings from the China Health and Retirement Longitudinal Study

Yan Zhang[1,2†], Lixing Zhou[1,2†], Meiling Ge[1,2], Xiufang Lin[1] and Birong Dong[1,2*]

[1]Center of Gerontology and Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [2]National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Introduction: Night sleep duration and total sleep duration are associated with frailty. However, the association between daytime nap duration and the risks of frailty has not been explored thoroughly.

Methods: This study used data from the China Health and Retirement Longitudinal Study (CHARLS). Participants aged 60 years and older at baseline were included in this study. Individuals with daytime nap duration were categorized into four groups: no napping, short napping (<30 min), moderate napping (30–89 min), and extended napping (≥90 min). Frailty was assessed using a modified Physical Frailty Phenotype (PFP) scale. Non-frail participants at baseline were followed up for 4 years. The association between nap duration and risks of frailty at baseline and incident frailty was evaluated by logistic regression and discrete-time Cox regression analyses, respectively.

Results: In total, 5,126 participants were included in this study. For individuals with night sleep duration of ≥9 h, short nappers showed higher odds [odds ratio (OR) = 4.08, 95% confidence interval (CI): 1.30–12.78] for frailty compared with non-habitual nappers at baseline, while moderate nappers were less likely to be frail (OR = 0.18, 95% CI: 0.04–0.73). In the follow-up study, short nappers showed higher risks for frailty compared with participants of the no napping group with night sleep duration of <6 h [hazard ratio (HR) = 1.91, 95% CI: 1.07–3.43] or 6–9 h (HR = 1.97, 95% CI: 1.18–3.30). Compared with short nappers, older adults with extended napping (HR = 0.41, 95% CI: 0.22–0.77) showed lower risks for frailty in those with night sleep duration of 6–9 h. For individuals with night sleep duration of ≥9 h, moderate napping (HR = 0.20, 95% CI: 0.05–0.77) decreased the risks for frailty compared with short napping.

Conclusion: Among older adults with night sleep duration of <9 h, short nappers posed higher risks for frailty compared with non-habitual nappers. Extended naps for those with a night sleep duration of 6–9 h or moderate naps for those with night sleep duration of ≥9 h could lower the risk of frailty compared with short naps. Future studies on the timing, purpose, frequency, and quality of daytime napping and objectively measured nap duration are needed to explore the association between daytime napping and risks of frailty.

KEYWORDS

nap, sleep duration, frailty, older adults, CHARLS

Introduction

Frailty is an age-related clinical syndrome that is characterized by an increased vulnerability to stressors caused by a cumulative decline in multiple physiologic systems (1, 2). Frailty could increase the risk of adverse outcomes, such as disability, hospitalization, falls, and death, which would be a threat to the quality of life and impose a heavy

economic burden on medical treatment and caregiving (3). However, frailty is not an irreversible condition. It has been shown that interventions targeted at risk factors for frailty may be effective strategies for frailty prevention and recovery (4, 5).

Sleep condition, especially sleep duration, is one of the risk factors which has been reported to be associated with frailty. According to two recent systematic reviews, both short and long sleep duration were associated with frailty (6, 7). However, since most of the studies included were cross-sectional, causal relationships between sleep duration and frailty could not be inferred. A longitudinal study showed that both short and long sleep duration were associated with incident frailty in Mexico (8), whereas Chen et al. reported that only long sleep duration was associated with increased risks of frailty among older adults in China (9). Another study found that short sleep duration was not associated with frailty at follow-up investigations (10). The aforementioned longitudinal studies on the association of sleep duration and risks of frailty barely investigated the effects of daytime nap duration or calculated only the total sleep duration per day and did not treat daytime nap duration as a primary independent variable.

Napping, an important part of sleep behavior, is very much prevalent among older adults (11–13). According to studies based on a nationally representative survey, more than half of the older adults were habitual nappers in China (14–16). Daytime napping, as a modifiable lifestyle factor impacting health, has been reported to increase or decrease the risks of adverse outcomes, such as cognitive decline, hypertension, diabetes, metabolic syndrome, stroke, and mortality (12, 17–21). However, a few studies focused on napping and the risks of frailty. A cross-sectional study in China that combined frailty and cognitive impairment found that long nap duration was associated with higher odds of cognitive frailty and physical frailty among older adults in nursing homes (22). Another cross-sectional study showed that long nap duration was associated with a lower likelihood of successful aging among community-dwelling older adults in China (23). Owing to the limited number and cross-sectional design of previous studies, knowledge gap in the association between napping and risks of frailty are still prevalent. Therefore, this study aimed to identify the relationship between daytime napping and the risks of frailty using data from the China Health and Retirement Longitudinal Study (CHARLS), a large sample size longitudinal study from China.

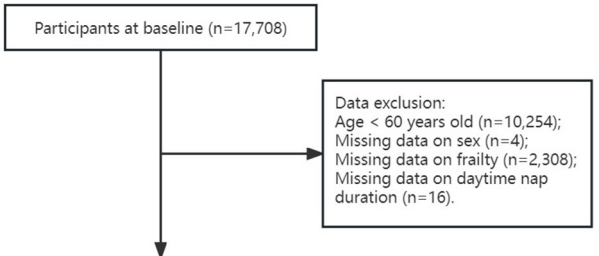


FIGURE 1
Flow chart of sample selection.

Methods

Study population

Data were obtained from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative longitudinal survey on community-dwelling adults aged 45 years and older from 28 provinces in China. The CHARLS was started in 2011 and included 17,708 participants at baseline, with follow-up surveys conducted every 2 years thereafter (2013, 2015, and 2018). Details of the CHARLS have been described previously (24). All participants provided informed consent. Ethical approval for data collection of all the CHARLS waves was obtained from the Institutional Review Board at Peking University (IRB00001052–11015). The present study used only data from baseline, wave 2 (2013), and wave 3 (2015), because wave 4 (2018) did not contain sufficient data on physical frailty phenotype. To focus better on older adults suffering from frailty, individuals aged 60 years and older were included in this study. In baseline data analyses, individuals with missing data on daytime napping time or frailty were excluded from this study. Participants with frailty at baseline in predicting the risk of developing frailty in the following surveys at wave 2 and wave 3 were excluded further from this study (see flowchart in Figure 1).

Measurements

Frailty

Frailty was measured using the modified Physical Frailty Phenotype (PFP) scale (25, 26) that consists of five criteria: weakness, slowness, exhaustion, shrinking, and inactivity. Individuals meeting three or more criteria were considered frail; otherwise, they were deemed non-frail.

Weakness

Weakness was defined using the maximum of the two-timed hand grip strength test of either hand, as being ≤20th percentile of the population within the four categories adjusted for sex and body mass index (BMI).

Slowness

Slowness was defined using the average gait speed of the two-timed walking tests over 2.5 m, as being ≤20th percentile of the population within the four categories classified by sex and sex-specific median height.

Exhaustion

Participants were asked if they could not get going or felt everything they did was an effort during the last week. Individuals

TABLE 1 Baseline characteristics of study sample grouped by daytime nap duration, the China Health and Retirement Longitudinal Study ($n = 5,126$).

Characteristics		Overall	Daytime nap duration				*P-value*
		($n = 5,126$)	No napping $n = 2,257$ (44.0%)	Short napping $n = 480$ (9.4%)	Moderate napping $n = 1,607$ (31.3%)	Extended napping $n = 782$ (15.3%)	
Age, mean ± SD		67.7 ± 6.4	67.5 ± 6.3	67.5 ± 6.3	67.9 ± 6.5	68.0 ± 6.5	0.16
Sex, *n* (%)	Male	2,630 (51.3)	977 (43.3)	260 (54.2)	904 (56.3)	489 (62.5)	<0.001
	Female	2,496 (48.7)	1,280 (56.7)	220 (45.8)	703 (43.7)	293 (37.5)	
Marital status, *n* (%)	Married	4,059 (79.2)	1,733 (76.8)	381 (79.4)	1,308 (81.4)	637 (81.5)	0.013
	Widowed	961 (18.7)	471 (20.9)	89 (18.5)	267 (16.6)	134 (17.1)	
	Others	106 (2.1)	53 (2.3)	10 (2.1)	32 (2.0)	11 (1.4)	
Current residence, *n* (%)	Urban	1,087 (21.2)	388 (17.2)	126 (26.3)	433 (27.0)	140 (17.9)	<0.001
	Rural	4,035 (78.8)	1,868 (82.8)	354 (73.8)	1,171 (73.0)	642 (82.1)	
Education, *n* (%)	No formal education or illiterate	1,838 (35.9)	945 (41.9)	141 (29.4)	499 (31.1)	253 (32.4)	<0.001
	Did not finish elementary school	1,018 (19.9)	442 (19.6)	75 (15.6)	340 (21.2)	161 (20.6)	
	Elementary school	1,344 (26.2)	556 (24.6)	145 (30.2)	419 (26.1)	224 (28.6)	
	Middle school	617 (12.0)	218 (9.7)	89 (18.5)	214 (13.3)	96 (12.3)	
	High school or above	308 (6.0)	95 (4.2)	30 (6.3)	135 (8.4)	48 (6.1)	
Smoking, *n* (%)	Non-smoker	2,897 (56.5)	1,370 (60.7)	274 (57.1)	881 (54.8)	372 (47.6)	<0.001
	Ex-smoker	624 (12.2)	237 (10.5)	67 (14.0)	217 (13.5)	103 (13.2)	
	Current smoker	1,605 (31.3)	650 (28.8)	139 (29.0)	509 (31.7)	307 (39.3)	
Drinking, *n* (%)	Never	3,535 (69.0)	1,656 (73.4)	338 (70.4)	1,060 (66.0)	481 (61.5)	<0.001
	Drink occasionally	351 (6.8)	119 (5.3)	36 (7.5)	129 (8.0)	67 (8.6)	
	Drink frequently	1,240 (24.2)	482 (21.4)	106 (22.1)	418 (26.0)	234 (29.9)	
Number of chronic conditions, *n* (%)	0	1,387 (27.6)	665 (30.1)	125 (26.6)	380 (24.1)	217 (28.1)	<0.001
	1	1,596 (31.8)	705 (31.9)	142 (30.2)	488 (31.0)	261 (33.8)	
	>1	2,043 (40.6)	839 (38.0)	203 (43.2)	707 (44.9)	294 (38.1)	
Cognition score, median (IQR)		10.5 (6.5, 13.5)	9.5 (5.5, 13.0)	11.0 (7.0, 13.5)	11.0 (7.0, 13.5)	10.5 (6.5, 13.5)	<0.001
Depression, *n* (%)	No	3,361 (68.8)	1,383 (64.6)	311 (68.2)	1,106 (71.9)	561 (74.9)	<0.001
	Yes	1,525 (31.2)	759 (35.4)	145 (31.8)	433 (28.1)	188 (25.1)	
Night sleep duration, *n* (%)	<6 h	1,743 (34.3)	912 (40.8)	149 (31.2)	496 (31.1)	186 (23.9)	<0.001
	6–9 h	2,931 (57.6)	1,153 (51.6)	286 (60.0)	997 (62.4)	495 (63.5)	
	≥9 h	412 (8.1)	168 (7.5)	42 (8.8)	104 (6.5)	98 (12.6)	
Night sleep duration, median (IQR)		6.0 (5.0, 8.0)	6.0 (4.0, 8.0)	6.0 (5.0, 8.0)	6.0 (5.0, 8.0)	7.0 (6.0, 8.0)	<0.001
Frailty, *n* (%)	Non-frail	4,690 (91.5)	2,054 (91.0)	439 (91.5)	1,482 (92.2)	715 (91.4)	0.62
	Frail	436 (8.5)	203 (9.0)	41 (8.5)	125 (7.8)	67 (8.6)	

SD, standard deviation; IQR, interquartile range.

who answered "Occasionally or a moderate amount of time (3–4 days)" or "Most or all the time (5–7 days)" to either of these two conditions were classified as exhausted.

Shrinking

Shrinking was defined as the self-reported weight loss of ≥5 kg in the previous year at baseline or a loss of ≥10% weight compared to

10.3389/fpubh.2022.1098609

TABLE 2 Association of daytime nap duration and frailty at baseline from the China Health and Retirement Longitudinal Study ($n = 5,126$).

	No napping	Short napping		Moderate napping		Extended napping	
		OR	95%CI	OR	95%CI	OR	95%CI
Model 1	Reference	0.94	(0.67, 1.34)	0.85	(0.68, 1.08)	0.95	(0.71, 1.27)
Model 2	Reference	0.96	(0.67, 1.37)	0.82	(0.65, 1.04)	0.91	(0.68, 1.23)
Model 3	Reference	1.08	(0.73, 1.60)	0.97	(0.74, 1.26)	1.09	(0.78, 1.52)
Subgroup analyses							
Night sleep duration <6 h							
Model 1	Reference	1.03	(0.61, 1.76)	1.13	(0.82, 1.58)	0.91	(0.55, 1.50)
Model 2	Reference	1.03	(0.59, 1.77)	1.07	(0.76, 1.51)	0.87	(0.52, 1.47)
Model 3	Reference	0.96	(0.53, 1.73)	1.18	(0.82, 1.71)	1.06	(0.59, 1.89)
Night sleep duration 6–9 h							
Model 1	Reference	0.74	(0.41, 1.33)	0.82	(0.57, 1.18)	1.13	(0.75, 1.70)
Model 2	Reference	0.75	(0.41, 1.36)	0.79	(0.55, 1.15)	1.08	(0.71, 1.65)
Model 3	Reference	0.82	(0.43, 1.57)	0.97	(0.65, 1.47)	1.19	(0.75, 1.90)
Night sleep duration ≥9 h							
Model 1	Reference	2.27	(0.94, 5.50)	0.33	(0.11, 1.01)	0.95	(0.42, 2.14)
Model 2	Reference	2.10	(0.84, 5.23)	0.28*	(0.09, 0.88)	0.80	(0.34, 1.86)
Model 3	Reference	4.08*	(1.30, 12.78)	0.18*	(0.04, 0.73)	0.61	(0.21, 1.76)

OR: odds ratio; 95%CI: confidence interval; *$p < 0.05$.
Model 1: unadjusted model; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex marital status, current residence, education level, smoking, drinking, number of chronic conditions, cognitive function, depression and night sleep duration (in the unstratified analyses).

the previous wave (in wave 2 and wave 3) or having a BMI of 18.5 kg/m^2 or less (27).

Inactivity

Participants were classified as being inactive if they answered no to the question if they walked for at least 10 min continuously in the course of a usual week.

Daytime nap duration

Daytime nap duration was assessed from the response to the following question: "During the past month, how long did you take a nap after lunch?" In accordance with previous studies (16, 28), individuals were categorized into four groups: no napping, 0 min per day; short napping, <30 min per day (not including 0 min); moderate napping, 30–89 min per day; and extended napping, ≥90 min per day.

Covariates

Covariates consisted of demographic variables and health and function variables. Demographic variables included age, sex, marital status (married, widowed, or others), current residence (urban or rural), and education level (no formal education or illiterate, did not finish elementary school, elementary school, middle school, or high school or above). Health and function variables included smoking (non-smoker, ex-smoker, or current smoker), drinking (never, drinks occasionally, or drinks frequently), number of chronic conditions, cognitive function, depression (no or yes), and night sleep duration. Drinking occasionally was defined as drinking less than one time a month in the last year. People drinking more than one time a month in the last year were categorized as drinking frequently. The number of chronic conditions was calculated by the total number of self-reported histories of hypertension, diabetes, cancer of the malignant tumor type, chronic lung diseases, liver disease, heart problems, stroke, kidney disease, stomach or other digestive diseases, and arthritis or rheumatism. According to the total number of chronic conditions, participants were divided into three groups (0, 1, and >1). Cognitive function was assessed by the Telephone Interview of Cognitive Status scale (TICS-10), episodic memory, and visuospatial abilities. The total score ranged from 0 to 21 and a higher score represented better cognitive function (29). Depression symptoms were assessed using the modified 10-item Center for Epidemiologic Studies Depression scale (CESD-10) (30), and individuals with a total score of 12 or more were categorized as having depression (31). Night sleep duration was assessed from the response to the following question: "During the past month, how many hours of actual sleep did you get at night?" Based on previous literature (32), participants were classified into three groups (<6, 6–9, or ≥9 h per day) according to their average sleep duration per night during the past month.

Statistical analyses

Descriptive analyses were presented as the mean ± standard deviation for normally distributed variables, the median (quartile) for abnormally distributed variables, and number (percentage) for categorical variables. Baseline characteristics of frailty status and covariates were grouped by nap duration and compared using *t*-tests, Wilcoxon's rank-sum test, and Pearson's chi-square test

TABLE 3 Association of daytime nap duration and incident frailty in the follow-up surveys (wave2–wave3) from the China Health and Retirement Longitudinal Study (n = 3,206).

	No napping	Short napping		Moderate napping		Extended napping	
		HR	95%CI	HR	95%CI	HR	95%CI
Model 1	Reference	1.50*	(1.06, 2.13)	1.02	(0.79, 1.33)	0.87	(0.62, 1.24)
Model 2	Reference	1.62**	(1.14, 2.29)	1.04	(0.80, 1.36)	0.87	(0.61, 1.24)
Model 3	Reference	2.01***	(1.40, 2.88)	1.16	(0.87, 1.54)	0.96	(0.66, 1.40)
Subgroup analyses							
Night sleep duration <6 h							
Model 1	Reference	1.59	(0.90, 2.79)	1.08	(0.71, 1.64)	1.17	(0.67, 2.06)
Model 2	Reference	1.54	(0.88, 2.72)	1.09	(0.71, 1.65)	1.08	(0.61, 1.91)
Model 3	Reference	1.91*	(1.07, 3.43)	1.28	(0.82, 2.00)	1.25	(0.69, 2.28)
Night sleep duration 6–9 h							
Model 1	Reference	1.52	(0.92, 2.51)	1.12	(0.77, 1.64)	0.81	(0.48, 1.36)
Model 2	Reference	1.69*	(1.02, 2.80)	1.17	(0.80, 1.72)	0.83	(0.49, 1.40)
Model 3	Reference	1.97**	(1.18, 3.30)	1.28	(0.85, 1.90)	0.81	(0.47, 1.39)
Night sleep duration ≥9 h							
Model 1	Reference	2.12	(0.81, 5.52)	0.69	(0.28, 1.71)	0.80	(0.32, 1.97)
Model 2	Reference	2.04	(0.78, 5.35)	0.61	(0.24, 1.53)	0.78	(0.31, 1.95)
Model 3	Reference	2.91	(0.87, 9.75)	0.57	(0.19, 1.73)	0.78	(0.26, 2.28)

HR: hazards ratio; 95%CI: 95% confidence interval; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Model 1: unadjusted model; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex marital status, current residence, education level, smoking, drinking, number of chronic conditions, cognitive function, depression and night sleep duration (in the unstratified analyses).

for normally distributed, abnormally distributed, and categorical variables, respectively. Logistic regression analysis was conducted to determine the association between nap duration and the risks of frailty at baseline, and discrete-time Cox regression analysis was used to examine the association between daytime napg duration and incident frailty in the follow-up studies. Subgroup analyses stratified by night sleep duration were performed in the aforementioned analyses. Multivariate analyses included three models: Model 1 was unadjusted. Model 2 was adjusted for age and sex; and Model 3 was adjusted for age, sex, marital status, current residence, education, smoking, drinking, the number of chronic conditions, cognitive function, depression, and night sleep duration.

Sensitivity analyses were performed. Mortality and/or incident frailty were set as composite outcomes to examine the competing effect of mortality for frailty.

Stata 15.1 (Stata Corp, College Station, TX, USA) was used for data analyses. A two-sided value of $p < 0.05$ was considered statistically significant.

Results

Sample characteristics

Table 1 shows the characteristics of the study population. A total of 5,126 participants were included in this study, of whom 2,257 (44.0%) individuals were non-habitual nappers, 480 (9.4%) older adults took naps <30 min per day, 1,607 (31.3%) participants took naps 30–89 min per day, and 782 (15.3%) extended nappers took naps ≥90 min per day during the past month at baseline. The average age of the participants was 67.7 ± 6.4 years, with 48.7% of participants being women. The prevalence of frailty showed no difference between the four nap duration groups. The non-habitual napping group showed a higher percentage of women (no napping: 56.7%, short napping: 45.8%, moderate napping: 43.7%, and extended napping: 37.5%), a higher percentage of rural residents (no napping: 82.8%, short napping: 73.8%, moderate napping: 73.0%, and extended napping: 82.1%), a higher prevalence of depression (no napping: 35.4%, short napping: 31.8%, moderate napping: 28.1%, and extended napping: 25.1%), and a lower cognition score (no napping: 9.5, short napping: 11.0, moderate napping: 11.0 and extended napping: 10.5). Extended napping group showed longer night sleep duration than other groups (no napping: 6.0, short napping: 6.0, moderate napping: 6.0, and extended napping: 7.0).

Association between daytime nap duration and the risks of frailty at baseline

No association was found between daytime nap duration and the risks of frailty at baseline in the unadjusted model and adjusted model (Table 2). However, in the subgroup analyses stratified by night sleep duration, this study found that, among older adults with night sleep duration of ≥9 h, short nappers showed higher odds (OR = 4.08, 95% CI: 1.30–12.78) for frailty in the fully adjusted model compared with the no napping group, while moderate nappers showed lower odds for frailty in Model 2 (OR = 0.28, 95% CI: 0.09–0.88) and Model 3 (OR = 0.18, 95% CI: 0.04–0.73).

Association between daytime nap duration and incident frailty in the follow-up surveys

The association between daytime nap duration and incident frailty in the follow-up surveys is shown in Table 3. Compared with the no napping group, older adults with a nap duration of <30 min showed a higher risk for incident frailty in all three models (Model 1: HR = 1.50, 95% CI: 1.06–2.13; Model 2: HR = 1.62, 95% CI: 1.14–2.29; and Model 3: HR = 2.01, 95% CI: 1.40–2.88). In subgroup analyses stratified by night sleep duration, a greater risk of incident frailty was found in the adjusted models for people with night sleep duration of <6 h (Model 3: HR = 1.91, 95% CI: 1.07–3.43) and 6–9 h (Model 2: HR = 1.69, 95% CI: 1.02–2.80; and Model 3: HR = 1.97, 95% CI: 1.18–3.30), respectively. However, no association was found for participants with night sleep duration of ≥9 h.

The present study examined further the association between nap duration and incident frailty when setting short napping as the reference group to find out whether moderate-to-long napping could lower the risks of frailty compared with short napping among habitual nappers (Supplementary Table S1). The results showed that, compared with the short napping group, individuals with no napping or moderate-to-long nap duration all had decreased risks for frailty. In subgroup analyses, for individuals with night sleep duration of 6–9 h, both no napping (HR = 0.51, 95% CI: 0.30–0.85) and extended napping (HR = 0.41, 95% CI: 0.22–0.77) showed lower risks of frailty compared with short napping. For individuals with night sleep duration of ≥9 h, moderate napping (HR = 0.20, 95% CI: 0.05–0.77) showed lower risks of frailty compared with short napping.

Sensitivity analyses

The results of sensitivity analyses were similar when exploring the association between daytime napping duration and incident mortality and/or frailty as a composite outcome (Supplementary Table S2).

Discussion

Although several studies showed that night sleep duration and total sleep duration were associated with frailty, daytime nap duration has not been investigated or considered as a primary independent factor in these studies. The relationship between daytime nap duration and the risks of frailty lacks clarity. The present study, therefore, aimed to explore the association between daytime nap duration and risks of frailty in a longitudinal study.

Napping is very common among older adults in China. They take naps for different reasons, including compensation for insufficient night sleep, beliefs in the beneficial impact of napping on health, low energy level, or feeling bored (33). According to the research mentioned in this study, over half of the older adults were habitual nappers, among whom more than half of them took naps with moderate duration (30–89 min).

In the baseline analyses, the present study found that, among participants with a night sleep duration of ≥9 h, those with short nap duration showed higher odds to be frail compared with those of the no napping group, while those with moderate nap duration showed the opposite result. In the longitudinal analyses of nap duration and incident frailty, older adults with short nap duration showed higher risks of frailty compared with non-habitual nappers. After stratification by night sleep duration, the association between short napping and higher risks of frailty was still significant for those with a night sleep duration of <9 h. The results of the present study were inconsistent with those of a previous cross-sectional study regarding nap duration and cognitive frailty, which indicated that short nap duration was associated with lower odds for physical prefrail, frailty, and cognitive frailty, while longer nap duration increased the odds for all three conditions (22). The discrepancy could be attributed to the different study populations. The former study was conducted among older adults living in nursing homes, while the present study was conducted among community-dwelling residents. In addition, the cross-sectional study design and different frailty assessment tools (i.e., the Fatigue, Resistance, Aerobic capacity, Illnesses, and Loss of weight (FRAIL) scale) used in the previous study could be the reasons for the different results. Nevertheless, a study focusing on the effects of short naps after sleep deprivation on physical performance found that a 20-min post-lunch nap after sleep deprivation is not sufficient for the recovery from most of the physical performance and subjective fatigue among soccer players. However, the aforementioned research was conducted among athletes, while a limited number of studies focused on napping and the incidence of frailty among older adults. The mechanisms of negative effects of short nap duration on incident frailty need to be explored further.

The present study also showed that, for individuals with a night sleep duration of 6–9 h, naps >90 min could lower the risks for incident frailty compared with short naps. For older adults with a night sleep duration ≥9 h, no association was found between napping and the risks of frailty when compared with no napping; however, naps with moderate duration could decrease the risks for frailty compared with short naps. A previous study focused on daytime napping and successful aging, which was defined as the coexistence of low probability of disease, no disease-related disability, high physical functioning, and active engagement with life for older adults, suggesting that those with daytime nap duration of >60 min per day had lower odds for successful aging compared with non-habitual nappers among older adults with night sleep duration of ≥8 h per night (23). Although successful aging and physical frailty are both age-related conditions and can both reflect the health status of older adults, the assessment tools of these two conditions contain different items and could result in different associations with daytime nap duration. Nevertheless, a systematic review reported that a longer nap, with a duration of 90 min suggested as the optimal, could result in an improvement in physical performance and decrease fatigue among athletes (34). The author speculated that a longer nap (i.e., 90 min) enables a complete sleep cycle with both non-rapid eye movement (NREM) and rapid eye movement (REM). NREM is beneficial for body restoration, which may result in higher performance (35). Therefore, compared with shorter naps, longer naps provide a sufficient time for NREM for body recovery, and individuals could wake up at the REM, which could reduce the severity of sleep inertia (36). In this vein, naps with longer duration may improve performance in components of frailty, such as slowness and exhaustion, compared with short naps. However, current studies on daytime nap duration and components of frailty were conducted

among young people. Research on the effects of nap duration on the development of frailty or items of frailty among older adults is needed in future studies.

The present study has several strengths. First, to our knowledge, this is the first study to explore the longitudinal association between daytime nap duration and the risks of frailty among older adults in China. Second, the CHARLS used in the present study is a nationally representative study with a large sample size of community-dwelling older adults in China. Furthermore, frailty in this study was assessed by a well-validated tool (26).

This study has some limitations. First, night sleep duration and daytime nap duration were all self-reported. Thus, an underestimation of nap duration among older adults may be possible, which could inevitably cause recall bias and lead to misclassification (37, 38). Studies with an objectively measured night sleep duration and daytime nap duration are expected. Second, compared with people included in this study, those who were excluded due to missing data on nap duration or frail status were older, and a higher percentage of them belong to female sex, were urban residents, had depression, and showed lower cognition scores (Supplementary Table S3). This aspect could have introduced bias in this study. Third, data were used from the CHARLS did not contain information on the timing, purpose, frequency of napping, and quality of night sleep and daytime napping, which were reported to have implications for health status (39, 40). These factors should be considered while determining the effects of napping on risks of frailty in future studies. Additionally, the present study examined the relationship between nap duration and incident frailty in a 4-year study, followed up with three waves. A longer follow-up duration could be expected to find either a positive or a negative association between nap duration and risks of frailty. Owing to the transient improvement in physical performance and other health-related functions after naps mentioned in previous studies, the short-term association between napping and the components of frailty, such as slowness and exhaustion, could be explored through a quicker assessment after napping. Finally, in the follow-up surveys, mortality could have had a competing effect on frailty since people may die before the onset of frailty or die with frailty but have not been recorded because of the 2-year interval between the two waves. However, in the sensitivity analyses, the results were unchanged when mortality was combined with frailty as a composite outcome (Supplementary Table S2).

Conclusion

Compared with non-habitual nappers, older adults with short napping were associated with higher risks of frailty for those with a night sleep duration of <9 h. For participants with a night sleep duration of 6–9 h, long daytime napping could decrease risks of frailty compared with short napping. For those with a night sleep duration of ≥ 9 h, moderate napping could lower the risks of frailty compared with short napping. Therefore, for non-habitual nappers, there was no need to dissuade them from taking naps. For older adults with a daytime nap duration of <30 min and a night sleep duration of ≥ 6 h per day, it would be better to extend their daytime nap duration to lower the risks of frailty. Given that napping habits are common and modifiable among older adults, it is of significance to change their napping habits to reduce the incidence of frailty and achieve healthy aging. Future studies should include an objectively measured nap duration, and information on the timing, frequency, purpose, and quality of napping is expected to provide a better understanding of the effect of napping on frailty and the underlying mechanisms behind them.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: http://charls.pku.edu.cn.

Ethics statement

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

Author contributions

YZ and LZ contributed to the conception and design of this study. YZ and MG performed data analyses. YZ, LZ, MG, XL, and BD contributed to drafting and revising the article. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Key R&D Program of China (2020YFC2005600, 2020YFC2005602, 2018YFC2002405, and 2017YFC0840101), National Natural Science Foundation of China (No. 81901411), China Postdoctoral Science Foundation (2021M692297, 2021T140491, and 2020M670061ZX), and National Clinical Research Center for Geriatrics, West China Hospital (Z2021JC003 and Z20201005).

Acknowledgments

The authors are grateful to the CHARLS team, and all the participants for their time and effort to make this study possible. The financial sponsors had no role in the design, implementation, analyses, or reporting of the results.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of

their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1098609/full#supplementary-material

References

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet.* (2013) 381:752–62. doi: 10.1016/S0140-6736(12)62167-9

2. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. *J Am Med Direct Assoc.* (2013) 14:392–7. doi: 10.1016/j.jamda.2013.03.022

3. Vermeiren S, Vella-Azzopardi R, Beckwee D, Habbig AK, Scafoglieri A, Jansen B, et al. Frailty and the prediction of negative health outcomes: a meta-analysis. *J Am Med Dir Assoc.* (2016) 17:1163 e1–e17. doi: 10.1016/j.jamda.2016.09.010

4. Marcucci M, Damanti S, Germini F, Apostolo J, Bobrowicz-Campos E, Gwyther H, et al. Interventions to prevent, delay or reverse frailty in older people: a journey towards clinical guidelines. *BMC Med.* (2019) 17:193. doi: 10.1186/s12916-019-1434-2

5. Jose Tarazona-Santabalbina F, Carmen Gomez-Cabrera M, Perez-Ros P, Miguel Martinez-Arnau F, Cabo H, Tsaparas K, et al. A multicomponent exercise intervention that reverses frailty and improves cognition, emotion, and social networking in the community-dwelling frail elderly: a randomized clinical trial. *J Am Med Direct Assoc.* (2016) 17:426–33. doi: 10.1016/j.jamda.2016.01.019

6. Pourmotabbed A, Boozari B, Babaei A, Asbaghi O, Campbell MS, Mohammadi H, et al. Sleep and frailty risk: a systematic review and meta-analysis. *Sleep Breath.* (2020) 24:1187–97. doi: 10.1007/s11325-020-02061-w

7. Sun R, Xie Y, Jiang W, Wang E, Li X. Effects of different sleep disorders on frailty in the elderly: a systematic review and meta-analysis of observational studies. *Sleep Breath.* (2022) 22:1–11. doi: 10.1007/s11325-022-02610-5

8. Moreno-Tamayo K, Manrique-Espinoza B, Morales-Carmona E, Salinas-Rodríguez A. Sleep duration and incident frailty: the rural frailty study. *BMC Geriatr.* (2021) 21:368. doi: 10.1186/s12877-021-02272-0

9. Chen S, Wang Y, Wang Z, Zhang X, Deng C, Ma B, et al. Sleep duration and frailty risk among older adults: evidence from a retrospective, population-based cohort study. *J Nutr Health Aging.* (2022) 26:383–90. doi: 10.1007/s12603-022-1766-z

10. Ensrud KE, Blackwell TL, Ancoli-Israel S, Redline S, Cawthon PM, Paudel ML, et al. Sleep disturbances and risk of frailty and mortality in older men. *Sleep Med.* (2012) 13:1217–25. doi: 10.1016/j.sleep.2012.04.010

11. Kitamura K, Watanabe Y, Nakamura K, Takano C, Hayashi N, Sato H, et al. Short daytime napping reduces the risk of cognitive decline in community-dwelling older adults: a 5-year longitudinal study. *BMC Geriatr.* (2021) 21:474. doi: 10.1186/s12877-021-02418-0

12. Zhang Z, Xiao X, Ma W, Li J. Napping in older adults: a review of current literature. *Curr Sleep Med Rep.* (2020) 6:129–35. doi: 10.1007/s40675-020-00183-x

13. Picarsic JL, Glynn NW, Taylor CA, Katula JA, Goldman SE, Studenski SA, et al. Self-reported napping and duration and quality of sleep in the lifestyle interventions and independence for elders pilot study. *J Am Geriatr Soc.* (2008) 56:1674–80. doi: 10.1111/j.1532-5415.2008.01838.x

14. Yang Y, Liu W, Ji X, Ma C, Wang X, Li K, et al. Extended afternoon naps are associated with hypertension in women but not in men. *Heart Lung.* (2020) 49:2–9. doi: 10.1016/j.hrtlng.2019.09.002

15. Fang Y, He Y, Huang Y, Ran L, Song W, Hao J, et al. Sleep duration, daytime napping, and risk of incident stroke: nuances by metabolic syndrome from the china health and retirement longitudinal study. *Front Cardiovasc Med.* (2022) 9:976537. doi: 10.3389/fcvm.2022.976537

16. Li C, Yan Y. Afternoon napping durations in chinese population over 60 years old: longitudinal associations with cognitive performance. *Front Public Health.* (2022) 10:911498. doi: 10.3389/fpubh.2022.911498

17. Sun J, Ma C, Zhao M, Magnussen CG Xi B. Daytime napping and cardiovascular risk factors, cardiovascular disease, and mortality: a systematic review. *Sleep Med Rev.* (2022) 65:101682. doi: 10.1016/j.smrv.2022.101682

18. Liu W, Wu Q, Wang M, Wang P, Shen N. Prospective association between sleep duration and cognitive impairment: findings from the china health and retirement longitudinal study (charls). *Front Med.* (2022) 9:971510. doi: 10.3389/fmed.2022.971510

19. Yang MJ, Zhang Z, Wang YJ Li JC, Guo QL, Chen X, et al. Association of nap frequency with hypertension or ischemic stroke supported by prospective cohort data and mendelian randomization in predominantly middle-aged european subjects. *Hypertension.* (2022) 79:1962–70. doi: 10.1161/HYPERTENSIONAHA.122.19120

20. Jin X, Chen H, Li Y, Xu W, Chen X, Tian L, et al. Association between daytime napping and stroke: a dose-response meta-analysis. *J Sleep Res.* (2021) 30:e13366. doi: 10.1111/jsr.13366

21. Wang L, Wang Y, Shu H, Wang K, Wang Y, Zhou P, et al. Association of midday napping with all-cause mortality in chinese adults: a 8-year nationwide cohort study. *Behav Med.* (2022) 2022:1–10. doi: 10.1080/08964289.2022.2061411

22. Liu S, Hu Z, Guo Y, Zhou F, Li S, Xu H. Association of sleep quality and nap duration with cognitive frailty among older adults living in nursing homes. *Front Public Health.* (2022) 10:963105. doi: 10.3389/fpubh.2022.963105

23. Xin C, Zhang B, Fang S, Zhou J. Daytime napping and successful aging among older adults in China: a cross-sectional study. *BMC Geriatr.* (2020) 20:2. doi: 10.1186/s12877-019-1408-4

24. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the china health and retirement longitudinal study (charls). *Int J Epidemiol.* (2014) 43:61–8. doi: 10.1093/ije/dys203

25. Wu C, Smit E, Xue QL, Odden MC. Prevalence and correlates of frailty among community-dwelling chinese older adults: the China health and retirement longitudinal study. *J Gerontol A Biol Sci Med Sci.* (2017) 73:102–8. doi: 10.1093/gerona/glx098

26. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* (2001) 56:M146–56. doi: 10.1093/gerona/56.3.M146

27. Shi H, Ge ML, Dong B, Xue QL. The framingham risk score is associated with incident frailty, or is it? *BMC Geriatr.* (2021) 21:448. doi: 10.1186/s12877-021-02387-4

28. Alqurashi YD, AlHarkan K, Aldhawyan A, Bahamdan A, Alabdulkader A, Alotaibi R, et al. Association between nap duration and cognitive functions among saudi older adults. *Front Neurosci.* (2022) 16:917987. doi: 10.3389/fnins.2022.917987

29. Wang Q, Zhu H, Dai R, Zhang T. Associations between total sleep duration and cognitive function among middle-aged and older chinese adults: does midday napping have an effect on it? *Int J Gen Med.* (2022) 15:1381–91. doi: 10.2147/IJGM.S343286

30. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the ces-d (center for epidemiologic studies depression scale). *Am J Prev Med.* (1994) 10:77–84.

31. Cheng ST, Chan AC. The center for epidemiologic studies depression scale in older chinese: thresholds for long and short forms. *Int J Geriatr Psychiatry.* (2005) 20:465–70. doi: 10.1002/gps.1314

32. Winer JR, Deters KD, Kennedy G, Jin M, Goldstein-Piekarski A, Poston KL, et al. Association of short and long sleep duration with amyloid-β burden and cognition in aging. *JAMA Neurol.* (2021) 78:1187–96. doi: 10.1001/jamaneurol.2021.2876

33. Lin JN. Correlates and influences of taking an afternoon nap on nocturnal sleep in chinese elderly: a qualitative study. *Geriatr Nurs.* (2018) 39:543–7. doi: 10.1016/j.gerinurse.2018.03.002

34. Souabni M, Hammouda O, Romdhani M, Trabelsi K, Ammar A, Driss T. Benefits of daytime napping opportunity on physical and cognitive performances in physically active participants: a systematic review. *Sports Med.* (2021) 51:2115–46. doi: 10.1007/s40279-021-01482-1

35. Venter RE. Role of sleep in performance and recovery of athletes: a review article. *South Afr J Res Sport Phys Educ Recreat.* (2012) 34:167–84. doi: 10.10520/EJC120506

36. Davies DJ, Graham KS, Chow CM. The effect of prior endurance training on nap sleep patterns. *Int J Sports Physiol Perform.* (2010) 5:87–97. doi: 10.1123/ijspp.5.1.87

37. McPhillips MV Li J, Hodgson NA, Cacchione PZ, Dickson VV, Gooneratne NS, et al. Daytime sleepiness and napping in nursing-home eligible community dwelling older adults: a mixed methods study. *Gerontol Geriatr Med.* (2020) 6:2333721420970730. doi: 10.1177/2333721420970730

38. Leng Y, Yaffe K. To nap or not to nap: more questions than answers. *Heart.* (2019) 105:1768–9. doi: 10.1136/heartjnl-2019-315442

39. Häusler N, Haba-Rubio J, Heinzer R, Marques-Vidal P. Association of napping with incident cardiovascular events in a prospective cohort study. *Heart.* (2019) 105:1793–8. doi: 10.1136/heartjnl-2019-314999

40. Lam KB, Jiang CQ, Thomas GN, Arora T, Zhang WS, Taheri S, et al. Napping is associated with increased risk of type 2 diabetes: the guangzhou biobank cohort study. *Sleep.* (2010) 33:402–7. doi: 10.1093/sleep/33.3.402

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 09 February 2023
DOI 10.3389/fpubh.2023.1048103

OPEN ACCESS

EDITED BY
Junhong Zhou,
Harvard Medical School, United States

REVIEWED BY
Maw Pin Tan,
University of Malaya, Malaysia
Sofia Cristina Iost Pavarini,
University Federal of São Carlo, Brazil

*CORRESPONDENCE
Young Ko
✉ moodory@gmail.com

SPECIALTY SECTION
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

RECEIVED 19 September 2022
ACCEPTED 23 January 2023
PUBLISHED 09 February 2023

CITATION
Choi K and Ko Y (2023) Cross sectional association between cognitive frailty and disability among community-dwelling older adults: Focus on the role of social factors. *Front. Public Health* 11:1048103. doi: 10.3389/fpubh.2023.1048103

Cross sectional association between cognitive frailty and disability among community-dwelling older adults: Focus on the role of social factors

Kyungwon Choi[1] and Young Ko[2]*

[1]Department of Nursing, Korea National University of Transportation, Chungju, Chungbuk, Republic of Korea, [2]College of Nursing, Gachon University, Incheon, Republic of Korea

Background: This study aimed to investigate the prevalence of cognitive frailty and the influence of social factors on the association between different levels of cognitive frailty and disability.

Methods: A nationally representative survey of non-institutionalized community-dwelling older adults in Korea was used. A total, 9,894 older adults were included in the analysis. We assessed the effects of social factors using social activities, social contacts, living arrangements, emotional support, and satisfaction with friends and neighbors.

Results: The prevalence of cognitive frailty was 1.6%, which was consistent with other population-based studies. Hierarchical logistic analysis demonstrated that the association between different levels of cognitive frailty and disability was attenuated when social participation, social contact, and satisfaction with friends and community were included in the model, and the magnitude of these effects differed across the levels of cognitive frailty.

Discussion: Considering the influence of social factors, interventions to enhance social relationships can help slow down the progression of cognitive frailty to disability.

KEYWORDS

cognition, frailty, social relationships, disability, elderly

1. Introduction

In the context of worldwide aging, frailty is considered a public health concern because it is directly related to adverse health outcomes such as disability, hospitalization, institutionalization, falls, and mortality. A broad consensus on the definition of frailty is that it is a multidimensional geriatric syndrome that manifests a critical reduction in the functional and physiological reserves of multiple organic systems (1). From a multidimensional perspective, psychosocial factors (2, 3), cognitive function (2–4), and environmental factors are considered in the context of frailty.

Studies have demonstrated that physical factors and cognition are crucial elements in predicting the risk of mortality (5, 6), and that frailty and cognitive impairment may happen at the early stages of disability and dementia (7–9). There is still insufficient to fully understand the complexities of the combined conditions of frailty and cognitive impairment, although significant relationship between frailty and cognitive impairment has been established in the literature (4, 10). In recognition of the importance of both physical and cognitive functions, the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics defined cognitive frailty as a heterogeneous clinical manifestation

characterized by the presence of both frailty and cognitive impairment in the absence of a clinical diagnosis of dementia (11). Subsequent studies revealed that people with cognitive frailty had a high risk of limitations on instrumental activities of daily living (IADLs), functional disability, poor quality of life, falls, hospitalization, death, and incident dementia (2–4). Therefore, appropriate support and timely interventions aimed at preventing or reducing the process of cognitive frailty and adverse health outcomes should be developed.

It is well-known that social inclusion positively influences health outcomes in older adults, such as physical frailty, cognitive impairment, and maintaining functional ability. Accordingly, high participation in social activity and frequent social contact have been associated with delayed progression to cognitive impairment (12, 13) and physical frailty (14, 15) among older adults. Similarly, the likelihood of functional decline is the highest in older adults with a lack of social contact (16, 17) or social participation (18, 19). A lack of satisfaction with social support (20, 21) or lack of good relations with relatives (17) was also associated with greater difficulties in activities of daily living (ADLs) and IADLs in older adults. However, few studies have explored whether social factors influence the association between cognitive frailty and adverse health outcomes, thus contributing to the slowing down of the transition from cognitive frailty to disability. Moreover, while most studies have not investigated the association between social factors and adverse health outcomes across levels of frailty, some have found that the effects of social factors on frailty varied across levels of physical frailty (22, 23).

Based on these findings, we aimed to investigate the prevalence of cognitive frailty in Korea and examine whether social factors influence the relationship between cognitive frailty and disability, and how the relationship differs across the levels of cognitive frailty. We hypothesized that social factors would impact the association between different levels of frailty and disability, and the effects of these factors would vary according to the level of cognitive frailty.

2. Materials and methods

2.1. Study design

This was a cross-sectional study with secondary data from the 2017 National Survey of Older Koreans (NSOK) (24). The protocol for the secondary analysis was approved by the Investigational Review Board of the university with which the researchers were affiliated (IRB No. 1044396-202107-HR-150-01).

2.2. Study setting and participants

NSOK has been conducted every 3 years since 1988. NOSK 2017 took place through in-person interviews in 934 survey areas from June 12 to August 28, 2017. The target population was non-institutionalized older adults aged 65 years or older and living in the community. A sample of older adults was selected using a stratified two-stage cluster sample design. The number of samples was calculated based on the 2010 population and housing census data (24). A total of 10,299 older adults participated in the 2017 survey; however, in this study, data from only 9,894 participants were used, after excluding those who had missing data on the main variables ($n = 405$) or were diagnosed with dementia ($n = 149$).

2.3. Measurement

2.3.1. Disability

Disability was measured using the Korean instrumental activities of daily living (K-IDL) scale (25). Disability was defined as requiring partial or full assistance for at least one activity.

2.3.2. Cognitive frailty

Cognitive frailty was operationally defined as a score ≥ 3 in the physical frailty criteria with cognitive impairment. Physical frailty was assessed using five items: fatigue, resistance, ambulation, illness, and weight loss (26). The five items were assessed and evaluated as follows: (i) Fatigue: 0 points for "no" and 1 point for "yes" to the question, "Have you lost a lot of activity or motivation these days?" (ii) Resistance: for the question "How difficult is it to climb 10 steps without any break?" "not difficult at all" or "slightly difficult" were scored 0 points, and "very difficult" or "not at all" were scored 1 point; (iii) Ambulation: for the question "How difficult is it to walk about one lap (400 m) on the playground?" "not at all difficult" or "slightly difficult" were scored 0 points, and "very difficult" or "not at all" were scored 1 point; (iv) Illness: 0 points if the number of diseases diagnosed by a doctor (hypertension, diabetes mellitus, cancer, chronic bronchitis/emphysema, angina pectoris/myocardial infarction, other heart disease, asthma, arthritis, cerebrovascular accident (cerebral infarction or stroke), chronic kidney disease) was 0–3, and 1 point for four or more diseases; and (v) Loss of weight: in the case of those who responded that they lost or gained more than 5 kg in weight despite not intentionally controlling their weight within 6 months, those who were underweight were scored 1 point, and the rest were scored 0 point. Based on these five criteria, those who fell into none of the above were defined as robust, those with one or two criteria were pre-frail, and those who fulfilled more than three criteria were defined as physically frail (27).

Cognitive function was assessed with the Mini-Mental State Examination for Dementia Screening (MMSE-DS) (28). The MMSE-DS consists of 19 items, and the total score is calculated by summing all items. Normal and cognitive impairments were classified using the criterion score based on gender, age, and educational level (28).

The participants were divided into four groups based on their levels of physical frailty and cognitive function. Participants without physical frailty and with normal cognitive function were classified as the "Robust" group. If the participants had no physical frailty but had cognitive impairment, they were part of the "Cognitively impaired" group. If the participants had physical frailty but no cognitive impairment, they were assigned to the "Physical frailty" group. Participants with physical frailty and cognitive impairment were classified into the "Cognitive frailty" group.

2.3.3. Social factors

Social factors included structural and functional variables in this study. We included living arrangements, frequency of participation in social activities, and the number of close persons as structural aspects. We included emotional support and satisfaction with friends and the community as the functional aspects. Living arrangements were

classified as follows: living alone, no spouse, living with others, and living with a spouse and/or others. The frequency of social activity participation per week was calculated by summing the frequency of seven social activities per week: club, social club, political and social group, volunteer activity, religious activity, senior citizen's center, and welfare center for seniors. The frequency of participation in social activities per week was classified as less than once per week, once per week, 2–3 times per week, and four or more times per week. Social contact was assessed using the question, "How many relatives, friends, neighbors, and acquaintances, including brothers and sisters, do you have close to (with whom you can confide in your mind)?" and classified as no social contact at all, 1–2 people, and three or more people.

The emotional support received from the participants' children, parents, or spouses was measured. Emotional support was measured based on the extent of assistance provided through counseling. An item was scored based on a Likert scale, where 1 was "extremely unlikely," 2 was "unlikely," 3 was "likely," and 4 was "extremely likely." The participant was assigned 0 when they did not have children, parents, or spouses. Higher scores indicated a higher level of support. Life satisfaction with friends and community was measured using the question "To what extent are you satisfied with relationships with friends and society?" The response options were: 1, very satisfied; 2, satisfied; 3, average; 4, not satisfied; and 5, not satisfied at all. "Very satisfied" and "satisfied" were classified as "satisfied," and "average," "dissatisfied" and "very dissatisfied" were classified as "dissatisfied."

2.3.4. Covariates

We considered covariate variables such as age, gender, educational attainment, equivalent family income, and subjective health status as possible factors influencing disability. Average household incomes were calculated by dividing the total household income by the square root of the number of household members. Equivalent family income was classified into quartile groups based on the distribution (lowest 25, 25–50, 50–75, and highest 25%). Subjective health status was measured on a 5-point scale in response to the question "How do you feel about your general health?" (1, very unhealthy; 2, unhealthy; 3, average; 4, healthy; and 5, very healthy).

2.4. Data collection

For the 2017 NSOK, a trained surveyor visited the participants' homes (dwellings) and conducted the survey directly with trusted respondents using a structured questionnaire. For this study, we were provided with data without personal identification information from the Korea Institute for Health and Social Affairs.

2.5. Data analysis

To analyze the general characteristics, social factors of participants and the prevalence of disability, descriptive statistics were used. The χ^2-test or ANOVA with Scheffe test were performed to compare the differences among four groups. Hierarchical logistic analysis was used to identify the influence of cognitive frailty on disability and the role of social factors in the association between the levels of cognitive frailty and disability. Disability was the dependent variable in these analyses. In Model 1, covariates (general characteristics and health-related characteristics) and cognitive frailty groups were entered. In Model 2–6, each of social factors was added to Model 1 and in model 7, covariates, social factors, and cognitive frailty groups were included. After adding social factors, the percentage of change in the odds ratio (OR) [explained fraction = [(OR model B-OR model A)/(OR model B-1)]×100] before [Model Before (B)] and after adding [Model After (A)] was presented to identify the degree of contribution of social factors. This is useful for measuring the direct and indirect contributions of social factors to the association between levels of cognitive frailty and disability (29). Statistical analyses were carried out with the SPSS software (version 26.0 for Windows; SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Characteristics of the participants and disability

Table 1 presents the general characteristics, social factors of the participants, and prevalence of disability. Regarding the classification of the cognitive frailty group, 79.3% were in the robust group, 14.8% in the cognitive impairment group, 4.2% in the physical frailty group, and 1.7% in the cognitive frailty group. Older persons in the cognitive frailty group had the lowest level of social participation, social support, emotional support, and showed least satisfaction with friends and community. Those in the physical frailty group showed higher levels of social support and satisfaction with friends and community than those in the cognitively impaired group. The percentage of older adults participating social activities for 2 and more days per week were higher in the physical frailty group than in the cognitively impaired group. The overall rate of disability was 22.2%. Among the four groups, the disability rate was highest in the cognitive frailty group. Significant differences in the prevalence of disability were observed in sex, age, educational attainment, equivalent family income, and subjective health status ($p < 0.001$). In addition, the prevalence of disability showed a significant difference in all social relation factors, such as living arrangement, social participation, social support, emotional support, and satisfaction with friends and community ($p < 0.001$).

3.2. Cognitive frailty and disability: Role of social factors

Table 2 shows the influence of cognitive frailty and social factors on disability. In Model 1, after adjusting for the covariates, the probability that the cognitive frailty group was disabled was 1.92 (1.65–2.24) times higher than that of the robust group. Compared to the robust group, the probability of having a disability was 7.01(5.41–9.09) times higher in the physical frailty group, and 15.36 (9.53–24.76) times higher in the cognitive frailty group than the robust group. In addition, the probability of having a disability was higher in those who were female, older than 74 years, with a low educational level, and low subjective health status.

In Models 2–6, each social relationship factor was sequentially added to Model 1 to explore the effect of each factor on the odds of cognitive frailty for disability. Living arrangement, social support,

TABLE 1 General characteristics and social factors according to cognitive frailty groups and prevalence of disability ($N = 9,894$).

Characteristics	Category	All	Robust group[a]	COI + robust group[b]	Non-COI + frail group[c]	COI + frail group[d]		Prevalence of disability
		n (%) or M ± SD	*n* (%) or M ± SD	*n* (%) or M ± SD	*n* (%) or M ± SD	*n* (%) or M ± SD	*p*	
Total		9,894 (100.0)	7,927 (79.3)	1,355 (14.8)	453 (4.2)	159 (1.7)		
Prevalence of disability		22.2	17.5	24.8				
Gender	Male	3,990 (42.8)	3,082 (41.0)	756 (58.7)	93 (22.2)	59 (36.2)	<0.001	13.9†
	Female	5,904 (57.2)	4,845 (59.0)	599 (41.3)	360 (77.8)	100 (63.8)		28.4
Age (years)	65–74	5,253 (58.6)	4,331 (60.3)	770 (61.6)	111 (28.6)	41 (26.8)	<0.001	11.8†
	≥75 years	4,641 (41.4)	3,596 (39.7)	585 (38.4)	342 (71.4)	118 (73.2)		36.9
Educational attainment	(0–22)	7.21 ± 4.59 (a,b > c,d)	7.36 ± 4.65	7.31 ± 4.05	4.84 ± 4.51	5.57 ± 4.39	<0.001	
	Elementary school	6,092 (57.7)	4,767 (55.9)	852 (60.8)	361 (76.6)	112 (72.4)	<0.001	30.4†
	Middle	1,581 (17.1)	1,264 (17.2)	248 (18.6)	42 (10.3)	27 (15.9)		12.6
	More than high	2,221 (25.2)	1,896 (26.9)	255 (20.6)	50 (13.1)	20 (11.7)		9.8
Equivalent family income (1,000 KRW)[a]	≤854.2	2,457 (22.9)	1,921 (22.2)	304 (20.8)	173 (38.6)	59 (34.3)	<0.001	32.6†
	854.3–1,282.7	2,477 (23.2)	1,976 (23.2)	337 (22.6)	123 (25.5)	41 (24.5)		24.0
	1,282.8–2,057.7	2,480 (25.7)	1,956 (25.1)	396 (30.5)	93 (20.4)	35 (23.5)		19.8
	≥2,061.3	2,480 (28.2)	2,074 (29.5)	318 (26.1)	64 (15.5)	24 (17.7)		14.3
Subjective health status	(1–5)	2.96 ± 0.98 (a,b > c,d)	3.05 ± 0.95	2.91 ± 0.97	1.89 ± 0.70	1.88 ± 0.75	<0.001	
	Unhealthy	4,040 (39.1)	2,883 (34.9)	584 (42.1)	401 (89.0)	142 (88.1)	<0.001	38.0†
	Average	2,320 (23.5)	1,984 (24.9)	296 (22.6)	30 (6.5)	10 (6.5)		18.2
	Healthy	3,554 (37.4)	3,060 (40.2)	475 (35.3)	22 (4.5)	7 (5.4)		8.2
Living arrangement	Living alone	2,502 (23.9)	2,021 (24.1)	279 (18.8)	163 (37.0)	39 (27.2)	<0.001	31.8†
	Elderly couple	4,895 (48.9)	3,960 (49.3)	279 (51.8)	163 (36.1)	39 (37.2)		15.9
	Living with others	2,497 (27.1)	3,960 (26.5)	703 (29.3)	166 (27.0)	66 (35.7)		25.1
Social participation (days per week)	<1 days	2,754 (28.5)	1,946 (25.0)	512 (38.8)	196 (43.4)	100 (66.6)	<0.001	30.9†
	1	2,422 (25.9)	1,981 (26.4)	331 (26.3)	86 (19.5)	24 (16.5)		16.6
	2–3	2,746 (27.3)	2,293 (28.7)	325 (22.3)	104 (23.9)	24 (11.2)		20.3
	≥4	1,972 (18.3)	1,707 (19.9)	187 (12.6)	67 (13.2)	11 (5.7)		19.2

(Continued)

10.3389/fpubh.2023.1048103

TABLE 1 (Continued)

Characteristics	Category	All	Robust group[a]	COI + robust group[b]	Non-COI + frail group[c]	COI + frail group[d]		Prevalence of disability
		n (%) or M ± SD	*n* (%) or M ± SD	*n* (%) or M ± SD	*n* (%) or M ± SD	*n* (%) or M ± SD	*p*	
Social support (person)		2.29 ± 2.67 (a,b > c,d)	2.40 ± 2.67	2.10 ± 2.78	1.43 ± 2.27	0.95 ± 1.48	<0.001	
	None	3,184 (31.6)	2,354 (28.9)	528 (38.8)	211 (46.7)	91 (57.2)	<0.001	32.6†
	1–2	3,277 (32.9)	2,647 (33.3)	421 (30.6)	161 (34.5)	48 (30.3)		22.0
	≥3	3,433 (35.6)	2,926 (37.9)	406 (30.7)	81 (18.8)	20 (12.5)		13.1
Emotional support	(0–4)	2.73 ± 0.71 (a > d)	2.75 ± 0.70	2.70 ± 0.69	2.66 ± 0.82	2.56 ± 0.99	<0.001	
	Less (0–2.9)	3,596 (38.0)	2,790 (36.8)	533 (41.5)	202 (44.4)	71 (46.0)	<0.001	22.5
	More (3–4)	6,298 (62.0)	5,137 (63.2)	822 (58.5)	251 (55.6)	88 (54.0)		22.0
Satisfaction with friends and community	(1–5)	2.48 ± 0.79 (a > c > b > d)	3.60 ± 0.75	3.35 ± 0.82	3.01 ± 0.96	2.71 ± 0.80	<0.001	
	Unsatisfied	3,793 (35.1)	2,724 (49.5)	651 (64.3)	287 (83.6)	131 (39.3)	<0.001	31.2†
	Satisfied	6,101 (64.9)	5,203 (50.5)	704 (35.7)	166 (16.4)	28 (60.7)		22.2

† < 0.01 for prevalence differences among different levels of each variable.

social participation, and satisfaction with friends and community accounted for 1.5, 5.9, 10.8, and 16.3% of the effect of cognitive frailty on disability, respectively. All the Odds ratios for social factors except emotional support in each model were statistically significant, indicating that poor social relationships increased the risk of disability in older adults.

In Model 7, after adding all social factors to Model 1, the probability that the cognitively impaired group had a disability was 1.76 (1.51–2.05) times higher than that in the robust group. It was decreased by 17.4% compared to the Odds ratio in the cognitively impaired group in Model 1. Compared with robust group, the Odds ratio of disability in the physical frailty group was 6.27 (4.82–8.15) times higher in Model 7. It was decreased by 12.3% compared to the Odds ratio in the physical frailty group in Model 1. The Odds ratio in the cognitive frailty group was also 12.32 (7.57–20.04) times higher than those of the robust group in Model 7. It was decreased by 21.1% compared to the Odds ratio in the cognitive frailty group in Model 1.

4. Discussion

This study investigated the prevalence of cognitive frailty in Korea and examined the impact of social factors on the association between the levels of cognitive frailty and disability. The prevalence rate of cognitive frailty (1.6%) in this study was in line with other population-based studies, which ranged from 1.0 to 4.4 in community-based settings (2, 30–33). In contrast, some studies in community-based settings have shown higher prevalence rates of cognitive frailty. In a study of 1,751 older persons aged 65 years and older from the Manitoba Study of Health and Aging (MSHA) (34) and in Xie's study of 1,586 Chinese older adults aged 75 years and older (35), the prevalence rates of CF were 12.0 and 7.2%, respectively. The higher prevalence rates in those studies may be explained by the higher mean age of the sample population compared to other studies (77.5 and 81.4, respectively).

The results of this study clearly showed that individuals with comorbidities of physical frailty and cognitive impairment have a higher risk of disability than older adults with either physical frailty or cognitive impairment alone, as well as healthy older adults. This is in line with previous studies which suggested that since both physical frailty and cognitive impairment may be related to an increased risk of adverse health outcomes, older adults with their co-occurrence are more likely to be at a particularly high risk (3, 36).

Specifically, we found that the association between different levels of cognitive frailty and disability was attenuated when social relationship variables were included in the model, and the magnitude of the attenuation was largest in cognitively frail adults, followed by older adults with cognitive impairment only. That is, our results reveal that the beneficial effects of social factors on the association between different levels of cognitive frailty and disability were greater for older adults with cognitive impairment than for those with physical frailty. This is in line with previous studies reporting that outcomes of the social dimension (22) and effects of intervention (37) vary depending on the level of frailty. These studies demonstrated that older adults with a transitional status—neither a progressive high frailty group nor stable as the least frail group—were more influenced by modifiable variables, including social support. Likewise, in this study, older adults in the cognitive frailty group were not only physically frail but cognitively impaired, which means that they

TABLE 2 Odds ratio and 95% confidence intervals (CI) for disability among Korean older persons aged 65 or older.

Characteristics	Comparison group (reference)	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gender	Female (male)	1.48 (1.30–1.68)**	1.39 (1.22–1.59)**	1.57 (1.38–1.78)**	1.56 (1.37–1.77)**	1.47 (1.30–1.67)**	1.52 (1.34–1.73)**	1.54 (1.34–1.76)**
Age	≥75 years (65–75 years)	2.78 (2.49–3.12)**	2.71 (2.42–3.04)**	2.83 (2.52–3.17)**	2.71 (2.42–3.04)**	2.79 (2.49–3.12)**	2.78 (2.48–3.11)**	2.68 (2.39–3.01)**
Equivalent family Income	Q1 (Q4)	1.07 (0.90–1.27)	1.17 (0.98–1.41)	1.06 (0.90–1.25)	1.04 (0.88–1.22)	1.05 (0.89–1.24)	1.03 (0.87–1.21)	1.09 (0.91–1.32)
	Q2 (Q4)	1.09 (0.92–1.30)	1.04 (0.87–1.24)	0.95 (0.80–1.12)	0.94 (0.80–1.11)	0.94 (0.80–1.11)	0.93 (0.79–1.10)	1.00 (0.84–1.20)
	Q3 (Q4)	1.08 (0.90–1.29)	1.02 (0.86–1.21)	0.97 (0.82–1.12)	0.96 (0.81–1.14)	0.96 (0.81–1.13)	0.95 (0.80–1.13)	1.01 (0.85–1.20)
Educational attainment		0.85 (0.84–0.86)**	0.85 (0.84–0.86)**	0.85 (0.84–0.86)**	0.85 (0.84–0.86)**	0.85 (0.84–0.86)**	0.85 (0.84–0.86)**	0.86 (0.84–0.87)**
Subjective health status		0.55 (0.51–0.58)**	0.55 (0.52–0.58)**	0.56 (0.52–0.59)**	0.56 (0.53–0.60)**	0.55 (0.52–0.58)**	0.57 (0.53–0.60)**	0.58 (0.54–0.61)**
Cognitive frail group	Cognitive impairment group (robust)	1.92 (1.65–2.24)**	1.91 (1.64–2.22)**	1.85 (1.58–2.15)**	1.87 (1.61–2.18)**	1.92 (1.65–2.24)**	1.83 (1.57–2.13)**	1.76 (1.51–2.05)**
	Physical frailty group (robust)	7.01 (5.41–9.09)**	7.00 (5.40–9.07)**	6.65 (5.13–8.63)**	6.86 (5.29–8.90)**	6.99 (5.40–9.06)**	6.36 (4.90–8.25)**	6.27 (4.82–8.15)**
	Cognitive frailty group (robust)	15.35 (9.53–24.76)**	15.13 (9.39–24.40)**	13.80 (8.53–22.33)**	14.51 (8.97–23.46)**	15.26 (9.47–24.60)**	13.01 (8.04–21.06)**	12.32 (7.57–20.04)**
Living arrangement	Living alone (living with spouse)		1.18 (1.02–1.35)*					1.21 (1.05–1.40)**
	Living with others (living with spouse)		1.33 (1.15–1.54)**					1.26 (1.09–1.47)**
Social participation (days per week)	1 (<1)			0.72 (0.62–0.84)**				0.79 (0.68–0.93)**
	2–3 (<1)			0.66 (0.57–0.77)**				0.76 (0.66–0.89)**
	≥4 (<1)			0.65 (0.56–0.77)**				0.77 (0.65–0.92)**
Social support (closed persons)	1–2 (none)				0.68 (0.59–0.77)**			0.71 (0.63–0.81)**
	≥3 (none)				0.63 (0.55–0.73)**			0.73 (0.63–0.84)**
Emotional support						0.96 (0.89–1.04)		1.03 (0.95–1.11)
Satisfaction for friends and community							0.77 (0.72–0.82)**	0.84 (0.78–0.91)**
Percentage change†	Cognitive impairment group (robust)		1.1%	7.6%	5.4%	0.0%	9.8%	17.4%
	Physical frailty group (robust)		0.2%	6.0%	2.5%	0.3%	10.8%	12.3%
	Cognitive frailty group (robust)		1.5%	10.8%	5.9%	0.6%	16.3%	21.1%

† Percentage change in ORs for disability compared with the reference model was calculated using the following formula: i.e., Model 1; [(OR (Model 1) – OR (Model 2–8) / (OR (Model 1) – 1) × 100]].

*$p < 0.05$, **$p < 0.001$.

OR, Odds ratio; CI, Confidence interval.

10.3389/fpubh.2023.1048103

have a higher risk of dementia (36) or disability (2, 32) than older adults with either physical frailty or cognitive impairment only. Our findings suggest that health care providers should develop and provide the continuous interventions to enhance social relationships for older adults with cognitive frailty as well as older adults with cognitive impairment or physical frailty only.

As expected, all associations between social factors and different levels of cognitive frailty and disability were in the same direction. However, the strength of the association and the relative importance of the social factors were different. Among social factors, the change in Odds of different levels of cognitive frailty in relation to disability was the largest when satisfaction with friends and the community was included in the model; the second largest change in OR was with the addition of social participation in the model. According to the theory of socioemotional selectivity proposed by Carstensen (38), social relationships change with age, which is the result of a selection process that develops over life, and older adults primarily maintain social relations to maximize emotional closeness. Thus, subjective satisfaction with relationships including friends, community may be more influential on the health outcomes of older adults than the structural aspects of social relationships, which is supported by previous studies (39, 40). Participation in social activities and social contacts was most consistently associated with preservation of global cognitive function (13, 41–43) and prevention or slowing down of the process of physical frailty (44) across all study types. The theory of "use it or lose it" (45) suggests that the brain can be considered a muscle; thus, social activities may stimulate the brain and contribute to the preservation of cognitive function. In addition, participation in social activities may decrease the risk of loneliness and depression, which are important risk factors for physical frailty (46). It also increases physical activity, which can improve the maintenance of physical function (9, 47, 48). According to the stress-buffering hypothesis, social activities may benefit health outcomes through their buffering effect on stress levels (49). Participation in social activities may provide opportunities for interacting with others in one's social network and increase the availability of various types of social support (46). These processes may influence cognitive functioning by reducing stress and lowering the levels of stress hormones (46).

Although it was not the primary aim of the current study, the results showed several previously observed associations between social factors and disability. As expected, social participation and social contact had a negative relationship with the risk of disability in older adults. Interestingly, however, the strength of the association did not show large differences across the frequencies of social participation, which was the same across the number of close persons, when all social factors were included in the model. Many studies have demonstrated that a higher level of social participation is associated with a higher level of functional status among older adults (19). A prospective study by Ide et al. (19) reported a dose-response relationship between social participation and functional decline; thus, a higher level of social participation is associated with a higher level of functional status among older adults. An exception is the study by Yokobayashi et al. (50), who reported that more frequent contact with friends was not associated with improved glycemic control, suggesting an optimal frequency of meeting friends (1–4 times per month) that may contribute to better glycemic control. Our result is in line with the study by Yokobayashi et al. (50), in that a higher frequency of social participation did not guarantee relatively stronger relationships with higher levels of health outcomes. Our findings suggest that the participation in social activities and social contact even once a week may play a role in slow down the progression of disability for older adults. However, we could not determine the causal relationship between the social factors and the different levels of cognitive frailty because the design of the present study was cross-sectional. Further prospective studies are needed to examine the strength of causal relationship.

There are more caveats in the interpretation of these results in addition to cross-sectional design of this study. We used the FRAIL and MMSE-K scales to assess level of frailty and cognitive function. Although the instruments for measuring frailty and cognitive function were consistent with previous research on older populations (2, 26, 36, 51, 52), we cannot rule out the possibility that the prevalence of cognitive frailty could vary if different measures are used. Moreover, we did not consider a broad spectrum of social activities or specific cognitive domains. Future studies should use multiple instruments to measure various aspects of the two concepts, such as capturing frequencies and types of social participation and specific cognitive ability, such as working memory, attention, verbal fluency, and processing speed. Despite these limitations, our study used a nationally representative sample weighted by census estimates, thereby increasing the generalizability of these findings. This study also shows the importance of social participation, social contacts, and satisfaction with friends and community in delaying the progression of cognitive frailty to disability, although each social variable has different effects across different levels of cognitive frailty and presents important implications for public health policy.

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.

Ethics statement

The studies involving human participants were reviewed and approved by Gachon University (IRB No. 1044396-202107-HR-150-01). The patients/participants provided their written informed consent to participate in this study.

Author contributions

KC and YK conceived and designed the study, analyzed the data, and wrote the first draft. Both authors contributed to revisions of the manuscript, critical discussion, read, and agreed to the published version of the manuscript.

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

References

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet.* (2013) 381:752–62. doi: 10.1016/S0140-6736(12)62167-9

2. Shimada H, Makizako H, Lee S, Doi T, Lee S, Tsutsumimoto K, et al. Impact of cognitive frailty on daily activities in older persons. *J Nutr Health Aging.* (2016) 20:729–35. doi: 10.1007/s12603-016-0685-2

3. Feng L, Nyunt MSZ, Gao Q, Feng L, Yap KB, Ng TP. Cognitive frailty and adverse health outcomes: Findings from the Singapore longitudinal ageing studies (SLAS). *J Am Med Dir Assoc.* (2017) 18:252–58. doi: 10.1016/j.jamda.2016.09.015

4. Panza F, Solfrizzi V, Barulli MR, Santamato A, Seripa D, Pilotto A, et al. Cognitive Frailty-epidemiological and neurobiological evidence of an age-related clinical condition: A systemic review. *Rejuvenation Res.* (2015) 18:389–412. doi: 10.1089/rej.2014.1637

5. Brigola AG, Rossetti ES, dos Santos BR, Neri AL, Zazzettta MS, Inouye K, et al. Relationship between cognition and frailty in elderly: A systemic review. *Dement Neuropsychol.* (2015) 9:110–9. doi: 10.1590/1980-57642015DN92000005

6. Cano C, Ternent RS, Snih SA, Markides K, Ottenbacher KJ. Frailty and cognitive impairment as predictors of mortality in older Mexican Americans. *J Nutr Health Aging.* (2012) 16:142–7. doi: 10.1007/s12603-011-0104-7

7. Fried LP, Tangen CM, Walston J, Newman AB, Gottdiener J, Seeman T, et al. Frailty in older adults: Evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* (2001) 56:M146–56. doi: 10.1093/gerona/56.3.M146

8. Makizako H, Shimada H, Doi T, Tsutsumimoto K, Suzuki T. Impact of physical frailty on disability in community-dwelling older adults: A prospective cohort study. *BMJ Open.* (2015) 5:e008462. doi: 10.1136/bmjopen-2015-008462

9. Peterson MJ, Giuliani C, Morey MC, Pieper CF, Evenson KR, Mercer V, et al. Physical activity as a preventative factor for frailty: The health, aging, and body composition study. *J Gerontol A Biol Sci Med Sci.* (2009) 64:61–8. doi: 10.1093/gerona/gln001

10. Borges KM, de Castro Cezar NO, Siqueira ASS, Yassuda M, Cesari M, Aprahamian I. The relationship between physical frailty and mild cognitive impairment in the elderly: A systemic review. *J Frailty Aging.* (2019) 8:192–7. doi: 10.14283/jfa.2019.29

11. Kelaiditi1 E, Cesari M, Canevelli M, van Kan GA, Ousset PJ, Gillette-Guyonnet S, et al. Cognitive frailty: Rational and definition from an (IANA/IAGG) international consensus group. *J Nutr Health Aging.* (2013) 17:726–34. doi: 10.1007/s12603-013-0367-2

12. Tan JH, Abdin E, Shahwan S, Zhang Y, Sambasivam R, Vaingankar JA, et al. Happiness and cognitive impairment among older adults: Investigating the mediational roles of disability, depression, social contact frequency, and loneliness. *Int J Environ Res Public Health.* (2019) 16:4954. doi: 10.3390/ijerph16244954

13. Hughes TF, Flatt JD, Fu B, Chang CC, Ganuli M. Engagement in social activities and progression from mild to severe cognitive impairment: The MYHAT study. *Int Psychogeriatr.* (2013) 25:587–95. doi: 10.1017/S1041610212002086

14. Duppen D, Van der Elst MCJ, Dury S, Lambotte D, De Donder L. D-SCOPE. The social environment's relationship with frailty: Evidence from existing studies. *J Appl Gerontol.* (2019) 38:3–26. doi: 10.1177/0733464816688310

15. Sun J, Kong X, Li H, Chen J, Yao Q, Li H, et al. Does social participation decrease the risk of frailty? Impacts of diversity in frequency and types of social participation on frailty in middle-aged and older populations. *BMC Geriatr.* (2022) 22:553. doi: 10.1186/s12877-022-03219-9

16. Avlund K, Lund R, Holstein BE, Due P. Social relations as determinant of onset of disability in aging. *Arch Gerontol Geriatr.* (2004) 38:85–99. doi: 10.1016/j.archger.2003.08.003

17. Cwirlej-Sozańska1 A, Wiśniowska-Szurlej A, Wilmowska-Pietruszyńska A, Sozański B. Determinants of ADL and IADL disability in older adults in southeastern Poland. *BMC Geriatr.* (2019) 19:297. doi: 10.1186/s12877-019-1319-4

18. Gao M, Sa Z, Li Y, Zhang W, Tian D, Zhang S, et al. Does social participation reduce the risk of functional disability among older adults in China? A survival analysis using the 2005-2011 waves of the CLHLS data. *BMC Geriatr.* (2018) 15:224. doi: 10.1186/s12877-018-0903-3

19. Ide K, Tsuji T, Kanamori S, Jeong S, Nagamine Y, Kondo K. Social participation and functional decline: A comparative study of rural and urban older people, using Japan gerontological evaluation study longitudinal data. *Int J Environ Res Public Health.* (2020) 17:617. doi: 10.3390/ijerph17020617

20. McLaughlin D, Leung J, Pachana N, Flicker L, Hankey G, Dobson A. Social support and subsequent disability: It is not the size of your network that counts. *Age Ageing.* (2012) 41:674–7. doi: 10.1093/ageing/afs036

21. Torres JL, Dias RC, Ferreira FR, Macinko J, Lima-Costa MF. Functional performance and social relations among the elderly in Greater Metropolitan Belo Horizonte, Minas Gerais State, Brazil: A population-based epidemiological study. *Cad Saude Publica.* (2014) 30:1018–28. doi: 10.1590/0102-311X00102013

22. Peek MK, Howrey BT, Ternent RS, Ray LA, Ottenbacher KJ. Social support, stressors and frailty among older Mexican American adults. *J Gerontol B Psychol Sci Soc Sci.* (2012) 67:755–64. doi: 10.1093/geronb/gbs081

23. Andrew MK, Keefe JM. Social vulnerability from a social ecology perspective: A cohort study of older adults from the National Population Health Survey of Canada. *BMC Geriatr.* (2014) 14:90. doi: 10.1186/1471-2318-14-90

24. Korea Institute for Health and Social Affairs. *National Survey of Older Koreans*. Sejong: Ministry of Health and Welfare (2017). p. 27–39.

25. Won CW, Rho YG, Sunwoo D, Lee YS. The validity and reliability of Korean instrumental activities of daily living scale. *J Korean Geriatr Soc.* (2002) 6:273–80.

26. van Kan GA, Rolland YM, Morley JE, Vellas B. Frailty: Toward a clinical definition. *J Am Med Dir Assoc.* (2008) 9:71–2. doi: 10.1016/j.jamda.2007.11.005

27. Morley JE, Malmstrom T, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging.* (2012) 16:601–8. doi: 10.1007/s12603-012-0084-2

28. Kim GW, Kim MH, Kim BG, Kim JR, Kim TH, Moon SW, et al. *Standardization of Diagnostic Tools for Dementia. Research Report. Report No.: 11-1351000-000589-01*. Seongnam: Bundang Seoul National University Hospital (2009).

29. Van Oort FV, Van Lenthe FJ, Mackenbach JP. Material, psychosocial, and behavioral factors in the explanation of educational inequalities in mortality in the Netherlands. *J Epidemiol Community Health.* (2005) 59:214–20. doi: 10.1136/jech.2003.016493

30. Moon JH, Huh JS, Won CW, Kim HJ. Is polypharmacy associated with cognitive frailty in the elderly? Results from the Korean frailty and aging cohort study. *J Nutr Health Aging.* (2019) 23:958–65. doi: 10.1007/s12603-019-1274-y

31. Kim KH, Awata S, Watanabe Y, Kojima N, Osuka Y, Motokawa K, et al. Cognitive frailty in community-dwelling older Japanese people: Prevalence and its association with falls. *Geriatr Gerontol Int.* (2019) 19:647–53. doi: 10.1111/ggi.13685

32. Roppolo M, Mulasso A, Rabaglietti E. Cognitive frailty in Italian community-dwelling older adults: Prevalence rate and its association with disability. *J Nutr Health Aging.* (2017) 21:631–63. doi: 10.1007/s12603-016-0828-5

33. Solfrizzi V, Scafato E, Seripa D, Lozupone M, Imbimbo B, D'Amato A, et al. Reversible cognitive frailty, dementia, and all-cause mortality. The Italian longitudinal study on aging. *J Am Med Dir Assoc*. (2017) 18:89.e1–8. doi: 10.1016/j.jamda.2016.10.012

34. John PD, Tyas SL, Griffith LE, Menec V. The cumulative effect of frailty and cognition on mortality-results of a prospective cohort study. *Int Psychogeriatr.* (2017) 29:535–43. doi: 10.1017/S1041610216002088

35. Xie B, Ma C, Chen Y, Wang J. Prevalence and risk factors of the co-occurrence of physical frailty and cognitive impairment in Chinese community-dwelling older adults. *Health Soc Care Community.* (2021) 29:294–303. doi: 10.1111/hsc.13092

36. Shimada H, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, Anan Y, et al. Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese People. *J Am Med Dir Assoc.* (2013) 14:518–24. doi: 10.1016/j.jamda.2013.03.010

37. Liao MY, Yeh CJ, Liao CC, Lee SH, Yang SF, Lee MC. Effects of receiving and providing family support on mortality in non-frail, pre-frail, and frail older adults in Taiwan: A 12-year follow-up longitudinal study. *Eur Geriatr Med*. (2018) 9:679-85. doi: 10.1007/s41999-018-0094-7

38. Carstensen LL. Social and emotional patterns in adulthood: Support for socioemotional selectivity theory. *Psychol Aging.* (1992) 7:331–8. doi: 10.1037/0882-7974.7.3.331

39. Kuiper JS, Zuidersma M, Zuidema SJ, Burgerhof JGM, Stolk RP, Voshaar RCO, et al. Social relationships and cognitive decline: A systematic review and meta-analysis of longitudinal cohort studies. *Int J Epidemiol.* (2016) 45:1169–206. doi: 10.1093/ije/dyw089

40. Costa-Cordella S, Arevalo-Romero C, Parada FJ, Rossi A. Social support and cognition: A systematic review. *Front Psychol.* (2021) 12:637060. doi: 10.3389/fpsyg.2021.637060

41. Hoogendijk EO, Smit AP, van Dam C, Schuster NA, de Breij S, Holwerda TJ, et al. Frailty combined with loneliness or social isolation: An elevated risk for mortality in later life. *J Am Geriatr Soc.* (2020) 68:2587–93. doi: 10.1111/jgs.16716

42. Dent E, Hoogendijk EO. Psychosocial factors modify the association of frailty with adverse outcomes: A prospective study of hospitalized older people. *BMC Geriatr.* (2014) 28:108. doi: 10.1186/1471-2318-14-108

43. Li Q, Zhang Q, Zhang S, Du M, Wang X, Hu S, et al. Relationship between frailty and cognitive decline in Chinese older patients with Alzheimer's disease: The mediating role of social contact. *Geritr Nurs.* (2022) 43:175–81. doi: 10.1016/j.gerinurse.2021.11.019

44. Zhang T, Ren Y, Shen P, Jiang S, Yang Y, Wang Y, et al. Prevalence and associated risk factors of cognitive frailty: A systematic review and meta-analysis. *Front Aging Neurosci.* (2022) 2022:755926. doi: 10.3389/fnagi.2021.755926

45. Wilson RS, Evans DA, Bienias JL, Mendes de Leon CF, Schneider JA, Bennett DA. Proneness to psychological distress is associated with risk of Alzheimer's disease. *Neurology.* (2003) 61:1479–85. doi: 10.1212/01.WNL.0000096167.56734.59

46. Berkman LF, Glass T, Bressette I, Seeman TE. From social integration to health: Durkheim in the new millennium. *Soc Sci Med.* (2000) 51:843–57. doi: 10.1016/S0277-9536(00)00065-4

47. Song J, Lindquist LA, Chang RW, Semanik PA, Ehrlich-Jones LS, Lee J, et al. Sedentary behavior as a risk factor for physical frailty independent of moderate activity: Results from the osteoarthritis initiative. *Am J Public Health.* (2015) 105:1439–45. doi: 10.2105/AJPH.2014.302540

48. Ishizaki T, Watanabe S, Suzuki T, Shibata H, Haga H. Predictors for functional decline among nondisabled older Japanese living in a community during a 3-year follow up. *J Am Geriatr Soc.* (2015) 48:1424–9. doi: 10.1111/j.1532-5415.2000.tb02632.x

49. Cohen S, Wills TA. Stress, social support, and the buffering hypothesis. *Psychol Bull.* (1985) 98:310–57. doi: 10.1037/0033-2909.98.2.310

50. Yokobayashi K, Kawachi I, Kondo K, Kondo N, Nagamine Y, Tani Y, et al. Association between social relationship and glycemic control among older Japanese: JAGES cross-sectional study. *PLoS ONE.* (2017) 12:e0169904. doi: 10.1371/journal.pone.0169904

51. Lee H, Chong J, Jung HW, Baek JY, Lee E, Jang IY. Association of the FRAIL scale with geriatric syndromes and health-related outcomes in Korean older adults. *Ann Geriatr Med Res.* (2021) 25:79–85. doi: 10.4235/agmr.20.0095

52. Sukkriang N, Punsawad C. Comparison of geriatric assessment tools for frailty among community elderly. *Heliyon.* (2020) 6:e04797. doi: 10.1016/j.heliyon.2020.e04797

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 15 February 2023
DOI 10.3389/fpubh.2023.1088833

OPEN ACCESS

EDITED BY
Jing Liao,
Sun Yat-sen University, China

REVIEWED BY
Jiaming Liang,
University of Southern California, United States
Kourosh Zarea,
Ahvaz Jundishapur University of Medical Sciences, Iran

*CORRESPONDENCE
Ping Yan
✉ yanping@xjmu.edu.cn

SPECIALTY SECTION
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

RECEIVED 03 November 2022
ACCEPTED 19 January 2023
PUBLISHED 15 February 2023

CITATION
Zhang N, Chen F, Wang C and Yan P (2023) Incidence of cognitive impairment after hypothetical interventions on depression, nighttime sleep duration, and leisure activity engagement among older Chinese adults: An application of the parametric g-formula. *Front. Public Health* 11:1088833. doi: 10.3389/fpubh.2023.1088833

Incidence of cognitive impairment after hypothetical interventions on depression, nighttime sleep duration, and leisure activity engagement among older Chinese adults: An application of the parametric g-formula

Nan Zhang[1], Fenghui Chen[2], Cui Wang[3] and Ping Yan[1]*

[1]Department of Surgical Nursing, School of Nursing, Xinjiang Medical University, Urumqi, Xinjiang, China, [2]Department of Internal Medicine Nursing, School of Nursing, Xinjiang Medical University, Urumqi, Xinjiang, China, [3]Department of Health Science, School of Nursing, Peking University, Beijing, China

Background: Cognitive impairment is an age-relevant intermediate stage where cognition declines to a state between the normal aging process and dementia. Earlier studies reported that depression, inappropriate nighttime sleep duration (NSD), and limited leisure activity engagement are cognitive impairment risk factors among older adults. Thus, we postulated that interventions on depression, sleep duration, and leisure activity engagement can reduce cognitive impairment risk. However, no earlier research ever explored this.

Methods: The data of 4,819 respondents aged 60 years and above, without cognitive impairment at baseline and with no prior history of memory-related diseases, including Alzheimer's disease, Parkinson's disease, and encephalatrophy, were obtained from the China Health and Retirement Longitudinal Study (CHARLS) between 2011 and 2018. The parametric g-formula, an analytic tool for estimating standardized outcome distributions using covariate (exposure and confounders)-specific estimates of the outcome distribution, was used to estimate 7-year cumulative cognitive impairment risks among older Chinese adults, under independent hypothetical interventions on depression, NSD, and leisure activity engagement, which was subdivided into social activity (SA) and intellectual activity (IA) for the different intervention combinations.

Results: The observed cognitive impairment risk was 37.52%. Independent intervention on IA was the most effective factor in reducing incident cognitive impairment, with a risk ratio (RR) of 0.75 (95% confidence interval [CI]: 0.67–0.82), followed by depression (RR: 0.89, 95% CI: 0.85–0.93) and NSD (RR: 0.88, 95% CI: 0.80–0.95). The joint intervention combining depression, NSD, and IA interventions could reduce the risk by 17.11%, with an RR of 0.56 (95% CI: 0.48–0.65). In subgroup analyses, independent interventions on depression and IA had analogously significant effects on men and women. However, interventions on depression and IA had stronger effects on literate than illiterate individuals.

Conclusions: Hypothetical interventions on depression, NSD, and IA reduced cognitive impairment risks among older Chinese adults, both independently and

jointly. The findings of the present study suggest that the intervention measures on depression, inappropriate NSD, limited intellectual activities, and their combination may prove to be effective strategies for preventing cognitive impairment among older adults.

KEYWORDS

older adults, cognitive impairment, sleep duration, depression, leisure activity, g-formula

Introduction

Cognitive impairment is an age-relevant intermediate stage of cognitive decline between the normal aging process and dementia, featuring cognition declines in memory, visuospatial ability, orientation, calculation, execution, and comprehension (1, 2). Older adults with cognitive impairment tend to have a significantly higher risk of dementia, with a progression rate of 10%−30% per year, whereas those adults without cognitive impairment have a progression rate of 1%−2% annually (3). Accordingly, it is important to identify older adults with cognitive impairment not only to develop interventions that alleviate individual suffering but also because this represents a population that is at an increased risk of developing dementia. Among older adults aged 60 years and above, the global prevalence of cognitive impairment ranges from 5.1% to 41.0% (4). In China, it is reported that the prevalence of cognitive impairment varies from 2.40% to 39.88% among older adults in different provinces, and approximately 36,000 additional cases of cognitive impairment occur annually (2, 5). The Chinese population is aging dramatically. In 2021, the population of people aged 60 years and above was 267 million, but it is projected to surpass the 400 million mark by 2035 (6). Therefore, China faces several challenges with regard to cognitive impairment among older adults, and early screening and intervention for cognitive impairment should receive more attention.

Evidence shows that women and individuals with low education levels are common risk factors for cognitive impairment (7, 8). An earlier study showed that overall cognitive impairment is more serious in women than in men (9). Consistent with this result, another study confirmed that Chinese women are significantly disadvantaged when it comes to cognitive functioning in old age (10). As regards education, a Chinese-based longitudinal study revealed that a low education level is associated with a high risk of cognitive impairment among older adults (5). As well as gender and education level, depression, inappropriate nighttime sleep duration (NSD), and limited leisure activity engagement are reported as other risk factors for cognitive impairment among older adults (11–13). Obvious issues with addressing the immutable characteristic of gender, and difficulty with changing the education level, especially in older adults, are prevalent. However, numerous studies revealed that treatments or interventions on depression, inappropriate NSD, and limited leisure activity engagement can not only ameliorate the symptoms themselves but may also be beneficial for improving cognitive performance and reducing the risk of cognitive impairment, although the results of these studies are mixed. For depression, reviews by Motter et al. (14) and Culpepper et al. (15), which examined the effectiveness of cognitive remediation therapy (CRT) in improving depression and cognition, revealed that CRT is effective in reducing depressive symptoms and improving cognitive functions. However, Wong et al. (16) and Adler et al. (17) demonstrated that, in cognitively impaired patients with depression, treatments are only effective in improving depression and not cognitive impairment. As regards the NSD, earlier studies reported that changes from long (≥9 h) to moderate (6–9 h) sleep duration (18), or from short (<6 h) to moderate (6–9 h) sleep duration (19), were negatively associated with cognitive impairment risks. Nevertheless, three other studies demonstrated that, compared with unchanged sleep durations in baseline and follow-ups, any increases or decreases in sleep durations were associated with worse cognitive performances or increased cognitive impairment risks, despite using the different sleep duration references (20–22). Participation in leisure activity and its subtypes, namely social activity (SA), physical activity (PA), and intellectual activity (IA), has been proven to be beneficial for the preservation of cognitive function (23). Several studies examining the association between leisure activity engagement and cognitive function in older adults demonstrated that SA and/or IA are relevant to decreased cognitive deficit and risks of dementia (24–26). Notably, changes in leisure activity engagement also have effects on subsequent trajectories of age-related cognitive performance, so individuals with more leisure activity engagement than before will have slower cognitive decline rates as they age (13). Although some, mostly observational, studies confirmed the risk factors of cognitive impairment to a certain extent, many limitations are prevalent with regard to not properly controlling confounding variates such as time-varying confounders in observational studies and a lack of, or inability to, estimate the causal effect of risk factors.

The standard for evaluating the comparative effectiveness and the causal effect of an intervention is a randomized controlled trial (RCT). However, when RCTs are not feasible or timely, the impact of potential treatment strategies can be informed empirically using observational data to emulate a target trial (27). Target trial emulation is the application of design principles from RCTs to the analysis of observational data, thereby explicitly tying the analysis to the trial it is emulating (28). This requires a clear specification of the trial protocol elements and, when assessing interventions sustained over time, an analytic method known as the g-formula is required to appropriately account for time-dependent confounding variate (27). The g-formula, first described by Robins (29) in 1986, is used to estimate the causal effect of arsenic on heart disease in an occupationally exposed cohort and is an analytic tool for estimating standardized outcome distributions using covariate (exposure and confounders)-specific estimates of the outcome distribution (30). It can be viewed as a generalized form of standardization of the conditional hazard under each treatment strategy to the joint distribution of the time-varying covariates so that it can appropriately adjust for time-varying confounders affected by prior exposures. It is especially well-suited

to estimating effects when the intervention involves multiple factors (joint interventions) or decisions that depend on the value of evolving time-dependent factors (31). Moreover, while observational analyses are restricted to a framework where one can only test interventions that have been explicitly carried out in the data, the g-formula enables one to simulate treatment strategies (also called hypothetical intervention) and to estimate their effect, even if those strategies have not been fully carried out in the data used to construct the model (32). Earlier studies using the parametric g-formula were conducted to measure hypothetical interventions on the levels of blood pressure, cholesterol, weight, PA, smoking, and alcohol intake for preventing stroke (33) and to estimate the risk of fall under single and joint interventions on sleep duration, SA, smoking, drinking, body mass index (BMI), systolic blood pressure, vision, depression, and activities of daily living scores (ADLs) (34). However, research using the parametric g-formula to investigate the risks of cognitive impairment under hypothetical interventions is limited. Therefore, the present study aimed at estimating the 7-year cumulative risks of cognitive impairment under independent interventions on depression, NSD, SA, and IA, as well as joint interventions consisting of different combinations thereof, using the parametric g-formula on the basis of a nationwide representative cohort of the China Health and Retirement Longitudinal Study (CHARLS). Such an estimation can help guide and provide intervention strategies and alternative treatments for the prevention of cognitive impairment among community-dwelling older Chinese adults.

Materials and methods

Data sources and participants

Data were extracted from four waves of CHARLS conducted in 2011 (wave 1), 2013 (wave 2), 2015 (wave 3), and 2018 (wave 4). CHARLS is a national longitudinal survey aimed at investigating and evaluating the aging issue of adults from 150 country-level units distributed in 28 provinces of China. It has been conducted by the Institute of Social Science Survey of Peking University since 2011, which updates the aforementioned survey every 2 years. The participants were informed of the research purpose and signed written informed consent forms to participate. Ethical approval was obtained from the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015) (35).

In total, 17,954 respondents were included in the first wave (2011), and these data were used as the baseline. To emulate hypothetical interventions on cognitive impairment risks, the inclusion and exclusion criteria were set according to the g-formula principle. The inclusion criteria of the present study were as follows: (1) participants aged 60 years and above, (2) participants who had no cognitive impairment at baseline, and (3) participants who had completed at least one follow-up. The exclusion criteria of the present study were as follows: (1) participants' key variables were missing and (2) participants were diagnosed with memory-related diseases including Alzheimer's disease, Parkinson's disease, and encephalatrophy at baseline. Finally, a total of 4,819 respondents were included in the analysis. The sample selection flowchart for this study is presented in Figure 1. For each participant, the follow-up was ended at the time of onset of cognitive impairment, when the patient was lost to follow-up, or when the patient was part of the examination of wave 4 (2018), whichever occurred first.

Cognitive impairment

The cognitive function was assessed by four dimensions comprising orientation, attention, episodic memory, and visuospatial ability. Cognition scores were calculated using the Telephone Interview for Cognitive Status (TICS-10), word recall, and picture redrawing. An overall cognition score (36) was considered the primary outcome of interest. The sum of all three TICS-10 scores (orientation and attention), word recall (episodic memory), and figure drawing (visual spatial ability) was then calculated to assess the global cognitive function, with the score ranging from 0 to 21. A higher score indicated a better cognitive function. Cronbach's α was 0.84 across all four waves.

Due to the discordancy of the criteria among multiple measurements, we used the concept of aging-associated cognitive decline (AACD) to define cognitive impairment, requiring at least one standard deviation (SD) below age-appropriate norms (10, 37). AACD—which is recommended by the International Psychogeriatric Association in collaboration with the World Health Organization (the WHO)—seeks evidence of cognitive decline within a broader range of cognitive domains, covering all criteria for estimating cognitive impairment. The AACD has been widely used as diagnostic criteria for estimating cognitive decline by both clinicians and scholars, therefore fitting the aim of this study (38). Respondents were divided into age groups, with each group representing a 5-year interval, and individuals with cognition scores lower than 1 SD from their group mean were defined as having cognitive impairment.

Intervention variables

Depressive symptoms were assessed using the 10-item Center for Epidemiologic Studies Depression (CES-D-10) Scale which comprised 10 depressive effects: bothered by things that usually did not bother them, trouble in concentration, feeling depressed, effort exerted to complete daily tasks, feeling fearful, restless sleep, loneliness, inability to "get going," feeling hopeful about the future, and feeling happy. Each of the 4-option responses to the item was scored from 0 to 3, and the total score was the sum of points for all 10 items. A total score of 10 or higher indicated clinical depression (39).

Nighttime sleep duration was obtained from the question "During the past month, how many hours of actual sleep did you get at night?" As reported in earlier studies, we took an NSD of 6 h as the reference duration (12) and classified participants into a 6-hr group and a non-6-hr group.

Leisure activity engagement was assessed through SA and IA (24). The SA items included: interacting with friends; going to a sport, social, or any other kind of club; taking part in a community-related organization; and doing volunteer or charity work. The IA items included: playing Mahjong, chess, or cards; attending an education or training course; stock investment; and surfing the Internet. The frequency of each activity was rated as never (score = 0), not regularly (score = 1), almost every week (score = 2), and almost daily (score = 3). All activity types were synthesized to a sum score ranging from

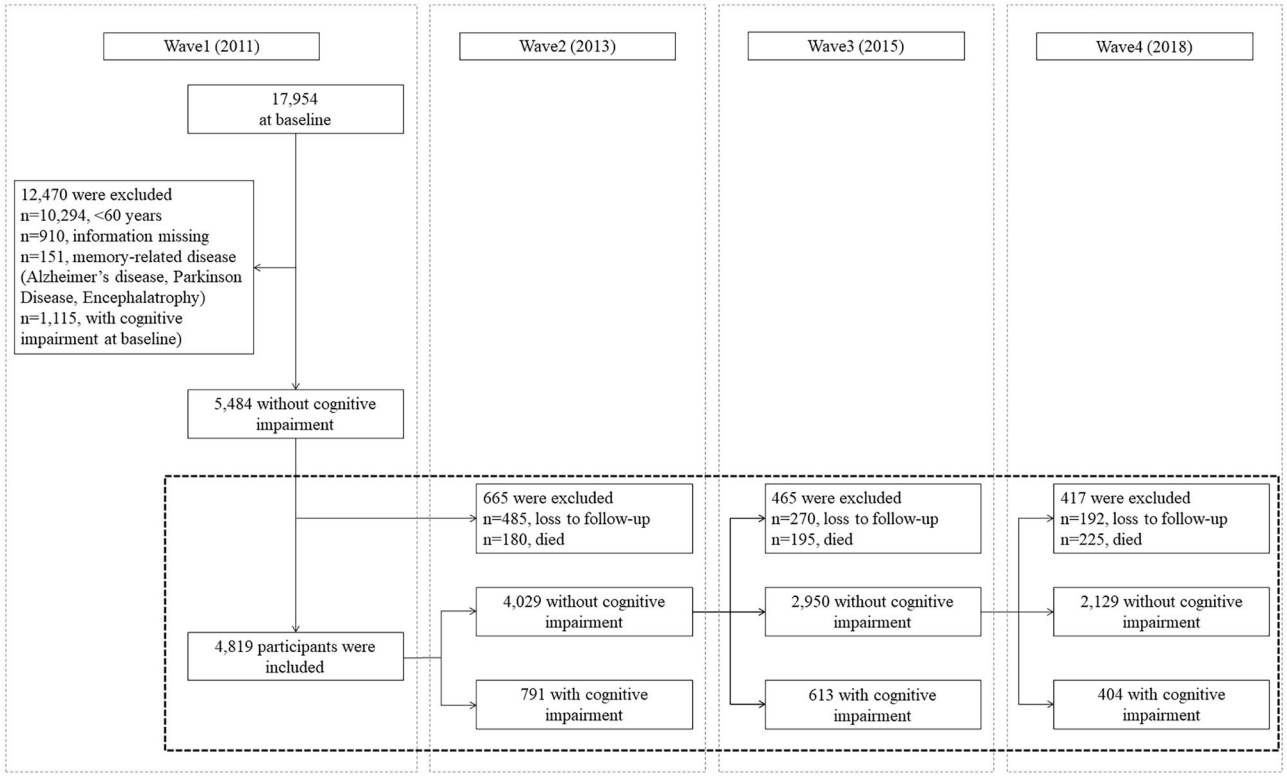


FIGURE 1
Sample selection flowchart based on the 2011–2018 China Health and Retirement Longitudinal Study (CHARLS) data.

0 to 12 based on the frequency level. Participants whose sum score was > 1 were categorized as "participating in SA/IA"; otherwise, they were regarded as "not participating in SA/IA."

Covariates

Baseline covariates included gender (male/female), age (continuous), education level (literate/illiterate), and marital status (married/other). Time-varying covariates included ADLs (restricted/unrestricted), instrumental activities of daily living scores (IADLs, restricted/unrestricted), chronic diseases (0/1–2 diseases/ ≥ 3 diseases), smoking status (none/quit/still smokes), drinking status (none of these/drinks but less than once a month/drinks more than once a month), and PA (continuous).

Functional disability was measured based on ADLs and IADLs. ADLs included six aspects: dressing, bathing or showering, eating, getting into or out of bed, using the toilet, and controlling urination and defecation. IADLs comprised five aspects: doing household chores, preparing hot meals, shopping, taking medications, and managing money. The response scale contained four options: "no, I do not have any difficulty," "I have difficulty but can still do it," "yes, I have difficulty and need help," and "I cannot do it." Participants whose responses were "no, I do not have any difficulty" for all items of ADLs or IADLs were classified as "unrestricted" to ADLs or IADLs; otherwise, they were classified as "restricted." Chronic diseases were determined by asking "Have you been diagnosed with the following conditions by a doctor?" and comprised the following 13 diseases: hypertension, dyslipidemia, diabetes, or hyperglycemia; cancer or malignant tumor; chronic lung disease; liver disease; heart attack; coronary heart disease; angina; congestive heart failure; stroke; kidney disease; stomach, emotional, nervous or psychiatric problems; arthritis or rheumatism; and asthma. Participants were classified as having no diseases, one to two chronic diseases, and over two chronic diseases based on their responses. PA comprised the amount of time a person spent on vigorous activities, moderate activities, and walking in a usual week. According to the responses, we indexed the amount of PA per day as 1 (<0.5 h), 2 (0.5–2 h), 3 (2–4 h), and 4 (>4 h). The weekly PA duration score was calculated by multiplying the number of days the activity was performed and the daily PA duration index for each activity. Finally, we generated the PA score variables using metabolic equivalent (MET) multipliers as follows: PA score = 8.0 × total vigorous activity weekly duration score + 4.0 × total moderate activity weekly duration score + 3.3 × total walking weekly duration score (40).

Hypothetical interventions

The parametric g-formula was used to estimate cognitive impairment risks under each of the following hypothetical interventions. Single interventions were as follows:

1. Depression: Intervention resolved all depressive symptoms in all participants.
2. NSD: Intervention resulted in all participants sleeping for 6 h per night.
3. SA: Intervention ensured that all participants took part in SA.

10.3389/fpubh.2023.1088833

4. IA: Intervention ensured that all participants took part in IA.

Joint interventions consisted of combinations of single interventions, which were significant in the last stage of analysis.

Statistical analysis

The 7-year cumulative risks of cognitive impairment under hypothetical interventions were estimated by applying the parametric g-formula. The g-formula directly models probabilities for a given outcome conditional upon covariates and exposures/interventions (32). For real-world datasets, directly modeling all conditional probabilities is not feasible, especially in the presence of continuous covariates. The parametric g-formula is an extension of the g-formula, where parametric models are used to model probabilities, instead of direct calculations. Under the assumptions of no unmeasured confounding and no model misspecification, this method can provide an estimate of the risk of outcomes under full adherence to different hypothetical sustained interventions (27). The standardized risk is estimated by a weighted average of the risks of cognitive impairment conditional on the given intervention and observed confounder history. The weights are probability distribution functions of the time-varying confounders estimated using parametric regression models. The weighted average is approximated through the Monte Carlo simulation (41). We used cognitive impairment as the outcome and simulated cognitive impairment risks under each single and joint intervention using the parametric g-formula with the following four-step algorithm (42):

1. Fit a parametric regression model for each time-varying covariate, as a function of the baseline covariate and covariate history among participants followed up to time *k*.
2. Estimate the conditional probability of cognitive impairment, as a function of conditional on intervention and covariate history and surviving and remaining uncensored among participants followed up to time *k*, using a pooled over-time logistic regression model to approximate time-to-failure risk.
3. Perform a Monte Carlo simulation to generate life histories for a pseudo-population of 10,000 simulated individuals, in which baseline covariates are randomly sampled with replacements from the original population. Time-varying covariates are drawn from the parametric distribution in Step 1, and intervention covariates are set based on the defined strategy, except for the natural course (no intervention) strategy.
4. Compute the intervention risk estimate of cognitive impairment at 7 years in the pseudopopulation. The risk ratio (RR)/risk difference (RD) can be constructed between each strategy and the natural course. Ninety-five percent confidence intervals (CIs) are computed by repeating the entire aforementioned steps in 500 bootstrap samples.

The aforementioned steps were repeated for each single and joint intervention to compute cognitive impairment risks, RRs, and RDs. We also conducted subgroup analyses to assess different effects of each single intervention according to gender (male and female) and education (illiteracy and literacy). To test the model reliability, sensitivity analyses were performed by changing the order of time-varying covariates. All analyses were conducted using the R 4.1.2 statistical package for the g-formula for Windows.

TABLE 1 The distribution of variables at baseline.

Characteristic	N (%)
Age (years, mean ± SD)	68.0 ± 6.6
60~	1,875 (38.9)
65~	1,229 (25.5)
70~	875 (18.2)
75~	499 (10.3)
80~	341 (7.1)
Gender (*n*/%)	
Male	2,647 (54.9)
Female	2,172 (45.1)
Education level (*n*/%)	
Illiterate	1,378 (28.6)
Literate	3,441 (71.4)
Marital status (*n*/%)	
Married	3,932 (81.6)
Others	887 (18.4)
ADLs (*n*/%)	
Restricted	994 (20.6)
Unrestricted	3,825 (79.4)
IADLs (*n*/%)	
Restricted	1,094 (22.7)
Unrestricted	3,725 (77.3)
Number of chronic diseases (*n*/%)	
None	1,252 (26.0)
1–2	2,504 (52.0)
≥3	1,063 (22.0)
Smoking status (*n*/%)	
None	2,596 (53.9)
Still smokes	1,614 (33.5)
Quit	609 (12.6)
Drinking status (*n*/%)	
None	3,225 (66.9)
Drink but less than once a month	380 (7.9)
Drink more than once a month	1,214 (25.2)
CES-D 10 (score, mean ± SD)	8.5 ± 6.1
With depression	1,827 (62.1)
Without depression	2,992 (37.9)
NSD (hours, mean ± SD)	6.3 ± 1.9
6 h	1,091 (22.6)
Others	3,728 (77.4)
SA (*n*/%)	
Participate	1,959 (40.7)
Not participate	2,860 (59.3)

(Continued)

TABLE 1 (Continued)

Characteristic	N (%)
PA (score, mean ± SD)	103.5 ± 77.6
IA (*n*/%)	
Participate	935 (19.4)
Not participate	3,884 (80.6)

ADLs, activities of daily living scores; IADLs, instrumental activities of daily living scores; NSD, nighttime sleep duration; SA, social activity; PA, physical activity; IA, intellectual activity.

Results

Baseline characteristics

Table 1 summarizes the sample characteristics at baseline. The mean age of respondents was 68.0 years, with an SD of 6.6 years. The proportion of men was larger than that of women: 54.9% and 45.1%, respectively. Among the population, 71.4% were literate and 81.6% were married. Over 75% were classified as being without restricted ADLs (79.4%) and IADLs (77.3%) at baseline. As regards chronic diseases, 52.0% of the individuals had 1–2 such diseases and 22.0% of them had more than two. Significantly more participants had never smoked (53.9%) or drank (66.9%) than participating in those actions. The mean CES-D-10 score and NSD were 8.5 points and 6.3 h, respectively. Accordingly, the prevalence of individuals without depression and of those who sleep 6 h at night was 37.9% and 22.6%, respectively. As regards leisure activity engagement, the mean score of PA was 103.5. The prevalence of older adults participating in SA and IA was 40.7% and 19.4%, respectively.

During the 7-year follow-up, 1,808 participants developed cognitive impairment, with a significantly lower prevalence in men than in women (28.9% vs. 48.1%); similarly, this tendency was observed in the literate and illiterate groups, with 25.3% and 68.1% prevalence, respectively.

Interventions in total population

The 7-year cumulative risks of cognitive impairment under four single hypothetical interventions, as estimated by the parametric g-formula, are shown in Table 2. The observed cognitive impairment risk was 37.52%, and the simulated risk in the natural course was 39.28% (95% CI: 35.99–44.12). Among the independent hypothetical interventions, participants who were in the IA intervention group showed the greatest risk reduction, with an RR of 0.75 (95% CI: 0.67–0.82). Notably, independent interventions for depression and NSD showed similar effects, with RRs of 0.89 (95% CI: 0.85–0.93) and 0.88 (95% CI: 0.80–0.95), respectively. However, participants who were in the SA intervention group did not show a decreased risk of cognitive impairment, with an RR of 1.00 (95% CI: 0.95–1.04).

Table 3 depicts the cognitive impairment risks under different combinations of joint interventions, after exclusion of the SA intervention due to its ineffectiveness. All joint interventions could significantly reduce cognitive impairment risks among older adults. Due to the similar effects of independent interventions on depression and NSD, the combination of "Depression + IA" and "NSD + IA" showed similar effects, with RRs of 0.66 (95% CI: 0.58–0.73) and 0.65 (95% CI: 0.58–0.70), respectively. The joint intervention of "Depression + NSD" could reduce the risk by 8.93%, with an RR of 0.77 (95% CI: 0.69–0.84). The "All factors" joint intervention, that combined interventions on depression, NSD, and IA, reduced the risk by 17.11%, with an RR of 0.56 (95% CI: 0.48–0.65).

Interventions in subgroups

In subgroup analyses, intervention on SA was excluded once more due to its lack of significance. The results showed a difference in independent intervention when stratified by gender (Table 4) and education level (Table 5). The cognitive impairment risk in men was lower than that in women (33.83% vs. 49.48%) in the natural course, similar to the literate and illiterate groups (26.79% vs. 72.62%). For gender subgroups, in men, only independent interventions on depression and IA had significant effects on reducing the risks of cognitive impairment, with RRs of 0.88 (95% CI: 0.83–0.94) and 0.74 (95% CI: 0.63–0.86), respectively. In contrast, for women, all three independent interventions on depression, NSD, and IA had significant effects, with RRs of 0.89 (95% CI: 0.83–0.94), 0.84 (95% CI: 0.74–0.94), and 0.76 (95% CI: 0.65–0.85), respectively (Figure 2). For education subgroups, in the literate group, all three independent interventions on depression, NSD, and IA had significant effects, with RRs of 0.80 (95% CI: 0.74–0.86), 0.85 (95% CI: 0.73–0.99), and 0.69 (95% CI: 0.59–0.79), respectively. Similarly, in the illiterate group, all three independent interventions on depression, NSD, and IA had significant effects, with RRs of 0.96 (95% CI: 0.92–1.00), 0.90 (95% CI: 0.81–1.00, and 0.80 (95% CI: 0.66–0.93), respectively (Figure 3).

Discussion

We estimated the 7-year cumulative risks of cognitive impairment under single and joint interventions on depression, sleep duration, and leisure activity engagement among older Chinese community-dwelling adults by applying the parametric g-formula to the nationally representative CHARLS cohort. The results of the present study suggest that single interventions on depression, NSD, and IA could reduce cognitive impairment risks, and that different combinations of these interventions reduced the risk further. Similar effects were observed in gender subgroups, with interventions on depression and IA reducing cognitive impairment risks. However, the effects of interventions on depression and IA were greater in literate than illiterate individuals.

The results of the present study showed that independent hypothetical interventions on depression, NSD, and IA could reduce cognitive impairment risks by 4.33%, 4.79%, and 9.94%, respectively, while the joint hypothetical intervention of all three factors could significantly reduce cognitive impairment risk by 17.11%. These findings confirmed the conclusions of earlier studies, wherein depression, inappropriate NSD, and limited IA were found to be risk factors for cognitive impairment among older adults (11–13). As the g-formula is a causal-effect analytic method, the results of the present study showed the causal effects of depression, inappropriate NSD, and limited IA engagement on the incidence of cognitive impairment. Thus, the social and public health implications of this finding are that it can provide both a theoretical and data-driven basis for future RCTs of interventions on depression, inappropriate

TABLE 2 Cognitive impairment risks at 7-year follow-up under natural course and single hypothetical interventions.

Intervention	Risk (%)	95% CI	RR	95% CI	RD (%)	95% CI
Natural course	39.28	35.99, 44.12	1.00			
Depression	34.96	31.01, 39.79	0.89	0.85, 0.93	−4.33	−5.85, −3.08
NSD	34.50	29.73, 40.03	0.88	0.80, 0.95	−4.78	−7.75, −2.12
SA	39.12	35.02, 44.16	1.00	0.95, 1.04	−0.16	−1.99, 1.59
IA	29.35	25.38, 34.01	0.75	0.67, 0.82	−9.94	−13.29, −7.03

NSD, nighttime sleep duration; SA, social activity; IA, intellectual activity, RR, risk ratio; RD, risk difference; CI, confidence interval.

TABLE 3 Cognitive impairment risks at 7-year follow-up under natural course and joint hypothetical interventions.

Intervention	Risk (%)	95% CI	RR	95% CI	RD (%)	95% CI
Natural course	39.28	35.99, 44.12	1.00			
Depression + NSD	30.36	25.68, 35.75	0.77	0.69, 0.84	−8.93	−12.11, −6.27
Depression + IA	25.89	21.99, 30.77	0.66	0.58, 0.73	−13.39	−16.78, −10.56
NSD + IA	25.51	21.69, 28.69	0.65	0.58, 0.70	−13.92	−17.02, −12.02
All factors	22.17	17.81, 27.40	0.56	0.48, 0.65	−17.11	−20.75, −13.91

NSD, nighttime sleep duration; IA, intellectual activity, RR, risk ratio; RD, risk difference; CI, confidence interval.

TABLE 4 Cognitive impairment risks at 7-year follow-up under natural course and single hypothetical interventions in subgroups stratified by gender.

Intervention	Risk (95% CI)		RD (95% CI)	
	Male	Female	Male	Female
Natural course	33.83 (27.24, 40.13)	49.48 (42.91, 55.58)		
Depression	29.91 (23.95, 36.02)	43.93 (36.79, 50.15)	−3.92 (−5.57, −2.03)	−5.55 (−8.03, −3.14)
NSD	31.23 (23.78, 38.62)	41.44 (33.56, 49.48)	−2.61 (−7.01, 1.17)	−8.03 (−12.57, −3.03)
IA	24.95 (19.19, 31.46)	37.54 (29.50, 45.11)	−8.89 (−12.54, −4.87)	−11.94 (−17.27, −7.28)

NSD, nighttime sleep duration; IA, intellectual activity, RD, risk difference; CI, confidence interval.

NSD, and limited IA engagement to prevent cognitive impairment among older adults. Moreover, our result is also helpful for community health service institutions to provide timely intervention for community-dwelling older adults with depression, inappropriate NSD, and limited IA engagement to reduce the risk of cognitive impairment. Nonetheless, it is unclear how these factors might increase cognitive impairment risks. Currently, researchers proposed several depression-relevant mechanisms as follows: (1) depressive symptoms can generate hyperactivity of the hypothalamic–pituitary–adrenal axis, thus increasing glucocorticoids, possibly leading to hippocampal damage and development of cognitive impairment (43). (2) Depression can cause hippocampal atrophy and accelerate the loss in hippocampal volume in women *via* the primary mediating mechanism of glucocorticoids (44). (3) Depression may also contribute to a cognitive decline through other pathways such as vascular disease, inflammation, impact on nerve growth factors, or by increasing β-amyloid accumulation (45). As regards the impact of NSD on cognition, evidence shows that the mechanisms of short and long sleep durations are different. Short sleep duration contributes to cognitive impairment *via* several different pathologies such as impaired β-amyloid clearance, pathological tau, impaired synaptic plasticity, atrophy of the cortex, and circadian rhythm disturbances. In contrast, long sleep duration is relevant to sleep fragmentation and chronic inflammation, which are linked to lower cognition (46). Moreover, Spira et al. (47) demonstrated that, among individuals with a normal cognitive function, sleep durations of <7 h and of >7 h may accelerate frontotemporal gray matter atrophy and subsequently increase the cognitive impairment risk. This result is not consistent with the results from both this study and an earlier one, which took 6 h as the reference sleep duration (12). These differences may have arisen due to differences in the study population such as race, study sample size, and population age bracket. The beneficial effects of IA engagement on impaired cognition risk reduction may be due to improved cognitive reserves. Excess β-amyloid can accumulate in the brain as plaques that block the gaps between synapses, which in turn affects the electrical signals used by the neurons to communicate with each other; moreover, the chemistry-imbalanced tau protein can entangle with other tau proteins to form tangles, which will destroy microtubules and prevent necessary nutrients from reaching nerve endings of neurons, thus causing the entire cell to become dysfunctional. All of these alterations can cause cognitive impairment (48). According to the cognitive reserve theory, IA can strengthen the functioning and plasticity of neural circuits, further increasing the cognitive reserve and decreasing the risk of cognitive impairment (25).

Cognitive impairment risks did not decrease under the SA intervention. A similar result was reported by Li et al. (48) who found that a higher participation in SA did not improve cognitive function. Moreover, an RCT conducted by Park et al. (49) also found that engagement in SA had limited

TABLE 5 Cognitive impairment risks at 7-year follow-up under natural course and single hypothetical interventions in subgroups stratified by education.

Intervention	Risk (95% CI)		RD (95% CI)	
	Illiteracy	Literacy	Illiteracy	Literacy
Natural course	72.62 (64.53, 79.40)	26.79 (21.65, 32.38)		
Depression	69.54 (60.57, 77.94)	21.52 (16.93, 26.69)	−3.09 (−5.71, −0.31)	−5.27 (−7.08, −3.58)
NSD	65.31 (54.82, 75.64)	22.90 (17.44, 29.57)	−7.32 (−13.32, −0.62)	−3.89 (−7.06, −3.72)
IA	58.21 (45.83, 70.26)	18.51 (13.62, 23.95)	−14.41 (−24.19, −4.96)	−8.29 (−11.07, −5.49)

NSD, nighttime sleep duration; IA, intellectual activity, RD, risk difference; CI, confidence interval.

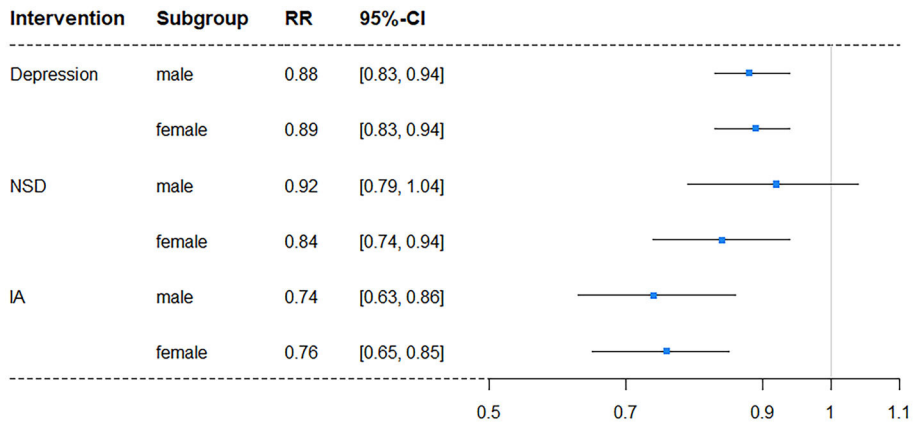


FIGURE 2
Forest plot of RR for depression risk in subgroups stratified by gender (NSD, nighttime sleep duration; IA, intellectual activity, RR, risk ratio; CI, confidence interval).

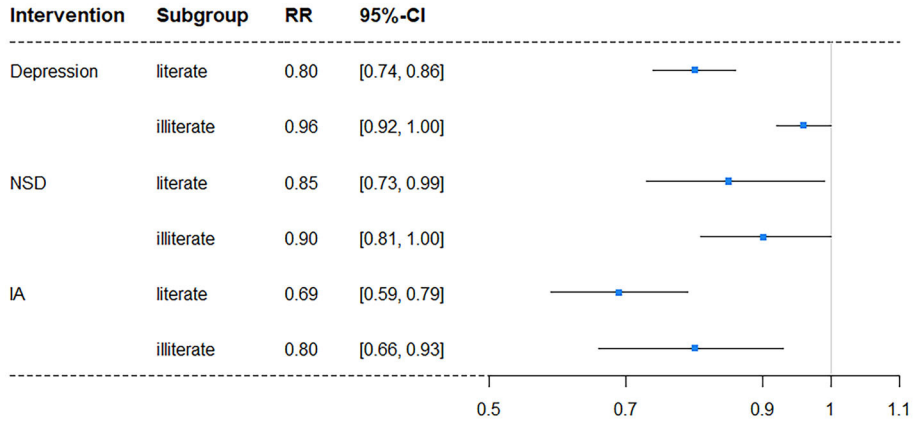


FIGURE 3
Forest plot of RR for depression risk in subgroups stratified by education level (NSD, nighttime sleep duration; IA, intellectual activity, RR, risk ratio; CI, confidence interval).

cognitive benefits. Interpretations for this phenomenon may be attributed to the fact that reduced social participation is an early manifestation of cognitive impairment rather than a cause (48). Additionally, simple SA is not particularly helpful in optimizing cognition in the long term because of the relatively passive participation and low cognitive demand. Such passivity may not be particularly beneficial for enhancing cognitive reserve (50). Therefore, monitoring changes of engagement in SA, rather than intervening to increase SA participation, may be beneficial to prevent cognitive impairment among older adults *via* timely identification and intervention.

Notably, in subgroup analyses, although similar effects of interventions on depression and IA for cognitive impairment risks were observed in gender subgroups, interventions on depression and IA displayed stronger effects in literate than illiterate participants. Several studies reported that education years and high education levels could predict and alleviate the severity of depression (51, 52). Accordingly, the intervention on depression was effective

for literate individuals, reducing cognitive impairment risks. As regards different effectiveness levels of interventions on IA for literate and illiterate individuals, as far as we know, we are the first to find a difference. We speculate that older adults with high education levels get more training and application during engagement because IA subtypes need more comprehend ability. As a result, intervention on IA was more effective for literate than for illiterate individuals. Recently, studies investigated the effectiveness of continuing education for the prevention of cognitive impairment and dementia. Thow et al. (53) reported that older adults who attended university courses over a period of 12 months showed significant improvement in their language processing capacity compared with healthy adult controls, but there was no change in their fluid cognitive function. However, another study, by Lenehan et al. (54), found that 92.5% of older individuals who undertook further education in 12-month part- or full-time university courses displayed a significantly linear increase in cognitive reserve over the 4 years of study, indicating that continuing education could improve cognitive function and offset cognitive decline. Because of these contradicting results, more studies focusing on the effectiveness of continuing education for the prevention of cognitive impairment and dementia are essential. If the possible preventive effects are confirmed, then interventions based on continuing education for older adults should be established and promoted in communities and nursing facilities.

The strengths of the present study are the population-based longitudinal design, standardized survey methods, rigorous case validation, and long follow-up time. We used the parametric g-formula to appropriately adjust for time-varying confounders and estimate the effects of independent and joint interventions on depression, NSD, and IA for a reduction in cognitive impairment risks. Thus, the estimates are more directly relevant and provide more information to guide public health and clinical decisions. However, the present study has several limitations. First, the validity of the g-formula approach relies on three common assumptions for observational research: no model misspecification, no measurement error, and no unmeasured confounding. We adjusted for many potential risk factors to alleviate the "no measurement error" and "no unmeasured confound issues," which were inevitable for this observational study. Evidence that simulated data under no intervention using the parametric g-formula were analogous to the observed data, indicating the condition of no model misspecification. Our sensitivity analyses also revealed that our results were robust across different specifications. Second, the precondition of generalizing our results to other populations is based on the condition that the target population should have the same distribution of effect modifiers and interference patterns as our study population because the calculation principle of the g-formula is based on the standardized risk to the distribution of risk factors. Due to the advantage of a population-based sample, we consider that the conclusion of this study has a certain degree of generalizability to some extent. Finally, we implicitly assumed that the counterfactual outcome for all scenarios should be the same as the observed outcome under the observed exposure history. It should be noted that, in real life, idealized intervention effects and complete adherence of participants are hard to accomplish; therefore, our estimates purely correspond to the best-case scenario, rather than the specific circumstances of each program.

Conclusions

By applying the parametric g-formula to a longitudinal sample from CHARLS, we found that hypothetical interventions on depression, NSD, and IA can reduce cognitive impairment risks among older Chinese adults, both independently and jointly. Furthermore, we observed similar effects of interventions on depression and IA in gender subgroups, but interventions on depression and IA had stronger effects in literate than illiterate individuals. Thus, the findings of the present study suggest that intervention measures for depression, inappropriate NSD, and limited intellectual activities and any combination thereof may prove to be effective strategies for the prevention of cognitive impairment among older adults.

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.

Ethics statement

The studies involving human participants were reviewed and approved by the Biomedical Ethics Committee, Peking University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

NZ: conceptualization, data curation, statistical analysis, methodology, drafting, manuscript editing, and graphics production. FC and CW: methodology and reviewing. PY: conceptualization, methodology, supervision, reviewing, and editing. All authors contributed to the article and approved the submitted version.

Funding

This research was supported by the Regional Collaborative Innovation Special Project of Autonomous Region—Science and Technology Aid Xinjiang Plan (No. 2022E02119) and the Xinjiang Medical University Doctoral Research Start-up Grant.

Acknowledgments

All authors thank CHARLS for providing data. They are grateful to those who designed, conducted, and participated in this study.

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

References

1. Xiong S, Liu S, Qiao Y, He D, Ke C, Shen Y. Estimation of losses of quality-adjusted life expectancy attributed to the combination of cognitive impairment and multimorbidity among Chinese adults aged 45 years and older. *BMC Public Health.* (2021) 21:24. doi: 10.1186/s12889-020-10069-w

2. Xue J, Li J, Liang J, Chen S. The prevalence of mild cognitive impairment in China: a systematic review. *Aging Dis.* (2018) 9:706–15. doi: 10.14336/ad.2017.0928

3. Falck RS, Davis JC, Best JR, Chan PCY Li LC, Wyrough AB, et al. Effect of a multimodal lifestyle intervention on sleep and cognitive function in older adults with probable mild cognitive impairment and poor sleep: a randomized clinical trial. *J Alzheimers Dis.* (2020) 76:179–93. doi: 10.3233/jad-200383

4. Pais R, Ruano L, Ofélia PC, Barros H. Global cognitive impairment prevalence and incidence in community dwelling older adults-a systematic review. *Geriatrics (Basel).* (2020) 5:84. doi: 10.3390/geriatrics5040084

5. Zhang Q, Wu Y, Han T, Liu E. Changes in cognitive function and risk factors for cognitive impairment of the elderly in China: 2005–2014. *Int J Environ Res Public Health.* (2019) 16:2847. doi: 10.3390/ijerph16162847

6. National Health Commission of the People's Republic of China. *Report of the State Council on the Progress of Strengthening and Promoting the Work on Aging. National Health Commission of the People's Republic of China* (2022). Available online at: https://www.nhc.gov.cn/wjw/mtbd/202209/2ca97b572ee34a38819cceaf5207dd1a.shtml (accessed November 3, 2022).

7. Millán-Calenti JC, Tubío J, Pita-Fernández S, González-Abraldes I, Lorenzo T, Maseda A. prevalence of cognitive impairment: effects of level of education, age, sex and associated factors. *Dement Geriatr Cogn Disord.* (2009) 28:455–60. doi: 10.1159/000257086

8. Alley D, Suthers K, Crimmins E. Education and cognitive decline in older Americans: results from the ahead sample. *Res Aging.* (2007) 29:73–94. doi: 10.1177/0164027506294245

9. Lee Y, Jean Yeung WJ. Gender matters: productive social engagement and the subsequent cognitive changes among older adults. *Soc Sci Med.* (2019) 229:87–95. doi: 10.1016/j.socscimed.2018.08.024

10. Zhang K, Zhang W. Adverse childhood experiences and mild cognitive impairment in later life: exploring rural/urban and gender differences using CHARLS. *J Appl Gerontol.* (2022) 41:1454–64. doi: 10.1177/07334648211064796

11. Mukku SSR, Dahale AB, Muniswamy NR, Muliyala KP, Sivakumar PT, Varghese M. Geriatric depression and cognitive impairment—an update. *Indian J Psychol Med.* (2021) 43:286–93. doi: 10.1177/0253717620981556

12. Wei Y, Lin JL, Chen G, Pei LJ. Association between sleep duration and cognitive impairment in Chinese people aged 65 years and older. *Zhonghua Liu Xing Bing Xue Za Zhi.* (2021) 42:2138–42. doi: 10.3760/cma.j.cn112338-20201106-01313

13. Armstrong NM, Tom SE, Harrati A, Casaletto K, Pa J, Arce Rentería M, et al. Longitudinal relationship of leisure activity engagement with cognitive performance among non-demented, community-dwelling older adults. *Gerontologist.* (2022) 62:352–63. doi: 10.1093/geront/gnab046

14. Motter JN, Pimontel MA, Rindskopf D, Devanand DP, Doraiswamy PM, Sneed JR. Computerized cognitive training and functional recovery in major depressive disorder: a meta-analysis. *J Affect Disord.* (2016) 189:184–91. doi: 10.1016/j.jad.2015.09.022

15. Culpepper L, Lam RW, McIntyre RS. Cognitive impairment in patients with depression: awareness, assessment, and management. *J Clin Psychiatry.* (2017) 78:1383–94. doi: 10.4088/JCP.tk16043ah5c

16. Wong MM, Chan CF Li SW, Lau YM. Six-month follow-up of cognitive impairment and depressive symptoms in late-onset depression. *East Asian Arch Psychiatry.* (2015) 25:146–9.

17. Adler G, Chwalek K, Jajcevic A. Six-month course of mild cognitive impairment and affective symptoms in late-life depression. *Eur Psychiatry.* (2004) 19:502–5. doi: 10.1016/j.eurpsy.2004.09.003

18. Zhu Q, Fan H, Zhang X, Ji C, Xia Y. Changes in sleep duration and 3-year risk of mild cognitive impairment in Chinese older adults. *Aging.* (2020) 12:309–17. doi: 10.18632/aging.102616

19. Hua J, Sun H, Shen Y. Improvement in sleep duration was associated with higher cognitive function: a new association. *Aging.* (2020) 12:20623–44. doi: 10.18632/aging.103948

20. Ferrie JE, Shipley MJ, Akbaraly TN, Marmot MG, Kivimäki M, Singh-Manoux A. Change in sleep duration and cognitive function: findings from the Whitehall II study. *Sleep.* (2011) 34:565–73. doi: 10.1093/sleep/34.5.565

21. Lian Y, Zhang J, Jia CX. Sleep duration change and cognitive function: a national cohort study of Chinese people older than 45 years. *J Nerv Ment Dis.* (2020) 208:498–504. doi: 10.1097/nmd.0000000000001159

22. Wu J, Cheng GH, Sheng LT, Feng L, Yuan JM, Chee M, et al. Prospective associations between change in sleep duration and cognitive impairment: findings from the Singapore Chinese health study. *J Affect Disord.* (2021) 281:125–30. doi: 10.1016/j.jad.2020.12.007

23. Wion RK, Hill NL, DePasquale N, Mogle J, Whitaker EB. The relationship between subjective cognitive impairment and activity participation: a systematic review. *Act Adapt Aging.* (2020) 44:225–45. doi: 10.1080/01924788.2019.1651188

24. Li H, Li C, Wang A, Qi Y, Feng W, Hou C, et al. Associations between social and intellectual activities with cognitive trajectories in Chinese middle-aged and older adults: a nationally representative cohort study. *Alzheimers Res Ther.* (2020) 12:115. doi: 10.1186/s13195-020-00691-6

25. Lee ATC, Richards M, Chan WC, Chiu HFK, Lee RSY, Lam LCW. Association of daily intellectual activities with lower risk of incident dementia among older Chinese adults. *JAMA Psychiatry.* (2018) 75:697–703. doi: 10.1001/jamapsychiatry.2018.0657

26. Su X, Huang X, Jin Y, Wan S, Han Z. The relationship of individual social activity and cognitive function of community Chinese elderly: a cross-sectional study. *Neuropsychiatr Dis Treat.* (2018) 14:2149–57. doi: 10.2147/ndt.s160036

27. Rojas-Saunero LP, Hilal S, Murray EJ, Logan RW, Ikram MA, Swanson SA. Hypothetical blood-pressure-lowering interventions and risk of stroke and dementia. *Eur J Epidemiol.* (2021) 36:69–79. doi: 10.1007/s10654-020-00694-5

28. Labrecque JA, Swanson SA. Target trial emulation: teaching epidemiology and beyond. *Eur J Epidemiol.* (2017) 32:473–5. doi: 10.1007/s10654-017-0293-4

29. Robins J, A. New approach to causal inference in mortality studies with sustained exposure periods—application to control of the healthy worker survivor effect. *Mathemat Modell.* (1986) 7:1393–512. doi: 10.1016/0270-0255(86)90088-6

30. Keil AP, Edwards JK, Richardson DB, Naimi AI, Cole SR. The parametric G-formula for time-to-event data: intuition and a worked example. *Epidemiology.* (2014) 25:889–97. doi: 10.1097/ede.0000000000000160

31. Taubman SL, Robins JM, Mittleman MA, Hernán MA. Intervening on risk factors for coronary heart disease: an application of the parametric G-formula. *Int J Epidemiol.* (2009) 38:1599–611. doi: 10.1093/ije/dyp192

32. Johnson KW, Glicksberg BS, Hodos RA, Shameer K, Dudley JT. Causal inference on electronic health records to assess blood pressure treatment targets: an application of the parametric G formula. *Pac Symp Biocomput.* (2018) 23:180–91. doi: 10.1142/9789813235533_0017

33. Vangen-Lønne AM, Ueda P, Gulayin P, Wilsgaard T, Mathiesen EB, Danaei G. Hypothetical interventions to prevent stroke: an application of the parametric G-formula to a healthy middle-aged population. *Eur J Epidemiol.* (2018) 33:557–66. doi: 10.1007/s10654-017-0344-x

34. Ren J, Li G, Zhang L, Zhang N, Ren J. Hypothetical Interventions for falls among older adults: an application of the parametric G-formula. *Front Med (Lausanne).* (2021) 8:732136. doi: 10.3389/fmed.2021.732136

35. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). *Int J Epidemiol.* (2014) 43:61–8. doi: 10.1093/ije/dys203

36. Wang J, Zhu WH Li YF, Zhu WW. Temporal precedence of cognitive function and functional abilities: a latent difference score model of the Chinese community-dwelling elders. *Int J Geriatr Psychiatry.* (2019) 34:1892–9. doi: 10.1002/gps.5206

37. Gilles C. Age-related mild cognitive deficit: a ready-to-use concept? *Dialog Clin Neurosci.* (2003) 5:61–76. doi: 10.31887/DCNS.2003.5.1/cgilles

38. Richards M, Touchon J, Ledesert B, Richie K. Cognitive decline in ageing: are AAMI and AACD distinct entities? *Int J Geriatr Psychiatry.* (1999) 14:534–40. doi: 10.1002/(sici)1099-1166(199907)14:7<534::aid-gps963>3.0.co;2-b

39. Liu H, Fan X, Luo H, Zhou Z, Shen C, Hu N, et al. Comparison of depressive symptoms and its influencing factors among the elderly in urban and rural areas: evidence from the China health and retirement longitudinal study (CHARLS). *Int J Environ Res Public Health.* (2021) 18:3886. doi: 10.3390/ijerph18083886

40. Zhang N, Wang C, Li Y, Yang M, Yang J, Chen F, et al. Gender-specific association between nighttime sleep duration and falls among community-dwelling middle-aged and older adults in China. *J Appl Gerontol.* (2022) 41:2511–9. doi: 10.1177/07334648221118904

41. Yang YI, Hodge AM, Dugué PA, Williamson EJ, Gardiner PA, Barr ELM, et al. Mortality effects of hypothetical interventions on physical activity and TV viewing. *Med Sci Sports Exerc.* (2021) 53:316–23. doi: 10.1249/mss.0000000000002479

42. McGrath S, Lin V, Zhang Z, Petito LC, Logan RW, Hernán MA, et al. Gformula: an R package for estimating the effects of sustained treatment strategies via the parametric g-formula. *Patterns (NY).* (2020) 1:100008. doi: 10.1016/j.patter.2020.100008

43. Vreeburg SA, Hoogendijk WJ, van Pelt J, Derijk RH, Verhagen JC, van Dyck R, et al. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch Gen Psychiatry.* (2009) 66:617–26. doi: 10.1001/archgenpsychiatry.2009.50

44. Brenowitz WD, Zeki Al Hazzouri A, Vittinghoff E, Golden SH, Fitzpatrick AL, Yaffe K. Depressive symptoms imputed across the life course are associated with cognitive impairment and cognitive decline. *J Alzheimers Dis.* (2021) 83:1379–89. doi: 10.3233/jad-210588

45. Byers AL, Yaffe K. Depression and risk of developing dementia. *Nat Rev Neurol.* (2011) 7:323–31. doi: 10.1038/nrneurol.2011.60

46. Hua J, Zhuang S, Shen Y, Tang X, Sun H, Fang Q. Exploring the bidirectional associations between short or long sleep duration and lower cognitive function: a 7-year cohort study in China. *Front Aging Neurosci.* (2021) 13:727763. doi: 10.3389/fnagi.2021.727763

47. Spira AP, Gonzalez CE, Venkatraman VK, Wu MN, Pacheco J, Simonsick EM, et al. Sleep duration and subsequent cortical thinning in cognitively normal older adults. *Sleep.* (2016) 39:1121–8. doi: 10.5665/sleep.5768

48. Li X, Zhang J, Hou R, Zheng M, Singh M, Li H, et al. Bidirectional associations of intellectual and social activities with cognitive function among middle-aged and elderly adults in China. *J Affect Disord.* (2022) 319:83–9. doi: 10.1016/j.jad.2022.09.031

49. Park DC, Lodi-Smith J, Drew L, Haber S, Hebrank A, Bischof GN, et al. The impact of sustained engagement on cognitive function in older adults: the synapse project. *Psychol Sci.* (2014) 25:103–12. doi: 10.1177/0956797613499592

50. Lam LC, Ong PA, Dikot Y, Sofiatin Y, Wang H, Zhao M, et al. Intellectual and physical activities, but not social activities, are associated with better global cognition: a multi-site evaluation of the cognition and lifestyle activity study for seniors in Asia (CLASSA). *Age Ageing.* (2015) 44:835–40. doi: 10.1093/ageing/afv099

51. Bień B, Bień-Barkowska K. Objective drivers of subjective well-being in geriatric inpatients: mobility function and level of education are general predictors of self-evaluated health, feeling of loneliness, and severity of depression symptoms. *Qual Life Res.* (2016) 25:3047–56. doi: 10.1007/s11136-016-1355-x

52. Chrzastek Z, Guligowska A, Soltysik B, Pigłowska M, Borowiak E, Kostka J, et al. Association of lower nutritional status and education level with the severity of depression symptoms in older adults-a cross sectional survey. *Nutrients.* (2021) 13:515. doi: 10.3390/nu13020515

53. Thow ME, Summers MJ, Saunders NL, Summers JJ, Ritchie K, Vickers JC. Further education improves cognitive reserve and triggers improvement in selective cognitive functions in older adults: the Tasmanian healthy brain project. *Alzheimers Dement (Amst).* (2018) 10:22–30. doi: 10.1016/j.dadm.2017.08.004

54. Lenehan ME, Summers MJ, Saunders NL, Summers JJ, Ward DD, Ritchie K, et al. Sending your grandparents to university increases cognitive reserve: the Tasmanian Healthy brain project. *Neuropsychology.* (2016) 30:525–31. doi: 10.1037/neu0000249

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 20 February 2023
DOI 10.3389/fpubh.2023.1103651

OPEN ACCESS

EDITED BY
Jing Liao,
Sun Yat-sen University, China

REVIEWED BY
Yun Zhang,
Columbia University Irving Medical Center, United States
Jingying Wang,
University of Florida, United States

*CORRESPONDENCE
Shuang Wang
✉ wangs0211@hotmail.com

SPECIALTY SECTION
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

RECEIVED 20 November 2022
ACCEPTED 01 February 2023
PUBLISHED 20 February 2023

CITATION
Sun Q-q, Tan K, Tang H-y, Liu Y-y, Zhu H, Qin H, Xia X, Zhang M, Chen Y-y, Nie S-s and Wang S (2023) Incidence and predictive value of social frailty among community-dwelling older adults in Southwest China: A prospective cohort study. *Front. Public Health* 11:1103651. doi: 10.3389/fpubh.2023.1103651

Incidence and predictive value of social frailty among community-dwelling older adults in Southwest China: A prospective cohort study

Qian-qian Sun[1,2], Ke Tan[3,4], Hui-yu Tang[1], Yan-yan Liu[1], Huan Zhu[1], Hai Qin[5], Xin Xia[2], Min Zhang[6], Yan-yu Chen[7], Shuang-shuang Nie[8] and Shuang Wang[1,2]*

[1]The Center of Gerontology and Geriatrics, Sichuan University West China Hospital, Chengdu, Sichuan, China, [2]National Clinical Research Center for Geriatrics, Sichuan University West China Hospital, Chengdu, Sichuan, China, [3]Department of Epidemiology and Health Statistics, Sichuan University West China Fourth Hospital, Chengdu, Sichuan, China, [4]Department of Clinic Development and Medical Affairs, Fosun Adgenvax Biopharmaceutical Co., Ltd., Chengdu, Sichuan, China, [5]Internal Medicine Department, Pingyi Community Health Service Center, Dujiangyan, Sichuan, China, [6]Department of Geriatrics, Sichuan Provincial People's Hospital, Sichuan Academy of Medical Science, Chengdu, Sichuan, China, [7]Department of Rheumatology and Immunology, Chongqing Emergency Medical Center, Chongqing, China, [8]Department of General Medicine, The Affiliated Qingdao Central Hospital of Qingdao University, Qingdao, Shandong, China

Background: Few studies have focused on the incidence and correlation of social frailty (SF) with adverse health events in Southwest China. This study aims to explore the predictive value of SF for adverse health events.

Methods: A 6-year prospective cohort study was employed, a total of 460 community-dwelling older adults aged 65 years and above were analyzed to provide a baseline in 2014. Participants completed two longitudinal follow-ups at 3 (2017, 426 participants involved) and 6 (2020, 359 participants involved) years later. A modified social frailty screening index was used in this study, and adverse health events such as physical frailty (PF) deterioration, disability, hospitalization, falls, and mortality were evaluated.

Results: Among these participants in 2014, the median age was 71 years, 41.1% were male, and 71.1% were married or cohabiting, up to 112 (24.3%) of them were classified as SF. It was observed that aging (OR = 1.04, 95% CI = 1.00–1.07, $P = 0.047$) and having family members die in the past year (OR = 2.60, 95% CI = 0.93–7.25, $P = 0.068$) were risk factors of SF, whereas having a mate (OR = 0.40, 95% CI = 0.25–0.66, $P = 0.000$) and having family members to help with care (OR = 0.53, 95% CI = 0.26–1.11, $P = 0.092$) were protective factors of SF. The cross-sectional study demonstrated that SF was only significantly associated with disability (OR = 12.89, 95% CI = 2.67–62.13, $P = 0.001$) at wave 1. Baseline SF significantly explained the incidence of mortality at the 3-year (medium-term, OR = 4.89, 95% CI = 2.23–10.71, $P = 0.000$) and 6-year follow-ups (long-term, OR = 2.22, 95% CI = 1.15–4.28, $P = 0.017$).

Conclusion: SF prevalence was higher in the Chinese older population. Older adults with SF had a significantly increased incidence of mortality at the longitudinal follow-up. Consecutive comprehensive health management of SF

(e.g., avoiding living alone and increasing social engagement) is urgently needed for the purposes of early prevention and multidimensional intervention in adverse health events, including disability and mortality.

KEYWORDS

social frailty (SF), community-dwelling older adults, adverse health events, mortality, prospective cohort study

Introduction

Among the worldwide aged population, frailty is an important health issue and is characterized by decreased physiological reserve and function across multiple physiologic systems (1, 2). It is associated with adverse events, including falls (3, 4), hospitalization, institutionalization (5), disability (6), lower quality of life and mortality (7). As a part of abnormal aging, frailty is a common public health problem with a prevalence of about 10% in the community-dwelling elderly population (1). Frailty has several phenotypes, such as physical, cognitive, psychological, nutritional and social frailty (8). Compared with other frail phenotypes, social frailty (SF) is the most unexplored component (9) because of the inconsistency of definition and measurement way of SF (10). Even though, the prevalence of SF were reported ranged from 7.7% (China), 11.1 or 18.0% (Japan) to 18.4% (Singapore) (9, 11–13) based on different screening tools. Therefore, social frailty is also accepted as an abnormal process of aging which contributed to disability (14), cognition impairment, depression (11), and mortality (15, 16), as same as physical frailty.

As for the screening tools, seven-item SF index was first constructed by Teo et al. (13) based on the Singapore Longitudinal Aging Studies Wave 1 (SLAS-1) cohort. However, this assessment method was time-consuming in practice. Bessa et al. (17) attempted to give an integrated conceptualization of SF which covered four aspects: measures general, social resources, social behaviors, and the satisfaction of basic social requirements (18). Then a modified SF index screen tool (19) based on those conception was developed by Nagai et al. (20) in Japan, who confirmed that briefly SF can predict future incidents of activity limitation and mortality in community-dwelling older adults (15). Yet, although the cultural may vary, the understanding of SF and its mechanisms remains the same; although general and social resources as well as social behaviors or activities may vary among different countries and cultures, they are still contribute to the social needs fulfillment (21). Considering that older adults must increasingly rely on their social relationships and social environment due to policy measures aimed at reducing the financing of formal care and support, the incidence of SF and its effect on adverse health events becomes even more important (21).

China has the largest older population in the world (8). China is a country that is changing rapidly including family cohesion and traditional family-based social support considerably weakened, which might contribute to the score of the SF index (16). However, the SF of older individuals in Chinese communities varies greatly, and few studies have reported the correlation of SF with adverse health events in Southwest China. Therefore, the core aim of this study was to identify the incidence of SF by using a modified SF index assessment tool and to explore the relationship between SF and deterioration of PF, disability, hospitalization, falls and all-cause mortality among community-dwelling older adults in both cross-sectional and longitudinal studies.

Methods

Study design, setting, and participants

All data were obtained from "the Survey on the Disease, Psychology and Social Support of the older Community-dwelling Population in Dujiangyan," a prospective cohort study for older individuals aged 65 years and older in China supported by Johnson & Johnson global novel project (2013), which has been described in detail in our previous study (22). The exclusion criteria included: (1) any disease in the acute phase cause life expectancy <6 months, such as acute heart, liver, kidney and respiratory failure were excluded for better follow-up; (2) severe visual/hearing impairment and severe dementia; and (3) unwillingness to be investigated and unable to communicate with the investigators. In Figure 1, a total of 1,117 older adults were first recruited in January 2014. Among them, 460 older adults finished the first survey (wave 1). The next two waves of follow-up were conducted in January 2017 (426 participants involved, wave 2) and January 2020 (359 participants involved, wave 3). The research protocol was reviewed and approved by the Ethics Review Committee of Sichuan University (registration number 2014-206), and informed written consent was obtained from all participants.

Measurements

Definition of social frailty

Taking the practicable and available into consideration, a modified social frailty index (15) (general and social resources, social behaviors, and the satisfaction of basic social requirements) was used to assess social frailty in this study, which was described as follows: (1) financial support: "Is your annual per capita income of households <RMB10,000?" (yes = 1 point, no = 0 points), (2) living status: "How many people do you live with?" (0 = 1 point, ≥1 = 0 points), (3) social activity: "Do you participate in any community activities regularly?" (no = 1 point, yes = 0 points), and (4) social contact: "Do you sometimes visit your friends and relatives?" (no = 1 point, yes = 0 points). Participants with summed

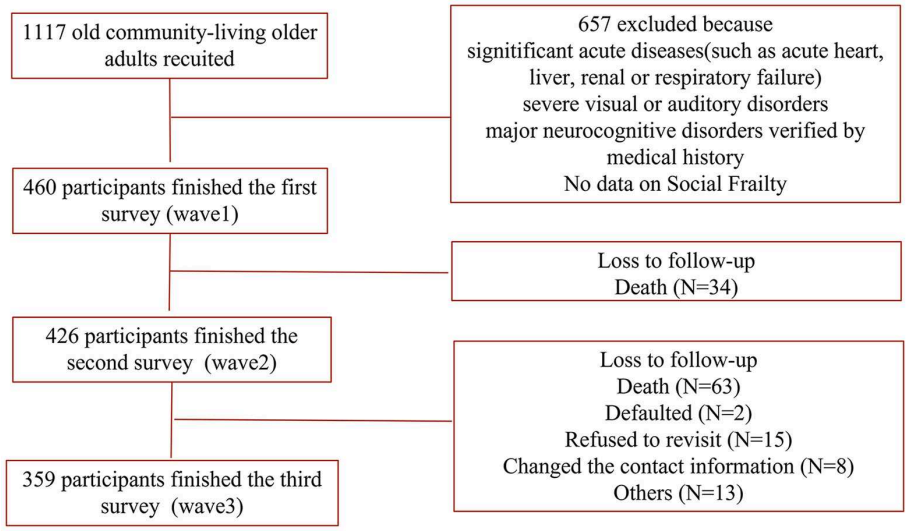


FIGURE 1
Flow chart demonstrating the process used to select the study participants.

scores of 2 or more were categorized as having SF. A score of 0–1 was regarded as non-social frailty.

Assessment of physical frailty

Physical frailty was defined using the Frail Scale comprising five components (18): fatigue, resistance, ambulation, illness, and loss of weight. Components were operationalized. Participants were considered physically frail (score = 3–5), prefrail (score = 1–2), and robust (score = 0) according to the summed score.

Adverse health events

Deterioration of PF was defined as from robust to pre-frail or frail and from pre-frail to frail.

Disability was defined as requiring assistance on one or more IADL (instrumental activities of daily living, eight items) or ADL (activities of daily living, seven items) item(s).

Hospitalization was assessed *via* self-reported hospitalizations or reviewing computerized HIS records from 2014 to 2020.

Falls were defined as any sudden drop from one surface to a lower surface. We assessed falls by asking the participants: "Did you fall in the previous year?" (response categories "yes" and "no").

Mortality data were collected by local government records or family members' self-reports.

Other covariates

A personal information questionnaire was used to collect the participants' characteristics. The sociodemographic covariates of participants included age, gender, marital status (with or without life partner), education level (according to the International Standard Classification of Education), self-rated sleep quality, self-reported memory status (good, average, and poor), Residency Period (<3, 3–10, >10 years), family member has died in 1 year. Social characteristics were assessed through the following dimensions: medical service support (medical insurance), expenditure (in debt), social engagement (whether having family members to help with care), and emotional support (willingness to make friends and with a confidant in one's life). Geriatric syndrome (malnutrition, depression, cognitive impairment, comorbidity, and polypharmacy) and physical profile (HbA1c, BMI, systolic BP, and diastolic BP).

Statistical analysis

The Statistical Package for Social Science (SPSS) for Windows version 21.0 (SPSS, Chicago, IL, USA) was used to calculate descriptive statistics and to obtain the frequency and percentage distributions. The characteristics of participants' at baseline were compared by using Mann–Whitney *U*, or chi-square tests according to the type of variables. Multivariate logistic regression using forward stepwise regression ($P < 0.10$ for variable inclusion criteria) were conducted with the aim of examining the association of SF with adverse health events in cross-sectional and predictive value of SF on adverse events in longitudinal scenarios.

Results

Participant characteristics

Table 1 summarizes the overall SF status and sociodemographic characteristics of participants at wave 1. Among these 460 participants in 2014, the median age was 71 years, 41.1% were male, and 71.1% were married or cohabiting. During the wave 2 follow-up, 34 participants died. The wave 3 visit and assessment were conducted in January 2020, during which 359 participants were completed, and 63 died. Another 38 participants were excluded as

TABLE 1 Demographic characteristics of SF in wave 1 ($N = 460$).

Variables	N-SF ($N = 348$)	SF ($N = 112$)	Total	*P*
Age (years)	71 (67–76)	73 (69–79.75)	71.0 (67.0, 77.0)	0.303
Sex (males; %)	200 (57.5)	71 (63.4)	189 (41.1)	0.268
Marital status (having a mate; %)	270 (77.6)	57 (50.9)	327 (71.1)	**0.000**
Education				**0.001**
Illiterate (%)	61 (17.5)	38 (33.9)	99 (21.5)	
Elementary school (%)	143 (41.1)	41 (36.6)	184 (40.0)	
Middle school or higher (%)	144 (41.4)	33 (29.5)	177 (38.5)	
Sleep quality (bad; %)	177 (50.9)	63 (56.3)	240 (52.2)	0.321
Self-reported memory status				0.944
Good (%)	92 (26.9)	30 (27.5)	131 (28.5)	
Normal (%)	138 (40.4)	42 (38.5)	180 (39.1)	
Bad (%)	112 (32.7)	37 (33.9)	149 (32.4)	
Residency period (year; %)				0.553
≤3	118 (34.0)	42 (37.5)	161 (35.0)	
3<x≤10	101 (29.1)	35 (31.3)	136 (29.6)	
>10	128 (36.9)	35 (31.3)	163 (35.4)	
Family member has died in 1 year (%)	10 (2.9)	8 (7.1)	18 (3.9)	**0.043**
With a confidant (%)	326 (93.9)	99 (88.4)	425 (92.4)	**0.051**
Having family members to take care (%)	63 (18.1)	11 (9.8)	74 (16.1)	**0.038**
SF four components				
Living alone (%)	19 (5.5)	38 (33.9)	57 (12.5)	**0.000**
Lack of social activity (%)	24 (6.9)	68 (60.7)	92 (20)	**0.000**
Lack of contact with neighbors (%)	147 (42.2)	102 (91.1)	249 (54.1)	**0.000**
Financial difficulties (%)	20 (5.8)	44 (39.3)	64 (14.0)	**0.000**
Physical frailty (PF)				0.173
Robust (%)	182 (52.3)	52 (46.4)	234 (50.9)	
Pre-frail (%)	148 (42.5)	49 (43.8)	197 (42.8)	
Frail (%)	18 (5.2)	11 (9.8)	29 (6.3)	
Adverse health events				
Disability (%)	3 (0.9)	11 (9.8)	14 (3.0)	**0.000**
Hospitalization within past 1 year (%)	170 (48.9)	63 (56.3)	74 (16.1)	0.173
Fall	25 (7.2)	8 (7.1)	33 (7.2)	0.988
Geriatric syndrome				
Malnutrition (%)	36 (10.3)	17 (15.2)	53 (11.5)	0.163
Depression (%)	9 (2.6)	5 (4.5)	14 (3.0)	0.490
Cognitive impairment (%)	39 (11.2)	25 (22.3)	64 (13.9)	**0.003**
Comorbidity	138 (39.7)	40 (35.7)	178 (38.7)	0.456
Polypharmacy	33 (9.5)	7 (6.3)	40 (8.7)	0.291
Physical profile				
HbA1C (%)	5.7 ± 0.8	5.7 ± 0.9	5.7 ± 0.8	0.540
BMI (kg/m^2)	24.8 ± 3.5	24.2 ± 3.5	24.6 ± 3.5	0.107
Systolic BP (mmHg)	139.5 ± 18.7	139.5 ± 19.5	139.5 ± 18.9	0.987
Diastolic BP (mmHg)	80.4 ± 11.0	81.9 ± 10.9	80.8 ± 11.0	0.188

SF, Social Frailty; PF, Physical Frailty; BMI, body mass index; HbA1c, glycated hemoglobin; BP, Blood Presure.
p-values < 0.05 are printed in bold.

TABLE 2 The overall social frailty status and adverse health events of participants at each visit.

Variables	2014 (wave 1; $N = 460$)	2017 (wave 2; $N = 426$)	2020 (wave 3; $N = 359$)
Social frailty (%)	112 (24.3)	123 (28.9)	217 (60.4)
Four components			
Living alone (%)	57 (12.5)	89 (20.9)	89 (24.8)
Lack of social activity (%)	92 (20)	147 (34.5)	266 (74.1)
Lack of contact with neighbors (%)	249 (54.1)	126 (29.6)	201 (56.0)
Financial difficulties (%)	64 (14.0)	72 (16.9)	36 (10.0)
Adverse health events			
Transitions in SF			
Deterioration (%)	-	72 (15.7)	154 (42.9)
Unchanging (%)	-	327 (71.1)	182 (50.7)
Improve (%)	-	61 (13.3)	23 (6.4)
Transitions in PF			
Deterioration (%)	-	67 (15.7)	78 (21.7)
Unchanging (%)	-	212 (49.8)	195 (54.3)
Improve (%)	-	147 (34.5)	86 (24.0)
Disability (%)	14 (3.0)	40 (9.4)	81 (22.6)
Hospitalization within past 1 year (%)	233 (50.7)	207 (48.6)	158 (44.0)
Fall (%)	33 (7.2)	29 (6.8)	96 (26.7)
Mortality (%)	-	34 (7.4)	63 (13.7)

SF, Social Frailty; PF, Physical Frailty.

they defaulted ($n = 2$), refused to revisit ($n = 15$), changed the contact information ($n = 8$), and other ($n = 13$; Figure 1).

Prevalence and risk factors for SF

The prevalence of SF increased with time and was 24.3% (112/460, wave 1), 28.9% (123/426 wave 2), and 60.4% (217/359 wave 3). During the two waves of follow-up, we observed a significant increase in SF deterioration [from 72 (15.7%) to 154 (42.9%)], and only 23 (6.4%) participants had improved in wave 3. A high prevalence of SF was observed among participants who were older, without a mate, had lower levels of education, with family members died in the last year, had family members to take care, who lacked social activity, who lacked contact with neighbors, had financial difficulties, had a disability or cognitive impairment. There were no significant difference between the two groups in terms of who had the worse sleep patterns, physical frailty, number of falls, hospitalizations within the past year and other geriatric syndromes (Tables 1, 2).

Multivariate logistic regression analysis was used to determine the possible associated factors for SF (wave 1) in Figure 2A. The risk factors of SF were significantly associated with aging (OR = 1.04, 95% CI = 1.00–1.07, $P = 0.047$) and having family members die in the past year (OR = 2.60, 95% CI = 0.93–7.25, $P = 0.068$), whereas, having a mate (OR = 0.40, 95% CI = 0.25–0.66, $P = 0.000$) and having family members to help with care (OR = 0.53, 95% CI = 0.26–1.11, $P = 0.092$) were protective factors of SF.

The incidence of different adverse health events

The prevalence of adverse health events from wave 1 to wave 3 (Table 2) was described as follows: disability was 3.0, 9.4, and 22.6%; falls were 7.2, 6.8, and 26.7%; hospitalization within the past 1 year was 50.7, 48.6, and 44.0%; and mortality was 7.4% (wave 2) and 13.7% (wave 3). In wave 2, the number of disabilities [40 (9.4%)] markedly increased, while the rates of falls [29 (6.8%)] and hospitalization [207 (48.6%)] were comparable to those in wave 1. By the end of wave 3, it was observed that 78 (21.7%) of patients had worsened into PF or pre-PF. A significant increase in the proportion of disabilities (22.6%), falls (26.7%) and mortality (13.7%) after 6 years were observed, but hospitalization (44.0%) was further decreased.

Relationship of SF with adverse health events: Cross-sectional and longitudinal analysis

Figures 2B–D presents the cross-sectional association of SF with adverse health events. At the first wave visit, after adjusting for background characteristics and adverse events, the logistic regression analyses demonstrated that SF was significantly associated with disability (OR = 12.83, 95% CI = 2.67–62.13, $P = 0.001$) and age (OR = 1.12, 1.04–1.21, $P = 0.004$). Poor sleep quality (OR = 2.20, 95% CI = 1.43–3.36, $P = 0.000$), residency period ($3<x\leq10$ years; OR = 0.48, 95% CI = 0.29–0.78, $P = 0.003$) and medical insurance (OR = 6.41, 95% CI = 2.34–17.57, $P = 0.000$) were related to hospitalization. Male participants (OR = 4.73, 95% CI = 1.62–13.87, $P = 0.005$) and those with poor sleep quality (OR = 3.12, 95% CI = 1.24–7.83, $P = 0.015$) at baseline had an increased risk of falling. However, baseline PF was not significantly associated with an increased risk of disability, hospitalizations or fall incidents.

Longitudinal analyses (waves 2) showed that SF significantly predicted the incidence of mortality (OR = 4.89, 95% CI = 2.23–10.71, $P = 0.000$), whereas SF did not have a significant effect on disability, hospitalizations, falls or PF deterioration. At the third wave of follow-up, the multivariate logistic regression analysis indicated that baseline SF significantly increased the risk of 6-year mortality (OR = 2.22, 95% CI = 1.15–4.28, $P = 0.017$). However, baseline SF was significantly associated with a decreased risk of hospitalization (OR = 0.57, 95% CI = 0.33–0.98, $P = 0.041$). No significant correlations with disability, falls or PF deterioration were found (Table 3, Supplementary Tables 1, 2).

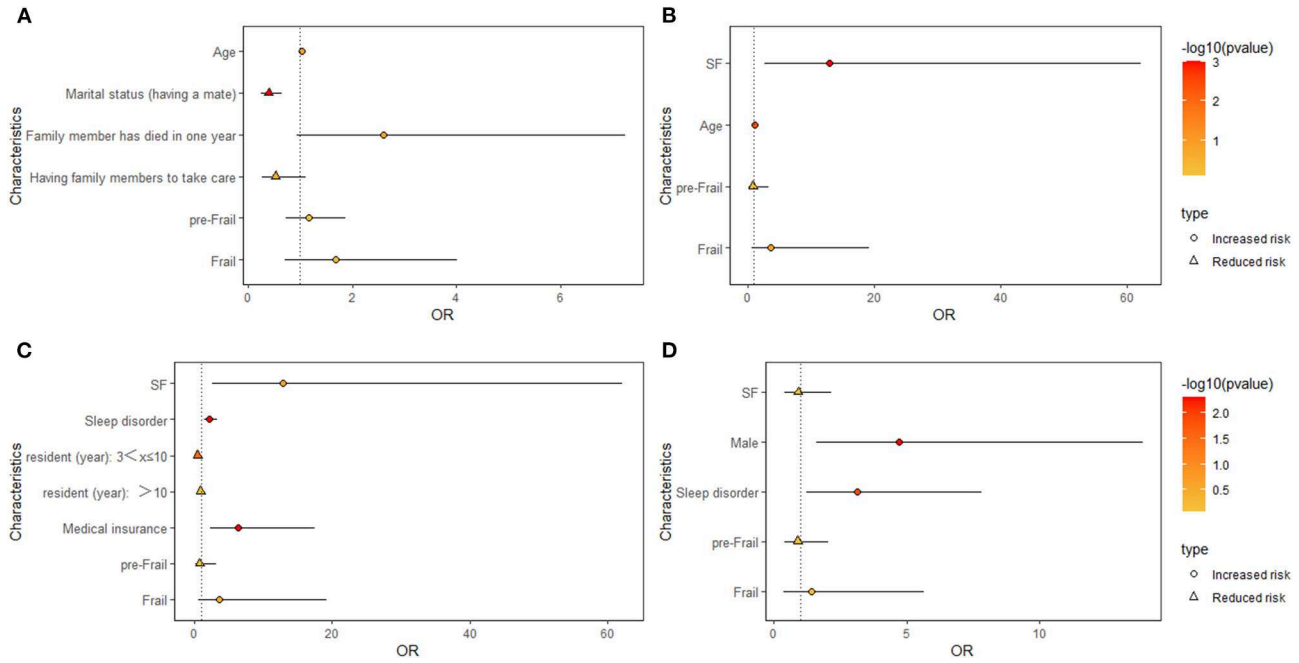


FIGURE 2
Forest plots showing the analysis of risk factors associated with SF **(A)** and cross-sectional analyses of baseline SF with adverse health events in wave 1 **(B–D)**. **(B)** Cross-sectional analyses of baseline SF with disability. **(C)** Cross-sectional analyses of baseline SF with hospitalization. **(D)** Cross-sectional analyses of baseline SF with fall.

Discussion

SF in aging populations is of grave concern because of social issues faced by older individuals, such as those related to income, family dynamics, and social inclusion (15). As a complex concept, SF is comprehensive, and there is still no consensus on the criteria. Comparing with some social terms, such as social isolation and social support alone, more directions (21) were taken into account. Among them, living alone and infrequent contact with family or friends might be the core of social frailty. So, the modified SF screen tool that consist of general and social resources ("is your annual per capita income of households <RMB10,000?"), social behaviors ("Do you participate in any community activities regularly?" and "Do you sometimes visit your friends and relatives?"), and the satisfaction of basic social requirements ("How many people do you live with?") was (21) chose in this study.

Our study found that the prevalence of SF in older individuals was 24.3%. At the end of our study, 60.4% of older adult participants were found to have SF. the baseline prevalence was higher than that of Ma et al. (16), who found that the prevalence of SF was 7.7% (aged ≥ 60 years) in Beijing by HALFT scale (inability to help others, limited social participation, loneliness, financial difficultly, and not having anyone to talk to) in 2004, 11.1% (mean age 71.9 years) in Japan (11) by the 5-item scale (living alone, going out less frequently compared to last year, visiting friends sometimes, feeling helpful to friends or family, and talking with someone every day) or 18.0% (mean age 75.2 years) by modified SF index screening questionnaire (financial support, living status, social activity, and social contact) (15), and 18.4% (mean age 66.1 years) in Singapore (13) by the Seven-item social frailty index (living alone, no education, absence of a confident, infrequent contact, infrequent social activities, financial difficulty and socioeconomic deprivation). Furthermore, our study reported the status changes of SF over time: half of participants had SF status stable (50.7%) while half deterioration (42.9%) at the end of 6 years. The potential reasons of high prevalence of SF in this study might be: (1) the mean age of our participants were older (mean age 71 years) than other studies; (2) reduced social activity and social contact by unique earthquake in 2008. Some older adults have to move to the present place of residence during the reconstruction of the disaster. They had fewer relatives and friends than before; (3) with the deterioration of aging and economic development of society, traditional family-based social support given to older community-dwelling adults was weakened gradually, the left-behind co-habitants were spouse or older adults were lived alone which contributed the living status changing; and (4) most of our participants were older adults lived in Urban-rural fringe, financial support was relatively limited (11).

We analysis the risk factor for SF by using baseline data. The results showed that participants with advanced age, marital status of no partner, lower education and cognitive impairment had a high prevalence of SF. Older age is a risk factor of SF An obviously increased proportion of SF was found in age group between 80 and 84 years old, which amounted to 22.0% and was even higher than 41.8% in patients 85 years of age and older (11). From this perspective, older age itself seems to be a risk factor of SF to come into being. Participants with a marital status of no partner were prone to isolation and loneliness, both linked to SF. It has been suggested that a decline in cognitive function may occur

TABLE 3 Longitudinal analyses of SF with adverse health events.

Variables	Follow-up		Longitudinal analysis (wave 2)	Longitudinal analysis (wave 3)
PF deterioration	Sig.		0.442	0.903
	Exp (B)		0.75	1.04
	95%	Lower	0.36	0.54
	C.I.	Upper	1.56	2.01
Disability	Sig.		0.142	0.285
	Exp (B)		1.95	0.71
	95%	Lower	0.8	0.37
	C.I.	Upper	4.73	1.34
Hospitalization	Sig.		0.85	**0.041**
	Exp (B)		1.05	0.57
	95%	Lower	0.63	0.33
	C.I.	Upper	1.75	0.98
Fall	Sig.		0.612	0.303
	Exp (B)		0.78	0.74
	95%	Lower	0.3	0.41
	C.I.	Upper	2.04	1.32
Mortality	Sig.		**0.000**	**0.017**
	Exp (B)		4.89	2.22
	95%	Lower	2.23	1.15
	C.I.	Upper	10.71	4.28

SF, Social Frailty; PF, Physical Frailty.
We used the stepwise logistic regression model to analyze the risk factors of SF. p-values < 0.05 are printed in bold.

concurrently with the presence of SF (23), which may lead to adverse health events, such as mortality, hospitalization, falls and disability. In addition, the study also found that aging (OR = 1.04, 95% CI = 1.00–1.07, $P = 0.047$) and having a family member who died within 1 year (OR = 2.60, 95% CI = 0.93–7.25, $P = 0.068$) were negative factors of SF, while having a mate (OR = 0.40, 95% CI = 0.25–0.66, $P = 0.000$) and having family members to help with care (OR = 0.53, 95% CI = 0.26–1.11, $P = 0.092$) were protective factors for SF in the Chinese culture. In the clinical setting, understanding who is more likely to deteriorate and who may remain stable, or even revert back to the better state, will allow clinicians to focus on those at the highest risk for early interventions (24). Despite many studies determining the effects of interventions on PF, the number of studies on interventions that target SF is limited (25). This study found that avoiding living alone (having a partner) and increasing social engagement (having family members to help with care) can contribute to preventing SF.

Furthermore, this study also provides evidence on the relationship between SF and adverse health events in both the medium- and long-term future. First, based on this cross-sectional analyses, it was found that SF was significantly correlated with disability and hospitalization. No relationship was found between falls and PF after adjusting for all the other variables in the model. In some studies, they found that the number of disabled persons among SF older increased by 2.30 times, and the number of severely disabled persons increased by 6.27 times (13). Other studies also found that SF status is negatively associated with physical functioning (26) and is associated with a higher incidence of disability (27). This study verified that SF, as an indicator of a decline in social function (28), is a risk factor for dependency (29). It shows that participants with baseline SF are ∼12 times more likely to have an incident related to disability than participants who are not SF. Some factors, such as age, male sex, poor sleep quality, medium period residence, and medical insurance, were also associated with adverse health outcomes, and these results were consistent with other studies (30–33).

Second, the regression analyses (longitudinal) revealed that SF was significantly associated with mortality during wave 2 (medium-term, OR = 4.89, 95% CI = 2.23–10.71, $P = 0.000$) and wave 3 (long-term, OR = 2.22, 95% CI = 1.15–4.28, $P = 0.017$), and medium-term mortality was higher than long-term mortality. Ma et al. (16) examined the correlation between SF and mortality among community-dwelling older adults. After adjusting for age and sex, the 8-year mortality hazard ratios were 2.5–4.3 for those with SF, and SF predicted 8-year mortality. Yamada et al. (15) conducted a prospective cohort study in 6,603 community-dwelling adults aged 65 years and older who were living independently in a city in Shiga prefecture in 2011 and found that 48.5% of those with SF died, indicating that community-dwelling older adults with SF (adjusted HR 1.71, 95% CI 1.54–1.90) were at higher risk of death over 6 years. Our data were higher than those studies, and participants with SF had a 4- and 2-fold incidence of mortality than those without SF, which was consistent with those results. Mortality is the most important variable among adverse health outcomes.

Third, some studies found that social factors could be associated with an increased incidence of hospitalizations. Social factors of self-neglect have been linked to poor social support, reduced nutritional intake and physical function (34), resulting in poor quality of life and increased falls, hospitalization and mortality. In a sample of 963 Brazilian people (35) aged 60 years and older, the TFI predicted hospitalization. However, in this study, baseline SF was significantly associated with a decreased risk of hospitalization (OR 0.57, 95% CI = 0.33–0.98, $P = 0.041$) during the 6-year follow-up. It is speculated that the baseline SF individuals were prone to having lower incomes and did not have equal hospitalizations; therefore, SF individuals in Southwest China predicted a decreased risk of hospitalization longitudinally.

Impaired falls in the older are a major source of injury resulting in disability (36). Although multiple longitudinal studies have investigated frailty as a predictor of future falls, the results were mixed (37). Gobbens et al. (38) found that SF was only correlated with disability and falls in a sample of 180 Dutch community-dwelling older people aged 70 years and older. The future fall risk according to frailty seemed to be higher in men than in women. SF is a factor associated with accelerated decline in both physical and mental functioning. In addition, it has been suggested that social roles gradually decrease before a decline in cognitive and physical functioning is reported (25). Makizako et al. (9) found

that participants who were SF at baseline had an increased risk of developing PF (OR = 3.93, 95% CI = 1.02–15.15) and physical prefrailty (OR = 2.50, 95% CI = 1.30–4.80). This indicates that those who are SF may be at greater risk of developing PF in the near future. However, this longitudinal study did not find that SF predicts PF deterioration in mid- and long-term studies. The reason for the lack of a relationship with falls and PF deterioration may be that there were more women among participants at the baseline. Another reason may be that participants came from the urban-rural fringe areas; many were labor workers and had better physical fitness.

In addition to SF, the current study also found that those resident <3 years and without a confidant also had an increased risk of developing adverse health events, such as falls and mortality. In the future, these factors should be taken into account as supplementary components of SF screening tools. This modified tool may better detect adverse health events, but it may need further validation.

This study also has some limitations. First, the instrument used to evaluate SF was self-reported, so it may be subject to potential recall bias despite all the questionnaires were conducted face-to-face one by one at all waves, and all investigators participated in the study were trained by standard protocol, so that the subjects had no understanding error. Second, due to the vary widely across regions and smaller geographic and cultural units, perhaps we miss an opportunity to take full advantage of this framing to educate the world outside China about those changes. Finally, considering these limitations, further studies will be needed to explore a consecutive comprehensive health management of SF for the purposes of early prevention and multidimensional intervention in adverse health outcomes.

Conclusion

This study reported the incidence of SF and its associated factors and highlights the predictive values of SF on adverse health events longitudinally. First, the incidence of SF was higher and its transitions was the majority of participants remained SF status stable or deteriorated at the end of 6 years in community-dwelling older adults in Southwest China. Second, this study found that avoiding living alone (having a partner) and increasing social engagement (having family members to help with care) can contribute to SF. Finally, older adults with SF had a significantly increased incidence of mortality at the longitudinal follow-up. Consecutive comprehensive health management of SF (e.g., avoiding living alone, increasing social engagement) is urgently needed for the purposes of early prevention and multidimensional intervention in adverse health events. The present study provided new, additional evidence for assessing SF in Chinese community-dwelling older people aiming to prevent or delay adverse events, including disability, hospitalization, and mortality.

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 Review Committee of Sichuan University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Q-qS wrote the manuscript and participated in all aspects of this research. KT, H-yT, Y-yL, HZ, and XX assisted with study design, data analysis, and interpretation. HQ, MZ, Y-yC, and S-sN helped in collecting data. SW reviewed the final article. All authors: revision of manuscript for important intellectual content and approval of final draft.

Funding

This work was supported by the Global Innovation Project of Johnson & Johnson Company (H1312124) and the Science and Technology of Sichuan Province of China (2018FZ0046 and 2021YFS0137).

Acknowledgments

The authors appreciate the staff of the Department of Geriatrics, Pingyi Community Health Service Center, and all participants and their legal proxies for their assistance in data collection.

Conflict of interest

KT was employed by Fosun Adgenvax Biopharmaceutical Co., Ltd.

The remaining 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/fpubh.2023.1103651/full#supplementary-material

References

1. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: A systematic review. *J Am Geriatr Soc.* (2012) 60:1487–92. doi: 10.1111/j.1532-5415.2012.04054.x

2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet.* (2013) 381:752–62. doi: 10.1016/S0140-6736(12)62167-9

3. Cheng MH, Chang SF. Frailty as a risk factor for falls among community dwelling people: Evidence from a meta-analysis. *J Nurs Scholarsh.* (2017) 49:529–36. doi: 10.1111/jnu.12322

4. Del Brutto OH, Mera RM, Peinado CD, Zambrano M, Sedler MJ. Frailty and risk of falls in community-dwelling older adults living in a rural setting. The Atahualpa project. *J Frailty Aging.* (2020) 9:150–4. doi: 10.14283/jfa.2019.36

5. Kojima G. Frailty as a predictor of nursing home placement among community-dwelling older adults: A systematic review and meta-analysis. *J Geriatr Phys Ther.* (2018) 41:42–8. doi: 10.1519/JPT.0000000000000097

6. Kojima G. Frailty as a predictor of disabilities among community-dwelling older people: A systematic review and meta-analysis. *Disabil Rehabil.* (2017) 39:1897–908. doi: 10.1080/09638288.2016.1212282

7. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: A systematic review and meta-analysis. *Age Ageing.* (2018) 47:193–200. doi: 10.1093/ageing/afx162

8. Rockwood K. What would make a definition of frailty successful? *Age Ageing.* (2005) 34:432–4. doi: 10.1093/ageing/afi146

9. Makizako H, Shimada H, Doi T, Tsutsumimoto K, Hotta R, Nakakubo S, et al. Social frailty leads to the development of physical frailty among physically non-frail adults: A four-year follow-up longitudinal cohort study. *Int J Environ Res Public Health.* (2018) 15:30490. doi: 10.3390/ijerph15030490

10. Quach LT, Primack J, Bozzay M, Madrigal C, Erqou S, Rudolph JL. The intersection of physical and social frailty in older adults. *R I Med J.* (2021) 104:16–9.

11. Tsutsumimoto K, Doi T, Makizako H, Hotta R, Nakakubo S, Makino K, et al. Association of social frailty with both cognitive and physical deficits among older people. *J Am Med Dir Assoc.* (2017) 18:603–7. doi: 10.1016/j.jamda.2017.02.004

12. Makizako H, Shimada H, Tsutsumimoto K, Lee S, Doi T, Nakakubo S, et al. Social frailty in community-dwelling older adults as a risk factor for disability. *J Am Med Dir Assoc.* (2015) 16:1003 e7–11. doi: 10.1016/j.jamda.2015.08.023

13. Teo N, Gao Q, Nyunt MSZ, Wee SL, Ng TP. Social frailty and functional disability: Findings from the Singapore longitudinal ageing studies. *J Am Med Dir Assoc.* (2017) 18:637 e13–637 e19. doi: 10.1016/j.jamda.2017.04.015

14. Teo N, Yeo PS, Gao Q, Nyunt MSZ, Foo JJ, Wee SL, et al. A bio-psycho-social approach for frailty amongst Singaporean Chinese community-dwelling older adults—Evidence from the Singapore Longitudinal Aging Study. *BMC Geriatr.* (2019) 19:350. doi: 10.1186/s12877-019-1367-9

15. Yamada M, Arai H. Social frailty predicts incident disability and mortality among community-dwelling Japanese older adults. *J Am Med Dir Assoc.* (2018) 19:1099–103. doi: 10.1016/j.jamda.2018.09.013

16. Ma L, Sun F, Tang Z. Social frailty is associated with physical functioning, cognition, and depression, and predicts mortality. *J Nutr Health Aging.* (2018) 22:989–95. doi: 10.1007/s12603-018-1054-0

17. Bessa B, Coelho T, Ribeiro O. Social frailty dimensions and frailty models over time. *Arch Gerontol Geriatr.* (2021) 97:104515. doi: 10.1016/j.archger.2021.104515

18. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging.* (2012) 16:601–8. doi: 10.1007/s12603-012-0084-2

19. Armstrong JJ, Andrew MK, Mitnitski A, Launer LJ, White LR, Rockwood K. Social vulnerability and survival across levels of frailty in the Honolulu-Asia Aging Study. *Age Ageing.* (2015) 44:709–12. doi: 10.1093/ageing/afv016

20. Nagai K, Tamaki K, Kusunoki H, Wada Y, Tsuji S, Itoh M, et al. Physical frailty predicts the development of social frailty: A prospective cohort study. *BMC Geriatr.* (2020) 20:403. doi: 10.1186/s12877-020-01814-2

21. Bunt S, Steverink N, Olthof J, van der Schans CP, Hobbelen MJS. Social frailty in older adults: A scoping review. *Eur J Ageing.* (2017) 14:323–34. doi: 10.1007/s10433-017-0414-7

22. Tang H, Zhu H, Sun Q, Qin H, Wang S. Transitions in the cognitive frailty states in community-living older adults: A 6-year prospective cohort study. *Front Aging Neurosci.* (2021) 13:774268. doi: 10.3389/fnagi.2021.774268

23. Makizako H, Tsutsumimoto K, Shimada H, Arai H. Social frailty among community-dwelling older adults: Recommended assessments and implications. *Ann Geriatr Med Res.* (2018) 22:3–8. doi: 10.4235/agmr.2018.22.1.3

24. Lee JS, Auyeung TW, Leung J, Kwok T, Woo J. Transitions in frailty states among community-living older adults and their associated factors. *J Am Med Dir Assoc.* (2014) 15:281–6. doi: 10.1016/j.jamda.2013.12.002

25. Dedeyne L, Deschodt M, Verschueren S, Tournoy J, Gielen E. Effects of multi-domain interventions in (pre)frail elderly on frailty, functional, and cognitive status: A systematic review. *Clin Interv Aging.* (2017) 12:873–96. doi: 10.2147/CIA.S130794

26. Pek K, Chew J, Lim JP, Yew S, Tan CN, Yeo A, et al. Social frailty is independently associated with mood, nutrition, physical performance, and physical activity: Insights from a theory-guided approach. *Int J Environ Res Public Health.* (2020) 17:124239. doi: 10.3390/ijerph17124239

27. Gutierrez-Robledo LM, Avila-Funes JA. How to include the social factor for determining frailty? *J Frailty Aging.* (2012) 1:13–7. doi: 10.14283/jfa.2012.3

28. Tanaka T, Takahashi K, Hirano H, Kikutani T, Watanabe Y, Ohara Y, et al. Oral frailty as a risk factor for physical frailty and mortality in community-dwelling elderly. *J Gerontol A Biol Sci Med Sci.* (2018) 73:1661–7. doi: 10.1093/gerona/glx225

29. Hironaka S, Kugimiya Y, Watanabe Y, Motokawa K, Hirano H, Kawai H, et al. Association between oral, social, and physical frailty in community-dwelling older adults. *Arch Gerontol Geriatr.* (2020) 89:104105. doi: 10.1016/j.archger.2020.104105

30. Enderlin C, Rooker J, Ball S, Hippensteel D, Alderman J, Fisher SJ, et al. Summary of factors contributing to falls in older adults and nursing implications. *Geriatr Nurs.* (2015) 36:397–406. doi: 10.1016/j.gerinurse.2015.08.006

31. Mojtabai R. Insurance loss in the era of the affordable care act: Association with access to health services. *Med Care.* (2019) 57:567–73. doi: 10.1097/MLR.0000000000001150

32. Denninger T. Disability and age-observations from an intersectional perspective. *Z Gerontol Geriatr.* (2020) 53:211–5. doi: 10.1007/s00391-020-01693-7

33. Denison HJ, Jameson KA, Sayer AA, Patel HP, Edwards MH, Arora T, et al. Poor sleep quality and physical performance in older adults. *Sleep Health.* (2021) 7:205–11. doi: 10.1016/j.sleh.2020.10.002

34. Schafer MH, Upenieks L, MacNeil A. Disorderly households, self-presentation, and mortality: Evidence from a national study of older adults. *Res Aging.* (2018) 40:762–90. doi: 10.1177/0164027517741347

35. Santiago LM, Gobbens RJJ, van Assen M, Carmo CN, Ferreira DB, Mattos IE. Predictive validity of the Brazilian version of the Tilburg Frailty Indicator for adverse health outcomes in older adults. *Arch Gerontol Geriatr.* (2018) 76:114–9. doi: 10.1016/j.archger.2018.02.013

36. Pfortmueller CA, Lindner G, Exadaktylos AK. Reducing fall risk in the elderly: Risk factors and fall prevention, a systematic review. *Minerva Med.* (2014) 105:275–81. doi: 10.1155/2014/256519

37. Kojima G. Frailty as a predictor of future falls among community-dwelling older people: A systematic review and meta-analysis. *J Am Med Dir Assoc.* (2015) 16:1027–33. doi: 10.1016/j.jamda.2015.06.018

38. Gobbens RJ, Boersma P, Uchmanowicz I, Santiago LM. The Tilburg Frailty Indicator (TFI): New evidence for its validity. *Clin Interv Aging.* (2020) 15:265–74. doi: 10.2147/CIA.S243233

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 07 March 2023
DOI 10.3389/fpubh.2023.1062843

OPEN ACCESS

EDITED BY
Narelle Warren,
Monash University, Australia

REVIEWED BY
Yun Zhang,
Columbia University Irving Medical Center, United States
Xun Luo,
Kerry Rehabilitation Medicine Research Institute, China

*CORRESPONDENCE
Lorena Villa-García
✉ lorena.v22@gmail.com

†These authors share first authorship

SPECIALTY SECTION
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

RECEIVED 06 October 2022
ACCEPTED 08 February 2023
PUBLISHED 07 March 2023

CITATION
Villa-García L, Davey V, Peréz LM, Soto-Bagaria L, Risco E, Díaz P, Kuluski K, Giné-Garriga M, Castellano-Tejedor C and Inzitari M (2023) Co-designing implementation strategies to promote remote physical activity programs in frail older community-dwellers. *Front. Public Health* 11:1062843. doi: 10.3389/fpubh.2023.1062843

Co-designing implementation strategies to promote remote physical activity programs in frail older community-dwellers

Lorena Villa-García[1,2,3*†], Vanessa Davey[1,4†], Laura M. Peréz[1], Luis Soto-Bagaria[1], Ester Risco[5,6], Pako Díaz[7], Kerry Kuluski[8,9], Maria Giné-Garriga[10,11], Carmina Castellano-Tejedor[1] and Marco Inzitari[1,12]

[1]Research Group on Aging, Frailty and Care Transitions in Barcelona, Parc Sanitari Pere Virgili and Vall d'Hebron Research Institute (VHIR), Barcelona, Spain, [2]Doctorate Program, Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain, [3]QIDA, Sabadell, Spain, [4]Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom, [5]Nursing Research Group, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA), Universitat Autònoma de Barcelona, Sabadell, Spain, [6]Nursing Department, Faculty of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain, [7]Centre d'Atenció Primària Bordeta-Magòria, Barcelona, Spain, [8]Bridgepoint Collaboratory for Research and Innovation, Bridgepoint Health, Toronto, ON, Canada, [9]Institute of Health Policy Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada, [10]Department of Sport Sciences, Faculty of Psychology, Education and Sport Sciences, Blanquerna, Universitat Ramon Llull, Barcelona, Spain, [11]Department of Physical Therapy, Faculty of Health Sciences, Blanquerna, Universitat Ramon Llull, Barcelona, Spain, [12]Faculty of Health Sciences, Universitat Oberta de Catalunya (UOC), Barcelona, Spain

Background: The "AGIL Barcelona (AGILBcn)" community-based integrated care program is a multicomponent healthy aging intervention for frail older adults. In this context, the present study aimed to identify implementation strategies to optimize the accessibility, acceptability, and adaptability of mobile health (mhealth) interventions to enhance physical activity in frail older adults, and to prioritize action points according to their importance and feasibility, through a co-design process.

Material and methods: A mixed methods approach was used. In the qualitative phase, a method adapted from the World Café was applied in 6 virtual groups to identify strategies to facilitate the virtual physical activity program. In the quantitative phase, prioritization and feasibility of the strategies was analyzed through surveys. Strategies were ranked based on priority vs. feasibility, revealing if strategies should either be: implemented first; if possible; taken into account for future consideration; or directly disregarded. The convenience sample included older adults ($n = 7$), community professionals ($n = 9$) and health professionals ($n = 13$). Qualitative data were analyzed by summative content analysis and quantitative data by nonparametric descriptive analyses.

Results: A total of 27 strategies were identified and grouped into four categories: general strategies for reducing barriers; specific strategies for facilitating the use of a digital application; specific strategies for facilitating participation in virtual exercise groups; and specific strategies for facilitating external support. According to the ranking of strategies, the first ones to be implemented included: digital literacy, digital capability assessment, family technology support, weekly telephone follow-up by professionals, personalizing exercises, and virtual exercises in small groups.

Conclusion: The active participation of all stakeholders enabled us to identify potential strategies for implementing person-oriented technology in physical activity programs and for engaging older adults.

KEYWORDS

older adults, frailty, aging, mhealth, World Café, integrated care, participatory methods, co-design

1. Introduction

The aging of the population is accompanied by an acceleration in the incidence of disability (1). Frailty, defined as a pre-disability state of initial impairment of intrinsic capacity, is a target for interventions aimed at improving function and delaying disability (2). Multicomponent lifestyle interventions aimed at promoting healthy aging have proven to be effective in the short term (3, 4).

During the COVID-19 pandemic, social distancing protocols and the subsequent demand for community spaces led to an increase in sedentary behavior in older adults (5), contributing to the progression of frailty and disability (6). An alternative approach to traditional face-to-face physical activity interventions that has gained special momentum is the use of mobile health (mhealth) (7). Technology-based interventions appear to positively influence physical activity levels in older adults (8) and offer the potential to reach individuals on a large scale while allowing for personalized programs. Despite the availability and potential of technology for enhancing physical activity (9), barriers to its adoption and use by older adults and in different care settings remain (10, 11).

It is widely recognized that there is a significant gap between the development of evidence-based interventions for public health and health promotion and their successful and sustainable implementation (12). Approaches for promoting physical activity in older adults using mhealth present unique challenges. Currently, most physical activity promotion interventions remain limited to the experimental or pilot phase, as their continuous implementation or scale-up poses large difficulties. These include a limited understanding of implementation strategies and a failure to match these to the needs of end users.

Engaging end users in the development of health promotion interventions and the design of digital solutions incorporating elements derived from participatory methodologies, conceived within the framework of patient and public involvement (PPI), is key to achieving strategies that are contextually adapted and conducive to their sustained adoption and implementation (13). Participatory design, now known as co-design, is hypothesized to have a strong and lasting impact on health outcomes and may represent a promising strategy for addressing complex health behaviors. Co-design in this context specifically refers to patients and caregivers working collaboratively with health and allied health professionals to improve service delivery by sharing knowledge and experience (14). Its goal is to optimize the implementation of evidence-based interventions according to the priorities and preferences of all stakeholders, enabling designed solutions to achieve maximum feasibility and sustainability.

The present study is part of the +AGIL Barcelona (AGILBcn) program (15), a complex community intervention co-designed by and for frail older adults, together with primary care teams and community stakeholders. The program encompasses different aspects of health including physical activity, nutrition, emotional wellbeing, sleep hygiene, cognitive screening and stimulation, loneliness, and medication review. The AGILBcn multicomponent exercise program consists of 10 face-to-face group sessions led by a physiotherapist in a primary care setting. The program is complemented by exercises performed at home and prescribed through the publicly available ViviFrail® App (16). Results showed a positive impact on physical function at 3 months (17).

Due to the COVID-19 pandemic and the ensuing challenges facing health services, pressure to redesign the program in a virtual or semi-virtual format increased. However, despite the great potential of digital technology to enhance the promotion of healthy lifestyles in older adults, a lack of specific implementation strategies could even exacerbate health inequalities, increase costs, and jeopardize implementation in routine practice.

This work aims to identify implementation strategies for optimizing the accessibility, acceptability, and adaptability of mHealth interventions aimed at increasing physical activity, within the framework of AGILBcn or similar programs, and to assess their level of priority and feasibility through a co-design process aimed at ensuring equal and equitable participation of multiple stakeholders.

2. Materials and methods

2.1. Study design

A mixed-methods study was designed, incorporating both qualitative and quantitative data and adopting a triangulation multilevel model, to elicit views from key stakeholders: older adults (OA) as end users; health professionals (HP); and professionals from the community and voluntary sector (CVS). We selected these key participants in order to assess the accessibility, acceptability and adaptability of the AGILBcn virtual program, aimed at older adults with frailty but absent or mild disability. Specific themes were addressed, including: barriers related to the "digital divide" that must be overcome, to ensure the viability of incorporating mHealth (app and virtual exercise sessions) into the program; logistics of exercising and conducting virtual exercise sessions from the homes of older adults; and monitoring, support and other factors that could affect uptake, motivation and adherence to the program.

The co-design process was carried out in two phases described below: (1) six virtual "World Café" (18) sessions (renamed as "AGIL Café" sessions) to identify implementation strategies for

facilitating the deployment of the AGILBcn virtual program; and (2) evaluation of the level of priority and feasibility of the strategies identified during the AGIL Café sessions, using digital surveys.

2.2. Settings and participants

Participation was sought to represent the main stakeholders in the community-based multi-component AGILBcn program (15). Participants included older adults, health professionals and professionals from the community. Purposive sampling was used to identify and select key participants capable of offering a wealth of information regarding the phenomenon of interest (19, 20). Inclusion criteria for participants were:

- Older adults with no or minimal disability in performing basic daily living activities, and with no acute diseases, aged 70–90 years, and presenting at least one sign of frailty (i.e., slow gait speed, weakness, memory complaints, involuntary weight loss, or poor social support), able to participate in videoconferences, fluent in Catalan or Spanish and without speech disorders.
- Health professionals (physicians, nurses, physiotherapists, neuropsychologists, occupational therapists, or social workers) with more than 6 months of work experience in primary care or geriatric services and in complex chronic conditions.
- Professionals from the community and voluntary sector: workers from third sector services targeted at older adults (municipal or non-profit programs).

Three researchers (LMP, LS, MI) were responsible for recruitment. Potential participants were contacted either by telephone (OA, previous or potential participants in AGILBcn) or e-mail (HP and CVS), to request participation and to explain the objectives, structure and format of the sessions. HP were recruited from an intermediate care hospital and a primary care center in Barcelona and were selected for diversity in profession, work area and professional experience. CVS were recruited based on the type of community organization they worked for (e.g., civic centers, pharmacies), and professional experience related to community programs targeting older adults (e.g., programs to increase physical activity, improve digital skills, reduce loneliness).

We aimed for between 6 and 12 participants per stakeholder group and invited 13 participants to each group to ensure participation. Sample size was determined based on the capacity of the selected sample to provide information and on a criterion of information redundancy in the identification of new codes or themes (20).

Of the 13 candidates from each group who were contacted for recruitment, 6 OA decided not to participate due to health-related problems or overlapping duties (which the research team had tried to accommodate), 4 CVS declined the invitation due to work commitments, and all HP agreed to participate. Finally, 7 OA, 9 CVS and 13 HP agreed to participate. No participants withdrew from the study.

2.3. Data collection

2.3.1. Phase 1: Procedure of AGIL Café

This study used the World Café participatory research approach (18) to facilitate structured and unstructured collaborative dialogue and knowledge generation for the resolution of common problems from the perspective of multiple stakeholders (21, 22). This method allows for obtaining the lived experience of the participants and their needs and preferences for services, dividing large groups into smaller ones while remaining part of a single, connected conversation (22). It has been used in a wide variety of settings, including the development and evaluation of health services (22) and for the improvement of care for older adults (23).

Six AGIL Café sessions (2 groups for each profile) were conducted. The decision to avoid mixed groups was made to give equal status to end users and thereby avoid the risk of reduced participation due to differentials in status and experience (24).

The AGIL Café sessions took place between December 2020 and March 2021, with a duration of 1.5 h per session, conducted in a virtual format (25). The Zoom® communication platform was chosen for its video and audio quality, functionalities and simplicity. Meetings were password protected. At the time of the meeting, attendees were sent to a waiting room where identity was confirmed. Sessions were video and audio recorded. The process was guided by a multidisciplinary research team with experience in primary, geriatric care, physical activity promotion programs and qualitative research experience. In each workshop, a member of the team acted as facilitator; an additional member admitted participants to the call and helped to solve technical problems during the session (LS); two recorded ideas (VD and MI); and two others acted as observers and evaluators of the process (LMP and LV). To stimulate the conversation, the team developed a script, adapted for each group, containing main questions and subsidiary prompts (Supplementary Table 1). These were guided by study objectives, existing literature, and independent and representative feedback on understandability and comprehensiveness. Sessions were conducted in rounds (introduction followed by a round for each question). To facilitate the participation of all attendees and to prevent any single participant from monopolizing the conversation, each participant was invited to respond by the moderator, who carefully monitored responses. After each round, time was allocated to unstructured discussion. The real-time LucidChart® app was used by the researchers to record and visualize ideas presented by participants using virtual "sticky notes" and graphics functions. This enabled the correction and clarification of suggestions made and permitted the continuous overview of ideas generated, facilitating reflection.

2.3.2. Phase 2: Prioritization and viability of changes identified in the co-design groups: Surveys

Based on the qualitative analysis of the AGIL Café sessions (phase 1), an *ad hoc* questionnaire was developed in Catalan, consisting of 27 potentially actionable strategies for facilitating the

AGILBcn virtual program, which were subdivided into 4 categories or blocks.

The questionnaire required that each item be ranked according to its perceived priority and feasibility using a 5-point Likert scale from P1/F1, representing the highest priority/highest feasibility, to P5/F5, representing the lowest priority/lowest feasibility (the range of options is described in Supplementary Table 2). A participant from each stakeholder group was asked to review the questionnaire prior to its dissemination, to identify any problems and rate its comprehensibility. The survey was conducted using the online platform LimeSurvey® between May and June 2021 with a 100% response rate. The survey was distributed to HP and CVS *via* email, with information on its purpose and objectives. The survey entry screen specified how data would be used and requested informed consent. Participants could withdraw at any time before submitting their final responses.

For OA, the survey was disseminated and completed *via* computer-assisted telephone interviewing to avoid any potential difficulties from the use of online platforms. Questions were read aloud directly from the online survey, and responses were recorded in real-time in the online system. A single trained interviewer (LS) conducted all surveys from the call center of the referral hospital.

2.4. Data analysis

2.4.1. Qualitative data

Content analysis (26, 27) was performed to identify all potentially actionable strategies raised by participants in the AGIL Café sessions using AtlasTi™, based on transcripts, field notes and visual record captured in Lucidchart™ for additional clarification. Some interpretation was required, to distinguish relevant material: two researchers worked together (LV, VD), thoroughly reviewing the material generated from each session, and carrying out analysis independently. Once finished, the codes, categories and themes were unified and agreed upon.

Once coded, frequencies and quotations were derived for all potentially actionable items and analyzed. Initially, 48 codes were identified, discussed and reviewed by the research team. Codes representing the same underlying concept were collapsed into one category, and codes were grouped into sections covering specific themes, resulting in the categorization of four umbrella categories and 27 codes. Questions for the survey were then developed to elicit views on the priority and feasibility of the proposed strategies, for practical purpose and to validating and triangulating the groups' data (28). We also analyzed the quantitative data to show the participation of stakeholders in the categories, and as such, their initial "ownership" of ideas; this provided a background to the interpretation of survey results and assisted in our appraisal of the co-design methodology.

2.4.2. Quantitative data

The Likert scale results for each of the 27 items of the phase 2 questionnaire were analyzed using non-parametric descriptive statistics. We assigned numerical values to the categorical ratings for priority (P) and feasibility (F) (separately) and converted all responses into numerical scores. Values were as follows: P1/F1 −100 (highest), P2/F2 −75 (high), P3/F3 −50 (medium), P4/F4 −25 (low), P5/F5 −0 (lowest). Using these values, we calculated:

- The "priority vs. feasibility score" (PvF score), which corresponds to the average of the priority and feasibility scores, providing an estimate of the global relevance of each item.
- The difference between the mean priority and feasibility score, which gives an idea of the agreement between P and F. We included this parameter because, although a strategy might rank high overall in PvF, it might show a gap between its P and F (e.g., high P and average or low F) reflecting a lack of agreement between priority and feasibility scores.

All scores were calculated for each of the participant profiles. Data were analyzed and processed using STATA® and Excel®.

2.5. Ethical and research approvals

Ethical approval was obtained from the Clinical Research Ethics Committee (CREC) of the Foundation University Institute for Primary Health Care Research Jordi Gol i Gurina (IDIAPJGol) (20/048-P) and by the Ethics Committee on Animal and Human Experimentation (Authorization Number CEEAH 5066) of the Universitat Autònoma de Barcelona (UAB). All participants received verbal and written information about the study and provided written consent for recording the sessions, using anonymized verbatim quotations in the reporting of data, and using audio, photograph and/or video recordings of the sessions in dissemination.

3. Results

3.1. Characteristics of study participants

The ages of participating OA ($n = 7$) ranged from 70 to 90 years (Table 1), in line with participants in the AGILBcn program. CVS was the most diverse in background, encompassing professionals working as part of neighborhood health plans ($n = 2$), a community project aimed at tackling loneliness ($n = 1$), a city community project for improving the situation of people in need of care and their caregivers ($n = 1$), a neighborhood civic center ($n = 1$), a community pharmacy ($n = 1$) and a foundation that assists older adults living alone ($n = 2$).

From the participating HP ($n = 13$), the most represented professions were medical doctors (5) and nurses (3). Other allied HP included a psychologist ($n = 1$), a physiotherapist ($n = 1$), an occupational therapist ($n = 1$), and a social worker ($n = 1$). We also included in this group an expert in healthcare information and communication technology ($n = 1$).

3.2. AGIL Café results

The results have been structured into 2 themes: (1) Suggested strategies that were, on the surface level: (i) actionable (to some

TABLE 1 Characteristics of the sample.

Participant	Sex	Age
OA1	Woman	82
OA2	Man	81
OA3	Woman	84
OA4	Woman	86
OA5	Woman	88
OA6	Woman	79
OA7	Woman	83
Participant	**Sex**	**Professionals from the community and voluntary sector**
CV1	Woman	Community Pharmacy
CV2	Man	Technician developing neighborhood health plans
CV3	Woman	Foundation that helps elderly people living alone
CV4	Man	Foundation that helps elderly people living alone
CV5	Man	Community project to tackle solitude
CV6	Woman	Technician developing neighborhood health plans
CV7	Woman	Departament Promoció persones grans
CV8	Woman	A city community project to improve the situation of people in need of care and their caregivers
CV9	Woman	Neighborhood Civic Center
Participant	**Sex**	**Profession**
HP1	Woman	Computer systems expert
HP2	Man	Physiotherapist
HP3	Woman	Doctor
HP4	Woman	Doctor
HP5	Woman	Neuropsychologist
HP6	Woman	Doctor
HP7	Woman	Nurse
HP8	Woman	Nurse
HP9	Woman	Nurse
HP10	Man	Doctor
HP11	Woman	Doctor
HP12	Woman	Occupational Therapist
HP13	Woman	Social Worker

degree) on the short term; (ii) within the boundaries of the project and, (iii) within the scope of influence of the actors involved, either at an individual or institutional level; and (2) Priorities for change that were wider in scope than the project and could not be actioned upon on the short term.

This paper focuses on the first theme. Our data coding and categorization process revealed four main categories and 27 codes of potentially actionable strategies (Table 2). The results are organized into four categories: (1) general strategies for reducing barriers to older adults participating in a virtual program (2) specific strategies for facilitating the use of a digital application to prescribe and teach individualized exercises and to monitor progress; (3) specific strategies for facilitating the participation of older adults in virtual exercise groups, performed at home *via* group video calls; and (4) specific strategies for facilitating external support, if needed.

Below, we provide an overview of how each stakeholder profile contributed to the set of actionable implementation strategies generated, with examples; observations are presented in accordance with the Consolidated group exercise for Reporting Qualitative Research guidelines (COREQ) (29).

3.2.1. Category 1: General strategies for reducing barriers to older adults in a virtual program

Strikingly, 85% ($n = 17$) of the strategies generated in this category came from HP, with lengthy discussions on concerns of lack of digital literacy among OA, much of which was from direct experience (Table 2). Early assessment of digital capacity was considered something that should become standard practice.

> "In geriatrics we are very used to using scales for everything, if there is a scale for a pre-measurement of their digital skills, it should be part of the holistic assessment of the person" (HP 3: Woman, health professional, Doctor).

Moving beyond this, pre-intervention face-to-face contact with end users and caregivers was perceived as key to guaranteeing an understanding of the program and of potential barriers for each person (and his/her caregiver), and to devising person-centered strategies to trying to reduce them.

> "There is a need for an initial visit, where they are accompanied. This is how to introduce physical activity, technology and stimulate involvement and motivation" (HP 4: Woman, health professional, Doctor).

All participating groups described the need for digital training programs, although suggestions varied. HP underlined the benefits of paper manuals, in combination with further scheduled contact during the intervention period:

> "At the time of seeing them, if you can, reinforce and review their ability to interact and use 'the app'... To do this, I have created written support, a mini-manual, with steps adapted to the person's ability" (HP 5: Woman, health professional, neuropsychologist).

3.2.2. Category 2: Specific strategies for facilitating the use of a digital application to prescribe and teach individualized exercises and to monitor progress

Relatively few suggestions ($n = 12$) were made on how to improve the accessibility and viability of using a digital application for personalized exercise plans for all groups (Table 2). End users'

10.3389/fpubh.2023.1062843

TABLE 2 Description and frequency of the main strategies (codes) suggested by the participants for implementing a virtual exercise program, grouped into four main categories.

Codes	All ($n = 29$)	CvS ($n = 9$)	HP ($n = 13$)	OA ($n = 7$)
General strategies for reducing barriers to older adults in a virtual program				
Assess digital capacity	8	0	8	0
Conduct educational meetings in advance to train and educate in the use of technology	3	0	3	0
Provide simple, paper-based educational materials on how to use technology	6	0	3	3
Inform family on the selected solutions to reinforce the use of technology	0	0	3	0
Assess the need for external support with technology and facilitate it, if necessary	5	1	4	0
Provide continuous technological support	6	4	2	0
Specific strategies to facilitating the use of a digital application to prescribe and teach individualized exercises and to monitor progress				
Provide feedback from a healthcare professional by phone, on individual progress	5	0	2	3
Use gamification techniques	3	0	2	1
Implement a formal digital "expert user" program (support by "peer champions")	3	2	1	0
Create a simple educational video on how to use technology and share it *via* chat	1	0	0	1
Specific strategies for facilitating the participation of older adults in virtual exercise groups, performed at home *via* group video calls				
Establish preferred platform for video calls	1	0	1	0
Implement systems for sending reminders with dates, *via* chat apps or phone calls	1	0	1	0
Inform caregiver or support volunteers about the class schedule	1	0	1	0
Provide a variety of physical exercises	3	0	0	3
Limit the size of the virtual group	3	0	0	3
Incorporate music in the sessions	9	0	0	9
Involve older adults in the co-design of the sessions	2	1	1	0
Provide feedback from a healthcare professional by phone, on group progress	5	0	2	3
Create peer-to-peer/group messaging in the chat application	3	1	2	0
Specific strategies for facilitating external support if needed				
Recruit local volunteers offering digital support	6	6	0	0
Organize peer support for technology	4	3	1	0
Develop an intergenerational technology literacy program with students	0	2	0	0
Custom referrals to local support services	9	5	4	0
Use local groups or volunteer networks to provide technological support	11	6	5	0
Prioritize any agency/group known to the individual as external support	9	8	0	1
Develop a formal support plan agreement/ social prescription of the program	13	7	6	0
Train primary care staff in support options and referral processes	2	1	1	0

CvS, professionals from the community and voluntary sector; HP, Health professionals; OA, older adults.
The numbers in the table represent the number of participants that suggested that particular strategy.

reactions to indirect support mechanisms such as training videos and paper guides were mixed. Some participants found using a video guide rather than written instructions more appealing, and vice versa. One person described following exercises at home alone with a paper or video guide as "sad". Support *via* trained expert users in digital literacy was mentioned by professionals, in line with expert patient programs to promote autonomy and self-care in people with chronic pathologies, but end users were unsure about this when it was suggested by the researchers. Most of the end users said, however, that they would be concerned about whether or not they were "getting it right". This was tied to a belief that performing the exercises incorrectly would result in not obtaining the desired improvement. They felt more confident if a professional followed up on the activity at regular intervals to "control results; if you have done it, or if you have not" (OA 2: Man, older adult). Weekly follow-up by a health professional was suggested only by a minority from this group; others spoke about capacity issues. Game elements, such as rewards and leveling up, were mentioned by a minority of HP and older adults, but signs of improvement were viewed by end users as the primary motivation:

> "As long as you see that [doing exercise like this] helps...that you notice that you're getting better..." (OA 2: Man, older adult).

3.2.3. Category 3: Specific strategies for facilitating the participation of older adults in virtual exercise groups, performed at home *via* group video calls

Older adults were most vocal in suggesting ways of making virtual exercise groups more accessible and appealing to them (68%) (Table 2). The option of participating in virtual exercise groups was seen by end users as preferable to being prescribed physical exercise alone through videos or a worksheet. Many said that, ultimately, face-to-face groups were more desirable to them for social interaction. Still, some mentioned that virtual groups might be easier because of mobility concerns, fear of falling, pain restricting mobility and fear of (COVID-19) infection:

> "For me, the greatest difficulty would be not being able to do it in the neighborhood without having to take public transport" (OA 4: Woman, older adult).

Limited group size was raised by many as necessary to ensure personalized attention. Some had had negative experiences attending large and overcrowded group exercise classes, targeted generally at their age range. Music featured heavily in the discussion. They felt that they would find it much more enjoyable and easier to perform if the accompanying music was adapted to the exercises to be performed.

3.2.4. Category 4: Specific strategies for facilitating external support if needed

In contrast to the first category, which was formed largely from HP input, "external support" mechanisms were predominantly raised by CVS, reflecting their work (Table 2). As with the first category, almost none of the strategies from this domain user were shared by our older adults' representatives. This was unsurprising, as all had some level of family support available for digital literacy:

> "..... I see my daughter every morning, I will tell her to teach me" (OP 1: Woman, older adult).

While there was much agreement on drawing on community support networks to assist people without family support, the potentially actionable strategies offered were diverse. Local groups or established support networks featured more frequently than the more loosely defined "local volunteers", with emphasis placed on making the most of existing resources (whatever they may be) at the neighborhood level. To this extent, CVS representatives encouraged mapping local resources including spaces, such as libraries and civic centers, which offered meeting points and internet connection. Many of the participants from the third sector spoke of the longer-term purpose of empowering older adults and fostering social relations. The needs of the virtual AGILBcn program, for ensuring accessibility and promoting adherence should be subsumed under other endeavors:

> "I think it would also be important to have the option of having two older people together who can receive the training, so we encourage something that is also very important... peer socialization" (CVS 5: Man, professional from the community).

3.3. Prioritization process

The AGIL Café sessions generated a large number of potentially actionable strategies (Table 2). There was also an obvious clustering of suggested by the professional group (HP vs. CVS). This created challenges for appraising the value and adaptability of possible strategies to optimize the accessibility, acceptability and adaptability of the virtual program. Consequently, the survey, eliciting views on prioritization, offered the participants the opportunity to evaluate all proposed strategies.

3.4. Priority vs. feasibility score

According to overall PvF score (Table 3), the top ten most valued strategies were related to: (a) improving group exercise through videoconference (limited group sizes, personalized exercises, choice of a preferred platform, reminders for the classes, and music); (b) general ways to overcome technological barriers (meetings to prepare and train users of technology, identification of a support person, shared information with family about the technology employed before the start of the program, and assessment of the need for external support with technology and facilitate it, if necessary and (c) the use of Apps (periodic follow-up calls to check on the use of the App and the progression of the program).

Average PvF score for all stakeholder groups tended to smoothen the contribution of each group, compounded by the uneven number of participants in each; thus, we also present the results stratified by groups (Table 3). Maintaining a person-centered approach was a priority, so it is important to note that 9/10 items prioritized by the users were concordant with the top ten from the overall ranking. Finally, CVS scores were systematically lower on all items, although the rank of priority was similar that of the other groups.

3.5. Differences between priority and feasibility scores

When looking at the difference between priority and feasibility (Table 3), the top three actions in terms of feasibility (group sessions through videoconference with a low number of participants and a high personalization of exercises, as well as setting-up a meeting specifically for preparing for the use of technology), seemed coherent in terms of both priority and feasibility. In contrast, the assessment of the need for external support, the identification of a support person and the provision of weekly follow-ups with users

TABLE 3 Comparison of priority (P) vs. feasibility (F) score (PvF) for each suggested strategy, and differences between average P and F for each item of the questionnaire.

	Blocks (4)	PvF Score				Difference (P, F)			
		All	CVS	HP	OA	All	CVS	HP	OA
n		29	9	13	7	29	9	13	7
Limit the size of the virtual group to facilitate personalized attention	Virtual groups	81	64	87	93	−3	0	−6	0
Provide a variety of physical exercises to be tailored to the individual	Virtual groups	75	54	83	89	−1	8	−7	0
Conduct educational meetings in advance to train and educate in the use of technology	General	74	65	80	73	−4	8	−17	4
Establish a preferred platform for video calls	Virtual groups	73	69	77	70	−6	−11	−6	0
Implement systems for sending reminders with dates *via* chat apps or phone calls	Virtual groups	73	58	85	70	1	6	−3	3
Provide continuous technological support	General	71	55	74	84	−12	0	−29	4
Incorporate music in the sessions	Virtual groups	71	51	77	84	1	−8	8	4
Inform family on the selected solutions to reinforce the use of technology	General	69	56	76	71	−8	6	−17	−7
Assess the need for external support with technology and facilitate it, if necessary	General	69	53	69	89	−14	0	−31	0
Provide feedback from a healthcare professional by phone, on the individual progress	App	69	65	65	82	−11	−8	−19	0
Assess digital capacity	General	68	65	77	55	−4	−3	−19	4
Provide simple, paper–based educational materials on how to use the technology	General	67	57	74	68	8	14	10	0
Provide feedback from a healthcare professional by phone, on the group progress	Virtual groups	67	51	72	78	−7	−3	−14	0
Create a simple educational video on how to use technology and share it *via* chat	App	66	64	68	64	6	17	2	0
Use gamification techniques	App	66	55	76	61	0	12	−10	0
Involve older adults in the co–design of the sessions	Virtual groups	64	36	83	66	−10	−12	−15	4
Inform caregiver or support volunteers about the class schedule	Virtual groups	63	51	68	68	−2	−3	−2	0
Use local groups or volunteer networks to provide technological support	External support	63	50	73	61	−7	8	−19	0
Recruit local volunteers offering digital support	External support	62	59	63	61	−9	−3	−19	0
Create peer-to-peer/group messaging in the chat application	Virtual groups	61	62	65	50	6	3	11	0
Custom referrals to local support services	External support	61	54	70	54	−11	0	−23	0
Prioritize any agency/group known to the individual as external support	External support	60	55	73	43	−9	−4	−16	0
Organize peer support for technology	External support	57	53	59	59	−16	−17	−21	−4
Implement a formal digital "expert user" program (support by "peer champions")	App	55	66	47	60	−15	0	−22	−19
Develop an intergenerational technology literacy program with students	External support	55	38	65	61	−8	−9	−12	0
Train primary care staff in support options and referral processes	External support	54	50	68	36	−14	−7	−22	0
Develop a formal support plan agreement/ social prescription of the program	External support	53	55	62	33	−5	18	−21	3
All		65	56	72	66	−6	<1	−12	<1

Items are ordered from highest to lowest PvS. Blocks (4) refer to the 4 categories into which the 27 strategies are grouped in Table 2.
PvF score, priority and feasibility score; CVS, professionals from the community and voluntary sector; HP, Health professionals; OA, older adults. PvF score is calculated as the averaging the mean priority and feasibility scores; the difference is between the mean priority and feasibility score. For the PvF score, the higher score, the best "compromise" between P and F, whereas for the Difference, a value close to 0 indicates the highest coherence between the 2 construct.

of digital apps correspond to actions with apparent lower feasibility than priority. End users tended to express the highest coherence in the feasibility of the actions with higher priority. On the other hand, HP had the lowest confidence in the feasibility of actions with the highest priority.

3.6. Prioritization of solutions by means of a prioritization matrix

The answers to the questionnaire were then plotted in a 4 × 4 matrix categorizing the combined priority and feasibility

10.3389/fpubh.2023.1062843

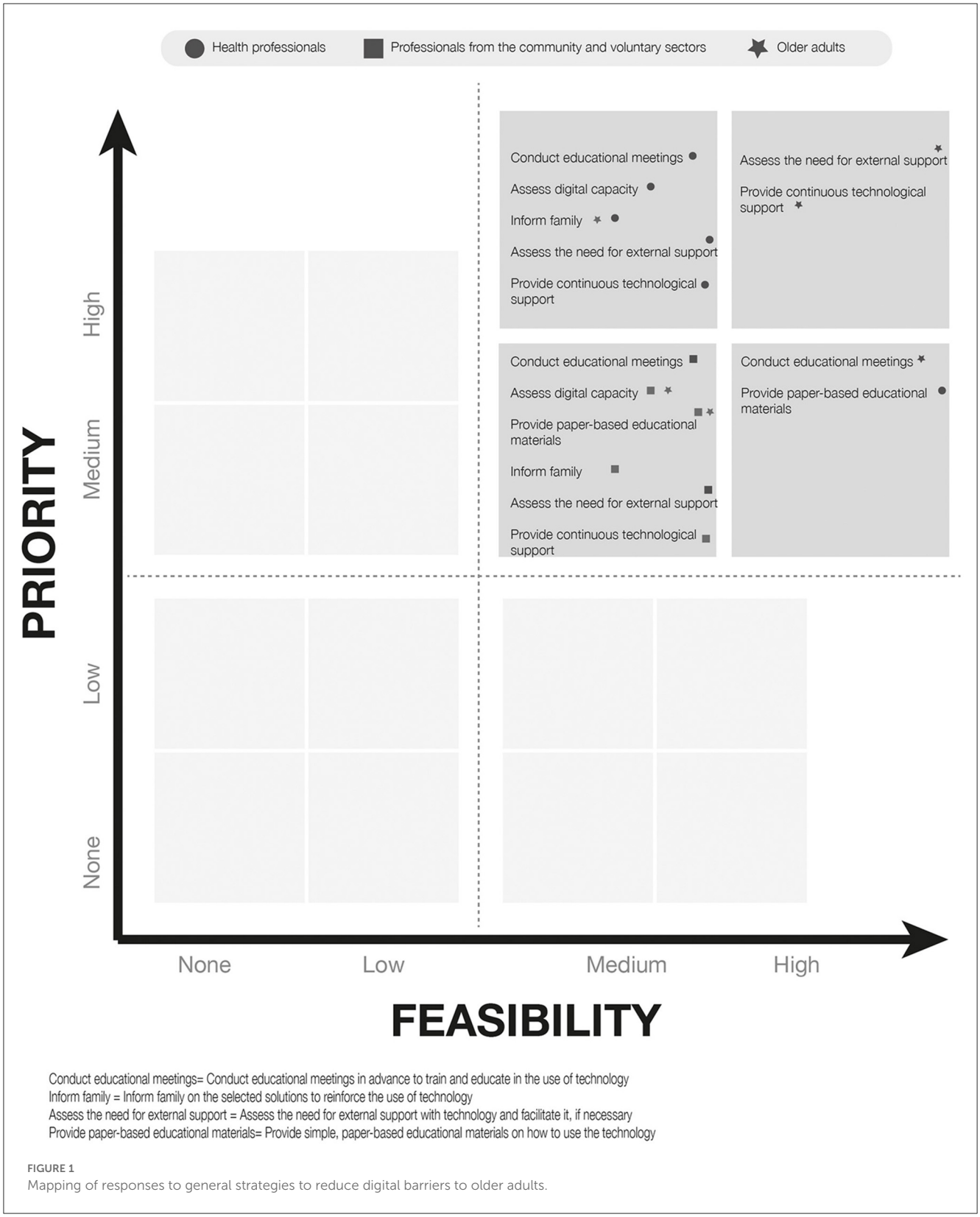
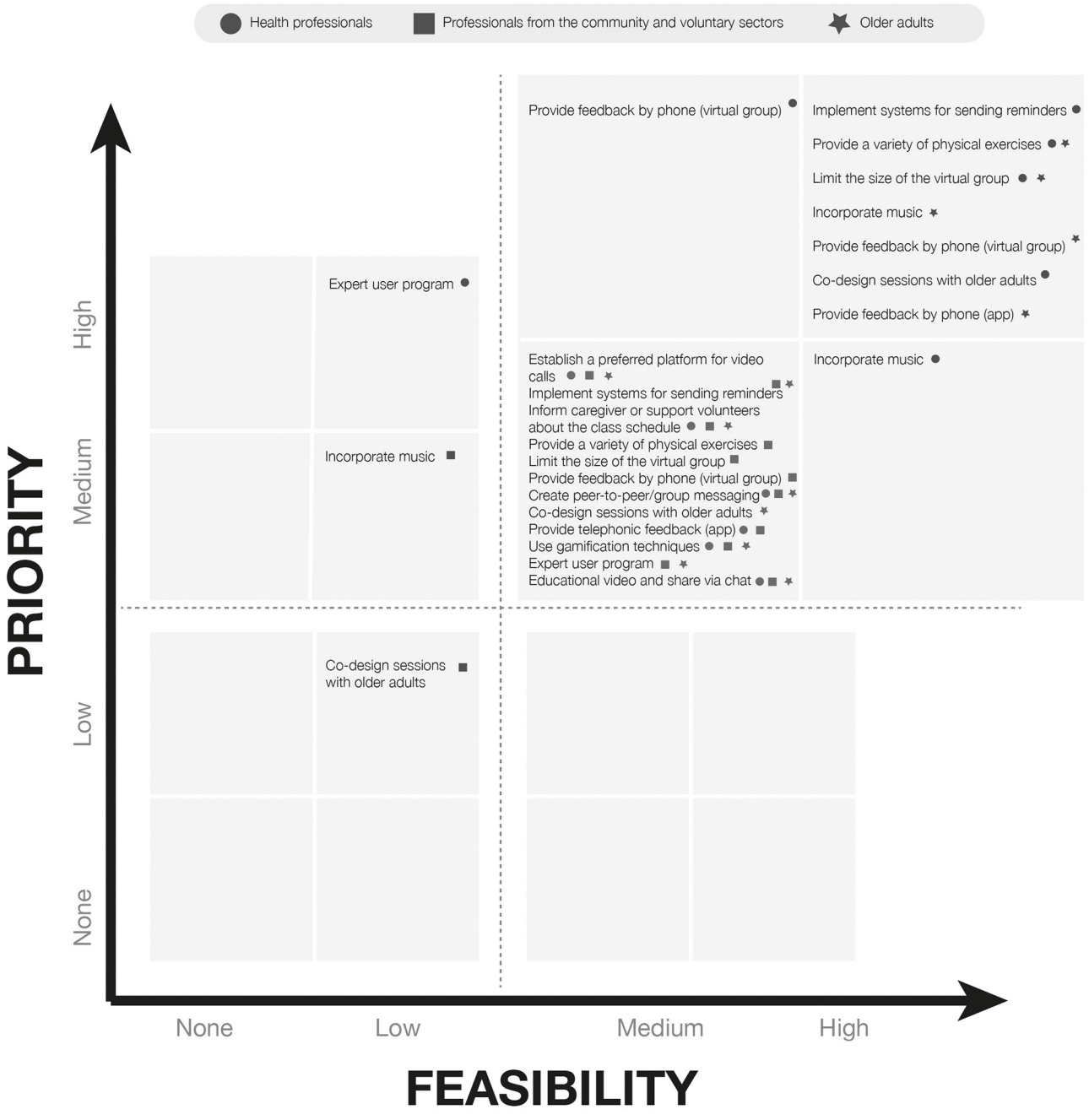


FIGURE 1
Mapping of responses to general strategies to reduce digital barriers to older adults.

response for each item ranging from top priority-top feasibility to no priority-no feasibility, according to the priority and feasibility scores for each item (score 75–100 = top, 50–74 = medium, 25–49 = low and 0–14 = no priority or feasibility (Supplementary Table 2). The responses for each sub-section of the questionnaire were plotted to create visual maps (Figures 1–3).

This procedure allowed us to map the proposed solutions in terms of their importance and feasibility or practical need for

10.3389/fpubh.2023.1062843



Expert user program= Implement a formal digital "expert user" program (support by "peer champions")
Co-design sessions with older adults= Involve older adults in the co-design of the sessions
Provide feedbak by phone (virtual group) = Provide feedback from a healthcare professional by phone, on the group progress
Implement systems for sending reminders = Implement systems for sending reminders with dates via chat apps or phone calls
Provide a variety of physical exercises = Provide a variety of physical exercises to be tailored to the individual
Limited the size of the virtual group = Limit the size of the virtual group to facilitate personalised attention
Provide feedback by phone (app) = Provide feedback from a health professional, on individual progress
Educational video and share via chat= Create a simple educational video on how to use technology and share it via chat

FIGURE 2
Mapping of responses to specific strategies to facilitate the use of physical activity App and specific strategies to facilitate the participation of the older adults in virtual exercise groups performed at home during group video calls.

action: must do, do first; important, do second; do if possible; bear in mind/ consider; and do not consider. Figure 4 represents the different proposed solutions as a "visual journey" of tasks that should be considered on a timeline, from the beginning to the end of a virtual exercise program, with each task coded according to this 4-category priority matrix. This map might add value in terms of a meaningful and workable way of looking at the results in order to guide the adaptation process, in accordance

10.3389/fpubh.2023.1062843

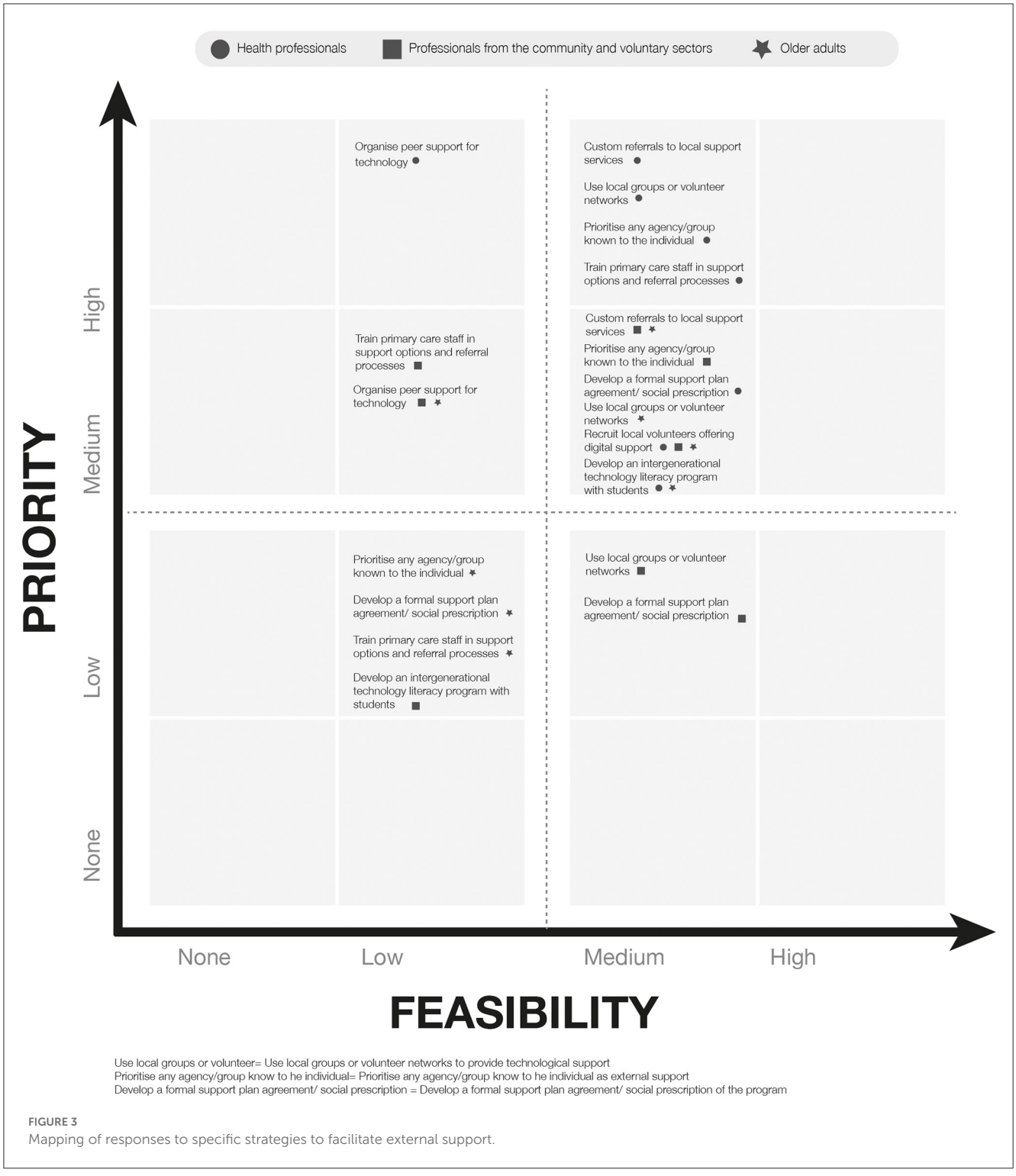


FIGURE 3
Mapping of responses to specific strategies to facilitate external support.

with the data generated from the co-design process. In particular, it ensures that the data on both priority and feasibility have an even influence on the results and that the results of each group have an even influence, despite the differences among groups in the respective number of participants. Consequently, one of the six items that appear as "must-do" does not match with the top six items according to the PvF score (weekly follow-up telephone calls to those using digital apps, substituting virtual exercise class reminders). The other "must do" items are coherent with the PvF score ranking (set up a preparation meeting, identify a support person for technology, assess the need for external support, limit the group size and personalize the exercises during videoconference groups). No solution was classified as "do if possible" or "do not consider".

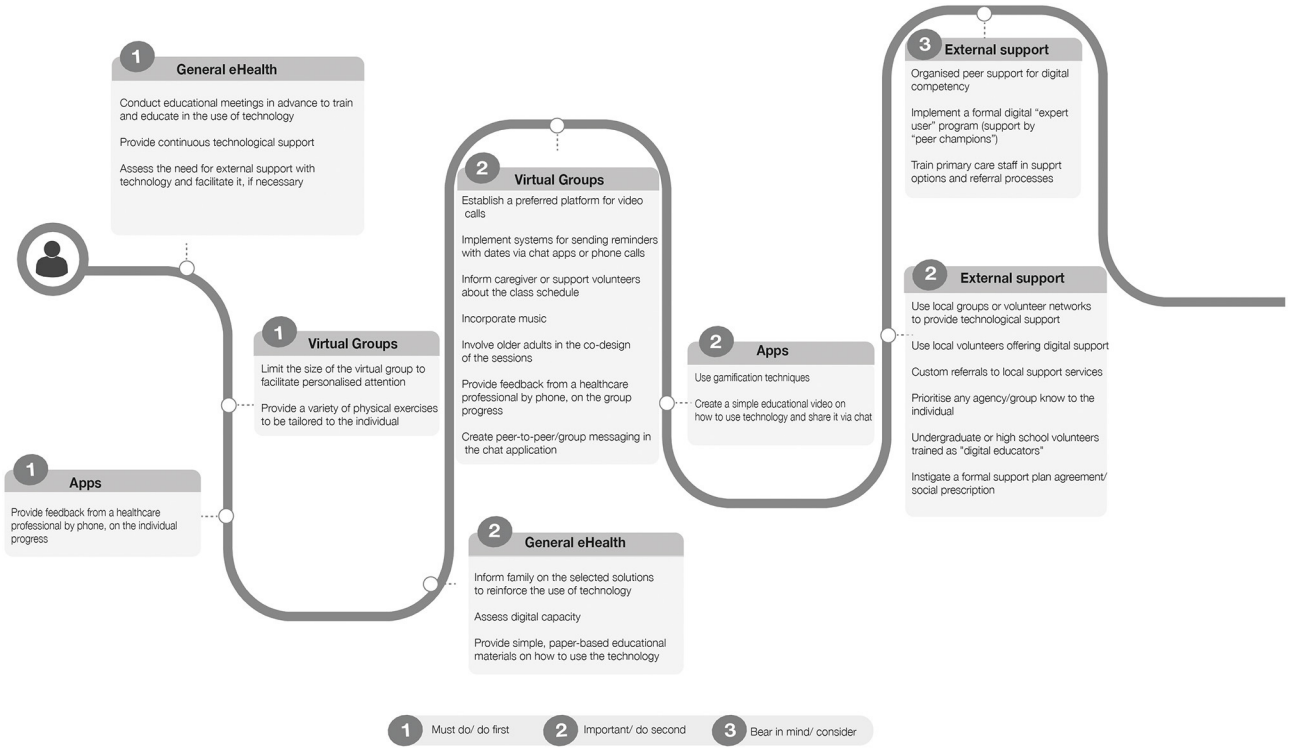


FIGURE 4
Graphic representation of the main suggestions from all groups, plotted along an ideal timeline, from the preparation to the execution of the mHealth solution to foster physical activity.

4. Discussion

Through the +AGIL Café sessions, 27 possible strategies were suggested to adapt a multicomponent program aimed at enhancing physical activity in older adults, based on accessibility, acceptability and adaptability. These were grouped into 4 categories: general strategies for reducing digital barriers; specific strategies for facilitating the use of a digital application; specific strategies for facilitating the participation in virtual exercise groups; and strategies for facilitating external support, if needed. The priorities included improvement of digital literacy, assessment of training and technology support needs, technological support from family members, telephone feedback, personalized exercises, and exercise conducted in small groups.

Although mhealth interventions appear to be beneficial for increasing physical activity levels in OA (8, 30), there are still barriers to large-scale implementation, on personal, social, technological, and organizational levels (10). We present solutions for program adaptation that vary in complexity from single-component strategies to multifaceted and multilevel strategies (31). The variety of strategies proposed by our participants appears in line with the characteristics that m-health interventions for physical activity promotion should have (8, 30) and with the theoretical constructs for promoting and sustaining behavior change (BCT) (32). First, according to the existing literature, an essential strategy for increasing physical activity levels is to develop digital health-literacy training resources (8, 33). In our study, educational sessions, collaborative learning and paper or video guides represented priorities to improve self-efficacy and digital literacy at the individual, interpersonal and social/community levels. Second, for the participating health professionals, the assessment of access to digital infrastructure, social support and digital skills should be systematically and universally added to the comprehensive assessment of older people; this is a core element of AGILBcn (15) and is consistent with previous studies (34). Our findings are also consistent with the need for social and community support for the adoption and use of technology by OAs, for the resolution of technical problems, and for a decrease in the potential digital divide, as highlighted by other authors (8). This support might be provided by family members or by local networks (e.g., volunteers or peers).

Social interaction in face-to-face groups has been shown to benefit the adoption, increase and maintenance of physical activity (35, 36). In our study, older adults recognized virtual group delivery as an opportunity to remove some of the existing barriers to participating in face-to-face group programs and as a means to interact with peers, avoiding exposure to COVID-19. In contrast, CVS highlighted that the potential benefits of virtual delivery are undeniable, but that the pandemic has amplified the barriers to technology in OA, increasing their social isolation and loneliness (11). Controversy exists regarding the positive or negative impact of technology on loneliness, connectedness, and social support (33). Future interventions should seek to mitigate the social connectedness paradox of COVID-19 (37). Our groups emphasized

the importance of combining non-digital alternatives to decrease the digital divide. Providing feedback is another important strategy to promote and maintain adherence to physical activity, and to trigger and sustain motivation for goal attainment (32). Among different options available [e.g., telephonic, *via* apps, wearable devices (38)], our participants still preferred to receive feedback by phone.

Attitudes of OA toward mhealth exercise vary (39). In our case, OA were willing to use technology-based exercise programs if they perceived them as useful or beneficial for achieving their goals. Interestingly, all participating groups paid little attention to safety and privacy in technology use, as compared to available evidence (10). OA focused on the adherence to and safety of home exercise performance, suggesting that technology is not an end in itself, but a mean.

While all the groups identified similar strategies, the results concerning priority and feasibility showed notable differences among groups. The OAs appreciated the limited size of participants in the virtual groups, the need for external support for participating in the intervention, personalization of the exercises, guarantee of access to technological support, incorporation of music in the virtual exercise sessions, and weekly telephone follow-up by HP. In contrast, significantly lower scores for these solutions were observed in CVS, and, in a smaller proportion, in HP.

CVSs scored lower on all items compared to the other two groups. In HPs, we observed a tendency to score higher for priority than for feasibility. This may be due to health professionals' experience regarding macro-, meso- and micro-level barriers to the implementation, scalability, integration and sustainability of mhealth interventions. Among the items for which HPs perceived feasibility to be higher than priority were: the use of messaging Apps (such as WhatsApp) to connect users, or as a vector for education; the creation of instruction booklets on the use of applications; and the incorporation of music in virtual exercise sessions. OAs perceived as a priority the design of an expert patient program and the sharing of information with family about the intervention, although ease of implementation was considered low, coinciding with HPs views. Conversely, the recruitment of local volunteers to provide support was deemed both a higher priority and a feasible step for all three groups.

We aimed to engage a wide range of stakeholders from an early stage to address the problem, identify strategies and prioritize them. This is in line with current policies, care practices and growing evidence on the importance of engagement and co-design for the development, implementation and adaptation of health promotion interventions and for the design of digital solutions (40, 41). However, there was some disparity in results regarding the potential benefits of this involvement concerning uptake and adoption (42). As in previous studies, the implementation of the co-design process was time- consuming, and it proved challenging to merge different stakeholder perspectives (43). In addition, involving OA in co-design was demanding, due to the extreme heterogeneity in physical and digital needs and capabilities (42).

As potential limitations of our study, the digital format of the AGIL Café sessions provided opportunities to participate in conversations during the COVID-19 pandemic, but was challenging due to technical limitations, such as signal loss, which resulted in certain segments in which the audio was missing (44). Although the platform allows the respondent to be seen, it is possible that we missed some non-verbal and body language cues, as participants often sit close to their cameras. Participants who were not technologically skilled required additional attention from the research team members, which led to a delay in the start of the sessions. The results should be interpreted with caution: the study was conducted in a particular area and with a particular group of participants, thus the results may not be completely generalizable; the integration of the different contributions made by the three different groups was limited to the final prioritization approach; and, finally, the phrasing of specific questions introduced the risk of being leading or suggestive (this, however, was necessary at the beginning of the sessions with OA, who had trouble understand more open questions).

As for strengths, the main advantage of the study was the combination of qualitative and quantitative research methods to provide complementary information. Another strength was the co-design approach involving all stakeholders, incorporating the diversity of perspectives of the AGILBcn program. Purposive sampling enabled us to recruit a wide range of participant types, although obviously selection bias cannot be completely excluded, as participation could have been skewed toward motivated individuals.

5. Conclusion

The present study provides practical solutions for implementing a technology-based, multicomponent program for older adults from a variety of perspectives, namely, those of older adults acting as end users, but also those of health professionals and professionals from the community. If confirmed by future studies in experimental and implementation research, these results might provide important considerations for policymakers, care providers, and practitioners, for designing, adapting, and implementing multicomponent, technology-based programs aimed to promoting physical activity in the older adult population. This can help to overcome barriers imposed by extreme conditions, such as the COVID-19 pandemic, and to improve adherence and enhance scalability to exercise 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 Clinical Research Ethics Committee (CREC) of the Foundation University Institute for Primary Health Care Research Jordi Gol i Gurina (IDIAPJGol) (20/048-P) and by the Ethical Commission of Animal and Human Experimentation (Authorization Number CEEAH 5066) of the Autonomous University of Barcelona. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LV-G, VD, LP, and MI contributed to the conceptualization of the study. LV-G, VD, LP, and LS-B performed the data collection. LV-G and VD were responsible for data curation and formal analysis. LV-G, VD, and MI were responsible for writing the initial draft. ER, PD, KK, MG-G, and CC-T reviewed and edited the draft. MI supervised the process of manuscript preparation. All authors agreed to be accountable for the content of the work. All authors contributed to the article and approved the submitted version.

Funding

LV-G was funded by the Industrial Doctorates Program [reference 2020 DI 76], promoted by the Government of Catalonia, Spain. This study received funding by the Barcelona Science Plan of the Cultural Institute of Barcelona-Barcelona City Council and by la Caixa Foundation [19S01576-006].

Acknowledgments

We extend our sincere gratitude to the participants who shared their time and effort in this study.

Conflict of interest

LV-G was employed by QIDA.

The remaining 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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1062843/full#supplementary-material

References

1. Cesari M, Prince M, Thiyagarajan JA, de Carvalho IA, Bernabei R, Chan P, et al. Frailty: an emerging public health priority. *J Am Med Dir Assoc.* (2016) 17:188–92. doi: 10.1016/j.jamda.2015.12.016

2. Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA.* (2014) 311:2387–96. doi: 10.1001/jama.2014.5616

3. Romera-Liebana L, Orfila F, Segura JM, Real J, Fabra ML, Möller M, et al. Effects of a primary care-based multifactorial intervention on physical and cognitive function in frail, elderly individuals : a randomized controlled trial. *J Gerontol A Biol Sci Med Sci.* (2018) 73:1668–74. doi: 10.1093/gerona/glx259

4. Tarazona-Santabalbina FJ, Gómez-Cabrera MC, Pérez-Ros P, Martínez-Arnau FM, Cabo H, Tsaparas K, et al. A multicomponent exercise intervention that reverses frailty and improves cognition, emotion, and social networking in the community-dwelling frail elderly: a randomized clinical trial. *J Am Med Dir Assoc.* (2016) 17:426–33. doi: 10.1016/j.jamda.2016.01.019

5. Pérez LM, Castellano-Tejedor C, Cesari M, Soto-Bagaria L, Ars J, Zambom-Ferraresi F, et al. Depressive symptoms, fatigue and social relationships influenced physical activity in frail older community-dwellers during the Spanish lockdown due to the COVID-19 pandemic. *J Gerontol A Biol Sci Med Sci.* (2021) 18:808. doi: 10.3390/ijerph18020808

6. Yamada M, Kimura Y, Ishiyama D, Otobe Y, Suzuki M, Koyama S, et al. Effect of the COVID-19 epidemic on physical activity in community-dwelling older adults in Japan: a cross-sectional online survey. *J Nutr Health Aging.* (2020) 24:948–50. doi: 10.1007/s12603-020-1501-6

7. Global strategy on digital health 2020-2025. (2021). Available online at: http://apps.who.int/bookorders. (accessed February 6, 2022).

8. Núñez de. Arenas-Arroyo S, Cavero-Redondo I, Alvarez-Bueno C, Sequí-Domínguez I, Reina-Gutiérrez S, Martínez-Vizcaíno V. Effect of eHealth to increase physical activity in healthy adults over 55 years: a systematic review and meta-analysis. *Scand J Med Sci Sports.* (2021) 31:776–89. doi: 10.1111/sms.13903

9. Schulz R, Wahl HW, Matthews JT, de Vito Dabbs A, Beach SR, Czaja SJ. Advancing the aging and technology agenda in gerontology. *Gerontologist.* (2015) 55:724–34. doi: 10.1093/geront/gnu071

10. Wilson J, Heinsch M, Betts D, Booth D, Kay-Lambkin F. Barriers and facilitators to the use of e-health by older adults: a scoping review. *BMC Public Health.* (2021) 21:1–12. doi: 10.1186/s12889-021-11623-w

11. Seifert A, Cotten SR, Xie B, A. Double burden of exclusion? Digital and social exclusion of older adults in times of COVID-19. *J Gerontol B Psychol Sci Soc Sci.* (2021) 76:e99–103. doi: 10.1093/geronb/gbaa098

12. Sansano-Nadal O, Giné-Garriga M, Brach JS, Wert DM, Jerez-Roig J, Guerra-Balic M, et al. Exercise-based interventions to enhance long-term sustainability of physical activity in older adults: a systematic review and meta-analysis of randomized clinical trials. *Int J Environ Res Public Health.* (2019) 16:2527. doi: 10.3390/ijerph16142527

13. Green LW, O'Neill M, Westphal M, Morisky D. The challenges of participatory action research for health promotion. *Promot Educ.* (1996) 3:3–5. doi: 10.1177/102538239600300401

14. Kuluski K, Ho JW, Cadel L, Shearkhani S, Levy C, Marcinow M, et al. An alternate level of care plan: co-designing components of an intervention with patients, caregivers and providers to address delayed hospital discharge challenges. *Health Expect.* (2020) 23:1155–65. doi: 10.1111/hex.13094

15. Inzitari M, Pérez LM, Enfedaque MB, Soto L, Díaz F, Gual N, et al. Integrated primary and geriatric care for frail older adults in the community: Implementation of a complex intervention into real life. *Eur J Intern Med.* (2018) 56:57–63. doi: 10.1016/j.ejim.2018.07.022

16. Izquierdo M, Rodriguez-Mañas L, Sinclair AJ, Vivifrail Investigators Group. Editorial: What is new in exercise regimes for frail older people - how does the erasmus vivifrail project take us forward?. *J Nutr Health Aging.* (2016) 20:736–7. doi: 10.1007/s12603-016-0702-5

17. Pérez Bazán LM, Enfedaque-Montes MB, Cesari M, Soto-Bagaria L, Gual N, Burbano MP, et al. A Community Program of Integrated Care for Frail Older Adults: +AGIL Barcelona. *J Nutr Health Aging.* (2019) 23:710–6. doi: 10.1007/s12603-019-1244-4

18. Fouché C. Light G. An invitation to dialogue: 'the world café' *Social Work Res.* (2010) 10:28–48. doi: 10.1177/1473325010376016

19. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. *Administration and Policy in Mental Health and Mental Health Services Research.* (2015) 42:533–44.

20. Saunders B, Sim J, Kingstone T, Baker S, Waterfield J, Bartlam B, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. *Qual Quant.* (2018) 52:1893–907. doi: 10.1007/s11135-017-0574-8

21. Brown J, Isaacs D. *The World Cafe: Shaping Our Futures Through Conversations That Matter* [Paperback]. (2005). p. 242.

22. Löhr K, Weinhardt M, Sieber S. *The "World Café" as a Participatory Method for Collecting Qualitative Data.* (2020). 19:1–15 doi: 10.1177/1609406920916976

23. Khong L, Bulsara C, Hill KD, Hill AM. How older adults would like falls prevention information delivered: fresh insights from a World Café forum. *Ageing Soc.* (2017) 37:1179–96. doi: 10.1017/S0144686X16000192

24. Litchfield I, Bentham L, Hill A, McManus RJ, Lilford R, Greenfield S. The impact of status and social context on health service co-design: an example from a collaborative improvement initiative in UK primary care. *BMC Med Res Methodol.* (2018) 18:1–10. doi: 10.1186/s12874-018-0608-5

25. McKimm J, Ramani S, Kusurkar RA, Fornari A, Nadarajah VD, Thampy H, et al. Capturing the wisdom of the crowd: health professions' educators meet at a virtual world café. *Perspect Med Educ.* (2020) 9:385–90. doi: 10.1007/S40037-020-00623-Y

26. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res.* (2005) 15:1277–88. doi: 10.1177/1049732305276687

27. Mayring P. Qualitative Content Analysis. *Forum Qualitative Sozialforschung/Forum: Qualitative Social Research*. (2000). p. 1.

28. Caillaud S, Flick U. *8 Focus Groups in Triangulation Contexts*.

29. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care.* (2007) 19:349–57. doi: 10.1093/intqhc/mzm042

30. Elavsky S, Knapova L, Klocek A, Smahel D. Mobile health interventions for physical activity, sedentary behavior, and sleep in adults aged 50 years and older: a systematic literature review. *J Aging Phys Act.* (2019) 27:565–93. doi: 10.1123/japa.2017-0410

31. Powell BJ, Warren G, Mmillen JC, Proctor EK, Carpenter CR, Griffey RT, et al. A compilation of strategies for implementing clinical innovations in health and mental health. *Med Care Res Rev.* (2012) 69:123–57. doi: 10.1177/1077558711430690

32. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med.* (2013) 46:81–95. doi: 10.1007/s12160-013-9486-6

33. Buyl R, Beogo I, Fobelets M, Deletroz C, van Landuyt P, Dequanter S, et al. E-Health interventions for healthy aging: a systematic review. *Syst Rev.* (2020) 9:1–15. doi: 10.1186/s13643-020-01385-8

34. Oh SS, Kim KA, Kim M, Oh J, Chu SH, Choi JY. Measurement of digital literacy among older adults: systematic review. *J Med Internet Res.* (2021) 23:e2614. doi: 10.2196/preprints.28211

35. Zengin Alpozgen A, Kardes K, Acikbas E, Demirhan F, Sagir K, Avcil E. The effectiveness of synchronous tele-exercise to maintain the physical fitness, quality of life, and mood of older people—a randomized and controlled study. *Eur Geriatr Med.* (1999) 1:3.

36. Lindsay Smith G, Banting L, Eime R, O'Sullivan G, van Uffelen JGZ. The association between social support and physical activity in older adults: a systematic review. *Int J Behav Nutr Phys Activity.* (2017) 14:1–21. doi: 10.1186/s12966-017-0509-8

37. Smith ML, Steinman LE, Ea C. Combatting social isolation among older adults in a time of physical distancing: the COVID-19 social connectivity paradox. Social Connect Paradox. *Front Public Health.* (2020) 8:403. doi: 10.3389/fpubh.2020.00403

38. McGarrigle L, Todd C. Promotion of physical activity in older people using mHealth and ehealth technologies: rapid review of reviews. *J Med Internet Res.* (2020) 22:e22201. doi: 10.2196/22201

39. Valenzuela T, Okubo Y, Woodbury A, Lord SR, Delbaere K. Adherence to technology-based exercise programs in older adults: a systematic review. *J Geriatric Physical Therapy.* (2018) 41:49–61. doi: 10.1519/JPT.0000000000000095

40. Sadler E, Sandall J, Sevdalis N, Wilson D. The contribution of implementation science to improving the design and evaluation of integrated care programmes for older people with frailty. *J Integrated Care.* (2019) 27:232–40. doi: 10.1108/JICA-07-2018-0048

41. Cole AC, Adapa K, Khasawneh A, Richardson DR, Mazur L. Codesign approaches involving older adults in the development of electronic healthcare tools: a systematic review. *BMJ Open.* (2022) 12:58390. doi: 10.1136/bmjopen-2021-058390

42. Fischer B, Peine A, Östlund B. The importance of user involvement: a systematic review of involving older users in technology design. *Gerontologist.* (2020) 60:513–23. doi: 10.1093/geront/gnz163

43. Kirk J, Bandholm T, Andersen O, Skov Husted R, Tjørnhøj-Thomsen T, Pedersen MM. Challenges in co-designing an intervention to increase mobility in older patients: a qualitative study. *J Health Organiz Manage.* (2021) 35:140–62. doi: 10.1108/JHOM-02-2020-0049

44. Seitz S. Pixilated partnerships, overcoming obstacles in qualitative interviews *via* Skype: a research. *Qualitative Res.* (2015) 16:229–35. doi: 10.1177/1468794115577011

frontiers | Frontiers in Public Health

TYPE Review
PUBLISHED 16 March 2023
DOI 10.3389/fpubh.2023.1086215

OPEN ACCESS

EDITED BY
Yurun Cai,
School of Nursing, University of Pittsburgh, United States

REVIEWED BY
Varalak Srinonprasert,
Mahidol University, Thailand
Yuan Lu,
Tongji University, China

*CORRESPONDENCE
Rhys Mantell
✉ r.mantell@unsw.edu.au

SPECIALTY SECTION
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

RECEIVED 03 November 2022
ACCEPTED 24 February 2023
PUBLISHED 16 March 2023

CITATION
Mantell R, Hwang YIJ, Radford K, Perkovic S, Cullen P and Withall A (2023) Accelerated aging in people experiencing homelessness: A rapid review of frailty prevalence and determinants. *Front. Public Health* 11:1086215. doi: 10.3389/fpubh.2023.1086215

Accelerated aging in people experiencing homelessness: A rapid review of frailty prevalence and determinants

Rhys Mantell[1]*, Ye In Jane Hwang[1,2], Kylie Radford[2,3,4], Silvija Perkovic[1], Patricia Cullen[1,5,6] and Adrienne Withall[1,2]

[1]School of Population Health, Faculty of Medicine and Health, University of New South Wales (UNSW), Sydney, NSW, Australia, [2]UNSW Ageing Futures Institute, University of New South Wales (UNSW), Sydney, NSW, Australia, [3]School of Psychology, Faculty of Science, University of New South Wales (UNSW), Sydney, NSW, Australia, [4]Neuroscience Research Australia (NeuRA), Sydney, NSW, Australia, [5]The George Institute for Global Health, University of New South Wales (UNSW), Sydney, NSW, Australia, [6]Ngarruwan Ngadju: First Peoples Health and Wellbeing Research Centre, University of Wollongong, Wollongong, NSW, Australia

Introduction: Older people experiencing homelessness (PEH) are a rapidly growing population at risk of accelerated aging and the early onset of geriatric conditions. One construct that shows promise in predicting age-related decline is frailty. Better understanding the rates and causes of frailty in PEH may improve understanding of its antecedents, thereby facilitating more targeted health and aged care service interventions. The aim of this study was to conduct a rapid review on the prevalence and determinants of frailty in adult PEH.

Methods: We conducted a rapid review of primary research papers studying PEH and frailty or frailty-related concepts.

Results: Fourteen studies were included, which indicate that frailty presents earlier and at higher rates in PEH than community-dwelling cohorts. A notable difficulty for many aging PEH was early-onset cognitive impairment which was associated with a range of negative functional outcomes. Another recurrent theme was the negative impact that drug and alcohol use and dependence can have on the health of PEH. Further, psychosocial and structural determinants such as loneliness, living in an impoverished neighborhood and being female had statistically significant associations with frailty and functional decline in PEH.

Discussion and implications: PEH in their 40s and 50s can be frail and experience geriatric conditions, including cognitive impairment. Factors that have important relationships to frailty and functional decline in PEH include cognitive deficits, drug and alcohol dependence and loneliness, as well as upstream determinants such as gender and ethnicity. More targeted data and research on these factors, including cohort studies to better investigate their potentially causal effects, is important for researchers and practitioners assessing and treating frailty in PEH, particularly those interested in early intervention and prevention.

Prospero registration ID: CRD42022292549.

KEYWORDS

frailty, homelessness, marginalized and vulnerable groups, accelerated aging, cognitive impairment, social determinants of health

Introduction

People experiencing homelessness (PEH) often face challenging living conditions and endure a complex interplay of health and social deprivation. The disadvantage facing PEH has previously been shown by the high rates of early morbidity and mortality that the group faces (1). Studies report mortality rates for PEH 3-to-12 times higher than the age-standardized general population rate (2–4). The burden facing PEH becomes particularly evident as individuals age, where physical and cognitive conditions become more common (1). Approximately two-thirds of older PEH in high-income countries have multiple physical health problems, most commonly cardiac disease, hypertension, diabetes and respiratory illness (5). A recent meta-analysis by Suh et al. (1) found that PEH experience higher rates of geriatric conditions at a younger age compared to community-dwelling adults. Unpacking the various health and social difficulties faced by older PEH is becoming increasingly important (6) as the number of older people in this situation is growing rapidly worldwide.

The cumulative disadvantage experienced by older people who are homeless has led many researchers, clinicians and policy makers to conclude that PEH are at risk of experiencing "accelerated aging," and consequently the early onset of geriatric conditions such as falls, functional and cognitive impairment, incontinence and immobility (1). There is no standard definition for accelerated aging, but it is generally recognized as a process where a person's physiological system deteriorates earlier and/or more rapidly than when compared to other people or cohorts of comparable age. There is evidence that the pathophysiology that causes this dysregulation is not necessarily related to a specific disease but to a cumulative process of physiological decline, or underlying biological alteration, which is caused by a combination of genetic, environmental and behavioral factors over time (7). Thus, the concept of accelerated aging is often used to examine the cumulative disadvantage of marginalized groups with relatively high morbidity and mortality who seem to "grow old before their time." In accordance with this, PEH are often considered "older" once they reach the age of 50 (1), as opposed to 65 years which is the nominal existing cut-off for aged care services in many countries.

The implications of accelerated aging can be particularly costly for PEH considering their challenging living environments, the lack of autonomy to modify these environments and the persistent barriers to regular service access that these environments can create or reinforce. In a group that is aging unequally, the concept of early intervention to reduce or slow the onset of geriatric conditions becomes increasingly important. However, one of the main obstacles to early identification and support for accelerated aging in PEH is effectively measuring, unpacking and responding to the underlying, often intersectional, causes of premature geriatric issues in such a diversely disadvantaged cohort (8).

Frailty as a construct to measure age-related decline

To more effectively identify the early signs of age-related decline, one construct that has gained considerable traction in recent decades is "frailty" (8). Although there is debate about an acceptable definition for the term, frailty can be broadly described as a decreased resilience to stressors, which renders people more vulnerable to disease, disability, hospitalization and social change (6). Similar to the concept of accelerated aging, the pathways that cause frailty are complex and multidimensional. However, unlike accelerated aging, frailty is readily measurable, with a number of validated frailty measures shown to predict various aging outcomes. In a study by Ritt et al. (9), it was found that frailty was a better predictor than disability for overall mortality. Likewise, in Bagshaw et al. (10), those who were frail were more likely to require ongoing help to live at home and also had higher in-hospital mortality compared to non-frail people. In other studies, frailty measures have outperformed chronological age as a predictor of mortality, disability, and cognitive decline, highlighting the relative sensitivity of the construct at capturing "biological" aging (11, 12). For these reasons frailty appears to be a useful approximation of accelerated aging, and may help to detect and/or unpack the complex causes of biological decline, which ultimately lead to the premature onset of geriatric conditions, disability and death (7).

Debates about how to measure and operationalize frailty have led to a variety of measures, frameworks and models (8). However, most measures stem from two dominant constructs: the phenotype model and the cumulative deficit model (6, 8). The phenotype model was developed by Fried et al. (13) through clinical observation and epidemiological research and operationalizes frailty as the presence of three or more of the following criteria: exhaustion, weight loss, weakness/loss of muscular strength, reduced gait speed and reduced energy/physical activity (Figure 1).

In contrast, the cumulative deficit model was developed by Rockwood et al. (14–16) through consideration of biological theories of aging. It argues frailty to be an accumulation of deficits including clinical signs and symptoms, diseases and disability (Figure 2). This model is often conceptualized as an aggregation of difficulties whereby the more predefined conditions an individual has the more likely they are to be frail (8, 17). In this model, frailty can be measured using a Frailty Index (FI), which for any individual represents the number of concerns present, divided by the number of concerns counted (16). An alternative measure of frailty using the foundations of the cumulative model is the Clinical Frailty Scale (CFS) (Figure 3). Although the CFS uses the concept of cumulative deficits to identify frailty, it is less prescriptive than a Frailty Index approach in determining what is measured and uses clinical judgement to assess a person's baseline health and frailty level (14). The judgment-based CFS is typically advantageous to use when clinicians are available who have experience in the care of older people; whereas the index approach is often useful when experts are unavailable or when a more data-driven measurement approach is desired (14).

Another noteworthy frailty measure is the Tilburg Frailty Indicator (TFI) [see (18–20)]. The TFI takes the foundational elements of the cumulative model of frailty and extends the construct to explicitly measure psychological and social elements. However, the TFI distinguishes itself from other cumulative model measures not only because of its focus on psychological and social elements of frailty, but also because it does not contain questions referring to disability nor disease. The typical questions asked in the user-friendly and self-reported TFI are summarized in Figure 4.

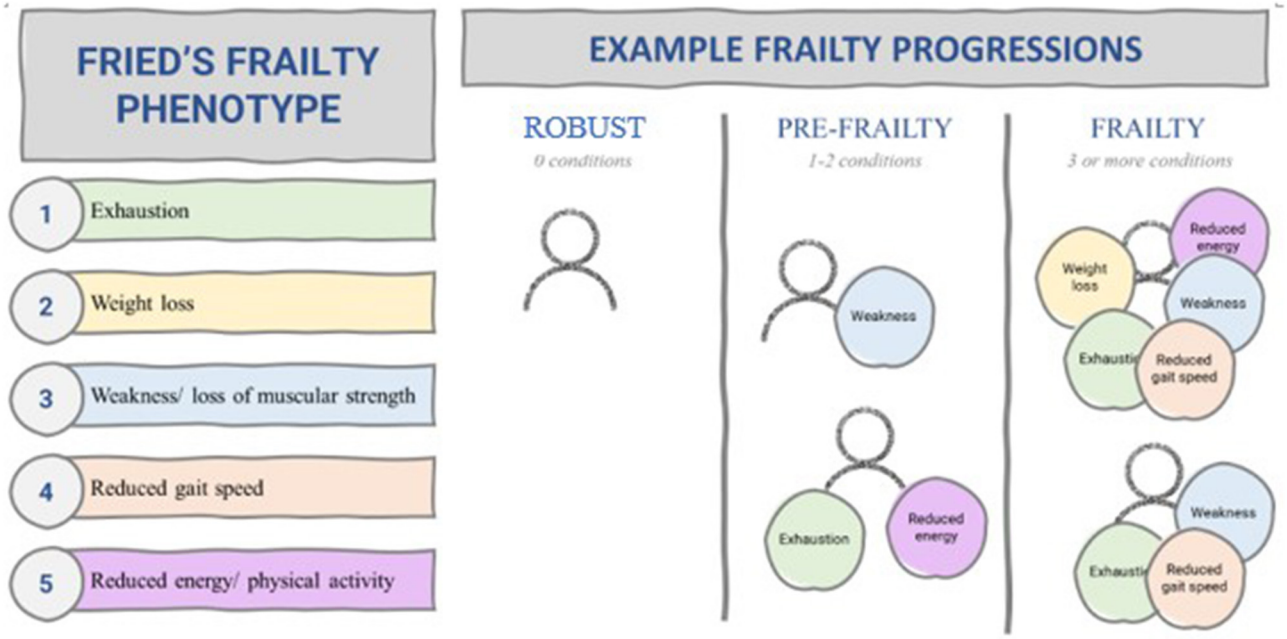


FIGURE 1
Fried's phenotype model of frailty (13).

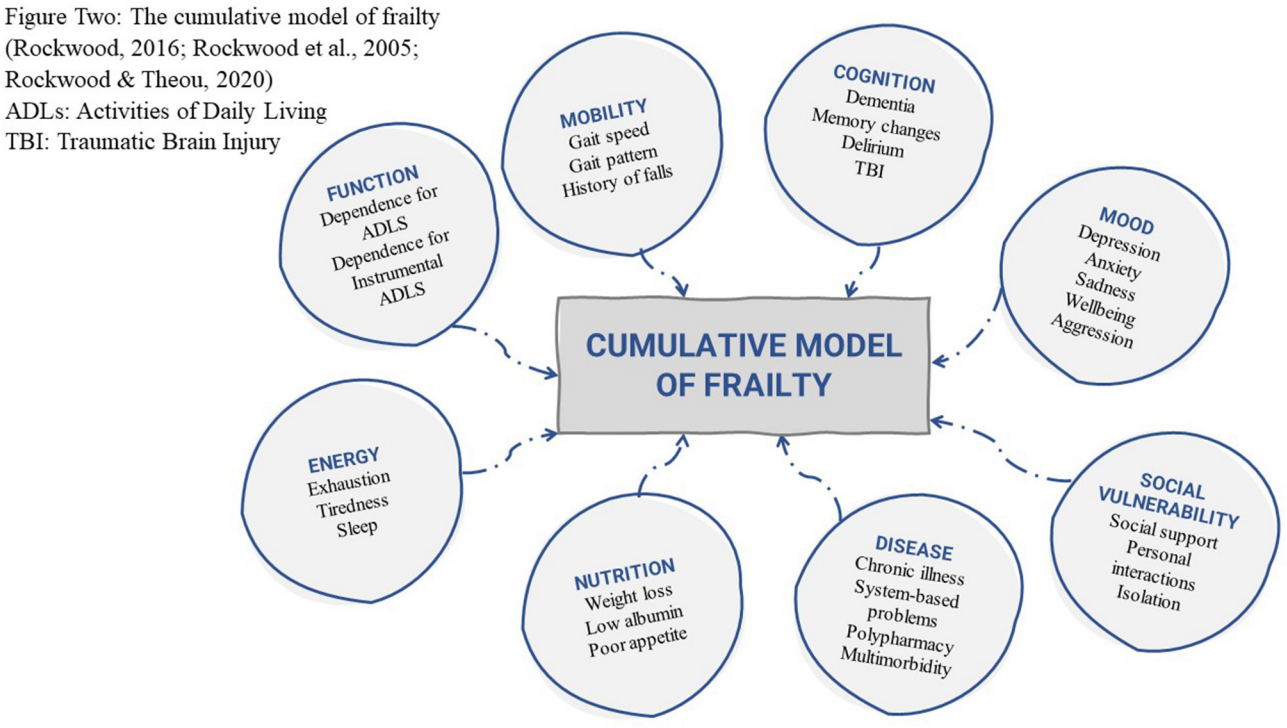


FIGURE 2
The cumulative model of frailty (14–16). ADLs, activities of daily living; TBI, traumatic brain injury.

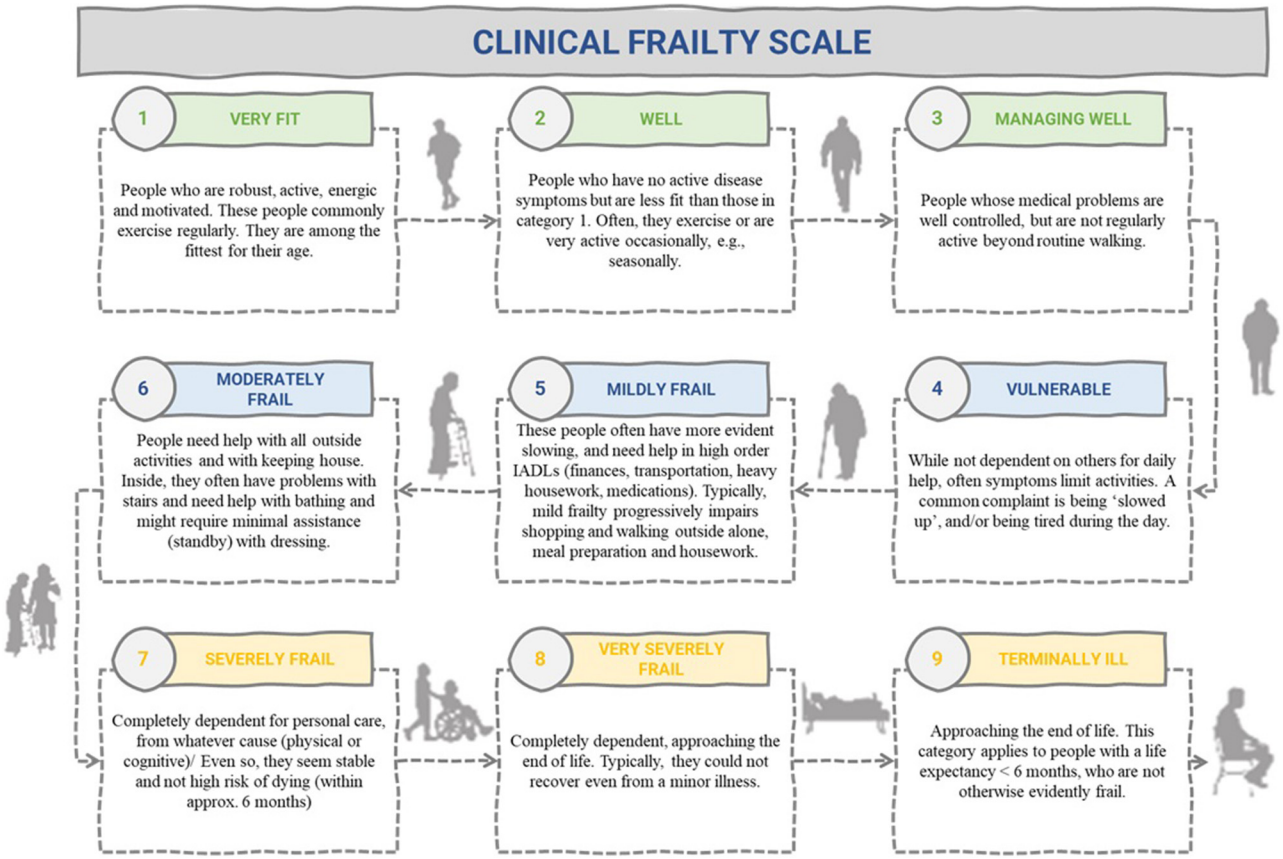


FIGURE 3
Clinical Frailty Scale (14).

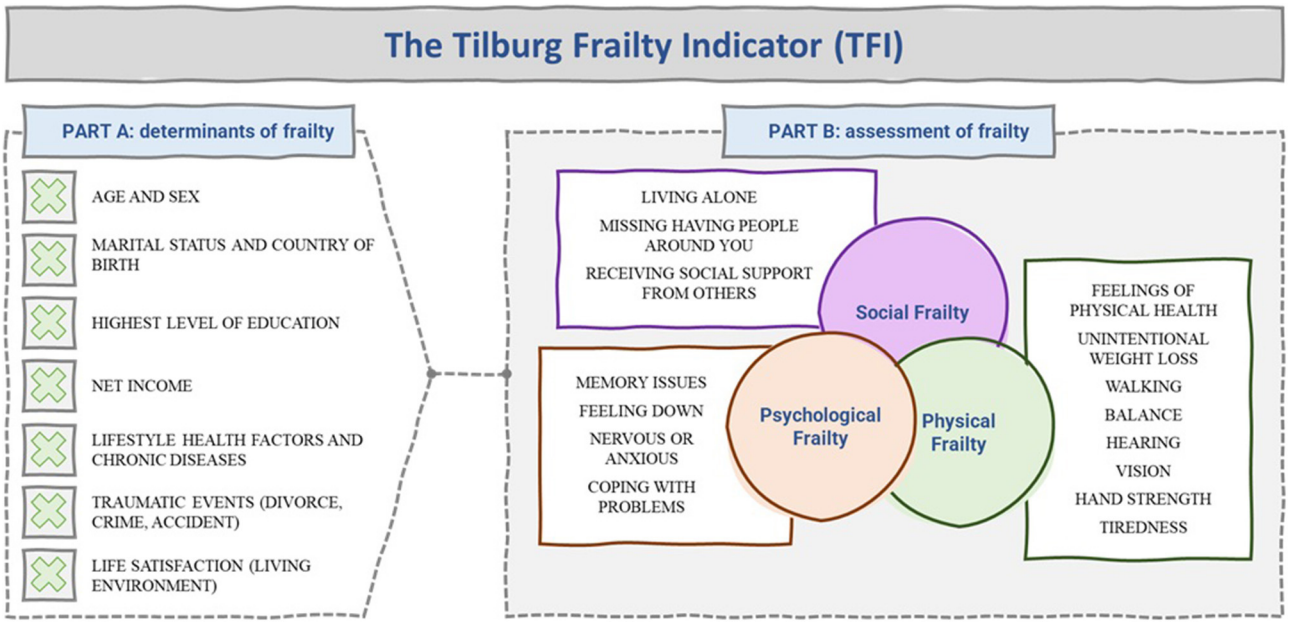


FIGURE 4
Tilburg Frailty Indicator (TFI) (18–20).

The TFI also has the important benefit of attempting to measure the determinants of frailty, not only assessing if someone is frail.

The frailty construct shows promise as a relatively quick, affordable and effective measure of the early signs of geriatric syndromes and premature aging. The broad application of such a measure in PEH could offer improved detection of premature geriatric conditions and early support to a group for whom health engagement can be a challenge. However, there are a vast range of different frailty measures and, as such, there is no gold standard assessment approach. This increases the complexity of applying and interpreting frailty measures. Further, much of the debate about the value of the frailty construct has not considered the application of the concept in the context of PEH; a group at risk of accelerated aging and the premature onset of geriatric conditions, with significant barriers addressing these conditions. There is ultimately a lack of research on the use of the frailty construct to assess and support PEH. Given the potential value of the frailty construct to predict adverse outcomes, its relative ease of use and potential capacity to measure the upstream determinants of geriatric conditions, including social and psychosocial factors, a synthesis of the frailty construct in the context of PEH is greatly needed to query the value of the construct for this group. This is particularly important as the number of older PEH grows rapidly across the world and, without intervention, will continue to do so over the coming decades.

Objectives

The aim of this study is to conduct a rapid review on the application of frailty in adult PEH. Specifically, this review aims to synthesize the findings of studies that have measured frailty or related geriatric constructs and investigated factors that contribute to frailty in PEH; which may in turn highlight existing opportunities for early intervention.

This rapid review aims to answer the following questions:

1. Do PEH experience higher levels and/or earlier onset of physical frailty and other frailty-related geriatric conditions when compared with 'housed' populations?
2. What are the most significant cognitive, psychological, and social determinants of frailty and other frailty-related geriatric conditions in PEH?

Methods

We conducted a rapid review which provides a streamlined version of a more traditional systematic review (21). Rapid reviews attempt to accelerate the review process, resulting in timely outputs that act as a rigorous summary of the literature rather than an in-depth synthesis (22). The adaptive methodology supported in rapid reviews suited the aims of this research, i.e., investigating the emerging and dynamic nature of the frailty construct [see (8)].

For the purposes of this work, methods included: independent and systematic searches by two researchers (RM and SP). Both screeners were independently involved in applying inclusion/exclusion criteria, underpinned by a comprehensive review strategy, for all search results using Covidence software. Where there was disagreement between the two screeners, the senior author (AW) screened these results. AW also acted as a triple screener of the titles and abstracts for 10% of studies to ensure fidelity of the process. Screening was followed by a thorough data extraction process audited by all authors to ensure consensus.

Search strategy

A search strategy was developed based on three intersecting concepts: Aging, homelessness and frailty. Given our interest in (a) accelerated aging and (b) cumulative geriatric difficulties, we also incorporated search terms which would capture these concepts, namely: premature, accelerated, onset and geriatric.

Data sources

Three electronic databases were searched: Medline, Embase and PsycINFO.

Original search query

(Old* OR elder* OR geriatric* OR gerontol* OR aging OR aged) AND (homeless* OR PEH OR unhoused) AND (health* OR frail* OR disease* OR infection* OR treat* OR illness* OR decline OR dementia OR functional OR onset OR premature OR accelerated).

Review criteria

We reviewed primary research papers studying PEH and which assessed frailty or frailty-related concepts between 2000 and 2021. Frailty-related concepts included studies on geriatric syndromes in PEH as well as studies which explicitly looked at an accumulation of deficits across two or more psychological, social and physical domains, which could have been reasonably included into a cumulative model of frailty. The latter search strategy required a level of interpretability by the research team. To ensure quality control and consistency the researchers implemented a further rule that to include a paper, it must:

- Explicitly involve a frailty measure or framework, *OR;*
- Measure cumulative geriatric syndromes or outcomes with high conceptual overlap with frailty (e.g., functional dependence, falls, incontinence), *OR;*
- Measure at least one physical geriatric deficit or condition *AND* at least one measure of either psychological, cognitive *OR* social burden.

It was deemed important to include the final point given the under-recognized contribution of social and psychological disadvantage in premature aging and physical frailty (23–25), and because the capacity to measure social and psychological deficits may enable early intervention or prevention of frailty (6).

For the purposes of this study, we defined homelessness to include primary, secondary and tertiary forms of homelessness. This excluded people in marginal housing, including permanent

supportive housing. An exception was made when studies incorporated samples with both homeless and precariously housed individuals, in which case a study was included.

This study aimed to investigate the onset of frailty in adult PEH and as such we did not actively define a minimum age threshold for presenting with geriatric conditions apart from the requirement that study sample populations were aged 18 or over.

Data extraction

Summary study information was extracted into a data workbook after a full text review. Data columns included Author(s); Year; Title; Journal; Location; Study design; Design Comments; Target population and/or setting; Sample Size; Age (Mean); Female (%); Frailty tool(s); Frailty tool(s) comments; Other tool(s) used; Study Aims; Main implications and/or insights. A summary version of the data extraction can be found in Table 1.

Results

Our initial database search yielded $n = 3{,}747$ papers. After removing duplicates and obvious exclusions, $n = 516$ papers were included for abstract screening and a further $n = 154$ were included for full screen review. Through our final search strategy and extraction process we identified $n = 14$ research papers that met the study criteria. Of these papers $n = 5$ used validated measures of physical frailty, and the other $n = 9$ adhered to cumulative model constructs of frailty (*defined above*) (Figure 5). All papers were cross-sectional or cohort studies. All papers were from anglophone countries with the exception of one paper from Peru (34). There were a diverse range of average ages across the studies—from 39 to 72 years. There were also some noticeable gender differences across the study samples; only two of the studies had more than 33% female participation. However, one of these papers (Salem et al., 2019) included only female participants. Finally, although there was some variance in the definition of PEH, all papers sampled participants from cohorts that conformed to our broad definition of homelessness.

Prevalence of physical frailty and other frailty-related geriatric conditions among PEH

The prevalence of physical frailty was measured directly in five studies of PEH (23, 25, 26, 32, 36). A further three studies (27, 28, 34) directly reported on geriatric conditions that were related to physical frailty. Although these papers did not explicitly measure frailty, the findings from these papers either directly or indirectly conform to a cumulative deficit model of frailty and thus highlight important geriatric difficulties for PEH. Findings are summarized in Table 2.

Physical frailty in PEH in the context of broader population studies

Of the eight papers which reported the rates of physical frailty and other frailty-related geriatric conditions in PEH, four were indirectly compared to frailty rates in other cohorts. In Rogans-Watson et al. (36), as assessment criteria were based on methods used in the English Longitudinal Study of Aging (ELSA), comparison to population data was feasible (37). When compared to ELSA data, the average frailty rates (2.6/5) of the PEH sample (average age 56) were equivalent to the mean for an 89-year-old in the general population in England (36).

In another study by Brown et al. (27), geriatric syndromes were measured using the same sample of older PEH as Brown et al. (26). Findings were subsequently compared with population-based cohorts to investigate differences in the prevalence of geriatric issues. When matched with Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) of Boston Study (MBS), PEH were less likely to report good, very good or excellent health ($p < 0.001$). Rates of physical frailty were significantly higher for PEH than the MBS cohort (16% vs. 10%) ($p < 0.001$). In Brown et al. (28), the authors compared their findings with the MBS cohort (27, 38, 39), as they did with a different PEH sample in 2012 (27). When compared to the MBS study sample ($n = 765$, mean age of 78.1), rates of several geriatric conditions were higher in the much younger PEH sample (median age 58). A second comparison was made with a cohort of community-dwelling adults aged 65 and older (mean age 71.7 years) with a very low-income (40). Low income was defined as income <200% of the United States poverty level. When compared to this much older and low-income group, PEH still had a significantly higher prevalence of falls (33.7% older PEH vs. 21.9% older adults living in poverty), visual impairment (45.1% vs. 12.0%), urinary incontinence (48.0% vs. 29.5%), and depression (38.3% vs. 11.3%) (28).

Finally, in Moquillaza-Risco et al. (34), the authors compared their findings with the Health, Welfare and Aging Survey (SABE, Spanish acronym), which was conducted in several Latin American and Caribbean countries (41). The SABE study indicated that between 10% and 25% of older survey participants had at least some kind of difficulty with ADLs and IADLs (41). This was noticeably lower than the 50% prevalence of *at least* partial functional impairments found in Moquillaza-Risco et al. (34).

Cognitive impairment and functional issues in PEH

An important finding highlighted by four studies (5, 29, 33, 34) in this rapid review, summarized in Table 3, is that many PEH present with significant cognitive deficits at relatively young ages.

In an Australian cross-sectional study by Rogoz and Burke (5) nearly half the sample indicated evidence of cognitive impairment. Further, in Moquillaza-Risco et al. (34), only 33.6% of the sample were assessed as having normal cognitive function. The likelihood of functional dependence increased with age for all degrees of cognitive impairment, except for severe cognitive impairment,

TABLE 1 Study characteristics.

References	Year	Location	Study design	Target population(s)	Sample size	Age (X)	Female (%)
Brown et al. (26)	2013	Boston, USA	Cross-sectional study	≥50 years PEH from emergency, transitional, and day shelters	250	56	19.20%
Brown et al. (27)	2012	Boston, USA	Cross-sectional study	PEH adults aged 50–69 recruited from emergency, transitional and day shelters	247	56	19.80%
Brown et al. (28)	2017	Oakland, USA	Cross-sectional study	≥50 years PEH from shelters open to older adults, all free and low-cost meal programs, recycling centers, and areas where adults slept unsheltered	350	58*	22.90%
Gicas et al. (29)	2020	Vancouver, Canada	Prospective cohort study	≥18 years PEH or precariously housed	375	44*	22.00%
Gicas et al. (30)	2021	Toronto, Canada	Prospective cohort study	≥18 years PEH, meeting criteria for a mental disorder (with or without a substance use disorder)	349	40	31.50%
Jutkowitz et al. (31)	2019	USA	Cross-sectional study	Veterans in a nursing home with a record of homelessness in the year prior to their nursing home admission	3,355	63	4.60%
Kiernan et al. (32)	2021	Dublin, Ireland	Cross-sectional study	PEH in an acute hospital inpatient facility ≥ 18	65	47	32.30%
Mahmood et al. (33)	2021	San Diego, USA	Cross-sectional study	PEH between 18 and 89	100	49	19.00%
Moquilazza-Risco et al. (34)	2015	Lima, Peru	Cross-sectional study	PEH ≥ 60 years	302	72	17.00%
Patanwala et al. (35)	2018	Oakland, USA	Prospective Cohort Study	PEH ≥ 50 at a community-based agency serving low-income older adults, overnight homeless shelters, low-cost, a recycling center, and places where unsheltered homeless adults stayed	350	59*	19.80%
Rogans-Watson et al. (36)	2020	London, UK	Cross-sectional study	Hostel for single PEH ≥30 years with complex needs	33	56	9.00%
Rogoz et al. (5)	2016	Sydney, Australia	Cross-sectional study	PEH ≥45 recruited from shelters (32.8%); hospital (12.9%); hostel (53.2%); and housing agencies (1.1%)	171	55	16.00%
Salem et al. (25)	2013	Los Angeles, USA	Cross-sectional study	PEH ≥40 without acute psychotic hallucinations and psychosis	150	52.4	50.00%
Salem et al. (23)	2019	Los Angeles and Pomona, USA	Cross-sectional study	Homeless ex-offending women; 18–65 with past drug use from community-based sites	130	39	100.00%

*Median age.

10.3389/fpubh.2023.1086215

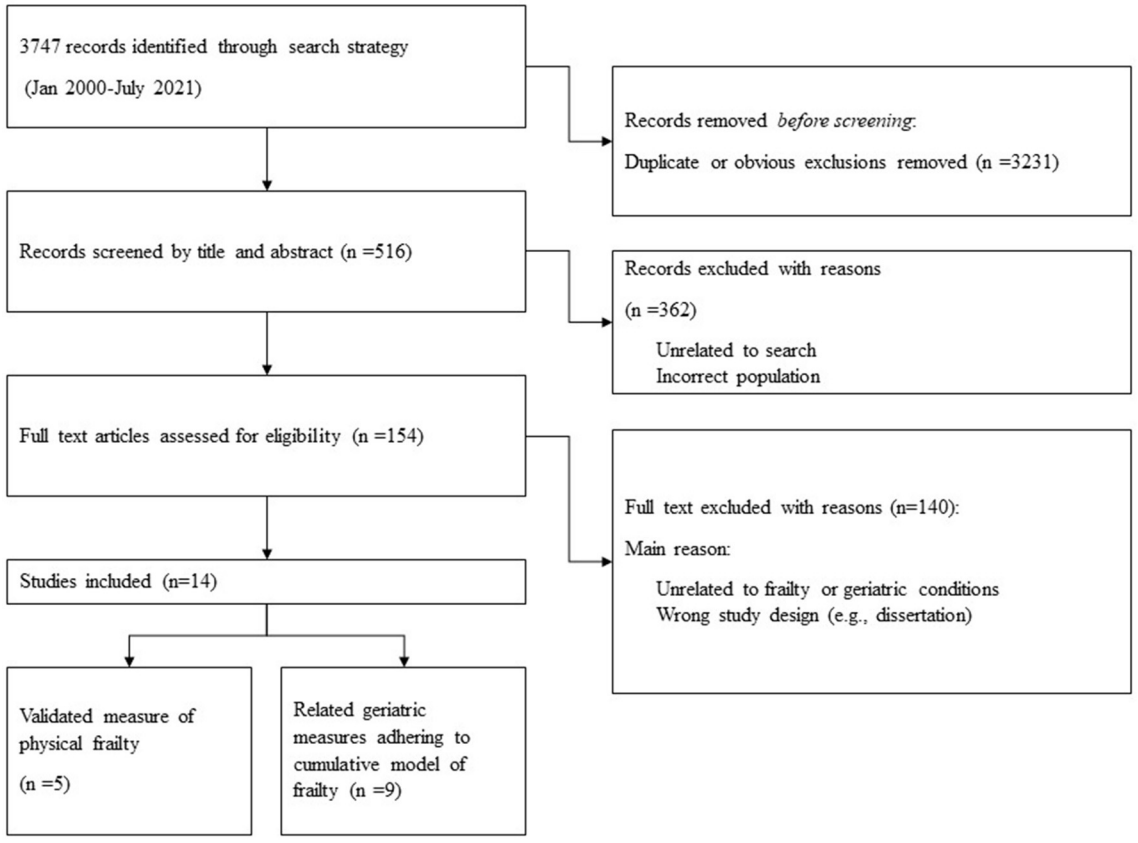


FIGURE 5
PRISMA diagram.

where the likelihood of dependence was close to 100% (i.e., fully dependent) at all ages.

In addition, the prevalence of cognitive impairment was fourfold higher among older PEH than among the SABE sample (34). These findings were reinforced in Gicas et al. (29), a nine-year community based longitudinal study of homeless and precariously housed people with a median age of 44 (age range 23–68). The study investigated the relationship between cognitive health and mortality. Across the study period, subsequent decline in verbal memory was most notable for individuals with a history of traumatic brain injury or alcohol dependence at baseline. Significant decline in inhibitory control was observed in the study, with greater decline for those who died during follow-up and for those who spent more years living in an impoverished environment. In the final model adjusted for comorbidities, inhibitory control remained a significant predictor of mortality.

In Mahmood et al. (33), there were significantly lower cognitive function scores (i.e., higher impairment rates) than expected in the general population ($p = 0.001$). MoCA scores were significantly associated with UPSA-B scores ($p < 0.001$), highlighting the strong connection between cognitive and functional performance, and reinforcing the interrelationship between the two (33).

The potential relationship between other psychosocial factors and frailty

The impact of a range of different psychosocial factors in PEH, and how they contribute to frailty, functional dependence and other geriatric conditions was reported in eight studies (23, 25, 26, 28–31, 35).

High levels of drug and alcohol dependence among PEH was found in numerous studies. In Brown et al. (26), drug use was associated with a 2.3 times higher total number of geriatric syndromes. In Brown et al. (28), nearly three-quarters (71.3%) of partipants had a history of mental health problems and more than half had a lifetime alcohol and/or drug use problem. In Gicas et al. (29), alcohol dependence was associated with greater impairment in learning, memory and motor functions. It was considered an important factor in the accelerated cognitive aging of this cohort (29). Similar patterns were observed in a cross-sectional study of $n = 3{,}355$ American veterans who were homeless in the year prior to their community nursing home admission (31). At the time of nursing home admission, participants were more likely to have had a diagnosis for a substance use disorder [Adjusted Relative Risk (ARR) = 2.18; 95% CI = (2.05–2.31)], dementia (ARR = 1.14; 95% CI = 1.04–1.25) and a mental health condition [ARR = 1.49; 95% CI = (1.45–1.54)] compared to those who were stably housed (31).

TABLE 2 The prevalence of frailty in PEH.

References	Sample size	Age (X)	Frailty (%)	Frailty tool	Other key findings
Rogan's-Watson et al. (36)	33	56	55% (i.e., 2.6/5)	Fried's phenotype	Frailty was also measured in the study using the Edmonton frail scale (55%) and Clinical Frailty Scale (48%)
Kiernan et al. (32)	65	47	23.3%	Clinical Frailty Scale (CFS)	Only one participant obtained a score of one (very fit) and only 31.7% were classified as being robust or "non-frail." The distribution of frailty scores was higher in females than males ($p = 0.023$) and there was no difference in frailty scores between age groups ($p > 0.05$)
Brown et al. (26)	250	56	16%	Fried's phenotype	Over 70% of participants reported having two or more geriatric conditions. Only 8.4% of the sample reported having no geriatric conditions and more than half reported they had fallen in the past year (53.4%). Nearly half had sensory impairment defined as hearing and/or vision impairment, and nearly half also reported urinary incontinence
Brown et al. (27)	247	56	N/A	Cumulation of geriatric syndromes	After multivariate adjustment, syndromes including functional and mobility impairment, depression, visual impairment and urinary incontinence, all indicative of cumulative frailty, were statistically more likely in PEH compared to matched samples (further discussed in next section)
Brown et al. (28)	350	58*	N/A	ADLs and IADLs	Over a third of all participants (38.9%) reported difficulty performing one or more ADLs and nearly one-fifth (17.1%) had difficulty performing three or more ADLs. Nearly half (49.4%) of the sample reported difficulty performing one or more instrumental activities of daily living (IADLs)
Moquilazza-Risco et al. (34)	302	72	N/A	KATZs	Nearly half the sample (48.9%) were at least partially dependent. Functional dependence was measured using the KATZ's index of independence, similar to a traditional ADL measure. In addition, during a logistical regression analysis, it was found that women were more likely than men to become functionally dependent
Salem et al. (23)	130	39	Physical psychological social	Tilburg Frailty Indicator (TFI)	37% had one frailty domain with a score above the median. Twenty-one percent had two frailty domains with domain scores above the median and 7% had all three domains with scores above the median. The number of domains with scores above the respective median was not significantly related to age
Salem et al. (25)	150	52.4	54%	Frailty Index (FI)	When comparing FI frailty scores to the holistic frailty framework among vulnerable populations (FFVP) measures (discussed further in Psychosocial section), there were significant moderate negative correlations between frailty and resilience, social support and nutrition

*Median age.

Further research has highlighted the relationship between a range of novel environmental and psychosocial factors and physical functioning in PEH. An important psychosocial finding in Gicas et al. (29) was that longer time living within an impoverished neighborhood was associated with greater decline in inhibitory control. The authors concluded that this finding may reflect *"the cumulative effects of socioeconomic disadvantage, unsafe living conditions and social stressors. Lack of community resources for cognitive enrichment in day-to-day life may also contribute" [(29), p. 6]*.

A study by Patanwala et al. (35) of PEH aged 50 and over (median age of 59 years) found over half (57.6%) of the participants had psychological symptoms and 26.5% had 'high regret'. In a multivariate regression model, it was established that being a woman [Adjusted OR = 2.54, 95% CI = (1.28–5.03)], having a history of childhood abuse [AOR = 1.88, CI= (1.00–3.50)], cannabis use [AOR = 2.59, CI = (1.38–4.89)], multimorbidity [AOR = 2.50, CI = (1.36–4.58)], anxiety [AOR = 4.30, CI = (2.24–8.26)], hallucinations [AOR = 3.77, CI = (1.36–10.43)], and loneliness [AOR = 2.32, CI = (1.26–4.28)] were all associated with moderate to high physical symptom burden. The authors also found an overall prevalence of loneliness (39.6%) higher than the estimated prevalence among older adults in the general population [estimated community prevalence reported from Ong et al. (42)]. The authors concluded that the high prevalence of loneliness in aging PEH could be an important contributor to functional decline in this group.

In a Canadian sample of 349 homeless adults with serious mental illness, and a relatively young average age of 39.8, the relationship between community functioning, cognitive health, Quality of Life (QoL), resilience and experiencing homelessness were investigated (30). After adjusting for select risk and protective factors, composite indices of verbal learning and memory, processing speed and cognitive flexibility, were all positively associated with community functioning, but not with QoL, over a 6-year period study period. Greater individual resilience levels were independently associated with better QoL. Cognition was the predominant predictor of community functioning, whereas select

TABLE 3 Summarizing the relationship between cognitive impairment and functional dependence in PEH.

References	Cognitive tool	Cognitive impairment	Relevance to frailty and adjacent age-related decline
Rogoz and Burke (5)	Mini-mental state examination (MMSE)	49.1% scored 26 or less, indicating evidence of cognitive impairment	Of PEH who scored as cognitively impaired, nearly 80% self-reported having mental health problems; and likewise mental health problems greatly increased the odds of also having cognitive impairment [OR = 7.16, 95% CI = (2.31, 22.19)]
Moquillaza-Risco et al. (34)	Pfeiffer's test	Mild cognitive impairment = 30.7%. Moderate cognitive impairment = 23.2%. Severe cognitive impairment = 12.5%	In a logistical regression model the probability of partial functional dependence, measured by the KATZ index, increased greatly with the severity of cognitive impairment, highlighting the interrelationship between functional impairment and degree of cognitive impairment
Gicas et al. (29)	Hopkins verbal learning test-revised Stroop test for inhibitory control	At baseline evaluation: 68.1% scored at or below the cut-off for verbal learning 62.9% scored at or below the cut-off for verbal memory. 10% scored as clinically impaired for inhibitory control	Survival analyses established that better inhibitory control was associated with a 6.6% decreased risk of mortality in the sample, and this protective effect of cognition became larger by 0.3% for every additional year of life, controlling for co-occurring chronic medical illnesses
Mahmood et al. (33)	Montreal cognitive assessment (MoCA)	65% impairment rate with a standard cut-off score of 26 and 30% with a cut-off of 23	Nearly half of the participants (47%) met criteria for functional impairment and 17% of the sample were not expected to be capable of living independently. Participants' functional abilities were assessed using the University of California, San Diego, Performance- Based Skills Assessment–Brief (UPSA-B) which measures functional capacity by asking participants to role play everyday tasks

risk and protective factors (childhood adversity and resilience, respectively) were specifically associated with QoL.

The frailty framework among vulnerable populations (FFVP) is a latent construct proposed by Salem et al. (25) which incorporates social and psychological elements into a holistic framework of frailty designed specifically for assessing and understanding marginalized populations.

The FFVP was tested or applied in two studies in this review (23, 25). In Salem et al. (25) a group of older PEH (average age 52.4) were assessed across a number of situational, health-related, behavioral, resource, biological, and environmental factors; designed to capture physical, psycholgical and social frailty. These assessments were subseuqently compared to a traditional frailty measure [Rockwood's Frailty Index (FI)], where the prevalence of frailty was 54%. When comparing FI frailty scores to the holsitic FFVP measures through a Pearson (r) bivariate correlation, significant moderate negative correlations between frailty and resilience ($r = -0.395$, $p < 0.01$), social support ($r = -0.377$, $p < 0.01$), and nutrition ($r = -0.652$, $p < 0.01$) were found. In the final model, age, gender, health care utilization, nutrition, and resilience were significantly related to frailty. The squared multiple correlation coefficients was 0.542, suggesting that 54.2% of the variance in frailty can be predicted by and age, gender, health care utilization, nutrition, and resilience (25).

In another study by Salem et al. (23), a sample of relatively young, formerly incarcerated women experiencing homelessness (average age 39 years), were assessed for physical frailty, psychological frailty and social frailty. These frailty outcomes were measured using the Tilburg Frailty Indicator (TFI) [see (18–20)]. In the sample, those who had a greater number of prior violent offenses had higher levels of physical frailty ($p = 0.001$); participants with a higher PTSD symptom score ($p = 0.012$), or a lower tangible support score ($p = 0.001$), had higher levels of physical frailty. Greater bodily pain was also associated with greater levels of psychological frailty ($p = 0.036$). Those with a higher drug dependency score had higher physical and psychological frailty ($p = 0.047$ and $p = 0.033$, respectively) and those who used a greater number of drugs had a higher likelihood of being socially frail ($p = 0.009$). Higher emotional regulation difficulty scores were also associated with higher levels of social frailty ($p < 0.001$) (23).

Discussion

The aim of this rapid review was to examine frailty in adult PEH. The findings establish collective evidence that frailty, either defined as phenotypical frailty, multidimensional frailty (*i.e., the TFI*) or the accumulation of relevant geriatric conditions, signs and symptoms (i.e., *indexed frailty/frailty scales*), presents earlier and at higher rates in PEH than community-dwelling cohorts. In some studies, the comparisons are quite stark. PEH aged in their 40s and 50s had similar frailty scores and geriatric conditions as people aged in their 70s and 80s (26, 27, 32, 36). These differences remained when PEH were compared to a cohort with very low incomes (28, 40). This high burden of early-onset geriatric difficulties provides further evidence that PEH are at risk of accelerated aging (7) and consequently premature functional decline, disability and death.

This review also synthesized novel insights regarding the antecedents of frailty in PEH, namely that psychosocial and structural determinants of health and wellbeing are associated with frailty onset and severity. For instance, loneliness (35), living in an impoverished neighborhood (29), resilience (25, 30), being female (32) and drug and alcohol use (23, 26, 31) were all associated with functional dependence and decline in PEH. However, given most

papers in this review were cross-sectional studies, it is not possible to make any general claims regarding the causal relationship between upstream determinants and frailty. This points to the urgent need for more cohort studies in this area. Regardless, these findings build upon previous work on early morbidity, mortality and accelerated aging in PEH (1) by mapping health decline to a validated construct, frailty; thereby providing a richer analysis of unequal aging and aging-related decline in PEH (8).

A notable difficulty for many aging PEH is cognitive impairment, which is associated with a range of negative outcomes, including early functional dependence, reduction in autonomy and reduced mobility. Rates of global cognitive impairment in PEH ranged from 25% to 65% across the studies in this review. Gicas et al. (29) found cognitive deficits, specifically in executive functioning, to be particularly debilitating for aging PEH. These deficits appeared for PEH in their 40s, decades earlier than healthy community-dwelling participants (29, 43). However, when interpreting these results it is important to note that high impairments scores in PEH could be related to the high incidence of mental illness such as depression or other psychiatric disorders in many of the PEH cohorts tested. For example, in a sample of PEH with cognitive impairments, 88.8% self-reported mental health problems (5). This high prevalence of mental health issues can have effects on cognitive performance scores and potentially overstate cognitive deficits. In addition, other upstream factors such as cultural or educational factors (including low literacy) are known to mediate cognitive performance scores in marginalized groups. These confounders need to be addressed in future research. Regardless, cognitive impairments in PEH appear to have an important, and interconnected, relationship with functional decline and dependence (33, 34), and these issues can emerge concerningly early in life.

This review found that the combination of poor mental and cognitive health difficulty greatly increases the risk of comorbid functional decline (5, 33, 34). These findings are reinforced by a large cross-sectional study (n = 1,500) of PEH with an average age of 41.1 (44). Stergiopoulos et al. (44) established that PEH with mental illness experience significant neurocognitive impairment; with nearly three quarters of PEH with mental illness showing evidence of neurocognitive impairment (44). Collectively, these findings indicate that cognitive impairment (both with or without mental health commodity) is an important contributor to functional decline in aging PEH, and subsequently the accelerated aging and premature frailty of the group. Efforts to assess cognitive health in PEH should be prioritized and seen as a vital underpinning to broader health and social care efforts to support aging PEH. Given the premature aging of the group, cognitive assessment efforts should be considered for PEH in their 40s and 50s. Further, given the relationship between functional dependence, cognitive impairment and other mental health issues, cognitive assessment should be carefully considered in the broader context of a person's physical and mental health and the high risk of comorbidities (including confounding disorders) across these domains.

Another recurrent theme in this review is the impact that drug and alcohol use and dependence can have on the health of PEH (26, 29, 30, 36). Drug and alcohol use can cause decline in cognitive functioning in PEH (29), particularly executive functioning. Chronic drug and alcohol use can also increase the risk of developing frailty by negatively impacting nutrition (45, 46) and sleep quality (47, 48). Further, drug and alcohol use by somebody once they are frail also increases the risk of serious falls (49), incontinence (27) and hospitalization (50). Prioritizing drug and alcohol assessment, treatment and management as a preventative measure to reduce the risks of accelerated aging and frailty in later life for PEH is of key importance.

Patanwala et al. (35) established that in an aging sample of PEH, loneliness was an independent predictor of both functional decline and mortality; and loneliness rates were higher in PEH than older community dwelling adults. Loneliness is being increasingly recognized as an important determinant of health and wellbeing. It is a key predictor of depression, substance disorders and cognitive decline in older people (51) and feelings of loneliness are of particular concern for those who are at increased risk of social disconnectedness and deprivation of genuine connection with family, friends and communities (52). Such risks are likely heightened for many aging PEH who live alone or in unpredictable environments. For instance, only 9.6% of the PEH sample in Moquillaza-Risco et al. (34) reported having a close relative. Loneliness appears to be an important consideration in the accelerated aging of PEH and warrants further attention (35). Importantly, with the exception of more holistic measures of frailty such as the TFI, the majority of traditional frailty measures do not adequately capture measures of social frailty like social exclusion, loneliness or sufficient social supports.

Although frailty measures tend to focus mainly on physical health deficits, this review has highlighted the importance of psychological, cognitive, psychosocial and environmental factors in relation to both the determinants of frailty, and the severity of frailty itself. For instance, using the frailty framework among vulnerable populations (FFVP) it was established that educational attainment, nutrition, greater number of years homeless, being divorced, poorer emotional regulation and those who identified as either being Black or female all were significantly associated with social, psychological and/or physical measures of frailty (23, 25). These findings are important as little research has been conducted into the etiologies of accelerated aging or premature frailty in PEH, and even less on intersectional aspects for this group. These findings also reinforce the upstream and structural social factors that often contribute to the cumulative health and social difficulties experienced by PEH. In this regard, frailty frameworks such as the FFVP and frailty measures such as the TFI- which actively include measures of psychological, cognitive and social frailty—appear relevant for PEH. However, there remains no gold standard assessment of frailty, and many measures (including the TFI) remain mostly underutilized and unvalidated for PEH and other marginalized groups at risk of accelerated aging. For instance, as summarized in Table 2, in the five studies that directly measured frailty captured in this review four different frailty tools were used, with only two of these directly collecting data on psychological or social issues. It appears important to further explore the psychosocial and environmental contributions of

frailty within marginalized groups in the context of the broader literature on physical frailty to ensure research consistency and clinical usefulness.

Limitations

This review has some limitations. None of the papers in this review examined the interrelationship between pathophysiological dysfunction at a biological level and the environmental or lifestyle determinants that may cause cellular deterioration. However, by measuring frailty and other related geriatric conditions and their associations with social, psychological and cognitive difficulties, a number of studies examined the contribution(s) of certain factors or determinants which appear to modify (accelerate) the aging process, i.e., functional decline, early mortality, etc.

As seems to be the case with much of the literature on frailty, which specific factors are most important in a single study depends on the way frailty is defined, measured and applied; and how these factors relate with the biological processes of aging, and in what context, is not always clear. This is certainly a barrier to the application of frailty research, but not necessarily a fatal one. As shown through this rapid review, you can analyze differential applications of the construct concurrently and identify patterns and overlap. An example of this is the lenient search strategy applied in this review to capture cognitive and psychosocial difficulties which have theoretical and practical links to frailty yet would not usually be included in traditional frailty research. Regardless, the fundamental differences between the two dominant approaches to frailty, as well as contemporary multidimensional measures and framework, have caused considerable practical and theoretical barriers to applying the construct over the last two decades, including disparate measures of predictive validity, different minimum data requirements and variable administration methods (53). Besides a lenient and dynamic search strategy and definition of frailty, no attempt to reconcile these differences was made in this review. Moving forward, a standardization of concepts should be attempted. This is increasingly important given the emergence of measures like the TFI and conceptual frameworks like the FFVP; which although add important contributions to the psychosocial and environmental elements of frailty, also increase the confusion surrounding the original construct.

Finally, the distinction between the concept of frailty and other related constructs, namely multimorbidity, is often difficult to define. The major distinction in the current literature is that multimorbidity refers exclusively to the coexistence of clinically manifest diseases, whereas frailty refers to an increased vulnerability to stressors which could include symptoms, signs, diseases, disabilities or laboratory, radiographic or electrocardiographic abnormalities (54). Although there is some attempt by the authors of this paper to distinguish between frailty and multimorbidity through a clear and comprehensive search criterion, the overlap between these concepts is substantial and requires further attention.

Implications

This rapid review has important implications for service provision. Service providers and clinicians should be aware that PEH aged in their 40s and 50s, or even earlier [e.g., (32)] can be physically frail and experience geriatric conditions as well as cognitive and functional impairments. For PEH, earlier onset geriatric conditions and concurrent chronic diseases, mental health issues and psychosocial problems are often accompanied by poor access to appropriate and effective treatment (5). This contributes to recurrent emergency department presentations (55) and high hospital readmission rates for PEH (56); with nearly four times the odds of being readmitted within 30-days as compared to low-income matched control participants (57). These difficulties further increase the complexity and cost of health treatment (50) and reduce the likelihood of health improvement, which underscores the importance of early intervention for PEH.

Importantly, the findings and recommendations presented in this rapid review should be seen as complementary to, and not a substitute for, long term housing strategies to reduce homelessness. Interventions to ensure stable and safe housing are essential supports for aging PEH to access community and/or aged care services, as well as reduce the cumulative health and social disadvantages that people who are currently homeless experience. As such, a suitable approach would be to strive for housing for PEH in parallel with more holistic, and equitable, service offerings to support PEH health and wellbeing.

To assist with timely detection of health issues, which may facilitate early intervention or even prevention of frailty and geriatric conditions before they emerge or progress (7), a presentation for one condition should trigger comprehensive health screening, including social determinants of health. Given the rates of frailty at a relatively young age for PEH, screening should be initiated early and often in this population. As highlighted by this review, a focus on co-occurring psychosocial and cognitive factors would be beneficial. Important psychosocial contributors to frailty and/or functional decline in PEH include cognitive decline (5, 29, 33, 34), drug and alcohol use (26, 29, 36, 58) and social isolation and loneliness (35). These factors are particularly important to detect for aging PEH as they can potentially lead to early modification and/or rehabilitation which may support proactive intervention in frailty pathways. It is recommended that research and practice exploring frailty in PEH incorporate minimum data on these three factors and explore interventions in these spaces. Measures such as the TFI are promising in this regard, however, require further research to establish psychometric validity for PEH at risk of accelerated aging. Regardless of what frailty tool is used, it should be considered as part of a broader suite of supports to reduce and manage frailty which often include exercise and nutrition interventions, sensible housing strategies and traditional geriatric services.

Finally, this review reported the structural, upstream and often intersectional determinants which can contribute to frailty, such as living in an impoverished neighborhood, educational attainment, being Black or female. It is important to appreciate that many of the contributors to accelerated frailty in PEH, including functional and cognitive decline, drug and alcohol use and loneliness are often

steeped in longer-term social difficulties and likely require more holistic and/or multidimensional intervention strategies (such as housing). Acknowledging these factors, and better understanding the dynamic and multidimensional burden facing PEH, which can manifest as accelerated aging and frailty conditions, is an important first step to better supporting the health and wellbeing of PEH.

Author contributions

SP, PC, AW, and KR contributed to the original conception and design of the study. SP, RM, and AW screened studies. RM and SP conducted the analysis, with guidance from AW, PC, and KR. RM wrote the first draft of the manuscript and final manuscript. YH wrote sections of the manuscript and edited the first draft. 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.

Publisher's note

References

1. Suh K, Beck J, Katzman W, Allen DD. Homelessness and rates of physical dysfunctions characteristic of premature geriatric syndromes: systematic review and meta-analysis. Physiother *Theory Pract.* (2020) 2020:1–10. doi: 10.1080/09593985.2020.1809045

2. Aldridge RW, Story A, Hwang SW, Nordentoft M, Luchenski SA, Hartwell G, et al. Morbidity and mortality in homeless individuals, prisoners, sex workers, and individuals with substance use disorders in high-income countries: a systematic review and meta-analysis. *Lancet.* (2018) 391:241–50. doi: 10.1016/S0140-6736(17)31869-X

3. Fazel S, Geddes JR, Kushel M. The health of homeless people in high-income countries: descriptive epidemiology, health consequences, and clinical and policy recommendations. *Lancet.* (2014) 384:1529–40. doi: 10.1016/S0140-6736(14)61132-6

4. Stenius-Ayoade A, Haaramo P, Kautiainen H, Gissler M, Wahlbeck K, Eriksson JG. Mortality and causes of death among homeless in Finland: a 10-year follow-up study. *J Epidemiol Community Health.* (2017). doi: 10.1136/jech-2017-209166

5. Rogoz A, Burke D. Older people experiencing homelessness show marked impairment on tests of frontal lobe function. *Int J Geriatr Psychiatry.* (2016) 31:240–6. doi: 10.1002/gps.4316

6. Quach LT, Primack J, Bozzay M, Madrigal C, Erqou S, Rudolph JL, et al. The Intersection of Physical and Social Frailty in Older Adults. *R I Med J.* (2013) 104:16–9.

7. Fried LP, Ferrucci L. Etiological role of aging in chronic diseases: from epidemiological evidence to the new geroscience. In: Sierra F, Kohanski R, editors. *Advances in Geroscience.* Cham: Springer International Publishing (2016). p. 37–51.

8. Spiers GF, Kunonga TP, Hall A, Beyer F, Boulton E, Parker S, et al. Measuring frailty in younger populations: a rapid review of evidence. *BMJ Open.* (2021) 11:e047051. doi: 10.1136/bmjopen-2020-047051

9. Ritt M, Ritt JI, Sieber CC, Gassmann KG. Comparing the predictive accuracy of frailty, comorbidity, and disability for mortality: a 1-year follow-up in patients hospitalized in geriatric wards. *Clin Interv Aging.* (2017) 12:293–304. doi: 10.2147/CIA.S124342

10. Bagshaw SM, Stelfox HT, McDermid RC, Rolfson DB, Tsuyuki RT, Baig N, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. *CMAJ.* (2014) 186:E95–102. doi: 10.1503/cmaj.130639

11. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr.* (2008) 8:24. doi: 10.1186/1471-2318-8-24

12. Jones DM, Song X, Rockwood K. Operationalizing a frailty index from a standardized comprehensive geriatric assessment. *J Am Geriatr Soc.* (2004) 52:1929–33. doi: 10.1111/j.1532-5415.2004.52521.x

13. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* (2001) 56:M146–56. doi: 10.1093/gerona/56.3.M146

14. Rockwood K, Theou O. Using the clinical frailty scale in allocating scarce health care resources. *Can Geriatr J.* (2020) 23:210–5. doi: 10.5770/cgj.23.463

15. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* (2005) 173:489–95. doi: 10.1503/cmaj.050051

16. Rockwood K. Conceptual models of frailty: accumulation of deficits. *Can J Cardiol.* (2016) 32:1046–50. doi: 10.1016/j.cjca.2016.03.020

17. Espinoza SE, Quiben M, Hazuda HP. Distinguishing comorbidity, disability, and frailty. *Curr Geriatr Rep.* (2018) 7:201–9. doi: 10.1007/s13670-018-0254-0

18. Gobbens RJ, van Assen MA, Luijkx KG, Wijnen-Sponselee MT, Schols JM. The Tilburg Frailty Indicator: psychometric properties. *J Am Med Dir Assoc.* (2010) 11:344–55. doi: 10.1016/j.jamda.2009.11.003

19. Gobbens RJ, van Assen MA, Luijkx KG, Schols JM. Testing an integral conceptual model of frailty. *J Adv Nurs.* (2012) 68:2047–60. doi: 10.1111/j.1365-2648.2011.05896.x

20. Gobbens RJ, Boersma P, Uchmanowicz I, Santiago LM. The Tilburg Frailty Indicator (TFI): new evidence for its validity. *Clin Interv Aging.* (2020) 15:265–74. doi: 10.2147/CIA.S243233

21. Garritty C, Gartlehner G, Nussbaumer-Streit B, King VJ, Hamel C, Kamel C, et al. Cochrane rapid reviews methods group offers evidence-informed guidance to conduct rapid reviews. *J Clin Epidemiol.* (2021) 130:13–22. doi: 10.1016/j.jclinepi.2020.10.007

22. Tricco AC, Langlois EV, Straus SE. *Rapid Reviews to Strengthen Health Policy and Systems: A Practical Guide.* Geneva: World Health Organization (2017).

23. Salem BE, Brecht ML, Ekstrand ML, Faucette M, Nyamathi AM. Correlates of physical, psychological, and social frailty among formerly incarcerated, homeless women. *Health Care Women Int.* (2019) 40:788–812. doi: 10.1080/07399332.2019.1566333

24. Salem BE, Nyamathi A, Phillips LR, Mentes JC, Sarkisian C, Brecht ML. Development of a frailty framework among vulnerable populations. *ANS Adv Nurs Sci.* (2014) 37:70–81. doi: 10.1097/ANS.0000000000000013

25. Salem BE, Nyamathi AM, Brecht ML, Phillips LR, Mentes JC, Sarkisian C, et al. Correlates of frailty among homeless adults. *West J Nurs Res.* (2013) 35:1128–52. doi: 10.1177/0193945913487608

26. Brown RT, Kiely DK, Bharel M, Mitchell SL. Factors associated with geriatric syndromes in older homeless adults. *J Health Care Poor Underserved.* (2013) 24:456–68. doi: 10.1353/hpu.2013.0077

27. Brown RT, Kiely DK, Bharel M, Mitchell SL. Geriatric syndromes in older homeless adults. *J Gen Intern Med.* (2012) 27:16–22. doi: 10.1007/s11606-011-1848-9

28. Brown RT, Hemati K, Riley ED, Lee CT, Ponath C, Tieu L, et al. Geriatric conditions in a population-based sample of older homeless adults. *Gerontologist.* (2017) 57:757–66. doi: 10.1093/geront/gnw011

29. Gicas KM, Jones AA, Thornton AE, Petersson A, Livingston E, Waclawik K, et al. Cognitive decline and mortality in a community-based sample of homeless and precariously housed adults: 9-year prospective study. *BJPsych Open.* (2020) 6:e21. doi: 10.1192/bjo.2020.3

30. Gicas KM, Mejia-Lancheros C, Nisenbaum R, Wang R, Hwang SW, Stergiopoulos V. Cognitive determinants of community functioning and quality of life

in homeless adults with mental illness: 6-year follow-up from the At Home/Chez Soi Study Toronto site. *Psychol Med.* (2021) 2021:1–9. doi: 10.1017/S0033291721001550

31. Jutkowitz E, Halladay C, McGeary J, O'Toole T, Rudolph JL. Homeless veterans in nursing homes: care for complex medical, substance use, and social needs. *J Am Geriatr Soc.* (2019) 67:1707–12. doi: 10.1111/jgs.15993

32. Kiernan S, Ni Cheallaigh C, Murphy N, Dowds J, Broderick J. Markedly poor physical functioning status of people experiencing homelessness admitted to an acute hospital setting. *Sci Rep.* (2021) 11:9911. doi: 10.1038/s41598-021-88590-0

33. Mahmood Z, Vella L, Maye JE, Keller AV, Van Patten R, Clark JMR, et al. Rates of cognitive and functional impairments among sheltered adults experiencing homelessness. *Psychiatr Serv.* (2021) 72:333–7. doi: 10.1176/appi.ps.202000065

34. Moquillaza-Risco M, León E, Dongo M, Munayco CV. Socio-demographics characteristics and health conditions of older homeless persons of Lima, Peru. *Rev Peru Med Exp Salud Publica.* (2015) 32:693–700. doi: 10.17843/rpmesp.2015.324.1760

35. Patanwala M, Tieu L, Ponath C, Guzman D, Ritchie CS, Kushel M. Physical, psychological, social, and existential symptoms in older homeless-experienced adults: an observational study of the hope home cohort. *J Gen Intern Med.* (2018) 33:635–43. doi: 10.1007/s11606-017-4229-1

36. Rogans-Watson R, Shulman C, Lewer D, Armstrong M, Hudson B. Premature frailty, geriatric conditions and multimorbidity among people experiencing homelessness: a cross-sectional observational study in a London hostel. *Housing Care Support.* (2020) 23:77–91. doi: 10.1108/HCS-05-2020-0007

37. Clemens S, Phelps A, Oldfield Z, Blake M, Oskala A, Marmot M, et al. *English Longitudinal Study of Ageing: Waves 0-8, 1998-2017, 30th Edn.* UK Data Service. SN: 5050. (2019). doi: 10.5255/UKDA-SN-5050-17

38. Kelsey JL, Berry SD, Procter-Gray E, Quach L, Nguyen US Li W, et al. Indoor and outdoor falls in older adults are different: the maintenance of balance, independent living, intellect, and Zest in the Elderly of Boston Study. *J Am Geriatr Soc.* (2010) 58:2135–41. doi: 10.1111/j.1532-5415.2010.03062.x

39. Leveille SG, Kiel DP, Jones RN, Roman A, Hannan MT, Sorond FA, et al. The MOBILIZE Boston Study: design and methods of a prospective cohort study of novel risk factors for falls in an older population. *BMC Geriatr.* (2008) 8:16. doi: 10.1186/1471-2318-8-16

40. Counsell SR, Callahan CM, Clark DO, Tu W, Buttar AB, Stump TE, et al. Geriatric care management for low-income seniors: a randomized controlled trial. *JAMA.* (2007) 298:2623–33. doi: 10.1001/jama.298.22.2623

41. Brevis C, Lebrão M, Diaz E, Ham-Chande R, Hennis A, Palloni A, et al. Encuesta Salud, Bienestar y Envejecimiento (SABE): metodología de la encuesta y perfil de la población estudiada. *Rev Panam Salud Pub.* (2005) 17:307–22. doi: 10.1590/S1020-49892005000500003

42. Ong AD, Uchino BN, Wethington E. Loneliness and health in older adults: a mini-review and synthesis. *Gerontology.* (2016) 62:443–9. doi: 10.1159/000441651

43. Salthouse TA. Trajectories of normal cognitive aging. *Psychol Aging.* (2019) 34:17–24. doi: 10.1037/pag0000288

44. Stergiopoulos V, Cusi A, Bekele T, Skosireva A, Latimer E, Schutz C, et al. Neurocognitive impairment in a large sample of homeless adults with mental illness. *Acta Psychiatr Scand.* (2015) 131:256–68. doi: 10.1111/acps.12391

45. Kamran U, Towey J, Khanna A, Chauhan A, Rajoriya N, Holt A. Nutrition in alcohol-related liver disease: physiopathology and management. *World J Gastroenterol.* (2020) 26:2916–30. doi: 10.3748/wjg.v26.i22.2916

46. Ni Lochlainn M, Cox NJ, Wilson T, Hayhoe RPG, Ramsay SE, Granic A, et al. Nutrition and frailty: opportunities for prevention and treatment. *Nutrients.* (2021) 13:2349. doi: 10.3390/nu13072349

47. Pourmotabbed A, Boozari B, Babaei A, Asbaghi O, Campbell MS, Mohammadi H, et al. Sleep and frailty risk: a systematic review and meta-analysis. *Sleep Breath.* (2020) 24:1187–97. doi: 10.1007/s11325-020-02061-w

48. Ebrahim IO, Shapiro CM, Williams AJ, Fenwick PB. Alcohol and sleep I: effects on normal sleep. *Alcohol Clin Exp Res.* (2013) 37:539–49. doi: 10.1111/acer.12006

49. Abbs E, Brown R, Guzman D, Kaplan L, Kushel M. Risk factors for falls in older adults experiencing homelessness: results from the HOPE HOME cohort study. *J Gen Intern Med.* (2020) 35:1813–20. doi: 10.1007/s11606-020-05637-0

50. Fisher DG, Reynolds GL, Khoiny N, Huckabay L, Rannalli D. Application of the frailty framework among vulnerable populations to hospitalization outcomes of individuals experiencing homelessness in Long Beach, California. *J Social Distress Homeless.* (2021) 2021:1–9. doi: 10.1080/10530789.2021.1908487

51. WHO. *Social isolation and Loneliness Among Older People: Advocacy Brief.* Geneva: World Health Organization (2021).

52. Joiner Jr TE, Van Orden KA, Witte TK, Rudd MD. *The Interpersonal Theory of Suicide: Guidance for Working With Suicidal Clients.* Washington, DC: American Psychological Association (2009). p. x, 246-x. doi: 10.1037/11869-000

53. Thillainadesan J, Scott IA, Le Couteur DG. Frailty, a multisystem ageing syndrome. *Age Ageing.* (2020) 49:758–63. doi: 10.1093/ageing/afaa112

54. Villacampa-Fernandez P, Navarro-Pardo E, Tarin JJ, Cano A. Frailty and multimorbidity: two related yet different concepts. *Maturitas.* (2017) 95:31–5. doi: 10.1016/j.maturitas.2016.10.008

55. Souza AM, Tsai JH, Pike KC, Martin F, McCurry SM. Cognition, health, and social support of formerly homeless older adults in permanent supportive housing. *Innov Aging.* (2020) 4:igz049. doi: 10.1093/geroni/igz049

56. Doran KM, Ragins KT, Iacomacci AL, Cunningham A, Jubanyik KJ, Jenq GY. The revolving hospital door: hospital readmissions among patients who are homeless. *Med Care.* (2013) 51:767–73. doi: 10.1097/MLR.0b013e31829fafbb

57. Saab D, Nisenbaum R, Dhalla I, Hwang SW. Hospital readmissions in a community-based sample of homeless adults: a matched-cohort study. *J Gen Intern Med.* (2016) 31:1011–8. doi: 10.1007/s11606-016-3680-8

58. Zhou LW, Panenka WJ, Al-Momen G, Gicas KM, Thornton AE, Jones AA, et al. Cerebral small vessel disease, risk factors, and cognition in tenants of precarious housing. *Stroke.* (2020) 51:3271–8. doi: 10.1161/STROKEAHA.120.030446

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 05 April 2023
DOI 10.3389/fpubh.2023.1055001

OPEN ACCESS

EDITED BY
Junhong Zhou,
Harvard Medical School,
United States

REVIEWED BY
Jingying Wang,
University of Florida,
United States
Yijian Yang,
The Chinese University of Hong Kong,
China

*CORRESPONDENCE
Chun-Qing Li
✉ lichuntsing@163.com

SPECIALTY SECTION
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

RECEIVED 27 September 2022
ACCEPTED 14 March 2023
PUBLISHED 05 April 2023

CITATION
Li C-Q, Kong H, Xu Z-Z, Ma J-H and Li X-Y (2023) Comparison of two frailty indices in predicting life-threatening morbidity and mortality among older patients undergoing elective high-risk abdominal surgery. *Front. Public Health* 11:1055001. doi: 10.3389/fpubh.2023.1055001

Comparison of two frailty indices in predicting life-threatening morbidity and mortality among older patients undergoing elective high-risk abdominal surgery

Chun-Qing Li[1]*, Hao Kong[1], Zhen-Zhen Xu[1], Jia-Hui Ma[1] and Xue-Ying Li[2]

[1]Department of Anaesthesiology, Peking University First Hospital, Beijing, China, [2]Department of Biostatistics, Peking University First Hospital, Beijing, China

Background: Frailty predicts an increased risk of postoperative morbidity and mortality. Comparison of the predictive performance between two deficit accumulation models of frailty, the modified frailty index (mFI) and the revised-Risk Analysis Index (RAI-rev), is poorly understood. This study compared the predictive abilities of the above two frailty indices in predicting life-threatening morbidity and mortality among older patients following elective high-risk abdominal surgery.

Methods: This retrospective cohort study extracted perioperative data of older patients (age ≥65years) undergoing elective high-risk abdominal surgery at a single institution between January 2018 and December 2020. Preoperative frailty was screened by mFI and RAI-rev scoring systems. The primary outcome was the composite of postoperative life-threatening morbidity and mortality during hospitalization. Multivariable logistic regression analyses were performed to investigate the association of the two frailty indices with the primary outcome. Receiver-operating characteristic (ROC) curve was employed to test the predictive performances of the two frailty instruments in predicting the composite primary outcome. The difference between the area under the curves (AUCs) was assessed by DeLong's test.

Results: 1,132 older patients (mean age, 73.4±6.2years; 63.9% male) were included. Of these, 107 (9.5%) developed postoperative life-threatening morbidity and mortality. In multivariable logistic regression analyses, rising continuous frailty scores (mFI: adjusted OR 1.319 per 0.09-point increase in score, 95% CI 1.151–1.511, $p<0.001$; RAI-rev: adjusted OR 1.052 per 1-point increase in score, 95% CI 1.018–1.087, $p=0.002$) as well as dichotomized frailty measures (mFI ≥0.27: adjusted OR 2.059, 95% CI 1.328–3.193, $p=0.001$; RAI-rev ≥45: adjusted OR 1.862, 95% CI 1.188–2.919, $p=0.007$) were associated with increased odds of the primary outcome separately. ROC curve analysis showed that the discrimination of mFI and RAI-rev scores for the life-threatening morbidity and mortality was poor and comparable (AUC: 0.598 [95% CI 0.569–0.627] vs. 0.613 [95% CI 0.583–0.641]; DeLong's test: $Z=0.375$, $p=0.7075$).

Conclusion: High mFI and RAI-rev scores were associated with an increased risk of life-threatening morbidity and mortality in older patients undergoing elective high-risk abdominal surgery. However, both frailty indices displayed poor discrimination for postoperative life-threatening morbidity and mortality.

KEYWORDS
frailty indices, high-risk surgery, older patient, morbidity, mortality

Introduction

With the rapid expansion of the aging population, frailty has constituted a critical public health issue for healthcare providers worldwide. Frailty is a multidimensional geriatric syndrome characterized by reduced physiologic reserve, accumulated deficits, and decreased resistance to stressors (1, 2). With older frail individuals increasingly presenting for surgical interventions, clinicians have to face the burden and challenges brought by frailty in perioperative settings (3, 4). Indeed, accumulating evidence demonstrates preoperative frailty is associated with increased risks of adverse system-centered outcomes (postoperative morbidity and mortality, prolonged hospital stay, readmissions, etc.) and patient-centered outcomes (disability, lower quality of life, etc.) across various surgical specialties (5–11). Preoperative frailty screening and interventions are strongly recommended across a wide range of surgical procedures, including elective high-risk procedures (12).

Compared with low-risk surgery, high-risk surgery exerts greater physiologic stress on older individuals and is prone to higher odds of major morbidity and mortality (13). It is imperative for clinicians and patients to adequately balance the risks and benefits of high-risk surgery during the shared decision-making process. Frailty assessment and its application in predicting postoperative outcomes have significant influences on the consideration of the tradeoff between the risks and benefits of surgery and the determination of overall goals of care for a patient, especially in the context of high-risk surgery. Furthermore, frailty screening can help guide the efficient allocation of perioperative care resources to high-risk patients as well as identify the modifiable domains as targets for tailored intervention to improve outcomes (12). A careful selection of a practical frailty screening tool can help improve the safety and quality of high-risk surgery among the vulnerable older population.

Over the past decades, dozens of frailty assessment tools have been developed (5, 6, 14–21). Generally, almost all frailty measurements are based on the subsections of the two most accepted frailty models, i.e., the frailty phenotype (20) and the frailty index (21). The frailty phenotype defines frailty as a pre-disability syndrome, which is suitable for the initial screening of non-disabled individuals at risk of adverse events (20); however, the presence of disability conditions may weaken its predictive ability for poor outcomes due to a sort of "ceiling effect" (22). The frailty index identifies frailty by evaluating "accumulated deficits" across multiple dimensions such as functional, medical, cognitive, nutritional, and social domains (21). Both the modified frailty index (mFI) and revised-Risk Analysis Index (RAI-rev) scoring systems are based on the deficit accumulation model of frailty. As a shortened scale derived from the Canadian Study of Health and Aging Frailty Index, the mFI comprises 11 components: 10 comorbidities and 1 item on functional status (5). RAI-rev is derived from the original RAI and consists of multiple domains, including aging, comorbidities, nutrition, cognitive ability, and functional and social status (6, 14). Evidence demonstrates that both frailty indices can predict adverse postoperative outcomes (5–10). Additionally, the two frailty indices can be readily obtained from routine clinical practice, either prospectively or retrospectively (5, 6). Given the association of the two frailty indices with poor postsurgical outcomes and the feasibility of their implementation, it is expected that they have the potential to efficiently utilize existing resources and improve the safety and quality of high-risk surgery in older patients. In highly-efficient perioperative settings, it is unrealistic and unnecessary to apply both frailty indices to a particular patient. Thus, it will be interesting to explore which one is more suitable to use in the context of high-risk operations. As far as we know, there is a lack of evidence on the head-to-head comparison between the above two frailty indices in predicting serious morbidity and mortality among older patients undergoing high-risk surgery.

The present study aimed to compare the performances of mFI and RAI-rev in predicting the composite outcome of life-threatening morbidity and mortality in older patients who underwent elective high-risk abdominal surgery.

Methods

This retrospective cohort study was conducted in Peking University First Hospital, a tertiary general hospital in Beijing, China. The ethical approval was provided by the Biomedical Research Ethics Committee of Peking University First Hospital (2019 [296]). The Ethics Committee agreed to waive the written informed consent from the participants due to the retrospective nature of the study and that no patient follow-up was carried out. The privacy of participants was strictly observed.

Patient selection

Older patients (≥65 years of age) who received elective high-risk abdominal surgery (including general and urologic surgical procedures) in Peking University First Hospital from January 2018 to December 2020 were screened for study inclusion. We utilized the Operative Stress Score (OSS) system to select patients who underwent high-risk surgery. OSS system rates common operations according to physiologic stress, i.e., OSS1, very low stress; OSS 2, low stress; OSS 3, moderate stress; OSS 4, high stress; and OSS 5, very high stress (23). We defined high-risk surgery as those with high or very high stress, i.e., OSS 4 and 5 operations (Supplementary Table S1). Patients with missing or incomplete important data were excluded. All data were extracted from our electronic medical records.

Frailty measurement by modified frailty index

The 11 frailty deficits contained in the mFI were collected based on the National Surgical Quality Improvement Program definitions;

each component was allocated the same weight of 1 point (Supplementary Table S2). The mFI score was calculated by dividing the sum of deficits present by 11. The resulting index thus ranges from 0 to 1.0, with higher scores indicating increasing frailty (5). Additionally, we dichotomized the continuous mFI scores into two categories based on our previous work (24), i.e., non-frail (mFI score <0.27) and frail (mFI score ≥0.27).

Frailty measurement by revised-Risk Analysis Index

RAI-rev score was obtained by evaluating 11 variables, i.e., age, sex, cancer, unintentional weight loss, poor appetite, renal failure, congestive heart failure, shortness of breath, residence other than independent living, functional status, and cognitive decline. The weight of each item is detailed in Supplementary Table S3. The total score is between 0 and 81, with higher scores implying a more severe frailty condition (6). In the event that more than one operation was performed on a patient during the same hospitalization period, only the first round of the surgery and the corresponding preoperative RAI-rev score were measured. We dichotomized the continuous RAI-rev scores into non-frail (RAI-rev score <45) and frail (RAI-rev score ≥45) according to previous literature (7).

Covariates

Baseline characteristics not covered by mFI or the RAI-rev were collected, including ASA physical status classification, body mass index (BMI), smoking status, current alcoholism, other major comorbidities, and main laboratory test results. Intraoperative data were also gathered, including risk stratification of surgery categorized by OSS (i.e., OSS 4 and 5) (23), duration of surgery, type of anesthesia, estimated blood loss, and intraoperative blood transfusion.

Postoperative outcomes

The primary endpoint was the composite postoperative outcome of life-threatening morbidity and mortality during hospitalization, i.e., defined as Clavien-Dindo (CD) grade IV and V complications (25). CD grade IV complications refer to life-threatening morbidity requiring intermediate care/intensive care unit (ICU) management, consisting of single and multiple organ dysfunction. CD grade V complication means the death of a patient (25). For patients who experienced multiple morbidities, we included the most serious one in the analysis. The clinical diagnostic criteria for life-threatening morbidity are detailed in Supplementary Table S4. The secondary outcomes included time to life-threatening morbidity and mortality (i.e., the time interval from surgery to the occurrence of life-threatening morbidity and mortality), postoperative ICU admission, prolonged hospital stay (defined as greater than the 75th percentile of the length of hospital stay for each type of surgery), and adverse discharge destination (defined as discharge to destinations other than home, such as skilled care facility or other hospitals).

Statistical analysis

The baseline and perioperative variables were compared between patients with life-threatening morbidity and mortality and those without. We also compared the postoperative outcomes between frail and non-frail patients according to the dichotomized frailty measures. Continuous variables were analyzed with the independent samples t-test or Mann–Whitney U test; the Kolmogorov–Smirnov test was performed to check for normality. Categorical variables were analyzed using χ^2 tests, continuity-corrected χ^2 tests, or Fisher's exact tests. Time-to-event variables were analyzed using the Kaplan–Meier estimator, with differences between groups assessed by the log-rank test.

Due to the non-normal distribution of the data, we used Spearman's correlation analysis to test the correlation of the two continuous frailty measures. The agreement of dichotomized measures was evaluated using the percentage of agreement and Cohen's Kappa coefficient.

We used univariate and multivariable logistic regression analyses to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of frailty in predicting life-threatening morbidity and mortality. We first analyzed the mFI score as a continuous variable and calculated the ORs and 95% CIs for the primary outcome per one-unit increase in mFI scores. Herein, to facilitate the clinical application of our findings, we defined one unit of the mFI score as 0.09 points (i.e., corresponding to 1 frailty trait). Potential confounding factors (not including the 11 variables covered by mFI) were screened by univariate analyses and tested for multicollinearity by variance inflation factor analysis. Factors with p values <0.10 in univariate analyses were then included in a multivariable model to examine the covariate-adjusted relationship between the rising mFI score and the primary outcome. Next, we analyzed the mFI score as a dichotomized measure and built another multivariable model to determine the adjusted association of frailty with the primary outcome. Likewise, the above statistical method was employed to explore the relationship of RAI-rev scores with the primary outcome. Herein, we defined each unit of the RAI-rev score as 1 point; similarly, the 11 variables included in RAI-rev were not enrolled in the corresponding multivariable models. All the multivariable analyses were performed with the backward stepwise method.

Besides, we conducted survival analysis to further explore the time effect of frailty (i.e., the two dichotomized frailty measures) on postoperative life-threatening morbidity and mortality. Herein, we adopted the 30-day life-threatening morbidity and mortality after surgery as the primary outcome in the survival analysis since almost all the primary endpoint events occurred within 30 days postoperatively in our study. The time to the endpoint event was calculated from the time of surgery to the date of the occurrence of life-threatening morbidity and mortality. Patients who were not observed to experience the primary outcome within 30 days and remained hospitalized after 30 days as well as those who did not undergo the endpoint event during hospitalization and were discharged from hospital within 30 days were all censored accordingly. Univariate analyses were performed using the Kaplan–Meier estimator with comparisons between frail and non-frail patients assessed by log-rank test. After multicollinearity screening, potential confounding factors (set at $p < 0.10$ in log-rank tests) were included in multivariable Cox proportional hazards regression models to examine the adjusted

relationship of frailty with the primary outcome. The factors included in the mFI and RAI-rev were not entered into the corresponding multivariable Cox regression model.

The predictive performances of mFI and RAI-rev were tested using the receiver-operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) was measured to test the discriminative power (ability to classify correctly) for the primary outcome. An AUC value of 1 indicates the best discrimination, whereas a value of 0.5 indicates that the predictor is no more reliable than chance. Generally, a predictor may be considered useful in clinical decision-making when the AUC exceeds 0.7 (26). Differences between AUCs were assessed by the DeLong' test.

For all analyses, two-tailed p values <0.05 were considered statistically significant. p-values were not corrected since no multiple comparison test was involved. All statistical analyses were performed with the SPSS version 26.0 (IBM Corp., Armonk, NY, United States) and MedCalc version 19.05 (Ostend, Belgium).

Results

Patient characteristics

From January 2018 to December 2020, 2,165 older patients (≥65 years of age) who experienced elective high-risk general and urologic surgical procedures were screened. Of these, 1,033 patients were excluded because they met the exclusion criteria (missing or ambiguous data on the components of mFI or RAI-rev, other ambiguous medical histories, or absence of necessary laboratory test results), leaving 1,132 patients in our analysis cohort (Figure 1).

The study population had a mean age of 73.4 ± 6.2 years; 63.9% (723/1132) were male. The median mFI and RAI-rev values of our cohort were 0.09 [IQR: 0.09–0.18] and 38 [IQR: 37–43], respectively. The distribution of the mFI and RAI-rev scores across the cohort is displayed in Figure 2. According to the mFI score cutoff of 0.27 or higher, 268 (23.7%) patients were classified as frail. Based on the RAI-rev value cutoff of 45 or greater, 251 (22.2%) patients were identified as frail. During surgery, 1,040 (91.9%) patients underwent high-stress procedures, and 92 (8.1%) experienced very high-stress procedures (Table 1; Supplementary Table S1). After surgery, 107 patients (9.5%) developed postoperative life-threatening morbidity and death during hospitalization, of whom 94 (8.3%) and 13 (1.1%) developed CD IV complications and death, respectively (Table 1; Supplementary Table S4). Other baseline and perioperative characteristics are reported in Table 1.

Postoperative outcomes according to frailty

Compared with patients with an mFI of <0.27, those with an mFI of ≥0.27 had a higher rate of the composite primary outcome or life-threatening morbidity, had a shorter time to develop the life-threatening morbidity and mortality, had more postoperative ICU admissions, stayed longer in hospital, and experienced more adverse discharge destinations (All $p < 0.05$). Similarly, there were significant differences in the above outcomes between the patients with an RAI-rev score of <45 and those with a score of ≥45 (all $p < 0.05$; Table 2). In addition, we observed that the patients with an RAI-rev score of ≥45 developed more in-hospital death than those with a score of <45 (3.6% vs. 0.5%, $p < 0.001$); whereas we found no significant difference in mortality between the two mFI subgroups (1.9% vs. 0.9%, $p = 0.351$; Table 2).

Correlation and agreement between the two frailty tools

Overall the Spearman's correlation coefficient for the continuous scores was 0.243 ($p < 0.001$), indicating a low correlation between the two frailty indices. The overall percentage of agreement between the two dichotomized measures was 72.2% (817/1132). Specifically, 102

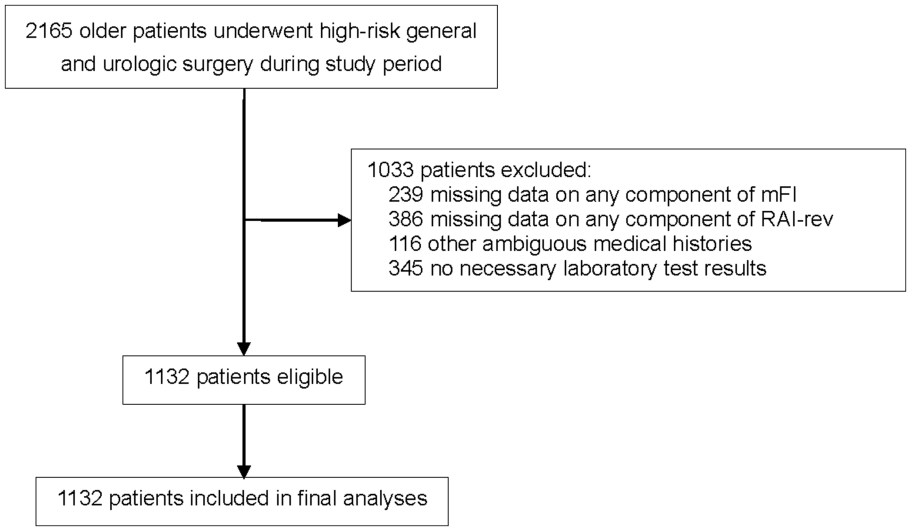


FIGURE 1
Flowchart of the study. MFI, modified frailty index; RAI-rev, revised- Risk Analysis Index.

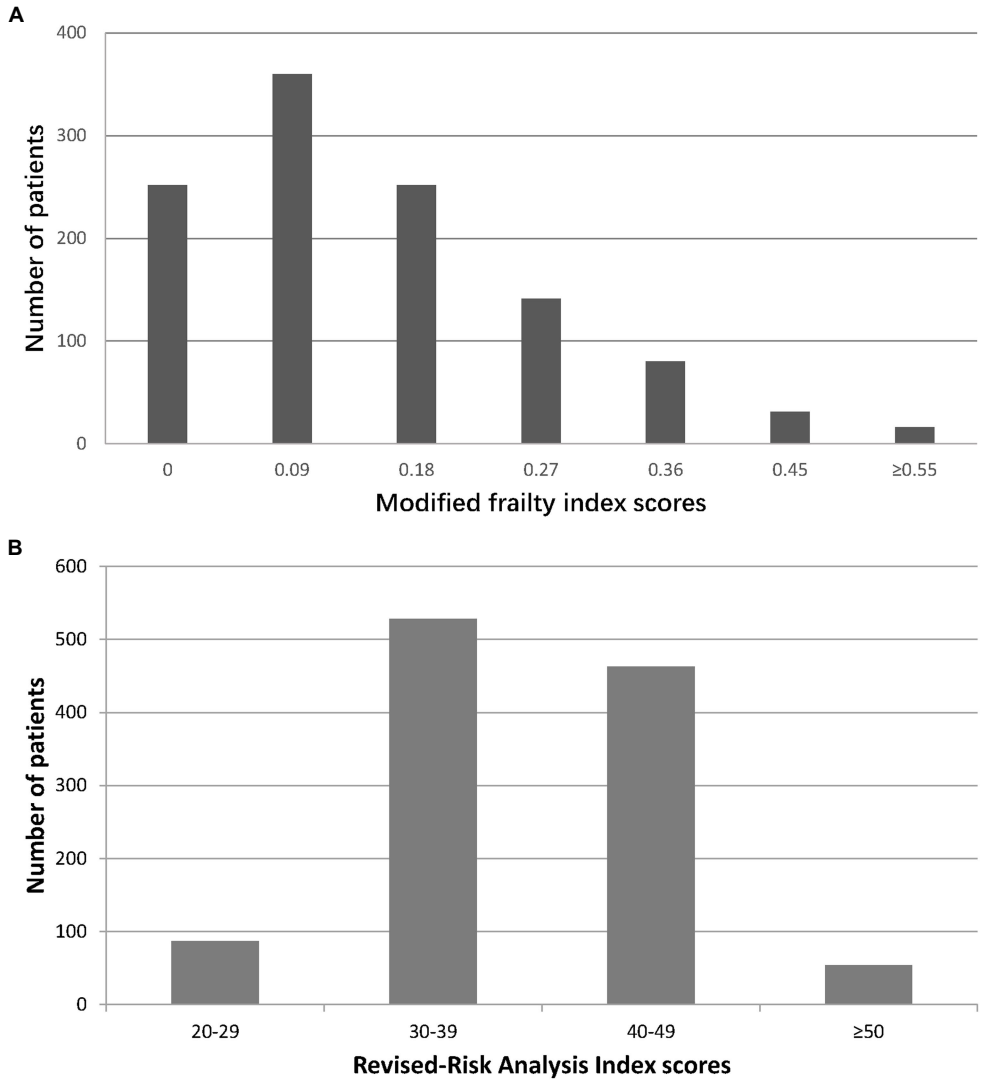


FIGURE 2
Distribution of frailty scores in the study cohort. **(A)** Modified frailty index; **(B)** Revised-Risk Analysis Index.

(9.0%) and 715 (63.2%) patients were identified as frail and non-frail by both measures, respectively. Cohen's Kappa test showed slight agreement between the two dichotomized measures (Cohen's Kappa coefficient: 0.213, $p < 0.001$; Table 3).

Association between mFI and life-threatening morbidity and mortality

The univariate logistic regression analysis showed that the odds of life-threatening morbidity and mortality increased by 34.5% with every unit (i.e., 0.09 points) increase in the mFI score (unadjusted OR 1.345 per 0.09-point increase in score, 95% CI 1.183–1.528, $p < 0.001$; Supplementary Table S5). After adjusting for confounding factors (i.e., age, body mass index, renal failure, hypoalbuminemia, hyponatremia, and risk stratification and duration of surgery), the rising mFI score remained to be significantly associated with an increased risk of life-threatening morbidity and mortality (adjusted OR 1.319 per 0.09-point increase in score, 95% CI 1.151–1.511, $p < 0.001$; Table 4; Supplementary Table S6).

Frailty, identified by mFI scores of ≥0.27, was associated with an increased risk of the primary outcome in both univariate analysis (unadjusted OR 2.184, 95% CI 1.440–3.313, $p < 0.001$; Supplementary Table S5) and multivariable analysis (adjusted OR 2.059, 95% CI 1.328–3.193, $p = 0.001$) after correcting for the above confounding factors (Table 4; Supplementary Table S6).

Association between RAI-rev and life-threatening morbidity and mortality

The univariate logistic regression analysis demonstrated that rising RAI-rev score was related to increased odds of life-threatening morbidity and mortality (unadjusted OR 1.066 per 1-point increase in score, 95% CI 1.032–1.100, $p < 0.001$; Supplementary Table S5). After correcting for confounding factors (i.e., body mass index, hypertension, coronary heart disease, previous stroke, diabetes

TABLE 1 Baseline and perioperative characteristics.

	All patients (*n* =1,132)	Without life-threatening morbidity and mortality (*n* =1,025)	With life-threatening morbidity and mortality (*n* =107)	*p* value
Baseline characteristics				
Age (years)	73.4 ± 6.2	73.2 ± 6.1	75.0 ± 6.1	**0.005**
Body mass index				**0.003**
<18.5 kg m^{-2}	68 (6.0%)	54 (5.3%)	14 (13.1%)	
18.5–23.9 kg m^{-2}	566 (50.0%)	522 (50.9%)	44 (41.1%)	
≥24 kg m^{-2}	498 (44.0%)	449 (43.8%)	49 (45.8%)	
Modified frailty index scores	0.09 [0.09–0.18]	0.09 [0.09–0.18]	0.18 [0.09–0.36]	**0.001**
Frailty identified by mFI of ≥0.27	268 (23.7%)	227 (22.1%)	41 (38.3%)	**<0.001**
Hypertension	558 (49.3%)	497 (48.5%)	61 (57.0%)	0.093
Coronary heart disease	206 (18.2%)	174 (17.0%)	32 (29.9%)	**0.001**
Peripheral vascular disease	142 (12.5%)	126 (12.3%)	16 (15.0%)	0.429
Diabetes mellitus	316 (27.9%)	275 (26.8%)	41 (38.3%)	**0.012**
COPD or current pneumonia	94 (8.3%)	81 (7.9%)	13 (12.1%)	0.130
CHF exacerbation within 30d	11 (1.0%)	6 (0.6%)	5 (4.7%)	**<0.001**
Myocardial infarction within 6 months	5 (0.4%)	3 (0.3%)	2 (1.9%)	0.073
Previous stroke	193 (17.0%)	165 (16.1%)	28 (26.2%)	**0.008**
Stroke with deficits	57 (5.0%)	53 (5.2%)	4 (3.7%)	0.519
Functional dependence	275 (24.3%)	238 (23.2%)	37 (34.6%)	**0.009**
Acutely impaired sensorium[a]	3 (0.3%)	2 (0.2%)	1 (0.9%)	0.258
Revised-Risk Analysis Index scores	38 [37–43]	38 [37–43]	41 [37–45]	**<0.001**
Frailty identified by RAI-rev of ≥45	251 (22.2%)	212 (20.7%)	39 (36.4%)	**<0.001**
Male sex	723 (63.9%)	648 (63.2%)	75 (70.1%)	0.159
Age				**0.037**
65–69	366 (32.3%)	343 (33.5%)	23 (21.5%)	
70–74	304 (26.9%)	278 (27.1%)	26 (24.3%)	
75–79	260 (23.0%)	229 (22.3%)	31 (29.0%)	
80–84	144 (12.7%)	124 (12.1%)	20 (18.7%)	
≥85	58 (5.1%)	51 (5.0%)	7 (6.5%)	
Cancer	1,006 (88.9%)	915 (89.3%)	91 (85.0%)	0.186
Weight loss[b]	260 (23.0%)	231 (22.5%)	29 (27.1%)	0.285
Poor appetite	358 (31.6%)	305 (29.8%)	53 (49.5%)	**<0.001**
Renal failure	11 (1.0%)	8 (0.8%)	3 (2.8%)	**0.130**
Congestive heart failure	11 (1.0%)	6 (0.6%)	5 (4.7%)	**<0.001**
Shortness of breath	6 (0.5%)	3 (0.3%)	3 (2.8%)	**0.013**
Residence other than independent living	7 (0.6%)	3 (0.3%)	4 (3.7%)	**0.002**
Cognitive decline	20 (1.8%)	17 (1.7%)	3 (2.8%)	0.638
Alzheimer's disease	5 (0.4%)	4 (0.4%)	1 (0.9%)	0.392
Vascular dementia	11 (1.0%)	10 (1.0%)	1 (0.9%)	>0.999
Parkinson's disease	8 (0.7%)	6 (0.6%)	2 (1.9%)	0.170

(Continued)

TABLE 1 (Continued)

	All patients (*n* =1,132)	Without life-threatening morbidity and mortality (*n* =1,025)	With life-threatening morbidity and mortality (*n* =107)	*p* value
Functional status				**0.002**
Independent	857 (75.7%)	787 (76.8%)	70 (65.4%)	
Partially dependent	263 (23.2%)	230 (22.4%)	33 (30.8%)	
Totally dependent	12 (1.1%)	8 (0.8%)	4 (3.7%)	
ASA classification				**<0.001**
I/II	629 (55.6%)	592 (57.8%)	37 (34.6%)	
III	458 (40.5%)	405 (39.5%)	53 (49.5%)	
IV	45 (4.0%)	28 (2.7%)	17 (15.9%)	
Current smoking[c]/quit ≤7 days	137 (12.1%)	124 (12.1%)	13 (12.1%)	0.987
Current alcoholism[d]	64 (5.7%)	56 (5.5%)	8 (7.5%)	0.391
Severe arrhythmia[e]	92 (8.1%)	80 (7.8%)	12 (11.2%)	0.219
Asthma	22 (1.9%)	20 (2.0%)	2 (1.9%)	>0.999
Mental disorders[f]	29 (2.6%)	27 (2.6%)	2 (1.9%)	0.877
Visual/hearing impairment	47 (4.2%)	43 (4.2%)	4 (3.7%)	>0.999
Chronic hepatic dysfunction[g]	60 (5.3%)	51 (5.0%)	9 (8.4%)	0.131
Chronic corticosteroid therapy[h]	41 (3.6%)	38 (3.7%)	3 (2.8%)	0.838
Hyper−/hypothyroidism	29 (2.6%)	27 (2.6%)	2 (1.9%)	0.877
Anemia[i]	376 (33.2%)	334 (32.6%)	42 (39.3%)	0.164
Blood coagulation disorder	15 (1.3%)	12 (1.2%)	3 (2.8%)	0.336
Dyslipidemia	614 (54.2%)	554 (54.0%)	60 (56.1%)	0.689
Hypoalbuminemia				**<0.001**
None	619 (54.7%)	576 (56.2%)	43 (40.2%)	
30.0–39.9 $g\,l^{-1}$	460 (40.6%)	408 (39.8%)	52 (48.6%)	
<30.0 $g\,l^{-1}$	53 (4.7%)	41 (4.0%)	12 (11.2%)	
Na^+ < 135.0 $mmol\,l^{-1}$	91 (8.0%)	74 (7.2%)	17 (15.9%)	**0.002**
Intraoperative data				
Risk stratification of surgery by OSS[j]				**0.002**
High stress	1,040 (91.9%)	950 (92.7%)	90 (84.1%)	
Very high stress	92 (8.1%)	75 (7.3%)	17 (15.9%)	
Duration of surgery (min)	237 [190–297]	231 [188–292]	256 [195–318]	**0.006**
Type of anesthesia				0.701
General	488 (43.1%)	440 (42.9%)	48 (44.9%)	
Combined regional-general	644 (56.9%)	585 (57.1%)	59 (55.1%)	
Estimated blood loss (ml)	100 [50–200]	100 [50–200]	150 [100–300]	**0.008**
Blood transfusion	130 (11.5%)	114 (11.1%)	16 (15.0%)	0.237
Postoperative outcomes				
CD grade IV	94 (8.3%)	–	94 (87.9%)	–
Death	13 (1.1%)	–	13 (12.1%)	–
ICU admission	344 (30.4%)	258 (25.2%)	86 (80.4%)	**<0.001**
Prolonged hospital stay[k]	378 (33.4%)	294 (28.7%)	84 (78.5%)	**<0.001**
Adverse discharge destination[l]	33 (2.9%)	9 (0.9%)	24 (22.4%)	**<0.001**

(Continued)

TABLE 1 (Continued)

Data are *n* (%), mean ± SD, or median [IQR]. *p*-values were derived from comparing the patients with life-threatening morbidity and mortality and those without. *p* values in bold indicate <0.05. COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; ASA, American Society of Anesthesiologists; Na^+, serum natremia concentration; OSS, operative stress score; CD, Clavien-Dindo classification of complication; ICU, intensive care unit.
[a]Refers to acute mental status changes and/or delirium in the context of the current illness. Patients with chronic or long-standing mental status changes secondary to chronic mental illness or chronic dementing illnesses are not included.
[b]Unintentional weight loss ≥10% from baseline within 6 months, or ≥5% within 3 months, or ≥2% within 1 month.
[c]Smoking refers to daily smoking of cigarettes up to half a pack for at least 2 years.
[d]Alcoholism refers to ethanol consumption ≥40 g/d for men and ≥20 g/d for women, lasting for more than 5 years. Ethanol (g) = alcohol consumption (ml) × ethanol content (%) × 0.8.
[e]Includes atrial fibrillation, frequent (>6 beats/min) or multifocal ventricular premature beat, paroxysmal supraventricular tachycardia, second/third-degree atrioventricular block, and sick sinus syndrome.
[f]Include diagnosed depression, anxiety, schizophrenia, phobia, and hallucination.
[g]Defined as Child-Pugh class B and C.
[h]With a duration of >1 month.
[i]Diagnosed according to the hemoglobin values from the last laboratory test before surgery, male: <120 $g l^{-1}$, female: <110 $g l^{-1}$.
[j]Identified the risk stratification of surgery by physiologic stress, i.e., operative stress score (OSS). The surgical procedures in the study were those with OSS level 4 (i.e., high stress) and OSS level 5 (i.e., very high stress) (23). Detailed data on surgery procedures is provided in Supplemental Table S1.
[k]Defined as greater than the 75th percentile of the length of hospital for each type of surgery.
[l]Defined as discharge to destinations other than home (e.g., skilled care facility or other hospitals).

TABLE 2 Postoperative outcomes according to frailty.

	Modified frailty index			Revised-Risk Analysis Index		
	<0.27 (*n* =864)	≥0.27 (*n* =268)	*P* value	<45 (*n* =881)	≥45 (*n* =251)	*p* value
The primary outcome	66 (7.6%)	41 (15.3%)	**<0.001**	68 (7.7%)	39 (15.5%)	**<0.001**
Life-threatening morbidity	58 (6.7%)	36 (13.4%)	**<0.001**	64 (7.3%)	30 (12.0%)	**0.018**
Mortality	8 (0.9%)	5 (1.9%)	0.351	4 (0.5%)	9 (3.6%)	**<0.001**
Time to life-threatening morbidity and mortality (day)[a]	27.826 (27.289–28.363)	25.567 (24.301–26.833)	**<0.001**	27.780 (27.230–28.330)	25.506 (24.209–26.802)	**<0.001**
Postoperative ICU admission	215 (24.9%)	129 (48.1%)	**<0.001**	231 (26.2%)	113 (45.0%)	**<0.001**
Prolonged hospital stay	249 (28.8%)	129 (48.1%)	**<0.001**	266 (30.2%)	112 (44.6%)	**<0.001**
Adverse discharge destination	20 (2.3%)	13 (4.9%)	**0.031**	17 (1.9%)	16 (6.4%)	**<0.001**

Data are *n* (%) or mean [95% CI]. *p* values in bold indicate <0.05. ICU, intensive care unit.
[a]Analyzed with Kaplan–Meier survival analysis (log-rank test).

mellitus, hypoalbuminemia, hyponatremia, and risk stratification and duration of surgery), the rising RAI-rev score remained to be an independent predictor of life-threatening morbidity and mortality (adjusted OR 1.052 per 1-point increase in score, 95% CI 1.018–1.087, $p = 0.002$; Table 4; Supplementary Table S7).

Frailty, based on RAI-rev scores of ≥45, predicted the primary outcome in both univariate analysis (unadjusted OR 2.199, 95% CI 1.443–3.353, $p < 0.001$; Supplementary Table S5) and multivariable analysis (adjusted OR 1.862, 95% CI 1.188–2.919, $p = 0.007$) after adjustment for the above confounding factors (Table 4; Supplementary Table S7).

Time effect of frailty on 30-day life-threatening morbidity and mortality

In the Kaplan–Meier analysis, when compared with non-frail (identified by mFI scores of <0.27) patients, the frail patients (determined by mFI scores of ≥0.27) had a shortened time to develop 30-day life-threatening morbidity and mortality (log-rank test: $p < 0.001$; Table 2; Supplementary Figure S1). Similar results were observed when frailty was diagnosed by RAI-rev scores of ≥45 (log-rank test: $p < 0.001$; Table 2; Supplementary Figure S2).

Multivariable Cox proportional hazards regression analyses demonstrated that frailty identified by mFI scores of ≥0.27 was associated with a 2-fold increased hazard of developing 30-day life-threatening morbidity and mortality (adjusted HR 2.042, 95% CI 1.353–3.083, $p = 0.001$; Supplementary Table S8). Similarly, frailty diagnosed by RAI-rev scores of ≥45 was linked with a 1.8-fold higher hazard of 30-day life-threatening morbidity and mortality (adjusted HR 1.822, 95% CI 1.198–2.770, $p = 0.005$; Supplementary Table S9).

Predictive performances of mFI and RAI-rev in predicting life-threatening morbidity and mortality

The AUCs of continuous mFI and RAI-rev scores in predicting life-threatening morbidity and mortality were 0.598 (95% CI 0.569–0.627) and 0.613 (95% CI 0.583–0.641), respectively. Although the

AUC of RAI-rev was slightly higher than that of mFI, no statistical difference between them was detected (DeLong's test: Z = 0.375, $p = 0.7075$; Figure 3).

As seen in Figure 3, the performances of dichotomized mFI (0.581 [95% CI 0.551–0.610]) and RAI-rev (0.579 [95% CI 0.549–0.608]) measures were also comparable in predicting the primary outcome (DeLong's test: Z = 0.0675, $p = 0.9462$).

Discussion

This retrospective cohort study determined that rising mFI and RAI-rev scores were associated with a higher risk of life-threatening morbidity and mortality in older patients after elective high-risk abdominal surgery. However, both the two frailty indices performed poor discriminative abilities for the occurrence of life-threatening morbidity and mortality.

In the present study, we found a low correlation and slight agreement between the two frailty indices. As shown in Table 3, among the 268 patients identified as frail by mFI, only 38% (102/268) were also diagnosed with frailty by RAI-rev; meanwhile, only 41% (102/251) of the RAI-rev frail patients were classified as frail by mFI. This finding was unsurprising since the two tools shared limited overlap between frailty spectrums and assigned different weights to components. The selection of cutoff values also affected the agreement between the two frailty indices. The slight agreement between them indicates the potential for combining the two measures to capture more useful patient-level information, which provides clues for further exploration.

TABLE 3 Two way cross-tabulation of dichotomized mFI and RAI-rev measures.

	Modified frailty index		
	Non-frail	Frail	Total
Revised-Risk Analysis Index			
Non-frail	715 (63.2%)	166 (14.7%)	881 (77.8%)
Frail	149 (13.2%)	102 (9.0%)	251 (22.2%)
Total	864 (76.3%)	268 (23.7%)	1,132 (100%)

Data are *n* (%). The overall percentage of agreement between the two dichotomized frailty measures was 72.2%. Cohen's Kappa coefficient was 0.213 ($P < 0.001$).

The effect of frailty on major postoperative morbidity and mortality has been extensively studied (5–11, 14, 17, 23, 24, 27). In a retrospective cohort study of 9,986 adult patients receiving pancreaticoduodenectomy, Mogal et al. (10) determined that increased mFI scores (≥0.27) predicted a 1.54-fold elevated risk of major complications or 30-day mortality. In the current study, we identified a stronger association between high mFI (≥0.27) and serious morbidity and mortality (adjusted OR: 2.06), which could be mainly attributed to the fact that our patients were older and performed worse baseline status (e.g., higher prevalence of functional dependence) than those in the above study. In another observational study of ambulatory patients undergoing minor surgery, Shah et al. (7) examined the relationship of RAI-sev with 1-year mortality and found that frailty (RAI-rev score: 45–52) and severe frailty (RAI-rev score: ≥53) were associated with hazard ratios of 2.76 and 4.83 for mortality (compared with normal status, i.e., RAI-rev score: 30–36), respectively. However, the above results were not corrected for any confounding factor. As far as we know, no previous studies have estimated the adjusted effects of rising RAI-sev score on the occurrence of serious morbidity and mortality after elective high-risk surgery. Our study filled this knowledge gap and expanded the existing evidence. Our findings highlighted the importance and urgent need to augment the application of routine frailty screening before surgery in older populations.

In the present study, ROC analysis results demonstrated that neither the mFI nor the RAI-rev was equipped with good discrimination for serious morbidity and mortality in older patients undergoing elective high-risk abdominal surgery. Our findings are congruent with previous studies that applicated frailty indices to predict postoperative morbidity (8, 9, 27). The poor discriminative abilities of the two frailty measures for postoperative morbidity might be explained by the following three reasons. First, the mFI fails to

TABLE 4 Association of frailty with life-threatening morbidity and mortality (logistic regression analyses).

	Univariate analyses		Multivariable analyses	
	Unadjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Modified frailty index scores[a]	1.345 (1.183–1.528)	<0.001	1.319 (1.151–1.511)	<0.001
Frailty based on mFI of ≥0.27[a]	2.184 (1.440–3.313)	<0.001	2.059 (1.328–3.193)	0.001
Revised-Risk Analysis Index scores[b]	1.066 (1.032–1.100)	<0.001	1.052 (1.018–1.087)	0.002
Frailty based on RAI-rev of ≥45[b]	2.199 (1.443–3.353)	<0.001	1.862 (1.188–2.919)	0.007

OR, odds ratio; CI, confidence interval; mFI, modified frailty index; RAI-rev, revised-Risk Analysis Index.

[a]After testing for multicollinearity, mFI (as continuous or dichotomous variable) and other factors with *p* values <0.10 in univariate logistic regression analyses (including age, body mass index, renal failure, hypoalbuminemia, hyponatremia, and risk stratification and duration of surgery) were included in the multivariable logistic regression model to identify the adjusted association between high mFI (per 0.09-point increase in mFI score or mFI of ≥0.27) and the primary outcome. The 11 variables covered by mFI were not separately enrolled in multivariable analyses. See Supplementary Table S6 for details.

[b]After testing for multicollinearity, RAI-rev (as continuous or dichotomous variable) and other factors with *p* values <0.10 in univariate logistic regression analyses (including body mass index, hypertension, coronary heart disease, previous stroke, diabetes mellitus, hypoalbuminemia, hyponatremia, and risk stratification and duration of surgery) were included in the multivariable logistic regression model to identify the adjusted association between high RAI-rev (per 1-point increase in RAI-rev score or RAI-rev of ≥45) and the primary outcome. The 11 variables covered by the RAI-rev were not separately enrolled in multivariable analyses. See Supplementary Table S7 for details.

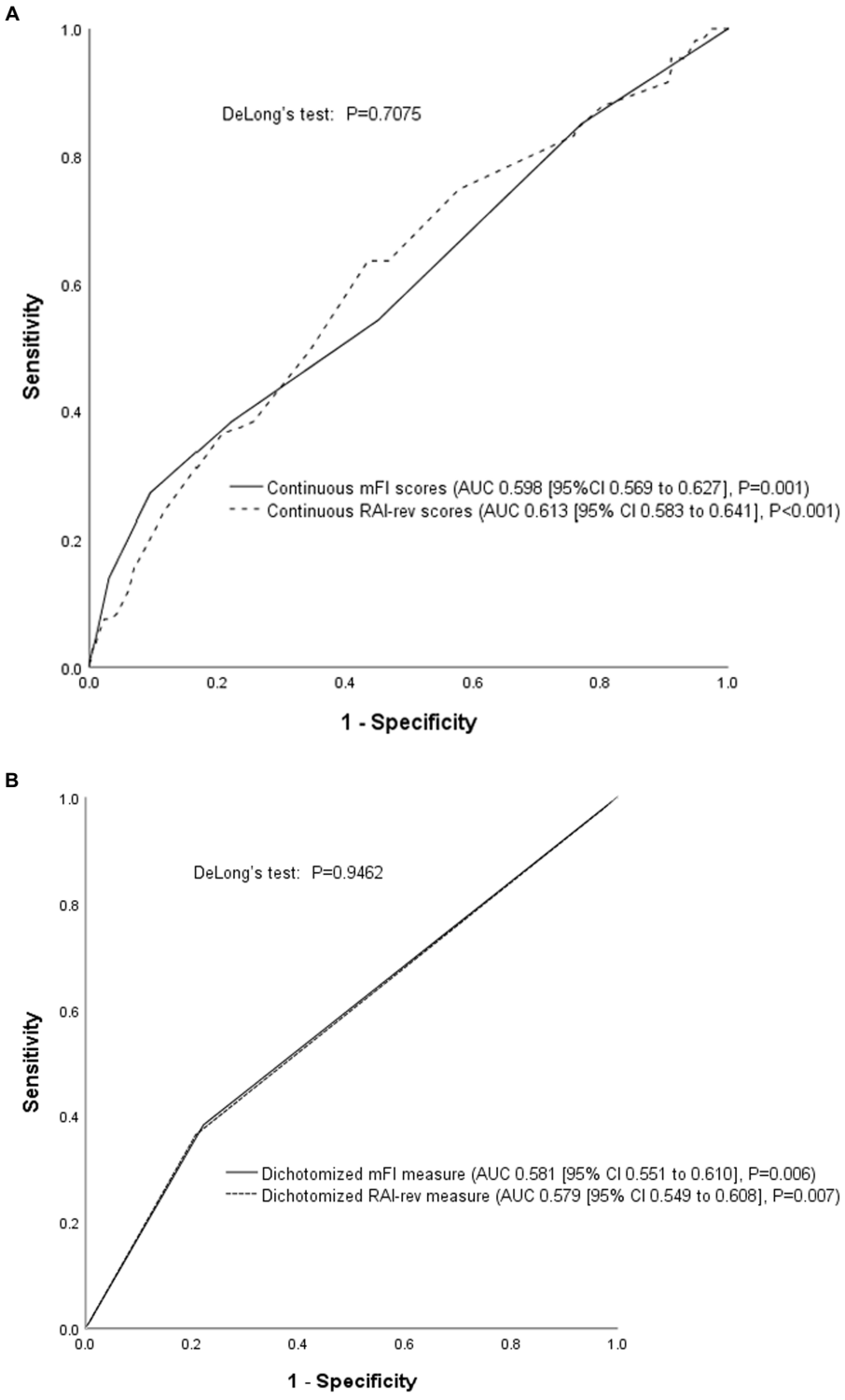


FIGURE 3
Receiver operating characteristic (ROC) curve analysis. **(A)** Comparison of the continuous mFI and RAI-rev scores; **(B)** Comparison of dichotomized mFI and RAI-rev measures. ROC curve analyses showed that the performances of mFI and RAI-rev were poor and comparable in predicting life-threatening morbidity and mortality. MFI, modified frailty index; RAI-rev, revised-Risk Analysis Index.

cover multiple frailty spectrums because it evaluates only two domains (comorbidity burden and functional impairment). Although the RAI-rev captures multiple frailty features, some of its elements are typically representative of acute disease processes, which are infrequent among elective high-risk surgery candidates. For example, the prevalence of congestive heart failure or shortness of breath was quite low in our cohort. Second, surgeons are always more cautious to determine the surgical candidacy of a patient when considering

the upcoming procedure as high risk. In most cases, the patient assessed as too frail may turn to conservative treatment instead of receiving aggressive high-risk surgery. Thus, the exclusion of severely frail patients might limit the predictive performance of frailty in this study cohort. Indeed, existing data suggest that the association between frailty and adverse outcomes is stronger in low-risk surgery than in high-risk surgery (23, 28, 29). Third, the etiology of postoperative morbidity is multifactorial, and the patient-level risk factors alone cannot adequately account for the variation in complication risk. Further studies should consider the combination of frailty with additional risk variables, such as other baseline characteristics and surgical-related risk factors, to predict the risk of postoperative morbidity.

Our findings demonstrated clinical significance and might play an important role in perioperative settings. Based on the multivariable logistic and Cox regression analysis results, frailty was significantly associated with a higher risk of life-threatening morbidity and mortality in older patients after elective high-risk abdominal surgery. This finding can help clinicians forecast the elevated risk of serious postoperative outcomes in frail older patients and improve the shared decision-making process. Once a patient is screened as frail, determining the goals of care and selecting the optimal approach to achieve the goals of care constitute crucial components of shared decision-making. It should be carefully considered whether aggressive surgical intervention or palliative care can get frail patients to their goals of care. Realistic expectations and appropriate decision-making may, in turn, decrease perioperative mortality (30). Furthermore, this finding can help guide the more efficient allocation of scarce perioperative care resources to high-risk patients, such as necessary postoperative ICU admission and active application of advanced invasive or non-invasive monitoring skills, thereby enhancing the safety and quality of high-risk surgery in older patients. Based on the ROC analysis results, the two frailty indices presented poor discriminative power in predicting the primary outcome. Despite this, the above finding generates clues for further research. It is anticipated that the combination of frailty with other baseline and perioperative risk factors may emerge as a potentially useful model to predict serious morbidity. Additionally, larger studies with the recruitment of more patients with severe frailty are needed to draw more reliable conclusions.

Besides the retrospective nature, our study had several notable limitations. First, as mentioned above, the patients with severe frailty were inevitably excluded from the study cohort due to the high-risk nature of the surgery, which might lead to selection bias. Second, the primary outcome was limited to in-hospital serious morbidity and mortality. The complications below CD grade IV were not included in our analysis and the post-discharge outcomes were not gathered, which might underestimate the rate of adverse outcomes. Finally, in our study, the composite endpoint rate was fairly low, especially mortality. Our relatively limited sample size could not enable us to fully elucidate the relationship between frailty and mortality. Despite these, our results demonstrate clinical significance and generate clues for further investigation.

Conclusion

In conclusion, this study determined that high mFI and RAI-rev scores were associated with an increased risk of life-threatening morbidity and mortality in older patients following elective high-risk abdominal surgery. However, both frailty indices displayed poor discrimination for the composite outcome of life-threatening morbidity and mortality.

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 Biomedical Research Ethics Committee of Peking University First Hospital. The ethics committee waived the requirement of written informed consent for participation.

Author contributions

C-QL contributed to the conception, study design, and supervision. C-QL, HK, and Z-ZX collected data. C-QL, J-HM, and X-YL analyzed and interpreted the data. C-QL drafted the manuscript. All authors critically revised the manuscript, agreed to submit it to the current journal, and gave final approval of the version to be published.

Acknowledgments

The authors gratefully acknowledge Yan Zhou (Department of Anesthesiology, Peking University First Hospital, Beijing, China) for his help during data collection.

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/fpubh.2023.1055001/full#supplementary-material

References

1. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. *Lancet*. (2019) 394:1376–86. doi: 10.1016/S0140-6736(19)31785-4

2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. (2013) 381:752–62. doi: 10.1016/S0140-6736(12)62167-9

3. Etzioni DA, Liu JH, Maggard MA, Ko CY. The aging population and its impact on the surgery workforce. *Ann Surg*. (2003) 238:170–7. doi: 10.1097/01.SLA.0000081085.98792.3d

4. Richards SJG, Frizelle FA, Geddes JA, Eglinton TW, Hampton MB. Frailty in surgical patients. *Int J Color Dis*. (2018) 33:1657–66. doi: 10.1007/s00384-018-3163-y

5. Velanovich V, Antoine H, Swartz A, Peters D, Rubinfeld I. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. *J Surg Res*. (2013) 183:104–10. doi: 10.1016/j.jss.2013.01.021

6. Arya S, Varley P, Youk A, Borrebach JD, Perez S, Massarweh NN, et al. Recalibration and external validation of the Risk Analysis Index: a surgical frailty assessment tool. *Ann Surg*. (2020) 272:996–1005. doi: 10.1097/SLA.0000000000003276

7. Shah R, Borrebach JD, Hodges JC, Varley PR, Wisniewski MK, Shinall MC Jr, et al. Validation of the Risk Analysis Index for evaluating frailty in ambulatory patients. *J Am Geriatr Soc*. (2020) 68:1818–24. doi: 10.1111/jgs.16453

8. Youngerman BE, Neugut AI, Yang J, Hershman DL, Wright JD, Bruce JN. The modified frailty index and 30-day adverse events in oncologic neurosurgery. *J Neuro-Oncol*. (2018) 136:197–206. doi: 10.1007/s11060-017-2644-0

9. George EM, Burke WM, Hou JY, Tergas AI, Chen L, Neugut AI, et al. Measurement and validation of frailty as a predictor of outcomes in women undergoing major gynaecological surgery. *BJOG*. (2016) 123:455–61. doi: 10.1111/1471-0528.13598

10. Mogal H, Vermilion SA, Dodson R, Hsu FC, Howerton R, Shen P, et al. Modified frailty index predicts morbidity and mortality after pancreaticoduodenectomy. *Ann Surg Oncol*. (2017) 24:1714–21. doi: 10.1245/s10434-016-5715-0

11. Melin AA, Schmid KK, Lynch TG, Pipinos II, Kappes S, Longo GM, et al. Preoperative frailty Risk Analysis Index to stratify patients undergoing carotid endarterectomy. *J Vasc Surg*. (2015) 61:683–9. doi: 10.1016/j.jvs.2014.10.009

12. Alvarez-Nebreda ML, Bentov N, Urman RD, Setia S, Huang JC, Pfeifer K, et al. Recommendations for preoperative management of frailty from the Society for Perioperative Assessment and Quality Improvement (SPAQI). *J Clin Anesth*. (2018) 47:33–42. doi: 10.1016/j.jclinane.2018.02.011

13. Schwarze ML, Barnato AE, Rathouz PJ, Zhao Q, Neuman HB, Winslow ER, et al. Development of a list of high-risk operations for patients 65 years and older. *JAMA Surg*. (2015) 150:325–31. doi: 10.1001/jamasurg.2014.1819

14. Hall DE, Arya S, Schmid KK, Blaser C, Carlson MA, Bailey TL, et al. Development and initial validation of the Risk Analysis Index for measuring frailty in surgical populations. *JAMA Surg*. (2017) 152:175–82. doi: 10.1001/jamasurg.2016.4202

15. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton frail scale. *Age Ageing*. (2006) 35:526–9. doi: 10.1093/ageing/afl041

16. Peters LL, Boter H, Buskens E, Slaets JP. Measurement properties of the Groningen frailty indicator in home-dwelling and institutionalized elderly people. *J Am Med Dir Assoc*. (2012) 13:546–51. doi: 10.1016/j.jamda.2012.04.007

17. Wang SL, Zhuang CL, Huang DD, Pang WY, Lou N, Chen FF, et al. Sarcopenia adversely impacts postoperative clinical outcomes following gastrectomy in patients with gastric cancer: a prospective study. *Ann Surg Oncol*. (2016) 23:556–64. doi: 10.1245/s10434-015-4887-3

18. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging*. (2012) 16:601–8. doi: 10.1007/s12603-012-0084-2

19. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. (2005) 173:489–95. doi: 10.1503/cmaj.050051

20. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. (2001) 56:M146–57. doi: 10.1093/gerona/56.3.M146

21. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *Sci World J*. (2001) 1:323–36. doi: 10.1100/tsw.2001.58

22. Cesari M, Gambassi G, van Kan GA, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. *Age Ageing*. (2014) 43:10–2. doi: 10.1093/ageing/aft160

23. Shinall MC Jr, Arya S, Youk A, Varley P, Shah R, Massarweh NN, et al. Association of preoperative patient frailty and operative stress with postoperative mortality. *JAMA Surg*. (2020) 155:e194620. doi: 10.1001/jamasurg.2019.4620

24. Li CQ, Zhang C, Yu F, Li XY, Wang DX. The composite risk index based on frailty predicts postoperative complications in older patients recovering from elective digestive tract surgery: a retrospective cohort study. *BMC Anesthesiol*. (2022) 22:7. doi: 10.1186/s12871-021-01549-6

25. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. (2004) 240:205–13. doi: 10.1097/01.sla.0000133083.54934.ae

26. McIsaac DI, Harris EP, Hladkowicz E, Moloo H, Lalu MM, Bryson GL, et al. Prospective comparison of preoperative predictive performance between 3 leading frailty instruments. *Anesth Analg*. (2020) 131:263–72. doi: 10.1213/ANE.0000000000004475

27. van der Windt DJ, Bou-Samra P, Dadashzadeh ER, Chen X, Varley PR, Tsung A. Preoperative Risk Analysis Index for frailty predicts short-term outcomes after hepatopancreatobiliary surgery. *HPB (Oxford)*. (2018) 20:1181–8. doi: 10.1016/j.hpb.2018.05.016

28. Castillo-Angeles M, Cooper Z, Jarman MP, Sturgeon D, Salim A, Havens JM. Association of frailty with morbidity and mortality in emergency general surgery by procedural risk level. *JAMA Surg*. (2021) 156:68–74. doi: 10.1001/jamasurg.2020.5397

29. McIsaac DI, Bryson GL, van Walraven C. Association of frailty and 1-year postoperative mortality following major elective noncardiac surgery: a population-based cohort study. *JAMA Surg*. (2016) 151:538–45. doi: 10.1001/jamasurg.2015.5085

30. Tang VL, Covinsky K. Frailty and surgical decision making. *Ann Intern Med*. (2016) 165:669–70. doi: 10.7326/M16-1866

frontiers | Frontiers in Public Health

TYPE Review
PUBLISHED 06 April 2023
DOI 10.3389/fpubh.2023.1147026

OPEN ACCESS

EDITED BY
Xin Jiang,
Shen Zhen People's Hospital,
China

REVIEWED BY
Kaiwu He,
Shenzhen Graduate School,
Peking University,
China
Tetsuya Goto,
Kagoshima University,
Japan

*CORRESPONDENCE
Wei Xiao
✉ sdws666@126.com
Keke Liu
✉ kekegood66@126.com

SPECIALTY SECTION
This article was submitted to Aging and Public Health, a section of the journal Frontiers in Public Health

RECEIVED 18 January 2023
ACCEPTED 02 March 2023
PUBLISHED 06 April 2023

CITATION
Wei T, Du Y, Hou T, Zhai C, Li Y, Xiao W and Liu K (2023) Association between adverse oral conditions and cognitive impairment: A literature review.
Front. Public Health 11:1147026.
doi: 10.3389/fpubh.2023.1147026

Association between adverse oral conditions and cognitive impairment: A literature review

Tianhao Wei[1], Yifeng Du[1,2], Tingting Hou[1,2], Chunjuan Zhai[3], Yuqi Li[1], Wei Xiao[1,2]* and Keke Liu[1,2,4]*

[1]Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China, [2]Department of Neurology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China, [3]Department of Cardiology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China, [4]Department of Infection Control, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China

Oral environment deterioration results from a lack of self-cleaning ability in patients with cognitive dysfunction but is also a risk factor for cognitive dysfunction. Adverse oral conditions can be alleviated and improved through a self-management and medical examination. In this review, the epidemiological evidence of previous studies is integrated to highlight the relationship between periodontitis, tooth loss, oral flora, oral dysfunction and cognitive dysfunction, emphasizing the importance of oral health for cognition. The results show that poor oral condition is associated with cognitive impairment. Although many previous studies have been conducted, there is a lack of higher-level research evidence, different judgment criteria, and conflicting research results. There is a bidirectional relationship between oral health and cognitive dysfunction. A comprehensive analysis of the relationship between oral health and cognitive dysfunction that explores the relationship and takes measures to prevent cognitive dysfunction and control the progression of such diseases is warranted in the future.

KEYWORDS

cognitive dysfunction, periodontitis, tooth loss, oral microflora, oral dysfunction

1. Introduction

Cognitive dysfunction manifests mainly as impaired memory, thinking, calculation, judgment, language, and other abilities, which seriously affect the normal life of patients. Cognitive dysfunction is a continuously developing process, from cognitive decline to mild cognitive impairment (MCI) to dementia. With the increase in global aging, dementia has gradually become a serious global public health problem. Compared with developed countries such as Europe and North America, the incidence of dementia continues to increase in low-income countries such as Asia and Africa (1). According to the World Health Organization, there are approximately 10 million new patients with dementia worldwide every year, and the number is expected to reach 82 million by 2030, with a cost of up to 2 trillion dollars (2). This will pose huge challenges for national healthcare and social welfare systems. Alzheimer's disease (AD) accounts for 60–80% of all dementia types (3); however, there are no effective treatments for any type of dementia to date, including AD and MCI. The main treatment method for patients with dementia involves symptomatic relief and access to necessary care and services to maximize the quality of life. Therefore, current research has focused on discovering risk factors

for cognitive dysfunction in advance and taking effective and reasonable intervention measures to effectively reduce and delay the occurrence of dementia.

The oral cavity is an important part of the human body and an essential organ for maintaining a normal life and normal social communication. In recent years, numerous studies have shown significant associations between the oral cavity and various systemic diseases (cirrhosis, diabetes, sepsis, arthritis, and atherosclerosis) (4, 5). In addition, other studies have shown that the oral cavity is related to nervous system diseases, and oral problems have a bidirectional correlation with cognitive dysfunction. Poor oral condition is a risk factor for cognitive dysfunction; in turn, poor cognition aggravates the deterioration of oral function (6). The correlation between oral problems and cognitive dysfunction has become a global research concern. In this review, we summarize the epidemiological studies on the effects of periodontal disease, tooth loss, oral flora, and oral function on cognitive dysfunction, providing scientific evidence for further oral and cognitive research.

2. Search strategy

We searched PubMed for articles published between 2000 and 2022 using combinations of the following terms: "Periodontitis," "Periodontal disease," "Tooth loss," "Oral bacteria," "Oral microbiome," "Oral microbiota," "Oral function," "Dental occlusion," "Dementia," "Alzheimer's disease," "Mild cognitive impairment," "Cognitive impairment," and "Cognitive function." Only articles published in English were considered.

The inclusion criteria were as follows: (1) cohort study or case–control study; (2) animal experiments and functional mechanism studies; (3) the main oral factors studied were periodontitis, tooth loss, oral flora, and oral dysfunction; (4) the article is in English.

In total, 1,211 articles were retrieved, and 659 articles remained after removing duplicates. The titles and abstracts were screened, and 170 articles remained after 489 articles that did not meet the title, and abstract criteria were excluded. Finally, another 124 articles were further excluded, and the final 46 articles were included in this review. Figure 1 shows a flowchart of the research article selection process.

3. Periodontitis and cognitive dysfunction

Periodontitis is a common dental disease that causes chronic inflammation of periodontal tissues through oral bacteria activity, which eventually leads to tissue destruction and tooth loss. Besides common dental inflammation, periodontitis can also induce chronic systemic inflammation leading to a serum proinflammatory response affecting neurological function and increasing the risk of cognitive impairment (7, 8). This manifests in the body as an increase in C-reactive protein and pro-inflammatory cytokine α in the blood and a decrease in anti-inflammatory markers (interleukin-10) (9). When the body is in a pro-inflammatory state for a long time, it can cause the expression of tight junctions that maintain the integrity of the blood–brain barrier to be reduced or misallocated, resulting in the interruption of the blood–brain barrier. At the same time, inflammatory factors have toxic effects on endothelial cells, leading to cell apoptosis and increasing the blood–brain barrier permeability. The presence of inflammatory factors can also increase blood–brain barrier permeability by activating microglia or stimulating astrocytes to secrete vascular endothelial growth factor-A (10). Due to the blood–brain barrier increased permeability and loss of complete protective function, inflammatory factors or endotoxins can penetrate the nervous system and eventually have an impact on brain function (11).

In a cross-sectional study of periodontitis and cognitive dysfunction published in 2008, Yu et al. found that periodontitis was more common in participants with low cognitive function scores (12). In recent years, some studies have also found that periodontitis is related to early cognitive dysfunction and AD. People with cognitive dysfunction have worse oral health and a higher incidence of periodontal diseases, such as sparse root tips, deepening periodontal pockets, and dental caries (13). In addition, several epidemiological studies have also shown a significant link between periodontitis and cognitive dysfunction. Noble et al. determined associations with cognitive function by measuring serum markers of periodontitis (14). They showed that individuals with higher *Porphyromonas gingivalis* immunoglobulin G levels had a higher rate of impaired performance in verbal memory and subdivision tests. This association persisted even after adjusting for confounding factors, such as social population and underlying diseases. In a Danish study, Kamer et al. used the digit symbol and block design tests to assess participants' cognitive function (15). Compared with participants without periodontitis, those with periodontitis had significantly lower digit symbol test scores ($p = 0.02$). A Japanese study analyzed the correlation between periodontal disease and cognitive impairment in an Asian population, and the European Consensus criteria for the periodontal disease were used to determine periodontal conditions and the Mini-Mental State Examination (MMSE) and Hasegawa Dementia Scale-Revised criteria were used to determine cognitive outcome variables (16). Periodontitis and cognitive score were still significantly correlated after adjusting for all co-variables. The former score was 2.21 (1.01–4.84, $p < 0.05$), and the latter score was 4.85 (1.29–18.15, $p < 0.05$). In a prospective cohort study of over 6,000 participants, Lee et al. found that periodontitis patients had a significantly higher risk of developing dementia than healthy controls. The risk increased after adjusting for sociodemographic characteristics (OR = 1.16, 95% CI = 1.01–1.32) (17). Chen et al. conducted a large retrospective cohort study including 27,963 people >50 years to determine the relationship between periodontitis and AD (18). Patients who had periodontitis for more than 10 years had more than a 1.7-fold risk of developing AD, which showed that long-term exposure to periodontitis has a significant effect on brain cognitive function. A large cross-sectional study by Sung et al. used Neurobehavioral Evaluation System 2 to judge cognitive function in participants and showed that severe periodontitis led to worse cognitive status, and the correlation remained significant after adjusting for confounding factors (19). Iwasaki et al. followed 179 participants for 5 years using two different definitions from the Periodontology Group and the American Academy of Periodontology to assess periodontitis severity (20). In this study, periodontitis severity was associated with cognitive impairment regardless of the standard definition.

In summary, studies have shown a correlation between periodontitis and cognitive dysfunction; to a certain extent, periodontitis is also a risk factor for cognitive impairment. However,

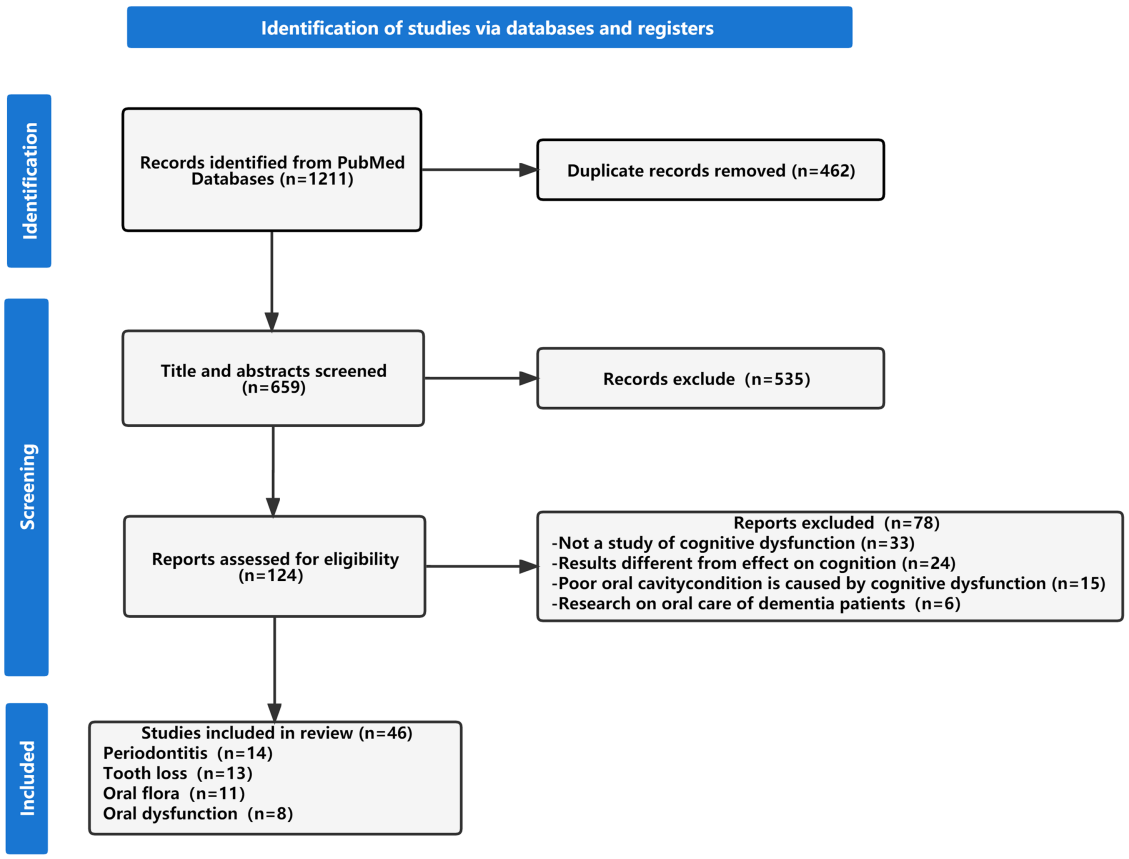


FIGURE 1
Flow chart of the literature search and study selection process.

most of the above studies were cross-sectional, so the causal relationship is difficult to explain. Although some were cohort studies, the cognitive judgment and diagnostic criteria for periodontitis may vary among them, which will inevitably lead to different results. In addition, the onset of dementia involves multiple mechanisms, and few studies have taken into account important confounding factors, such as family history, the susceptibility gene apolipoprotein E, nutrition level, and education level. In addition, periodontitis severity may also have different effects on cognition, but only one study considered the relationship between periodontitis severity and cognition (20). Therefore, this association requires further study. At present, there are few cohort studies in the field of periodontitis, and further large-population studies with the same diagnostic criteria are needed to clarify the mechanism of action linking periodontitis and cognitive dysfunction.

4. Tooth loss and cognitive dysfunction

Tooth loss is a common oral disease that is more common in the elderly population and is associated with age, smoking, economic status, poor diet, and various oral pathological factors (21). Evidence shows that tooth loss is related to oral health and cognitive function. A lack of nutrients, such as B vitamins, may have an impact on cognition due to changes in eating habits caused by missing teeth (22, 23). Animal experiments have confirmed that prolonged molar deprivation can reduce the expression levels of brain-derived neurotrophic factor (BDNF), which is related to hippocampal learning and memory. Decreased BDNF expression is also present in patients with AD, and the number of hippocampal vertebral cells is decreased, leading to cognitive dysfunction (24, 25). In imaging studies, patients with tooth loss showed significant gray matter shrinkage in brain areas responsible for memory and cognition, such as the hippocampus, caudate nucleus, and temporal pole (26). In addition, tooth loss was associated with decreased total gray matter volume in the brain (27), suggesting that tooth loss increases the risk of shrinking brain regions associated with memory, learning, and cognition.

A prospective study including 597 older American men showed that each tooth lost per decade increased the risk of MMSE score reduction by 9–12% over 32 years of follow-up (28). In a 5-year follow-up study of 11,140 patients with type 2 diabetes, Batty et al. found that participants with no teeth had a significantly higher risk of dementia and cognitive decline than those with 1–22 or more teeth (29). In a cross-sectional study of 3,063 participants, patients with dementia averaged 18.7 missing teeth, compared with 11.8 and 9.3 for patients with MCI and normal cognition, respectively, and >16 lost teeth were significantly associated with dementia (OR: 1.5, 95% CI: 1.12–2.18), indicating that tooth number is associated with cognitive function (30). In a longitudinal cohort study of aging in the

United Kingdom, participant memory was assessed using the number of words they could recall. Patients without teeth had worse memory, recalling 0.88 fewer words than patients with teeth, as well as worse motor ability (31). The association between memory and motor ability differed significantly by age, and it was more significant in the elderly aged 60–74 years. A 13-year longitudinal study in China conducted by Li et al. found that cognitive function gradually declined with time but retained a significant correlation with the number of teeth (32). Evidently, the MMSE score decreased by 0.01 points for each missing tooth, and the number of teeth significantly correlated with the time passage. This suggests that older adults with more teeth have a better cognitive function and a slower rate of cognitive decline. A 5-year Japanese cohort study analyzed the relationship between the number of remaining teeth and all-cause dementia, AD, and vascular dementia (33). The study showed a significant association between all-cause dementia and tooth number, which was preserved after model adjustment. The number of remaining teeth was negatively associated with the risk of AD, but this association was not statistically significant after model adjustment. A prospective cohort study also partially confirmed the association between tooth loss and higher risk of dementia. In a cross-sectional study, Kato et al. (34) evaluated cognitive diagnosis in elderly Japanese communities and showed that MMSE scores decreased along with the number of teeth. In addition, participants with >20 total teeth (including natural teeth and dentures) had significantly higher MMSE scores than those with <19 total teeth, suggesting that denture use may exert a protective effect on cognitive function.

In conclusion, the above studies show a significant association between tooth loss and cognitive dysfunction, which has been verified in longitudinal studies in Asian, European, and American populations. Two cross-sectional studies found similar results, where tooth loss indicated poorer cognitive function. Some studies use MMSE as a diagnostic assessment tool for cognition; however, considering its limitations, it can be combined with better diagnostic criteria to obtain more accurate results. In addition, cognitive diagnostic criteria are worth considering, as the diagnosis workload will inevitably increase due to the large number of patients involved and the time-consuming nature of longitudinal cohort studies. Moreover, different studies have used different criteria to count the number of teeth. In their study, Li et al. used the number of self-reported teeth as the standard, and subsequent data cleaning and examination were carried out, which inevitably increased the workload and greatly reduced data reliability (32). Cohort studies by Batty et al. (29) and Takeuchi et al. (33) counted "complete/partial attachment to the gums as a tooth" and "healthy, treated or repaired teeth," respectively, but the mechanism by which teeth affect cognitive function puts more emphasis on chewing. Therefore, it is worth studying the criterion of "complete, healthy, functional teeth after treatment or repair." In addition, the effect of dentures on cognitive function has rarely been mentioned in cohort studies, and their long-term protective effect still requires further demonstration in large, high-quality epidemiological studies.

5. Oral flora and cognitive dysfunction

Oral cavity is a gathering place for many microorganisms, whose balance is essential for maintaining overall health. Oral microbial imbalance is the main cause of various oral diseases and an important risk factor for cardiovascular, digestive, and nervous system diseases (5). Some studies have found the presence of *Porphyromonas gingivalis* and *Treponema* in brain tissue, trigeminal ganglion, and cortex samples of patients with AD (35, 36). Therefore, oral bacteria appear to be involved in the development of cognitive dysfunction. Human immunity and saliva are crucial for maintaining oral health and regulating the balance of oral flora. However, with age increase, saliva secretion decreases, and immune function weakens, reducing the body's ability to inhibit oral flora overgrowth and non-oral species invasion (37, 38), eventually leading to a pro-inflammatory response and weakening the protective effect of the blood–brain barrier. The spread of bacteria to the brain impacts brain function. In addition, oral bacteria can produce toxins such as lipopolysaccharides, arg-gingipain, and lys-gingipain, which damage the tau protein, which is responsible for neuronal function (39). Oral bacteria can also cross the blood–brain barrier and cause transient encephalitis, which leads to short-term memory impairment. Meanwhile, the persistent infection produces lasting cognitive damage in the brain (40).

Liu et al. used 16S rRNA sequencing to analyze the differences between the saliva microflora of patients with AD and healthy people (41). The variety and richness of saliva microflora from patients with AD were significantly lower than those of healthy controls, and the abundance of *Moraxella*, *Leptotrichia micronomyces*, and *Sphaerochaeta* in patients with AD increased, while *Rhodotella* abundance decreased. In addition, salivary flora diversity decreased in patients with AD, the bacterial community was disturbed, and it invaded the brain to affect neurological function. Yang et al. collected oral samples from 68 patients with MCI and a control group, analyzed the characteristics of oral microorganisms and explored their association with MCI inflammation markers (42). There was no difference in alpha- and beta-diversity between the two groups and no change in oral microflora. Several inflammatory factors related to cognitive function, such as matrix metallopeptidase 10 and chemokines in the cerebrospinal fluid of the MCI group, were different from those of the control group, and there was a correlation between the oral microbiome and inflammation. Wu et al. (43) analyzed the bacteria in the dental plaque of patients with AD and a control group and used alpha diversity to assess the difference between groups. Oral microflora diversity in the AD group was lower than that in the control group, and the number of *Lactobacillus*, *Streptococcus*, and *Bacteroides* increased significantly in patients with AD, while the number of *Clostridium* decreased significantly. Holmer et al. collected 95 subgingival specimens to identify oral microflora in three case groups (AD, MCI, and subjective cognitive dysfunction). The microbial alpha diversity of subjective cognitive dysfunction was significantly higher than that of the control group, and the microflora of the MCI group was particularly rich and diverse. Compared with non-dementia patients, the oral microbiota showed consistent changes and was significantly associated with periodontal disease in three case groups (44). A Canadian case–control study with 90 participants collected oral specimens from the salivary glands on both sides of the mouth and under the tongue, also using 16S microbial sequencing technology (45). Contrary to Wu et al. (43), this study showed higher alpha diversity of oral microorganisms and decreased *Streptococcus* and *Actinomyces* abundance in patients with AD, compared with controls.

In conclusion, although studies have shown no significant difference in oral flora between patients with MCI and healthy participants, oral microbes are associated with inflammatory factors (42), and the MCI group showed a high degree of diversity in a subsequent study (44). MCI is the early stage of dementia, whose development can be effectively controlled by detecting risk factors and adopting countermeasures. At present, there are few research studies in this field, and more large-cohort studies are needed to verify the current results. Moreover, four studies have analyzed the oral microbiota of patients with AD, two of which showed reduced diversity. Two of the low-diversity studies included Chinese people (Asian), and the other two included Swedes and Canadians (Caucasian), so it is worth exploring the impact of race or dietary differences. Moreover, confounding factors, such as daily habits, socioeconomic conditions, and drug use, were not taken into account in the study. Oral specimens were also collected from different sites in different studies, and the number of participants was small, which may also impact the results. For pathogenic bacteria, the distance from the mouth to the brain is shorter than that from other organs. Studies have shown that oral bacteria can penetrate the blood–brain barrier and affect brain neurological functions by causing neuroinflammation through soluble surface proteins or the production of lipopolysaccharides, exotoxins, and other substances (39, 46). Therefore, an in-depth exploration of the relationship between oral microbes and cognitive dysfunction may provide a feasible method to reduce the risk of cognitive dysfunction.

6. Oral and cognitive dysfunction

Commonly, oral dysfunction includes decreased chewing ability, decreased tongue motor ability, decreased tongue pressure, subjective eating, and swallowing difficulties (47). These problems can be summarized as "oral fragility," a term introduced by Japan's Ministry of Health, Labor, and Welfare in 2013 to emphasize the role of oral function in overall health. Evidence suggests that oral fragility significantly increases the risk of frailty, sarcopenia, disability, and death in older adults and is associated with cognitive impairment (4, 48).

Some studies have found that chewing can increase blood perfusion and stimulate neural activity in the brain (4), exerting a positive impact on memory and improving cognitive ability (49). On the contrary, declining chewing function may negatively impact brain function and cause cognitive dysfunction (50). In a cross-sectional study of 502 participants, Cardoso et al. determined the number of functional masticatory units in participants through visual examination and analyzed its association with cognitive function (51). A positive correlation was seen between the number of functional masticatory units and the Mini Cognitive Examination score, as more chewing units indicated better cognitive function. Han et al. achieved similar results in a longitudinal cohort study involving 411 participants (52), where more functional teeth and occlusal units indicated a lower probability of cognitive decline. These two studies provide strong epidemiological evidence for an association between chewing function and cognitive dysfunction.

A cross-sectional study on oral and cognitive function involving 1,118 people in Japan revealed that tongue pressure and oral diadochokinesis were significantly associated with MMSE scores after adjusting for relevant factors (53). Moreover, pathway analysis showed that tongue pressure was related to decreasing MMSE scores, and it affected cognitive function through oral diadochokinesis. Egashira et al. used the Japanese version of the Montreal Cognitive Assessment Form to assess cognitive status in a 50-person dental outpatient cross-sectional study, showing that tongue pressure and tooth count were significantly lower in the cognitively declining group than in the healthy group (54). A cross-sectional study by Suzuki et al. showed that the maximum bite force of patients with cognitive dysfunction was significantly reduced, and a high proportion of patients had tongue and lip dysfunction (55). After adjusting for gender and age, bite force was still correlated with cognitive function.

The above research shows that traditional oral diseases, such as periodontitis and tooth loss, are associated with cognitive dysfunction, as is oral dysfunction. Epidemiological studies have shown an association between reduced chewing function and cognitive impairment, but the accuracy of their results is questionable, given that assessments were based on direct oral examination, and they did not take into account socioeconomic levels, malnutrition caused by mastication, and other factors associated with cognitive impairment. The cross-sectional design used in studies of bite force, tongue pressure, oral coherent movement, and cognitive function could not establish causality and included a small number of participants. In all studies, scales were used to judge cognitive function. However, in an ideal situation, neuropsychological tests and imaging results should be used to diagnose cognition in each participant. Therefore, more longitudinal cohort studies in large populations are required to further clarify the correlation and causal relationship between oral function and cognitive dysfunction. Oral cavity is an important organ of the human body. Exploring the functional relationship between the oral cavity and brain organs may produce a new understanding of brain cognitive function. At present, most of the studies on oral function have been conducted in Asian populations. To further understand the relationship between oral function and cognitive function, besides longitudinal studies in large populations, different regions should be discussed to obtain more convincing results.

7. Conclusion

This review focused mainly on the relationship between periodontitis, tooth loss, oral flora, oral dysfunction, and cognitive dysfunction, and its results showed that adverse oral conditions would greatly impact patient cognitive function (Figure 2). Most studies on periodontitis and tooth loss used different judgment criteria for oral and cognitive status, and the included confounding factors were not comprehensive. Oral flora has a great impact on cognitive function, but the results of changes in oral flora in patients with cognitive impairment are conflicting. At present, there are few studies on oral dysfunction and cognition in which the study population is relatively concentrated and oral function is diverse. Longitudinal studies with large populations can better clarify the association. Moreover, most of the existing studies have analyzed a single adverse oral condition, so it was necessary to try to analyze the association between multiple adverse oral factors and cognition in the same population, which helps

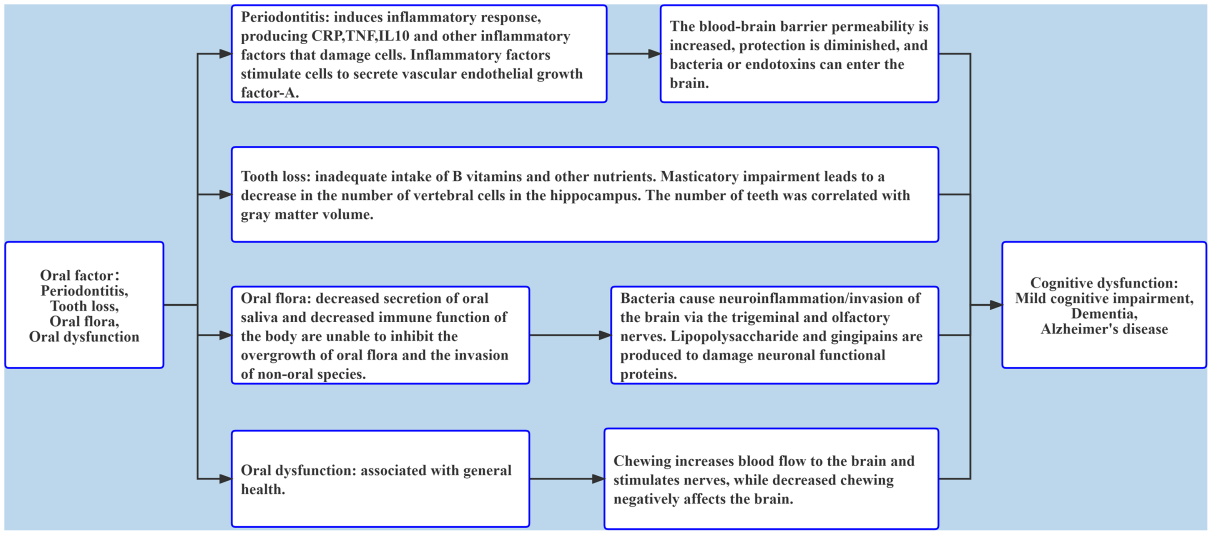


FIGURE 2
The role of oral factors including periodontitis, tooth loss, oral flora, and oral dysfunction in cognitive dysfunction.

find the association and take timely measures. To a large extent, poor oral health can be improved or treated with current medical technology. Therefore, it is of great significance to comprehensively explore the association between oral health status and cognitive dysfunction for the prevention or early detection of risk factors for cognitive dysfunction. However, one limitation of this review was that different studies included no uniform definition for cognitive dysfunction and oral conditions, as well as many influencing factors. Therefore, the final research results should be observed with caution. In future studies, unified standards should be adopted, research methods should be carefully designed, more rigorous tests should be conducted, and longitudinal cohort studies of large populations should be adopted more frequently to ensure representative results. Current medical technology can improve or treat adverse oral conditions to a large extent. Therefore, the relationship between oral problems and cognitive dysfunction is certainly invaluable to preventing and facilitating early detection of oral risk factors related to cognitive dysfunction.

Author contributions

YD, WX, and KL contributed to the conception and design of the study. TW, TH, and YL organized the database. TW, WX, CZ, and KL wrote the manuscript. All authors contributed to the manuscript revision and read and approved the submitted version.

Funding

This work was supported by grants from the Clinical Medicine Technology Innovation Program (grant no. 202019080), the Natural Science Foundation of Shandong Province (grant no. ZR2022QH106), the National Natural Science Foundation of China (grant nos. 81861138008 and 81772448, 82011530139, and 82171175), the National Key R&D Program of China Ministry of Sciences and Technology (grant nos. 2017YFC1310100 and 2022YFC3501404), the Academic Promotion Program of Shandong First Medical University (grant no. 2019QL020), the Integrated Traditional Chinese and Western Medicine Program in Shandong Province (grant no. YXH2019ZXY008), and the Brain Science and Brain-Like Intelligence Technology Research Projects of China (grant nos. 2021ZD0201801 and 2021ZD0201808), and Shandong Provincial Key Research and Development Program (grant no. 2021LCZX03). The funding agencies had no role in the study design, data collection and analysis, the writing of this article, and in the decision to submit the work for publication.

Acknowledgments

We would like to thank all team members of the Multimodal Interventions to Delay Dementia and Disability in Rural China (MIND-CHINA) Project.

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

References

1. Wang Y, Du Y, Li J, Qiu C. Lifespan intellectual factors, genetic susceptibility, and cognitive phenotypes in aging: Implications for interventions. *Front Aging Neurosci*. (2019) 11:129. doi: 10.3389/fnagi.2019.00129

2. World Health Organization. *Risk reduction of cognitive decline and dementia: WHO guidelines*. Geneva: WHO (2019).

3. Ming Y, Hsu SW, Yen YY, Lan SJ. Association of oral health-related quality of life and Alzheimer disease: A systematic review. *J Prosthet Dent*. (2020) 124:168–75. doi: 10.1016/j.prosdent.2019.08.015

4. Nakamura T, Zou K, Shibuya Y, Michikawa M. Oral dysfunctions and cognitive impairment/dementia. *J Neurosci Res*. (2021) 99:518–28. doi: 10.1002/jnr.24745

5. Gao L, Xu T, Huang G, Jiang S, Gu Y, Chen F. Oral microbiomes: More and more importance in oral cavity and whole body. *Protein Cell*. (2018) 9:488–500. doi: 10.1007/s13238-018-0548-1

6. Daly B, Thompsell A, Sharpling J, Rooney YM, Hillman L, Wanyonyi KL, et al. Evidence summary: The relationship between oral health and dementia. *Br Dent J*. (2017) 223:846–53. doi: 10.1038/sj.bdj.2017.992

7. Nascimento PC, Castro MML, Magno MB, Almeida A, Fagundes NCF, Maia LC, et al. Association between periodontitis and cognitive impairment in adults: A systematic review. *Front Neurol*. (2019) 10:323. doi: 10.3389/fneur.2019.00323

8. Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. *J Clin Periodontol*. (2008) 35:277–90. doi: 10.1111/j.1600-051X.2007.01173.x

9. Ide M, Harris M, Stevens A, Sussams R, Hopkins V, Culliford D, et al. Periodontitis and cognitive decline in Alzheimer's disease. *PLoS One*. (2016) 11:e0151081. doi: 10.1371/journal.pone.0151081

10. Huang X, Hussain B, Chang J. Peripheral inflammation and blood-brain barrier disruption: Effects and mechanisms. *CNS Neurosci Ther*. (2021) 27:36–47. doi: 10.1111/cns.13569

11. Shoemark DK, Allen SJ. The microbiome and disease: Reviewing the links between the oral microbiome, aging, and Alzheimer's disease. *J Alzheimers Dis*. (2015) 43:725–38. doi: 10.3233/jad-141170

12. Yu YH, Kuo HK. Association between cognitive function and periodontal disease in older adults. *J Am Geriatr Soc*. (2008) 56:1693–7. doi: 10.1111/j.1532-5415.2008.01847.x

13. Holmer J, Eriksdotter M, Schultzberg M, Pussinen PJ, Buhlin K. Association between periodontitis and risk of Alzheimer's disease, mild cognitive impairment and subjective cognitive decline: A case-control study. *J Clin Periodontol*. (2018) 45:1287–98. doi: 10.1111/jcpe.13016

14. Noble JM, Borrell LN, Papapanou PN, Elkind MS, Scarmeas N, Wright CB. Periodontitis is associated with cognitive impairment among older adults: Analysis of NHANES-III. *J Neurol Neurosurg Psychiatry*. (2009) 80:1206–11. doi: 10.1136/jnnp.2009.174029

15. Kamer AR, Morse DE, Holm-Pedersen P, Mortensen EL, Avlund K. Periodontal inflammation in relation to cognitive function in an older adult Danish population. *J Alzheimers Dis*. (2012) 28:613–24. doi: 10.3233/jad-2011-102004

16. Iwasaki M, Kimura Y, Yoshihara A, Ogawa H, Yamaga T, Sato M, et al. Oral health status in relation to cognitive function among older Japanese. *Clin Exp Dent Res*. (2015) 1:3–9. doi: 10.1002/cre2.2

17. Lee YT, Lee HC, Hu CJ, Huang LK, Chao SP, Lin CP, et al. Periodontitis as a modifiable risk factor for dementia: A nationwide population-based cohort study. *J Am Geriatr Soc*. (2017) 65:301–5. doi: 10.1111/jgs.14449

18. Chen CK, Wu YT, Chang YC. Association between chronic periodontitis and the risk of Alzheimer's disease: A retrospective, population-based, matched-cohort study. *Alzheimers Res Ther*. (2017) 9:56. doi: 10.1186/s13195-017-0282-6

19. Sung CE, Huang RY, Cheng WC, Kao TW, Chen WL. Association between periodontitis and cognitive impairment: Analysis of national health and nutrition examination survey (NHANES) III. *J Clin Periodontol*. (2019) 46:790–8. doi: 10.1111/jcpe.13155

20. Iwasaki M, Kimura Y, Ogawa H, Yamaga T, Ansai T, Wada T, et al. Periodontitis, periodontal inflammation, and mild cognitive impairment: A 5-year cohort study. *J Periodontal Res*. (2019) 54:233–40. doi: 10.1111/jre.12623

21. Kawahara H, Inoue M, Okura K, Oshima M, Matsuka Y. Risk factors for tooth loss in patients with ≥25 remaining teeth undergoing mid-long-term maintenance: A retrospective study. *Int J Environ Res Public Health*. (2021) 18:7174. doi: 10.3390/ijerph18137174

22. Selhub J, Bagley LC, Miller J, Rosenberg IH. B vitamins, homocysteine, and neurocognitive function in the elderly. *Am J Clin Nutr*. (2000) 71:614s–20s. doi: 10.1093/ajcn/71.2.614.

23. Tucker KL, Qiao N, Scott T, Rosenberg I, Spiro A 3rd. High homocysteine and low B vitamins predict cognitive decline in aging men: The veterans affairs normative aging study. *Am J Clin Nutr*. (2005) 82:627–35. doi: 10.1093/ajcn.82.3.627

24. Takeda Y, Oue H, Okada S, Kawano A, Koretake K, Michikawa M, et al. Molar loss and powder diet leads to memory deficit and modifies the mRNA expression of brain-derived Neurotrophic factor in the hippocampus of adult mice. *BMC Neurosci*. (2016) 17:81. doi: 10.1186/s12868-016-0319-y

25. Oue H, Miyamoto Y, Okada S, Koretake K, Jung CG, Michikawa M, et al. Tooth loss induces memory impairment and neuronal cell loss in app transgenic mice. *Behav Brain Res*. (2013) 252:318–25. doi: 10.1016/j.bbr.2013.06.015

26. Kobayashi T, Kubota M, Takahashi T, Nakasato A, Nomura T, Furuya J, et al. Effects of tooth loss on brain structure: A voxel-based morphometry study. *J Prosthodont Res*. (2018) 62:337–41. doi: 10.1016/j.jpor.2017.12.007

27. Dintica CS, Rizzuto D, Marseglia A, Kalpouzos G, Welmer AK, Wårdh I, et al. Tooth loss is associated with accelerated cognitive decline and volumetric brain differences: A population-based study. *Neurobiol Aging*. (2018) 67:23–30. doi: 10.1016/j.neurobiolaging.2018.03.003

28. Kaye EK, Valencia A, Baba N, Spiro A 3rd, Dietrich T, Garcia RI. Tooth loss and periodontal disease predict poor cognitive function in older men. *J Am Geriatr Soc*. (2010) 58:713–8. doi: 10.1111/j.1532-5415.2010.02788.x

29. Batty GD, Li Q, Huxley R, Zoungas S, Taylor BA, Neal B, et al. Oral disease in relation to future risk of dementia and cognitive decline: Prospective cohort study based on the action in diabetes and vascular disease: Preterax and diamicron modified-release controlled evaluation (advance) trial. *Eur Psychiatry*. (2013) 28:49–52. doi: 10.1016/j.eurpsy.2011.07.005

30. Luo J, Wu B, Zhao Q, Guo Q, Meng H, Yu L, et al. Association between tooth loss and cognitive function among 3063 Chinese older adults: A community-based study. *PLoS One*. (2015) 10:e0120986. doi: 10.1371/journal.pone.0120986

31. Tsakos G, Watt RG, Rouxel PL, de Oliveira C, Demakakos P. Tooth loss associated with physical and cognitive decline in older adults. *J Am Geriatr Soc*. (2015) 63:91–9. doi: 10.1111/jgs.13190

32. Li J, Xu H, Pan W, Wu B. Association between tooth loss and cognitive decline: A 13-year longitudinal study of Chinese older adults. *PLoS One*. (2017) 12:e0171404. doi: 10.1371/journal.pone.0171404

33. Takeuchi K, Ohara T, Furuta M, Takeshita T, Shibata Y, Hata J, et al. Tooth loss and risk of dementia in the community: The Hisayama study. *J Am Geriatr Soc*. (2017) 65:e95–e100. doi: 10.1111/jgs.14791

34. Kato H, Takahashi Y, Iseki C, Igari R, Sato H, Sato H, et al. Tooth loss-associated cognitive impairment in the elderly: A community-based study in Japan. *Intern Med*. (2019) 58:1411–6. doi: 10.2169/internalmedicine.1896-18

35. Poole S, Singhrao SK, Kesavalu L, Curtis MA, Crean S. Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. *J Alzheimers Dis*. (2013) 36:665–77. doi: 10.3233/jad-121918

36. Riviere GR, Riviere KH, Smith KS. Molecular and immunological evidence of oral *Treponema* in the human brain and their association with Alzheimer's disease. *Oral Microbiol Immunol*. (2002) 17:113–8. doi: 10.1046/j.0902-0055.2001.00100.x

37. Sureda A, Daglia M, Argüelles Castilla S, Sanadgol N, Fazel Nabavi S, Khan H, et al. Oral microbiota and Alzheimer's disease: Do all roads lead to Rome? *Pharmacol Res*. (2020) 151:104582. doi: 10.1016/j.phrs.2019.104582

38. Orr ME, Reveles KR, Yeh CK, Young EH, Han X. Can oral health and oral-derived biospecimens predict progression of dementia? *Oral Dis*. (2020) 26:249–58. doi: 10.1111/odi.13201

39. Costa MJF, de Araújo IDT, da Rocha Alves L, da Silva RL, dos Santos Calderon P, Borges BCD, et al. Relationship of *Porphyromonas gingivalis* and Alzheimer's disease: A systematic review of pre-clinical studies. *Clin Oral Investig*. (2021) 25:797–806. doi: 10.1007/s00784-020-03764-w

40. Wu Y, du S, Johnson JL, Tung HY, Landers CT, Liu Y, et al. Microglia and amyloid precursor protein coordinate control of transient Candida cerebritis with memory deficits. *Nat Commun*. (2019) 10:58. doi: 10.1038/s41467-018-07991-4

41. Liu XX, Jiao B, Liao XX, Guo LN, Yuan ZH, Wang X, et al. Analysis of salivary microbiome in patients with Alzheimer's disease. *J Alzheimers Dis*. (2019) 72:633–40. doi: 10.3233/jad-190587

42. Yang I, Arthur RA, Zhao L, Clark J, Hu Y, Corwin EJ, et al. The oral microbiome and inflammation in mild cognitive impairment. *Exp Gerontol*. (2021) 147:111273. doi: 10.1016/j.exger.2021.111273

43. Wu YF, Lee WF, Salamanca E, Yao WL, Su JN, Wang SY, et al. Oral microbiota changes in elderly patients, an indicator of Alzheimer's disease. *Int J Environ Res Public Health*. (2021) 18:4211. doi: 10.3390/ijerph18084211

44. Holmer J, Aho V, Eriksdotter M, Paulin L, Pietiäinen M, Auvinen P, et al. Subgingival microbiota in a population with and without cognitive dysfunction. *J Oral Microbiol*. (2021) 13:1854552. doi: 10.1080/20002297.2020.1854552

45. Cirstea MS, Kliger D, MacLellan AD, Yu AC, Langlois J, Fan M, et al. The oral and fecal microbiota in a Canadian cohort of Alzheimer's disease. *J Alzheimers Dis*. (2022) 87:247–58. doi: 10.3233/jad-215520

46. Wang XL, Zeng J, Yang Y, Xiong Y, Zhang ZH, Qiu M, et al. Helicobacter pylori filtrate induces Alzheimer-like tau hyperphosphorylation by activating glycogen synthase kinase-3β. *J Alzheimers Dis*. (2014) 43:153–65. doi: 10.3233/jad-140198

47. Izumi M, Akifusa S. Tongue cleaning in the elderly and its role in the respiratory and swallowing functions: Benefits and medical perspectives. *J Oral Rehabil*. (2021) 48:1395–403. doi: 10.1111/joor.13266

48. Tanaka T, Takahashi K, Hirano H, Kikutani T, Watanabe Y, Ohara Y, et al. Oral frailty as a risk factor for physical frailty and mortality in community-dwelling elderly. *J Gerontol A Biol Sci Med Sci*. (2018) 73:1661–7. doi: 10.1093/gerona/glx225

49. Hirano Y, Obata T, Kashikura K, Nonaka H, Tachibana A, Ikehira H, et al. Effects of chewing in working memory processing. *Neurosci Lett*. (2008) 436:189–92. doi: 10.1016/j.neulet.2008.03.033

50. Tada A, Miura H. Association between mastication and cognitive status: A systematic review. *Arch Gerontol Geriatr*. (2017) 70:44–53. doi: 10.1016/j.archger.2016.12.006

51. Cardoso MG, Diniz-Freitas M, Vázquez P, Cerqueiro S, Diz P, Limeres J. Relationship between functional masticatory units and cognitive impairment in elderly persons. *J Oral Rehabil*. (2019) 46:417–23. doi: 10.1111/joor.12763

52. Han JH, Lee HJ, Han JW, Suh SW, Lee JR, Byun S, et al. Loss of functional dentition is associated with cognitive impairment. *J Alzheimers Dis*. (2020) 73:1313–20. doi: 10.3233/jad-190971

53. Kugimiya Y, Ueda T, Watanabe Y, Takano T, Edahiro A, Awata S, et al. Relationship between mild cognitive decline and oral motor functions in metropolitan community-dwelling older Japanese: The Takashimadaira study. *Arch Gerontol Geriatr*. (2019) 81:53–8. doi: 10.1016/j.archger.2018.11.008

54. Egashira R, Mizutani S, Yamaguchi M, Kato T, Umezaki Y, Oku S, et al. Low tongue strength and the number of teeth present are associated with cognitive decline in older Japanese dental outpatients: A cross-sectional study. *Int J Environ Res Public Health*. (2020) 17:8700. doi: 10.3390/ijerph17228700

55. Suzuki H, Furuya J, Hidaka R, Miyajima S, Matsubara C, Ohwada G, et al. Patients with mild cognitive impairment diagnosed at dementia clinic display decreased maximum occlusal force: A cross-sectional study. *BMC Oral Health*. (2021) 21:665. doi: 10.1186/s12903-021-02027-8

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 03 May 2023
DOI 10.3389/fpubh.2023.1165753

OPEN ACCESS

EDITED BY
Junhong Zhou,
Harvard Medical School, United States

REVIEWED BY
Jingying Wang,
University of Florida, United States
Fan Chen,
University of Massachusetts Lowell, United States

*CORRESPONDENCE
Lianlian Wang
✉ llian_w@163.com
Xun Lei
✉ leixun521@cqmu.edu.cn

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

RECEIVED 14 February 2023
ACCEPTED 05 April 2023
PUBLISHED 03 May 2023

CITATION
Yang J, Zhang Y, Shen S, Yu H, Yang L, Zhao Y, Xiong Y, Su J, Wang L and Lei X (2023) Instrumental activities of daily living trajectories and risk of mild cognitive impairment among Chinese older adults: results of the Chinese longitudinal healthy longevity survey, 2002–2018.
Front. Public Health 11:1165753.
doi: 10.3389/fpubh.2023.1165753

Instrumental activities of daily living trajectories and risk of mild cognitive impairment among Chinese older adults: results of the Chinese longitudinal healthy longevity survey, 2002–2018

Jialu Yang[1,2,3†], Yangchang Zhang[1,2,3,4†], Shisi Shen[5], Han Yu[6], Luran Yang[5], Yao Zhao[7], Yang Xiong[8], Jiayi Su[9], Lianlian Wang[10,11*] and Xun Lei[1,2,3,4*]

[1]School of Public Health and Management, Chongqing Medical University, Chongqing, China, [2]Research Center for Medicine and Social Development, Chongqing Medical University, Chongqing, China, [3]The Innovation Center for Social Risk Governance in Health, Chongqing Medical University, Chongqing, China, [4]Research Center for Public Health Security, Chongqing Medical University, Chongqing, China, [5]The First School of Clinical Medicine, Chongqing Medical University, Chongqing, China, [6]The Second School of Clinical Medicine, Chongqing Medical University, Chongqing, China, [7]The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China, [8]The West China Hospital, Sichuan University, Chengdu, China, [9]The Jiang Jin Central Hospital of Chongqing, Chongqing, China, [10]Department of Reproductive Center, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [11]State Key Laboratory of Maternal and Fetal Medicine of Chongqing Municipality, Chongqing Medical University, Chongqing, China

Background: The association between the instrumental activities of daily living (IADL) score and the risk of initial cognitive function impairment is inconclusive. We aimed to identify distinctive IADL trajectories and examine their relationship with the onset of mild cognitive impairment (MCI) among Chinese older people.

Methods: The study used six-wave longitudinal data from the Chinese Longitudinal Healthy Longevity Survey conducted between 2002 and 2018. It included a total of 11,044 Chinese people aged 65years or older. A group-based trajectory model was used to identify distinctive trajectories of the IADL score, and the Cox proportional hazards model was used to explore the hazard ratio of various trajectories at the onset of MCI. Interaction analysis was used to analyze individual modification between the IADL trajectories and the onset of MCI. Finally, we adopted four types of sensitivity analysis to verify the robustness of the results.

Results: During a median follow-up of 16years, the incidence of MCI was 6.29 cases per 1,000 person-years (95% confidence interval [CI] 5.92–6.68). Three distinct IADL trajectory groups were identified: a low-risk IADL group (41.4%), an IADL group with increasing risk (28.5%), and a high-risk IADL group (30.4%). Using the Cox proportional hazards model after adjusting for covariates, we found that compared with the low risk IADL group, the hazard ratio of the IADL group with increasing risk was 4.49 (95% CI=3.82–5.28), whereas that of the high-risk IADL group was 2.52 (95% CI 2.08–3.05). Treating the IADL group with increasing risk as the reference, the hazard ratio for the high-risk IADL group was 0.56 (95% CI 0.48–0.66). Interaction analyses showed that age and residence were significant moderators (*P* for interaction <0.05).

Conclusion: A group-based trajectory model was developed to classify older people into three distinct trajectory groups of the IADL score. The IADL group

with increasing risk had a greater risk of MCI than the high-risk IADL group. In the IADL group with increasing risk, city residents of ≥80years were the most likely to develop MCI.

KEYWORDS

CLHLS, GBTM, IADL, MCI, Chinese older adults

1. Introduction

Mild cognitive impairment (MCI) is an intermediate state between normal aging and dementia, which mostly takes the form of Alzheimer's disease (1). According to a meta-analysis in China, the prevalence of MCI has reached 12.2% (95% confidence interval [CI] 10.6–14.2) in community residents aged over 55 years (2). To reduce the health burden and enhance the quality of life of older adults, the prevention of dementia is essential (3). Moreover, the onset of MCI is associated with a significant risk of cognitive impairment, which is exhibited by a decline in social activity (4).

Instrumental activities of daily living (IADL) are measured to assess the ability of older adults in independent living, social communication, and completing family tasks (5). If an older adult has lower functioning measured with IADL, it means that their capacity for social activity is seriously hampered (6). Studies on IADL have mainly focused on the prediction and assessment of chronic and critical diseases. The results of a longitudinal cohort study recently indicated that inclusion of IADL impairment in the MCI construct improves the prediction of future dementia (7). Several studies have reported that cognitive impairment and increased age are risk factors for IADL impairment in the social context of China (8–10).

Instrumental activities of daily living impairment and MCI development have been linked through ongoing research. Patients with MCI and dementia have impaired functioning measured with IADL to varying degrees. The functioning in the dementia group was greater impaired than in the MCI group, which is greater than the normal group ($p < 0.05$) (11). With an impairment in cognitive ability, the capacity for complicated social activities shows a dynamic decline, first displayed as a loss in instrumental ability and afterward as an impairment in instrumental activities with lower cognitive requirements (12). This trend has been reported to serve as a dynamic monitoring mechanism for assessing cognitive ability (7), thus providing a new method for predicting the diagnosis of dementia (13). Despite this, some disagreements have arisen in the actual application of the IADL tools, such as in the scoring method (14) and the threshold item division (15). The IADL of older people exhibit complex and varied patterns over time, which add complexity to the study of IADL trajectories.

A group-based trajectory model (GBTM) is an algorithm that can characterize dynamic changes in variables while simultaneously separating a group into multiple trajectory groups and constructing trajectory models within each group (16). In the current study, we used a GBTM to examine and identify relationships and changes within various latent trajectories of IADL.

There is currently a lack of a consistent methodology to accurately identify the risk of MCI. Therefore, we had two main aims in the current study involving longitudinal data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS; 2002–2018): first, to investigate the dynamic IADL trajectories of community-dwelling Chinese elders *via* GBTM, and second, to predict MCI by a Cox proportional hazards model.

2. Materials and methods

2.1. Study population

2.1.1. Study sample

This research used data from CLHLS. The project was jointly conducted by the Centre for Healthy Aging and Development Studies at Peking University and the Chinese Centre for Disease Control and Prevention. It explored the changes in lifestyle and health status of middle-aged and older people in the changing social environment. The collected information included sociodemographic characteristics, lifestyle, health status, psychological and cognitive status, living environment, and death data.

Eight waves of national surveys have now been conducted by the CLHLS (1998, 2000, 2002, 2005, 2008, 2011, 2014, and 2018). The CLHLS includes 21 provinces, accounting for about 85% of the population of the nation, which makes it the largest longitudinal study of the elderly in developing nations (10). Targeted random sampling is used to select participants in CLHLS. In each province, roughly half of the cities (counties) are chosen to serve as the primary investigative units. To balance the age and sex of older adults, CLHLS uses a multistage stratified random sampling method to follow one nonagenarian, one octogenarian, and three people aged between 65 and 79 years from the same street, village, or town in a primary sampling unit. CLHLS is regarded as a high-quality database because of its robust results of reliability/validity testing, little missing data, and its high response rate (17). Visit the following website to learn details about the CLHLS sampling plan: https://www.icpsr.umich.edu/web/NACDA/studies/36179.

2.1.2. Inclusion and exclusion criteria

For inclusion, participants had to be 65 years or older from the Chinese community, with normal baseline cognitive abilities (based on the clinical diagnosis of dementia) and without dementia or a Mini-Mental State Examination (MMSE) score of ≥24. All participants voluntarily signed the informed consent form in person. Exclusion criteria were a lack of baseline information on living capacity ($n = 29$) and an absence of baseline information on cognitive function measurement ($n = 2{,}606$).

Investigating the risk prediction of early cognitive impairment based on long-term IADL score changes was necessary for the overall research objective. Consequently, we chose a fixed cohort from 2002,

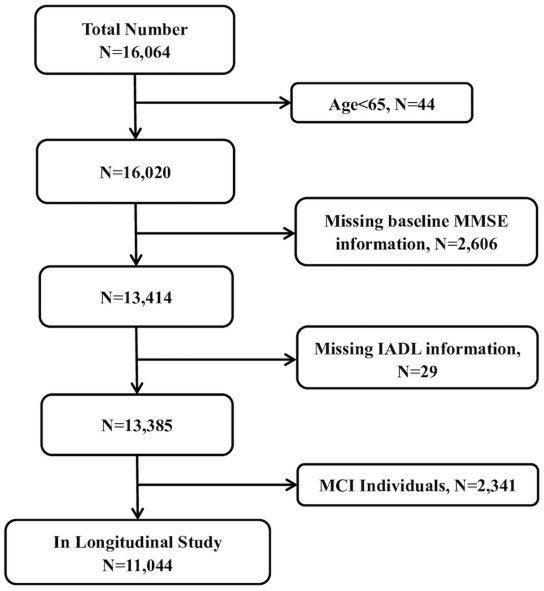


FIGURE 1
The flow chart of sample selection in the present study. MMSE, Mini Mental State Examination; IADL, instrumental activities of daily living; MCI, mild cognitive impairment.

with data available from six waves of investigations. The participants were 11,044 community-dwelling seniors aged 65 years and over (Figure 1).

2.2. Measurements

2.2.1. Instrumental activities of daily living

Instrumental activities of daily living was primarily included in this study's model as a significant independent variable, which measured the health status associated with the social ability of older people in Chinese communities. There are eight sub-items in the IADL, including the following questions: (1) Can you visit your neighbors by yourself? (2) Can you go shopping by yourself? (3) Can you cook a meal by yourself when necessary? (4) Can you wash clothes by yourself when necessary? (5) Can you walk a kilometer at a time by yourself? (6) Can you lift a weight of 5 kg, such as a heavy bag of groceries? (7) Can you continuously squat and stand up three times? (8) Can you take public transportation by yourself? In the CLHLS survey, a score of three negative answers indicates "yes, very limited," a score of two negative answers denotes "yes, slightly limited," and one negative answer signifies "not limited." According to an empirical study, if all the eight indicators of IADL are not limited, it indicates that the elderly individual is fully self-dependent. If one or more items shows that the individual cannot take care of themselves, it suggests that, in respect to IADL, they are disabled (18). The overall score in this study, which ranged from 8 to 24, served as a reference for the participant's level of IADL disability. The higher the score, the greater the participant's level of IADL disability (10).

Basic activities of daily living (ADL) reflect the ability of the respondents to live independently. Once ADL are impaired, it means that the patient needs long-term care from nursing staff or family members to ensure their basic living needs. A higher score indicates a greater degree of ADL disability, with an overall score ranging from 6 to 18 points.

2.2.2. Mini-mental state examination

Mini-Mental State Examination has been widely used to assess the cognitive state of older adults. It contains 11 questions related to time and place orientation, reaction, attention, numeracy, memory, and language (19). The participants were required to complete the MMSE questions in person as part of CLHLS to increase the validity of the assessment of cognitive function. A nurse and an investigator assessed the participants' fundamental cognitive abilities during the evaluation. The question was marked as "unable to answer" if the patient was unable to respond (a score of 0). Higher scores on the MMSE, which range from 0 to 30, indicate better cognitive function (20). As recommended by a geriatric epidemiological survey, MCI was classified by education using the MMSE scale and Petersen criteria (21, 22). For participants who had never received education, an MMSE score of 17 or less was considered as cognitive impairment; for those who had less than 6 years of education, an MMSE score of 20 or less was considered as cognitive impairment; and for those who had more than 6 years of education, an MMSE score of 24 or less was considered as cognitive impairment. For each level of education, scores above the threshold were considered cognitively normal. Beginning in 2002, MMSE was followed up every 2–3 years until MCI occurred or the follow-up period was over.

2.2.3. Covariates

This survey included the collection of sociodemographic and lifestyle factors using a structured questionnaire. The socioeconomic factors included years of schooling (illiterate, primary, and high school), residence (urban and rural), marital status (living without spouse and living with spouse), and income (recoded into tertiles as low, medium, and high). Physical exercise was also divided into three categories, depending on whether or not do it regularly: "never", "formal", "present". Classification variables were also used to describe smoking and drinking status: never, former, and present. Health variables, including physical indicators (age, weight, and chronic disease) and mental indicators (depression), were collected *via* self-reports and objective measurement. The weight of the respondents was measured in kilograms by having them stand on an electronic counting scale after removing their jackets or coats. Chronic diseases, such as hypertension, diabetes, heart disease, pneumonia, and pulmonary tuberculosis, were logged through self-reports. Depression levels were assessed by a series of questions: (1) "Do you always look on the bright side of things?," (2) "Do you often feel fearful or anxious?," (3) "Can you make your own decisions concerning your personal affairs?," (4) "Do you feel the older you get, the more useless you are?," and (5) "Are you as happy as when you were younger?." The overall scores ranged from 5 to 25 points, with higher scores indicating lower levels of depression.

2.3. Statistical analysis

Stata 16.0 (StataCorp LLC., College Station, TX, United States) was used for descriptive analysis and statistical inference. Continuous variables were described as mean ± standard deviation, whereas categorical variables were expressed as numbers and proportions (%).

We constructed GBTM to identify distinctive IADL trajectory groups and create profiles of the characteristics of these groups. In the analysis, we included all participants who had data on IADL scores collected during six waves from 2002 to 2018. The survey wave was used as a timescale for the trajectories. As a potential class growth model, GBTM was used to analyze longitudinal data and explore heterogeneity. Assuming that there are numerous potential subgroups with various developmental trajectories or patterns in the population, the goal of GBTM is to investigate how many subgroups with various developmental trends are present in the population and to identify the developmental trajectory of each subgroup (16). GBTM predicts the trajectory of each group, the shape of each trajectory, analyzes the individual's probability of belonging to a group, and places individuals in the group for which they have the highest probability. The first step in GBTM is to determine the number of trajectory groups to include in the model. The fitting effect of the model is reflected in the Bayesian information criterion (BIC) and Akaike information criterion. When the values reach a relative minimum, the best number of trajectory groups is finalized. In addition, the average posterior probability, which reflects the probability of group members belonging to the trajectory, ought to be higher than 0.70 for each group. Moreover, to identify the functional form of the model, each trajectory group is fitted starting from the high-order polynomial to the low-order. If the high-order parameters are not statistically significantly reflected in p values or the BIC of the model, the low-order parameters continue to be fitted.

A Cox proportional hazards model was used to investigate the hazard ratios (HRs) of the different trajectories at the onset of MCI, with 95% CIs. Model 1 was adjusted for age and sex; Model 2 was further adjusted for education level, income, marital status, and residence; Model 3 was further adjusted for smoking, alcohol consumption, physical activity, and social activity; and Model 4 was further adjusted for weight, depression, and chronic diseases. Possible modification effects were identified through an interaction effect analysis. The principle of the semiparametric Cox proportional hazards model was to use the product formula to obtain the risk probability related to the baseline risk. The model compensated for the limitations of the univariate Kaplan–Meier survival estimate, which is unable to examine continuous factors (23, 24).

Four distinct sensitivity studies were conducted to confirm the robustness of the results. The first excluded participants who died in the first wave of follow-up. The second excluded participants with baseline chronic diseases. The third involved a multiple interpolation method: a chained equation approach was used to specify the distribution of interpolation variables as the Gaussian normal distribution, while the continuous iterative interpolation method was used to interpolate the missing values. Five sets of data were interpolated, and the regression operation was performed. Finally, the regression coefficients and standard errors of the five sets of regression models were combined (25). In the fourth sensitivity study, a generalized linear mixed model was used. The IADL trajectories were taken as the key independent variable, the MMSE score was taken as the dependent variable, and the individual ID was coded as the second-level variable for model estimation. The hypotheses were tested at a two-sided significance level of $\alpha = 0.05$, and statistical significance was accepted when p-values were < 0.05 (two-sided).

3. Results

A total of 11,044 respondents (without MCI at baseline) were included in the group-based trajectory analysis (Table 1). During a median follow-up of 16 years, the incidence of MCI was 6.29 (95% CI 5.92–6.68). The average age of the participants was 82.8 ± 11.0 years, and 53.4% ($n = 5,896$) of participants were female. The average weight was 50.4 ± 10.5 kg, 53.0% ($n = 5,852$) of the respondents lived in rural areas, 57.6% ($n = 6,359$) were illiterate, and 37.1% ($n = 4,096$) lived with their spouses. In terms of income, 34.9% ($n = 3,858$) of the respondents had a low income, 33.8% ($n = 3,727$) had a middle income, and 31.3% ($n = 3,459$) had a high income. Additionally, 38.5% ($n = 4,251$) of the participants did physical exercise regularly, but only 14.8% ($n = 1,640$) and 2.4% ($n = 266$) of the participants attended social activities sometimes and often, respectively. In terms of smoking and drinking, 62.8% ($n = 6,920$) had never smoked and 66% ($n = 7,274$) had never consumed alcohol. In terms of mental and physical status, the average depression score was 11.4 ± 3.2, the average IADL score was 11.8 ± 4.9, the average ADL score was 6.4 ± 1.3, and the average MMSE score was 25.6 ± 3.2. Among the 11,044 participants, 34.5% ($n = 3,809$) had one or more chronic diseases.

The Akaike information criterion and BIC results showed that the model with three trajectory groups with up to quadratic order terms had the best fit (BIC −7,241.49) and captured the essential features of the data in a more comprehensible and analytically tractable manner (Table 2). Table 3 shows the fitting information of the GBTM, including the testing intercept and linear, quadratic, and cubic specifications for the trajectory shapes. Three distinct trajectories of the community-dwelling Chinese older people were identified (Figure 2). Those in Group 1 (41.1%) who had an IADL score below 2.5 were referred to as the low-risk IADL group. Those in Group 2 (28.5%) who had an IADL score linearly increasing between 2.3 and 3.1 were referred to as the IADL group with increasing risk. Lastly, those in Group 3 (30.4%) who exhibited high levels of IADL between 2.8 and 3.1 during all waves were referred to as the high-risk IADL group.

Table 4 shows the associations between the IADL trajectory groups and the risk of MCI by four Cox proportional hazards models (Group 1 was used as the reference). The HRs were significant in all the models. The HRs for the IADL group with increasing risk and the high-risk IADL group compared with the low-risk IADL group were 4.49 (95% CI 3.82–5.28) and 2.52 (95% CI 2.08–3.05), respectively, as shown in Model 4. Analyzing the sexes separately, the research results of the Cox proportional hazards models were similar to those for the whole group (Supplementary Tables S1, S2). When the IADL group with increasing risk was used as the reference (Supplementary Table S3), the HR for the high-risk IADL group was 0.56 (95% CI 0.48–0.66).

The interaction analysis results showed that age was a significant moderator (P for interaction <0.01). Specifically, participants aged 80 years and above in the IADL group with increasing risk (HR 7.49, 95% CI 5.55–10.12, compared with Group 1) were more likely to develop MCI than those younger than 80 years. In addition, when the risk of IADL was increasing, participants living in urban areas had a greater risk of MCI (P for interaction <0.05) than rural residents. Treating Group 1 as the reference, in the urban population, the HR of the IADL group with increasing risk was 5.99 (95% CI 4.53–7.92). The

TABLE 1 The baseline data for participants of CLHLS in 2002.

Variables	Total
	N=11,044
Depression, mean (SD)	11.4 ± 3.2
IADL, mean (SD)	11.8 ± 4.9
ADL, mean (SD)	6.4 ± 1.3
MMSE, mean (SD)	25.6 ± 3.2
Age (years), mean (SD)	82.8 ± 11.0
Weight (kilogram), mean (SD)	50.4 ± 10.5
Sex, *n* (%)	
Male	5,148 (46.6%)
Female	5,896 (53.4%)
Years of Schooling, *n* (%)	
Illiterate	6,359 (57.6%)
Primary school	3,423 (31.0%)
High school	1,262 (11.4%)
Residence, *n* (%)	
Rural	5,852 (53.0%)
City	5,192 (47.0%)
Marital status, *n* (%)	
Living without spouse	6,948 (62.9%)
Living with spouse	4,096 (37.1%)
Income, *n* (%)	
Low	3,858 (34.9%)
Medium	3,727 (33.8%)
High	3,459 (31.3%)
Smoking, *n* (%)	
Never smoking	6,920 (62.8%)
Former smoking	1,807 (16.3%)
Present smoking	2,300 (20.9%)
Drinking, *n* (%)	
Never drinking	7,274 (66.0%)
Former drinking	1,287 (11.6%)
Present drinking	2,465 (22.4%)
Social activity, *n* (%)	
Never	9,138 (82.8%)
Sometimes	1,640 (14.8%)
Always	266 (2.4%)
Physical activity, *n* (%)	
Never	5,825 (52.9%)
Former	952 (8.6%)
Present	4,251 (38.5%)
Chronic disease, *n* (%)	
No	7,234 (65.5%)
Yes	3,809 (34.5%)

CLHLS, the Chinese Longitudinal Healthy Longevity Survey; IADL, instrumental activities of daily living; ADL, activities of daily living; MMSE, Mini-Mental State Examination.

onset of MCI was not associated with sex, education level, income, or marital status when controlling for covariates (Table 5).

Four sensitivity analysis protocols were also conducted (Table 6). With the multiple interpolation method, the HR in the IADL group with increasing risk was 4.46-fold higher than that in the low-risk IADL group (HR 4.46, 95% CI 3.79–5.24). The HR of MCI in the high-risk IADL group was 2.48-fold higher than that in the low-risk IADL group (HR 2.48, 95% CI 2.05–3.00). After participants who passed away during the first wave of follow-up were excluded, the adjusted HR was 3.13 (95% CI 2.65–3.70) for the IADL group with increasing risk and 3.15 (95% CI 2.60–3.82) for the high-risk IADL group. After eliminating participants with chronic disease at baseline, the adjusted HRs in the IADL group with increasing risk and the high-risk IADL group were 4.55 (95% CI 3.75–5.23) and 2.59 (95% CI 2.05–3.27), respectively, compared with the low-risk IADL group. The average MMSE score for the IADL group with increasing risk was 1.33-fold lower than that of the low-risk IADL group (95% CI −1.47, −1.19), and for the high-risk IADL group it was 2.29-fold lower (95% CI −2.45, −2.13) than that of the low-risk IADL group.

4. Discussion

To the best of our knowledge, this was the first study to divide IADL into three trajectory groups in an older Chinese community-dwelling population to investigate the relationship between IADL trajectories and the onset of MCI. The IADL group with increasing risk and the high-risk IADL group both had greater risks of developing MCI than the low-risk IADL group. The IADL group with increasing risk had the highest risk of developing MCI. In adults over 80 years of age living in cities, the risk of MCI rose with increasing IADL impairment, according to the interaction analysis.

In the CLHLS, the prevalence of MCI was 17.5% in the Chinese community aged 65 years and over at baseline. According to previous surveys in China, the prevalence of MCI (using the Petersen criteria) ranged from 11.33 to 20.80% among individuals of 65 years of age and older (26–28). Although the survey results show heterogeneity as a result of various research designs, social background differences, and sampling errors, a Chinese meta-analysis reported the combined prevalence of MCI in adults over 55 years at 12.2% (2). The findings reveal a latent MCI trend in Chinese communities. Therefore, effective assessment tools and MCI prevention strategies are necessary.

Group-based trajectory model was used to classify IADL into three distinctive trajectory groups in this longitudinal study: the low-risk IADL group, the IADL group with increasing risk, and the high-risk IADL group. Most previous studies on the evolution of older people's daily living skills have focused on IADL. A cohort study conducted in Chinese community-living older people found that IADL trajectories either showed a sharp decline from a high starting point or a rapid decline from a low starting point (29). We included groups with increasing risk (linear change) and static high-risk or low-risk (constant level) related to IADL during follow-up. Among the three trajectory groups, the HRs for MCI were highest for the IADL group with increasing risk, intermediate for the high-risk IADL group, and lowest for the low-risk IADL group. Similar conclusions were made in a UK health and retirement study, which was based on a latent growth trajectory model. It reported that in middle-aged people

TABLE 2 Summary information on good-of-fit of IADL trajectory.

Group	AIC	BIC	AvePP		
			Trajectory Group 1	Trajectory Group 2	Trajectory Group 3
1	−11814.78	−11833.05	1		
2	−8630.77	−8660.01	0.918	0.899	
3	−7201.28	−7241.49	0.751	0.801	0.882

AIC, Akaike information criterion; BIC, Bayesian information criterion; AvePP, the average posterior probability.

TABLE 3 Procedure for selecting an IADL trajectory.

Group	Trajectory group	Growth parameter	Est.	*SE*	*T*-value	*p*-value
1	1	Intercept	2.40	0.003	663.47	<0.001
		Linear	0.02	0.003	6.33	<0.001
		Quadratic	−0.003	0.001	−5.21	<0.001
		Cubic	0.0001	0.001	5.49	<0.001
2	1	Intercept	2.19	0.004	586.30	<0.001
		Linear	0.007	0.002	4.49	<0.001
		Quadratic	0.001	0.001	7.61	<0.001
	2	Intercept	2.70	0.006	469.56	<0.001
		Linear	0.05	0.003	18.81	<0.001
		Quadratic	−0.002	0.001	−6.82	<0.001
3	1	Intercept	2.18	0.004	543.47	<0.001
		Linear	−0.01	0.002	−8.34	<0.001
		Quadratic	0.002	0.001	16.93	<0.001
	2	Intercept	2.257	0.006	371.85	<0.001
		Linear	0.06	0.001	59.35	<0.001
	3	Intercept	2.83	0.006	459.36	<0.001
		Linear	0.058	0.004	16.42	<0.001
		Quadratic	−0.003	0.001	−8.01	<0.001

Est., parameter estimate; SE, standard error of parameter estimate.

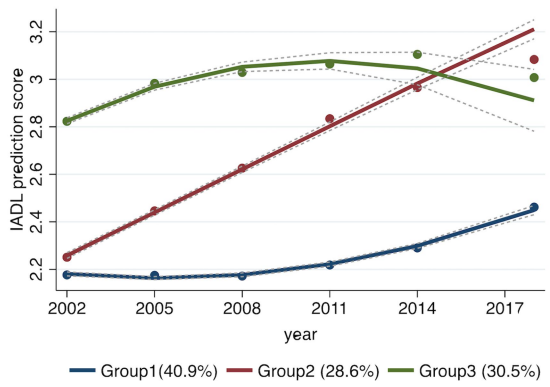


FIGURE 2
Instrumental activities of daily living (IADl) trajectory groups showing differences across waves. Group 1 named as "low-risk IADL group," Group 2 named as "IADL group with increasing risk," and Group3 named as "high-risk IADL group." IADL, instrumental activities of daily living.

(50–64 years), worse ADL and IADL outcomes were closely associated with cognitive impairment (non-dementia) and predicted dementia in later life (30).

What are the underlying mechanisms that explain why the IADL group with increasing risk had the highest MCI risk among the three trajectory groups? The disability of the individuals in the high-risk IADL group cannot be ignored, and thus corresponding nursing and medical measures are taken promptly. By contrast, the performance of the individuals in the IADL group with increasing risk might be hidden by functional compensation, making disability harder to recognize. The "disability paradox" claims that senior citizens with self-reported severe disability still report high quality of life even though the disability is linked to higher healthcare costs, premature death, and impaired quality of life (31–33). Therefore, the "paradox" is influenced by the social context and external environment of the individual (34).

Dynamic switching between different disability states can occur in older people. For example, a multimodal model of disability transition among Chinese older people was developed to analyze the

transition rate of four modes: no disability, mild disability, severe disability, and death. According to this study, aging significantly reduced the rate of change from a disabled to a non-disabled status (35). From the perspective of social stratification, rural areas had a higher rate of mild disability rehabilitation than urban areas (35). The transition to severe disability was more common than improvement among individuals older than 85 years of age (36).

TABLE 4 Cox proportional hazards model for hazard ratio of MCI according to changes in IADL.

Model	IADL Trajectory Group, HR (95%CI)		
	Low-risk IADL group	IADL group with increasing risk	High-risk IADL group
Model 1	1.00	4.44 (3.78–5.20)	2.38 (1.99–2.84)
Model 2	1.00	4.39 (3.74–5.15)	2.41 (2.01–2.89)
Model 3	1.00	4.45 (3.97–5.22)	2.49 (2.07–2.99)
Model 4	1.00	4.49 (3.82–5.28)	2.52 (2.08–3.05)

Model 1 adjusted for age, sex. Model 2 adjusted for variables in Model 1 and education level, income, marital status, and residence. Model 3 adjusted for variables in Model 2 and smoking, alcohol consumption, physical activity, and social activity. Model 4 adjusted for variables in Model 3 and weight, depression, and chronic diseases.

We found that in the IADL group with increasing risk, individuals over 80 years of age and those living in the city had a higher risk of developing MCI than those under 80 and those living in rural areas ($p < 0.05$). In China's rural areas, the standard of medical and health care is lower, and high-quality medical care facilities are more sparsely concentrated (37). Senior residents in rural areas also tend to have less medical knowledge, which could contribute to a shorter life span than their urban counterparts (38). In the absence of health education and exercise facilities, rural residents have a low self-reported rate of regular physical exercise (39). However, the rural residents in our study had a significantly lower risk of MCI than urban residents in the IADL group with increasing risk, indicating that the environment had an impact on the disability of these community elders. An underlying mechanism related to "survival choice" needs to be taken into consideration. Owing to the poorer access to medical services in rural areas, older people who are frail in these areas may die prematurely, whereas the older people who survive may have some stronger characteristics (such as genes and behaviors) against disability. This process leads to regional inequality in MCI related to IADL disability (40).

Increasing age was identified as an essential factor regulating IADL from an individual perspective, consistent with the findings of previous studies. Elderly people have weaker immune systems, are less physically active, and have less capacity for recovery compared with

TABLE 5 Interaction analysis of hazard ratio of IADL trajectory on MCI.

Variables	IADL trajectory group, HR (95%CI)					*P* for interaction
	Low-risk IADL group	IADL group with increasing risk		High-risk IADL group		
Age (year)						<0.001
≤80	1.00	3.27	(2.65–4.04)	2.05	(1.44–2.94)	
>80	1.00	7.49	(5.55–10.12)	3.93	(2.91–5.30)	
Sex						0.89
Male	1.00	4.61	(3.63–5.85)	2.53	(1.86–3,43)	
Female	1.00	4.39	(3.51–5.49)	2.49	(1.94–3.20)	
Years of schooling						0.18
Illiterate	1.00	3.90	(3.14–4.84)	2.42	(1.90–3.07)	
Primary school	1.00	5.18	(3.84–6.98)	2.69	(1.85–3.92)	
High school	1.00	5.82	(3.80–8.91)	2.35	(1.26–4.38)	
Residence						0.02
Rural	1.00	3.81	(3.12–4.66)	2.36	(1.87–2.99)	
City	1.00	5.99	(4.53–7.92)	2.85	(2.06–3.94)	
Income						
Low	1.00	4.03	(3.16–5.13)	2.50	(1.88–3.33)	0.40
Medium	1.00	4.29	(3.22–5.71)	2.17	(1.55–3.04)	
High	1.00	5.85	(4.15–8.25)	3.22	(2.17–4.80)	
Marital status						0.27
Never married	1.00	4.99	(4.01–6.21)	2.79	(2.20–3.53)	
Married	1.00	3.78	(2.94–4.86)	2.21	(1.54–3.16)	

HR (95%CI) adjusted for age, sex, years of schooling, income, marital status, smoking, alcohol consumption, physical activity, social activity, weight, depression, and chronic diseases (remove grouping variables). HR, hazards ratio.

TABLE 6 Sensitivity analysis of hazard risks of IADL trajectory on MCI.

IADL trajectory groups	Model 1, HR (95% CI)[a]	Model 2, HR (95% CI)[b]	Model 3, HR (95% CI)[c]	Model 4, β (95% CI)[d]
Low-risk IADL group	1	1	1	1
IADL group with increasing risk	4.46 (3.79,5.24)	3.13 (2.65,3.70)	4.55 (3.75,5.23)	−1.33 (−1.47, −1.19)
High-risk IADL group	2.48 (2.05,3.00)	3.15 (2.60,3.82)	2.59 (2.05,3.27)	−2.29 (−0.2.45, −2.13)

[a]Multivariate Cox regression results after multiple interpolation; [b]Multivariate Cox regression results after excluding patients who died in the first circle; [c]Cox regression results excluding patients with chronic diseases at baseline; [d]Adopt the generalized mixed-effect model. Covariates such as age, sex, education level, income, marital status, smoking, alcohol consumption, physical activity, social activity, weight, depression, and chronic diseases were adjusted for all sensitivity analyses. HR, hazard ratio.

younger older people, which reduces their chances of recovering from injuries or illnesses (41). Moreover, a "male–female health-survival paradox" has been reported in which male people typically have fewer disabilities than female people but have shorter lives (42). In the sensitivity analyses, to limit the effect of the choice paradox, we excluded participants with chronic diseases at baseline or those who had died by the first follow-up to confirm that the results were still robust. This supported our findings that IADL impairment increased the risk of MCI and that this risk was higher for the IADL group with increasing risk than for the high-risk IADL group.

Our study had several strengths. First, we used GBTM to classify older individuals into three distinct trajectory groups of the IADL score to examine the risk of MCI in these different groups. To our knowledge, this is the first study to document the connection between the trajectory of IADL and MCI risk. We assessed the effect of the IADL trajectory on MCI using the Cox proportional hazards model. The long-term follow-up from 2002 to 2008 and the sizable sample size offered adequate statistical power. Furthermore, four types of sensitivity analyses were used to confirm that the IADL trajectory estimations were reliable as indicators of MCI risk.

There were some limitations to our study. First, as the participants were older individuals, there were deaths during the follow-up period, resulting in loss of some sample information to estimate the model. Most variables in the present study were obtained by self-reported questionnaires, especially in terms of information on chronic diseases. More physical examinations and laboratory objective indicators should be considered in future to reduce the Hawthorne effect. In addition, five depression-related questions were self-compiled by CLHLS investigators to assess the depressive status of the respondents before 2018; thus, a complete depression scale was lacking. Finally, the MMSE scale was used to measure MCI. Although this method has been verified in population studies, it is not a method used in clinical diagnoses. Some objective means, such as molecular targets and iconography methods, may be more helpful in clarifying the diagnosis of MCI.

5. Conclusion

A GBTM was developed to classify community-dwelling Chinese seniors into three distinct trajectory groups of the IADL score. The participants' age and place of residence had various effects on how IADL impairment affected MCI incidence. Individuals of ≥80 years of age living in urban rather than rural locations in the IADL group with increasing risk were the most likely to develop MCI. Our study provides evidence for monitoring IADL change in older adults. In terms of MCI management, the findings underline the need for basic medical and health services for older people living in cities.

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 authors.

Ethics statement

All the procedures used to support this work were carried out in agreement with the necessary standards and laws. The datasets used to support this work are available to the public through the CLHLS project. It received approval from Peking University's research ethics committees (IRB00001052–13074). All the participants signed a written informed consent.

Author contributions

JY, YCZ, LW, and XL designed the study. SS, HY, LY, YOZ, YX, and JS collected and systematized the data. YCZ analyzed the data. JY drafted the manuscript. LW and XL polished the manuscript. All authors contributed to the article and have approved the submitted version.

Funding

The present study was supported by the National Natural Science Foundation of China (Grant No. 72174033) and the Science and Technology Research Project of Chongqing Education Commission (Grant No. KJQN202100432).

Acknowledgments

The Centre for Healthy Aging and Development Studies of Peking University and Duke University jointly conducted the "Chinese Longitudinal Longevity Survey" (CLHLS), which supplied the data used in this study. The U.S. National Institute on Aging (NIA), the China Natural Science Foundation, the China Social Science Foundation, and UNFPA all provided funding for CLHLS.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1165753/full#supplementary-material

References

1. Jongsiriyanyong S, Limpawattana P. Mild cognitive impairment in clinical practice: a review article. *Am J Alzheimers Dis Other Dement*. (2018) 33:500–7. doi: 10.1177/1533317518791401

2. Lu Y, Liu C, Yu D, Fawkes S, Ma J, Zhang M, et al. Prevalence of mild cognitive impairment in community-dwelling Chinese populations aged over 55 years: a meta-analysis and systematic review. *BMC Geriatr*. (2021) 21:10. doi: 10.1186/s12877-020-01948-3

3. Anderson ND. State of the science on mild cognitive impairment (MCI). *CNS Spectr*. (2019) 24:78–87. doi: 10.1017/S1092852918001347

4. Jian W, Shi J. Activities of daily living rating for differentiating mild cognitive impairment and dementia. *Chin J Gerontol*. (2014) 34:865–8.

5. Vergara I, Bilbao A, Orive M, Garcia-Gutierrez S, Navarro G, Quintana JM. Validation of the Spanish version of the Lawton IADL scale for its application in elderly people. *Health Qual Life Outcomes*. (2012) 10:130. doi: 10.1186/1477-7525-10-130

6. Jekel K, Damian M, Wattmo C, Hausner L, Bullock R, Connelly PJ, et al. Mild cognitive impairment and deficits in instrumental activities of daily living: a systematic review. *Alzheimers Res Ther*. (2015) 7:17. doi: 10.1186/s13195-015-0099-0

7. Di Carlo A, Baldereschi M, Lamassa M, Bovis F, Inzitari M, Solfrizzi V, et al. Daily function as predictor of dementia in cognitive impairment, no dementia (CIND) and mild cognitive impairment (MCI): an 8-year follow-up in the ILSA study. *J Alzheimers Dis*. (2016) 53:505–15. doi: 10.3233/JAD-160087

8. Lipnicki DM, Crawford JD, Dutta R, Thalamuthu A, Kochan NA, Andrews G, et al. Age-related cognitive decline and associations with sex, education and apolipoprotein E genotype across ethnocultural groups and geographic regions: a collaborative cohort study. *PLoS Med*. (2017) 14:e1002261. doi: 10.1371/journal.pmed.1002261

9. Qi SG, Wang ZH, Wang LM, Wang H, Zhang H, Li ZX. Incidence of activities of daily living disability and related factors in community-dwelling older adults in China. *Zhonghua Liu Xing Bing Xue Za Zhi*. (2019) 40:272–6.

10. Zhang Y, Xiong Y, Yu Q, Shen S, Chen L, Lei X. The activity of daily living (ADL) subgroups and health impairment among Chinese elderly: a latent profile analysis. *BMC Geriatr*. (2021) 21:30. doi: 10.1186/s12877-020-01986-x

11. Kalligerou F, Fieo R, Paraskevas GP, Zalonis I, Kosmidis MH, Yannakoulia M, et al. Assessing functional status using the IADL-extended scale: results from the HELIAD study. *Int Psychogeriatr*. (2020) 32:1045–53. doi: 10.1017/S1041610219001091

12. Hsiung GY, Alipour S, Jacova C, Grand J, Gauthier S, Black SE, et al. Transition from cognitively impaired not demented to Alzheimer's disease: an analysis of changes in functional abilities in a dementia clinic cohort. *Dement Geriatr Cogn Disord*. (2008) 25:483–90. doi: 10.1159/000126499

13. Apostolo J, Holland C, O'Connell MD, Feeney J, Tabares-Seisdedos R, Tadros G, et al. Mild cognitive decline. A position statement of the cognitive decline Group of the European Innovation Partnership for active and healthy ageing (EIPAHA). *Maturitas*. (2016) 83:83–93. doi: 10.1016/j.maturitas.2015.10.008

14. Jette AM. How measurement techniques influence estimates of disability in older populations. *Soc Sci Med*. (1994) 38:937–42. doi: 10.1016/0277-9536(94)90426-X

15. Park J, Lee YJ. Patterns of instrumental activities of daily living and association with predictors among community-dwelling older women: a latent class analysis. *BMC Geriatr*. (2017) 17:158. doi: 10.1186/s12877-017-0557-6

16. Nagin D, Odgers C. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol*. (2010) 6:109–38. doi: 10.1146/annurev.clinpsy.121208.131413

17. Zhang H, Wang Y, Wu D, Chen J. Evolutionary path of factors influencing life satisfaction among Chinese elderly: a perspective of data visualization. *Data*. (2018) 3:35. doi: 10.3390/data3030035

18. Chen N, Wang C. A study of urban-rural difference of self-care ability of seniors ——an empirical analysis based on CLHLS(2014)data. *Popul Dev*. (2021) 27:135–44.

19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. (1975) 12:189–98. doi: 10.1016/0022-3956(75)90026-6

20. Zeng Yi JWV. Functional capacity and self–evaluation of health and life of oldest old in China. *J Soc Issues*. (2010) 58:733–48.

21. Cui GH, Yao YH, Xu RF, Tang HD, Jiang GX, Wang Y, et al. Cognitive impairment using education-based cutoff points for CMMSE scores in elderly Chinese people of agricultural and rural Shanghai China. *Acta Neurol Scand*. (2011) 124:361–7. doi: 10.1111/j.1600-0404.2010.01484.x

22. Zhang MY, Katzman R, Salmon D, Jin H, Cai GJ, Wang ZY, et al. The prevalence of dementia and Alzheimer's disease in Shanghai, China: impact of age, gender, and education. *Ann Neurol*. (1990) 27:428–37. doi: 10.1002/ana.410270412

23. Lei Q, Tian H, Xiao Z, Wu W, Liang X, Zhao Q, et al. Association between body mass index and incident dementia among community-dwelling older adults: the Shanghai aging study. *J Alzheimers Dis*. (2022) 86:919–29. doi: 10.3233/JAD-215517

24. Yang Y, Du Z, Liu Y, Lao J, Sun X, Tang F. Disability and the risk of subsequent mortality in elderly: a 12-year longitudinal population-based study. *BMC Geriatr*. (2021) 21:662. doi: 10.1186/s12877-021-02611-1

25. Beesley LJ, Bondarenko I, Elliot MR, Kurian AW, Katz SJ, Taylor JM. Multiple imputation with missing data indicators. *Stat Methods Med Res*. (2021) 30:2685–700. doi: 10.1177/09622802211047346

26. Jia J, Wei C, Chen S, Li F, Tang Y, Qin W, et al. The cost of Alzheimer's disease in China and re-estimation of costs worldwide. *Alzheimers Dement*. (2018) 14:483–91. doi: 10.1016/j.jalz.2017.12.006

27. Ma F, Wu T, Zhao J, Ji L, Song A, Zhang M, et al. Prevalence of mild cognitive impairment and its subtypes among Chinese older adults: role of vascular risk factors. *Dement Geriatr Cogn Disord*. (2016) 41:261–72. doi: 10.1159/000446507

28. Rao D, Luo X, Tang M, Shen Y, Huang R, Yu J, et al. Prevalence of mild cognitive impairment and its subtypes in community-dwelling residents aged 65 years or older in Guangzhou. *China Arch Gerontol Geriatr*. (2018) 75:70–5. doi: 10.1016/j.archger.2017.11.003

29. Xiaolan W, Ji L. A study on developmental trajectories of activities of daily living for the elderly in China. *Popul J*. (2018) 40:59–71.

30. Wu B, Toseef MU, Stickel AM, González HM, Tarraf W. Associations between midlife functional limitations and self-reported health and cognitive status: results from the 1998-2016 health and retirement study. *J Alzheimers Dis*. (2022) 85:1621–37. doi: 10.3233/JAD-215192

31. Akosile CO, Mgbeojedo UG, Maruf FA, Okoye EC, Umeonwuka IC, Ogunniyi A. Depression, functional disability and quality of life among Nigerian older adults: Prevalences and relationships. *Arch Gerontol Geriatr*. (2018) 74:39–43. doi: 10.1016/j.archger.2017.08.011

32. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*. (2004) 59:255–63. doi: 10.1093/gerona/59.3.m255

33. Walter LC, Brand RJ, Counsell SR, Palmer RM, Landefeld CS, Fortinsky RH, et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA*. (2001) 285:2987–94. doi: 10.1001/jama.285.23.2987

34. Albrecht GL, Devlieger PJ. The disability paradox: high quality of life against all odds. *Soc Sci Med*. (1999) 48:977–88. doi: 10.1016/S0277-9536(98)00411-0

35. Hou C, Ma Y, Yang X, Tao L, Zheng D, Liu X, et al. Disability transitions and health expectancies among elderly people aged 65 years and over in China: a nationwide longitudinal study. *Aging Dis*. (2019) 10:1246–57. doi: 10.14336/AD.2019.0121

36. van Houwelingen AH, Cameron ID, Gussekloo J, Putter H, Kurrle S, de Craen AJ, et al. Disability transitions in the oldest old in the general population. The Leiden 85-plus study. *Age (Dordr)*. (2014) 36:483–93. doi: 10.1007/s11357-013-9574-3

37. Lustria ML, Smith SA, Hinnant CC. Exploring digital divides: an examination of eHealth technology use in health information seeking, communication and personal health information management in the USA. *Health Informatics J*. (2011) 17:224–43. doi: 10.1177/1460458211414843

38. Anand S, Fan VY, Zhang J, Zhang L, Ke Y, Dong Z, et al. China's human resources for health: quantity, quality, and distribution. *Lancet*. (2008) 372:1774–81. doi: 10.1016/S0140-6736(08)61363-X

39. Blair SN, Kohl HR, Barlow CE, Paffenbarger RJ, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA*. (1995) 273:1093–8. doi: 10.1001/jama.1995.03520380029031

40. Glymour MM, Weuve J, Chen JT. Methodological challenges in causal research on racial and ethnic patterns of cognitive trajectories: measurement, selection, and bias. *Neuropsychol Rev*. (2008) 18:194–213. doi: 10.1007/s11065-008-9066-x

41. Bootsma-van DWA, Gussekloo J, de Craen AJ, van Exel E, Knook DL, Lagaay AM, et al. Disability in the oldest old: can do or do? *J Am Geriatr Soc*. (2001) 49:909–14. doi: 10.1046/j.1532-5415.2001.49181.x

42. Oksuzyan A, Juel K, Vaupel JW, Christensen K. Men: good health and high mortality. Sex differences in health and aging. *Aging Clin Exp Res*. (2008) 20:91–102. doi: 10.1007/BF03324754

frontiers | Frontiers in Public Health

TYPE Review
PUBLISHED 04 May 2023
DOI 10.3389/fpubh.2023.1171243

OPEN ACCESS

EDITED BY
Junhong Zhou,
Harvard Medical School, United States

REVIEWED BY
Matheus Uba Chupel,
Sunnybrook Research Institute (SRI), Canada
Jingying Wang,
University of Florida, United States

*CORRESPONDENCE
Dilorom Sass
✉ dilorom.sass@gmail.com;
✉ dilijon08@gmail.com

RECEIVED 21 February 2023
ACCEPTED 07 April 2023
PUBLISHED 04 May 2023

CITATION
Sass D, Parmelee Streck B, Guedes VA, Cooper D, Guida JL and Armstrong TS (2023) Blood-based biomarkers of frailty in solid tumors: a systematic review.
Front. Public Health 11:1171243.
doi: 10.3389/fpubh.2023.1171243

Blood-based biomarkers of frailty in solid tumors: a systematic review

Dilorom Sass[1]*, Brennan Parmelee Streck[2], Vivian A. Guedes[1], Diane Cooper[3], Jennifer L. Guida[2] and Terri S. Armstrong[1]

[1]Neuro-Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, United States, [2]Basic Biobehavioral and Psychological Sciences Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Rockville, MD, United States, [3]Office of Research Services, National Institutes of Health Library, National Institutes of Health, Bethesda, MD, United States

This review examines the current literature to identify biomarkers of frailty across patients with solid tumors. We conducted the systematic review using preferred reporting items for systematic reviews and meta-analysis guidelines (PRISMA). PubMed, Web of Science, and Embase databases were searched from their inception to December 08, 2021, for reports of biomarkers and frailty. Two reviewers independently screened titles, abstracts, and full-text articles. A quality assessment was conducted using NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, and Quality Assessment of Case-Control Studies. In total, 915 reports were screened, and 14 full-text articles were included in the review. Most studies included breast tumors, were cross-sectional in design, and measured biomarkers at baseline or pre-treatment. Frailty tools varied with Fried Frailty Phenotype and the geriatric assessment most frequently used. Increased inflammatory parameters (i.e., Interleukin-6, Neutrophil Lymphocyte Ratio, Glasgow Prognostic Score-2) were associated with frailty severity. Only six studies were rated as good quality using assessment ratings. Together, the small number of studies and heterogeneity in frailty assessment limited our ability to draw conclusions from the extant literature. Future research is needed to identify potential target biomarkers of frailty in cancer survivors that may aid in early detection and referral.

KEYWORDS

biomarkers, molecular biomarkers, solid tumors, frailty, deficit accumulation, cancer survivors

1. Introduction

Cancer and cancer therapies may contribute to the development of early onset frailty, a geriatric syndrome that is indicative of multi-system decline and often precipitates mortality (1–4). The prevalence of frailty has been reported to range from 8% in adult survivors of childhood cancer to 59 percent in older adult cancer survivors using phenotypic and deficit accumulation frailty measures (5). Sustained or worsening phenotypic frailty measured prior-to post-cancer diagnosis significantly increases the risk of mortality in patients with solid tumors (breast, lung, colorectal, ovarian, and endometrial) (6). Thus, there is an increased need for early identification of patients at risk for developing frailty to aid in timely therapeutic interventions.

Two commonly used, but conceptually distinct constructs of frailty, include: (i) phenotypic frailty, where frailty is a defined and measurable state (e.g., fried frailty phenotype) (7) and (ii)

the accumulation of deficits, where frailty is more of a stochastic process, in which random deficits lead to increased vulnerability (8). While phenotypic frailty evaluates signs/symptoms (e.g., weight loss, exhaustion, and weakness) and may exist independent of medically classified conditions as a pre-disability syndrome, deficit accumulation frailty is based on a long checklist of signs/symptoms and medically classified conditions, including disability (9). Phenotypic frailty is most useful if the goal is to define risk factors and mechanisms with a degree of specificity for sub-clinical and clinical frailty because individuals are stratified into distinct risk categories and specific pathways can be identified for prevention and remediation. Stochastic deficit accumulation frailty may be helpful for individual prognostication and targeting shared risk factors or biological mechanisms (10). To encompass the two conceptual definitions, in this review, frailty will be operationalized as both phenotypic frailty (7) and deficit accumulation frailty (8).

Cancer and cancer treatments may accelerate aging which may be measured using correlates or biomarkers representative of hallmarks of aging (e.g., telomere attrition, epigenetic alteration, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, senescence, and inflammation) and may in turn lead to early frailty states (2, 5, 11). Indeed, several studies report that completion of primary cancer therapy (post-treatment) accelerates biological aging in cancer survivors, as evidenced by increased expression of cytokines (12, 13), senescence-associated $p16^{INK4}$ (13), and decreased telomere length (14). However, little is known about the association of these biological measures of aging with frailty in cancer survivors with solid tumors. For example, several recent reviews and/or meta-analyses evaluated common frailty biomarkers in older adults, but few included oncologic studies (15–18). The search for sensitive and specific biomarkers of frailty in oncological populations is crucial for early detection of aging-related consequences of cancer and its treatments on cancer survivors (2). Such biomarkers may offer diagnostic and prognostic utility by aiding clinical assessment of frailty signs/symptoms and may help evaluate the effectiveness of interventions designed to mitigate (or potentially reverse) phenotypic and deficit accumulation frailty. Given the heterogeneity in the biology, treatments, and frailty rates (19, 20) between hematologic and solid cancers, this review evaluates biomarkers of frailty specific to cancer survivors with solid tumors.

Potential target biomarkers of frailty may be used to identify cancer survivors at risk for the development of frailty. To fill this gap, this systematic review synthesizes current literature by examining (i) frailty measures and (ii) biomarkers evaluated in association with phenotypic frailty and deficit accumulation in patients with solid tumors across all age groups.

2. Methods

A systematic review was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (21).

2.1. Eligibility criteria

Inclusion criteria were: (a) published in the English language, (b) molecular measures that correlate with the aging process (hallmarks of aging) (11): telomere attrition, epigenetic alteration, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, senescence, and inflammation, (c) evaluated phenotypic frailty or deficit accumulation, and (d) measured an association between the biomarker and phenotypic frailty/deficit accumulation. Studies with non-solid tumors and non-human subjects were excluded.

2.2. Literature search strategy

A medical librarian (D.C.) conducted electronic database searches of PubMed, Web of Science, and Embase databases of publications from the date of inception to December 08, 2021. Frailty was operationalized as both the phenotypic frailty (7) and deficit accumulation frailty (8) consistent with prior reviews on frailty and biomarkers (15, 16). The search terms included: solid tumors (brain, breast, colon, lung, pancreatic, prostate, and ovarian), biomarkers (cytokines, extracellular vesicles, microRNA, mitochondrial DNA, telomere length, cell senescence markers, inflammageing, epigenetic alterations, mitochondrial dysfunction, and stem cell exhaustion), and outcomes (accelerated aging, frailty, functional decline, and deficit accumulation). The complete search strategy with MeSH terms and Boolean operators for each database is detailed in Supplementary Table S1. References from retrieved reviews and Google Scholar were scanned for additional studies using key search terms.

2.3. Data collection

Two reviewers (D.S. and B.P.S.) independently screened titles and abstracts and subsequently full-text articles for study eligibility using the covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Any incongruencies were resolved upon discussion and consultation with the third researcher (T.S.A.). Two reviewers (D.S. and B.P.S.) completed data abstraction and D.S. reviewed all the final abstracted information. To preserve integrity of the data, the authors kept written communication records of decisions on incongruencies related to data abstraction. Data were extracted using a standardized form for key variables (sample, tumor type, stages, time points, study design, frailty instruments, molecules measured, statistical methods, and key findings).

2.4. Risk of bias assessment

Risk of bias assessment was conducted using the National Heart, Lung, and Blood Institute quality assessment tool for observational cohort and cross-sectional studies and a tool for case–control studies (22). The tools consist of 12–14 methodological quality items rated as "yes," "no," or "other (cannot determine, not reported, not applicable)" (Supplementary Table S2). The questions evaluate the internal validity of each study, considering the potential risk of biases such as information bias, measurement bias, or outcome bias. The greater the bias (higher number of items rated as "no"), the lower the assigned rating. Reviewers (D.S. and B.P.S.) conducted independent quality assessments. Incongruencies were discussed with the third reviewer's input (T.S.A.) and concordance was reached upon discussion. To

grade the overall quality of the studies, the percentage of items free of bias (items rated as "yes") out of all possible items was calculated. Studies were assigned overall quality ratings according to the following categories: poor (<50%), fair (≥50% and ≤70%), and good (>70%).

2.5. Data analysis

Descriptive statistics were calculated (such as mean, range, and standard deviation) for variable age using either the reported mean or median. Where available, data on race/ethnicity (white vs. non-white) and sex (male vs. female) was extracted.

3. Results of synthesis

3.1. Study selection

The study selection process is detailed in a PRISMA flow diagram (Figure 1). Briefly, 910 reports were retrieved from the databases. Five additional articles were identified through screening references of relevant reviews and Google Scholar using the search criteria. After removing 19 duplicate reports, search results were uploaded to the covidence software where an additional five reports were identified as duplicates. Two reviewers (D.S. and B.P.S.) independently screened 888 titles and abstracts, of which 844 reports were deemed irrelevant (Supplementary Table S3). Five additional reports were located through Google Scholar and 49 reports were retrieved for full-text review. In total, 14 full-text articles were included in the review. Of the 35 excluded reports, 13 did not measure frailty, 12 were conference abstracts, six were not primary research studies, two were not in human subjects, and two did not measure an association between frailty and biomarkers. Although the study by Falandry and authors (23) did not explicitly use the term "frailty," the study met the inclusion criteria for measuring "decline in functional reserve" using the geriatric vulnerability score consistent with deficit accumulation definition.

3.2. Study and participant characteristics

Characteristics of the included studies are presented in Table 1. All 14 studies were observational study designs. Seven studies were longitudinal cohort studies (23, 26–31), six were cross-sectional (32–37), and one study was a case-control design (38). Across the 14 studies, a total of 2,178 participants were included, with the sample size of each study ranging from 20 to 581. The mean age across all studies was 72 years (standard deviation = 7, range: 53–80 years). Thirteen studies reported information on sex and the distribution was 63% female and 37% male. Four studies reported information on race/ethnicity (28, 29, 37, 38), of which 82% of participants were white and 18% non-white.

The most commonly studied solid tumor was breast ($n = 6$, 43%) (27–29, 32–34), followed by prostate tumor ($n = 3$, 21%) (26, 36, 38) (Table 1). Stages of cancer varied greatly ranging from stage I to IV (or localized to metastasized) and most studies were initiated at pre-treatment (i.e., at the diagnosis, pre-inclusion, prior to surgery or adjuvant treatments) ($n = 11$) (23, 27–35, 37) (Table 1). Among

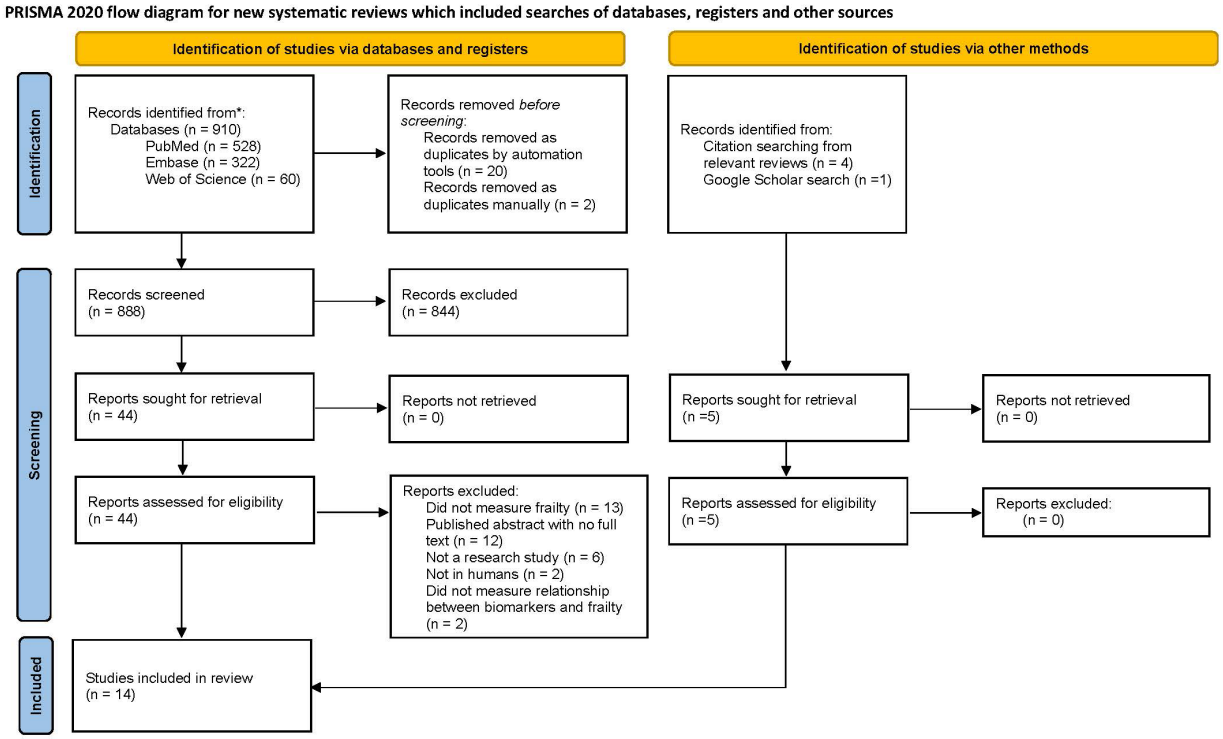


FIGURE 1
PRISMA flow diagram.

TABLE 1 Study and participants characteristics.

Author Year Journal Country	Sample	Tumor Type Stages Time Points	Study design	Frailty instruments	Molecules measured	Statistical methods	Key findings[a,b]
Brouwers 2015 Aging Belgium	162 participants (old group) **Age**: (median 76) **Sex**: Not reported **Race/ethnicity**: Not reported *Note*: only old group had frailty assessment and is included in this review	**Breast Cancer** **Stages**: Grade I-III Unknown **Time Points**: Pre-treatment	**Cross-sectional**	• Balducci score • Leuven Oncogeriatric Frailty Score (LOFS) **Balducci Frail criteria**: presence of any of the below criteria (24): ≥85 years ≥1 ADl dependence ≥1 Comorbidity ≥1 Geriatric syndrome **Components of LOFS**: • ADL • Comorbidities • iADL • Mental state • Nutritional scale	• IGF-1 • IL-6 • MCP-1 • RANTES • Telomere length	• Kruskal-Wallis test (Balducci score) • Spearman correlation (LOFS)	**Balducci score**: • IL-6 was higher in pre-frail and frail groups **LOFS**: • IL-6 also correlated with worse LOFS. **Limitations**: • Did not report power analysis • Frailty and biomarker measurements are limited to old group alone • Did not report post-hoc or multivariate analyses
Buigues 2020 Cancers Spain	39 participants 31% Frail 65% Pre-Frail 17% Robust *Note*: at follow up, 59% had worsening frailty while 41% improved. **Age**: (mean 71.9, SD 9.8) **Sex**: Male 100% **Race/ethnicity**: Not reported	**Prostate Cancer** **Stages**: all stages **Time Points**: • During treatment (≥6 months of ADT) • Follow-up (~1 year follow-up)	**Prospective longitudinal**	• **Fried Frailty Phenotype** **Components of Assessment**: • Fatigue • Physical activity • Walking speed • Weakness • Weight loss	• Basophils • CRP • Eosinophils • Fibrinogen • IL-1β • IL-6 • IL-8 • Lymphocytes • Monocytes • Neutrophils • TNF-α	Kruskal–Wallis test followed by multinomial logistic regression controlling for age, gleason score, presence of metastatic disease, prostatectomy, and comorbidity index.	**≥6 months on ADT**[a] • Higher IL-6, IL-8, and lymphocyte count associated with frailty **Follow up**[a] • IL-6 associated with frailty **Progression**[a] • Higher baseline IL-6 and lower lymphocytes associated with frailty progression. **Limitations**: • Did not report power analysis • Small sample

(Continued)

10.3389/fpubh.2023.1171243

TABLE 1 (Continued)

Author Year Journal Country	Sample	Tumor Type Stages Time Points	Study design	Frailty instruments	Molecules measured	Statistical methods	Key findings[a,b]
Bylow 2011 Urology United States	134 participants • 63 ADT group • 71 Control (non-ADT) group **Age**: ADT group (mean 72.1, SD 7.0) Control group (mean 70.5, SD = 6.3) **Sex**: Male 100% **Race/ethnicity**: **ADT group**: African-American 32% White 67% Other 2% **Control group**: African American 45% White 46% Other 4%	**Prostate Cancer** **Stages**: Not reported **Time Points**: During treatment (≥6 months on ADT) *Note*: control group was post-surgery or radiation without ADT	**Case-Control**	• **Fried Frailty Phenotype** • **Modified Fried Frailty Phenotype** • **Components of Assessment – Fried Frailty Phenotype**: • Exhaustion • Physical activity • Walking speed • Weakness • Weight loss • **Modified Fried Frailty Phenotype**: • Weight loss replaced by obesity	• Albumin • CRP • Hemoglobin • HDL • Glucose • IL-6 • LDL • Total cholesterol • Triglycerides	T-tests and Fisher's Exact test	Hemoglobin was lower in ADT compared to non-ADT group. *Note*: ADT group had higher percentage of frail participants using modified FFP. **Limitations**: • Did not report power analysis • Small sample Did not report multivariate analyses for molecular correlates (hemoglobin)

(Continued)

10.3389/fpubh.2023.1171243

TABLE 1 (Continued)

Author Year Journal Country	Sample	Tumor Type Stages Time Points	Study design	Frailty instruments	Molecules measured	Statistical methods	Key findings[a,b]
Corona 2014 Journal of Cellular Physiology Italy	89 participants • 49 Fit • 23 Unfit • 17 Frail **Age**: (median 77, range 70–97) **Sex** Female 100% **Race/ethnicity**: Not reported	**Breast Cancer** **Stages**: Mixed **Time Points**: Pre-treatment	**Cross-sectional**	• **Comprehensive Geriatric Assessment (CGA)** **Components of Assessment**: No description of components	40 acylcarnitines 45 aminoacids 150 phospholipids	ANOVA post residual model adjusting for age.	• **Unfit &Frail (compared to Fit)**[a]: greater age-adjusted 3-methyl-hystidine • **Unfit & Frail (compared to Fit)**[a]: depletion of several age-adjusted sphingolipids and glycerol-phospholipids (SM (OH) C16:1, SM (OH) C24:1, PC aa C32:3, PC aa C34:4, PC aa C36:3, PC aa C36:4, PC aa C38:5, PC ae C32:2, PC ae C34:0, PC ae C34:1, PC ae C34:2, PC ae C34:3, PC ae C36:2, PC ae C36:3, PC ae C36:4, PC ae C36:5, PC ae C38:4, PC ae C38:5, PC ae C42:2, lysoPC a C18:1, lysoPC a C20:4). **Limitations**: ■ Did not report power analysis ■ Small sample

(Continued)

10.3389/fpubh.2023.1171243

TABLE 1 (Continued)

Author Year Journal Country	Sample	Tumor Type Stages Time Points	Study design	Frailty instruments	Molecules measured	Statistical methods	Key findings[a,b]
Dalmasso 2018 BioMed Central (BMC) Cancer Belgium	89 participants • 46 Chemotherapy (chemo) group • 43 Non-chemo group **Age** retrieved from (25): • Chemo group ($n = 57$, median = 73.5, range = 70–80) ($n = 52$, median 75, range = 70–90) **Sex**: Female 100% **Race/ethnicity**: Not reported *Note*: Demographic and clinical data was reported on full sample (25)	**Breast Cancer** **Stages**: • Locally-advanced • Non-metastatic **Time Points**: • Inclusion/Pre-treatment (post-surgery and pre-chemo for chemo group) • 3 months after inclusion or the day of last chemo for chemo group • 1 year after inclusion	**Prospective longitudinal**	• **Balducci score*** • **LOFS** • **Flemish Triage Risk Screening Tool (fTRST)*** • **G8*** **Components of LOFS**: • ADL • Comorbidity Index • iADL • Mental state • Nutritional state *Note*: Balducci, fTRST and G8 components not described.	• miR-34a • miR-320b • miR-378a • miR-20a • miR-30b • miR-106b • miR-191 • miR-301a • miR-374a *Note*: authors also measured telomere length, IL-6, IL-10, TNF-α, RANTES, MCP-1, IGF-1, but did not correlate to frailty.	Spearman correlation followed by multivariable model	Associations with frailty reported at inclusion not separated by groups: **LOFS**[a]: • Higher LOFS associated with higher miR374a and lower miR-320b levels **fTRST**[b]: • miR-301a negatively correlated with higher frailty **G8**[a]: • Lower miR-106b, miR-191, miR320b and higher miR374a served as predictors for total G8 *Note*: No correlations with Balducci score[a] **Limitations**: • Did not report power analysis • Small sample
Falandry 2015 Aging France	109 participants **Age**: (median 78, range 70–93) **Sex**: Female 100% **Race/ethnicity**: Not reported	**Ovarian Cancer** **Stages**: FIGO Stage III-IV **Time Points**: Pre-treatment	**Prospective longitudinal**	• **Geriatric Vulnerability Score** **Components of Assessment**: • ADL • iADL • HADS • Hypoalbumenia • Lymphopenia	Telomere length (TL)	Linear regression	GVS ≥3[a] associated with shorter TL group cross-sectionally **Limitations**: • Did not report power analysis for effect of TL on GVS

(Continued)

10.3389/fpubh.2023.1171243

TABLE 1 (Continued)

Author Year Journal Country	Sample	Tumor Type Stages Time Points	Study design	Frailty instruments	Molecules measured	Statistical methods	Key findings[a,b]
Gilmore 2020 Journal of Geriatric Oncology United States	286 participants • 144 Cancer group • 142 Non-cancer group **Age**: Cancer group (mean = 60, range 50–76) Non-cancer group (mean 59, range 50–81) **Sex**: Female 100% **Race/ethnicity**: **Cancer group**: 90% White 10% Non-White **Non-cancer group**: 96% White 4% Non-White	**Breast Cancer** **Stages**: I-IIIC Unknown **Time Points**: • Pre-treatment (within 7 days prior to chemotherapy) • Post-treatment (4 weeks after chemotherapy completion)	**Prospective longitudinal**	• **Modified Fried Frailty Phenotype** **Components of Assessment**: • Exhaustion • Physical activity • Walking speed • Weakness	• IL-6 • sTNFRI • sTNFRII	Linear regression controlling for pre-chemotherapy frailty scores	**Cancer group**[a]: • Greater levels of pre-chemo IL-6, sTNFRI and sTNFRII associated with worse post-chemo frailty in cancer groups *Note*: No associations were found in non-cancer group **Limitations**: • Did not report power analysis • Cytokines levels are dichotomized due to skewed pre-treatment cytokine distributions
Gilmore 2021 Breast Cancer Research United States	• 581 Pre-chemotherapy • 547 post-chemotherapy • 506 six months post-chemotherapy **Age**: (baseline mean 53.4, range 22–81) **Sex**: Female 100% **Race/ethnicity**: White 89% Non-White 11%	**Breast Cancer** Stages: I-IIIC **Time Points**: • Pre-treatment (within 7 days) • Post-treatment (within 4 weeks after) • Post-treatment (6 months after)	**Retrospective longitudinal**	• **Modified Fried Frailty Phenotype** **Components of Assessment**: • Exhaustion • Physical activity • Walking speed • Weakness	• Albumin • Hemoglobin • Hematocrit • Lymphocytes • LMR • Monocytes • Neutrophils • NLR • Platelets • Total WBC	Linear regression analyses controlling for baseline frailty, age, race, marital status, and education, and number of days between blood draw and start or last day of chemo	**Pre-chemo**[a]: • Total WBC, neutrophils, NLR associated with pre-chemo frailty **Post-chemo**[a]: • Increase from pre-to-post chemo levels of total WBC, neutrophils, and NLR associated with post-chemo (4 weeks after treatment) frailty and in participants who received growth factors with chemo. *Note*: no significant associations from pre-chemo to 6 months post-chemo .**Limitations**: • Did not report power analysis

(Continued)

10.3389/fpubh.2023.1171243

TABLE 1 (Continued)

Author Year Journal Country	Sample	Tumor Type Stages Time Points	Study design	Frailty instruments	Molecules measured	Statistical methods	Key findings[a,b]
Harneshaug 2019 Journal of Geriatric Oncology Norway	255 participants • 127 Frail • 128 Non-frail **Age**: (mean = 76.7) Frail group (mean = 77.4) Non-frail (mean 75.5) **Sex**: Female 44% Male 56% **Race/ethnicity**: Not reported	**Mixed Sample**: • Breast • Prostate • Other GI • Lung • Colorectal • Other **Stages**: • Localized • Locally-advanced • Metastatic **Time Points**: Pre-treatment	**Prospective longitudinal**	• **Modified GA domains for Balducci's criteria** **Components of Assessment**: • ADL • Comorbidity Cognitive function • Depressive symptoms • Falls • Nutritional status • Physical function • Polypharmacy	• GPS (ratio of *Albumin* and *CRP*) • IL-6 • TNF-α	Logistic regression controlling for tumor type, stage of disease, BMI, use of anti-inflammatory meds.	• **GPS 2**[a] significantly associated with frailty **Limitations**: • Heterogenous sample and treatment modalities • Higher detection level on ELISAs (higher ULD) • Did not report power analysis
Hatse 2014 Public Library of Science (PLOS) One Belgium	*20 Validation Cohort* • 10 Older Fit • 10 Older Frail *Note*: only validation cohort of older adults received frailty assessment and is included in this review. **Age**: Older fit (mean 78, range 71–83) Older non-fit (mean 78, range 73–91) **Sex**: Female 100% **Race/ethnicity**: Not reported	Breast Cancer **Stages**: I-III **Time Points**: Pre-treatment	**Cross-sectional**	• **Balducci** • **LOFS** **Balducci**: presence of any of the below criteria (24): ≥85 years ≥1 ADl dependence ≥1 Comorbidity ≥1 geriatric syndrome **Components of LOFS**: • ADL • iADL • Comorbidities • Mental state • Nutritional scale	miR-320b miR-301a miR-210 miR-21 miR-376a miR-378 miR-374a miR-423-5p miR-20a-3p let-7d miR-191 miR-200c miR-30b-5p miR-140-5p miR-106b	Two group tests with Dunn-Bonferroni correction	No differences between fit and frail groups (Balducci and LOFS) **Limitations**: • Did not report power analysis • Small sample size • Did not report multivariate analyses

(Continued)

10.3389/fpubh.2023.1171243

TABLE 1 (Continued)

Author Year Journal Country	Sample	Tumor Type Stages Time Points	Study design	Frailty instruments	Molecules measured	Statistical methods	Key findings[a,b]
Lealdini 2015 Journal of Geriatric Oncology Brazil	52 participants **Age**: (median 72.5, range 65–97) **Sex**: 56% Male 44% Female **Race/ethnicity**: Not reported	**Mixed Sample**: Breast Prostate Stomach Colorectal Head and Neck Lung Endometrial **Stages**: Localized Metastasized **Time Points**: Pre-treatment	**Cross-sectional**	• **Edmonton Frailty Scale (EFS)** **Components of Assessment**: • ADL • Cognition • Depression/mood • General health status • Incontinence • Nutrition • Physical function • Polypharmacy • Social support	mGPS, (ratio of *Albumin* and *CRP*)	ANOVA with Bonferroni test or Student T test followed by logistic regression to establish relative risk.	**mGPS 0:** • Patients with lower mGPS (0) had lower scores on EFS compared to the mGPS of 2 **mGPS 2**[a]: • Patient with mGPS of 2 were 7.5 more likely to have severe frailty **Limitations**: • Did not report power analysis • Small sample size • Did not report multivariate analyses
Navarro-Martinez, 2019 In Urologic Oncology: Seminars and Original Investigations Spain	92 participants 46 Cancer group 46 Control group **Age** (cancer group): (mean 72.2, SD = 9.4) **Sex** (cancer group): Male 100% **Race/ethnicity**: Not reported	**Prostate Cancer** **Stages**: I-IV **Time Points**: During treatment (ADT)	**Cross-sectional**	• Fried Frailty Phenotype **Components of Assessment**: • Exhaustion • Physical activity • Walking speed • Weakness • Weight loss	• CRP • Creatinine • Erythrocytes • Fibrinogen • Glomerular filtration rate • Glucose • Hemoglobin • IL-1β • IL-6 • IL-8 • Leukocytes • Lymphocytes • Platelets • TNF-α	ANOVA or Kruskal Wallis with posthoc Tukey test for CBC values ANOVA or Kruskal Wallis followed by logistic regression for cytokines	• **Cancer group**[a]: higher log IL-6 and fibrinogen were associated with higher odds ratio of being frail • **Control group**: significant difference in IL-6, IL-8, CRP with frailty syndrome (Kruskal Wallis). **Limitations**: • Demographic data not reported for the control group • Did not report post-hoc or multivariate analyses for the control group • Did not report power analysis • Small sample

(Continued)

10.3389/fpubh.2023.1171243

TABLE 1 (Continued)

Author Year Journal Country	Sample	Tumor Type Stages Time Points	Study design	Frailty instruments	Molecules measured	Statistical methods	Key findings[a,b]
Nishijima 2017 Aging United States	133 participants **Age**: (median 74, range 65–92) **Sex**: Female 80% Male 20% **Race/ethnicity**: White 88% Non-White 12%	**Mixed Sample**: Breast Genitourinary Gastrointestinal Lung Other **Stages**: I–IV **Time Points**: Pre-treatment	**Cross-sectional**	• **Carolina Frailty Index (CFI)** **Components of Assessment**: • iADL • Cognitive Function • Comorbidities • Hearing • Falls • Medications • Mental health • Mobility • Nutritional status • Physical function • Social activity • Vision	• Lymphocytes • LMR • Neutrophils • NLR • Monocytes • Platelets • PLR • Total WBC	Spearman correlation test followed by multivariable linear and logistic regression controlling for age, sex, race, education, marital status, cancer type, cancer stage	• NLR positively correlated with CFI **Pre-frail *vs* frail**[a]: • Patients with NLR at top teritles had higher odds of being pre-frail and frail. **Limitations**: • Did not report power analysis
Ronning 2010 Age and Aging Norway	137 participants **Age**: (median 80 range 70–94) **Sex**: Female 55% Male 45% **Race/ethnicity**: Not reported	**Colorectal Cancer Stages**: • Localized • Regional lymph Node metastases • Distant metastasis • Not determined **Time Points**: Pre-treatment	**Prospective longitudinal**	• **Fried Frailty phenotype** • **CGA frailty categories** **Components of Fried frailty phenotype**: • Exhaustion • Walking speed • Weakness • Weight loss • Low physical activity **Components of CGA frailty**: • ADL • Comorbidities • Cognitive function • Depression • Functional Dependence • Nutritional Status • Polypharmacy	• CRP • IL-6 • TNF-a • D-dimer	Kruskal-Wallis followed by Mann–Whitney U test with Bonferroni correction	**FFP results**[b]: • CRP and IL-6 were higher in frail versus pre-frail groups for both frailty phenotypes • TNF-α levels were also significantly higher in pre-frail versus robust group **CGA results**[b]: • CRP and IL-6 were higher in intermediate versus fit and frail versus intermediate groups • TNF-α was significantly higher in frail than intermediate group **Limitations**: • Did not report power analysis • Did not report multivariate analyses for frailty outcomes • Small sample

(Continued)

10.3389/fpubh.2023.1171243

studies which included participants on treatment ($n = 6$, 43%), three studies in prostate cancer ($n = 3$, 21%) had patients receiving ADT and three studies with participants with breast cancer had patients on adjuvant or neoadjuvant chemotherapy and/or endocrine treatment.

Evaluation of the association between biomarker levels and frailty occurred cross-sectionally in 11 studies (Figure 2). Two studies reported an evaluation of the association between the biomarker and frailty at multiple time points (26, 29). Buigues and authors (26) evaluated the association during treatment (six months or greater on treatment) and at one-year follow-up, notably, authors do not indicate one-year follow-up as post-treatment. Another study (29) evaluated the association of pre-treatment cell counts with pre-treatment frailty scores and an increase in cell counts from pre-treatment to four weeks or six months post-treatment with post-treatment frailty scores. Gilmore and authors (28) evaluated pre-treatment levels of cytokines as predictors of post-treatment frailty, but not at each time point.

3.3. Assessments of phenotypic frailty/ deficit accumulation

Frailty measurements varied greatly across the 14 studies. Fried frailty phenotype (FFP) was the most common instrument used ($n = 6$). The instrument's prespecified criteria were applied across four studies (26, 31, 36, 38), where "frail" was defined as the presence of three or more components, "pre-frail" with one to two components, and "robust" with zero components (7). However, three studies used a modified version of the FFP, where two reports did not include unintended weight loss (28, 29) and one study replaced unintended weight loss with obesity (38).

Eight studies measured frailty as a deficit accumulation index or geriatric vulnerability scores using the Leuven Oncogeriatric Frailty Score (27, 32, 34), Balducci criteria (27, 30, 32, 34), Flemish Triage Risk Screening Tool (fTRST) (27), G8 (27), geriatric assessment domains (30, 31), the geriatric vulnerability score (23), the Edmonton frailty scale (35), and the Carolina frailty index (37). One study (23) used geriatric assessment domains that also included hypoalbuminemia and lymphopenia as two additional vulnerabilities calculated into the total geriatric vulnerability score. Two studies did not report which domains were assessed in comprehensive geriatric assessment (CGA) (33), Flemish Triage Risk Screening Tool, Balducci, or the G8 (27).

Four studies used multiple deficit accumulation frailty tools (Table 1). Two reports used the Balducci frailty category together with Leuven Oncogeriatric Frailty Score (32, 34); whereas, one study added the Flemish Triage Risk Screening Tool and G8, in addition to Balducci and Leuven Oncogeriatric Frailty Score (27). Although the frailty scores differed based on the instrument applied to either continuous scoring and/or frailty group categories, the authors reported frailty scores and their association with biomarkers across all the tools used (27, 31, 32, 34).

3.4. Blood-based biomarkers

Peripherally circulating blood-based markers were measured across all 14 studies to evaluate their association with frailty. Only one

TABLE 1 (Continued)

ADL, activities of daily living; ADT, androgen deprivation therapy; iADL, instrumental ADL; α, alpha; CFI, Carolina frailty index; IL, interleukin; IGF, insulin-like growth factor 1; MCP-1, monocyte chemoattractant protein-1; RANTES, regulated upon activation, normal T cell expressed and secreted; fTRST, Flemish triage risk screening tool; HADS, Hospital anxiety depression scale; EFS, edmonton frailty scale; CGA, comprehensive geriatric assessment; GA, geriatric assessment; TNF-α, tumor necrosis factor -α; SD, standard deviation; TST, time since treatment; CRP, C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; LOF, Leuven Oncogeriatric Frailty Score; miRNA, micro RNA; GPS, Glasgow prognostic score; mGPS, modified GPS; sTNFR I, soluble TNF receptor I; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; WBC, white blood cells; ECOG-PS, Eastern cooperative oncology group performance scale.

[a]Denotes findings that remained significant after inclusion in multivariate analyses.

[b]Denotes findings that remained significant after post hoc analyses.

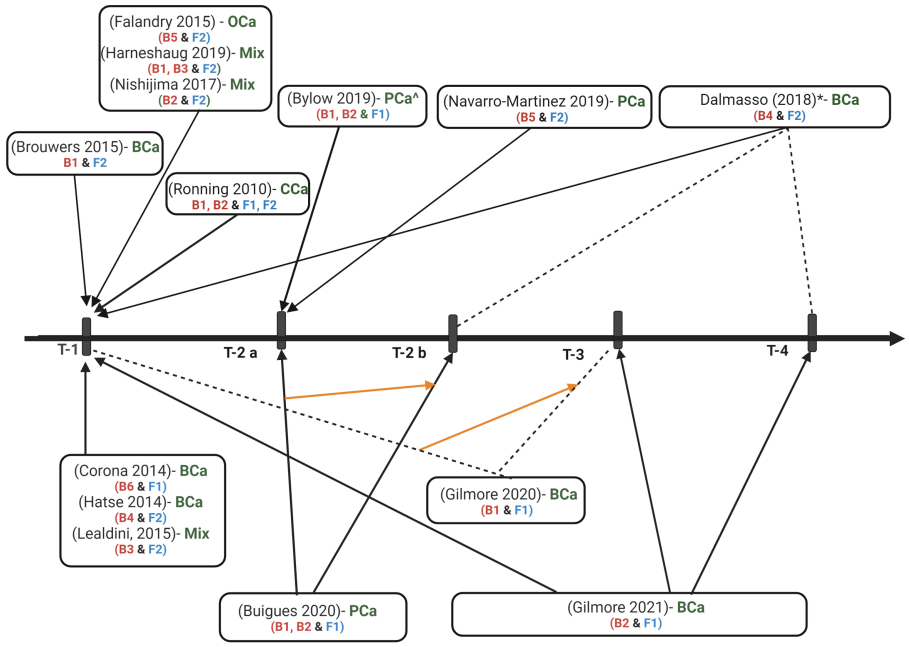


FIGURE 2
Time-points for frailty and biomarker assessments. T-1=pre-treatment (pre-surgery or post-surgery but pre-adjunctive therapy), T-2 a=during treatment (T-2 b=follow up since treatment beginning but not post-treatment), T-3=4weeks post-treatment, T-4=6months or greater post-treatment, BCa=breast cancer, PCa=prostate cancer, mix=mix solid tumors, Oca=ovarian cancer, CCa=colorectal cancer, B1=cytokines, cytokine receptors, and acute phase proteins, B2=molecules from complete blood count, lipid panel, or chemistry panel, B3=glasgow prognostic score (GPS), B4=micro RNAs, B5=telomere length, B6=metabolomics, F1=physical frailty phenotype measured by fried frailty phenotype tool, F2=deficit accumulation or geriatric vulnerability based frailty measured by geriatric assessment (GA) or GA domains (Balducci score, Leuven Oncogeriatric Frailty Score, Comprehensive Geriatric Assessment, Flemish Triage Risk Screening Tool, geriatric vulnerability score, Edmonton Frailty Scale, and Carolina Frailty Index). *=timeline is the same for cancer group with chemotherapy and without. ^control group with history of PCa, post-surgery or radiation therapy. Biomarker levels, frailty scores, and the association was measured between the two, pre-treatment biomarkers were associated with post-treatment frailty scores, biomarker levels and frailty scores were measured but did not evaluate the association between the two.

report found no significant association with frailty in any of the markers measured (34). The statistically significant findings (p values < 0.05) identified in this review are presented below and categorized into six categories: cytokines/cytokine receptors and acute phase reactants; complete blood count; Glasgow Prognostic Score; microRNAs; telomere length; and metabolomics (Figure 3).

3.5. Cytokines, cytokine receptors, and acute phase reactants

Cytokines, cytokine receptors, and acute phase reactants associated with frailty included: interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α, soluble TNF receptor I (TNFR I), soluble TNFR II, C-reactive protein (CRP), and fibrinogen (Figure 3). Results are separated by frailty construct and time points for frailty measurements.

3.5.1. Phenotypic frailty: pre-treatment

Pre-treatment levels of IL-6, TNF-α, and CRP were significantly associated with increased phenotypic frailty in colorectal tumors (31). Of note, while Gilmore and authors (28) measured pre-treatment levels of IL-6, the associations were tested with post-treatment frailty scores, therefore, the results are described below.

3.5.2. Phenotypic frailty: during treatment

Higher levels of IL-6 were associated with higher phenotypic frailty in prostate cancer during androgen deprivation treatment (ADT) (26, 36) and at one-year follow-up (26). However, IL-6 and CRP were not associated with higher phenotypic frailty on six months of ADT in another prostate cancer cohort (38). While Buigues and authors (26) found that higher levels of IL-8 were associated with frailty at inclusion (six months or greater on ADT), IL-8 was no longer associated with frailty at one-year follow-up from inclusion. Similarly, another study (36) reported null findings during treatment, whose cohort had an average of 106 months from diagnosis. The two cohorts reported mixed findings on the association of fibrinogen with phenotypic frailty, where Navarro-Martinez and authors (36) found that higher levels of fibrinogen were associated with frailty, but Buigues and authors (26) reported null findings. Findings were also null for CRP, IL-1β, and TNF-α in these two prostate cancer cohorts (26, 36).

Of note, while Navarro-Martinez and authors (36) also included a non-cancer control group, the adjusted results with posthoc analysis were reported for the ADT group but not the control group, making their comparison challenging. Unadjusted higher levels of CRP, IL-6, and IL-8 were associated with greater frailty in the non-cancer control group.

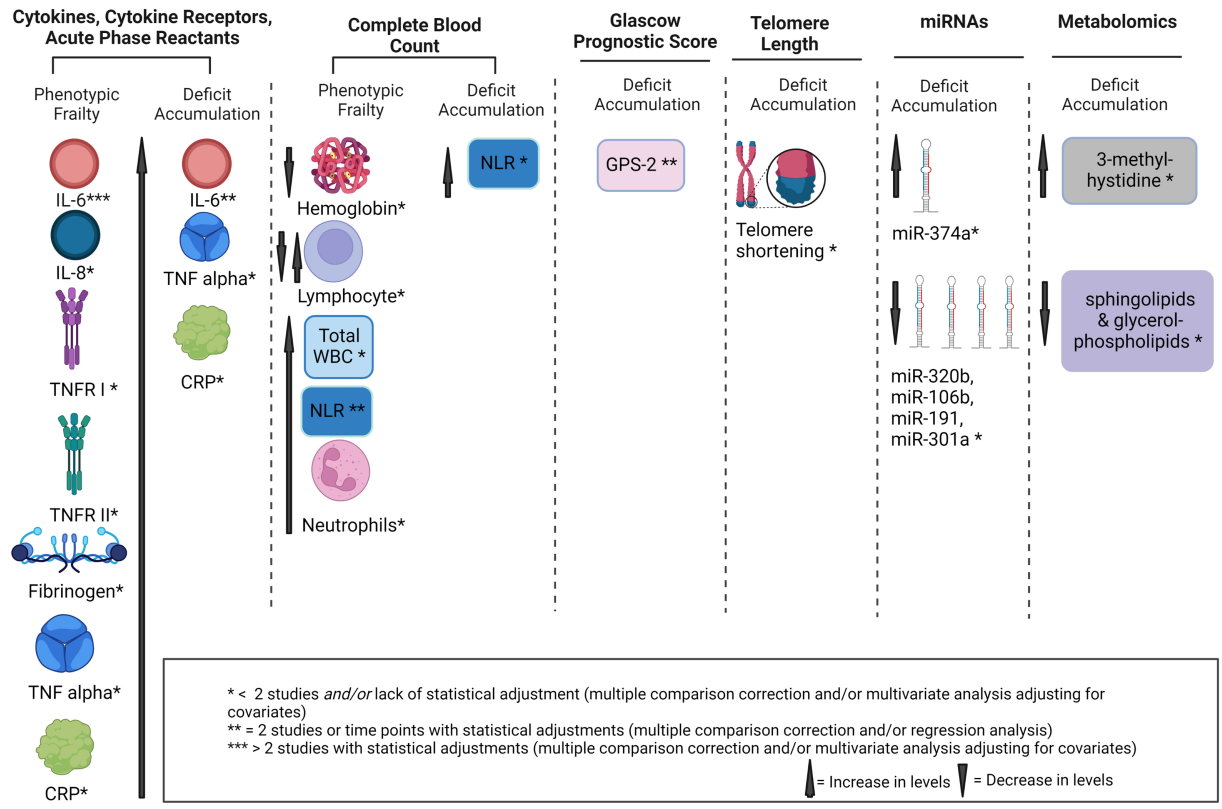


FIGURE 3
Potential biomarkers of frailty in solid tumors. IL, interleukin, GA, geriatric assessment, TNF-α, tumor necrosis factor-α, CRP, C-reactive protein, miRNA, micro RNA, GPS, glasgow prognostic score, sTNFR I, soluble TNF receptor I, NLR, neutrophil to lymphocyte ratio, WBC, white blood cells.

3.5.3. Phenotypic frailty: post-treatment

Pre-treatment levels of IL-6, soluble TNFR I and II were significantly associated with four weeks post-treatment phenotypic frailty in the breast cancer group. Notably, no associations were found with any of the biomarkers in the age-matched non-cancer group (28).

3.5.4. Deficit accumulation frailty: pre-treatment

In pre-treatment studies, IL-6 was significantly associated with increased deficit accumulation frailty (Balducci and Leuven Oncogeriatric Frailty Score) in breast cancer (32). In patients with colorectal cancer (31), authors reported increasing trends of IL-6 and CRP across stratified levels of deficit accumulation frailty (geriatric assessment domains) ranging from fit to frail. Authors also found higher levels of TNF-α in frail versus intermediate groups (31). However, no association between IL-6 or TNF-α and greater frailty (Balducci criteria) was found in mixed solid tumors (30).

3.6. Complete blood count

Five studies investigated the association between markers of complete blood count and frailty (26, 29, 36–38).

3.6.1. Phenotypic frailty: pre-treatment

At pre-treatment, greater total white blood cell (WBC) count, neutrophils, and neutrophil-lymphocyte ratio (NLR) were associated with phenotypic frailty in patients with breast cancer (29). However, hemoglobin was not associated with frailty in the same cohort (29).

3.6.2. Phenotypic frailty: during treatment

During ADT, Buigues and authors (26) found that a higher lymphocyte count was associated with significant odds of being frail in patients six months or greater on ADT. In contrast, a lower lymphocyte count was associated with frailty progression at a one-year follow-up (26). In another prostate cancer cohort, lower hemoglobin was found in the ADT group compared to the non-ADT control group (38). The authors did not find a significant association with other cell markers. Similarly, total WBC, leukocyte counts, or hemoglobin did not predict frailty states in another study (36).

3.6.3. Phenotypic frailty: post-treatment

Pre-to post-treatment increases in WBC, neutrophils, and NLR predicted greater four-week post-treatment frailty in breast cancer, however, none of these markers were significant predictors of six months post-treatment frailty (29). Null findings were reported for

hemoglobin or other cell markers in breast cancer post-treatment (29).

3.6.4. Deficit accumulation frailty: pre-treatment

One study was found to evaluate complete blood count with deficit accumulation frailty at pre-treatment in mixed tumor types. Authors (37) found that greater NLR was associated with frailty (Carolina Frailty Index), however, they found null findings in total WBC or other cell counts.

3.7. Glasgow prognostic score

3.7.1. Deficit accumulation frailty: pre-treatment

Glasgow Prognostic Score (GPS), the ratio between CRP and albumin, was tested as a biomarker of frailty in two studies (30, 35). Both studies included patients with mixed solid tumors in the pre-treatment phase (30, 35) and found GPS 2 (elevated CRP and hypoalbuminemia) to be significantly associated with deficit accumulation frailty (Balducci criteria and Edmonton Frailty Scale).

3.8. MicroRNAs

3.8.1. Deficit accumulation frailty: pre-treatment

Two studies evaluated microRNAs (miRNAs) as biomarkers of deficit accumulation frailty (Balducci, Leuven Oncogeriatric Frailty Score, Flemish Triage Risk Screening Tool, G8) in patients with breast cancer (27, 34) at pre-treatment. Dalmasso and authors (27) found that higher miR374a and lower miR-320b levels were associated with lower frailty using the Leuven Oncogeriatric Frailty Score and levels of miR-301a negatively correlated with frailty using Flemish Triage Risk Screening Tool scores. In addition, lower miR-106b, miR-191, miR-320b, and higher miR-374a emerged as independent predictors of deficit accumulation frailty using G8 (27). In comparison, Hatse and authors (34) reported null findings for 15 evaluated miRNAs and deficit accumulation frailty (Balducci, Leuven Oncogeriatric Frailty Scores).

3.9. Telomere length

3.9.1. Deficit accumulation frailty: pre-treatment

Two studies evaluated the relationship between telomere length and deficit accumulation frailty (Balducci, Leuven Oncogeriatric Frailty Score, geriatric vulnerability score) at pre-treatment (23, 32). In patients with ovarian cancer, shorter telomere length was associated with a geriatric vulnerability score $\geq$3 (23). However, findings were null in patients with breast cancer (32).

3.10. Metabolomics

3.10.1. Deficit accumulation frailty: pre-treatment

The search yielded only one study that evaluated a metabolomic profile of different amino acids, acylcarnitines, and phospholipids as biomarkers of deficit accumulation frailty (comprehensive geriatric assessment) in patients with breast cancer (33). The authors found greater age-adjusted ß3-methyl-hystidine levels in unfit and frail groups compared to the fit group. Similarly, they found depletion of several sphingolipids and glycerol-phospholipids in unfit and frail groups compared to fit (Table 1).

3.11. Risk of bias and quality assessment

The risk of bias and quality assessment results are presented in Table 2. Interrater reliability for cross-sectional and cohort studies between the two reviewers was 83 and 67% for the case–control study. Six studies were rated as good (23, 26, 27, 29–31), while the remaining eight were rated as fair. Several areas of potential bias in this body of literature were identified: participant sampling procedures, power analyses, measurement biases, instrumentation, and statistical methods. Most of the cohort studies (12/13) reported selecting participants during the same period and applying inclusion criteria uniformly (23, 26–35, 37). One study selected prostate cancer group undergoing ADT and the control group from nursing home facilities, thus the two groups differed in diagnosis, active treatment, clinical setting and therefore were rated as dissimilar or "no" for the criterion on sampling methodology (question 4) (36).

None of the included studies reported sample size justification through power analysis. Among the observational longitudinal cohorts, four studies (23, 28, 30, 31) measured biomarkers at only one-time points, while reporting longitudinal outcomes such as survival. Thus, these four studies received a "no" rating for the repeated exposure measurement criterion. Among the evaluation of outcome (frailty), over half of the reports either did not use previously validated cut-off scores or modified existing tools without prior validation. All studies were either missing blinding procedures or failed to report them, thus potential risk for bias could not be determined. Only seven studies (23, 26–30, 37) controlled for confounders through multivariate analyses. Lack of multivariate analyses may introduce potential confounding bias in overestimation or underestimation of markers' impact on frailty. In the single case-control study, the investigators did not provide sample size justification or blinding procedures (38). The investigators also did not specify if concurrent controls were used or if 100% of eligible cases were recruited, thus, it was unclear if participants in the control group were recruited at the same time as cases. Measures of association or effect sizes were not reported or partially reported in seven included studies (28, 31–33, 35, 36, 38; Supplementary Table S4).

4. Discussion

In our review evaluating biomarkers of frailty in solid tumors, we identified IL-6, NLR, and GPS 2 as potential biomarkers of frailty found across two or more studies. To our knowledge, this is the first systematic review evaluating existing biomarkers of frailty in patients with solid tumors. While the inclusion criteria included all solid tumors, the search yielded findings in breast, prostate, mixed solid tumors, ovarian, and colorectal cancers with no studies identified in brain, pancreatic, lung, or other solid organ cancers. The included

TABLE 2 Quality assessment.

Author and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	# of items free of bias	% of items free of bias	Qualitative rating
Observational cohort[a]																	
Buigues et al. 2020	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes	Yes	12	86	Good
Dalmasso et al. 2018	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	CD	Yes	Yes	11	79	Good
Falandry et al. 2015	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	CD	Yes	Yes	11	79	Good
Gilmore et al. 2020	Yes	Yes	NR	Yes	No	Yes	Yes	Yes	Yes	No	No	CD	Yes	Yes	9	64	Fair
Gilmore et al. 2021	Yes	Yes	NR	Yes	No	Yes	Yes	Yes	Yes	Yes	No	CD	Yes	Yes	10	71	Good
Harneshaug et al. 2019	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	CD	Yes	Yes	10	71	Good
Ronning et al. 2010	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	CD	Yes	No	10	71	Good
Cross-sectional[a]																	
Brouwers et al. 2015	Yes	Yes	NR	Yes	No	No*	No*	Yes	Yes	No*	No	CD	No*	No	5	50	Fair
Corona et al. 2014	Yes	Yes	Yes	Yes	No	No*	No*	Yes	Yes	No*	No	CD	No*	No	6	60	Fair
Hatse et al. 2014	Yes	Yes	Yes	Yes	No	No*	No*	Yes	Yes	No*	No	CD	No*	No	6	60	Fair
Lealdini et al. 2015	Yes	Yes	NR	Yes	No	No*	No*	Yes	Yes	No*	Yes	CD	No*	No	6	60	Fair
Navarro-Martinez et al. 2019	Yes	Yes	NR	No	No	No*	No*	Yes	Yes	No*	Yes	CD	No*	CD	5	50	Fair
Nishijima et al. 2017	Yes	Yes	NR	Yes	No	No*	No*	Yes	Yes	No*	Yes	CD	No*	Yes	7	70	Fair
Case–control[b]																	
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**	**Q12**	**# of items free of bias**	**% of items free of bias**	**Qualitative rating**		
Bylow et al. 2011	Yes	Yes	No	Yes	Yes	Yes	CD	CD	Yes	Yes	CD	No	7	58	Fair		

*Questions that were not applicable to cross-sectional design studies were not counted toward overall score.[a]Cohort and cross-sectional studies were evaluated using NIH quality assessment tool for observational cohort and cross-sectional.
[b]Case-control study was evaluated using the quality assessment tool for case-control studies.
[c]Cancer group had multivariate analyses but not the control group.

10.3389/fpubh.2023.1171243

studies used two distinct frailty constructs, phenotypic frailty and deficit accumulation, which are described in prior literature (10, 39, 40). These distinct frailty paradigms make synthetization challenging. We found that biomarkers were most frequently evaluated and associated with phenotypic and deficit accumulation frailty at pre-treatment although associations were found across the cancer continuum.

Inflammatory molecules were most frequently measured and significantly associated with phenotypic and deficit accumulation frailty, on par with prior reviews that evaluated biomarkers of frailty primarily in older individuals with mixed diagnoses (15–18). Cytokines, cytokine receptors, and acute phase reactants were among the most commonly measured, perhaps due to their role as modulators of cell-to-cell communication in inflammatory responses and cancer biology (41, 42).

Five studies reported elevated levels of IL-6, a pleiotropic pro-inflammatory cytokine, in patients with higher phenotypic and deficit accumulation frailty across the breast, prostate, and colorectal tumors (26, 28, 31, 32, 36). Elevated levels of IL-6 have been documented in aging, cancer progression, and the development of cancer cachexia (43). Moreover, IL-6 can be elevated in both acute and chronic immune responses by exerting stimulatory effects on T and B cells and producing acute-phase reactants (44). Included studies reported higher levels of IL-6 associated with phenotypic and deficit accumulation frailty evaluated at pre-treatment, during treatment, and four weeks post-treatment. However, two studies reported null findings: six months on ADT with phenotypic frailty (38) and with pre-treatment deficit accumulation frailty (30). Bylow and authors (38) did not find significance when comparing their ADT group (more frail group) to their non-ADT group (less frail group), which suggested that ADT-associated frailty may not be related to circulating increases in IL-6. Harneshaug and authors (30) found a significant association with pre-treatment deficit accumulation frailty, but the findings were null after adjustment for confounders. That coupled with the absence of multivariate analyses in the studies with positive findings (31, 32), suggests elevated IL-6 may be related to the clinical confounders and analytical adjustments are necessary to parse the relationships. IL-6, as a multifaceted cytokine, has been shown to be elevated in chronic inflammatory states such as aging, cancer, obesity (43, 45) and plays a role in underlying pathology of worsening disease states (18). We hypothesize that elevated levels of IL-6 in worsening frailty may be explained by a greater number of inflammation related symptoms and conditions (18).

IL-8, a pro-inflammatory chemokine, was evaluated in two of the studies (26, 36) and found to serve as a correlate of frailty during treatment (six months or greater on ADT), but not at one-year follow-up (26). In contrast, null findings were reported during treatment in another prostate cancer group (36). Although both studies (26, 36) studied IL-8 and phenotypic frailty during ADT, their discrepant findings may be owed to their analytical methods: namely, post-hoc statistical adjustment versus multivariate regression. Additionally, Navarro-Martinez and authors (36) did not report a list of variables included in the multinomial regression which made it difficult to compare to Buigues and authors (26). Thus, although IL-8 has been postulated to rise during ADT (46), the evidence remains inconclusive and is limited by these two studies with varying methods and small sample sizes (26, 36). A possible explanation for the association between IL-8 and frailty could be that frail individuals may be more susceptible to acute inflammatory response during treatment, which may manifest as reduced physical activity and increased frailty symptomology (2).

TNF-α was evaluated in four reports (26, 30, 31, 36) and found to associate with pre-treatment phenotypic and deficit accumulation frailty in colorectal cancer (31). The associations were null in pre-treatment deficit accumulation in mixed tumors (30) or during treatment with phenotypic frailty in prostate tumors (26, 36). The incongruencies for phenotypic frailty may relate to the heterogeneity in tumor types and time from treatment: pre-treatment (31) versus during treatment (26, 36). Findings were also incongruent for pre-treatment deficit accumulation frailty, where one study (31) found higher levels of TNF-α in the frail group, but another (30) had null findings after adjustment for confounding variables in the multivariate analysis. Importantly, the study by Ronning and authors (31) lacked multivariate adjustments altogether. Soluble TNFR I and II, members of the TNF superfamily, were measured only in one study with post-treatment phenotypic frailty, and findings, albeit significant, are exploratory and thus warrant additional corroborations (28). Thus, the relationships between phenotypic and deficit accumulation frailty severity and TNF-α, soluble TNFR I and II remain unclear.

Consistent with a previous meta-analysis of frailty biomarkers in primarily non-cancer diagnoses of older adults (18), CRP and fibrinogen emerged as correlates of phenotypic and deficit accumulation frailty at pre-treatment (31) and with phenotypic frailty during treatment (36). Importantly, CRP was not significant in three studies of patients with prostate tumors on ADT (26, 36, 38), whereas fibrinogen was not significant in one report (26). The finding by Ronning and authors (31) of elevated pre-treatment CRP in frail groups may correlate with tumor-mediated inflammatory response (47). However, further extrapolation would yield ambiguous conclusions, given the cross-sectional time points and lack of pre-treatment levels for comparison across all four reports. Collectively, findings for IL-6, IL-8, TNF-α, CRP, and fibrinogen suggest that higher levels of pro-inflammatory cytokines and acute phase reactants may play a role in frailty states in patients with solid tumors. Increased levels of inflammation markers may be related to cancer and its treatment effects on frail and pre-frail cancer survivors. Additionally, although we did not restrict the age of the participants for the inclusion criteria in this review, the average age across 14 studies was 72 years. Older age has a linear relationship with low grade chronic inflammation and is subsequently associated with increased comorbidity and higher vulnerability to disease, which may, in turn, be manifested as frailty signs/symptoms such as weakness, decreased physical activity, and exhaustion (16, 18).

Perturbations in neutrophils, lymphocytes, total WBC, and NLR may be related to both tumor promoting and immune suppressive roles associated with poor outcomes in solid tumors (48–52). Across the five studies that evaluated markers of complete blood counts, NLR, a quotient of neutrophil and lymphocyte counts, emerged as a significant predictor of pre-treatment and post-treatment phenotypic frailty in breast cancer (29) and pre-treatment deficit accumulation frailty in mixed tumor types (37). High NLR has been shown to associate with greater phenotypic and deficit accumulation frailty in

cancer survivors, patients with cardiovascular disease, and community dwelling older adults (15). Notably, the study by Gilmore and authors (29) found associations between increased NLR, total WBC, neutrophils and frailty scores pre-chemotherapy and four weeks post-chemotherapy; however these markers and frailty scores returned to baseline six months post treatment. We hypothesize the observed elevations in NLR, total WBC, neutrophils and their association with increased frailty symptomology may be related to an acute inflammatory response to cancer pathology and treatment effects.

Higher lymphocyte levels were associated with phenotypic frailty during treatment in patients on ADT six months or greater prior to inclusion; however, when evaluating progression to frailty at one year follow-up, lower lymphocyte levels associated with the likelihood of being frail (26). The discrepancy may relate to the frailty scores at inclusion versus one year follow-up, reflecting the long-term effect of ADT on frailty progression and the potential effect on lymphopoiesis (53). Additionally, decreased physical activity (a component of frailty phenotype) was previously reported to be associated with lower lymphocyte counts, whereas increased physical activity was associated with higher lymphocyte counts. Prior scoping review also documented an association between lower lymphocyte counts in the presence of frailty (15). Lymphocyte counts did not associate with phenotypic frailty pre-or post-treatment in the breast (29) or pre-treatment deficit accumulation in mixed solid tumors (37). The discrepant findings across the three studies may be related to heterogeneity in the types of solid tumors and frailty definitions.

Hemoglobin, a marker of anemia, was evaluated in three studies and was found to be associated with phenotypic frailty in patients with prostate tumors six months on ADT (38). However, this association was not corroborated by the other two reports with phenotypic frailty before and during treatment in neither prostate nor breast tumors (29, 36). The association found by Bylow and authors (38) may relate to the inverse relationship between androgen deprivation treatment and hemoglobin levels, where treatment may cause decline in hemoglobin (53). ADT-related lower hemoglobin (i.e., anemia) has been associated with symptoms such as fatigue and decreased activity (53), thus, it is plausible that lower hemoglobin in the study by Bylow and authors (38) may be related to the exhaustion and decreased physical activity symptoms/components of the phenotypic frailty.

GPS, the ratio between CRP and albumin, has been extensively validated as a biomarker of poor prognosis in cancer (54). GPS includes scores of 0, 1, 2, with scores $\geq$2 signifying both hypoalbuminemia (<35 g/L) and elevated CRP levels (>10 mg/L) (54). While CRP is a pro-inflammatory molecule, hypoalbuminemia reflects poor nutritional status associated with increased mortality in patients with cancer (55). In this review, two reports found GPS 2 to significantly associate with deficit accumulation frailty at pre-treatment with moderate to excellent specificity (30, 35). Previously, GPS 2 was shown to associate with cancer-related cachexia, weight loss, and poor performance status (54, 56); however, the two reports which evaluated frailty with GPS in the present review did not measure weight loss. Additionally, pronounced inflammatory response induces hypoalbuminemia (57), and the aging process, itself has been linked to lower levels of albumin (58). Because the patients included in the aforementioned reports were >70 years of age with mixed solid tumors, stages, and treatments (30, 35), we hypothesize that GPS 2 (i.e., elevated CRP and hypoalbuminemia) may be related to the physiological processes underlying cancer, aging, and geriatric vulnerabilities which comprised the deficit accumulation frailty scores.

Epigenetic alterations are another hallmark of aging (11) and are causally related to miRNA dysregulations in cancer (59). Among the reports included, two studies evaluated aging-related miRNAs as molecular correlates of pre-treatment deficit accumulation frailty. Dalmasso and authors (27) found an association between higher levels of aging-related miR-320b and higher frailty using the Leuven Oncogeriatric Frailty Score (LOFS) but not with the Balducci score. They also report an inverse relationship with G8 scores and miR-106b, miR-191, and miR320b, suggesting lower levels are associated with higher scores. Given the established link between the miRNAs with aging process (11) and their dysregulation in cancer biology (59), we hypothesize the exploratory findings reported by Dalmasso and colleagues (27) may be related to the older age of participants included (median age > 74 years), cancer biology, and amalgamation of geriatric deficits comprising LOFS and G8. In contrast, a report by Hatse and authors (34) did not find these associations in a smaller cohort of older frail ($n = 10$) patients with breast cancer. The validation study by Hatse and authors (34) was used as pilot validation cohort and nonsignificant findings in relation to frailty may relate to the smaller sample size. Additional studies are warranted to further extrapolate relationship between aging miRNAs and phenotypic/deficit accumulation frailty phenotypes.

Telomere length also associates with pre-treatment deficit accumulation frailty. Telomeres are nucleoprotein structures located at the chromosomal ends and telomere length attrition is attributed to telomerase deficiency and lack of DNA repair (11, 60). Telomere dysfunction, linked to cell senescence, apoptosis (11), and tissue inflammation, gives rise to diseases with inflammatory components such as cancer (60). While shorter telomere length was associated with greater pre-treatment deficit accumulation frailty in patients with ovarian cancer (23), findings were null in patients with breast cancer (32). This discrepancy may be due to the varying geriatric domains that comprise the geriatric vulnerability score (23), Baducci, and the Leuven Oncogeriatric Frailty Score (32). Given the previously established bidirectional link between inflammation and telomere attrition (61), it is plausible that the shorter telomere length found in the ovarian cancer cohort (23) relates to inflammation and hypoalbuminemia components of GVS. Conversely, shortened telomere length may also relate to differences in stages of cancer: stages I–III in the breast cancer cohort (32) compared to stages III–IV in the ovarian cancer cohort (23). The evidence presented here does not support the extrapolation of the link between shorter telomere length and frailty state in solid tumors. Additional studies investigating telomere capacity as biomarkers of frailty are needed to compare frail versus non-frail cohorts with similar age, disease, and treatment before this finding can be confirmed.

Only one study incorporated a global approach by using metabolomics to investigate a comprehensive profile of amino acids, acylcarnitines, and phospholipids in association with pre-treatment deficit accumulation frailty (33). Metabolomics is

a powerful tool that enables researchers to profile endogenous metabolites and metabolic pathways underlying disease (62, 63). Researchers propose that metabolomics may capture the multifactorial frailty profiles (63). Corona and authors (33) found that age-adjusted 3-methylhistidine (3MHis) was elevated and levels of sphingolipids and glycerophospholipids were decreased in frail patients with breast cancer. Higher 3MHis relates to skeletal muscle loss observed with older age (64) in healthy adults, whereas the dysregulation of sphingolipids and glycerophospholipids relates to the progression of metabolic disease (65). A recent study evaluating the metabolomic profile of frailty phenotype in healthy older adults stratified by gender identified modulators of prefrailty phosphatidylglycerol (26:1) and dimethyloxazale for men and threonine, fructose, mannose, dihydroxyphenyl acetic acid, and 2,4-aminobutyric acid for women (66). While the metabolites in the two studies differed, the metabolomics results suggest perturbations in the metabolites may be associated with frailty, but further validation in each solid tumor type is needed.

Interpreting these results requires caution due to several limitations. First, the studies' frailty instruments measured different constructs of frailty, including phenotypic versus deficit accumulation frailty. Our findings here highlight variations in the constructs, operationalization, and instruments used to assess frailty, of which some were validated. These issues are echoed by findings from previous reviews (40, 67) and a clinician survey (68) of limited validity across instruments and different operationalizations of the frailty concept. Modification of existing tools and lack of validity and reliability support for novel tools collectively threaten the internal and external validity of findings in this body of literature.

Second, great heterogeneity in analysis was found across studies. While some reports incorporated multiple logistic regression, others used bivariate correlations and tests by three groups (e.g., Kruskal-Wallis) to draw associations between the molecular correlates and frailty scores. We found that several studies did not report multiple comparison corrections and adjustments for significant covariates, which would introduce type II error and the potential for multicollinearity. The variation in statistical approach makes it difficult to synthesize findings across studies.

Third, included studies did not report power analyses, although the majority reported smaller sample sizes. This indicates that the evidence is, at this point, largely exploratory and warrants larger corroborative investigations. Moreover, only half the included studies reported measures of association/effect sizes for statistically significant results, which limits our ability to comment on clinically meaningful effect. Future investigations would benefit from reporting effect size calculations to better inform science of biomarker discovery for frailty phenotypes. Fourth, molecule selections were often limited to a few nonspecific markers of inflammation. This reflects the state of science in biomarker development for frailty. Fifth, most of the included studies lacked control groups (i.e., non-cancer or healthy controls), thus it was challenging to determine the strength of association with frailty in the absence of solid tumors and treatments. In addition, IL-6, TNF-α, and CRP are repeatedly found to be elevated in a myriad of conditions linked to inflammation, such as obesity and smoking (45, 69). Therefore, future studies should include these relevant health characteristics as covariates in biomarker discovery studies. Additionally, there was heterogeneity in the type of treatments received among studies during treatment and/or post-treatment. Future studies may benefit from comparing the effects of different treatment types and modalities on frailty profiles and biomarker oscillation. Lastly, current literature lacks stratification by sex, race, and ethnicity, which decreases the generalizability and specificity of the results, and may also hinder our progress in developing targeted interventions.

5. Conclusion

In summary, IL-6, NLR, and GPS 2 emerged as potential biomarkers of frailty found in two or more of the included studies (Figure 3). Although IL-6 emerged as potential biomarker in five out of seven reports that measured this cytokine, findings remain inconsistent. Findings are inconclusive and were limited by number of reports found for all other measures. Our findings show that the current literature employs varying conceptual definitions of and instruments measuring frailty and that the genesis of frailty in solid tumors may be multifactorial, impacted by time since cancer diagnosis, treatments, and unique biology of individual solid tumors. Our findings highlight a need for further instrument validations and clear conceptual and operational definitions of frailty within the oncology field. Only two reports evaluated associations with biomarkers longitudinally. These two reports found that higher levels of inflammatory markers may serve as predictors of phenotypic frailty four weeks post-treatment (29) or at one year follow-up in patients with prostate cancer on ADT (26), however, further investigations are warranted with longer follow-up times. Post-treatment phenotypic frailty was captured four weeks (28, 29) and six months post-treatment (29), without data for pre-treatment (28) or during treatment (28, 29). The evidence highlights a substantial gap in long-term survivorship and frailty biomarkers evaluated longitudinally from pre-treatment to months and years post-treatment.

Collectively, the reports included in this review suggest that inflammatory pathways related to the proliferation of immune cells at the time of diagnosis and treatment are associated with frailty development and symptomology. Limited reports (one each) also implicate telomere shortening and epigenetic alterations such as perturbations in aging miRNAs as potential correlates of deficit accumulation frailty. Additionally, metabolic pathways underlying deficit accumulation frailty may be of potential value when identifying target biomarkers. Given the paucity of evidence across the diverse set of biomarkers searched, the field of frailty biomarkers in solid tumors is largely underexplored. Future studies will benefit from longitudinal studies with a comprehensive set of biomarkers adjusted for cancer stages, time since diagnosis and treatment, and type of treatment; larger sample sizes, robust control groups, and multiple time points by sex, gender, and race/ethnicity. Such investigations will aid the development of robust biomarker profiles, early identification of cancer survivors at risk for developing frailty, and timely referral to therapeutic interventions.

Author contributions

DS and TA: conceptualization. DS, BP, DC, and TA: data curation and methodology. DS: formal analysis, project administration, and visualization. DS and BP: investigation and validation. TA: supervision. TA and DC: resources. DS, BP, VG, JG, and TA: writing—original draft. DS, BP, VG, DC, JG, and TA: writing—review and editing. All authors contributed to the article and approved the submitted version.

Funding

This research was supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health.

Acknowledgments

Our research team would like to thank Nancy Touchette, Ph.D., National Institutes of Health Office of Intramural Training & Education writer and editor, for manuscript editing assistance.

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/fpubh.2023.1171243/full#supplementary-material

References

1. Hurria A, Jones L, Muss HB. Cancer treatment as an accelerated aging process: assessment, biomarkers, and interventions. *Am Soc Clin Oncol Educ Book*. (2016) 35:e516–22. doi: 10.1200/EDBK_156160

2. Guida JL, Ahles TA, Belsky D, Campisi J, Cohen HJ, DeGregori J, et al. Measuring aging and identifying aging phenotypes in cancer survivors. *JNCI*. (2019) 111:1245–54. doi: 10.1093/jnci/djz136

3. Henderson TONess KK, Cohen HJ. Accelerated aging among cancer survivors: from pediatrics to geriatrics. *Am Soc Clin Oncol Educ Book*. (2014) 34:e423–30. doi: 10.14694/EdBook_AM.2014.34.e423

4. Hayek S, Gibson TM, Leisenring WM, Guida JL, Gramatges MM, Lupo PJ, et al. Prevalence and predictors of frailty in childhood cancer survivors and siblings: a report from the childhood cancer survivor study. *J Clin Oncol*. (2020) 38:232–47. doi: 10.1200/JCO.19.01226

5. Ness KK, Wogksch MD. Frailty and aging in cancer survivors. *Transl Res*. (2020) 221:65–82. doi: 10.1016/j.trsl.2020.03.013

6. Feliciano EMC, Hohensee C, Rosko AE, Anderson GL, Paskett ED, Zaslavsky O, et al. Association of prediagnostic frailty, change in frailty status, and mortality after cancer diagnosis in the women's health initiative. *JAMA Netw Open*. (2020) 3:e2016747. doi: 10.1001/jamanetworkopen.2020.16747

7. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol Ser A Biol Med Sci*. (2001) 56:M146–57. doi: 10.1093/gerona/56.3.m146

8. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. *J Am Geriatr Soc*. (2010) 58:681–7. doi: 10.1111/j.1532-5415.2010.02764.x

9. Cesari M, Gambassi G, Abellan van Kan G, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. *Age Ageing*. (2014) 43:10–2. doi: 10.1093/ageing/aft160

10. Kuchel GA. Frailty and resilience as outcome measures in clinical trials and geriatric care: are we getting any closer? *J Am Geriatr Soc*. (2018) 66:1451–4. doi: 10.1111/jgs.15441

11. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cells*. (2013) 153:1194–217. doi: 10.1016/j.cell.2013.05.039

12. Alfano CM, Peng J, Andridge RR, Lindgren ME, Povoski SP, Lipari AM, et al. Inflammatory cytokines and comorbidity development in breast cancer survivors versus noncancer controls: evidence for accelerated aging? *J Clin Oncol*. (2017) 35:149–56. doi: 10.1200/JCO.2016.67.1883

13. Sanoff HK, Deal AM, Krishnamurthy J, Torrice C, Dillon P, Sorrentino J, et al. Effect of cytotoxic chemotherapy on markers of molecular age in patients with breast cancer. *J Natl Cancer Inst*. (2014) 106:1–8. doi: 10.1093/jnci/dju057

14. Lee J-J, Nam C-E, Cho S-H, Park K-S, Chung I-J, Kim H-J. Telomere length shortening in non-Hodgkin's lymphoma patients undergoing chemotherapy. *Ann Hematol*. (2003) 82:492–5. doi: 10.1007/s00277-003-0691-4

15. Navarro-Martínez R, Cauli O. Lymphocytes as a biomarker of frailty syndrome: a scoping review. *Diseases*. (2021) 9:53. doi: 10.3390/diseases9030053

16. Picca A, Coelho-Junior HJ, Calvani R, Marzetti E, Vetrano DL. Biomarkers shared by frailty and sarcopenia in older adults: a systematic review and meta-analysis. *Ageing Res Rev*. (2022) 73:101530. doi: 10.1016/j.arr.2021.101530

17. Ramakrishnan P, Alyousefi N, Abdul-Rahman P, Kamaruzzaman S, Chin A, Tan M. A systematic review of studies comparing potential biochemical biomarkers of frailty with frailty assessments. *Eur Geriatr Med*. (2017) 8:397–407. doi: 10.1016/j.eurger.2017.07.010

18. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing Res Rev*. (2016) 31:1–8. doi: 10.1016/j.arr.2016.08.006

19. Ho Y-W, Tang W-R, Chen S-Y, Lee S-H, Chen J-S, Hung Y-S, et al. Association of frailty and chemotherapy-related adverse outcomes in geriatric patients with cancer: a pilot observational study in Taiwan. *Aging*. (2021) 13:24192–204. doi: 10.18632/aging.203673

20. Ness KK, Krull KR, Jones KE, Mulrooney DA, Armstrong GT, Green DM, et al. Physiologic frailty as a sign of accelerated aging among adult survivors of childhood cancer: a report from the St Jude Lifetime cohort study. *J Clin Oncol*. (2013) 31:4496–503. doi: 10.1200/JCO.2013.52.2268

21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The prisma 2020 statement: an updated guideline for reporting systematic reviews. *Int J Surg*. (2021) 88:105906. doi: 10.1136/bmj.n71

22. NHLBI. Study Quality Assessment Tools (2021) (cited 2022). Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

23. Falandry C, Horard B, Bruyas A, Legouffe E, Cretin J, Meunier J, et al. Telomere length is a prognostic biomarker in elderly advanced ovarian cancer patients: a multicenter Gineco study. *Aging*. (2015) 7:1066–74. doi: 10.18632/aging.100840

24. Balducci L, Extermann M. Management of the frail person with advanced cancer. *Crit Rev Oncol Hematol*. (2000) 33:143–8. doi: 10.1016/s1040-8428(99)00063-3

25. Brouwers B, Hatse S, Dal Lago L, Neven P, Vuylsteke P, Dalmasso B, et al. The impact of adjuvant chemotherapy in older breast cancer patients on clinical and biological aging parameters. *Oncotarget*. (2016) 7:29977–88. doi: 10.18632/oncotarget.8796

26. Buigues C, Navarro-Martínez R, Sánchez-Martínez V, Serrano-Carrascosa M, Rubio-Briones J, Cauli O. Interleukin-6 and lymphocyte count associated and predicted the progression of frailty syndrome in prostate cancer patients undergoing antiandrogen therapy. *Cancers*. (2020) 12:1716. doi: 10.3390/cancers12071716

27. Dalmasso B, Hatse S, Brouwers B, Laenen A, Berben L, Kenis C, et al. Age-related micrornas in older breast cancer patients: biomarker potential and evolution during adjuvant chemotherapy. *BMC Cancer*. (2018) 18:1–15. doi: 10.1186/s12885-018-4920-6

28. Gilmore N, Kadambi S, Lei L, Loh KP, Mohamed M, Magnuson A, et al. Associations of inflammation with frailty in patients with breast cancer aged 50 and over receiving chemotherapy. *J Geriatr Oncol*. (2020) 11:423–30. doi: 10.1016/j.jgo.2019.04.001

29. Gilmore N, Mohile S, Lei L, Culakova E, Mohamed M, Magnuson A, et al. The longitudinal relationship between immune cell profiles and frailty in patients with breast cancer receiving chemotherapy. *Breast Cancer Res*. (2021) 23:19–1. doi: 10.1186/s13058-021-01388-w

30. Harneshaug M, Kirkhus L, Benth JŠ, Grønberg BH, Bergh S, Whist JE, et al. Screening for frailty among older patients with cancer using blood biomarkers of inflammation. *J Geriatr Oncol*. (2019) 10:272–8. doi: 10.1016/j.jgo.2018.07.003

31. Rønning B, Wyller TB, Seljeflot I, Jordhøy MS, Skovlund E, Nesbakken A, et al. Frailty measures, inflammatory biomarkers and post-operative complications in older surgical patients. *Age Ageing*. (2010) 39:758–61. doi: 10.1093/ageing/afq123

32. Brouwers B, Dalmasso B, Hatse S, Laenen A, Kenis C, Swerts E, et al. Biological aging and frailty markers in breast cancer patients. *Aging*. (2015) 7:319–33. doi: 10.18632/aging.100745

33. Corona G, Polesel J, Fratino L, Miolo G, Rizzolio F, Crivellari D, et al. Metabolomics biomarkers of frailty in elderly breast cancer patients. *J Cell Physiol*. (2014) 229:898–902. doi: 10.1002/jcp.24520

34. Hatse S, Brouwers B, Dalmasso B, Laenen A, Kenis C, Schöffski P, et al. Circulating micrornas as easy-to-measure aging biomarkers in older breast cancer patients: correlation with chronological age but not with fitness/frailty status. *PLoS One*. (2014) 9:e110644. doi: 10.1371/journal.pone.0110644

35. Lealdini V, Trufelli DC, da Silva FBF, Normando SRC, Camargo EW, de Matos LL, et al. Applicability of modified glasgow prognostic score in the assessment of elderly patients with cancer: a pilot study. *J Geriatr Oncol*. (2015) 6:479–83. doi: 10.1016/j.jgo.2015.09.001

36. Navarro-Martínez R, Serrano-Carrascosa M, Buigues C, Fernández-Garrido J, Sánchez-Martínez V, Castelló-Domenech AB, et al. Frailty syndrome is associated with changes in peripheral inflammatory markers in prostate cancer patients undergoing androgen deprivation therapy. *Urol Oncol*. (2019) 37:976–87. doi: 10.1016/j.urolonc.2019.08.005

37. Nishijima TF, Deal AM, Williams GR, Guerard EJ, Nyrop KA, Muss HB. Frailty and inflammatory markers in older adults with cancer. *Aging*. (2017) 9:650–64. doi: 10.18632/aging.101162

38. Bylow K, Hemmerich J, Mohile SG, Stadler WM, Sajid S, Dale W. Obese frailty, physical performance deficits, and falls in older men with biochemical recurrence of prostate cancer on androgen deprivation therapy: a case-control study. *Urology*. (2011) 77:934–40. doi: 10.1016/j.urology.2010.11.024

39. Huisingh-Scheetz M, Walston J. How should older adults with cancer be evaluated for frailty? *J Geriatr Oncol*. (2017) 8:8–15. doi: 10.1016/j.jgo.2016.06.003

40. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: a review. *Eur J Intern Med*. (2016) 31:3–10. doi: 10.1016/j.ejim.2016.03.007

41. O'Shea JJ, Gadina M, Siegel RM. Cytokines and cytokine receptors. *Clin Immunol Elsevier*. (2019):127–155.e1. doi: 10.1016/B978-0-7020-6896-6.00009-0

42. Pang WW, Abdul-Rahman PS, Wan-Ibrahim WI, Hashim OH. Can the acute-phase reactant proteins be used as cancer biomarkers? *Int J Biol Markers*. (2010) 25:1–11. doi: 10.1177/172460081002500101

43. Brábek J, Jakubek M, Vellieux F, Novotný J, Kolář M, Lacina L, et al. Interleukin-6: molecule in the intersection of cancer, aging and COVID-19. *Int J Mol Sci*. (2020) 21:7937. doi: 10.3390/ijms21217937

44. Gabay C. Interleukin-6 and chronic inflammation. *Arthritis Res Ther*. (2006) 8:S3–6. doi: 10.1186/ar1917

45. Khaodhiar L, Ling PR, Blackburn GL, Bistrian BR. Serum levels of interleukin-6 and C-reactive protein correlate with body mass index across the broad range of obesity. *J Parenter Enter Nutr*. (2004) 28:410–5. doi: 10.1177/0148607104028006410

46. Lopez-Bujanda ZA, Haffner MC, Chaimowitz MG, Chowdhury N, Venturini NJ, Patel RA, et al. Castration-mediated Il-8 promotes myeloid infiltration and prostate cancer progression. *Nat Cancer*. (2021) 2:803–18. doi: 10.1038/s43018-021-00227-3

47. Hart PC, Rajab IM, Alebraheem M, Potempa LA. C-reactive protein and cancer—diagnostic and therapeutic insights. *Front Immunol*. (2020) 11:595835. doi: 10.3389/fimmu.2020.595835

48. Howard R, Kanetsky PA, Egan KM. Exploring the prognostic value of the neutrophil-to-lymphocyte ratio in cancer. *Sci Rep*. (2019) 9:1–10. doi: 10.1038/s41598-019-56218-z

49. Coffelt SB, Kersten K, Doornebal CW, Weiden J, Vrijland K, Hau C-S, et al. Il-17-producing γδ t cells and neutrophils conspire to promote breast cancer metastasis. *Nature*. (2015) 522:345–8. doi: 10.1038/nature14282

50. Ocana A, Nieto-Jiménez C, Pandiella A, Templeton AJ. Neutrophils in cancer: prognostic role and therapeutic strategies. *Mol Cancer*. (2017) 16:1–7. doi: 10.1186/s12943-017-0707-7

51. Zhao J, Huang W, Wu Y, Luo Y, Wu B, Cheng J, et al. Prognostic role of pretreatment blood lymphocyte count in patients with solid tumors: a systematic review and meta-analysis. *Cancer Cell Int*. (2020) 20:15–4. doi: 10.1186/s12935-020-1094-5

52. Weng M, Zhao W, Yue Y, Guo M, Nan K, Liao Q, et al. High preoperative white blood cell count determines poor prognosis and is associated with an immunosuppressive microenvironment in colorectal cancer. *Front Oncol*. (2022) 12:1–15. doi: 10.3389/fonc.2022.943423

53. Grossmann M, Zajac JD. Hematological changes during androgen deprivation therapy. *Asian J Androl*. (2012) 14:187–92. doi: 10.1038/aja.2011.102

54. McMillan DC. The systemic inflammation-based glasgow prognostic score: a decade of experience in patients with cancer. *Cancer Treat Rev*. (2013) 39:534–40. doi: 10.1016/j.ctrv.2012.08.003

55. Ñamendys-Silva SA, González-Herrera MO, Texcocano-Becerra J, Herrera-Gómez A. Hypoalbuminemia in critically ill patients with cancer: incidence and mortality. *Am J Hosp Palliative Med*. (2011) 28:253–7. doi: 10.1177/1049909110384841

56. Dolan RD, McMillan DC. The prevalence of cancer associated systemic inflammation: implications of prognostic studies using the glasgow prognostic score. *Crit Rev Oncol Hematol*. (2020) 150:102962. doi: 10.1016/j.critrevonc.2020.102962

57. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. *J Parenter Enter Nutr*. (2019) 43:181–93. doi: 10.1002/jpen.1451

58. Gomi I, Fukushima H, Shiraki M, Miwa Y, Ando T, Takai K, et al. Relationship between serum albumin level and aging in community-dwelling self-supported elderly population. *J Nutr Sci Vitaminol*. (2007) 53:37–42. doi: 10.3177/jnsv.53.37

59. Suzuki H, Maruyama R, Yamamoto E, Kai M. Epigenetic alteration and microrna dysregulation in cancer. *Front Genet*. (2013) 4:258. doi: 10.3389/fgene.2013.00258

60. Chakravarti D, LaBella KA, DePinho RA. Telomeres: history, health, and hallmarks of aging. *Cells*. (2021) 184:306–22. doi: 10.1016/j.cell.2020.12.028

61. Zhang J, Rane G, Dai X, Shanmugam MK, Arfuso F, Samy RP, et al. Aging and the telomere connection: an intimate relationship with inflammation. *Ageing Res Rev*. (2016) 25:55–69. doi: 10.1016/j.arr.2015.11.006

62. Vinayavekhin N, Homan EA, Saghatelian A. Exploring disease through metabolomics. *ACS Chem Biol*. (2010) 5:91–103. doi: 10.1021/cb900271r

63. Picca A, Coelho-Junior HJ, Cesari M, Marini F, Miccheli A, Gervasoni J, et al. The metabolomics side of frailty: toward personalized medicine for the aged. *Exp Gerontol*. (2019) 126:110692. doi: 10.1016/j.exger.2019.110692

64. Trappe T, Williams R, Carrithers J, Raue U, Esmarck B, Kjaer M, et al. Influence of age and resistance exercise on human skeletal muscle proteolysis: a microdialysis approach. *J Physiol*. (2004) 554:803–13. doi: 10.1113/jphysiol.2003.051755

65. Rodriguez-Cuenca S, Pellegrinelli V, Campbell M, Oresic M, Vidal-Puig A. Sphingolipids and glycerophospholipids–the "Ying and Yang" of lipotoxicity in metabolic diseases. *Prog Lipid Res*. (2017) 66:14–29. doi: 10.1016/j.plipres.2017.01.002

66. Pujos-Guillot E, Pétéra M, Jacquemin J, Centeno D, Lyan B, Montoliu I, et al. Identification of pre-frailty sub-phenotypes in elderly using metabolomics. *Front Physiol*. (2019) 9:1903. doi: 10.3389/fphys.2018.01903

67. Theou O, Cann L, Blodgett J, Wallace LM, Brothers TD, Rockwood K. Modifications to the frailty phenotype criteria: systematic review of the current literature and investigation of 262 frailty phenotypes in the survey of health, aging, and retirement in Europe. *Ageing Res Rev*. (2015) 21:78–94. doi: 10.1016/j.arr.2015.04.001

68. Bruyère O, Buckinx F, Beaudart C, Reginster J-Y, Bauer J, Cederholm T, et al. How clinical practitioners assess frailty in their daily practice: an international survey. *Aging Clin Exp Res*. (2017) 29:905–12. doi: 10.1007/s40520-017-0806-8

69. Aldaham S, Foote JA, Chow H-HS, Hakim IA. Smoking status effect on inflammatory markers in a randomized trial of current and former heavy smokers. *Int J Inflamm*. (2015) 2015:1–6. doi: 10.1155/2015/439396

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 10 May 2023
DOI 10.3389/fpubh.2023.1154809

OPEN ACCESS

EDITED BY
Jing Liao,
Sun Yat-sen University, China

REVIEWED BY
Xun Luo,
Kerry Rehabilitation Medicine Research Institute, China
Yun Zhang,
Columbia University Irving Medical Center, United States

*CORRESPONDENCE
Fan Wu
✉ wufan@shmu.edu.cn

RECEIVED 31 January 2023
ACCEPTED 17 April 2023
PUBLISHED 10 May 2023

CITATION
Qin F, Guo Y, Ruan Y, Huang Z, Sun S, Gao S, Ye J and Wu F (2023) Frailty and risk of adverse outcomes among community-dwelling older adults in China: a comparison of four different frailty scales. *Front. Public Health* 11:1154809. doi: 10.3389/fpubh.2023.1154809

Frailty and risk of adverse outcomes among community-dwelling older adults in China: a comparison of four different frailty scales

Fei Qin[1], Yanfei Guo[2,3], Ye Ruan[2], Zhezhou Huang[2], Shuangyuan Sun[2], Shuna Gao[4], Jinghong Ye[5] and Fan Wu[1]*

[1]School of Public Health, Fudan University, Shanghai, China, [2]Division of Chronic Non-communicable Disease and Injury, Shanghai Municipal Center for Disease Control and Prevention, Shanghai, China, [3]School of Public Health and Community Medicine, Institution of Medicine, University of Gothenburg, Sahlgrenska Academy, Gothenburg, Sweden, [4]Department of Chronic Non-communicable Disease, Shanghai Huangpu Center for Disease Control and Prevention, Shanghai, China, [5]Department of Chronic Non-communicable Disease, Shanghai Hongkou Center for Disease Control and Prevention, Shanghai, China

Background: Data on which frailty scales are most suitable for estimating risk in Chinese community populations remain limited. Herein we examined and compared four commonly used frailty scales in predicting adverse outcomes in a large population-based cohort of Chinese older adults.

Methods: A total of 5402 subjects (mean age 66.3 ± 9.6 years, 46.6% male) from the WHO Study on global AGEing and adult health (SAGE) in Shanghai were studied. Frailty was measured using a 35-item frailty index (FI), the frailty phenotype (FP), FRAIL, and Tilburg Frailty Indicator (TFI). Multivariate logistic regression models were performed to evaluate the independent association between frailty and outcomes including 4-year disability, hospitalization, and 4- and 7-year all-cause mortality. The accuracy for predicting these outcomes was determined by evaluating the area under the curve (AUC). The prevalence of frailty, sensitivity, and specificity were calculated using our proposed cut-off points and other different values.

Results: Prevalence of frailty ranged from 4.2% (FRAIL) to 16.9% (FI). FI, FRAIL and TFI were comparably associated with 4-year hospitalization, and 4- and 7-year mortality (adjusted odds ratios [aORs] 1.44–1.69, 1.91–2.22 and 1.85–2.88, respectively). FRAIL conferred the greatest risk of 4-year disability, followed by FI and TFI (aOR 5.55, 3.50, and 1.91, respectively). FP only independently predicted 4- and 7-year mortality (aOR 1.57 and 2.21, respectively). AUC comparisons showed that FI, followed by TFI and FRAIL, exhibited acceptable predictive accuracy for 4-year disability, 4- and 7-year mortality (AUCs 0.76–0.78, 0.71–0.71, 0.65–0.72, respectively), whereas all scales poorly predicted 4-year hospitalization (AUCs 0.53–0.57). For each scale, while specificity estimates (85.3–97.3%) were high and similar across all outcomes, their sensitivity estimates (6.3–56.8%) were not sufficient yet. Prevalence of frailty, sensitivity, and specificity varied considerably when different cut-off points were used.

Conclusion: Frailty defined using any of the four scales was associated with an increased risk of adverse outcomes. Although FI, FRAIL and TFI exhibited

fair-to-moderate predictive accuracy and high specificity estimates, their sensitivity estimates were not sufficient yet. Overall, FI performed best in estimating risk, while TFI and FRAIL were additionally useful, the latter perhaps being more applicable to Chinese community-dwelling older adults.

KEYWORDS

frailty, predictive accuracy, older Chinese, population-based, longitudinal study, adverse outcomes

1. Introduction

Frailty describes a non-specific state reflecting cumulative declines in multiple physiological systems with aging, leading to decreased resilience to stressors (1). Routine screening for frailty among older adults has been called for (2); however, no uniformly accepted operational definition for frailty is currently available (1, 3). Most commonly, frailty has been operationalized as the frailty phenotype (FP) based on the biologic syndrome model proposed by Fried and colleagues (4). In comparison, the frailty index (FI) was developed as a scale of deficit accumulation model to measure the cumulative burden of, for example, diseases, symptoms, and conditions (5). Furthermore, the FRAIL, proposed by the International Academy of Nutrition Health and Aging (IANA) and developed as a simple measure that combines elements from both the FI and FP models, as well as the Tilburg Frailty Indicator (TFI), described in line with an integral conceptual model of frailty by a group of Canadian researchers based on interview-based questions, are also frequently used (6).

A substantial number of frailty scales including the four above, irrespective of the frailty definition used, have been shown to predict a variety of adverse outcomes (7), while in practice choosing a scale is sometimes arbitrary, e.g., based solely on available data, yet how frailty is conceptualized affects aging research. For example, given that multiple frailty-related health outcomes, such as disability, hospitalization and all-cause death, can affect lots of people, it is crucial to determine whether one frailty scale has advantages over others in identifying and predicting high-risk groups. As a result, comparisons between frailty scales in estimating risk have been performed but the results are still controversial (8–11), partially attributed to differences in study populations, settings, outcomes, follow-up periods, and even the criteria selected to operationalize frailty. This highlights the need for careful examination of the predictive properties of frailty scales for health outcomes in different populations and settings for subsequent research.

In China, the largest developing country with a rapidly aging population, several longitudinal cohorts have explored frailty and risk of adverse outcomes, including the Chinese Longitudinal Health and Longevity Study (CLHLS) (12, 13), the Beijing Longitudinal Study of Aging (BLSA) (14, 15) and the Rugao Longevity and Aging Study (RuLAS) (16, 17), the majority of which focus on the relationship between FI and/or FP and mortality. In an earlier longitudinal study of 4,000 Hong Kong Chinese aged 65 and older (8), the FRAIL scale was found comparable with FI and FP in the prediction of mortality and physical limitations over 4 years of follow-up. Recently, another longitudinal study of 302 Chinese hospitalized older patients (median age 86 years) found that four different frailty scales showed similar performance in predicting 1-year in-hospital mortality (18). However, data on the relationship between multiple frailty scales and adverse outcomes are still limited, and even to date, no longitudinal studies have compared multiple frailty scales in predicting long-term health outcomes within the same timeframe in the same mainland Chinese community-dwelling population, making it difficult to determine which frailty scale should be used as an outcome measure.

To fill the above gap, we analyzed the results of a population-based cohort study involving 5,402 Chinese community-dwelling adults aged 50 and older, in which four frailty scales were explored and compared. Some related frailty scales were not included because they are more focused on relatively small scopes (e.g., timed-up-and-go test, scarcopenia) or are less directly applicable to population-based settings (e.g., laboratory-based biomarkers), or cannot be constructed using the present data (e.g., Clinical Frailty Scale). In this longitudinal study, we sought to examine and compare the utility of four commonly used frailty scales adapted from existing frailty approaches in identifying frailty, together with their ability to predict several adverse outcomes (4-year disability, hospitalization, and 4- and 7-year all-cause mortality), for the sake of identifying at-risk groups and potentially reversing established frailty status.

2. Materials and methods

2.1. Study sample

Participants were drawn from a large ongoing population-based cohort study, the WHO Study on global AGEing and adult health (SAGE) in Shanghai. Details concerning the SAGE have been previously described (19). Briefly, SAGE is a longitudinal study on the health and wellbeing of adults aged 50 and older in six low- and middle-income countries (LMICs): China, Ghana, India, Mexico, Russian and South Africa. In China, the study was constructed including wave 1, implemented in 2009/10, wave 2 in 2014/15 and wave 3 in 2018/19. We enlarged the sample size of SAGE in Shanghai, China to obtain a sub-state representative sample using the same multistage clustered sampling method and survey assessment. In particular, wave 2 served as the baseline and wave 3 as the follow-up of the current study, as they contained a more comprehensive set of assessments. A longer follow-up through December 31, 2021 was additionally conducted

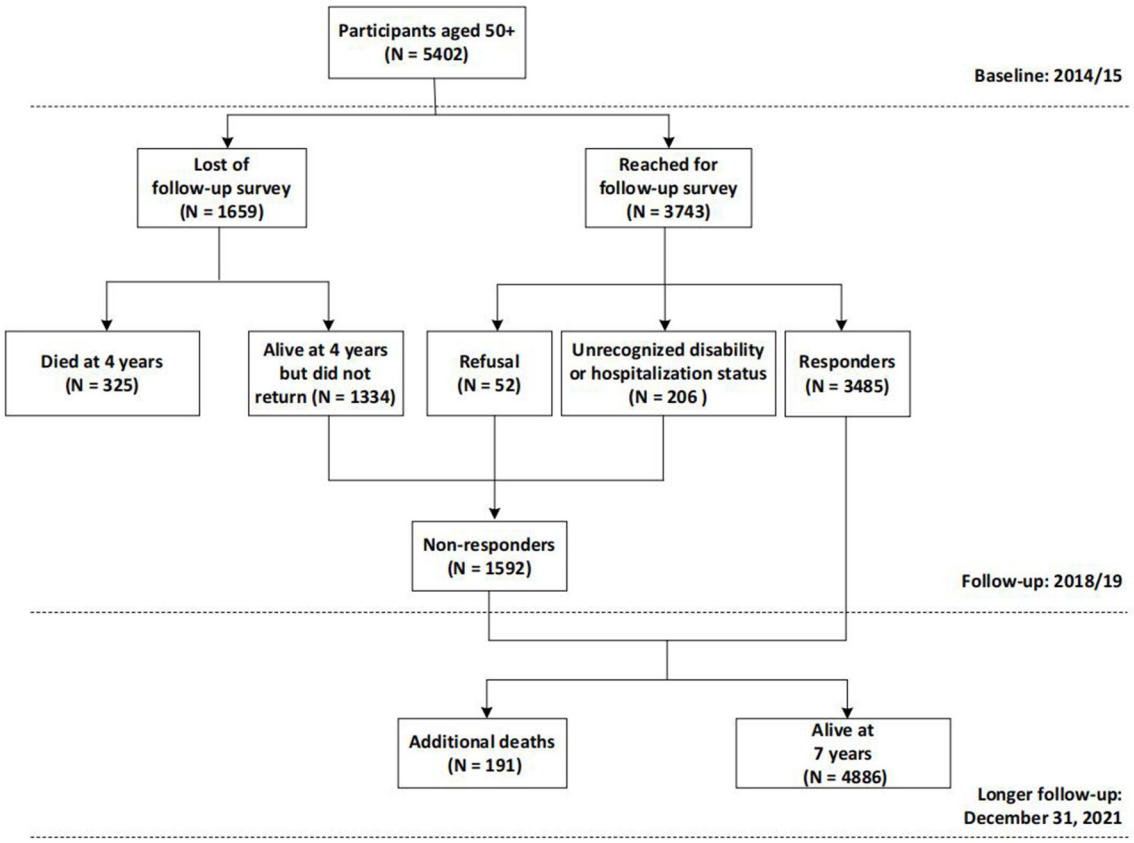


FIGURE 1
Flow chart of the selection of subjects for the cohort study.

to ascertain the participants' survival status. At baseline (2014/15), 5,402 community dwellers aged 50 and older were recruited from five districts of Shanghai, China and included in the analysis for mortality. After 4 years, 5,077 subjects (325 had died) were invited to undergo the follow-up assessment, while 1,592 were excluded (1334 did not return, 52 declined, and 206 had unrecognized disability or hospitalization); leaving 3,485 participants eligible for the analysis for disability and hospitalization (Figure 1). Comparisons of the non-responders with respondents in terms of baseline age, sex, and frailty status were conducted (see Supplementary material S1) and results suggested that the issue of the representativeness should not represent a potential bias, despite a response rate of 68.6%.

2.2. Frailty scales

The four frailty scales are briefly described below. An overview of all items constructed in each scale can be found in Supplementary material S2. In particular, to maximize the use of available data, a scale was included in subsequent analyses if no more than 20% of all items were missing (11); meanwhile, missing items for FP, FRAIL, and TFI were imputed with 0 (having no this deficit), whereas no substitution procedure was required for FI because of its distinctive derivation method used in this study.

Frailty index (FI). The FI is based on the cumulative deficit model that identifies frailty based on a range of variables across multiple domains, such as diseases, symptoms, and conditions, collectively referred to as deficits. It has been suggested that an index with 30–40 variables is sufficiently accurate for predicting adverse outcomes. Following a standard procedure (20), we created a 35-item FI comprising 7 components: self-rated health, medically diagnosed conditions (9 items), medical symptoms (6 items), functional activities assessments (11 items), cognitive function assessments (5 items), body mass index (BMI), and physical performance tests (2 items). The included variables were dichotomous, ordinal or continuous. Dichotomous variables were coded as 0 as non-deficit and 1 being a deficit; ordinal and continuous variables were converted as a certain proportion of the deficit. For each participant, these deficits were summed up and then divided by the total possible deficit to derive the FI. In line with previous SAGE studies in Chinese populations (21, 22), individuals with an index of 0.20 or greater were considered to be frail.

Frailty phenotype (FP). The FP was constructed using an adapted phenotypic definition based on the criteria of five components proposed by Fried et al. (4): slowness, weight loss, low grip strength, exhaustion, and low physical activity. It has been previously operationalized in SAGE (23–25), and the same criteria were applied in this study. In short, exhaustion and physical activity are self-report questions, while slowness, weight loss and low grip strength are performance-based measures.

TABLE 1 Baseline characteristics and the difference between participants with and without adverse outcomes.

Variable	All ($n = 5402$)	4-year disability ($n = 125$)		4-year hospitalization ($n = 720$)		4-year mortality ($n = 325$)		7-year mortality ($n = 516$)	
		Value	$p^{\dagger}$	Value	$p^{\dagger}$	Value	$p^{\dagger}$	Value	$p^{\dagger}$
Mean (SD)									
Age (years)	66.3 (9.6)	72.6 (9.1)	<0.001	67.1 (8.4)	<0.001	78.3 (9.7)	<0.001	78.5 (9.8)	<0.001
BMI (kg/m^2)	19.5 (3.0)	19.0 (2.9)	0.026	19.6 (3.1)	0.730	18.8 (3.4)	<0.001	18.8 (3.4)	<0.001
Number (%)									
Sex (male)	2515 (46.6)	56 (44.8)	0.856	357 (49.6)	0.016	170 (52.3)	0.032	265 (51.4)	0.022
Marital status			<0.001		0.507		<0.001		<0.001
Not partnered	767 (14.2)	28 (22.4)		93 (12.9)		116 (35.7)		183 (35.5)	
Partnered	4635 (85.8)	97 (77.6)		627 (87.1)		209 (64.3)		333 (64.5)	
Educational level			<0.001		<0.001		<0.001		<0.001
No education	1049 (19.4)	48 (38.4)		166 (23.1)		129 (39.7)		198 (38.4)	
Less than primary	718 (13.3)	20 (16.0)		128 (17.8)		49 (15.1)		68 (13.2)	
Primary	1026 (19.0)	24 (19.2)		157 (21.8)		49 (15.1)		84 (16.3)	
Secondary	1534 (28.4)	24 (19.2)		168 (23.3)		49 (15.1)		90 (17.4)	
Higher	1075 (19.9)	9 (7.2)		101 (14.0)		49 (15.1)		76 (14.7)	
Smoking status			0.475		0.904		0.440		<0.001
Never smoked	3825 (70.8)	92 (73.6)		518 (72.0)		235 (61.7)		334 (64.7)	
Former smoker	232 (4.3)	7 (5.6)		29 (4.0)		17 (7.0)		35 (6.8)	
Current smoker	1345 (24.9)	26 (20.8)		173 (24.0)		73 (31.3)		147 (28.5)	
Frailty status (frail)*									
FI	888 (16.9)	64 (51.2)	<0.001	150 (21.0)	<0.001	154 (55.0)	<0.001	258 (56.8)	<0.001
FP	648 (12.6)	26 (20.8)	0.002	109 (15.2)	0.002	63 (30.6)	<0.001	117 (34.1)	<0.001
FRAIL	224 (4.2)	32 (25.6)	<0.001	45 (6.3)	<0.001	56 (19.5)	<0.001	91 (19.6)	<0.001
TFI	385 (7.3)	28 (22.4)	<0.001	72 (10.0)	<0.001	75 (27.3)	<0.001	117 (26.2)	<0.001

SD, Standard Deviation; BMI = Body Mass Index; FI, Frailty Index; FP, Frailty Phenotype; TFI, Tilburg Frailty Indicator.

†p value for comparison of difference between adverse outcome groups: t-test or Wilcoxon rank-sum test (depending on distribution) for continuous variables, Chi-square test for categorical variables.

*Due to missing data, small differences between n and numbers of participants reported for each scale can occur.

10.3389/fpubh.2023.1154809

TABLE 2 Comparison of adverse outcomes between baseline frail and non-frail participants during follow-up.

	4-year disability		4-year hospitalization		4-year mortality		7-year mortality	
	Adjusted[a] OR (95% CI)	*p*	Adjusted[a] OR (95% CI)	*p*	Adjusted[a] OR (95% CI)	*p*	Adjusted[a] OR (95% CI)	*p*
FI	3.50 (2.19, 5.61)	<0.001	1.44 (1.11, 1.88)	0.006	2.22 (1.42, 3.48)	<0.001	2.88 (2.03, 4.08)	<0.001
FP	1.06 (0.64, 1.76)	0.816	1.15 (0.89, 1.50)	0.278	1.57 (1.12, 2.20)	0.008	2.21 (1.53, 3.20)	<0.001
FRAIL	5.55 (3.20, 9.62)	<0.001	1.64 (1.07, 2.52)	0.024	1.91 (1.05, 3.46)	0.035	2.29 (1.43, 3.66)	<0.001
TFI	1.91 (1.12, 3.27)	0.018	1.69 (1.21, 2.37)	0.002	1.94 (1.18, 3.20)	0.010	1.85 (1.24, 2.76)	0.003

FI, Frailty Index; FP, Frailty Phenotype; TFI, Tilburg Frailty Indicator; OR, Odds Ratio; CI, Confidence Interval.
[a]Logistic regression models adjusted for baseline age, sex, educational level, marital status, BMI, and smoking status.

Likewise, participants were classified as frail if 3 or more criteria were present.

FRAIL scale. We used an adaption of the IANA FRAIL scale (26), which considers deficits accumulated in five domains: fatigue, resistance, ambulation, illness, and loss of weight. FRAIL has not been explored in SAGE before. Fatigue was measured on a 5-point Likert scale by asking respondents whether they had enough energy for daily activities. This criterion was considered present if participants answered "Not at all" or "A little". Resistance and ambulation were obtained by asking "Do you have any difficulty standing for long periods" and "Do you have any difficulty walking 1 kilometer", respectively. Resistance or ambulation was considered present if subjects answered "Severe" or "Extreme/Cannot do". Participants were classified as ill if they had 5 or more out of 9 self-reported chronic diseases including diabetes mellitus, stroke, cataracts, angina pectoris, arthritis, asthma, chronic lung disease, depression and hypertension. The weight loss criterion was ascertained based on the lowest quintile of BMI. Individuals with 3 or more criteria were recognized as frail.

Tilburg Frailty Indicator (TFI). The TFI, developed as an integral conceptual model of frailty, comprises two subscales (27). One subscale addresses the determinants of frailty such as socio-demographics, the latter addresses the level of frailty across physical (8 items), psychological (4 items) and social domains (3 items), and is used in this study, yet it has not previously been explored in SAGE. Memory problems were measured using a delayed recall memory test and the cut-off point was the worst-performing 10th centile. Anxiety was assessed using a question about irritability, and coping was obtained by asking the individual "How often have you found that you could not cope with all the things that you had to do?", and was considered present if people answered, "Fairly often" or "Very often". Social deficits were assessed by asking the individual "What is the total number of people who live in your household?", "How satisfied are you with your personal relationships" and "Were you supported for the last time when you needed it?". Theoretical scores of the TFI range from 0 to 15, with a score of 5 or greater defining frailty.

2.3. Outcome measures

Outcome measures were new development of disability, hospitalization at 4 years, and 4- and 7-year all-cause mortality.

Disability was assessed both during 2014/15 and 2018/19 using eight activities of daily living (ADL) tasks (moving around, bathing, dressing, maintaining appearance, getting up from lying down, eating, toileting, and controlling urine) (28). For each ADL task, participants were asked, "Do you have difficulty in" performing the task in the preceding 30 days? The response was in a Likert scale format ranging from "None" to "Extreme/Cannot". Respondents were considered to have ADL disability if they reported severe or extreme difficulties in performing at least one of the eight tasks listed above; then, the onset of a new disability was defined as a newly identified disability during 2018/19. For hospitalization, participants were asked "whether you had stayed at least overnight in a hospital since the last interview, i.e., in the prior 4 years?" during 2018/2019. Finally, 4- and 7-year all-cause mortality was determined by linking data to the Shanghai Death Registry during 2018/2019 and on December 31, 2021, respectively.

2.4. Covariates

Using the literature on disability, hospitalization, and mortality in older adults as a guide (9, 16, 17), commonly cited risk factors were selected as potential covariates and then identified in the dataset. Hence, covariates included age, sex (male or female), marital status (partnered [married/cohabiting], not partnered [separated/divorced/widowed or never married]), educational level achieved (no education, less than primary, primary, secondary or higher), smoking status (never smoked, current smoker or former smoker) and body mass index (BMI). For smoking status, respondents were first asked "Have you ever smoked tobacco or used smokeless tobacco?" Those who answered "No" were classified as never smoked, while those who answered "Yes" were then asked "Do you currently use (smoke, sniff or chew) any tobacco products such as

cigarettes, cigars, pipes, chewing tobacco or snuff?" If the respondents answered "Yes" again, they were classified as current smokers, otherwise they were classified as former smokers. Measured height and weight were used to calculate a standard BMI (calculated as weight in kilograms divided by height in meters squared).

2.5. Statistical analysis

Descriptive statistics were presented as either means (standard deviations) or frequencies (percentages), with comparisons between four different outcome groups using *t*-tests/Wilcoxon rank-sum tests or chi-square tests, as appropriate. Logistic regression models were measured to investigate the association of dichotomized frailty status [frail, non-frail (reference)] identified by each scale with adverse outcomes, with results reported as odds ratios (ORs) and 95% confidence intervals (CIs). All regression models were performed and adjusted for the same multiple covariates above (fixed model). For each outcome, a receiver operator characteristic (ROC) curve based on the continuous scores of each scale was created and the area under the curve (AUC) was calculated with their corresponding 95% CIs to assess the unadjusted ability of each scale to differentiate between the frail and non-frail participants; AUCs between frailty scales were then compared using Wilcoxon tests to ascertain if there is a statistical difference. The prevalence of frailty, sensitivity and specificity for each scale and for each outcome were also calculated using our proposed cut-off points as well as those points one above and one below our proposed values (0.05 for the FI). We used the following acceptable minimum thresholds: ≥0.60 for AUC (29), ≥0.8 for sensitivity (30), and ≥0.6 for specificity (30). Statistical analyses were performed using the SAS software (version 9.4, SAS Institute, Inc., Cary, NC), and a 2-sided $p < 0.05$ was considered statistically significant.

3. Results

The baseline characteristics of the cohort are described in Table 1. Of 5,402 participants, 2,515 (46.6%) were men and 2,887 (53.4%) were women. The participants ranged in age from 50 to 97 years, with a mean age of 66.3 (SD: 9.6) years. Most (85.8%) of the participants were currently partnered, while few (19.4%) were illiterate. Approximately one-quarter (24.9%) of the participants were current smokers. The prevalence of frailty varied between scales: FRAIL, 4.2%; TFI, 7.3%; FP, 12.6%; FI, 16.9%, although between 103 (1.9%) and 244 (4.5%) participants were unable to be assessed by the four scales due to missing data (>20% items) (see Supplementary material S3).

After 4 years of follow-up, 325 (6.0%) of 5,402 participants had died; of 3,485 responders, 125 (3.6%) developed a new disability and 720 (20.7%) reported one or more new hospitalizations, respectively. Additionally, after a longer 7-year follow-up, a total of 516 participants died, resulting in a greater mortality rate of 9.6%. Compared with their counterparts, those with adverse outcomes generally were older, less educated, and frailer using any scale at baseline (all $p < 0.01$) (Table 1).

For each scale of interest, Table 2 details the risk of selected adverse outcomes in frail compared to non-frail participants. Multivariate logistic regression found frailty by any of the FI, FP, FRAIL, and TFI scales to be a strong predictor of all-cause mortality (all $p < 0.05$), with adjusted ORs of 2.22, 1.57, 1.91, and 1.94 for 4-year mortality, 2.88, 2.21, 2.29, and 1.85 for 7-year mortality, respectively. The risk of 4-year disability was also associated with frailty by any scale (except FP), but the association was stronger for FRAIL (adjusted OR 5.55) than for either FI (adjusted OR 3.50) or TFI (adjusted OR 1.91) (all $p < 0.05$). Frailty by these three scales was additionally comparably associated with 4-year hospitalization (adjusted ORs 1.44–1.69, all $p < 0.05$). Of note, the independent association with risk of 4-year either disability or hospitalization did not reach statistical significance for FP (both $p > 0.05$).

We further estimated and compared the predictive accuracy of each scale for each adverse outcome in Figure 2. Per adverse outcome, AUC comparisons showed that the four scales had distinctive predictive accuracy; regarding 4-year disability, 4- and 7-year mortality, FI was more predictive than the other scales (AUC 0.76–0.78), followed by TFI (AUC 0.71) and FRAIL (AUC 0.65–0.72), which performed better than FP (AUC 0.57–0.59) (Figures 2A, C, D). By contrast, all scales had poor accuracy in predicting new hospitalizations at 4-year follow-up, with FI (AUC 0.57) being a better predictor than FRAIL, which was equivalent to both FP and TFI (AUC 0.53–0.54) (Figure 2B).

We also determined the prevalence of frailty as well as the associated sensitivity and specificity based on different cut-off points, as described in Table 3. With our proposed cut-offs in the current study, the prevalence of frailty in this population varied. Regarding the associated diagnostic values, each scale showed high and similar levels of specificity for all outcomes (FI: 85.3–87.7%, FP: 88.2–89.0%, TFI: 93.8–95.0%, FRAIL: 96.7–97.3%). In contrast, sensitivity estimates varied widely within lower ranges: for 4-year disability, 4- and 7-year mortality, each scale showed similar levels of sensitivities, while FI had higher estimates (51.2%, 55.0% and 56.8%, respectively) compared to the other three scales, the latter showed similar sensitivity estimates at lower levels (range 20.8–34.1% for FP, 19.5–25.6% for FRAIL, and 22.4–27.3% for TFI, respectively); for 4-year hospitalization, lowest sensitivity estimates were found across all scales (FI 21.0%, FP 15.2%, FRAIL 6.3%, TFI 10.0%). Furthermore, the sensitivity and specificity for each scale were found to vary considerably when higher or lower cut-off points were applied. For all frailty scales, with increasing levels of frailty, the specificity fell and the sensitivity increased, and yet no scale had both acceptable sensitivity and specificity.

4. Discussion

To date, this large-scale prospective cohort study has been the first attempt to simultaneously identify and compare the four validated frailty scales for their utility in identifying frailty, together with their ability to predict adverse outcomes in mainland Chinese community dwellers. In this study, we found a low prevalence of frailty as assessed by the FI, FP, FRAIL, and TFI among Chinese community-dwelling older adults. With four frailty scales, frailty was associated with multiple adverse outcomes, including 4-year disability (except FP), hospitalization (except FP),

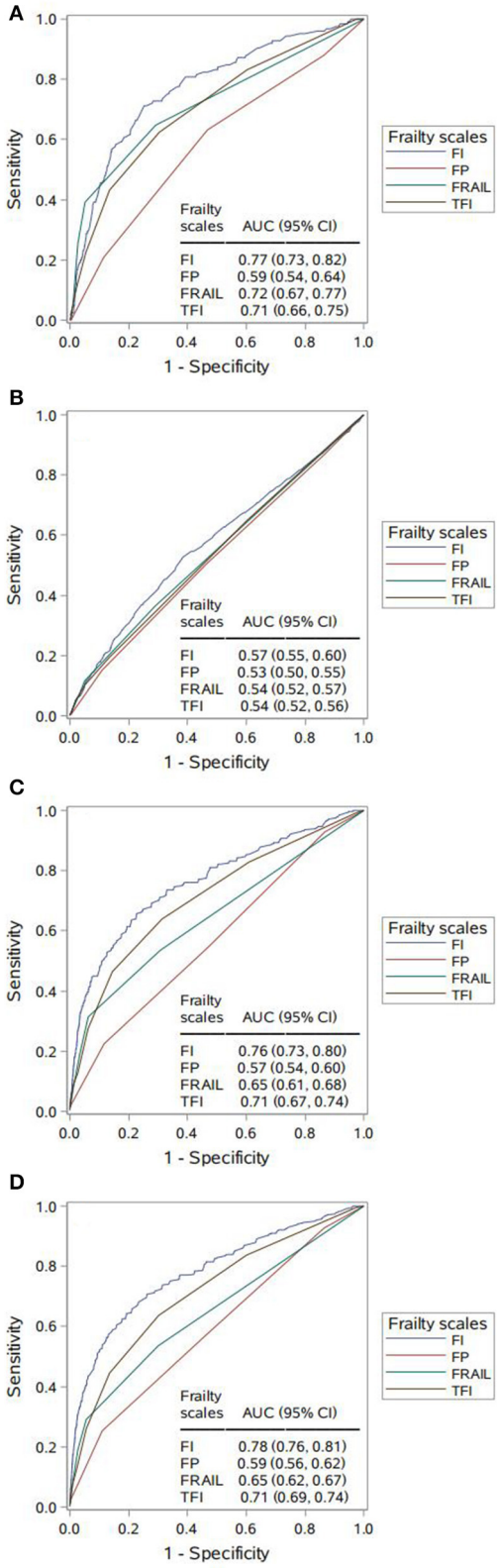


FIGURE 2
Comparing area under the curve (AUC) for the four frailty scales per adverse outcome. **(A)** 4-year disability. AUC contrasts: Frailty Index (FI) vs. Frailty Phenotype (FP), $p < 0.001$; FI vs. FRAIL, $p = 0.018$; FI vs. Tilburg Frailty Indicator (TFI), $p = 0.002$; FP vs. FRAIL, $p < 0.001$; FP vs. TFI, $p < 0.001$; FRAIL vs. TFI, $p = 0.549$. **(B)** 4-year hospitalization. AUC contrasts: FI vs. FP, $p < 0.001$; FI vs. FRAIL, $p = 0.014$; FI vs. TFI, *(Continued)*

FIGURE 2 (Continued)
$p = 0.001$; FP vs. FRAIL, $p = 0.135$; FP vs. TFI, $p = 0.256$; FRAIL vs. TFI, $p = 0.722$. **(C)** 4-year mortality. AUC contrasts: FI vs. FP, $p < 0.001$; FI vs. FRAIL, $p < 0.001$; FI vs. TFI, $p < 0.001$; FP vs. FRAIL, $p < 0.001$; FP vs. TFI, $p < 0.001$; FRAIL vs. TFI, $p < 0.001$; **(D)** 7-year mortality. AUC contrasts: FI vs. FP, $p < 0.001$; FI vs. FRAIL, $p < 0.001$; FI vs. TFI, $p < 0.001$; FP vs. FRAIL, $p < 0.001$; FP vs. TFI, $p < 0.001$; FRAIL vs. TFI, $p < 0.001$.

and 4- and 7-year all-cause mortality. However, the four frailty scales showed mixed predictive accuracy as well as associated sensitivity and specificity for the outcomes of interest, indicating that different frailty scales may point to various risks of further adverse outcomes.

In this large representative sample of Chinese community dwellers, we found 4.2% up to 16.9% of Chinese adults aged 50 years or older were frail between the scales. The low frailty prevalence estimates in our cohort are consistent with previous studies (14, 21), although widely varying frailty prevalence estimates have also been observed among community dwellers in LIMICs (31) due to differences in population and the myriad of frailty scales used. By using the most commonly used scales, FI and FP, more than 10% of our cohort fulfilled the criteria for frailty, whereby only 7.3% or 4.2% would have been frail by TFI or FRAIL, respectively. In a European study (32), albeit among hospitalized patients, a higher proportion of the cohort was considered frail on FI and TFI compared with the FRAIL scale. We found that, unlike the multidimensional FI and TFI, FRAIL did not capture psychological and social components, which may have contributed to its lower detection rates of frailty. In addition, compared with FRAIL and TFI, FP was largely guided by physical performance, including walking speed and grip strength, yielding a higher prevalence estimate of frailty.

Previous studies have simultaneously validated the studied scales longitudinally in different European populations. However, these results may not be generalizable because the exposure pattern and disease spectrum of Europeans are quite different from those of the Chinese, especially for older adults. FI, FRAIL, and TFI demonstrated independent predictive validity against all outcomes of interest in this study, suggesting that they could identify high-risk Chinese older adults, as measured by 4-year disability, hospitalization, and 4- and 7-year all-cause mortality. The results are consistent with those of other studies (10, 11, 18), although most of them focus on mortality. Furthermore, while these three scales were comparably associated with 4-year hospitalization and 4- and 7-year mortality, their strengths of association with 4-year disability were different; FRAIL conferred the greatest risk, followed by FI and TFI (adjusted OR 5.55, 3.50 and 1.91, respectively, all $p < 0.05$). Notably, there was no evidence of an independent association between FP and 4-year disability or hospitalization in the multivariate analysis, which contrasted with previously published data (33, 34). This discrepancy may be attributable to the partially modified components as well as different covariates adjustments used in our study. Nevertheless, we found that FP was independently associated with mortality, even allowing for different follow-up periods.

10.3389/fpubh.2023.1154809

TABLE 3 Prevalence of frailty, sensitivity, and specificity for different cutoffs of each scale for each outcome.

Frailty scale	Cutoff	Frail [n (%)]*	4-year disability		4-year hospitalization		4-year mortality		7-year mortality	
			Sens (%)	Spec (%)	Sens (%)	Spec (%)	Sens (%)	Spec (%)	Sens (%)	Spec (%)
FI	≥ 0.15	1704 (32.4)	72.8	71.7	39.6	72.6	70.0	69.8	71.2	71.3
	≥ 0.20	**888 (16.9)**	**51.2**	**87.3**	**21.0**	**87.7**	**55.0**	**85.3**	**56.8**	**86.9**
	≥ 0.25	560 (10.6)	33.6	92.8	13.0	93.1	45.0	91.3	44.9	92.6
FP	≥ 2	2482 (48.1)	63.2	53.0	51.1	53.3	69.4	52.8	71.7	53.6
	≥ 3	**648 (12.6)**	**20.8**	**88.5**	**15.2**	**89.0**	**30.6**	**88.2**	**34.1**	**89.0**
	≥ 4	26 (0.5)	0	99.6	0.4	99.6	2.9	99.6	3.2	99.7
FRAIL	≥ 2	406 (7.7)	39.2	94.8	11.7	95.0	31.7	93.7	29.5	94.4
	≥ 3	**224 (4.2)**	**25.6**	**97.3**	**6.3**	**97.1**	**19.5**	**96.7**	**19.6**	**97.3**
	≥ 4	78 (1.5)	4.8	99.0	2.1	99.1	7.7	98.9	7.5	99.1
TFI	≥ 4	847 (16.1)	43.2	86.5	19.3	86.7	45.8	85.6	44.4	86.6
	≥ 5	**385 (7.3)**	**22.4**	**94.6**	**10.0**	**95.0**	**27.3**	**93.8**	**26.2**	**94.5**
	≥ 6	171 (3.2)	11.2	97.6	5.2	97.9	12.7	97.3	12.8	97.6

FI, Frailty Index; FP, Frailty Phenotype; TFI, Tilburg Frailty Indicator; Sens, Sensitivity; Spec, Specificity.
The proposed cutoff values used in this study are highlighted in bold.
*Due to missing data, small differences between n and numbers of participants reported for each scale can occur.

Notably, differences were also evident between our unadjusted logistic models where the predictive accuracy (estimated using AUC) of FI was significantly higher than that of either FRAIL or TFI, all of which offered an advantage over FP. This is perhaps unsurprising, as multidimensional geriatric measures may provide better identification of frailty-related outcomes than a unidimensional index exclusively focused on muscular fitness. Moreover, regarding 4-year disability and 4-and 7-year mortality, AUCs for FI, FRAIL and TFI were acceptable and slightly higher than those of other population-based studies (16, 33, 35); all studied scales, however, were least able to discriminate 4-year hospitalization, which was consistent with these studies. For example, FI, FP, and FRAIL were investigated in the African American Health (AAH) cohort (10), and the findings showed AUCs of 0.69, 0.66 and 0.68 respectively, for 9-year disabilities, 0.64, 0.57 and 0.53 for 9-year mortality. A retrospective study in the Australian Longitudinal Study of Aging (ALSA) (33) revealed that both FI and FP had a low ability to discriminate hospitalization (AUC <0.6). In short, we demonstrated that in this Chinese older population, FI, FRAIL, and TFI are useful predictors for predicting 4-year disability and 4- and 7-year all-cause mortality, whereas none of the four scales should be used as the sole tool for screening for risk of hospitalization.

Another interesting finding in our study was that although the AUC for adverse outcomes was different between the scales, similar performances were found in their diagnostic values of sensitivity and specificity. The high and similar specificity estimates indicated that all frailty scales can be comparably useful in identifying non-frail participants in those without adverse outcomes. Correspondingly, sensitivity estimates for different frailty scales varied within low ranges; regarding 4-year disability and 4- and 7-year mortality, the FI showed similar levels of sensitivity (range 51.2–56.8%), and the other three scales showed similar sensitivity at poor levels (range 20.8–34.1% for FP, 19.5–25.6% for FRAIL, and 22.4–27.3% for TFI, respectively), and lowest sensitivities were found for each scale in the prediction of 4-year hospitalization (range 6.3-21.0%). These findings were consistent with those of a previous study conducted in an older Australian population (33), and the low sensitivity suggested a lack of identification of frail participants at risk for adverse outcomes with our proposed cut-off points. Recently, a similar population-based study (9) of Dutch community-dwelling older people examined the predictive accuracy of FI, FP, and TFI for adverse outcomes including death, hospitalization, and ADL dependency, with a 2-year follow-up. It reported comparable specificity values for FP 79.6–86.2%; however, the sensitivity values were slightly better: 24.7–44.5%. For TFI, the Dutch study reported higher sensitivity values of 70.5–80.6% than those of 10.0–27.3% in the present study, while its specificity values were lower (36.5–45.7%). In addition, compared to the FI used in the Dutch study with a cut-off value of 0.25, the FI with a lower cut-off value of 0.2 used in our Chinese population was found to have higher sensitivity (except for hospitalization) and specificity. A possible reason for this disparity is that our study used the cut-off points proposed by the original authors for FP, FRAIL, and TFI, however, these cutoffs may not be sensitive enough to detect small changes in frailty status when applied to the Chinese population, especially given that we observed higher sensitive values when lower cut-offs were applied (Table 3). Previous studies (36, 37) on the validation of frailty scales also suggested that for the TFI and FRAIL scales used in Chinese community-dwelling older adults, the optimal cut-off points for frailty were 4 and 2, respectively, which were slighter

lower than the original values. Additionally, we speculate that different components of the scales and definitions of the outcomes may also have contributed to this disparity.

In general, good frailty scales should have high predictive ability and sensitivity, the latter of which will be the most relevant criterion, as higher sensitivity means a lower risk of withholding additional investigation and, if available, possible treatments from people who might need it. In the current study, while the scales (except FP) showed distinctively acceptable predictive ability, none of them had both acceptable sensitivity and specificity, nor when the cutoffs were increased or decreased. Therefore, we recommend that choosing a scale will greatly depend on the purpose and setting for frailty assessment. From this perspective, FI, TFI, and FRAIL are useful predictors and frailty screening tools for the development of disability and death in intervention programs such as being inclusion criteria for clinical trials, in which higher specificity is preferred over sensitivity, as it is preferable to correctly identify frail individuals, although some frail individuals will be missed. When screening for geriatric conditions in primary care, a highly sensitive test is preferred, as it is better to identify as many frail individuals as possible, rather than to miss those who are actually frail. Considering our low sensitivity across all scales, the used cut-off points of specific scales can be changed. A strategy for maximizing the feasibility of frailty screening would be to conduct a stepwise process of increasingly more detailed assessment, that is, to combine the existing frailty scales for a comprehensive geriatric assessment. In addition, as good frailty scales should also be simple to apply, another consideration when choosing a scale is the time that is needed to complete it. FRAIL has the advantage of being easy and quick to administer, score and interpret. Conversely, while FI and TFI provide broader coverage of deficits and allow for better identification of high-risk individuals, they are more time-consuming. Thus, we suggest that while FI performs best for estimating risk, the FRAIL scale may be more practical to apply in the Chinese community-dwelling population. However, the increasing use of electronic health records (e.g., general practices) enables ready access to health measures across multiple domains. Then, both FI and TFI can be easily used as screening tools.

Strengths of this research include the longitudinal cohort design, a large, well-defined population-based sample, a wide range of baseline age, and a repeated comprehensive set of health-related assessments. These enable the operationalization and comparison of these four scales in the same Chinese population within the same timeframe.

Our study also has several potential limitations. A potential limitation is the reliance on self-reported questionnaires. We cannot rule out recall bias (e.g., regarding hospitalization over the past 4 years). Furthermore, the scales used here were adapted from the original definitions to utilize the data available from SAGE in shanghai, some important aging-specific variables, therefore, were not included, which may have influenced how each scale predicted outcomes. In particular, we used the lowest BMI for self-reported weight loss, which may have modified the scale characteristics, although this modification has been used previously in many studies. The modified measures, however, may be advantageous. For example, our measure of memory performance (assessed using a verbal recall test instead of a single self-reported question) can predict functional decline (38) and, unlike the self-reported memory used in the original scale, relies on objective assessment. A third limitation is that those who were excluded from the analyses of a scale due to missing data had a higher proportion of 4- and 7-year mortality (see Supplementary material S3). This study may slightly underestimate the ability of scales to predict all-cause mortality. Future studies could focus on verifying the usefulness of our operational approaches to frailty by replicating and extending our findings in other populations and settings.

5. Conclusion

In conclusion, we found that different approaches to frailty result in different estimates for the prevalence of at-risk individuals. Frailty defined using FI, FP, FRAIL, and TFI was independently associated with 4-year disability (except FP), hospitalization (except FP), and 4- and 7-year all-cause mortality in Chinese community-dwelling older adults. However, only FI, FRAIL and TFI were able to reliably predict these outcomes (except 4-year hospitalization), with fair-to-moderate predictive accuracy. Moreover, all four scales, while performing well at ruling out high-risk groups through high specificity estimates, were likely to miss large numbers of frail individuals as measured by adverse outcomes due to low sensitivity estimates. According to our study, FI performs best in estimating risk, while TFI and FRAIL are additionally useful, especially the latter, as a simple and faster screening tool, which may be more practical to apply in Chinese community-dwelling older adults either for the screening or diagnosis of frailty.

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 Shanghai Center for Disease Control and Prevention Ethical Review Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FQ did the statistical analyses, conducted the literature search, and wrote the first draft of the manuscript. All authors critically revised the manuscript for important intellectual content, approved the final version, and contributed to the study concept and design, acquisition, analysis, or interpretation of data.

Funding

This work was supported by the WHO and the US National Institute on Aging through Interagency Agreements (OGHA 04034785, YA1323-08-CN-0020, and Y1-AG-1005-01) and through a research grant (R01-AG034479), the Program for Outstanding Medical Academic Leader, Shanghai, China (2019LJ24), and Shanghai Municipal Health Commission

(20204Y0196, 2020YJZX0113, and 201840118). The sponsor had no role in the design and conduct of the study, the collection, analysis, and interpretation of data, the preparation of the manuscript, and the review or approval of the manuscript.

Acknowledgments

The authors wish to thank all the participants in the study as well as the departments involved in their recruitment.

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/fpubh.2023.1154809/full#supplementary-material

References

1. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *Lancet.* (2019) 394:1365–75. doi: 10.1016/S0140-6736(19)31786-6

2. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc.* (2013) 14:392–7. doi: 10.1016/j.jamda.2013.03.022

3. Pilotto A, Custodero C, Maggi S, Polidori MC, Veronese N, Ferrucci L, et al. Multidimensional approach to frailty in older people. *Ageing Res Rev.* (2020) 60:101047. doi: 10.1016/j.arr.2020.101047

4. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol Ser A-Biol Sci Med Sci.* (2001) 56:M146–M56. doi: 10.1093/gerona/56.3.M146

5. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* (2005) 173:489–95. doi: 10.1503/cmaj.050051

6. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue QL, et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. *Ageing Res Rev.* (2016) 26:53–61. doi: 10.1016/j.arr.2015.12.003

7. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: a review. *Eur J Intern Med.* (2016) 31:3–10. doi: 10.1016/j.ejim.2016.03.007

8. Woo J, Leung J, Morley JE. Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. *J Am Geriatr Soc.* (2012) 60:1478–86. doi: 10.1111/j.1532-5415.2012.04074.x

9. Veld LPMOh, Beurskens AJHM, de Vet HCW, van Kuijk SMJ, Hajema K, Kempen GIJM, et al. The ability of four frailty screening instruments to predict mortality, hospitalization and dependency in (instrumental) activities of daily living. *Eur J Age.* (2019) 16:387–94. doi: 10.1007/s10433-019-00502-4

10. Malmstrom TK, Miller DK, Morley JE. A comparison of four frailty models. *J Am Geriatr Soc.* (2014) 62:721–6. doi: 10.1111/jgs.12735

11. Theou O, Brothers TD, Mitnitski A, Rockwood K. Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. *J Am Geriatr Soc.* (2013) 61:1537–51. doi: 10.1111/jgs.12420

12. Gu D, Dupre ME, Sautter J, Zhu H, Liu Y, Yi Z. Frailty and mortality among Chinese at advanced ages. *J Gerontol.* (2009) 64:279–89. doi: 10.1093/geronb/gbn009

13. Yang F, Gu D. Predictability of frailty index and its components on mortality in older adults in China. *BMC Geriatr.* (2016) 16:145. doi: 10.1186/s12877-016-0317-z

14. Zheng Z, Guan S, Ding H, Wang Z, Zhang J, Zhao J, et al. Prevalence and incidence of frailty in community-dwelling older people: beijing longitudinal study of aging Ii. *J Am Geriatr Soc.* (2016) 64:1281–6. doi: 10.1111/jgs.14135

15. Wang C, Ji X, Wu X, Tang Z, Zhang X, Guan S, et al. Frailty in relation to the risk of Alzheimer's disease, dementia, and death in older chinese adults: a seven-year prospective study. *J Nutr Health Aging.* (2017) 21:648–54. doi: 10.1007/s12603-016-0798-7

16. Shi G-P, Ma T, Zhu Y-S, Wang Z-D, Chu X-F, Wang Y, et al. Frailty phenotype, frailty index and risk of mortality in Chinese elderly population- rugao longevity and ageing study. *Arch Gerontol Geriatr.* (2019) 80:115–9. doi: 10.1016/j.archger.2018.11.001

17. Zhu Y, Liu Z, Wang Y, Wang Z, Shi J, Xie X, et al. Agreement between the frailty index and phenotype and their associations with falls and overnight hospitalizations. *Arch Gerontol Geriatr.* (2016) 66:161–5. doi: 10.1016/j.archger.2016.06.004

18. Zhang D, Tang W, Dou L-Y, Luo J, Sun Y. Four different frailty models predict health outcomes in older patients with stable chronic obstructive pulmonary disease. *BMC Geriatr.* (2022) 22:1. doi: 10.1186/s12877-022-02750-z

19. Kowal P, Chatterji S, Naidoo N, Biritwum R, Fan W, Lopez Ridaura R, et al. Data resource profile: the world health organization study on global ageing and adult health (Sage). *Int J Epidemiol.* (2012) 41:1639–49. doi: 10.1093/ije/dys210

20. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K, A. Standard procedure for creating a frailty index. *BMC Geriatr.* (2008) 8:24. doi: 10.1186/1471-2318-8-24

21. Biritwum RB, Minicuci N, Yawson AE, Theou O, Mensah GP, Naidoo N, et al. Prevalence of and factors associated with frailty and disability in older adults from China, Ghana, India, Mexico, Russia and South Africa. *Maturitas.* (2016) 91:8–18. doi: 10.1016/j.maturitas.2016.05.012

22. Ruan Y, Guo Y, Kowal P, Lu Y, Liu C, Sun S, et al. Association between anemia and frailty in 13,175 community-dwelling adults aged 50 years and older in China. *BMC Geriatr.* (2019) 19:327. doi: 10.1186/s12877-019-1342-5

23. Anand A. Categorical frailty phenotype and continuous frailty index: a conceptual overview of frailty and its components among older persons in India. *Italian J Public Health.* (2019) 16:4. doi: 10.2427/13212

24. Gonzalez-Bautista E, Manrique-Espinoza B, Avila-Funes JA, Naidoo N, Kowal P, Chatterji S, et al. Social determinants of health and frailty are associated with all-cause mortality in older adults. *Salud Publica Mex.* (2019) 61:582–90. doi: 10.21149/10062

25. Hoogendijk EO, Rijnhart JJM, Kowal P, Perez-Zepeda MU, Cesari M, Abizanda P, et al. Socioeconomic inequalities in frailty among older adults in six low- and middle-income countries: results from the who study on global ageing and adult health (Sage). *Maturitas.* (2018) 115:56–63. doi: 10.1016/j.maturitas.2018.06.011

26. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (frail) predicts outcomes in middle aged African Americans. *J Nutr Health Aging.* (2012) 16:601–8. doi: 10.1007/s12603-012-0084-2

27. Gobbens RJJ, Luijkx KG, Wijnen-Sponselee MT, Schols J. Towards an integral conceptual model of frailty. *J Nutr Health Aging.* (2010) 14:175–81. doi: 10.1007/s12603-010-0045-6

28. World Health Organization. *Measuring Health and Disability: Manual for WHO Disability Assessment Schedule (WHODAS 2.0).* World Health Organization (2010). Available online at: https://apps.who.int/iris/handle/10665/43974?locale-attribute=en& (accessed August 16, 2022).

29. Royston P, Moons KGM, Altman DG, Vergouwe Y. Prognosis and prognostic research: developing a prognostic model. *BMJ.*(2009) 338:b604. doi: 10.1136/bmj.b604

30. Apostolo J, Cooke R, Bobrowicz-Campos E, Santana S, Marcucci M, Cano A, et al. Predicting risk and outcomes for frail older adults: a protocol

for an umbrella review of available frailty screening tools. *JBI.* (2016) 13:14–24. doi: 10.1097/01.XEB.0000511332.11553.51

31. Siriwardhana DD, Hardoon S, Rait G, Weerasinghe MC, Walters KR. Prevalence of frailty and prefrailty among community-dwelling older adults in low-income and middle-income countries: a systematic review and meta-analysis. *BMJ Open.* (2018) 8:e018195. doi: 10.1136/bmjopen-2017-018195

32. Chong E, Ho E, Baldevarona-Llego J, Chan M, Wu L, Tay L, et al. Frailty in hospitalized older adults: comparing different frailty measures in predicting short- and long-term patient outcomes. *J Am Med Dir Assoc.* (2018) 19:450–7 e3. Epub 2017/11/21. doi: 10.1016/j.jamda.2017.10.006

33. Widagdo IS, Pratt N, Russell M, Roughead EE. Predictive performance of four frailty measures in an older australian population. *Age Ageing.* (2015) 44:967–72. doi: 10.1093/ageing/afv144

34. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Cawthon PM, Stone KL, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Arch Intern Med.* (2008) 168:382–9. doi: 10.1001/archinternmed.2007.113

35. Forti P, Rietti E, Pisacane N, Olivelli V, Maltoni B, Ravaglia G, et al. Comparison of frailty indexes for prediction of adverse health outcomes in an elderly cohort. *Arch Gerontol Geriatr.* (2012) 54:16–20. doi: 10.1016/j.archger.2011.01.007

36. Dong L, Liu N, Tian X, Qiao X, Gobbens RJJ, Kane RL, et al. Reliability and validity of the tilburg frailty indicator (Tfi) among chinese community-dwelling older people. *Arch Gerontol Geriatr.* (2017) 73:21–8. doi: 10.1016/j.archger.2017.07.001

37. Dong L, Qiao X, Tian X, Liu N, Jin Y, Si H, et al. Cross-cultural adaptation and validation of the frail scale in chinese community-dwelling older adults. *J Am Med Dir Assoc.* (2018) 19:12–7. doi: 10.1016/j.jamda.2017.06.011

38. Park J-H, Park H, Sohn SW, Kim S, Park KW. Memory performance on the story recall test and prediction of cognitive dysfunction progression in mild cognitive impairment and Alzheimer's dementia. *Geriatr Gerontol Int.* (2017) 17:1603–9. doi: 10.1111/ggi.12940

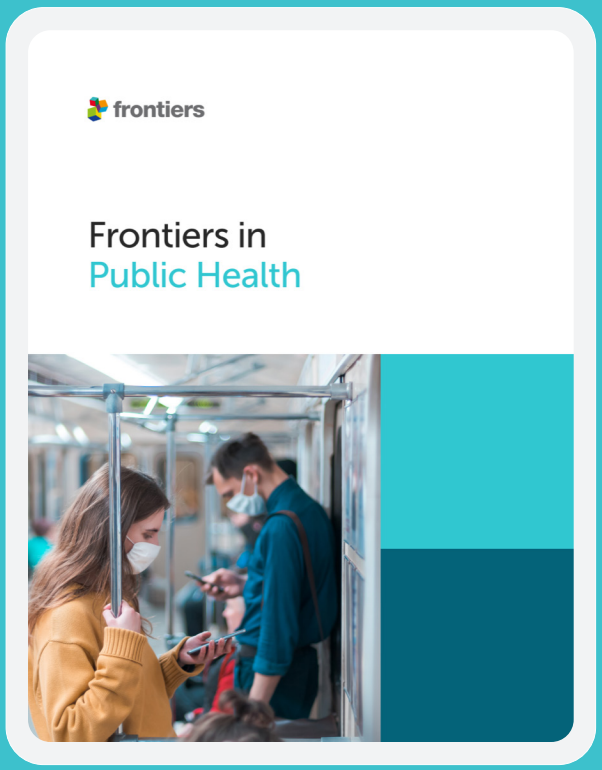
Frontiers in Public Health

Explores and addresses today's fast-moving healthcare challenges

One of the most cited journals in its field, which promotes discussion around inter-sectoral public health challenges spanning health promotion to climate change, transportation, environmental change and even species diversity.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact