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Frailty: Risks and management

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Frailty: Risks and management

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Editorial: Frailty: Risks and management

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KEYWORDS

frailty, older adults, geriatric syndrome, aging, geriatric medicine

Editorial on the Research Topic
Frailty: Risks and management

The Research Topic "Frailty: Risks and management" aims to investigate the recent advances in the risk assessment and management of frailty in older adults, a growing major public health burden due to population aging, through relevant articles proposed by research groups from different countries.

The selected articles address the typical problems associated with this geriatric multifactorial condition from different perspectives and points of view, highlighting emerging epidemiological aspects alongside consolidated ones, analyzing risk factors specific to sex, reporting the potential role of new diagnostic tools and helping to propose the multidisciplinary approach as an essential resource in the care of elderly people.

Cognitive decline is extremely common among older adults, and cognitive frailty represents an emerging nosological entity that selectively associates it with frailty, as a potentially reversible syndrome (1). Focusing on a population of 1,390 older adults from the Geriatrics Service of the Centro Médico Naval in Peru, Vargas-Torres-Young et al. found that cognitive frailty and its specific components (cognitive impairment and modified Fried Phenotype criteria) were associated with higher risk of mortality, stimulating discussion on the role of interventions aimed at reversing this condition.

Interventions aimed at treating frailty are the subject of intense debate, given that their effectiveness is conditioned by multiple factors. At this regard, Coelho-Júnior and Uchida investigated the effects of resistance training programs on frailty status, physical performance, cognitive function and blood pressure in 60 Brazilian pre-frail and frail older adults, randomly allocated to low-speed and high-speed exercises. The results are particularly interesting because, although both resistance trainings reversed frailty status and enhanced physical performance, different patterns of improvement were observed between frailty degrees, with effects probably mediated by the heterogeneity of the aging process.

The use of diagnostic tools in the management of frailty is of great relevance, and muscle ultrasound is attracting increasing attention in the scientific community, especially in the assessment of sarcopenia (2). This tool is the topic of two manuscripts published in the present collection. Lv et al. enrolled 150 people aged ≥65 years from the First Hospital Affiliated to Nanjing Medical University who had undergone the anterior ultrasound of ulnar, vastus lateralis and anterior tibial muscles. The authors demonstrated that frailty phenotype (Fried's model) (3) was closely related to muscle thickness and quality, especially vastus lateralis muscle, and that muscle quality also deteriorated in the prefrailty stage, earlier than thickness. Bencivenga et al. employed Rockwood's Frailty Index (4) and ultrasound of rectus femoris plus vastus intermedius muscles of dominant arm to assess the association between frailty and muscle thickness in

a population of 136 hospitalized older adults. The authors found that frailty index resulted significantly and independently associated with age and muscle thickness. Both studies stimulate discussion on the opportunity to consider muscle ultrasound as an additional imaging domain of frailty.

In recent years, several pieces of literature have been focusing on the variability patterns of measurable variables as measures of the altered state of homeostatic mechanisms underlying the development of frailty, especially in cardiovascular medicine (5). In this context, the review by Arantes et al. propose that heart rate variability can constitute a potential marker of frailty, as epiphenomenon of changes in cardiac autonomic modulation. They provide an overview on the tools to monitor the heart rate variability and summarize the evidence on its association with frailty.

In the era of personalized medicine, with a tailored preventive and therapeutic approach to older adults, studies on epidemiology that take into account the specific risk factors for frailty in individual countries and cultures are needed. Wang, Lv, et al., based on the results from 13,859 participants in the Chinese Longitudinal Healthy Longevity Study (CLHLS), reported a high prevalence of pre-frail and frail participants (54.1 and 26.3%, respectively) and provided a comprehensive insight into the epidemiology of this syndrome and related adverse outcomes. In their second article (Wang, Zhang, et al.) included in the present collection, a corresponding paper on the epidemiology of frailty, the authors presented a wide range of sex-specific contributors to frailty. Indeed, focusing on a group of 3,327 participants from the CLHLS, they reported risk factors that were common for both sexes and others more associated with the male or female sex. The protective effect of greater household income, higher level of physical activity and fresh fruit and vegetable consumption was shown for both sexes.

The two above-mentioned Chinese studies are accurately supplemented by the results of the prospective observational China Health and Retirement Longitudinal Study (CHARLS). Huang et al. found in their 2-year follow-up project that undertaking frequent intellectual activities (including playing Ma-jong, chess or cards, attending courses or surfing the web) corresponded with decreased risk of frailty syndrome in older adults aged 60 years and more. When considering frailty risk factors from a wider perspective, iatrogenic harms come to the fore. In their prospective cohort study of hospitalized patients treated with intravenous infusions, Cao et al. reported that the risk of frozen shoulder within 1 year of hospital discharge was as high as 5.2%. The risk factors for its onset included longer time of intravenous infusion, longer hospital stay, older age and comorbidities.

The current global economic and political crises recall the key role of socio-economic support on the state of health of the various age groups of the population, with a medium-long term impact. In this context the research question of the research proposed by Gao et al. on the relation between hunger in childhood and frailty in old age, seems particularly important. In their cross-sectional analysis of data obtained from the 2018 Chinese Longitudinal Healthy Longevity Survey, the authors showed that experience of childhood hunger was linked to frailty in late life, mediated by age and financial resources.

Taking advantage of the multidisciplinary approach, which is strongly advocated for the proper management of the complexity of frailty syndrome, geriatricians should go hand in hand with ophthalmologists when working with middle-aged and older patients. The opinion paper included in our collection by Crooke et al. presented a comprehensive scope of presbyopia as an opportunity for the timely detection of pre-frailty and frailty.

A key component of the aging process is represented by comorbidities, which, together with chronological age, constitute the main factors associated with frailty. Granata et al. propose a systematic review to evaluate the use of Clinical Frailty Scale, a screening tool based on clinical judgment (6), for frailty assessment, with a specific focus on chronic and noncommunicable diseases. From the 56 studies included, this tool was associated with a variety of disease-related characteristics, and was a good predictor of clinical outcomes, life expectancy, hospitalizations, and quality of life.

In summary, appreciating the high impact of frailty on national health systems, the articles in this Research Topics collection provide a meaningful and up-to-date scenario on some key aspects of this syndrome, also pointing out interesting potential innovations and stimulating new concepts. The Research Topic "Frailty: Risks and management" represents an important contribution to the body of scientific evidence in the field of geriatric medicine and also reveal current research gaps, stimulating ideas for future research on the topic.

Author contributions

LB and KP wrote and approved the editorial. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Associations Between Intellectual and Social Activities With Frailty Among Community-Dwelling Older Adults in China: A Prospective Cohort Study

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Background: Frailty is one of the most important global health challenges. We aimed to examine the associations between frequency of intellectual and social activities and frailty among community-dwelling older adults in China.

Methods: This is a prospective analysis of older adults (aged ≥60 years) who had intellectual and social activity data and were free of frailty from the national representative China Health and Retirement Longitudinal Study (CHARLS). The exposure was frequency of intellectual and social activities. Frailty was measured by the frailty index (FI) and defined as FI ≥ 0.25. Frailty incidents were followed up for 2 years. We estimated the relative risks (RRs) with 95% confidence intervals (CIs) using log-linear binominal regression adjusting for potential confounders.

Results: We documented 655 frailty cases over the past 2 years. Participants who had frequent intellectual activities had a lower frailty risk compared with participants who did not have intellectual activity (adjusted RR = 0.65, 95%CI = 0.47–0.90). The adjusted RRs were 0.51 (95%CI = 0.33–0.77) for participants who did not have a slip or a fall accident and 1.06 (95%CI = 0.65–1.75) for participants who had experienced slip and fall accidents ($P = 0.01$ for interaction). Having frequent social activities was not associated with a significant decrease in frailty risk compared with participants who did not have social activity (adjusted RR = 0.93, 95%CI = 0.78–1.12).

Conclusions: This observational study showed that having frequent intellectual activities was associated with a decreased frailty risk. The association was likely to be stronger in participants without a slip or a fall accident. Randomized controlled trials are needed to confirm this observational finding.

Keywords: frailty, intellectual activity, social activity, prospective cohort study, CHARLS

INTRODUCTION

Frailty, as an extreme consequence of the normal aging process, is one of the most serious global health challenges (1). A recent systematic review and meta-analysis has reported that the pooled prevalence of frailty was 17.4% among community-dwelling older adults in low-income and middle-income countries (2). Frailty is an unstable status in which the physiological reserves are reduced, causing disorders in homeostatic systems (1, 3). This would lead to rapid deterioration in functional capacity across many physiological systems and, thus, significantly increased risks of adverse health outcomes, such as falls, disability, hospitalization, and death (1, 3). Therefore, the identification of and interventions to slow the progression of frailty are essential for healthcare systems in an aging society (4, 5).

Insights into the key risk factors of frailty would be very helpful in determining effective strategies for frailty prevention. Many cross-sectional and longitudinal studies have been conducted to explore factors associated with frailty (2, 6–22). The identified potential factors included sociodemographic factors (6–9), socioeconomic status (2, 7, 14, 15), physical and biological factors (20–22), and lifestyle and clinical factors (7, 11–14, 18, 19). Most of these risk factors could be modified by regular physical activities and adequate nutritional intake (23).

Several studies have shown that participation in social and intellectual activities could improve the cognitive reserve and reduce functional decline and disabilities (12, 23, 24). Social and intellectual activities, along with physical activities and nutritional intake, play an important role in frailty prevention (2, 12). The associations between social or intellectual activities and physical frailty have been investigated in many studies (25–32). For example, a 4-year cohort study in Japan found that social frailty was a significant risk factor that leads to physical frailty (25). Another study in Japan showed that social activities decreased the functional disability risks (32). Wang et al. conducted a cross-sectional study among seniors from Singapore (28). They found that participation in intellectual activities was likely to be associated with a lower frailty prevalence (28).

To date, prospective cohort evidence for the associations between intellectual and social activities and frailty is still lacking in China. In addition, the associations between the different frequencies of intellectual or social activity participation and frailty development also needed to be further investigated (3, 33–35). We therefore conducted this prospective study to evaluate the associations between the frequency of intellectual and social activities and frailty among Chinese community-dwelling older adults.

METHODS

Study Population and Design

The analyses were performed based on the China Health and Retirement Longitudinal Study (CHARLS) (36). In brief, CHARLS is a biennial national study that collects a representative sample of Chinese residents using a multistage stratified probability proportionate to size technique. High-quality information of the included residents was collected. The details of the objectives and methods of CHARLS were published in a previous report (36). The survey in 2015–2016 and the follow-up survey in 2017–2018 were available for the analyses in this study. The CHARLS was approved by the Biomedical Ethics Review Committee of Peking University. Written informed consent was obtained from all participants. The ethical approval number of CHARLS is IRB00001052-11015.

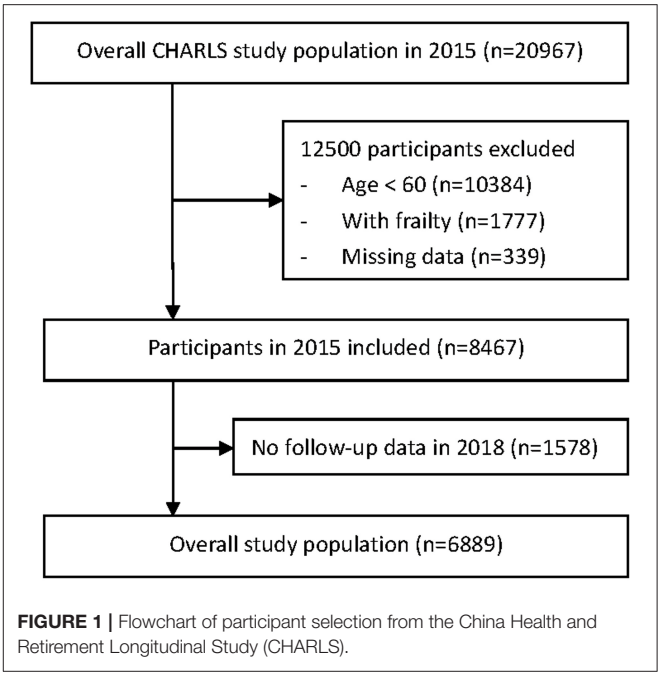

FIGURE 1 | Flowchart of participant selection from the China Health and Retirement Longitudinal Study (CHARLS).

For the current analysis, we restricted the participants to those aged 60 years or above. We also excluded participants without frailty information. For each participant, the intellectual and social performances were collected in 2015–2016. Each participant had a 2-year follow-up. The ascertainment of frailty was carried out in 2017–2018. The participants who did not respond to the 2018 survey were considered as lost to follow-up (see **Figure 1**). The data in this study were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (37).

Assessment of the Frequencies of Intellectual and Social Activities

In the 2015–2016 CHARLS survey, participants were asked about their intellectual and social activities in the past month. Intellectual activities include playing Ma-jong, chess, cards; attending an educational or training course; investing in stock; and surfing the Internet. Social activities include interacting with friends; going to a sport, social, or other kinds of club; taking part in a community-related organization; and doing voluntary or charity work. The frequency of each activity was rated as follows: almost daily (score = 3), almost every week (score = 2), not regularly (score = 1), or never (score = 0). The total

scores for intellectual and social activities ranged from 12 to 0 points and were categorized as ≥3, 1–2, and 0, where "≥3" referred to frequent participation, "1-2" referred to non-regular participation, and "0" referred to no participation in intellectual and social activities (30).

Ascertainment of Frailty

Frailty was measured by using a frailty index (FI). The construction of the FI was based on a standard procedure (38). The detailed method for the calculation of FI was reported in previous published studies (13, 17). In brief, a total of 39 deficit variables that were associated with FI in the CHARLS were selected, including 15 comorbidity variables, 5 disability variables, and 19 variables on activities of daily living. All of these 39 variables were scored from 0 to 1, where "0" indicated no deficit and "1" indicated the presence of a deficit. For each participant, FI was calculated by adding the scores of all the deficits and dividing by the total number of deficits. Frailty was defined as FI ≥ 0.25 (13, 16, 17, 39, 40).

Assessment of Covariates

The following information were obtained: sociodemographic factors, including age and sex; socioeconomic factors, including economic development regions (>$10,000, from $10,000 to >7,000, and ≤$7,000) (41); lifestyle and health factors, including hours of actual sleep (≥6 h or <6 h), smoking (yes or no), and whether one had experienced slip and fall accidents (yes or no). The participants were deemed to have slip and fall accidents if they responded "yes" when asked "Have you fallen down?" The main comorbidities in medical history included cancer, diabetes mellitus, heart disease, hypertension, and stroke.

Statistical Analysis

Baseline characteristics were compared among the different intellectual and social activity scores by using one-way analysis of variance (ANOVA) for continuous measures and using the Mantel–Haenszel test for proportion trends. The associations between intellectual and social activities and frailty were estimated as relative risks (RRs) with 95% confidence intervals (CIs) using log-linear binominal regression with a multivariable-adjusted model. In the multivariable-adjusted model 1, we adjusted for age and sex. To control potential confounding from socioeconomic status, we additionally adjusted for economic development regions in the multivariable-adjusted model 2. In the multivariable-adjusted model 3, we additionally controlled for lifestyle and health factors, such as sleep, smoking, and experiences of slip and fall accidents. Moreover, we finally introduced a model 4 to additionally adjust for the main comorbidities such as cancer, diabetes mellitus, heart disease, hypertension, and stroke. A multivariate logistic regression analysis was used in model 4. Odd ratios (ORs) with 95% CIs were reported.

Based on a review of previous literature (8, 16, 17), whether one had experienced slip and fall accidents was a potential effect modifier that may modify the associations between intellectual and social activities and frailty. Therefore, subgroup analysis was conducted based on whether the participants had experienced slip and fall accidents.

A number of sensitivity analyses were performed to examine the robustness of the associations between intellectual and social activities and frailty. Firstly, the impacts of lowering the cutoff value of FI were estimated, as FI ≥ 0.24 and FI ≥ 0.23. Secondly, only participants aged 65 years or older were included. Thirdly, we included only the participants without missing data. A p-value <0.05 was considered significant. All the analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

This study included 6,889 participants. **Table 1** presents the baseline characteristics according to the intellectual activity and social activity scores. Of the sample, 78.3% of the participants had an intellectual activity score of 0 and 62.4% had a social activity score of 0. Among the different intellectual activity scores, there were differences in the baseline characteristics such as age, sex, economic development region, actual sleep, smoking, cancer, diabetes, and heart disease. Among the different social activity scores, there were differences in the baseline characteristics such as age, sex, slip and fall accidents, smoking, diabetes, heart disease, and hypertension.

We observed 655 frailty cases over the past 2 years. In the fully adjusted model (model 3), participants with frequent intellectual activities (score ≥ 3) had a lower frailty risk compared with participants who did not have intellectual activity (scores = 0), with multivariable-adjusted RR of 0.65 (95%CI = 0.47–0.90). Participants who had non-regular intellectual activities (score = 1–2) had a lower frailty risk compared with participants who did not have intellectual activity, with multivariable-adjusted RR of 0.60 (95%CI = 0.44–0.80).

Results from the adjusted model (model 3) showed that participants who had non-regular social activities (score = 1–2) had a lower frailty risk compared with participants who had no social activity (score = 0), with multivariable-adjusted RR of 0.68 (95%CI = 0.54–0.86). However, having frequent social activities (score ≥ 3) was not associated with a decreased frailty risk compared with participants who had no social activity (score = 0), with multivariable-adjusted RR of 0.93 (95%CI = 0.78–1.12) (**Table 2**).

Subgroup analysis was conducted to detect whether having experienced slip and fall accidents was an interaction that modified the effect of intellectual activity on frailty. We found evidence of an interaction effect of "slip and fall accidents" when comparing participants who had frequent intellectual activities (score ≥ 3) to those who did not have intellectual activity (score = 0). Among the participants who did not have a slip or a fall accident, having frequent intellectual activities (score ≥ 3) was associated with a significant decrease in frailty risk compared with participants who did not have intellectual activity (score = 0). However, among the participants who had experienced slip and fall accidents, having frequent intellectual activities (score ≥ 3) was not associated with a decreased frailty risk compared with participants who had no intellectual activity (score = 0). The p-value for the "slip and fall accidents" interaction was 0.0103 (**Table 3**).

TABLE 1 | Baseline characteristics according to the intellectual activity and social activity scores.

	Intellectual activity scores				Social activity scores			
	0	1–2	≥3	*P*-value[a]	0	1–2	≥3	*P*-value[a]
No. of participants	5,395	848	646		4,302	1,147	1,440	
Age, mean (SD) (years)	67.4 (6.1)	66.4 (5.5)	67.0 (5.8)	<0.0001	67.2 (5.9)	66.9 (5.8)	67.7 (6.3)	0.0023
Male, *n* (%)	2547 (47.2)	533 (62.9)	403 (62.4)	<0.0001	2,273 (52.8)	594 (51.8)	616 (42.8)	<0.0001
Economic development region, *n* (%)				0.0084				0.5143
>$10,000	1,883 (34.9)	294 (34.8)	235 (36.4)		1,508 (35.1)	418 (36.5)	486 (33.8)	
$10,000 to > 7,000	2,487 (46.2)	439 (51.9)	319 (49.4)		2,038 (47.4)	511 (44.6)	696 (48.4)	
≤$7,000	1,019 (18.9)	113 (13.4)	92 (14.2)		752 (17.5)	217 (18.9)	255 (17.8)	
Actual sleep <6 h, *n* (%)	1,974 (36.6)	264 (31.1)	188 (29.1)	<0.0001	1,556 (36.2)	378 (33.0)	492 (34.2)	0.0816
Without falling down experience, *n* (%)	4,395 (81.6)	704 (83.0)	541 (83.8)	0.1114	3,565 (83.0)	926 (80.7)	1,149 (79.8)	0.0033
Never smoker, *n* (%)	3,032 (58.0)	337 (41.0)	276 (44.0)	<0.0001	2,208 (53.0)	587 (52.4)	850 (60.8)	<0.0001
Medical history, *n* (%)								
Cancer	87 (1.6)	21 (2.5)	18 (2.8)	0.0112	69 (1.6)	24 (2.1)	33 (2.3)	0.0728
Diabetes mellitus	606 (11.5)	107 (12.9)	117 (18.6)	<0.0001	469 (11.2)	157 (14.0)	204 (14.5)	0.0003
Heart disease	1,014 (19.6)	191 (23.6)	151 (25.2)	0.0001	774 (18.8)	250 (22.7)	332 (24.5)	<0.0001
Hypertension	2,146 (42.4)	321 (40.2)	274 (45.1)	0.5427	1,687 (41.8)	428 (39.5)	626 (46.4)	0.0154
Stroke	385 (7.2)	48 (5.8)	58 (9.2)	0.3467	297 (7.0)	69 (6.1)	125 (8.8)	0.0621

[a]*Mantel–Haenszel test for proportion trends and one-way ANOVA for continuous measures.*

TABLE 2 | Risk of frailty according to the intellectual activity and social activity scores.

Scores	No. of cases	Multivariable-adjusted model 1		Multivariable-adjusted model 2		Multivariable-adjusted model 3		Multivariable-adjusted model 4	
		Relative risk (95%CI)	*P*-value	Relative risk (95%CI)	*P*-value	Relative risk (95%CI)	*P*-value	Odds ratio (95%CI)	*P*-value
Intellectual activity scores									
0	567/5,395	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–
1–2	48/848	0.64 (0.48–0.86)	0.0027	0.64 (0.48–0.86)	0.0026	0.60 (0.44–0.80)	0.0007	0.51 (0.35–0.73)	0.0003
≥3	40/646	0.67 (0.49–0.92)	0.0119	0.67 (0.49–0.91)	0.0116	0.65 (0.47–0.90)	0.0092	0.40 (0.26–0.61)	<0.0001
Social activity scores									
0	441/4,302	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–
1–2	77/1,147	0.70 (0.55–0.88)	0.0024	0.70 (0.56–0.89)	0.0032	0.68 (0.54–0.86)	0.0016	0.57 (0.42–0.77)	0.0003
≥3	137/1,440	0.92 (0.76–1.10)	0.3604	0.92 (0.76–1.10)	0.3615	0.93 (0.78–1.12)	0.4654	0.93 (0.73–1.18)	0.5453

Multivariable-adjusted model 1: adjusted for age and sex.
Multivariable-adjusted model 2: additionally adjusted for economic development regions (>$10,000, $10,000 to >7,000, and ≤$7,000).
Multivariable-adjusted model 3: additionally adjusted for sleep (≥6 h or <6 h), smoking (never, past, or current), and whether one had a fall experience (yes or no).
Multivariable-adjusted model 4: additionally adjusted for cancer, diabetes mellitus, heart disease, hypertension, and stroke. Multivariate logistic regression analyses were used in model 4.

In the sensitivity analyses, all the results were generally unchanged, indicating the robustness of the identified associations (**Table 4**).

DISCUSSION

In this prospective analysis of 6,889 elderly Chinese participants, 655 frailty cases were identified over the 2-year follow-up. We found that having frequent intellectual activities was associated with a 35% lower risk of frailty. The association was likely to be stronger among participants who did not experience a slip or a fall accident, with a 49% lower risk of frailty. These associations showed robustness in a series of sensitivity analyses. On the contrary, having frequent social activities was not associated with a significant decrease in frailty risk compared with participants who did not have social activity.

Previous studies have shown that risk factors for the onset of frailty span across a broad range, including sociodemographic, socioeconomic, lifestyle-related, and biological and clinical aspects (2, 6–22). Feng et al. conducted a systematic review and meta-analysis to investigate protective factors that were associated with frailty among elderly people (7). A wider range of factors was identified, including psychological and social factors (7). Our study is in agreement with these previous findings.

The identification of essential modifiable risk and protective factors is very important for frailty prevention (1, 3, 42).

TABLE 3 | Subgroup analyses of the intellectual activity and social activity scores and the risk of frailty.

Scores	Slip and fall experience	Relative risk (95%CI)	*P* interaction[a]
Intellectual activity scores			
1–2 vs. 0	Yes	0.72 (0.43–1.18)	0.3511
	No	0.56 (0.38–0.81)	
≥3 vs. 0	Yes	1.06 (0.65–1.75)	0.0103
	No	0.51 (0.33–0.77)	
Social activity scores			
1–2 vs. 0	Yes	0.81 (0.54–1.22)	0.2918
	No	0.64 (0.48–0.86)	
≥3 vs. 0	Yes	1.04 (0.75–1.45)	0.1983
	No	0.88 (0.70–1.10)	

[a]*Estimated effects were adjusted on the fully adjusted model 3 (see footnote in* ***Table 2****).*

Previously, the preventive strategies mainly focused on physical-related interventions, such as taking regular physical activities and providing adequate nutritional intake (4, 33, 43). Recently, loneliness and social isolation have been proven to have negative effects on health (10, 44, 45). More attention should be paid to the association between psychosocial factors and frailty development. In a 4-year cohort study, Makizako et al. found that social frailty leads to physical frailty in a relatively short period of time (25). Based on a 2-year cohort, the results from the study of Ye et al. showed that social participation was associated with a higher prefrail improvement (29). Kim et al. conducted a cross-sectional study to investigate the frequency of social activity participation and its association with the different levels of frailty (27). They found that social activities such as leisure and club activities at a frequency of once a week were associated with frailty prevention (27). The results of this study were in agreement with these previous findings, despite the differences in the setting population, the frailty index domains, and details in the social and intellectual activities included between this study and the previous studies. In addition, we found that non-regular participation in social activities has a positive impact on frailty prevention. However, having frequent social activities (such as an almost daily participation) was not associated with a decrease in frailty risk.

Understanding the associations between intellectual activity participation and frailty development was also important. In a cross-sectional study, Wang et al. found that engaging in intellectual activities in late-life was associated with a lower frailty prevalence, especially among female elderly people (28). To date, evidence from prospective cohort studies is still lacking for the impact of intellectual activities on frailty. The present study showed that participation in intellectual activity was associated with a significant decrease in frailty risk compared with non-participation in intellectual activity. Frailty often coexists with cognitive impairment (45, 46). Lack of intellectual activity increases the risks of cognitive impairment (30, 47, 48). In the future, strategies for frailty prevention should be more focused on improving participation in intellectual activities. In addition, intellectual training, when combined with physical training, could have a positive effect on preserving the function of physiological systems and, thus, slowing the progression of cognitive frailty (12, 48, 49), despite the underlying biological and psychological mechanisms still far from being understood (1, 48, 50).

Effective strategies are needed to prevent or slow the progression of frailty. To date, solid evidence, such as randomized controlled trials (RCTs), is still lacking to evaluate the effectiveness of intervention strategies on frailty development. Most of the previous studies were observational. They were mainly focused on physical activity and nutritional strategies, such as exercise and muscle training and sufficient protein intake (1, 4, 5, 51). Since the current observational evidence showed a significant association between participation in intellectual activities and decreased frailty risk, it is encouraged to include intellectual activities in the intervention strategies on frailty in the future. Individually tailored intellectual and social activity programs could be added into traditional frailty intervention strategies. Moreover, high-quality RCTs are also needed to examine the effectiveness of these intellectual activity programs on frailty prevention.

STRENGTHS AND LIMITATIONS OF THIS STUDY

To our knowledge, this is the first prospective observational study investigating the associations between intellectual and social activities and frailty risks. We identified that having frequent intellectual activities is associated with decreased frailty risks whereas having frequent social activities is not compared with non-participation in intellectual and social activities. In addition, fall was a significant interaction for the effect of intellectual activity on frailty. The findings in this study would provide useful evidence for the management of and prevention strategies on frailty.

However, two potential limitations should be noted. Firstly, the current research was an observational cohort study. Despite potential confounders being adjusted in the log-linear binominal regression by multivariable-adjusted models, the results may still be biased by other potential important confounders, for example, nutrient intake, musculoskeletal function, and laboratory parameters such as serum uric acid levels (7). On the one hand, the analyses in this study were based on secondary data, so important factors such as nutrition and exercise were precluded. On the other hand, due to model limitation, the number of cases was too small to include enough adjusted variables in the adjusted model. In the future, RCTs are needed to determine the effect of the different levels of intellectual and social activities on frailty. Then, both the known and unknown confounders would be controlled in well-designed RCTs. Secondly, frailty should be detected reliably. Although multiple screening instruments for frailty have been developed and validated, to date, there is still a lack of the most effective instruments to detect frailty. There is also a lack of agreement between the different screening instruments. Nevertheless, in this study, multiple sensitivity analyses with different cutoff values of the FI were performed and the results were robust.

TABLE 4 | Sensitivity analyses: risk of frailty according to the intellectual activity and social activity scores.

	No. of cases	Multivariable-adjusted model 1		Multivariable-adjusted model 2		Multivariable-adjusted model 3		Multivariable-adjusted model 4	
		Relative risk (95%CI)	*P*-value	Relative risk (95%CI)	*P*-value	Relative risk (95%CI)	*P*-value	Odds ratio (95%CI)	*P*-value
SA1	**Intellectual activity scores**								
0	653/5,395	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–
1–2	57/848	0.65 (0.50–0.85)	0.0016	0.65 (0.50–0.85)	0.0015	0.62 (0.47–0.81)	0.0005	0.54 (0.38–0.75)	0.0003
≥3	46/646	0.66 (0.50–0.89)	0.0058	0.66 (0.50–0.89)	0.0056	0.65 (0.48–0.88)	0.0050	0.40 (0.27–0.59)	<0.0001
	Social activity scores								
0	502/4,302	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–
1–2	93/1,147	0.74 (0.60–0.91)	0.0053	0.75 (0.61–0.92)	0.0067	0.72 (0.58–0.90)	0.0030	0.59 (0.45–0.79)	0.0003
≥3	161/1,440	0.95 (0.80–1.12)	0.5394	0.95 (0.80–1.12)	0.5458	0.96 (0.81–1.14)	0.6601	0.97 (0.77–1.22)	0.7917
SA2	**Intellectual activity scores**								
0	731/5,395	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–
1–2	69/848	0.70 (0.56–0.89)	0.0039	0.70 (0.55–0.89)	0.0038	0.67 (0.52–0.85)	0.0013	0.58 (0.42–0.79)	0.0006
≥3	56/646	0.72 (0.56–0.94)	0.0147	0.72 (0.56–0.94)	0.0147	0.72 (0.55–0.94)	0.0164	0.47 (0.33–0.68)	<0.0001
	Social activity scores								
0	564/4,302	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–
1–2	110/1,147	0.77 (0.64–0.94)	0.0086	0.78 (0.64–0.94)	0.0110	0.76 (0.63–0.93)	0.0069	0.64 (0.49–0.84)	0.0011
≥3	182/1,440	0.94 (0.81–1.10)	0.4715	0.94 (0.81–1.10)	0.4691	0.95 (0.81–1.11)	0.5145	0.95 (0.77–1.19)	0.6732
SA3	**Intellectual activity scores**								
0	539/4,953	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–
1–2	45/760	0.65 (0.48–0.87)	0.0042	0.65 (0.48–0.87)	0.0039	0.61 (0.45–0.83)	0.0015	0.51 (0.35–0.75)	0.0005
≥3	38/588	0.68 (0.49–0.94)	0.0178	0.68 (0.49–0.94)	0.0180	0.65 (0.47–0.91)	0.0125	0.39 (0.25–0.60)	<0.0001
	Social activity scores								
0	419/3,939	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–
1–2	74/1,040	0.71 (0.56–0.90)	0.0044	0.72 (0.57–0.91)	0.0058	0.69 (0.54–0.88)	0.0025	0.57 (0.42–0.78)	0.0005
≥3	129/1,322	0.90 (0.75–1.09)	0.2952	0.90 (0.75–1.09)	0.2902	0.92 (0.76–1.11)	0.4011	0.92 (0.72–1.18)	0.5217
SA4	**Intellectual activity scores**								
0	549/5,226	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–
1–2	44/820	0.61 (0.45–0.83)	0.0014	0.61 (0.45–0.83)	0.0014	0.60 (0.44–0.80)	0.0007	0.51 (0.35–0.73)	0.0003
≥3	37/628	0.64 (0.46–0.88)	0.0062	0.64 (0.46–0.88)	0.0063	0.65 (0.47–0.90)	0.0092	0.40 (0.26–0.61)	<0.0001
	Social activity scores								
0	425/4,161	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–
1–2	72/1,119	0.68 (0.53–0.86)	0.0016	0.68 (0.54–0.87)	0.0019	0.68 (0.54–0.86)	0.0016	0.57 (0.42–0.77)	0.0003
≥3	133/1,394	0.94 (0.78–1.13)	0.4816	0.93 (0.77–1.12)	0.4366	0.93 (0.78–1.12)	0.4654	0.93 (0.73–1.18)	0.5453

Multivariable-adjusted model 1: adjusted for age and sex.
Multivariable-adjusted model 2: additionally adjusted for economic development regions (>$10,000, $10,000 to >7,000, and ≤$7,000).
Multivariable-adjusted model 3: additionally adjusted for sleep (≥6 h or <6 h), smoking (never, past, or current), and whether one had a fall down experience (yes or no).
Multivariable-adjusted model 4: additionally adjusted for cancer, diabetes mellitus, heart disease, hypertension, and stroke. Multivariate logistic regression analyses were used in model 4.
SA1: defined frailty as FI ≥ 0.24 in sensitivity analysis 1.
SA2: defined frailty as FI ≥ 0.23 in sensitivity analysis 2.
SA3: included only those participants ≥65 years old in sensitivity analysis 3.
SA4: included only the participants without missing data in sensitivity analysis 4.
SA, sensitivity analysis.

CONCLUSIONS

Overall, this prospective analysis study showed that having frequent intellectual activities was associated with a decreased risk of frailty, particularly in those participants who did not have slip and fall accidents. Non-regular participation in social activities was associated with a decreased risk of frailty compared with no social activity, whereas frequent social activity participation was not. These conclusions were based on observational evidences. In the future, more well-designed cohort studies and RCTs are still required to confirm our findings.

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 at: This analysis uses

data or information from the Harmonized China Health and Retirement Longitudinal Study (CHARLS) dataset and Codebook, version C, which was developed by the Gateway to Global Aging Data (https://g2aging.org). The development of the Harmonized CHARLS was funded by the National Institute on Aging (grants R01 AG030153, RC2 AG036619, and R03 AG043052). Further inquiries can be directed to the corresponding authors. Data can also be obtained on request (yafang@ccmu.edu.cn; xyguo@ccmu.edu.cn).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Biomedical Ethics Review Committee of Peking University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XG and YH contributed to conception of the study and drafted the manuscript. YH, XG, JD, and YL helped with acquisition, analysis, or interpretation of data. YH, XG, and JD critically revised the manuscript for important intellectual content. YH, XG, and YL performed statistical analysis. XG and YH provided administrative, technical, or material support, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

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Effects of Low-Speed and High-Speed Resistance Training Programs on Frailty Status, Physical Performance, Cognitive Function, and Blood Pressure in Prefrail and Frail Older Adults

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Aim: The current study investigated the effects of low-speed resistance training (LSRT) and high-speed resistance training (HSRT) on frailty status, physical performance, cognitive function and blood pressure in pre-frail and frail older people.

Material and Methods: Sixty older adults, 32 prefrail and 28 frail, were randomly allocated into LSRT, HSRT, and control group (CG). Before and after intervention periods frailty status, blood pressure, heart rate, and a set of physical performance capabilities and cognitive domains were assessed. Exercise interventions occurred over 16 weeks and included four resistance exercises with 4–8 sets of 4–10 repetitions at moderate intensity.

Results: The prevalence of frailty criteria in prefrail and frail older adults were reduced after both LSRT and HSRT. In prefrail, LSRT significantly improved lower-limb muscle strength, while mobility was only improved after HSRT. Muscle power and dual-task performance were significantly increased in both LSRT and HSRT. In frail, LSRT and HSRT similarly improved lower-limb muscle strength and power. However, exclusive improvements in dual-task were observed after LSRT. Memory was significantly increased in prefrail and frail, regardless of the type of resistance training. No significant changes were observed in blood pressure and heart rate.

Conclusion: Findings of the present study indicated that both LSRT and HSRT reversed frailty status and improved physical performance in prefrail and frail older adults. Notably, different patterns of improvement were observed among RT protocols. Regarding frailty status, LSRT seemed to be more effective in reverse prefrailty and frailty when compared to HSRT. Greater improvements in muscle strength and power were also observed after LSRT, while HSRT produced superior increases in mobility and dual-task performance. One-leg stand performance was significantly reduced in LSRT, but not HSRT and CG, after 16 weeks. In contrast, RT programs similarly improved verbal memory in prefrail. Finally, no changes in blood pressure and heart rate were observed, regardless of the type of RT.

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Trial Registration: The protocol was approved by the University of Campinas Human Research Ethics Committee (Protocol No. 20021919.7.0000.5404) and retrospectively registered at ClinicalTrials.gov Protocol Registration and Results System: NCT04868071.

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INTRODUCTION

Frailty refers to a reversible state of increased vulnerability to adverse outcomes, including disability and mortality, which occurs separated and faster than the normal aging process in response to a multisystem impairment of the human body and lack of psychosocial support (1–4). Frailty is highly incident in older adults (2, 4) with occurrence rates of 44 new cases per 1,000 person-years (5). In South America, a recent pooled analysis indicated an average prevalence of prefrailty and frailty in community-dwelling older adults of 46.8 and 21.7%, respectively (6). People living in long-term institutions (LTI) are the most affected, so that one-in-two are identified as frail.

With frailty progression, people become more vulnerable to negative events (7–11). Particularly, findings from cross-sectional studies suggested that cognitive function declines across frailty statuses in non-demented older adults (12–14). In addition, frail older people seemed to be at higher risk of dementia in relation to robust individuals (15–17). High blood pressure (BP) levels have also been frequently found in frail people (18–22). A possible explanation for these observations is based on the fact that sustained elevation in arterial BP might predispose to the development of frailty as a result of disturbances in cerebral microcirculation, inflammation and oxidative stress, to quote a few (18–22).

This scenario is especially concerning, since reduced physical performance and declining cognitive function depict the paradigm of unsuccessfully aging (23), while high BP represents a major risk factor for cardiovascular and cerebrovascular diseases (24). As such, frailty represents a major public health problem (25).

The treatment of frailty is under intense debate (26, 27). Among the possible alternatives, considerable attention has been attributed to low-speed resistance training (LSRT), a type of physical exercise in which muscle contractions are performed against a resistance at low-to-moderate velocity (28). Such interest relies in the fact that numerous studies (29–32) have found improvements in frailty-related parameters in older adults who performed LSRT protocols. These findings are reinforced by a recent systematic review (33), which indicated that LSRT might considerably increase lower-limb muscle strength and mobility in frail older adults.

Although these findings are encouraging, just a few of the included studies had identified frailty using a valid scale and investigated exercise programs based on LSRT alone. Moreover, trials have been considered methodologically limited, examined robust people, and have not adopted frailty status as an outcome measure (26, 27). Hence, more studies are still necessary to support the use of LSRT as a first-line therapy to counteract frailty.

Notably, many investigations in the early 2000's started to suggest that muscle power, the capacity to exert force in a short time interval, was more associated with mobility tasks than muscle strength (34–36). These findings led researchers (37–41) to examine whether high-speed resistance training (HSRT), a modality of physical exercise in which muscle contractions are performed as fast as possible (28), could cause greater improvements in mobility tasks than LSRT.

This assumption has been confirmed by numerous investigations conducted with robust (37, 38, 40, 41) and mobility-limited older adults (39), but no studies were performed in frail people. Systematic reviews and metanalyses (42, 43) have supported these results but authors emphasized that data must be carefully extrapolated to the clinical, given that meaningless differences were found among exercise protocols.

Expert opinions (44–48) have encouraged the inclusion of HSRT on exercise programs for frail older adults. According to researchers, perform concentric muscle contractions as fast as possible might be crucial to improve mobility and restore independence. However, empirical evidence comparing the impact of LSRT and HSRT programs on frailty status and related parameters in frail people are scarce (26, 27).

Based on these premises, the current study investigated the effects of LSRT and HSRT on frailty status in pre-frail and frail older people. Secondarily, we examined the effects of both resistance training (RT) programs on physical performance, cognitive function, and BP, given its close association with frailty.

MATERIALS AND METHODS

Study Design

This is a three-arm randomized parallel controlled trial that investigated the effects of two types of RT on frailty status, physical performance, cognitive function, and BP of prefrail and frail older adults. Ethics approval was granted by the University of Campinas Human Research Ethics Committee (Protocol No. 20021919.7.0000.5404) and the study was retrospectively registered at ClinicalTrials.gov (NCT04868071). All participants provided written informed consent prior to participating. All study procedures were conducted following the principles of the Declaration of Helsinki. The present study is in accordance with the CONSORT statement (49).

Participants

Candidate participants were recruited from two different places, between January 2017 and January 2019. Prefrail volunteers (60–76 years) were recruited from the Senior Center of the city of Poá, SP, Brazil. People were invited to participate by direct contact and through posters placed in the senior center. Volunteers lived

alone and were on a waiting list to take part of the exercise programs offered by the senior center. Some of them attended for routine medical appointments.

Frail volunteers (66–99 years) were recruited from a LTI also located in the city of Poá, SP, Brazil. The nursing home is a philanthropic institution structured with accommodations, kitchen, dining and TV rooms, nursing and rehabilitation units, and psychological stimulation room. Most residents arrived at the nursing home due to abandonment, maltreatment, and/or financial, cognitive, and physical disabilities. Patients are accommodated in the rooms according to gender and health status. Residents commonly wake up around 07:00 a.m., are monitored by nurses, and attend to the rehabilitation unit according to their self-will. Physiotherapists offer analgesia, massages, and physical stimulation without overload in individual sessions up to 45 min. In the evenings, older patients watch movies, perform artworks, receive visits, and/or remain in the garden. Visits to theaters, cinemas, parks, and other places occur at least once a month. Meals are offered five times per day and no specific nutritional recommendations (e.g., protein consumption) for older adults are followed.

All candidate participants met the following inclusion criteria: (a) aged 60 years or over; (b) were prefrail or frail according to Fried's criteria (50); (c) performed the sit-to-stand test alone, with a mobility aid, or with the help of a researcher, who provided support but did not interfere in the test performance; (d) possessed sufficient physical and cognitive abilities to understand and perform exercise sessions; and (e) had a physician authorization to participate of physical exercise programs. Exclusion criteria included the clinical diagnosis of orthostatic hypotension, having participated in a structured physical exercise training program in the past 6 months, prescription of hormone replacement therapy and/or psychotropic drugs, and any unstable cardiovascular event (e.g., myocardial infarction) or complication in the past 6 months. Volunteers who had missed four or more exercise sessions in a recurrent and sequential manner according to the records were also excluded.

The power of the sample size was determined using G*Power version 3.1.9.2 on the basis of the magnitude of the mean differences among the groups (i.e., for prefrail and after frail). Considering an effect size of 0.75 based on changes in muscle strength (51), a power of 80%, a level of significance set at 5%, and a dropout of 16.9% (52), the sample size necessary was estimated to be of 66 volunteers. Sample size was calculated according to changes in muscle strength, given the lack of studies that used frailty status as a study outcome (26, 27).

A computer-generated list of random numbers was used by an independent researcher to allocate participants into one of three experimental groups using a ratio of 1 1 1 according to age, body mass index (BMI), and sit-to-stand performance: Low-speed resistance training (LSRT), High-speed resistance training (HSRT), and control group (CG), before baseline evaluations.

Clinical Characteristics

Clinical characteristics were measured at baseline for sample characterization. Body mass and height were measured using an analog weight scale with a Filizola® (Brazil) stadiometer. BMI was calculated according to the following formula:

(a) BMI = body mass (kg)/ height (m^2);

Information pertaining to disease conditions, medication, schooling, and time of institutionalization was collected through self-report and careful review of medical charts.

Primary Outcome

Frailty Status

The frailty phenotype was adapted from Fried et al. (50) and incorporates measures of multiple physical domains, including weight loss, exhaustion, weakness, slowness, and sedentary behavior (53, 54). Participants were respectively identified as prefrail and frail according to the presence of 1–2 and ≥3 of the following criteria: (1) unintentional weight loss of ≥5 kg in the prior 6 months; (2) self-reported fatigue; (3) weakness, based on isometric handgrip strength (IHG); (4) slowness, based on walking speed (WS); and (5) low physical activity levels according to the short form of the International Physical Activity Questionnaire (IPAQ) (54). Gender-specific and gender- and height-specific cutoff points based on the median values of older adults from Poá, Brazil (55) were used for IHG and WS, respectively. Gender-specific cutoffs were used for physic activity levels (54).

Secondary Outcomes

Physical Performance

Physical performance tests were administered by experienced exercise physiologists and physiotherapists. One examiner was responsible for detailing the operational procedures, showing the test before the assessment, quantifying performance and evaluating motor patterns. The other examiner ensured participants' safety by providing occasional verbal and/or tactile cueing if needed. Particularly, most frail participants needed physical support for performing mobility tests, which was provided by the research team without interfering in the performance. After the explanation and before each test, prefrail participants performed a familiarization trial to ensure they had fully understood each test, while frail participants were requested to verbally explain the tests, to avoid fatigue. Except for the 6-min walking test (6MWT), participants performed all tests twice with the mean result used for analysis. Tests were administered in a sequential order with a 2–10-min rest interval, as follows: (1) IHG (56), (2) muscle strength of knee extensors, hip flexors, and ankle extensors (57); (3) one-leg stand (58); (4) balance tests of the Short Physical Performance Battery (SPPB) (59); (5) sit-to-stand (59); (6) Timed "Up and Go" (TUG) (60); (7) WS at usual and fast paces (61); and (8) 6MWT (59). A detailed description of physical performance tests and test reliability values are available in **Supplementary Material 1**.

COGNITIVE FUNCTION

Cognitive tests were administered face-to-face in a private silent room by a trained researcher. Global cognitive function was assessed using the mini-mental state examination (MMSE)

(62, 63) and the clock drawing test (CDT) (64). Attention, inhibitory control, and reaction time (ms) were assessed using a computerized version of the Stroop test (TESTINPACSTM) (65, 66). The Rey's auditory verbal learning test (RAVLT) (67–70) was used to assess episodic and delayed memory, and susceptibility to interference. The test consists of read-aloud two lists (A and B) of 15 substantives each (with a 1-s interval between each word). At the beginning of the test, list A was read five consecutive times by a researcher. Then, participants were requested to recall as many words were possible after each trial (A1-A5). The list B, interference list, with new 15 substantives was read after A5 and words were retrieved (B1). Finally, participants were asked to recall the words from list A immediately after the interference list (A6, immediate recall) and after a delay of 20 min (A7, delayed recall), without listening to the list A again.

Four summary scores were calculated (71), as follows:

(b) Verbal learning (VL) score = $\sum$A1-A5–(5 * A1);
(c) Proactive interference (PI) = B1/A1;
(d) Retroactive interference (RI) = A6/A5;
(e) Forgetting speed (FS) = A7-A6;

Final scores are provided as continuous data and no specific cutoff points were used.

A detailed description of cognitive tests is available in **Supplementary Material 1**.

Blood Pressure and Heart Rate

BP was measured accordingly to the VII Joint National Committee of High Blood Pressure (JNC7) (72). Pre- and post-intervention BP values were based on the mean values measured in three consecutive visits in three different days. For BP evaluation, participants remained seated in a comfortable chair in a room with artificial light. BP and heart rate (HR) were blindly measured in the left arm using automated oscillometric equipment (BP 3BT0A, Microlife AG, Widnau, Switzerland) (73). At the end of each measurement, the equipment provided systolic BP (SBP), diastolic BP (DBP), and HR.

Exercise Interventions

Exercise interventions were carried out over a total of 16 weeks in the mornings (08:00 a.m.−12:00 a.m.) under the supervision of fitness instructors and physiotherapists. Exercise sessions for frail participants were performed individually and occurred in the LTI, while prefrail people attended to the senior center and performed exercise sessions in groups of 3–4 older adults. The first 4 weeks were dedicated to participants' familiarization. In this period, four exercises for lower limbs: (1st) squat on the chair, (2nd) seated unilateral hip flexion, (3rd) seated unilateral knee extension, and (4th) bilateral calf raise with 12–15 submaximal repetitions avoiding fatigue (i.e., inability to complete a repetition in a full range of motion) were performed. The number of sets was increased linearly during the first month, so that one set was performed in the 1st week, two sets in the 2nd week, 3 sets in the 3rd week, and 4 sets in the 4th week. The main exercise period occurred in the consecutive 12 weeks. After a brief warm-up, participants performed the same four exercises utilized during the familiarization period using adjustable weight vests and ankle weights (DOMYOS®, Shanghai, China). The total volume (sets × repetitions × load) was equalized among the groups. However, LSRT and HSRT were designed according to the peculiarities of each type of RT (28, 74). Hence, the LSRT group performed four sets of 8–10 repetitions at 70–75% of 1-repetition maximum (1RM). The concentric and eccentric phases were carried out for ∼2.5-s. For HSRT, exercises were performed 8 times (sets) with 3–5 repetitions at 70–75% of 1RM. The concentric phase was performed as fast as possible, and the eccentric phase was carried out for ∼2.5-s. No maximal strength test was conducted to determine the load of bilateral calf raise, so that participants performed this exercise using the same load that was used to seated unilateral knee extension exercise. A researcher was responsible for monitoring and ensuring that the velocity of muscle contractions was adequate to the protocol. Verbal encouragement was provided to HSRT.

Ten-Repetition Maximum Test (10RM)

10RM tests were performed prior, monthly, and at the end of the exercise programs in the following three exercises: squat on the chair (until 90° knee flexion), seated unilateral hip flexion, and seated unilateral knee extension. Before the tests, individuals performed a brief specific warm-up using light loads. Afterwards, the 10RM load was determined up to five attempts, with a 3-min interval between the attempts. The resistance was increased according to the capacity of the volunteer to perform more than one successful repetition maximum with the proper technique. The test was completed when participants were unable to perform more than 10 repetitions using a proper technique (75). All trials were performed with participants using the full range of motion. Subsequently, the 1RM was calculated based on the following formula:

(f) 1RM = (10RM/(1.0278−[0.0278 × 10])) (76).

Control Group

The CG performed flexibility sessions for 20 min once a week.

Statistical Analysis

Normality of data was ascertained using the Kolmogorov-Smirnov test. Data are presented as mean ± standard deviation (SD) or absolute numbers (percentages) for continuous and categorical variables, respectively. A group × time repeated-measures ANOVA followed by Bonferroni *post hoc* analyses were performed to determine whether there were significant differences between groups. For all tests, the level of significance was set at 5% ($p < 0.05$). All analyses were conducted using GraphPad Prism 6.0. (San Diego, CA).

RESULTS

One-hundred twenty-two older adults were recruited and evaluated according to the eligibility criteria. Of these, 37 were identified as robust and seven could not attend exercise training in the mornings, leaving a total of 78 older adults, 39 prefrail and 39 frails, who were randomized into the three groups (i.e., LSRT, HSRT, and CG). Adherence to exercise sessions was above 95% in both prefrail and frail groups. Five prefrail

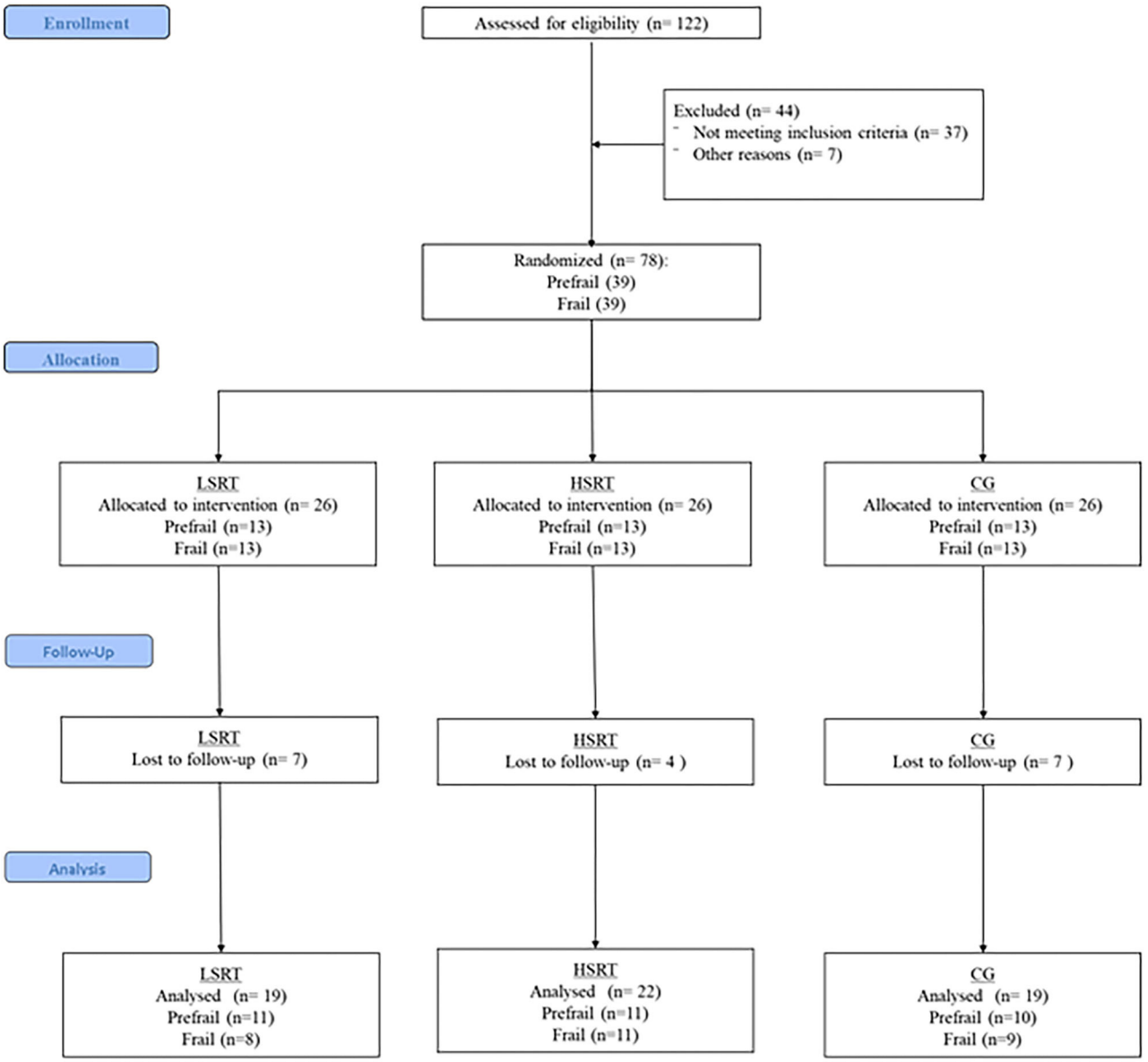

FIGURE 1 | Flowchart of the present study. LSRT, Low-speed resistance training; HSRT, High-speed resistance training; CG, Control group.

and 11 frail participants withdrew from the trial. In prefrail, three participants from the CG withdrew to start a programmed exercise program, while two, one from the HSRT and one from the LSRT, withdrew after 2 weeks because they were not randomized to the same exercise group. In frail, four participants withdrew due to personal reasons, two participants due to the 10RM test, one start to take psychotropic drugs, one could not attend for exercise sessions for 2 months due to substantial weight loss and complains of muscle fatigue, one had a stroke, one had urinary tract infection, and one died. The flowchart of the present study is shown in **Figure 1**.

Most frail participants complained of extraneous muscle fatigue during the familiarization period, but not in the main period. Two participants reported joint pain and one frail participant from the HSRT group reported epigastric discomfort and nausea during the performance of the squat on the chair exercise. No falls were recorded in pre-frail community dwelling-older adults during the protocol. In frail, six falls (four in the same participant) were registered in the HSRT, four in LSRT, and four in the CG. All falls occurred on days other than training days.

Clinical Characteristics

Table 1 shows the clinical characteristics of prefrail and frail participants according to group allocation. There were no significant differences in clinical characteristics between experimental and CG groups, regardless of frailty status. Frail

participants were older and had less formal education in comparison to prefrail. The average BMI was within normal limits for both groups. Hypertension and type II diabetes were highly prevalent in prefrail and frail, while osteoarthritis, stroke, and Parkinson's disease were most notorious in frail. There were significant differences in physical performance between exercise and CG in prefrail and frail. In prefrail, LSRT showed higher right and left muscle strength of knee extensors, right hip flexor, and balance on one-leg stand test. In addition, CG showed higher TUG performance when compared to LSRT. In frail, LSRT showed higher right and left muscle strength of knee extensors in comparison with HSRT and CG, and lower TUG performance in comparison to HSRT. No differences in cognitive function or BP were observed in any group.

Frailty Status

The effects of RT on frailty status are shown on **Figure 2**. Both LSRT and HSRT reduced the prevalence of frailty criteria in prefrail and frail older adults. Six (54.5%) prefrail participants returned to robust condition after LSRT, while two (18.1%) participants became robust after HSRT. RT improved weakness (LSRT, $n = 1$; HSRT, $n = 0$), slowness (LSRT, $n = 2$; HSRT, $n = 1$), and exhaustion (LSRT, $n = 8$; HSRT, $n = 6$) in prefrail. In frail, 10 participants, five in each intervention group (62.5%, 45.4%), returned to prefrail condition, and two participants (12.5%, 9.0%), one in each intervention group, returned to robust condition after LSRT and HSRT, respectively. RT improved weight loss (LSRT, $n = 3$; HSRT, $n = 2$), sedentary behavior (LSRT, $n = 8$; HSRT, $n = 11$), and exhaustion (LSRT, $n = 5$; HSRT, $n = 5$).

Physical Function

The effects of RT on physical function in prefrail and frail are shown in **Tables 2**, **3** and **Supplementary Figures 1**, **2**, respectively. LSRT and HSRT caused different patterns of improvements in physical function in prefrail. LSRT improved muscle strength of the right knee extensors ($P = 0.01$), right ($P = 0.01$) and left ($P = 0.001$) hip flexors, and right ($P = 0.001$) and left ($P = 0.01$) ankle extensors, while the right ($P < 0.001$) and left ($P = 0.01$) one-leg stand performances were significantly reduced. In contrast, TUG at fast pace ($P = 0.01$), TUG associated with a verbal task ($P = 0.001$), TUG associated with motor and verbal tasks ($P < 0.001$), and tandem balance ($P = 0.01$) were only improved after HSRT. Performance time ($P < 0.001$), power ($P = 0.05$, $P < 0.001$), and the velocity of muscle contraction ($P < 0.001$) in the sit-to-stand test, TUG at usual pace ($P = 0.01$, $P < 0.001$), and TUG associated with a motor task ($P = 0.01$, $P < 0.001$) were significantly improved in response to both LSRT and HSRT. CG showed a significant increase in the time on the sit-to-stand ($P < 0.001$) test. At the end of the protocol, higher TUG performance ($P < 0.001$) and muscle strength of the right ($P < 0.001$) and left knee extensors ($P < 0.001$) were observed in exercise groups in comparison to CG, while only LSRT showed lower right and left one-leg stand performances ($P < 0.001$) and higher muscle strength of the right ($P = 0.01$) and left ($P < 0.01$) hip flexors, and right ($P < 0.01$) and left ($P < 0.01$) ankle extensors in comparison to CG. Significant differences in TUG associated with motor task ($P = 0.01$), TUG associated with motor and verbal tasks ($P = 0.01$), and power ($P = 0.01$) in the sit-to-stand test were found between LSRT and HSRT.

RT improved fewer physical parameters in frail in comparison to prefrail. Power ($P < 0.01$) in the sit-to-stand test, muscle strength of the left knee extensors ($P = 0.01$) and right ($P = 0.001$) left ($P = 0.001$) hip flexors were improved after both LSRT and HSRT. Particularly, exclusive improvements in TUG associated with a motor task ($P = 0.01$), TUG associated with motor and verbal tasks ($P = 0.01$), and time in the sit-to-stand test ($P = 0.01$) were found in LSRT, while only HSRT improved muscle strength of the left ankle extensors ($P = 0.001$) and the velocity of the muscle concentric contraction in the sit-to-stand test ($P = 0.01$). Exercise groups showed higher performance ($P = 0.001$) and power ($P = 0.001$) in the sit-to-stand tests in comparison to CG. There were no significant differences among exercise groups.

Fourteen participants, six in the HSRT, four in the LSRT, and four in the CG, performed the sit-to-stand test with mobility aids or researchers' help at baseline. In contrast, four participants in the LSRT and three in the HSRT no longer needed help after exercise protocols.

Cognitive Parameters

The effects of RT on cognitive parameters in prefrail and frail people are shown in **Figures 3**, **4**. There were no within- and between-group differences on MEEM, CDT, and STROOP in prefrail. On the other hand, higher verbal learning was observed after both LSRT and HSRT when compared to CG. In frail, no significant within- and between-group differences were observed on MEEM and STROOP performances. However, RAVLT performance ($P = 0.01$) was significantly improved after HSRT.

Blood Pressure and Heart Rate

There were no within- and between-group differences on BP and HR in response to any intervention in prefrail and frail.

DISCUSSION

The main findings of the present study indicated that RT reversed frailty status and improved physical function in prefrail and frail older adults. Nevertheless, different improvements were observed among the groups in response to LSRT and HSRT. In addition, prefrail older adults showed higher RAVLT performance after both RT protocols in comparison to CG. Finally, no changes in BP and HR were observed in any group. A summary of the results is shown in **Table 4**.

Effects of RT on Frailty Status

RT reversed frailty status in both prefrail and frail older adults. Our findings are supported by prior investigations that observed reductions in frailty status after exercise training protocols (77–83). However, most studies combined RT with other types of exercise and/or health interventions (81), limiting inferences regarding the impact of RT alone on frailty (84). In addition,

TABLE 1 | Main characteristics of study participants.

	Prefrail ($n = 32$)				Frail ($n = 28$)			
	LSRT ($n = 11$)	HSRT ($n = 11$)	CG ($n = 10$)	Total ($n = 32$)	LSRT ($n = 8$)	HSRT ($n = 11$)	CG ($n = 9$)	Total ($n = 28$)
Variables								
Clinical characteristics								
Age, years	65 ± 3.5	65 ± 2.8	65 ± 3.5	65 ± 3.2	75 ± 4.6	73 ± 7.5	75.0 ± 9.2	76 ± 7.2
Gender, female/male	9/2	11/0	11/0	31/2	6/2	6/5	6/3	18/10
BMI, kg/m^2	26.8 ± 5.7	24.5 ± 2.4	25.5 ± 3.3	26.3 ± 4.5	25.3 ± 3.1	24.6 ± 3.5	25.7 ± 2.4	24.8 ± 5.3
Schooling, years	7 ± 2.9	4 ± 2.1	8 ± 2.1	6 ± 2.8	2 ± 4.5	0 ± 1.0	1.8 ± 2.4	1.5 ± 2.7
Time of institutionalization, years	—	—	—	—	2 ± 0.9	2 ± 3.1	2 ± 1.5	2 ± 2.2
Comorbidities, %								
Hypertension	72.7	36.6	100	78.7	87.5	63.6	44.4	64.3
Osteoarthritis	27.2	27.2	36.3	34.3	25.0	36.3	66.6	45.5
Stroke	0	0	0	0	12.5	9.0	11.1	10.7
Diabetes	9.0	27.2	9.0	17.4	37.5	9.0	11.1	17.8
Parkinson's disease	0	0	0	0	0	9.0	0	3.5
Frailty phenotype, %								
Weakness	45.4	72.7	0	40.6	87.5	72.7	77.7	78.5
Slow walking speed	18.1	45.4	20.0	28.1	87.5	81.8	66.6	78.5
Unintentional weight loss	0	9.0	40.0	15.6	50	63.6	77.7	64.2
Exhaustion	45.4	72.7	81.8	66.2	100	100	100	100
Low activity level	0	9.0	20.0	9.3	100	100	100	100
Physical performance								
Right IHG, kg	25.0 ± 4.0	21.9 ± 5.7	25.9 ± 3.2	24.2 ± 4.7	6.2 ± 5.5	4.8 ± 6.4	13.8 ± 13.7[a,b]	8.1 ± 9.8
Left IHG, kg	25.5 ± 6.1	21.3 ± 6.0	25.7 ± 3.6	24.2 ± 5.7	8.5 ± 9.5	9.6 ± 9.3	12.7 ± 12.4[a,b]	10.3 ± 10.2
Right knee extensor, kgf	17.3 ± 4.2	11.7 ± 2.3[a]	10.1 ±1.9[a]	13.4 ± 4.4	7.0 ± 1.9	7.1 ± 2.8	7.0 ± 5.7	6.6 ± 4.1
Left knee extensor, kgf	14.8 ± 3.1	12.3 ± 3.4[a]	10.3 ± 2.3[a]	12.7 ± 3.5	6.6 ± 2.0	6.1 ± 3.7	6.6 ± 5.0	6.2 ± 3.9
Right hip flexor, kgf	11.1 ± 3.2	8.2 ± 3.3[a]	8.6 ± 3.6[a]	9.4 ± 3.5	6.0 ± 1.7	5.4 ± 2.2	4.7 ± 2.8	5.0 ± 2.6
Left hip flexor, kgf	10.1 ± 2.7	8.1 ± 2.8	8.3 ± 2.5	8.9 ± 2.8	5.4 ± 1.1	5.1 ± 2.5	4.3 ± 2.5	4.8 ± 2.3
Right ankle extensor, kgf	6.8 ± 2.1	6.4 ± 1.8	5.8 ± 1.1	6.4 ± 1.8	5.6 ± 1.5	4.3 ± 2.6	3.8 ± 2.3	4.2 ± 2.5
Left ankle extensor, kgf	7.1 ± 1.7	6.4 ± 1.8	6.4 ± 1.1	6.7 ± 1.6	3.8 ± 2.8	4.4 ± 2.4	3.7 ± 2.6	3.9 ± 2.6
Right one-leg stand, s (30 s max)	19.4 ± 9.7	10.9 ± 11.6[a]	12.5 ± 12.0[a]	14.4 ± 11.4	0.1 ± 0.3	0.1 ± 0.4	2.2 ± 3.1	0.8 ± 2.0
Left one-leg stand, s (30 s max)	16.4 ± 11.0	13.0 ± 12.2	7.3 ± 10.4[a]	12.4 ± 11.6	0.0 ± 0.2	0.2 ± 0.4	2.3 ± 4.4	0.9 ± 2.6
Normal balance, s (10 s max)	10.0 ± 0.0	9.8 ± 0.6	10.0 ± 0.0	9.9 ± 0.4	1.2 ± 3.5	1.8 ± 4.0	4.4 ± 5.2	2.5 ± 4.4
Semi tandem balance, s (10 s max)	10.0 ± 0.0	9.8 ± 0.6	10.0 ± 0.0	9.9 ± 0.4	0.0 ± 0.0	1.0 ± 3.0	4.4 ± 5.2	1.9 ± 3.9
Tandem balance, s (10 s max)	10.0 ± 0.0	6.9 ± 0.6	10.0 ± 0.0	8.9 ± 3.1	0.0 ± 0.0	0.8 ± 2.7	5.5 ± 5.2	0.7 ± 2.5
Sit-to-stand, s	8.4 ± 1.1	10.0 ± 2.3	8.0 ± 0.6	8.9 ± 2.0	26.7 ± 11.6	26.2 ± 13.3	28.6 ± 10.9	25.3 ± 10.4
TUG at usual pace, s	8.0 ± 0.8	10.2 ± 2.7	6.2 ± 1.4[a]	8.3 ± 2.5	119.8 ± 180.2	20.8 ± 27.3[a]	46.4 ± 36.3	57.3 ± 104.0
TUG at fast pace, s	6.5 ± 1.1	8.4 ± 2.5	5.6 ± 0.9	6.9 ± 2.0	38.0 ± 46.3	17.4 ± 22.8[a]	28.5 ± 25.4	26.9 ± 31.9
TUG with verbal task, s	8.3 ± 1.0	10.7 ± 3.9	7.1 ± 1.2	8.8 ± 2.9	69.0 ± 109.8	18.4 ± 24.1	37.5 ± 43.2	36.6 ± 62.5
TUG with motor task, s	8.7 ± 1.7	10.1 ± 2.1	8.0 ± 0.8	9.0 ± 1.9	14.2 ± 13.0	7.1 ± 12.9	16.1 ± 20.7	11.5 ± 15.4
TUG with both verbal and motor tasks, s	8.3 ± 1.1	11.6 ± 3.2	10.9 ± 1.4	10.3 ± 2.5	17.6 ± 19.7	8.3 ± 18.7	17.7 ± 23.2	12.8 ± 19.8
WS at usual pace, m/s	1.3 ± 0.3	1.2 ± 0.2	1.3 ± 0.3	1.3 ± 0.3	0.41 ± 0.37	0.81 ± 0.99	0.51 ± 0.41	0.50 ± 0.35
WS at fast pace, m/s	1.8 ± 0.3	1.5 ± 0.3	1.9 ± 0.3	1.8 ± 0.4	0.46 ± 0.41	0.66 ± 0.91	0.62 ± 0.50	0.57 ± 0.40
6MWT, m	480 ± 137	460 ± 151	589 ± 179	507.7 ± 161.2	150 ± 174	100 ± 136	91.4 ± 107	78.1 ± 118.4
Cognitive function								
MMSE, points	24.3 ± 1.9	23.2 ± 1.8	23.4 ± 1.5	24.4 ± 2.4	15.6 ± 4.5	13.8 ± 3.7	16.0 ± 2.0	14.9 ± 3.6
CDT, points	1.6 ± 0.8	1.6 ± 0.7	2.0 ± 0.7	1.7 ± 0.6	5.5 ± 1.4	5.5 ± 1.3	4.4 ± 1.4	5.2 ± 1.3
Hemodynamic parameters								
SBP, mmHg	130.4 ± 14.9	131.6 ±19.5	137.8 ± 13.5	133.0 ± 16.1	124.0 ± 21.6	114.3 ± 17.0	140.1 ± 15.4	124.8 ± 20.5
DBP, mmHg	68.0 ± 23.0	72.0 ± 10.0	79.8 ± 11.8	73.1 ± 16.4	81.9 ± 15.5	67.8 ± 9.4	79.2 ± 11.7	76.4 ± 13.8
HR, bpm	73.7 ± 11.6	73.7 ± 9.6	73.1 ± 4.2	73.6 ± 8.8	65.9 ± 5.6	70.5 ± 12.2	86.7 ± 12.3	80.2 ± 12.9

BMI, Body mass index; IHG, isometric handgrip strength; TUG, Timed "Up-and-Go"; 6MWT, 6-min walking test; MMSE, Mini mental state examination; CDT, Clock Drawing Test; SPB, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; LSRT, Low-Speed Resistance Training; HSRT, High-Speed Resistance Training; CG, Control Group; [a]$P < 0.05$ vs. LSRT; [b]$P < 0.05$ vs. HSRT.

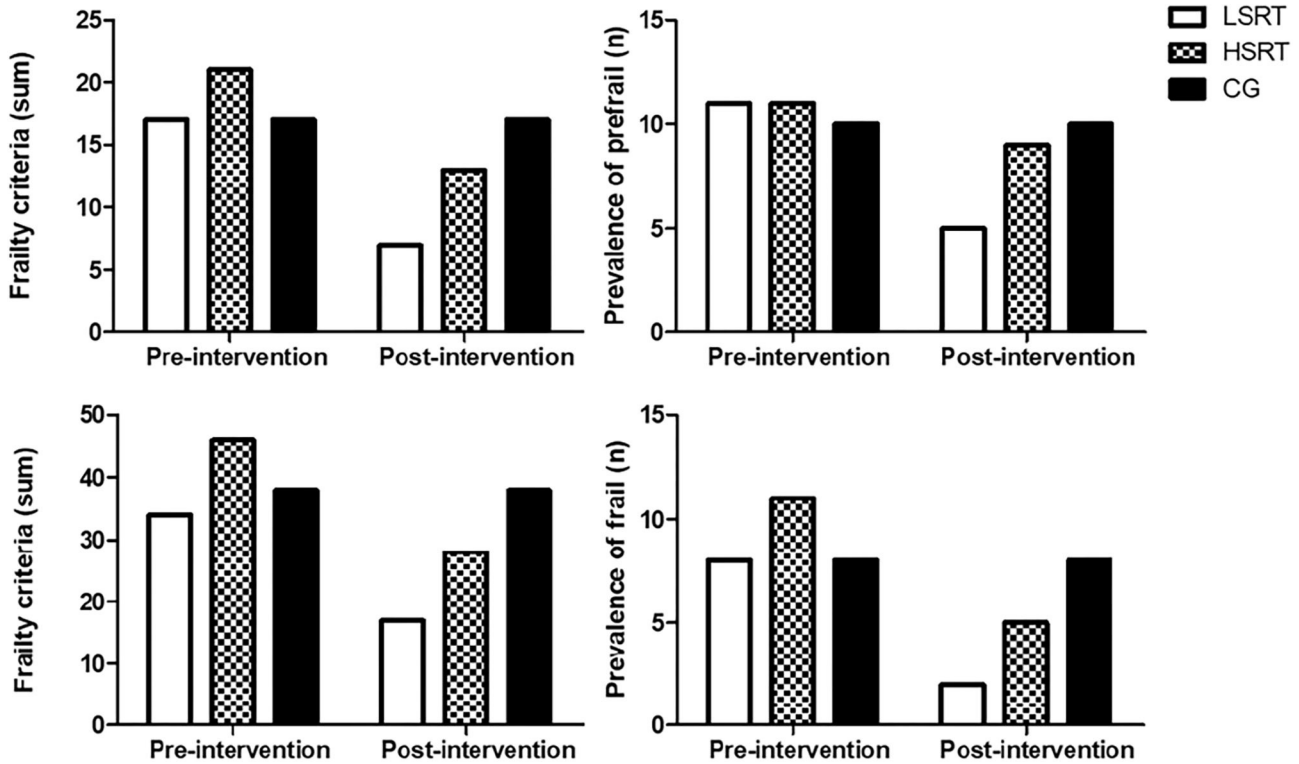

FIGURE 2 | Effects of RT on Frailty Status in prefrail and frail older adults. LSRT, Low-speed resistance training; HSRT, High-speed resistance training; CG, Control group.

the majority of the studies have focused on frailty components, whereas frailty status was only investigated in a few trials (33, 77).

Notably, RT improved weakness, slowness, and exhaustion in prefrail; and weight loss, sedentary behavior, and exhaustion in frail. Although surprising, similar results were found in the LIFE-P study (78), given that changes on frailty status were not associated with improvements on slowness and weakness, but physical activity levels.

A possible explanation for these findings is that prefrail individuals have more preserved physical function in comparison to frail counterparts, so that improvements on weakness (IHG) and slowness (WS) are easier to achieve cutoff values for robustness. In contrast, some frail participants in the present study had IHG values close to zero and took more than 60 s to perform WS test.

In this context, improvements in physical function may have contributed to reduce perceived fatigue (85), motivating frail participants to increase physical activity levels. Regarding weight loss, muscle hypertrophy is a well-established product of RT (86, 87) and it is possible to suggest that our RT programs reduced weight loss by modulating muscle mass.

These findings have important clinical implications by demonstrating that 16-weeks lower-limb LSRT and HSRT programs reversed frailty status in prefrail and frail older adults, possibly reducing the risk of negative events in these people (7–11). Particularly, some studies have reported low adherence to multicomponent exercise training programs, mainly in institutionalized frail older adults (80, 82), which might occur due to the fact the frail patients cannot support very-long exercise sessions (88). In addition, aerobic and gait exercises are not feasible and hard to prescribe in frail nursing home residents due to the high prevalence of mobility limitations (89). On the other hand, RT programs may be fully performed with individuals sitting in bed or in a chair without the need for transferring or walking, prioritizing some muscle groups, using body weight, free weights, or elastic bands (28, 90).

Effects of RT on Muscle Strength and Power

Lower-limb muscle strength (i.e., knee extensors, hip flexors, ankle extensors) and power (i.e., time and power in the sit-to-stand) were significantly increased in prefrail and frail. Nevertheless, greater improvements were observed in LSRT relative to HSRT and CG.

These findings are in concordance with prior original articles (31, 79, 91–93) and systematic reviews (33) that investigated LSRT (79, 91, 92) and HSRT (91–93). However, just a few studies compared the effects of LSRT and HSRT in prefrail and, for the best of our knowledge, there are no investigations in frail people.

Several mechanisms may potentially explain why greater improvements were found after LSRT, including the time under

TABLE 2 | Effects of resistance training on physical performance of pre-frail older adults.

	Baseline			16-week		
	LSRT	**HSRT**	**CG**	**LSRT**	**HSRT**	**CG**
Physical performance						
Right IHG, kg	25.0 ± 4.0	21.9 ± 5.7	25.9 ± 3.2	27.4 ± 5.3	20.7 ± 4.0	25.7 ± 2.9
Left IHG, kg	25.5 ± 6.1	21.3 ± 6.0	25.7 ± 3.6	27.3 ± 6.3	20.0 ± 4.9	25.6 ± 3.0
Right knee extensor, kgf	17.3 ± 4.2	11.7 ± 2.3	10.1 ±1.9	19.2 ± 5.0[a]	13.5 ± 3.5	9.8 ± 1.8[b,c]
Left knee extensor, kgf	14.8 ± 3.1	12.3 ± 3.4	10.3 ± 2.3	16.8 ± 4.3	14.3 ± 3.8	9.7 ± 2.3
Right hip flexor, kgf	11.1 ± 3.2	8.2 ± 3.3	8.6 ± 3.6	12.8 ± 3.6[a]	9.1 ± 3.7	8.1 ± 3.3[b]
Left hip flexor, kgf	10.1 ± 2.7	8.1 ± 2.8	8.3 ± 2.5	12.5 ± 3.9[a]	8.7 ± 2.5	8.2 ± 2.6[b]
Right ankle extensor, kgf	6.8 ± 2.1	6.4 ± 1.8	5.8 ± 1.1	8.7 ± 2.9[a]	7.6 ± 1.5	5.6 ± 1.3[b]
Left ankle extensor, kgf	7.1 ± 1.7	6.4 ± 1.8	6.4 ± 1.1	8.7 ± 2.7[a]	7.5 ± 1.3	6.2 ± 1.3[b]
Right one-leg stand, s (30 s max)	19.4 ± 9.7	10.9 ± 11.6	12.5 ± 12.0	6.6 ± 0.7[a]	14.2 ± 12.0	11.9 ± 12.2[b]
Left one-leg stand, s (30 s max)	16.4 ± 11.0	13.0 ± 12.2	7.3 ± 10.4	5.5 ± 0.9[a]	17.9 ± 12.7	9.9 ± 11.5[b]
Normal balance, s (10 s max)	10.0 ± 0.0	9.8 ± 0.6	10.0 ± 0.0	10.0 ± 0.0	10.0 ± 0.0[a]	10.0 ± 0.0
Semi tandem balance, s (10 s max)	10.0 ± 0.0	9.8 ± 0.6	10.0 ± 0.0	10.0 ± 0.0	10.0 ± 0.0	10.0 ± 0.0
Tandem balance, s (10 s max)	10.0 ± 0.0	6.9 ± 0.6	10.0 ± 0.0	10.0 ± 0.0	7.3 ± 4.2[a]	10.0 ± 0.0
Sit-to-stand, s	8.4 ± 1.1	10.0 ± 2.3	8.0 ± 0.6	6.6 ± 0.8[a]	7.3 ± 2.0[a]	9.0 ± 1.1[a]
Sit-to-stand, power	49.0 ± 11.4	34.6 ± 8.8	46.5 ± 5.8	54.2 ± 13.3[a]	42.1 ± 12.6[a,b]	43.9 ± 5.6
Sit-to-stand, concentric contraction, m/s	1.3 ± 0.2	0.8 ± 0.3	1.2 ± 0.2	1.7 ± 0.4[a]	1.2 ± 0.4[a]	1.1 ± 0.1
Sit-to-stand, eccentric contraction, m/s	1.1 ± 0.5	1.2 ± 0.4	1.3 ± 0.4	1.0 ± 0.4	1.0 ± 0.4	1.3 ± 0.4
TUG at usual pace, s	8.0 ± 0.8	10.2 ± 2.7	6.2 ± 1.4	7.5 ± 0.8[a]	9.4 ± 2.5[a]	6.3 ± 1.4[b,c]
TUG at fast pace, s	6.5 ± 1.1	8.4 ± 2.5	5.6 ± 0.9	6.1 ± 1.0	7.8 ± 2.1[a]	6.0 ± 1.1
TUG with verbal task, s	8.3 ± 1.0	10.7 ± 3.9	7.1 ± 1.2	7.4 ± 0.5	9.1 ± 2.6[a]	7.4 ± 1.2
TUG with motor task, s	8.7 ± 1.7	10.1 ± 2.1	8.0 ± 0.8	7.8 ± 1.2[a]	9.4 ± 2.2[a,b]	8.2 ± 0.9
TUG with both verbal and motor tasks, s	8.3 ± 1.1	11.6 ± 3.2	10.9 ± 1.4	7.7 ± 0.8[a]	9.8 ± 2.5[a,b]	11.1 ± 1.2[a]
WS at usual pace, m/s	1.3 ± 0.3	1.2 ± 0.2	1.3 ± 0.3	1.5 ± 0.1	1.4 ± 0.2	1.2 ± 0.2
WS at fast pace, m/s	1.8 ± 0.3	1.5 ± 0.3	1.9 ± 0.3	1.8 ± 0.3	1.4 ± 0.2	2.1 ± 0.4
6MWT, m	480 ± 137	460 ± 151	589 ± 179	511 ± 135	478 ± 159	589 ± 179

LSRT, Low-speed resistance training; HSRT, High-speed resistance training; CG, Control group. 6MWT, 6-min walking test; IHG, Isometric handgrip strength; TUG, Timed "Up and Go"; WS, Walking speed; [a]P < 0.05 vs. Pre-intervention; [b]P < 0.05 vs. LSRT; [c]P < 0.05 vs. HSRT.

tension (TUT), range of motion (ROM), the prevalence of comorbidities, and cognitive status.

Prior studies reported that TUT might impact strength gains in response to RT in healthy older adults (86, 94). Indeed, larger increases in dynamic and isometric strength have been observed in RT programs based on muscular contractions that lasted 6–7 s in comparison to those performed for ∼2 s (86, 95, 96). Slow muscle contractions might reduce oxygen supply to the muscle (94) and increase the accumulation of products of cellular metabolism (95, 96). This scenario predisposes the recruitment of type II muscle fibers, those more associated with force generation and muscle hypertrophy (97), and additional motor units, according to the size principle of Henneman et al. (98), in an attempt to maintain force production (99). Hence, longer muscle contractions performed during LSRT (∼5 s vs. ∼2.5 s in HSRT) might have produced greater improvements on muscle strength by creating a more challenging metabolic environment, inducing the recruitment of type II muscle fibers and large motor units, resulting in superior neuromuscular adaptations.

Alternatively, the time under tension has been associated with increased myofibrillar protein synthesis and phosphorylation of anabolic signaling proteins (i.e., p70S6K, 4EBP1, and p90RSK) (100), likely inducing muscle hypertrophy (101). However, skeletal muscle mass was not assessed in the present study.

Notably, such greater improvements in muscle strength might have contributed to the development of muscle power in LSRT, given that force plays a key role in power production (102, 103) and muscle strength serve as the main driver for the ability to express high power outputs (103).

Another possible explanation for our results is based on the fact that most frail participants had reduced joint ROM due to high prevalence of lower limb osteoarthritis and the long-time using wheelchairs and mobility aids. The length-tension curve relationship states that exercises performed at optimal muscle length evokes greater myosin and actin interaction, and so strength (104), while exercises performed at partial ROM commonly produce less neuromuscular adaptations, restricted to the specific ROM in which muscle contractions occurred (105). Considering that sit-to-stand performance involves total knee and hip extensions, older adults with joint limitations might have performed exercises with reduced ROM, limiting the development of muscle strength and mainly power.

TABLE 3 | Effects of resistance training on physical performance of frail older adults.

	Baseline			16-weeks		
	LSRT	**HSRT**	**CG**	**LSRT**	**HSRT**	**CG**
Physical performance						
Right IHG, kg	6.2 ± 5.5	4.8 ± 6.4	13.8 ± 13.7	9.0 ± 9.9	7.0 ± 6.9	13.6 ± 13.9
Left IHG, kg	8.5 ± 9.5	9.6 ± 9.3	12.7 ± 12.4	11.2 ± 9.0	12.3 ± 12.0	13.7 ± 12.5
Right knee extensor, kgf	7.0 ± 1.9	7.1 ± 2.8	7.0 ± 5.7	10.6 ± 5.3	7.9 ± 7.2	6.8 ± 5.2
Left knee extensor, kgf	6.6 ± 2.0	6.1 ± 3.7	6.6 ± 5.0	9.7 ± 4.9[a]	9.2 ± 7.5[a]	6.2 ± 5.3
Right hip flexor, kgf	6.0 ± 1.7	5.4 ± 2.2	4.7 ± 2.8	7.4 ± 2.9[a]	6.6 ± 5.6[a]	5.0 ± 3.0
Left hip flexor, kgf	5.4 ± 1.1	5.1 ± 2.5	4.3 ± 2.5	6.8 ± 2.5[a]	7.1 ± 3.8[a]	4.7 ± 2.8
Right ankle extensor, kgf	5.6 ± 1.5	4.3 ± 2.6	3.8 ± 2.3	6.1 ± 1.7	4.3 ± 4.0	3.8 ± 2.6
Left ankle extensor, kgf	3.8 ± 2.8	4.4 ± 2.4	3.7 ± 2.6	4.5 ± 3.2	5.9 ± 3.0[a]	3.2 ± 2.3
Right one-leg stand, s (30 s max)	0.1 ± 0.3	0.1 ± 0.4	2.2 ± 3.1	1.0 ± 1.8	2.0 ± 5.7	2.8 ± 4.9
Left one-leg stand, s (30 s max)	0.0 ± 0.2	0.2 ± 0.4	2.3 ± 4.4	0.2 ± 0.4	1.7 ± 5.0	3.3 ± 7.8
Normal balance, s (10 s max)	1.2 ± 3.5	1.8 ± 4.0	4.4 ± 5.2	2.5 ± 4.6	2.7 ± 4.6	4.4 ± 5.2
Semi tandem balance, s (10 s max)	0.0 ± 0.0	1.0 ± 3.0	4.4 ± 5.2	1.2 ± 3.5	1.8 ± 4.0	4.4 ± 5.2
Tandem balance, s (10 s max)	0.0 ± 0.0	0.8 ± 2.7	5.5 ± 5.2	1.2 ± 3.5	0.9 ± 3.0	1.1 ± 3.3
Sit-to-stand, s	26.7 ± 11.6	26.2 ± 13.3	28.6 ± 10.9	17.1 ± 11.7[a]	18.9 ± 10.0	37.1 ± 19.3[b,c]
Sit-to-stand, power	13.9 ± 2.7	16.4 ± 7.1	11.9 ± 4.8	28.5 ± 10.6[a]	27.5 ± 13.8[a]	12.8 ± 3.6[b,c]
Sit-to-stand, concentric contraction, m/s	0.35 ± 0.30	0.26 ± 0.20	0.17 ± 0.10	0.55 ± 0.50	0.50 ± 0.43[a]	0.19 ± 0.0
Sit-to-stand, eccentric contraction, m/s	0.53 ± 0.51	0.53 ± 0.46	0.82 ± 0.46	0.65 ± 0.53	0.56 ± 0.46	0.86 ± 0.36
TUG at usual pace, s	119.8 ± 180.2	20.8 ± 27.3	46.4 ± 36.3	64.2 ± 4.7.4	23.9 ± 20.1	48.7 ± 37.4
TUG at fast pace, s	38.0 ± 46.3	17.4 ± 22.8	28.5 ± 25.4	45.0 ± 26.8	16.7 ± 16.7	25.8 ± 23.7
TUG with verbal task, s	69.0 ± 109.8	18.4 ± 24.1	37.5 ± 43.2	52.0 ± 50.0	20.8 ± 25.9	38.3 ± 45.3
TUG with motor task, s	14.2 ± 13.0	7.1 ± 12.9	16.1 ± 20.7	22.2 ± 22.2[a]	5.9 ± 11.1	13.7 ± 18.5
TUG with both verbal and motor tasks, s	17.6 ± 19.7	8.3 ± 18.7	17.7 ± 23.2	29.6 ± 39.0[a]	6.0 ± 13.8	17.1 ± 23.4
WS at usual pace, m/s	0.41 ± 0.37	0.81 ± 0.99	0.51 ± 0.41	0.41 ± 0.38	0.48 ± 0.38	0.58 ± 0.41
WS at fast pace, m/s	0.46 ± 0.41	0.66 ± 0.91	0.62 ± 0.50	0.48 ± 0.42	0.61 ± 0.34	0.65 ± 0.42
6MWT, m	150 ± 174	100 ± 136	91.4 ± 107			

LSRT, Low-speed resistance training; HSRT, High-speed resistance training; CG, Control group. 6MWT, 6-min walking test; IHG, Isometric handgrip strength; TUG, Timed "Up and Go"; WS, Walking speed; [a]P < 0.05 vs. Pre-intervention; [b]P < 0.05 vs. LSRT; [c]P < 0.05 vs. HSRT.

According to experts in the field (44), the prescription of HSRT to older adults with disabilities should take into consideration other factors than the variables of RT. Particularly, researchers have emphasized that participants must be continuously monitored and stimulated to keep concentric muscle contractions at high velocity (44). In the present study, exercise sessions were closely monitored and the HSRT protocol was composed by a few repetitions in an attempt to maintain participants' concentration. In addition, only older adults cognitively able to understand exercise and testing instructions were included. Nevertheless, the possibility that HSRT was not performed with the maximal power output cannot be ruled out.

Effects of RT on Mobility, Dual-Task Performance, and Balance

HSRT is expected to produce greater improvement in mobility than LSRT (44, 45, 47, 90, 106). Bean et al. (39) found similar improvements in SPPB after non-equalized 16-weeks LSRT and HSRT programs in older adults. However, HSRT exhibited better effects when only older adults with mobility limitations were analyzed (39). Miszko et al. (37), Botaro et al. (107), and Ramírez-Campillo et al. (40) confirmed these findings by indicating that HSRT programs produced greater improvements in physical performance relative to LSRT, while Lopes et al. (41) reported exclusive improvements in sit-to-stand and TUG performances after HSRT.

Although these findings are supported by systematic review and metanalyses (42, 43), a wide confidence interval was observed between studies, suggesting that the effects of both LSRT and HSRT are still compatible with a clinically non-relevant difference. In addition, most studies were based on physically healthy older adults, short-term RT protocols, and expensive exercise machines, limiting extrapolations for prefrail and frail older adults.

In this context, findings of the present study are unique and add to the current knowledge by indicating that HSRT produced greater improvements in TUG performance in comparison to LSRT in prefrail older adults. A question that remains from these findings, then, is "how HSRT caused greater improvements in mobility without provoke larger increases in muscle strength and power?"

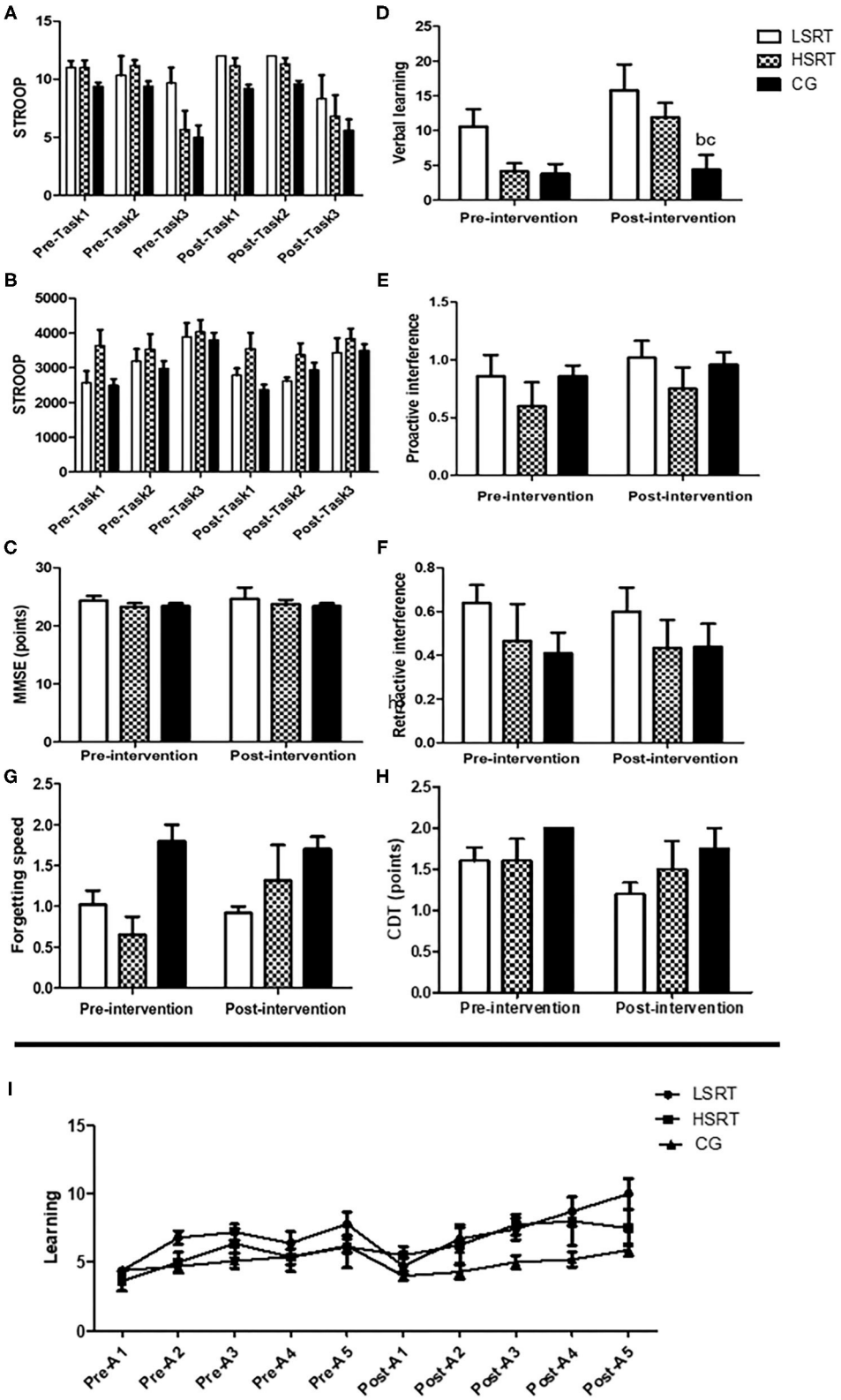

FIGURE 3 | Effects of RT on cognitive parameters in prefrail older adults. Stroop test **(A,B)**, Mini-mental state examination (MMSE; **C**), The Rey's auditory verbal learning test **(D–G,I)** and Clock Drawing Tests **(H)**. LSRT, Low-speed resistance training; HSRT, High-speed resistance training; CG, Control group; MMSE, $^{b}P < 0.05$ vs. LSRT; $^{c}P < 0.05$ vs. HSRT.

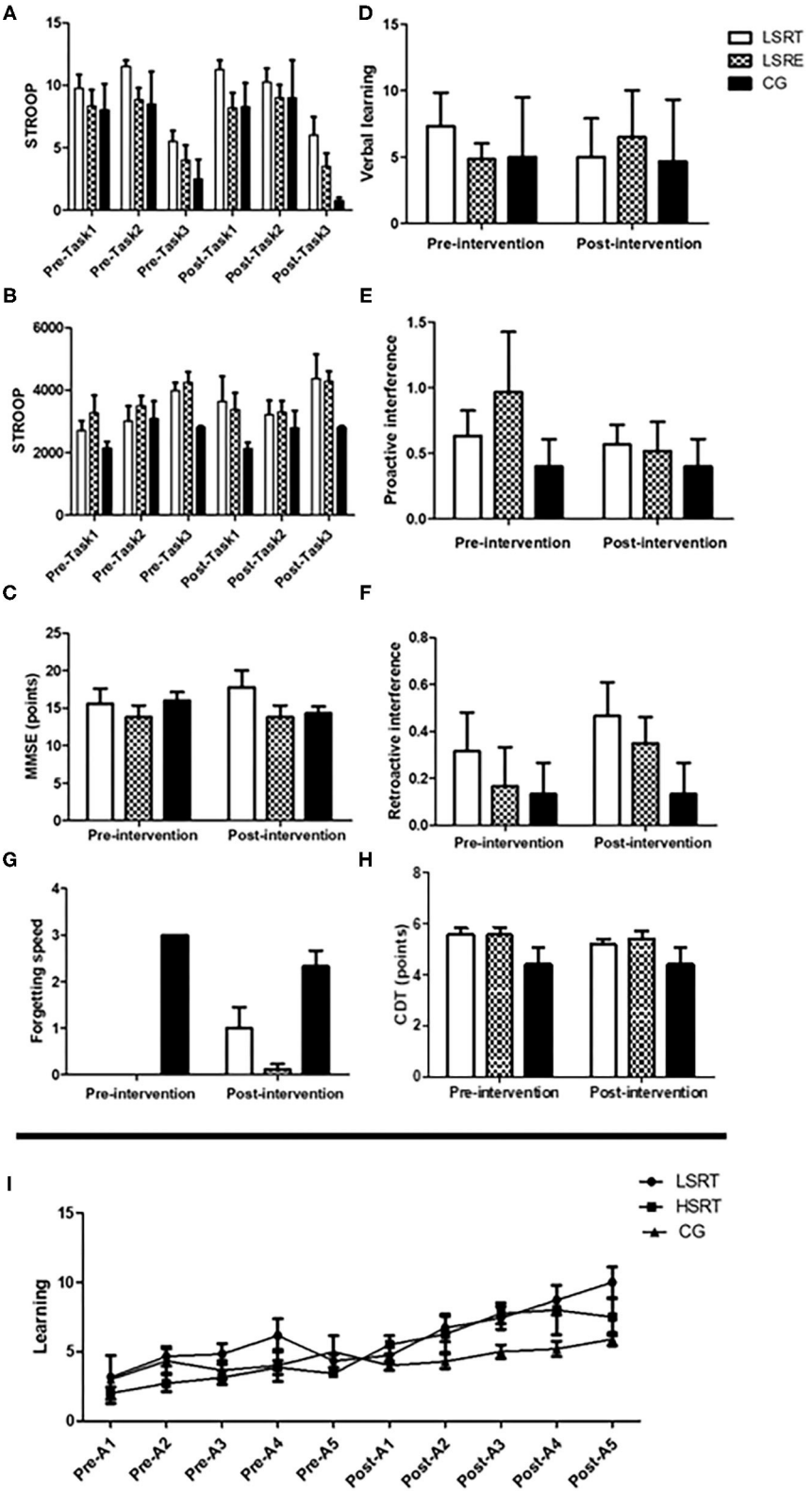

FIGURE 4 | Effects of RT on cognitive parameters in prefrail older adults. Stroop test **(A,B)**, Mini-mental state examination (MMSE; **C**), The Rey's auditory verbal learning test **(D–G,I)** and Clock Drawing Tests **(H)**. LSRT, Low-speed resistance training; HSRT, High-speed resistance training; CG, Control group; MMSE.

TABLE 4 | Effects of RT on frailty status, physical performance, cognitive function, and blood pressure and heart rate of prefrail and frail people.

	Prefrail			Frail		
Variable	**LSRT**	**HSRT**	**CG**	**LSRT**	**HSRT**	**CG**
Frailty status						
Weakness	↑	↔	↔	↑	↔	↔
Slow walking speed	↑	↑	↔	↔	↔	↔
Unintentional weight loss	↔	↔	↔	↑	↑	↔
Exhaustion	↑	↑	↔	↑	↑	↔
Low activity level	↔	↔	↔	↑	↑	↔
Physical performance						
Upper-limb muscle strength	↔	↔	↔	↔	↔	↔
Lower-limb muscle strength	↑↑	↑	↔	↑↑	↑	↔
Lower-limb muscle power	↑↑	↑	↔	↑	↑	↔
Mobility	↑	↑↑	↔	↔	↔	↔
Dual-task	↑	↑↑	↔	↑	↑	↔
Balance	↓	↑	↔	↔	↔	↔
Cognitive function						
Global	↔	↔	↔	↔	↔	↔
RAVLT	↑	↑	↔	↔	↔	↔
STROOP	↔	↔	↔	↔	↔	↔
Hemodynamic parameters						
SBP	↔	↔	↔	↔	↔	↔
DBP	↔	↔	↔	↔	↔	↔
HR	↔	↔	↔	↔	↔	↔

LSRT, Low-speed resistance training; HSRT, High-speed resistance training; CG, Control group; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR, Heart rate; ↑Improved vs. Pre-intervention; ↑↑Improved vs. Pre-intervention and CG and/or experimental group; ↓Reduced vs. Pre-intervetion; ↔Unchanged.

A likely explanation is that muscle power was improved in other muscle actions than those assessed in the present study. TUG involves the interaction among several body movements, including sit-to-stand transition, walking, turn and stand-to-sit transition (108). In fact, TUG performance requires power of the ankle flexors and extensors to stride velocity (35) and fast response to perturbations to turn (109).

Despite the similar improvements in muscle power, mobility was unaffected by LSRT and HSRT in frail. These results should be interpreted cautiously, given that most participants of the current study needed researchers' help or were not able to perform mobility tests at baseline, causing a wide variability in the results. Indeed, although no significant within-group differences were observed in WS and TUG, seven participants became independent to perform mobility tests after RT protocols. This scenario might also have influenced frailty status and indicates that long-term RT protocols seem to be necessary to reverse physical dysfunction in institutionalized frail older adults.

Notably, the improvements observed in muscle power might also account for the observed differences in balance in prefrail (36). However, it should be noted that all participants in LSRT and CG groups achieved the highest performance in normal and tandem tests in both pre- and post-intervention periods. In HSRT, only one participant did not complete the test at baseline but showed significant improvements after 16 weeks. These results suggest that LSRT and HSRT have limited effects on balance. In fact, neither LSRT nor HSRE significantly improved one-leg stand.

Another important finding is that prefrail participants showed better dual-task performance after HSRT, while LSRT was most effective in frail people. These results suggest that the effects of RT on dual-task performance might be dependent on frail status.

Effects of RT on Cognitive Function, Blood Pressure, and Heart Rate

There is still no consensus on the effects of RT on the cognitive function of older adults (110) and only a few studies have examined prefrail and frail people. Mollinedo Cardalda et al. (93) and Yoon et al. (111) observed that RT improved overall cognitive function in frail older adults. This view was expanded by van de Rest et al. (52), who found increased digit span, attention, and working memory performances in prefrail and frail older adults who took part of a 24-weeks LSRT program. To the best of our knowledge, only Yoon et al. (112) compared the effects of HSRT and LSRT, and results revealed similar improvements in overall cognitive function.

The current study contributes to the growing literature by indicating that LSRT and HSRT improved verbal memory in community-dwelling prefrail older adults, regardless of the velocity of muscle contraction. However, our findings differ from prior investigations, given that no significant changes were found

in global cognition, middle-term memory, inhibitory capacity, and attention in prefrail and frail older adults.

Differences in the results might be partially attributed to sample characteristics (52, 111, 112), since some studies combined prefrail and frail participants, cognitive status (e.g., mild-cognitive impairment) (93, 111–113), mobility levels (mobility-limited vs. able to walk) (93, 111, 112), cognitive assessment tools (52, 93, 111, 114), and RT programs (52, 93, 111, 114).

Our findings refuted the hypothesis that RT might reduce blood pressure and heart rate in prefrail and frail older adults. The majority of the studies on the effects of RT on blood pressure have examined robust community-dwelling older adults (112, 115–118) and no prior investigations included prefrail or frail participants. A possible explanation for our results may be the fact that the pathophysiology and progression of frailty involve the dysregulation of numerous mechanisms that predispose to increased blood pressure values (7, 119–121), which may not be counterregulated by neither LSRT nor HSRT.

Practical Applications

Two main features of the current RT protocols should be highlighted. First, both LSRT and HSRT were low price, given that all equipment cost around $127,82, and seems feasible to public health programs. Second, the short duration of exercise sessions, which lasted ∼25 min. Another practical aspect of the current study is that the reversion of frailty was influenced by the nursing home environment. Indeed, when frail participants showed minimal ability and resistance to walking few steps, a non-structured walking program was created. In this program, frail participants walked from 10 to 25 min at short intervals with the assistance of nursing students. It is worth mentioning that an affinity loop was created between researchers and study participants, and we deeply believe that this scenario contributed with participants' well-being and the adherence to exercise protocols. Finally, the question that remains is "What is the best RT protocol to improve frailty status and its related parameters in prefrail and frail older adults?" Taking into consideration all limitations of the present study, both exercise programs seem to be important in these populations improving different domains and reversing frailty status. Notably, LSRT seemed to be more effective in reverse prefrailty and frailty when compared to HSRT. Moreover, health practitioners should keep in mind that people with joint limitations and with probable cognitive impairments, as older adults living in LTI, might need more attention and auxiliary treatments (e.g., flexibility exercise) to properly perform HSRT. In any case, the next step would be to verify the effects of combined LSRT and HSRT programs.

Limitations

Differences on age and on the context where participants were recruited are the two major limitations that avoid comparisons between pre-frail and frail older adults. Indeed, a mean difference of 10 years of age was observed between the groups. Age might indirectly influence the effects of RT on frailty and its associated parameters by impacting sedentary behavior, dietary habits, educational level, and social engagement (122–124). In addition, the main mechanisms underlying the effects of RT on neuromuscular function and cognition seems to be significantly affected by age (125–128). Regarding the setting of recruitment, older adults admitted to LTI are often socially isolated, have more depressive symptoms, a high prevalence of disability and multimorbidity, and increased cognitive decline (129–131). In the course of time, institutionalization can make things worse by contributing with the exacerbating of pre-existing conditions and with the development of new ones (132–135). Hence, it is possible that different results might be found in pre-frail and frail community-dwellers. However, it is important to note that the prevalence of frailty increases with age, and it is most commonly observed in LTI, with might explain our sample characteristics, so that future studies are still necessary to confirm our findings. Several additional limitations must be mentioned. First, participants were not screened for dementia since they were only required to understanding exercise commands. Second, the current findings are prevalently based on older women and extrapolations should be carefully performed. Third, although LSRT and HSRT had no effects on blood pressure, prior studies have noted that frailty was associated with ambulatory blood pressure, but not office blood pressure (18). Fourth, according to Vellas et al. (136) intervention periods longer than 12 months might be required to observe improvements in the cognitive function of older adults. Fifth, our sample size and inclusion criteria limited further analysis (e.g., respondents and non-respondents) (137, 138). Sixth, the possible mechanisms underlying the effects of RT on physical function were not investigated. Seventh, prefrail and frail older adults were recruited from different settings. Eighth, sample size calculation was based on changes on muscle strength, so that it might not be adequate to the other study outcomes, including frailty. Finally, additional covariables [e.g., high inflammatory status (139)] that could influence the current results were not controlled.

Conclusions

Findings of the present study indicated that both LSRT and HSRT reversed frailty status and improved physical performance in prefrail and frail older adults. Notably, different patterns of improvement were observed among RT protocols. Regarding frailty status, LSRT seemed to be more effective in reverse prefrailty and frailty when compared to HSRT. Greater improvements in muscle strength and power were also observed after LSRT, while HSRT produced superior increases in mobility and dual-task performance. One-leg stand performance was significantly reduced in LSRT, but not HSRT and CG, after 16 weeks. In contrast, RT programs similarly improved verbal memory in prefrail. Finally, no changes in BP and HR were observed, regardless of the type of RT.

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 University of Campinas Human Research Ethics

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

AUTHOR CONTRIBUTIONS

HC-J and MU: methodology, analysis, writing-original draft preparation, and writing-review and editing. HC-J: data collection and project administration. MU: supervision. Both authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.702436/full#supplementary-material

Supplementary Figure 1 | Effects of RT on physical performance in prefrail older adults. LSRT, Low-speed resistance training; HSRT, High-speed resistance training; CG, Control group. 6MWT, 6-minute walking test; IHG, Isometric handgrip strength; TUG, Timed "Up and Go"; WS, Walking speed; $^{a}P < 0.05$ vs. Pre-intervention; $^{b}P < 0.05$ vs. LSRT; $^{c}P < 0.05$ vs. HSRT.

Supplementary Figure 2 | Effects of RT on physical performance in frail older adults. LSRT, Low-speed resistance training; HSRT, High-speed resistance training; CG, Control group. 6MWT, 6-minute walking test; IHG, Isometric handgrip strength; TUG, Timed "Up and Go"; WS, Walking speed; $^{a}P < 0.05$ vs. Pre-intervention; $^{b}P < 0.05$ vs. LSRT; $^{c}P < 0.05$ vs. HSRT.

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Age- and Gender-Specific Prevalence of Frailty and Its Outcomes in the Longevous Population: The Chinese Longitudinal Healthy Longevity Study

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Background: Frailty is an epidemic age-related syndrome addressing heavy burden to the healthcare system. Subject to the rarity, age-, and gender-specific prevalence of frailty and its prognosis among the longevous population remains under-investigated.

Methods: Based on the Chinese Longitudinal Healthy Longevity Study (CLHLS, 2008–2018), individuals aged ≥ 65 years having complete data of frailty were recruited. Modified Fried criteria (exhaustion, shrink, weakness, low mobility, and inactivity) were adopted to define pre-frailty (1–2 domains) and frailty (≥3 domains), respectively. The association between pre-frailty/frailty and adverse outcomes (frequent hospitalization, limited physical performance, cognitive decline, multimorbidity, and dependence) was analyzed using logistic regression models. The association between pre-frailty/frailty and mortality was analyzed using Cox proportional hazards models. Age- and gender-stratified analyses were performed.

Results: Totally, 13,859 participants aged 85.8 ± 11.1 years, including 2,056 centenarians, were recruited. The overall prevalence of pre-frailty and frailty were 54.1 and 26.3%, respectively. Only 5.0% of centenarians were non-frailty whereas 59.9% of the young-old (65–79 years) showed pre-frailty. Both pre-frailty and frailty were associated with the increased risk of multiple adverse outcomes, such as incident limited physical performance, cognitive decline and dependence, respectively ($P < 0.05$). Frail males were more vulnerable to the risk of mortality (hazard ratio [HR] = 2.3, 95% confidence interval [CI], 2.1–2.6) compared with frail females (HR = 1.9, 95%CI, 1.7–2.1). The strongest association between frailty and mortality was observed among the young-old (HR = 3.6, 95%CI, 2.8–4.5). Exhaustion was the most common domain among patients with pre-frailty (74.8%) or frailty (83.2%), followed by shrink (32.3%) in pre-frailty and low mobility (83.0%) in frailty. Inactivity among females aged 65–79 years showed the strongest association with the risk of mortality (HR = 3.50, 95%CI, 2.52–4.87).

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Conclusion: A huge gap exists between longer life and healthy aging in China. According to the age- and gender-specific prevalence and prognosis of frailty, the strategy of frailty prevention and intervention should be further individualized.

Keywords: frailty, prognosis, longevous population, age- and gender-disparity, all-cause mortality

INTRODUCTION

Frailty is a series of age-related clinical conditions showing the deterioration of strength and physiologic malfunction (1–5). It is strongly associated with the susceptibility of stressors, manifested as the vulnerability to multiple diseases and the delayed recovery (1, 3, 4). Studies in Europe indicated that frail individuals cost three to five times of healthcare services compared with non-frail ones (6, 7). Thus, frailty significantly increases the pressure to the healthcare system to cope with the challenge of aging. Since frailty is a biological syndrome of aging, the prevalence of frailty grows in keeping with the rapid expansion of the aging population (4–6). Previous studies reported the prevalence of frailty among the population aged 60 years or older as 4.0–59.1% in high-income countries (8) and 3.9–65.3% in low- and middle-income countries (9–11). However, subject to the rarity of longevous population and the difficulty of their long-term response to the follow-up, the burden of frailty among the longevous population remains under-investigated. Recently, Herr et al. (12) explored the prevalence of frailty among 1,253 centenarians in five high-income countries and reported the prevalence of frailty as 64.7% (12). Although all participants included in this study were from developed countries, Herr et al. (12) reported the association between residence of country and the risk of frailty among centenarians. It further stressed the necessity to explore the burden of frailty in different regions.

As the largest developing country, China shows unique process of aging due to the one-child policy and rapid development of social economy (13, 14). Owing to the size and globalization, the evaluation of the burden of frailty in China has potentially scientific implications to the global strategy to promote healthy aging (15). According to the data from the National Bureau of Statistics, there were 176 million people aged≥65 years in China in 2019 (1), while this number was predicted as 400 million (26.9% of the total population) in 2050 and 150 million of them were aged 80 years or older (13). The number of the oldest population (≥80 years) increases roughly 10% annually in China and around one quarter of the global oldest population will live in China by 2050 (16). However, a huge gap exists between long life expectancy and healthy aging. Previous studies reported the prevalence of frailty as 3.1–25.0% in China, while few of them investigated the prevalence and the outcomes among the large sample size of the oldest people with a long period of follow-up (9–11, 17–21). As an essential clinical manifestation among the aging people, evaluating the burden of frailty among the longevous population in China, which should contain the insight of both the prevalence and the outcomes, would supplement the insight of global frailty and evidence the modification of the frailty management among the oldest population.

The Chinese Longitudinal Healthy Longevity Surveys (CLHLS) is an ongoing nationally representative cohort drawing data from the longevous population (22–25). Till 2018, 67.4% of participants in CLHLS were people aged 80 years or older, and the CLHLS had interviewed over 20 thousand person-times of centenarian, nonagenarian and octogenarian, respectively (23). Based on this precious cohort, the present study investigated the prevalence of pre-frailty and frailty among the community-dwelling population with advanced age. The association between pre-frailty/frailty and multiple adverse outcomes was also investigated. Given the disparity of frailty between genders and age groups (1, 4), gender- and age-stratified analyses were performed.

METHODS

Population

The CLHLS was conducted in a randomly-selected half of the counties and cities in 22 of the 31 provinces, which covering 85% of population of China (22–26). The CLHLS recruited a large sample size of centenarians and the approximately equal numbers of nonagenarians, octogenarians, and young-old (aged 65–79 years) in both genders living in the same area with the centenarians so as to ensure the representativeness (23). From 1998 on, the interview was conducted every 3–4 years using the structured questionnaires. Detailed description of CLHLS could be found elsewhere (22–26).

The present study was conducted based on the 2008 cohort of CLHLS including interviews of 2008, 2011, 2014, and 2018 (23, 26). A total of 16,954 participants were included in the cohort, 2,710 of them were excluded because of the absence of frailty-related data. Another 385 individuals aged <65 years were also excluded. Ultimately, 13,859 participants aged ≥ 65 years and having complete data on frailty were included in the current analyses.

The CLHLS was approved by the Research Ethics Committee of Peking University (IRB00001052-13074). All participants provided written informed consent.

Covariates

Age groups was defined as 65–79, 80–89, 90–99, and ≥100 years. The level of education was categorized as illiteracy, primary school, and middle school or above in accordance with the years being educated. The levels of household income were recorded as quartiles. Status of smoke and drink were recorded as never, past, and current. Body mass index (BMI, kg/m^2) was calculated as weight divided by height square and categorized into normal (18.5–23.9 kg/m^2), underweight (<18.5 kg/m^2), overweight (24.0–27.9 kg/m^2), and obesity (≥28.0 kg/m^2). Activities of

daily living (ADL) was evaluated through six daily activities (eating, dressing, transferring, using the toilet, bathing, and continence). Impaired ADL was defined if the participant need help for one or more activities; dependency was defined if the participant could not complete one or more activities with or without help. Self-reported comorbidity was recorded including hypertension, diabetes, heart disease, cerebrovascular disease, chronic pulmonary disease (chronic bronchitis, emphysema, or asthma), eye disease (cataract or glaucoma), cancer, Parkinson's disease, dementia, mental disease, arthritis, gastrointestinal ulcer, hepatitis, and others.

Criteria for Frailty

The modified Fried criteria was adopted to define the frailty status (2, 12, 17). Five domains including exhaustion, shrink, weakness, low mobility, and inactivity were evaluated using self-report data.

Exhaustion was defined if the participant answered "always," "often," or "sometimes" to either of the questions "I felt old and useless" or "I felt everything I did was an effort" (17, 27). Shrink was defined as BMI < 18.5 kg/m^2 (12, 17, 28). Weakness was defined if the participant failed to lift a bag weighting 5 kg (12, 28). Low mobility was defined if the participant failed to walk for 1 km (29). Inactivity was defined if the participant did the following activities 1 time per week or less: housework, outside activity, gardening, keeping a pet, livestock breeding, playing cards or moh-jong, and social activity (27).

Participant meeting 1–2 domains was defined as pre-frailty. Participant meeting $\geq$3 domains was defined as frailty. The prevalence of pre-frailty and frailty was defined according to the 2008 interview.

Outcomes

Outcomes were defined using the data of the 2011, 2014, and 2018 waves. Frequent hospitalization was defined if the participant been in hospital $\geq$3 times due to severe illness during the past 2 years before the interview. Incident limited physical performance was defined if the participant completed the objective performance-based tests at baseline but failed during the follow-up (22). Incident cognitive decline was defined if the participant had the MMSE score $\geq$ 23 at baseline but $<$23 during the follow-up (22). Incident multimorbidity was defined if the participant reported 0–2 comorbidities at baseline while $\geq$3 comorbidities during the follow-up (30). Incident dependency was defined if the participant showed normal or impaired ADL at baseline but being dependency during the follow-up. All-cause mortality was recorded. The median duration of follow-up was 55 (IQR 25–95) months.

Statistics

Demographic characteristics (age, gender), socioeconomic characteristics (education, household income), lifestyles (smoke, drink), physical health status (BMI, comorbidity count) and follow-up duration were presented by the status of frailty at baseline (non-frailty, pre-frailty, and frailty). Chi-square tests, oneway ANOVA, and Kruskal–Wallis tests were applied for the comparison of categorical, normal distributed continuous, and skewed distributed continuous variables, respectively. The prevalence of frailty domains (exhaustion, shrink, weakness, low mobility, and inactivity) was analyzed. Age- and gender-stratified analyses of frailty status and frailty domains were calculated, respectively.

Multivariate logistic regression models were adopted to separately analyze the association between the frailty status (non-frailty, pre-frailty, and frailty) and the risk of frequent hospitalization, incident limited physical performance, incident cognitive decline, incident multimorbidity, and incident dependency. Covariates including age, gender, education, household income, smoke, and comorbidity count were adjusted. Results were presented as odds ratio (OR) with 95% confidence interval (CI). Gender-stratified analyses were performed.

Cox proportional hazards regression models were adopted to analyze the association between frailty status (non-frailty, pre-frailty, and frailty), domains of frailty (exhaustion, shrink, weakness, low mobility, and inactivity) and the risk of all-cause mortality, respectively. Covariates including education, household income, smoke, and comorbidity count were adjusted. Age- and gender-stratified analyses were performed. Hazard ratio (HR) and 95% CI was calculated.

All analyses were two tailed and $P < 0.05$ was considered to be statistical significance. Stata version 16.0 (Stata Corp LP, College Station, TX, USA) were used for all statistical analyses.

RESULTS

Population Characteristics

A total of 13,859 participants aged 85.8 $\pm$ 11.1 (range 65–116) years were included. Among them, 2,056 (14.8%) were centenarians and 3,690 (26.6%) were nonagenarians. Totally, 59.2% of participants were in rural area and 59.7% of participants were illiteracy. Underweight (31.4%) was more common compared with obesity (2.8%) among the studied population. Altogether 27.4, 31.7, 9.8, and 8.0% of participants showed limited physical performance, cognitive decline, dependency and multimorbidity at baseline, respectively (**Table 1**).

As to participants with pre-frailty, although they were at high-risk of frailty, 1,524 (20.3%) and 1,420 (19.0%) pre-frail individuals were current smokers and drinkers, respectively. The highest proportion of illiteracy (75.4%) and the lowest proportion of obesity (2.0%) were observed among the frail population. Limited physical performance (62.6%), impaired ADL (13.4%), dependency (30.8%) cognitive decline (64.0%), and having comorbidities (58.9%) were more common among frail population compared with non-frail ones (**Table 1**).

Prevalence of Pre-frailty and Frailty

In accordance with the modified Fried criteria, 7,497 participants with pre-frailty and 3,647 participants with frailty were identified, respectively. The overall prevalence of pre-frailty and frailty was 54.1 and 26.3%, respectively (**Table 1**). Nearly doubled prevalence was observed among females compared with males (females vs. males: 33.2 vs. 17.9%) while slightly higher

TABLE 1 | Comparison of characteristics among participants in different status of frailty at baseline.

Characteristics	Overall	Non-frailty	Pre-frailty	Frailty	*P*-value
In total, No. (%)	13,859 (100.0)	2,715 (19.6)	7,497 (54.1)	3,647 (26.3)	
Follow-up duration, IQR, month	55 (25,95)	71 (42,118)	65 (30,106)	28 (14,54)	<0.001
Mean age, years, mean (SD)	85.8 (11.1)	79.2 (10.0)	84.2 (10.5)	93.8 (8.2)	<0.001
Age group, No. (%)					<0.001
65–79 years	4,180 (30.2)	1,475 (54.3)	2,505 (33.4)	200 (5.5)	
80–89 years	3,933 (28.4)	729 (26.9)	2,440 (32.6)	764 (21.0)	
90–99 years	3,690 (26.6)	408 (15.0)	1,811 (24.2)	1,471 (40.3)	
≥100 years	2,056 (14.8)	103 (3.8)	741 (9.9)	1,212 (33.2)	
Gender, No. (%)					<0.001
Male	6,252 (45.1)	1,538 (56.7)	3,593 (47.9)	1,121 (30.7)	
Female	7,607 (54.9)	1,177 (43.4)	3,904 (52.1)	2,526 (69.3)	
Regions, No. (%)					<0.001
Urban	5,648 (40.8)	1,295 (47.7)	2,814 (37.5)	1,539 (42.2)	
Rural	8,211 (59.2)	1,420 (52.3)	4,683 (62.5)	2,108 (57.8)	
Education, No. (%)					<0.001
Illiteracy	8,279 (59.7)	1,110 (40.9)	4,421 (59.0)	2,748 (75.4)	
Primary school	4,082 (29.5)	1,081 (39.8)	2,311 (30.8)	690 (18.9)	
Middle school or above	1,498 (10.8)	524 (19.3)	765 (10.2)	209 (5.7)	
Household income, No. (%)					<0.001
Quartile 1	4,152 (30.0)	632 (23.3)	2,492 (33.2)	1,028 (28.2)	
Quartile 2	2,980 (21.5)	582 (21.4)	1,576 (21.0)	822 (22.5)	
Quartile 3	3,859 (27.8)	834 (30.7)	2,042 (27.2)	983 (27.0)	
Quartile 4	2,868 (20.7)	667 (24.6)	1,387 (18.5)	814 (22.3)	
Smoke, No. (%)					<0.001
Never	9,095 (65.7)	1,574 (58.0)	4,747 (63.3)	2,774 (76.2)	
Past	2,233 (16.1)	492 (18.1)	1,224 (16.3)	517 (14.2)	
Current	2,524 (18.2)	649 (23.9)	1,524 (20.3)	351 (9.6)	
Drink, No. (%)					<0.001
Never	9,484 (68.5)	1,681 (61.9)	5,019 (67.0)	2,784 (76.4)	
Past	1,912 (13.8)	371 (13.7)	1,055 (14.1)	486 (13.3)	
Current	2,454 (17.7)	662 (24.4)	1,420 (19.0)	372 (10.2)	
BMI, No. (%)					<0.001
Normal	7,557 (54.5)	2,086 (76.8)	4,044 (54.0)	1,427 (39.1)	
Underweight	4,352 (31.4)	0 (0.0)	2,418 (32.3)	1,934 (53.0)	
Overweight	1,563 (11.3)	516 (19.0)	834 (11.1)	213 (5.8)	
Obesity	387 (2.8)	113 (4.2)	201 (2.7)	73 (2.0)	
Limited physical performance, No. (%)					<0.001
No	10,057 (72.6)	2,506 (92.4)	6,189 (82.6)	1,362 (37.4)	
Yes	3,798 (27.4)	207 (7.6)	1,308 (17.5)	2,283 (62.6)	
Cognitive decline, No. (%)					<0.001
No	9,464 (68.4)	2,430 (89.5)	5,723 (76.4)	1,311 (36.0)	
Yes	4,383 (31.7)	284 (10.5)	1,773 (23.7)	2,326 (64.0)	
ADL, No. (%)					<0.001
Normal	11,709 (84.5)	2,653 (97.7)	7,020 (93.6)	2,036 (55.8)	
Impaired	791 (5.7)	42 (5.3)	261 (3.5)	488 (13.4)	
Dependency	1,359 (9.8)	20 (0.7)	216 (2.9)	1,123 (30.8)	
Count of comorbidity, No. (%)					<0.001
None	5,888 (45.6)	1,241 (48.0)	3,274 (46.9)	1,373 (41.0)	
1–2 comorbidities	5,984 (46.4)	1,165 (45.1)	3,181 (45.6)	1,638 (48.9)	
≥3 comorbidities	1,036 (8.0)	178 (6.9)	522 (7.5)	336 (10.0)	

SD, standard deviation; BMI, body mass index; ADL, activity of daily live.

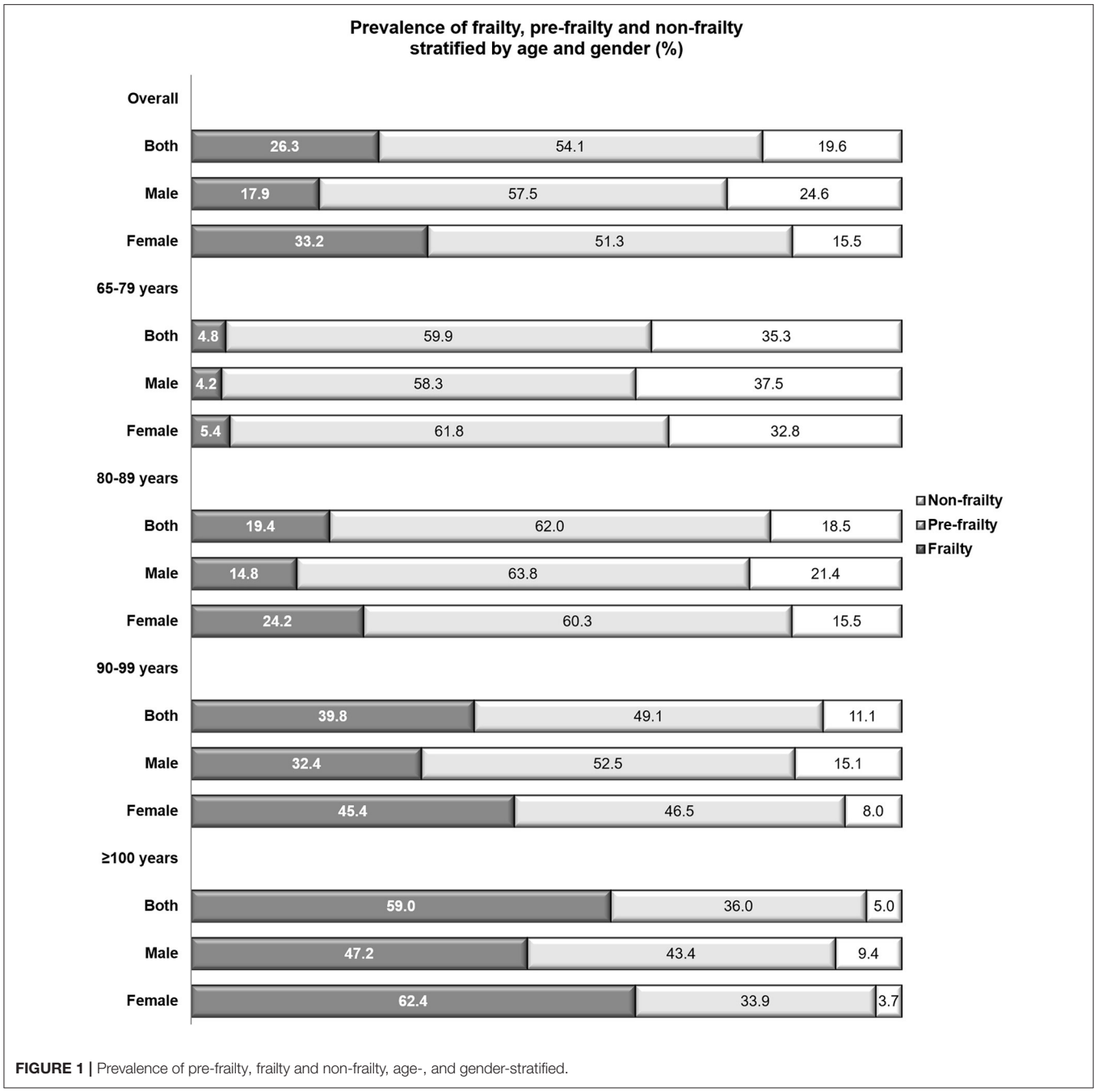

FIGURE 1 | Prevalence of pre-frailty, frailty and non-frailty, age-, and gender-stratified.

prevalence of pre-frailty was observed among males in contrast to females (males vs. females: 57.5 vs. 51.3%; **Figure 1**).

According to the age-stratified analyses, the prevalence of frailty among the young-old (<80 years), octogenarians, nonagenarians and centenarians was 4.8, 19.4, 39.9, and 59.0%, respectively. The prevalence of pre-frailty peaked among the octogenarians (62.0%) and decreased with aging (centenarians: 36.0%) (**Figure 1**). The gender-stratified analyses showed that females were with higher prevalence of frailty compared with males in all age groups and males showed higher prevalence of pre-frailty compared with females in groups aged ≥80 years. The highest prevalence of pre-frailty was observed among males aged 80–89 years (63.8%) and the highest prevalence of frailty was observed among females aged ≥ 100 years (62.4%) (**Figure 1**).

Domains of Frailty

Among pre-frail population, exhaustion (74.8%), shrink (32.3%), and inactivity (14.6%) were the most frequent domains. The prevalence of exhaustion decreased with age while that of shrink, weakness, low mobility, and inactivity increased with age. Females were more likely to be shrink in all age groups

TABLE 2 | Association between pre-frailty/frailty and the risk of multiple adverse outcomes.

Outcomes	Case no.	Adjusted OR[a] (95% CI)	*P*-value
Frequent hospitalization			
Non-frailty	138	Ref.	Ref.
Pre-frailty	318	1.2 (1.0–1.5)	0.090
Frailty	68	1.9 (1.3–2.7)	0.001
Incident limited physical performance			
Non-frailty	2,025	Ref.	Ref.
Pre-frailty	5,422	1.2 (1.1–1.4)	0.004
Frailty	1,344	5.2 (2.9–9.2)	<0.001
Incident cognitive decline			
Non-frailty	402	Ref.	Ref.
Pre-frailty	1,277	1.4 (1.1–1.7)	0.003
Frailty	307	5.2 (3.0–9.0)	<0.001
Incident multimorbidity[b]			
Non-frailty	447	Ref.	Ref.
Pre-frailty	990	1.3 (1.0–1.7)	0.050
Frailty	401	17.3 (5.3–56.1)	<0.001
Incident dependence			
Non-frailty	327	Ref.	Ref.
Pre-frailty	1,142	1.4 (1.2–1.7)	0.001
Frailty	448	5.7 (3.8–8.7)	<0.001

[a]*Adjusted for: age, gender, education, household income, smoke status, and comorbidity count at baseline.*
[b]*Adjusted for: age, gender, education, household income, and smoke status.*
OR, odds ratio; CI, confidence interval.

and males were obviously inactive except for centenarians (**Supplementary Table 1**).

Among frail population, exhaustion (83.2%), low mobility (83.0%), and weakness (82.5%) were the most frequent domains. The prevalence of exhaustion peaked among the young-old (<80 years, 91.0%). The prevalence of low mobility (88.8%) exceeded that of exhaustion (78.7%) and became the most common domains among the centenarians. Gender-specific analyses showed that shrink, weakness, and low mobility were more common among females in all age groups whereas inactivity was more common among males (**Supplementary Table 1**).

Pre-frailty, Frailty, and Adverse Outcomes

After adjusting for confounders, pre-frailty was significantly associated with the risk of limited physical performance (OR = 1.2, 95%CI, 1.1–1.4), incident cognitive decline (OR = 1.4, 95%CI, 1.1–1.7) and dependency (OR = 1.4, 95%CI, 1.2–1.7), respectively. Frailty was strongly associated with nearly doubled risk of frequent hospitalization and more than five times increased risk of incident limited physical performance, incident cognitive decline, and incident dependency, respectively (**Table 2**).

Subject to the number of incident cases, gender-stratified analyses were only performed regarding outcomes of incident limited physical performance, incident cognitive decline, and incident dependency. Females with pre-frailty, instead of males, were with the increased risk of incident limited physical performance (OR = 1.3, 95%CI, 1.1–1.6), cognitive decline (OR = 1.4, 95%CI, 1.1–1.9), and dependency (OR = 1.7, 95%CI, 1.3–2.2). Frailty was significantly associated with the risk of these adverse outcomes in both genders and showed more intensive influence to males compared with females ($P < 0.001$; **Supplementary Table 2**).

Frailty Status and All-Cause Mortality

After adjusting for confounders, both pre-frailty and frailty were strongly correlated to the increased risk of mortality ($P < 0.001$). The association between pre-frailty and the risk of mortality peaked among centenarians (HR = 1.7, 95%CI, 1.3–2.2). The strongest association between frailty and mortality was observed among the group aged 65–79 years (HR = 3.6; 95% CI, 2.8–4.5). Among the age groups ≥ 80 years, frail males were much vulnerable to the risk of mortality in contrast to frail females (**Figure 2**).

Domains of Frailty and All-Cause Mortality

All of the domains of frailty were significantly associated with the increased risk of all-cause mortality (**Figure 3**; **Supplementary Table 3**) According to the age- and gender-stratified analyses, the association between exhaustion and the risk of mortality showed U-shaped trend with aging in both genders and was more influential to males in contrast to females (**Figure 3A**). Shrink was significantly associated with the increased risk of mortality among females aged 65–79 years (HR = 1.46, 95%CI, 1.16–1.82) and males aged 80–89 years (HR = 1.19, 95%CI, 1.05–1.36) (**Figure 3B**; **Supplementary Table 3**). Males aged 65–79 years with weakness (HR = 2.78, 95%CI, 1.99–3.89) and with low mobility (HR = 3.15, 95%CI, 2.33–4.24) were with the highest risk of mortality in contrast to females and males in other age groups (**Figures 3C,D**; **Supplementary Table 3**). The strongest association between inactivity and the risk of mortality was observed among females aged 65–79 years (HR = 3.50, 95%CI, 2.52–4.87) (**Figure 3E**; **Supplementary Table 3**).

DISCUSSION

Based on the nationwide cohort study of the longevous population, the present study reported the prevalence of pre-frailty and frailty among the population with a mean age of 85 years, which were 54.1 and 26.3%, respectively. Females were predominant among frail population in all age groups whereas males were dominant among pre-frail individuals aged ≥ 80 years. Both pre-frailty and frailty were strongly associated with multiple adverse outcomes. Males and the young-old (<80 years) were the most susceptible to the risk of mortality. Although all of the domains were significantly associated with adverse outcomes, physical deficits including weakness, low mobility and inactivity showed stronger association with the risk of mortality compared with exhaustion and shrink. The current results supplemented previous data on the prevalence of frailty among the longevous population and provided clues to develop the strategy of frailty treatment. Intensified prevention and treatment

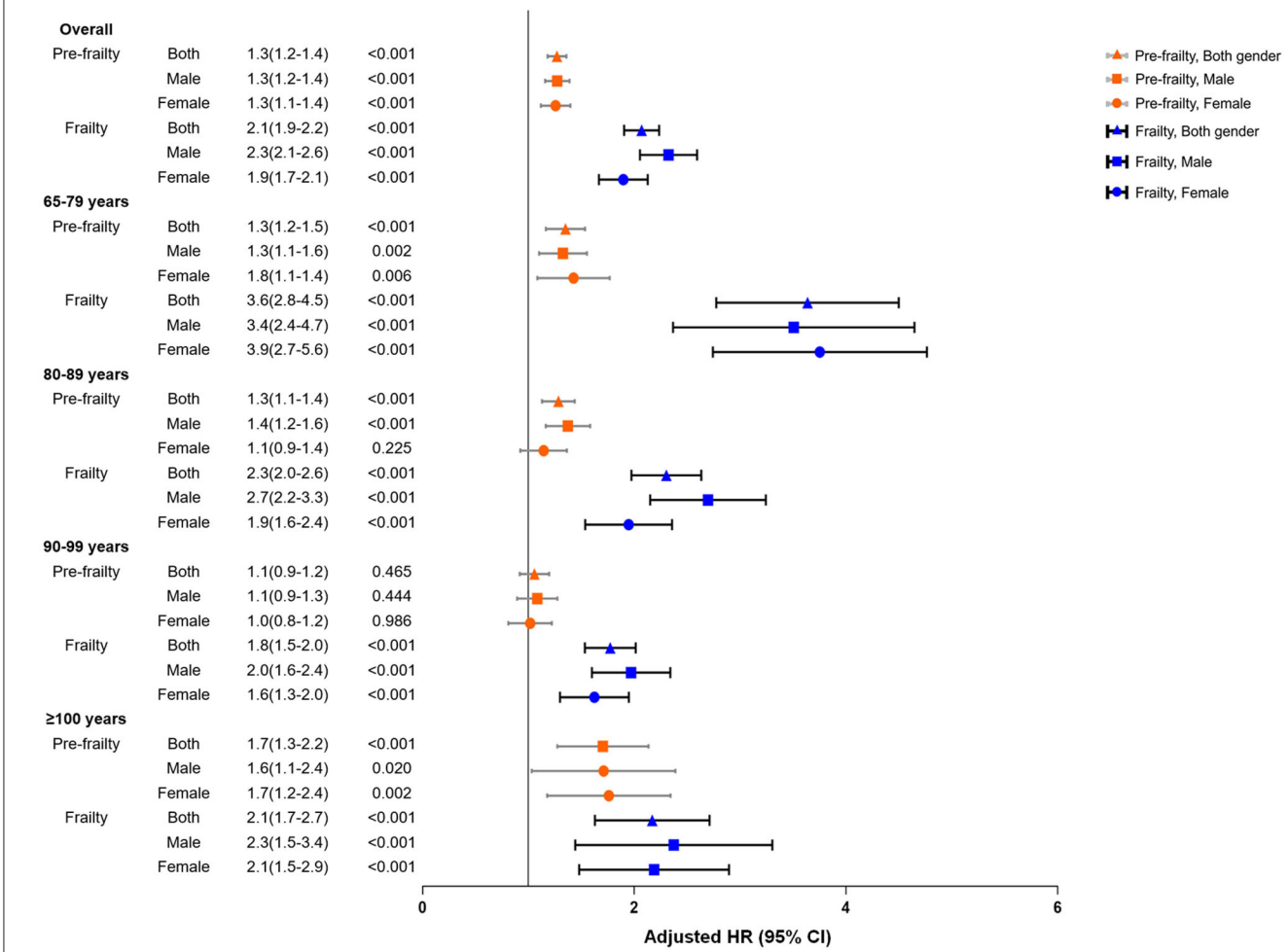

FIGURE 2 | All-cause mortality for pre-frailty and frailty at baseline, stratified by age and gender. Adjusted for education, household income, smoke status, and comorbidity count at baseline.

of frailty should be applied in China. The gender-specific strategy should be developed.

Healthy aging is an important goal of the public health in the 21st century. However, a huge gap exists between longer life and healthy aging. The present study indicated the high prevalence of pre-frailty and frailty among the Chinese longevous population, which is consistent with the results from 1,253 centenarians in the 5-COOP countries (Japan, France, Switzerland, Sweden, and Denmark) (12). It demonstrated that the heavy burden of frailty among the longevous population was globally substantial. Notably, only 5% of centenarians and 11.1% of nonagenarians were non-frailty in the present study. Similar results were observed among centenarians in the 5-COOP countries (12). Additionally, the present results comprehensively demonstrated the association between pre-frailty, frailty, and the risk of multiple adverse outcomes. It implies not only the high consumption of healthcare resources of the frail elderly, but also the suffering of patients themselves. Hence, the epidemic of frailty could be considered as one of the great barriers of healthy aging. The healthcare system in the developing countries, such as China, should be changed as soon as possible so as to better prevent and treat frailty and cope with the challenge of aging.

The current results found the strongest association between frailty and the risk of mortality among the young-old although the prevalence of frailty was the lowest in this group. Similar results were reported in previous studies (31–34). Dupre et al. (35) investigated frailty and the type of death among aged people in China, which was categorized according to the bedridden and suffering before death. They found that the young-old (65–79 years) with any levels of frailty showed the longest period of bedridden with suffering before death in contrast to other older groups. Abraham et al. (36) analyzed suffering at the end of life among individuals without acknowledged physical distress and found that the mean age of moderate-to-severe suffering

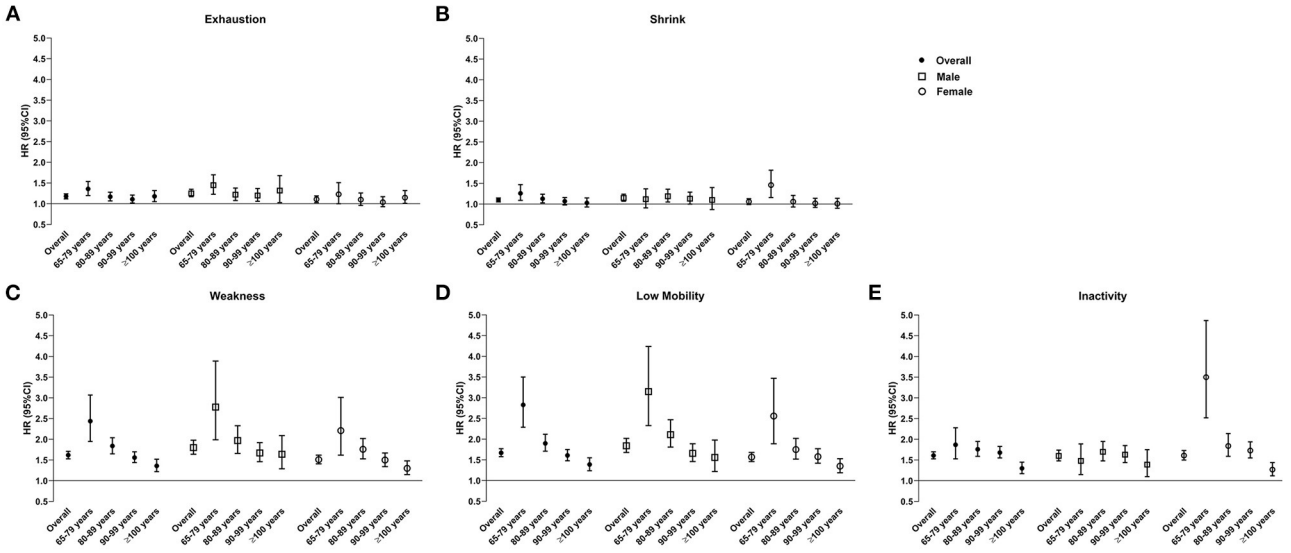

FIGURE 3 | Association between domains of frailty [**(A)** exhaustion, **(B)** shrink, **(C)** weakness, **(D)** low mobility, and **(E)** inactivity] and the risk of all-cause mortality, age-, and gender-stratified. Adjusted for: education, household income, smoke status, and comorbidity count at baseline.

group was significantly younger than no-to-mild suffering group (65 vs. 75 years, $P < 0.05$). It indicated that a distinguishing mechanism of deathbed or mortality might exist among the young-old population compared with those with advanced age. However, to our knowledge, rare studies explored the underlying mechanisms. In contrast to the chronological age, frailty is a much specific indicator of physical and biological senescence (27) and shows significantly gender-specific association with multiple adverse outcomes. Although the underlying mechanism of frailty and premature death remains to be explored, the present results provide validate results to strongly stress the importance to prevent and treat frailty among the young-old population.

The gender-specific prevalence of frailty and its association between mortality were found in the present study, which is consistent with previous studies (37, 38). Corbi et al. (37) investigated the inter-relationship between gender, frailty, and the 10-year survival among 1,284 adults with a mean age of 74.2 years. Although more females with frailty were found compared with males (50.3 vs. 29.5%), female gender was associated with the reduced risk of mortality (HR = 0.43, 95%CI: 0.299–0.561). Zhang et al. (38) reported the higher prevalence of frailty among females (8.8 vs. 5.4%) and the higher mortality among frail males (22.5 vs. 8.5%). In addition to the community-dwelling population, the gender difference of prevalence of frailty was also found among patients with HIV-infection (39). It strongly suggests the necessity to develop the gender-specific strategies for management and prevention of frailty. Previously, Serra-Prat et al. (40) conducted a randomized controlled trial and demonstrated the effectiveness of an intervention focused on physical activity and nutrition to prevent frailty in pre-frail population. However, according to the present results of gender-difference of frailty, the gender-specific effectiveness of intervention on activity and nutrition should be further investigated. According to the study of Zhang et al. (38), heart disease and nephritis were the leading causes of death among the frail males and females, respectively. Komici et al. (41) reviewed the cardioprotective effects of dietary phytochemicals and reported the gender-differences of the adsorption, distribution, metabolism, and elimination of dietary phytochemicals. For instance, a better effect of quercetin against atherosclerosis was found among females, which might be influenced by the better absorption among females, while a lower kidney elimination of the conjugated phenolic compounds was found among females. In sum, the impact of gender on the pathogenesis of frailty should be further explored and the development of the gender-specific strategies for prevention and management of frailty should fully consider the epidemiological factors and the underlying mechanisms of the gender-differences.

Heterogeneity is one of the major characteristics of the natural course of frailty, it increases the challenge of early management of frailty (1). Previous studies investigating the phenotype and progression of frailty were mainly from Caucasians in developed countries. Results from the Women's Health and Aging Study II (42) (included 420 females aged 70–79 years) indicated weakness as the initial manifestation whereas results from the Longitudinal Aging Study Amsterdam and the Netherlands (LASA, $n = 1{,}440$) and the Invecchiare in Chianti, aging in the Chianti area (InCHIANTI, $n = 998$) Study showed that exhaustion was the first manifestation of frailty (43). According to the present results, exhaustion was the predominant domain among pre-frail population while the prevalence of physical deficits, such as weakness and low mobility, obviously increased among the frail population. It showed that the progression of frailty among the Chinese longevous population was from exhaustion to physical deficits. It is consistent with results from LASA and InCHIANTI study. Additionally, the present study

demonstrated the association between domains of frailty and the risk of all-cause mortality. Although weakness, low mobility and inactivity emerged later and dominated in frailty among the longevous population, these physical deficits showed significantly stronger association with the risk of mortality compared with exhaustion. Our results indicated the importance of prevention of exhaustion among the aging population and stressed the prevention and treatment of physical deficits among pre-frail and frail population. Family- and community-based system of multicomponent training, such as exercise and social activities, would be feasible and beneficial (44). Besides, high prevalence of shrink among females and inactivity among males indicated the necessity of gender-specific strategy of frailty management. Caregivers should enhance the nutrition supplement especially among females and improve the physical activity especially among males.

The present study has limitations. First, data of comorbidity was self-reported. Influenced by awareness, the status of multimorbidity might be under-estimated. Second, given the heterogeneity of existing tools for frailty screening (1), studies generating and using other tools to quantify frailty are still expected although the criteria adopted in the present study has been widely used. Third, the determinants of mortality in addition to the status of frailty were not investigated in the present study subject to the availability of data. Fourth, the possibility of residual confounding exists.

In conclusion, frailty is prevalent among the longevous population in China. The association between pre-frailty, frailty, and multiple adverse outcomes emphasized the importance to prevent and treat frailty in the elderly. Given the disparity of frailty between genders and age groups, gender-, and age-specific strategies should be developed to prevent the adverse outcomes.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: the datasets analyzed during the current study are available in the Chinese Longitudinal Healthy Longevity Surveys repository, https://opendata.pku.edu.cn/dataverse/CHADS.

ETHICS STATEMENT

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

DISCLOSURE

All authors listed meet the criteria for authorship, have approved the submission and release the copyright for publication.

AUTHOR CONTRIBUTIONS

HYW designed the study, analyzed the data, interpreted the results, and wrote the manuscript. XL advised the methodology and interpreted the results. JD and GK revised the manuscript. LZ supervised the study, revised the manuscript, and is the study garantor. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.719806/full#supplementary-material

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Sex-Specific Association Between Socioeconomic Status, Lifestyle, and the Risk of Frailty Among the Elderly in China

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Background: Lifestyle contributors to frailty among the elderly were previously reported in the developed Western countries, while evidence from the less developed East Asian regions was still lacking. Due to the well-acknowledged sex-based disparity of frailty and sex-difference of socioeconomic status and lifestyle, it is worth investigating the sex-specific association between the social and behavioral contributors and the risk of frailty among the East Asian longevous population.

Methods: The present study was an observational study based on the four waves of interviews of the Chinese Longitudinal Healthy Longevity Survey (CLHLS) from 2008 to 2018. The participants aged ≥65 years and without frailty at baseline were included. Fried criteria (exhaustion, shrink, weakness, low mobility, and inactivity) were adopted to identify the incidence of frailty (≥3 domains) and pre-frailty (1–2 domains) during the follow-up. The sex-specific association between lifestyle (smoke status, drinking status, food intake, sleep, exercise, and physical activity) and the risk of incident pre-frailty and frailty was analyzed using the multinomial logistic regression models.

Results: Altogether, 3,327 participants aged 81.2 ± 10.3 (range 65–116) years were included. In total, 964 (29.0%) and 1,249 (37.5%) participants were recognized as having incident pre-frailty and frailty, respectively. Older women were disproportionately uneducated, frequently did housework and labor work, but seldom did exercise. Men had diverse dietary and recreational activities but were frequently exposed to tobacco and alcohol. The protective effects of higher income, exercise, doing housework, and daily intake of fresh fruits/vegetables were found in both the sexes ($P < 0.05$). Sleep disorders (odds ratio [*OR*] = 2.16, 95% *CI*: 1.28–3.62) and labor work (*OR* = 2.18, 95% *CI*: 1.42–3.33) were associated with the increased risk of frailty among women. For men, diverse dietary (four types of food added: *OR* = 0.21, 95% *CI*: 0.09–0.50) showed a protective effect on the risk of frailty, but daily intake of pickled vegetables showed the opposite effect (*OR* = 1.86, 95% *CI*: 1.12–3.07).

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Conclusion: Socioeconomic status, lifestyle, and the association with the risk of frailty showed substantial difference between the sexes among the longevous population in China. To establish the individualized strategy of behavioral improvement for the frailty prevention should consider the sex disparity.

Keywords: frailty, lifestyle, socioeconomic status, sex disparity, the longevous population

INTRODUCTION

Frailty is an age-related syndrome characterized by the deficits of physical function, deterioration of physiological reserves, and vulnerability to stressors (1, 2). It was considered as a natural course of aging and was increasingly used as an indicator of biological aging (2, 3). Thanks to the striking development of society and medicine, global life expectancy has increased continuously (4), which is accompanied by the increase of frail population (1, 2). The prevention and intervention of frailty have become major challenges to the public health. Sex disparity of frailty and its health-mortality paradox were widely acknowledged (5, 6). In contrast to men, women were more likely to be frail but often showed the lower risk of mortality (5, 6). Although the pathophysiological pathways of frailty and the sex difference were not clear yet, the previous studies indicated the essential roles of the combination of biological, behavioral, and social factors (5).

Several clinical guidelines of frailty management suggested that the modifiable risk factors of frailty, such as unhealthy diet and insufficient physical activity, should be prevented earlier (7, 8). Multiple dietary quality scores were suggested to predict the risk of frailty (9), and an individualized physical activity program was strongly recommended to prevent and treat frailty (7). However, it should be noted that few of the previous studies included a large sample size of the longevous population (e.g., aged over 80 years) (9–14). Additionally, lifestyle is obviously affected by culture and socioeconomic status. Women, especially those residing in the less developed Asian countries, are more likely to overwork and be over-committed to family but endure the persistent shortage of care and economic support (15–18). The previous studies were mainly conducted in the developed Western countries or developed Asian countries such as Japan (9, 10, 12, 14). The sex-specific association between socioeconomic status, lifestyle and the risk of frailty among the longevous population in the less developed Asian countries is still under-investigation that means evidence for the sex-specific strategy of lifestyle improvement among the elderly in the developing countries is still lacking.

As to the largest developing country China, the Chinese population who were born in the early twentieth century and became the longevous people in the twenty-first century experienced the World War II, famine, poverty, and rapid prosperity of the country. Since the foundation of the People's Republic of China in 1949, the social status of the Chinese women has undergone enormous changes (15). Social status of women was changed from an oppressed and enslaved group in the past thousands of years to masters of their own fate. The progress of culture and socioeconomic status alters the sex-specific lifestyles and further influences the health. Insight into sex-specific socioeconomic status, lifestyle and frailty of the longevous population could not only be a supplement to the understanding of sex difference of frailty in low-income countries, but also guide the prevention and management of frailty among the East Asian older adults. The Chinese Longitudinal Healthy Longevity Survey (CLHLS) is a nationally representative cohort study in China, which recruited a large sample size of octogenarians, non-agenarians, and centenarians and followed up more than 10 years (19, 20). It provides a precious opportunity to investigate the sex-specific influence of socioeconomic status and lifestyles to the risk of frailty among the oldest-old population in a developing country. Hence, based on the CLHLS, the present study comprehensively investigated the sex-specific association among socioeconomic status, lifestyle, and the risk of frailty among the elderly in China. The effects of sex-specific dietary patterns and types of daily physical activity on the risk of frailty were further evaluated so as to provide more clues for the improvement of lifestyle.

METHODS

Population

The present study was conducted based on the 2008–2018 cohort study of CLHLS (21). The CLHLS was conducted in a random-sample design, which recruited participants in 22 of the 31 provinces, covering about 85% population of China. Centenarians in the sampled counties and cities were invited to the survey and number-matched residents aged from 65 to 99 years living near to the centenarians were recruited either. With this design, the representativeness of the population in CLHLS was ensured. Also, social and behavioral data collected by the CLHLS are feasible to investigate the determinants of healthy aging in China (19, 21). The information of the Participants, such as demographic characteristics, socioeconomic status, lifestyle, and health status was collected using the structured questionnaires. Data from the four waves of interviews (2008, 2012, 2014, 2018) were adopted. Altogether, 9,494 participants aged $\geq$65 years at baseline (2008) and having complete data of frailty during the follow-up were included. The participants who had frailty ($n = 3,647$) or at the baseline of pre-frailty ($n = 2,036$) were excluded. Another 484 participants were excluded due to the absence of data related to lifestyle. Ultimately, 3,327 participants were eligible for the present study. The criteria for frailty and pre-frailty are mentioned below (Methods, *Outcome* section).

The CLHLS was approved by the Research Ethics Committee of Peking University (IRB00001052-13074) (22, 23). All the

participants provided written informed consent. Detailed information of the CLHLS could be found elsewhere (20, 23).

Covariates

The age groups were categorized into 65–79, 80–89, 90–99, and ≥100 years. Multimorbidity was defined as having more than three comorbidities, such as hypertension, diabetes, heart disease, cerebrovascular disease, chronic pulmonary disease, eye disease (cataract or glaucoma), cancer, Parkinson's disease, dementia, mental disease, arthritis, gastrointestinal ulcer, and hepatitis (24–26). Body mass index (BMI) was calculated as weight divided by height square and categorized into normal (18.5–23.9 kg/m^2), underweight (<18.5 kg/m^2), overweight (24.0–27.9 kg/m^2), and obesity (≥28.0 kg/m^2). Low accessibility of healthcare was defined if the participants answered "No" to the question "Would you timely see a doctor if you suffered from a severe illness?"

Socioeconomic Status

The levels of education were defined as uneducated (never being educated), primary school (being educated for 1–6 years), and middle school or above (being educated for 7 years or more). Household income was recorded as quartiles.

Lifestyles

Smoke status was recorded as never, past, and current (22). Drinking status was recorded as never, past, low risk drinking (alcohol consumption: ≤25 g for men, ≤15 g for women), and high risk drinking (alcohol consumption: >25 g for men, >15 g for women) (27). Sleep was defined as normal (5–10 h/day and no sleep disorder), excessive (>10 h/day) and insufficient (<5 h/day or having sleep disorder) (28–30). Exercise was defined as never, past, and current.

Physical Activity

According to social and cultural background, the CLHLS collected type and frequency of the most common physical activities among the longevous population in China (21). The following physical activities were recorded in the frequency of <1 time/week or ≥1 time/week: radio/TV/reading, playing cards, social activity, outdoor activity, gardening/keeping a pet, housework/childcare, and raising domestic animals.

The intensity of activity was defined as low-to-medium intensive activity (radio/TV/reading, playing cards, social activity, outdoor activity, and gardening/keeping a pet), and high-intensive activity (housework/childcare and raising domestic animals).

Food Intake

Food intake was recorded as daily, sometimes (weekly/monthly), or rarely intake of meat, fish/seafoods, eggs, dairy, legumes, fresh fruits/vegetables, tea, garlic, and pickled vegetables (22).

The categories of food intake were defined as the following groups: meat/fish/seafoods/eggs, fresh fruits/vegetables, diary/legumes, and tea/garlic (27). In accordance with the daily food category, dietary diversity was defined as staple food only (mainly eat rice/wheat/corn but rarely eat other types of food, such as meat, fruits/vegetables, and dairy products), one type added, two types added, three types added, and four types added. The participants added four types of food to staple food were defined as having diverse diet.

Outcome

The modified Fried criteria (exhaustion, shrink, weakness, low mobility, and inactivity) were adopted to identify the incident pre-frailty and frailty (31).

Exhaustion was defined if the participant answered "always," "often," or "sometimes" to questions "I felt old and useless" or "I felt everything I did was an effort" (26, 32, 33). Shrink was defined as BMI < 18.5 kg/m^2 (26, 33). Weakness was defined if the participant was unable to lift a bag weighted 5 kg (34). Low mobility was defined if the participant was unable to walk for 1 km (35). Inactivity was defined if the participants did all the following activities less than one time/week: playing cards, social activity, gardening/keeping a pet, outdoor activity, housework/childcare, and raising domestic animals (32).

Incidence of pre-frailty and frailty was identified if the participants arose 1–2 domains and ≥3 domains during the follow-up, respectively. The participants showed no domains during the follow-up were defined as non-frailty (31, 32).

Statistics

The demographic characteristics (age and sex), socioeconomic status (education and household income), health status (multimorbidity and accessibility of healthcare), and lifestyles (smoke status, drinking status, sleep, exercise, intensity of physical activity, dietary diversity, types of physical activity, and type of food intake) were presented according to the status of non-frailty, incident pre-frailty, and incident frailty, respectively. Chi-square tests and one-way ANOVA were applied for the comparison of categorical and normal-distributed continuous variables, respectively. The baseline characteristics were compared between the sexes (1, 5).

The multinomial logistic regression models were used to analyze the factors associated with the risk of incident pre-frailty and frailty, respectively. Following factors at baseline (2008) were analyzed as the categorical variables such as age, sex, education, household income, multimorbidity, smoke status, drinking status, sleep, exercise, intensity of physical activity, and dietary diversity. Odds ratio (*OR*) and 95% *CI* were separately calculated for the incident pre-frailty and frailty, each in reference to non-frailty. The sex-stratified analyses were conducted.

The association among the types of physical activity, types of food intake at baseline (2008), and the risk of incident pre-frailty and frailty was analyzed using the multinomial regression models, respectively. The covariates, such as age, sex, education, household income, and multimorbidity were adjusted. The results were presented in *OR* and 95% *CI*. The sex-stratified analyses were conducted.

All the analyses were two tailed and p value < 0.05 was considered to be statistically significant. All the statistical analyses were performed using Stata version 16.0 (Stata Corp LP, College Station, TX, USA).

TABLE 1 | Comparison of the characteristics at baseline according to the status of frailty during the follow-up.

Characteristics	Overall	Non-frailty	Pre-frailty	Frailty	*P* value
In total (*n*, %)	3,327 (100.0)	1,114 (33.5)	964 (29.0)	1,249 (37.5)	
Mean age (years, mean ± SD)	81.2 ± 10.3	81.3 ± 10.9	75.8 ± 8.7	85.4 ± 8.9	<0.001
Age group (*n*, %)					<0.001
65–79 years	1,060 (31.9)	375 (33.7)	525 (54.5)	160 (12.8)	
80–89 years	935 (28.1)	268 (24.1)	272 (28.2)	395 (31.6)	
90–99 years	1,011 (30.4)	356 (32.0)	139 (14.4)	516 (41.3)	
≥100 years	321 (9.7)	115 (10.3)	28 (2.9)	178 (14.3)	
Sex (*n*, %)					<0.001
Men	1,684 (50.6)	649 (58.3)	551 (57.2)	484 (38.8)	
Women	1,643 (49.4)	465 (41.7)	413 (42.8)	765 (61.3)	
Multimorbidity (*n*, %)	664 (21.1)	220 (20.7)	178 (19.3)	266 (22.8)	0.141
Uneducated (*n*, %)	1,600 (35.5)	462 (41.5)	348 (36.1)	790 (63.3)	<0.001
Low household income (*n*, %)†	858 (25.8)	208 (18.7)	251 (26.0)	399 (32.0)	<0.001
Low accessibility to healthcare (*n*, %)	115 (3.5)	21 (1.9)	18 (1.9)	76 (6.1)	<0.001
Having diverse diet (*n*, %)‡	400 (12.0)	174 (15.6)	128 (13.3)	98 (7.9)	<0.001
Smoke status (*n*, %)					<0.001
Never	2,052 (61.7)	672 (60.3)	533 (55.3)	847 (67.8)	
Past	566 (17.0)	213 (19.1)	157 (16.3)	196 (15.7)	
Current	709 (21.3)	229 (20.6)	274 (28.4)	206 (16.5)	
Drinking status (n, %)					<0.001
Never	2,188 (66.9)	714 (65.1)	572 (60.9)	902 (73.0)	
Past	432 (13.2)	155 (14.1)	122 (13.0)	155 (12.6)	
Low risk drinking	159 (4.9)	68 (6.2)	48 (5.1)	43 (3.5)	
High risk drinking	492 (15.0)	160 (14.6)	197 (21.0)	135 (10.9)	
High-intensive activity (n, %)	2,519 (77.6)	842 (75.6)	818 (84.9)	859 (83.4)	<0.001
Exercise (n, %)					<0.001
Never	1,805 (54.3)	504 (45.2)	523 (54.3)	778 (62.3)	
Past	331 (10.0)	97 (8.7)	78 (8.1)	156 (12.5)	
Current	1,191 (35.8)	513 (46.1)	363 (37.7)	315 (25.2)	
Sleep disorder (n, %)					<0.001
Excessiveness	187 (5.6)	65 (5.8)	47 (4.9)	75 (6.0)	
Insufficiency	320 (9.6)	72 (6.5)	82 (8.5)	166 (13.3)	

†*Low household income: the participants whose household income <25% of the population were defined as having low household income.*
‡*Diverse diet: based on staple food, the participants added four types of food were defined as having diverse diet.*

RESULTS

Population Characteristics

In total, 3,327 participants with an age of 81.2 ± 10.3 (range 65–116) years were included. Among them, 1,011 (30.4%) were aged 90–99 years and 321 (9.7%) were centenarians (**Table 1**). Till 2018, 964 (29.0%) and 1,249 (37.5%) participants were recognized as incident pre-frailty and incident frailty, respectively. Compared with the non-frail participants, those with incident pre-frailty were significantly younger, whereas those with incident frailty were significantly older ($P < 0.001$) (**Table 1**). Men (57.2%) and women (61.5%) were predominant among pre-frail and frail population, respectively ($P < 0.001$) (**Table 1**).

The highest proportions of current smokers (28.4%) and excessive drinkers (21.0%) were observed among the population with incident pre-frailty. Compared with the non-frail participants, those with incident frailty were more likely to be inactive, have single diet and insufficient sleep ($P < 0.001$) (**Table 1**). The proportions of participants raising domestic animals daily were higher in the groups of incident pre-frailty (33.7%) and incident frailty (26.8%) as compared with the non-frail group (22.9%) ($P < 0.001$) (**Table 2**).

Sex-Specific Characteristics at Baseline

Comparison of characteristics between sexes is shown in **Figure 1**. Compared with men, more women were centenarians (12.1 vs. 7.3%), uneducated (69.5 vs. 27.2%), and more likely to have low accessibility of healthcare (4.1 vs. 2.8%) (**Figure 1A**).

Men were more frequently exposed to tobacco and alcohol but had a diversified diet ($P < 0.001$) (**Figure 1B**). Women were more likely to have insufficient sleep, did high-intensive activity but never did exercise ($P < 0.001$) (**Figure 1C**). Men preferred

TABLE 2 | Comparison of types of food intake and types of physical activity at baseline according to the status of frailty during the follow-up.

Types (*n*, %)	Overall	Non-frailty	Pre-frailty	Frailty	*p* value
Physical activity					
Radio/TV/reading					<0.001
<1 time/week	757 (22.8)	191 (17.2)	127 (13.2)	439 (35.2)	
≥1 times/week	2,570 (77.3)	923 (82.9)	837 (86.8)	810 (64.9)	
Playing cards					<0.001
<1 time/week	2,824 (84.9)	907 (81.4)	787 (81.6)	1,130 (90.5)	
≥1 times/week	503 (15.1)	207 (18.6)	177 (18.4)	119 (9.5)	
Social activity					<0.001
<1 time/week	3,042 (91.4)	977 (87.7)	861 (89.3)	1,204 (96.4)	
≥1 times/week	285 (8.6)	137 (12.3)	103 (10.7)	45 (3.6)	
Gardening/keeping a pet					<0.001
<1 time/week	2,738 (82.3)	851 (76.4)	758 (78.6)	1,129 (90.4)	
≥1 times/week	589 (17.7)	263 (23.6)	206 (21.4)	120 (9.6)	
Outdoor activity					<0.001
<1 time/week	1,022 (30.7)	262 (23.5)	287 (29.8)	473 (37.9)	
≥1 times/week	2,305 (69.3)	852 (76.5)	677 (70.2)	776 (62.1)	
Housework/childcare					<0.001
<1 time/week	951 (28.6)	313 (28.1)	184 (19.1)	454 (36.4)	
≥1 times/week	2,376 (71.4)	801 (71.9)	780 (80.9)	795 (63.7)	
Raising domestic animals					<0.001
<1 time/week	2,412 (72.5)	859 (77.1)	639 (66.3)	914 (73.2)	
≥1 times/week	915 (27.5)	255 (22.9)	325 (33.7)	335 (26.8)	
Food intake					
Meat					<0.001
Rarely	604 (18.2)	178 (16.0)	143 (14.8)	283 (22.7)	
Sometimes	1,656 (49.8)	539 (48.4)	501 (52.0)	616 (49.3)	
Daily	1,067 (32.1)	397 (35.6)	320 (33.2)	350 (28.0)	
Fish/seafoods					<0.001
Rarely	1,148 (34.5)	341 (30.6)	296 (30.7)	511 (40.9)	
Sometimes	1,894 (56.9)	651 (58.4)	583 (60.5)	660 (52.8)	
Daily	285 (8.6)	122 (11.0)	85 (8.8)	78 (6.2)	
Eggs					0.071
Rarely	576 (17.3)	189 (17.0)	147 (15.3)	240 (19.2)	
Sometimes	1,558 (46.8)	508 (45.6)	460 (47.7)	590 (47.2)	
Daily	1,193 (35.9)	417 (37.4)	357 (37.0)	419 (33.6)	
Dairy					<0.001
Rarely	2,044 (61.4)	628 (56.4)	587 (60.9)	829 (66.4)	
Sometimes	589 (17.7)	178 (16.0)	193 (20.0)	218 (17.5)	
Daily	694 (20.9)	308 (27.7)	184 (19.1)	202 (16.2)	
Legumes					0.025
Rarely	898 (27.0)	301 (27.0)	231 (24.0)	366 (29.3)	
Sometimes	1,760 (52.9)	572 (51.4)	532 (55.2)	656 (52.5)	
Daily	669 (20.1)	241 (21.6)	201 (20.9)	227 (18.2)	
Fresh fruits/vegetables					<0.001
Rarely	668 (20.1)	161 (14.5)	171 (17.7)	336 (26.9)	
Sometimes	2,100 (63.1)	707 (63.5)	621 (64.4)	772 (61.8)	
Daily	559 (16.8)	246 (22.1)	172 (17.8)	141 (11.3)	
Tea					<0.001
Rarely	1,736 (52.2)	551 (49.5)	433 (44.9)	752 (60.2)	
Sometimes	281 (8.5)	91 (8.2)	92 (9.5)	98 (7.9)	
Daily	1,310 (39.4)	472 (42.4)	439 (45.5)	399 (32)	

(Continued)

TABLE 2 | Continued

Types (*n*, %)	Overall	Non-frailty	Pre-frailty	Frailty	*p* value
Garlic					<0.001
Rarely	1,440 (43.3)	453 (40.7)	375 (38.9)	612 (49)	
Sometimes	1,110 (33.4)	371 (33.3)	362 (37.6)	377 (30.2)	
Daily	777 (23.4)	290 (26)	227 (23.6)	260 (20.8)	
Pickled vegetables					<0.001
Rarely	1,764 (53.0)	649 (58.3)	449 (46.6)	666 (53.3)	
Sometimes	898 (27.0)	283 (25.4)	283 (29.4)	332 (26.6)	
Daily	665 (20.0)	182 (16.3)	232 (24.1)	251 (20.1)	

sedentary or recreational activities, whereas women frequently did high-intensive activities such as housework/childcare and raising domestic animals ($P < 0.001$) (**Figure 1D**). Men consumed more nutritious food, whereas women mostly had pickled vegetables ($P < 0.001$) (**Figure 1E**).

Socioeconomic Status

As to the risk of incident pre-frailty, those aged over 80 years and with higher levels of household income were associated with the reduced risk of incident pre-frailty ($P < 0.05$) (**Table 3**).

As to the risk of incident frailty, women sex and aging were the risk predictors ($P < 0.001$). High levels of education and household income were associated with the reduced risk of frailty ($P < 0.05$). The sex-stratified analyses showed that the levels of education were more influential to women, whereas the levels of income affected men more ($P < 0.001$) (**Table 3**).

Lifestyles

High risk drinking was associated with the increased risk of incident pre-frailty ($OR = 1.84$, 95% CI: 1.24–2.75). Current smoke was associated with the increased risk of frailty among men ($OR = 1.67$, 95% CI: 1.04–2.68). Insufficient sleep was the risk factor of frailty ($OR = 1.75$, 95% CI: 1.20–2.54), especially among women ($OR = 2.16$, 95% CI: 1.28–3.62). Currently, doing sport ($OR = 0.60$, 95% CI: 0.45–0.79) and high-intensive activity ($OR = 0.61$, 95% CI: 0.45–0.83) showed strongly protective effects on frailty. Diversified diet was associated with the reduced risk of frailty among men (four types added: $OR = 0.21$, 95% CI: 0.09–0.50), but not for women ($P > 0.05$) (**Table 3**).

Physical Activity

As to the risk of incident pre-frailty, social activity showed the protective effect ($OR = 0.72$, 95% CI: 0.52–0.98) while raising domestic animals it showed an adverse effect ($OR = 1.41$, 95% CI: 1.03–1.93) (**Table 4**).

As to the risk of incident frailty, physical activities including radio/TV/reading, gardening/keeping a pet, outdoor activity and housework/childcare were significantly associated with the reduced risk of frailty ($P < 0.001$). Benefits of radio/TV/reading and gardening/keeping a pet on the incident frailty were observed among men ($P < 0.001$), but not among women. Raising domestic animals was significantly associated with the increased risk of frailty ($OR = 1.69$, 95% CI: 1.25–2.29), especially among women ($OR = 2.18$, 95% CI: 1.42–3.33) (**Table 4**).

Food Intake

Daily intake of pickled vegetables was associated with the increased risk of incident pre-frailty ($OR = 1.69$, 95% CI: 1.19–2.41), especially among men ($OR = 2.15$, 95% CI: 1.33–3.48) (**Table 4**).

Sometimes or daily intake of fresh fruits/vegetables showed the protective effect on the incident frailty in both sexes ($P < 0.05$). Daily intake of dairy was associated with the reduced risk of frailty among men ($OR = 0.45$, 95% CI: 0.28–0.73), while daily intake of pickled vegetables showed adverse effect on the risk of frailty among men ($P < 0.05$) (**Table 4**).

DISCUSSION

Based on the nationally representative cohort of the elderly in China, the present study comprehensively investigated the sex-specific association between socioeconomic status, lifestyle, and the risk of pre-frailty and frailty, respectively. The protective effects of high levels of income, exercise, high-intensive activity, and fresh fruits/vegetables on the risk of frailty were found in both the sexes. For older women, the improvement in education and sleep and the avoidance of labor work might be beneficial for the prevention of frailty. For older men, cessation of tobacco, reduction of pickled vegetables' intake but increase of dairy intake might be beneficial for the prevention of frailty.

The disparity of frailty between sexes was well-recognized (2, 5, 36, 37). The present results of sex disparity are consistent with the previous studies, while its underlying reasons seem different from developed countries. Various studies in Western countries reported that much positive healthcare-seeking behavior and better perception of healthcare partly contributed to the high rate of diagnosis and early intervention of frailty among women (5). This phenomenon suggested the influence of awareness and the use of healthcare resources on the management of frailty (5, 38). However, in the present study, the Chinese older women were disproportionately uneducated, and more women showed low accessibility of healthcare as compared with men, especially among rural residents. The proportion of uneducated women in rural areas was 62.7% while in urban areas it was 37.7%. A higher proportion of women residents in rural areas

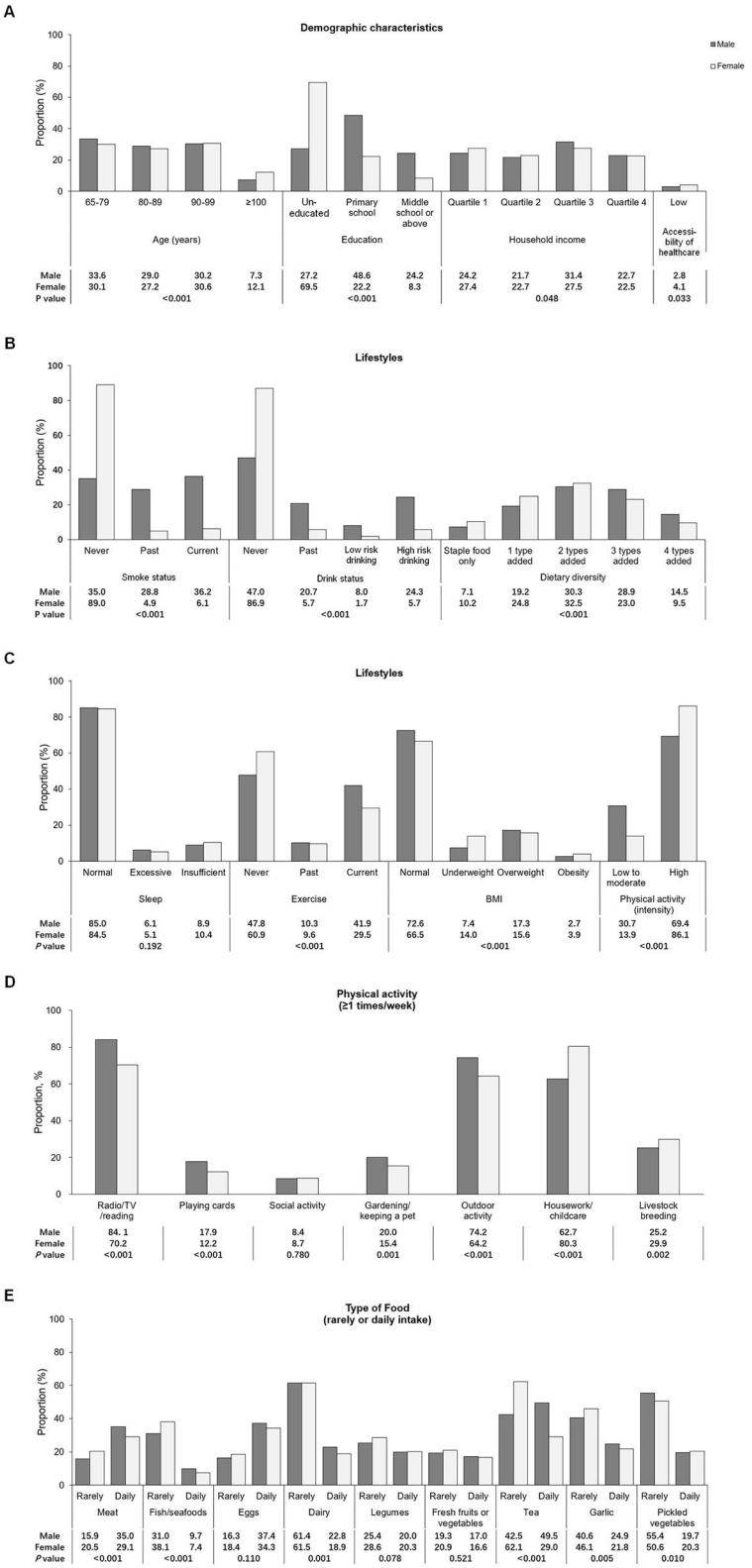

FIGURE 1 | Comparison of characteristics between genders. **(A)** The demographic characteristics and accessibility of healthcare. **(B)** Lifestyles, such as the status of smoke, drinking, and the diversity of diet. **(C)** Lifestyles, such as sleep conditions, habits of exercise, and daily physical activity categorized by intensity and the category of body mass index. **(D)** Type of daily physical activity. **(E)** Type of food intake. The comparison of types of food intake between genders was conducted using three groups of intake including rarely, sometimes and daily, of which the significance was presented in the current figure. The percentage of rarely and daily intake was presented using the bars whereas the percentage of food sometimes intake was not shown in this figure.

TABLE 3 | Factors associated with pre-frailty, frailty, and sex stratified.

Variables	Overall				Men				Women			
	Pre-frailty vs. non-frailty		Frailty vs. non-frailty		Pre-frailty vs. non-frailty		Frailty vs. non-frailty		Pre-frailty vs. non-frailty		Frailty vs. non-frailty	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Socioeconomic status												
Education												
Uneducated	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Primary school	1.26 (0.90–1.76)	0.178	0.89 (0.66–1.21)	0.455	1.64 (1.02–2.64)	0.043	1.18 (0.77–1.81)	0.452	1.00 (0.60–1.65)	0.992	0.70 (0.44–1.09)	0.114
Middle school or above	1.11 (0.74–1.68)	0.611	0.53 (0.35–0.81)	0.004	1.54 (0.87–2.70)	0.136	0.68 (0.38–1.19)	0.175	0.79 (0.41–1.54)	0.486	0.39 (0.19–0.77)	0.007
Household income												
Quartile 1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Quartile 2	0.66 (0.44–1.00)	0.052	0.61 (0.41–0.89)	0.011	0.67 (0.38–1.19)	0.171	0.55 (0.31–0.97)	0.037	0.69 (0.36–1.31)	0.256	0.68 (0.40–1.17)	0.165
Quartile 3	0.49 (0.33–0.73)	<0.001	0.57 (0.40–0.81)	0.002	0.42 (0.24–0.71)	0.001	0.59 (0.35–0.98)	0.043	0.57 (0.32–1.04)	0.065	0.59 (0.36–0.98)	0.041
Quartile 4	0.59 (0.39–0.89)	0.013	0.45 (0.31–0.66)	<0.001	0.49 (0.27–0.86)	0.014	0.39 (0.22–0.70)	0.002	0.68 (0.37–1.25)	0.218	0.52 (0.31–0.87)	0.012
Lifestyles												
Smoke status												
Never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Past	1.04 (0.69–1.58)	0.843	1.33 (0.89–1.98)	0.166	1.30 (0.81–2.08)	0.276	1.42 (0.88–2.28)	0.151	0.52 (0.17–1.56)	0.242	1.33 (0.57–3.12)	0.515
Current	1.24 (0.84–1.83)	0.283	1.34 (0.90–1.98)	0.146	1.54 (0.97–2.43)	0.065	1.67 (1.04–2.68)	0.034	1.22 (0.55–2.69)	0.625	0.73 (0.33–1.61)	0.438
Drinking												
Never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Past	0.89 (0.58–1.37)	0.59	0.86 (0.57–1.29)	0.456	0.80 (0.49–1.33)	0.394	1.03 (0.64–1.68)	0.896	1.17 (0.49–2.79)	0.721	0.52 (0.23–1.19)	0.121
Low risk drinking	1.13 (0.61–2.10)	0.701	0.88 (0.49–1.58)	0.657	1.01 (0.51–1.99)	0.977	0.88 (0.44–1.77)	0.724	1.39 (0.26–7.35)	0.696	1.13 (0.32–3.94)	0.853
High risk drinking	1.84 (1.24–2.75)	0.003	0.81 (0.53–1.24)	0.335	1.88 (1.18–2.99)	0.008	1.02 (0.62–1.69)	0.941	1.46 (0.63–3.37)	0.381	0.41 (0.18–0.91)	0.030
Sleep												
Normal	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Excessive	0.97 (0.52–1.81)	0.918	0.67 (0.39–1.17)	0.163	0.90 (0.42–1.96)	0.799	0.51 (0.22–1.19)	0.119	1.10 (0.37–3.23)	0.867	0.79 (0.36–1.74)	0.560
Insufficient	1.27 (0.84–1.92)	0.263	1.75 (1.20–2.54)	0.003	1.47 (0.82–2.63)	0.195	1.42 (0.81–2.51)	0.224	1.07 (0.58–1.98)	0.833	2.16 (1.28–3.62)	0.004
Exercise												
Never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Past	0.85 (0.52–1.40)	0.528	1.36 (0.89–2.06)	0.153	0.70 (0.35–1.43)	0.333	1.46 (0.81–2.64)	0.206	1.09 (0.53–2.25)	0.822	1.30 (0.70–2.41)	0.402
Current	0.97 (0.72–1.31)	0.855	0.60 (0.45–0.79)	<0.001	1.21 (0.81–1.81)	0.361	0.66 (0.44–0.99)	0.047	0.81 (0.51–1.28)	0.359	0.59 (0.40–0.88)	0.009
Physical activity												
Low to medium	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
High	0.99 (0.69–1.42)	0.936	0.61 (0.45–0.83)	0.002	0.99 (0.65–1.51)	0.949	0.67 (0.45–1.00)	0.049	0.86 (0.39–1.9)	0.706	0.46 (0.27–0.77)	0.003

(Continued)

TABLE 3 | Continued

Variables	Overall				Men				Women			
	Pre-frailty vs. non-frailty		Frailty vs. non-frailty		Pre-frailty vs. non-frailty		Frailty vs. non-frailty		Pre-frailty vs. non-frailty		Frailty vs. non-frailty	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Dietary diversity												
Staple food only	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1 type added	0.92 (0.50–1.68)	0.781	0.74 (0.44–1.22)	0.235	1.21 (0.49–3.00)	0.684	0.53 (0.24–1.18)	0.121	0.65 (0.28–1.51)	0.319	0.89 (0.46–1.69)	0.716
2 types added	1.04 (0.59–1.86)	0.887	0.59 (0.36–0.96)	0.034	0.77 (0.32–1.85)	0.555	0.37 (0.18–0.80)	0.011	1.43 (0.65–3.17)	0.377	0.75 (0.40–1.41)	0.364
3 types added	1.26 (0.70–2.27)	0.436	0.58 (0.35–0.95)	0.031	0.79 (0.33–1.92)	0.605	0.33 (0.15–0.71)	0.005	2.11 (0.93–4.80)	0.075	0.87 (0.44–1.69)	0.672
4 types added	0.93 (0.48–1.79)	0.830	0.41 (0.23–0.75)	0.003	0.69 (0.27–1.76)	0.436	0.21 (0.09–0.50)	<0.001	1.42 (0.52–3.85)	0.493	0.78 (0.32–1.92)	0.590

Adjusted for age, sex, and multimorbidity.

(5.75%) showed low accessibility of healthcare compared with that in urban areas (2.17%). Besides, proportions of un-education among women having low income in urban and rural areas were 81.5 and 80.6%, respectively. Hence, the high rate of incident frailty among women in the present study was more likely to be the integrated consequence of the long-term exposure to a series of unhealthy lifestyles and limited resources. According to the present results, women frequently did high-intensive activities including housework, childcare, and raising domestic animal but infrequently did exercise, which was more likely to accumulate the functional and physical impairments and further led to the high incidence of frailty. Generally, higher income was considered as the protective factor of frailty (2, 39), while in the present study, women were less influenced by household income compared with men. It might be a consequence of the women adaptability, generated from the long-term enduring of limited economic and care resources. It should be noted that the studied population was born from the 1890s to the 1940s. In that era, the turmoil of Chinese society strongly limited the education and economy. Additionally, the lagging feudal thought of "men are priority to women" exacerbated the problem of un-education and shortage of resources among women. It should be noted that the enormous improvement of sex disparity of socioeconomic status has been achieved during the past 70 years (15, 40). The association between socioeconomic status and the risk of frailty and its underlying reasons in the present results might be different among the population who were born in the new era of China (e.g., people born in the 1990s experienced flourishing of China after the reform and opening-up policy).

The significant differences in lifestyle and their association with frailty were found between sexes among older adults in China. In contrast to men, less diverse diet and less intake of nutritious food, such as meat, fish/seafoods, dairy products, tea, and garlic, were found among older women. Age-related reduction of appetite might contribute to the less diverse diet among older women (7). Besides, the determinants of socioeconomic factors on eating habits should be considered. Although women had significantly less diverse diet, the milder influence of dietary diversity on the risk of frailty was found among women. Meanwhile, the less influence of income on the risk of frailty further evidenced adaptability of women to behavioral nutrition based on a relatively poor socioeconomic status. The highest percentage of current smokers, mainly men, was found in the population with incident pre-frailty. Cessation of tobacco use among the elderly should be further intensified.

By analyzing the patterns of physical activity, the present study found that the men pattern of activity was much similar to the sedentary lifestyle, whereas women did more high-intensive activities including housework/childcare and raising domestic animals. Compared with men, fewer older women spent time on reading, watching TV, or listening to the radio. The levels of education may contribute to the low utilization of media among women, and the beneficial effects of media among men might be resourced from the healthcare information acquired from these media. It was noteworthy that women did more high-intensive activities compared with men, but only a few of them did exercise. Additionally, the risk effect of labor work was found

TABLE 4 | Association among the types of physical activity, types of food intake and the risk of pre-frailty, frailty, and sex stratified.

Variables	Overall				Men				Women			
	Pre-frailty vs. non-frailty		Frailty vs. non-frailty		Pre-frailty vs. non-frailty		Frailty vs. non–frailty		Pre–frailty vs. non–frailty		Frailty vs. non–frailty	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Types of physical activity (Ref. <1 times/week)												
Radio/TV/reading	1.37 (0.90–2.08)	0.142	0.67 (0.48–0.92)	0.013	0.97 (0.52–1.82)	0.929	0.48 (0.29–0.82)	0.007	1.71 (0.97–3.04)	0.066	0.82 (0.54–1.24)	0.340
Playing cards	1.03 (0.74–1.45)	0.857	0.77 (0.54–1.10)	0.156	1.13 (0.73–1.74)	0.586	0.85 (0.51–1.41)	0.522	0.90 (0.52–1.57)	0.716	0.71 (0.42–1.20)	0.200
Social activity	0.91 (0.61–1.36)	0.646	0.71 (0.45–1.12)	0.141	1.22 (0.71–2.09)	0.474	0.57 (0.26–1.27)	0.170	0.70 (0.38–1.29)	0.254	0.72 (0.40–1.30)	0.275
Gardening/keeping a pet	1.04 (0.77–1.41)	0.793	0.51 (0.36–0.71)	<0.001	1.01 (0.68–1.51)	0.948	0.32 (0.19–0.54)	<0.001	1.10 (0.67–1.81)	0.715	0.79 (0.49–1.29)	0.351
Outdoor activity	0.72 (0.52–0.98)	0.039	0.54 (0.40–0.71)	<0.001	0.79 (0.50–1.25)	0.310	0.45 (0.29–0.70)	<0.001	0.66 (0.42–1.05)	0.077	0.64 (0.43–0.95)	0.027
Housework/childcare	0.87 (0.63–1.21)	0.415	0.49 (0.36–0.65)	<0.001	0.95 (0.65–1.38)	0.772	0.60 (0.41–0.88)	0.009	0.70 (0.35–1.41)	0.316	0.36 (0.22–0.58)	<0.001
Raising domestic animals	1.41 (1.03–1.93)	0.031	1.69 (1.25–2.29)	0.001	1.02 (0.66–1.56)	0.944	1.24 (0.78–1.96)	0.368	2.01 (1.25–3.23)	0.004	2.18 (1.42–3.33)	<0.001
Food intake (Ref. rarely)												
Meat												
Sometimes	1.28 (0.86–1.91)	0.221	0.79 (0.56–1.13)	0.194	1.15 (0.66–1.99)	0.631	0.70 (0.42–1.19)	0.189	1.55 (0.85–2.83)	0.151	0.89 (0.54–1.47)	0.660
Daily	1.23 (0.79–1.90)	0.357	0.90 (0.61–1.32)	0.590	1.12 (0.61–2.05)	0.708	0.86 (0.49–1.52)	0.610	1.43 (0.74–2.77)	0.290	0.97 (0.57–1.68)	0.927
Fish/seafoods												
Sometimes	0.91 (0.65–1.27)	0.591	1.20 (0.89–1.61)	0.243	1.27 (0.80–1.99)	0.311	1.38 (0.89–2.15)	0.150	0.60 (0.36–1.01)	0.053	1.02 (0.67–1.56)	0.915
Daily	0.76 (0.45–1.26)	0.283	0.77 (0.47–1.27)	0.307	0.70 (0.36–1.38)	0.308	0.60 (0.28–1.28)	0.184	0.80 (0.35–1.84)	0.595	0.93 (0.45–1.92)	0.842
Eggs												
Sometimes	1.02 (0.68–1.53)	0.925	1.02 (0.71–1.48)	0.903	1.01 (0.58–1.76)	0.965	1.06 (0.61–1.84)	0.837	1.02 (0.55–1.87)	0.960	1.02 (0.61–1.69)	0.948
Daily	1.16 (0.76–1.77)	0.488	1.07 (0.73–1.57)	0.725	0.98 (0.55–1.74)	0.936	0.84 (0.47–1.49)	0.549	1.44 (0.76–2.75)	0.263	1.45 (0.85–2.45)	0.170
Dairy												
Sometimes	0.86 (0.58–1.27)	0.455	0.79 (0.55–1.13)	0.200	1.05 (0.61–1.81)	0.855	0.94 (0.54–1.61)	0.808	0.85 (0.47–1.52)	0.586	0.69 (0.42–1.12)	0.132
Daily	0.74 (0.52–1.05)	0.093	0.53 (0.38–0.74)	<0.001	0.66 (0.41–1.05)	0.080	0.45 (0.28–0.73)	0.001	0.81 (0.46–1.42)	0.455	0.64 (0.39–1.03)	0.068
Legumes												
Sometimes	1.43 (1.02–2.02)	0.038	1.56 (1.15–2.12)	0.004	1.3 (0.82–2.06)	0.268	1.80 (1.14–2.85)	0.012	1.63 (0.96–2.74)	0.069	1.35 (0.88–2.07)	0.172
Daily	1.10 (0.72–1.70)	0.653	1.32 (0.89–1.95)	0.170	1.02 (0.57–1.84)	0.948	1.33 (0.74–2.41)	0.341	1.2 (0.62–2.32)	0.599	1.28 (0.73–2.23)	0.385
Fresh fruits/vegetables												
Sometimes	0.97 (0.67–1.39)	0.849	0.58 (0.42–0.79)	0.001	0.70 (0.44–1.13)	0.148	0.5 (0.32–0.79)	0.003	1.36 (0.76–2.45)	0.298	0.63 (0.41–0.98)	0.040
Daily	1.05 (0.66–1.67)	0.843	0.43 (0.28–0.67)	<0.001	0.69 (0.37–1.30)	0.249	0.51 (0.27–0.95)	0.034	1.76 (0.85–3.67)	0.128	0.39 (0.21–0.73)	0.004

(Continued)

TABLE 4 | Continued

Variables	Overall				Men				Women			
	Pre-frailty vs. non-frailty		Frailty vs. non-frailty		Pre-frailty vs. non-frailty		Frailty vs. non-frailty		Pre-frailty vs. non-frailty		Frailty vs. non-frailty	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Tea												
Sometimes	1.48 (0.91–2.41)	0.117	0.90 (0.55–1.46)	0.658	1.47 (0.74–2.93)	0.268	0.95 (0.46–1.96)	0.884	1.53 (0.74–3.16)	0.246	0.87 (0.44–1.71)	0.692
Daily	1.3 (0.97–1.74)	0.080	0.98 (0.74–1.29)	0.882	1.06 (0.72–1.56)	0.757	0.89 (0.61–1.30)	0.555	1.92 (1.19–3.08)	0.007	1.21 (0.79–1.85)	0.383
Garlic												
Sometimes	0.94 (0.69–1.29)	0.710	0.88 (0.65–1.18)	0.388	0.88 (0.58–1.36)	0.573	0.83 (0.54–1.28)	0.400	0.96 (0.59–1.56)	0.870	0.87 (0.57–1.32)	0.509
Daily	0.74 (0.52–1.03)	0.077	0.79 (0.58–1.09)	0.154	0.64 (0.40–1.01)	0.057	0.65 (0.41–1.05)	0.078	0.88 (0.52–1.49)	0.622	0.94 (0.6–1.48)	0.800
Pickled vegetables												
Sometimes	1.16 (0.83–1.61)	0.386	0.96 (0.71–1.31)	0.812	1.36 (0.87–2.12)	0.177	1.04 (0.66–1.64)	0.850	0.92 (0.55–1.52)	0.740	0.91 (0.59–1.41)	0.683
Daily	1.69 (1.19–2.41)	0.004	1.38 (0.98–1.95)	0.064	2.15 (1.33–3.48)	0.002	1.86 (1.12–3.07)	0.016	1.22 (0.71–2.11)	0.476	1.06 (0.65–1.72)	0.813

Adjusted for age, sex, education, household income, and multimorbidity.

among older women. Given the higher rate of sarcopenia among older women in contrast to men (5), it raised the concern that whether the excessive activity based on the relatively insufficient physiological reserve played adverse roles in the pathogenesis of frailty. Nascimento et al. reported the importance of exercise on the intervention of both sarcopenia and frailty (41). Combined with the current results, we recommended the avoidance of labor work and the increase of exercise among older women.

Collectively, the present study revealed the sex-specific evidence for the improvement of diet and physical activity among the elderly in China, which would supplement the existing policy and guidelines for healthy aging. The Chinese government previously released a detailed plan called "Healthy China Initiative (2019–2030)," which presented the recommendations on diet, physical activity, social support, and healthcare for healthy aging in detail (42, 43). Intake of meat, seafood, egg, milk, and legume was recommended by the Initiative. According to the present results, intake of fresh fruit and vegetables should be also recommended and the use of pickled vegetables should be reduced. As to physical activity, in addition to exercise and physical training recommended by the Initiative, benefits of activity in daily life, such as housework, gardening, and outdoor activity, were observed in the present study, which should be supplemented in the recommendations. Considering the lower socioeconomic levels of aging women in China compared with men, forces from the society, community, and family should take part in the support of aging women to modify their lifestyles and prevention from chronic diseases including frailty.

It has to be admitted that the present study has limitations. First, only self-reported frequency of food intake was recorded. Data of processing and cooking method and quantity of intake, which may alter the nutrients of the identical food, were unavailable in the present study. Lack of detailed data might be the reason because no significant association between the daily intake of meat and reduced risk of frailty was found in the present study. Second, data on diet and physical activity were collected by questionnaires, recall bias exists. Third, the data of outcomes (incident pre-frailty and incident frailty) were collected from the interviews of 2011, 2014, and 2018. The exact dates of outcomes were unavailable. Hence, the logistic regression models, instead of Cox regression models, were adopted in the present study. Fourth, multimorbidity was defined using self-reported data and its prevalence might be underestimated because of awareness. In a previous study, Herr et al. reported that around 50% of the population aged over 70 years had at least three comorbidities (26), while the prevalence of multimorbidity in the present study was 21.1%. The underestimated prevalence might be influenced the results on the association between multimorbidity and the risk of frailty. Lastly, subject to the observational feature, no causal conclusion could be made in the present study.

CONCLUSION

In conclusion, socioeconomic status and lifestyle were significantly associated with the incidence of frailty among

the elderly in China. Social and behavioral factors which should be improved varied between genders. Individualized strategy for the frailty prevention should consider the substantial sex disparity of socioeconomic status, lifestyle, and its association with frailty.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: https://opendata.pku.edu.cn/dataverse/CHADS.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee of Peking University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HYW designed the study, analyzed the data, interpreted the results, wrote the manuscript, and is study guarantor. MZ and XS interpreted the results and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Application of Muscle Thickness and Quality Measured by Ultrasound in Frailty Assessment in China

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To explore the correlation between Fried Frailty Phenotype (FFP) and the muscle thickness and quality of local muscle, and to provide a reasonable basis for the application of ultrasound measurement in the frailty assessment. A total of 150 people (age ≥ 65 years, 58 women, 92 men) were included from the First Hospital Affiliated to Nanjing Medical University. They were divided into Normal group (40 cases), Prefrailty group (69 cases) and Frailty group (41 cases). The thickness and the quality of local muscle were detected by ultrasound. Participants in the prefrailty group had a higher grayscale value of the vastus lateralis muscle, indicating the deterioration of muscle quality. At the frailty stage, the muscle thickness and quality of the vastus lateralis muscle and the anterior tibialis muscle decreased significantly compared with the normal and the prefrailty group. Pearson's correlation analysis also showed FFP was negatively correlated with muscle thickness and quality of the lower limbs. In multiple regression model, FFP was positively associated with gray value (Vastus lateralis muscle:$\beta = 0.457$, $p < 0.001$; Anterior tibialis muscle: $\beta = 0.220$, $p = 0.037$) and inversely associated with muscle thickness (Vastus lateralis muscle:$\beta = -0.973$, $p = 0.031$; Anterior tibialis muscle: $\beta = -4.551$, $p = 0.004$) in the frailty stage. Together, FFP was closely related to muscle thickness and quality, especially vastus lateralis muscle. Moreover, Muscle quality has deteriorated in the prefrailty stage, which is earlier than muscle thickness.

Keywords: Fried Frailty Phenotype (FFP), ultrasound, muscle thickness (MT), muscle quality, local muscle

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KEY POINTS

1. A rapid and accurate screening test is needed to assess frailty, as current assessments are complex and time-consuming.
2. Ultrasound can measure muscle thickness and quality simultaneously.
3. Fried Frailty Phenotype (FFP) was closely related to muscle thickness and quality, especially vastus lateralis muscle.
4. Muscle quality has deteriorated in the stage of prefrailty, which is earlier than muscle thickness.
5. Our findings highlight the practicability of ultrasonic measures of local muscle with frailty assessment.

INTRODUCTION

With the global aging and the improvement of people's living standards, frailty has gradually become a research hotspot in the field of geriatrics (1). Frailty is caused by a variety of factors, a clinical syndrome characterized by reduced strength, stamina, and reduced physical function that causes increased fragility in the individual and ultimately leads to fall, disability, and/or death (2). So far, various methods of frailty assessment have been used, but there is no unified standard and they are all complicated and time-consuming (3, 4).

Sarcopenia is often considered as an early manifestation of frailty, an important risk factor for accelerating the occurrence and development of frailty, and a core element of frailty (5). With the deepening of the research on sarcopenia, it has been reported that the speed of sarcopenia caused by aging is not consistent in all regions of the body (6). As a new tool for the evaluation of sarcopenia, ultrasound has the advantage of accurately evaluating the local muscle thickness of the body and the muscle quality simultaneously (7, 8). Muscle quality refers to the micro and macro changes in muscle structure and composition, as well as the muscle function transmitted per unit in muscle mass (9). At present, several studies have shown that the changes of muscle mass and muscle strength are inconsistent, indicating muscle quality may play an important role and is a reliable indicator of muscle strength (10, 11).

However, the relationship between local muscle thickness, muscle quality and frailty assessment is not clear. Therefore, we selected the same part of the anterior ulnar muscle and the vastus lateral muscle and anterior tibia muscle to detect their muscle thickness by ultrasound. Meanwhile, QLab software was used to analyze the gray value of the Region Of Interest (ROI). The purpose of this study was to investigate the correlation between Fried frailty assessment and the muscle thickness and muscle quality of anterior ulnar muscle, vastus lateralis muscle and anterior tibial muscle, and to provide a reasonable basis for the application of ultrasound measurement in the assessment of frailty.

MATERIALS AND METHODS

Study Participants

Data of patients hospitalized in the Department of Geriatrics Endocrinology from January 2020 to January 2021 were collected. A total of 150 inpatients were included in this study, including 92 men and 58 women. Their inclusion criteria were: (1) they were older than 65 years old; (2) they had the ability of independent activities and were in good general condition. Exclusion criteria:(1) patients with autoimmune diseases, musculoskeletal diseases, or thyroid dysfunction; (2) Patients with severe heart, liver and kidney function impairment or with tumor, severe infection and other diseases; (3) recent operation or serious external injury; (4) People who cannot move autonomously and suffer from mental illness; (5) exclude other endocrine diseases, such as the pituitary, adrenal, parathyroid and other diseases; (6) take sex hormones, glucocorticoids, thyroid hormones, antiepileptic drugs, antidepressants and other drugs that affect muscle metabolism. This clinical study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (No. 2019-SR-481).

Biochemical Analysis

Height and weight were measured by standard methods with participants wearing light clothing without shoes. Body mass index (BMI) was calculated as BMI (kg/m^2) = Weight (kg)/height^2 (m^2).

After overnight fasting, blood samples of participants were obtained and centrifuged at 4.0°C for 10 min at 1,000 rpm and subsequently analyzed. Plasma glucose was determined using the YSI 2300 STAT Plus glucose oxidase assay (Yellow Springs Instruments, Yellow Springs, OH, USA). Serum insulin was measured using a radioimmunoassay (EMD Millipore, Billerica, MA, USA). Serum triglycerides (TG) and cholesterol were analyzed using enzymatic methods with an automated platform (Roche Modular Diagnostics, Indianapolis, IN, USA). Serum triiodothyronine (FT3), thyroxine (FT4), and thyroid stimulating hormone (TSH) levels were measured using the Abbott AxSYM Immunoassay system (Abbott Laboratories, Abbott Park, IL, USA) with intra- and inter-assay coefficients of variation of $<$10% for all measurements.

Ultrasound Measurements

A B-mode ultrasound (Philips iU Elite, Bothell, WA, USA) with a linear transducer (5–12 MHz) was used to evaluate muscle thickness (MT) and muscle quality. When measuring the anterior ulnar muscle, MT was obtained on the anterior of the right forearm (at 30% proximal between the styloid process and the head of the radius) when the participants were in the supine position with their elbow extended, relaxed and their forearm supinated. When measuring the vastus lateralis muscle, the probe was placed at the junction of the greater trochanter of femur and the middle and lower third of the femur, with the long axis perpendicular to the long axis of femur, and the maximum thickness of the vastus lateralis muscle was measured. When measuring the anterior tibialis muscle, the probe was placed at the midpoint of the horizontal line between the lower edge of the patella and the lateral condyle of the fibula. The long axis of the probe was perpendicular to the long axis of the fibula to measure the thickest part of the anterior tibial muscle.

When measuring the muscle quality, select the same part of the muscle, adjust the inspection depth to 5 cm, freeze the image, analyze it with QLAB software, use the default 5 mm square sampling frame, avoid the blood vessels, obtain the region of interest (ROI), and then measure the gray value of ROI.

All measurements were performed by the same sonographer with 5 years of experience. All data were measured three times, and the average value was used for further analysis.

Depression and Nutritional Assessment

The severity of depressive mood was evaluated using the 30-item Geriatric Depression Scale (GDS-30) developed by Yesavage et al. (12). The GDS-30 was rater-administered in a standardized manner. All items in the GDS-30 are rated as 0 or 1; specifically, 1 = "No" and 0 = "Yes" for some items (1, 5, 7, 9, 15,

19, 21, 27, 29, 30) but 0 = "Yes" and 1 = "No" for the remaining items. Item scores are summed, resulting in a possible total score of 0–30. High scores represent more severe depression.

Nutritional status was evaluated by Mini Nutritional Assessment (MNA) composed of simple measurements and brief questions. Discriminant analysis was used to compare the nutritional status determined by the extensive nutritional assessment including complete anthropometric, clinical biochemistry and dietary parameters. The sum of the MNA score distinguishes between elderly patients with: 1. Adequate nutritional status (MNA > or = 24); 2. Malnutrition (MNA < 17; 3); 3. At risk of malnutrition (MNA between 17 and 23.5).

Frailty Measures

Frailty status was assessed at discharge with a modified version of the frailty phenotype by Fried (13) including unintentional weight loss, feelings of exhaustion, weakness (grip strength), gait speed, and independence in Activities of Daily Living (ADL) measured with the Katz Index (14). Weight loss and exhaustion relied on participant self-report. Grip strength was assessed by dynamometry, and walking speed was based on a 15-foot timed gait. Cut-off scores, as defined by Fried, were used for gait speed and grip strength.

The overall frailty status of the patient was assessed based on the above domains. Patients with problems in ≥ 3 domains were considered as frail and 1–2 domains were considered as pre-frail.

Ethical and Legal Considerations

The participants themselves gave their written informed consent to participate in the study and were informed that they could refuse to participate at any stage.

Statistical Analysis

Descriptive data are presented as the means ± SDs. The associations between Fried Frailty Phenotype (FFP) and muscle mass, muscle quality were examined using Pearson's correlation analysis. Comparison between multiple groups was performed by one-way ANOVA. Multivariate logistics regression analysis models were used to analyze muscle mass, muscle quality and the FFP using age, BMI data and so on as confounding variables. All statistical analyses were performed using SPSS V.20.0 (IBM Corp, Armonk, New York, USA), and $p < 0.05$ was considered statistically significant.

RESULTS

General Characteristics and Fried Frailty Phenotype of Participants

Table 1 shows the participant's demographic characteristics. The analysis included data from 150 older inpatients, of whom 92 were men and 58 were women. According to Fried diagnostic criteria, the patients in the three groups were divided into three groups: normal group (FFP 0 points), pre-frailty group (FFP 1–2 points), and frailty group (FFP 3 points). The average age of the patients in the three groups was over 65 years old. The mean GDS-30 scores in the frailty and pre-frailty groups were 9.17 ± 5.16 and 6.38 ± 5.99 points, respectively. The MNA scores of the three groups were within the range of adequate nutritional status.

TABLE 1 | Anthropometrics, depression assessment and Fried Frailty Phenotype (FFP) of the participants.

	Normal	Prefrailty	Frailty
n	**40**	**69**	**41**
Age (years)	72.77 ± 6.41	75.58 ± 8.32	85.38 ± 6.72$^{***\#\#\#}$
Weight (cm)	67.38 ± 6.74	66.27 ± 10.67	62.86 ± 12.20
Height (cm)	164.54 ± 8.26	164.71 ± 8.11	163.30 ± 7.21
BMI (kg/m2)	24.85 ± 3.27	24.44 ± 3.62	23.55 ± 4.33
HbA1c (%)	6.57 ± 1.20	6.69 ± 1.56	7.22 ± 2.40*
Glucose (mmol/L)	5.93 ± 1.51	5.78 ± 1.46	6.70 ± 2.43*
TC (mmol/L)	4.43 ± 1.24	4.42 ± 1.14	4.24 ± 1.13
TG (mmol/L)	1.32 ± 0.51	1.45 ± 0.69	1.32 ± 0.73
HDL-C (mmol/L)	1.23 ± 0.25	1.16 ± 0.32	1.14 ± 0.32
LDL-C (mmol/L)	2.57 ± 0.82	2.62 ± 0.83	2.51 ± 0.74
VD (ng/ml)	66.54 ± 24.02	52.42 ± 25.95*	48.65 ± 17.85***
FT3 (pmol/L)	4.0.70 ± 1.27	4.34 ± 0.82	3.76 ± 0.58$^{***\#\#}$
FT4 (pmol/L)	15.97 ± 2.01	16.34 ± 2.06	16.59 ± 3.18
TSH (mIU/L)	2.49 ± 1.51	2.64 ± 1.42	2.88 ± 2.20
Depression	5.07 ± 6.63	6.38 ± 5.99	9.17 ± 5.16**
MNA	29.88 ± 3.57	28.42 ± 4.39	28.33 ± 5.42
FFP	0	1.65 ± 0.48***	3.62 ± 0.50$^{***\#\#\#}$

*Variables are expressed as mean ± SD; BMI, body mass index; HAc1%, glycated hemoglobin; TC, cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FT3, triiodothyronine; FT4, thyroxine; TSH, thyroid stimulating hormone; MNA, Mini Nutritional Assessment; FFP, Fried Frailty Phenotype. *compared with normal; #compared with prefrailty. *P < 0.05; ** and ##P < 0.01; *** and ###P < 0.001.*

The age of the frailty group was significantly higher than that of the normal group. Compared with the normal group, weight, height, body mass index, lipid levels, TSH, MNA score of the frailty group and the pre-frailty group were not statistically significant. Vitamin D and FT3 in the frailty group were lower than those in the normal group. The HbA1c, fasting plasma glucose and depressed mood were higher than those of the normal group.

Local Muscle Thickness and Muscle Quality of Upper and Lower Extremities

All patients underwent ultrasonic detection of the thickness of the anterior ulnar muscle (**Figure 1A**), the vastus lateralis muscle (**Figure 1B**) and the anterior tibial muscle (**Figure 1C**), and placed the 5 mm square sampling frame in the corresponding intramuscular image and obtain the Region Of Interest (ROI). The gray value was analyzed by QLAB software to represent muscle quality (**Figures 1D–F**).

As shown in **Table 2**, at the stage of prefrailty, the muscle thickness of the three parts did not change significantly compared with the normal group, but the grayscale value of the vastus lateralis muscle increased significantly, indicating the deterioration of muscle quality. At the frailty stage, the muscle thickness and quality of the vastus lateralis muscle and the anterior tibialis muscle of the lower extremities

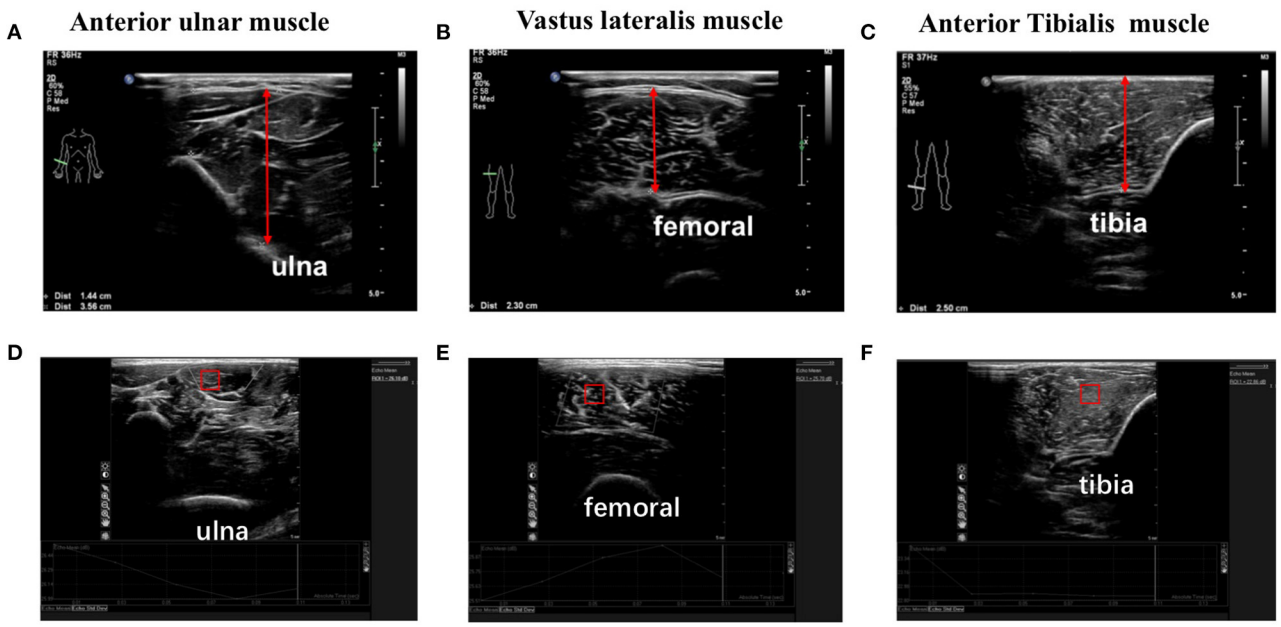

FIGURE 1 | The thickness and quality of anterior ulnar muscle, vastus lateralis muscle and anterior tibialis muscle were detected by ultrasound. **(A–C)** The thickness of anterior ulnar muscle, vastus lateralis muscle, and anterior tibialis muscle were detected by ultrasound; **(D–F)** The gray value of anterior ulnar muscle, vastus lateralis muscle and anterior tibialis muscle were analyzed by QLAB software to detect the muscle quality. Square sampling frame represents Region Of Interest (ROI).

decreased significantly compared with the normal group and the prefrailty stage, but the muscle thickness of the anterior tibialis muscle of the upper extremities did not change, only the muscle quality decreased significantly compared with the normal group.

Correlation Between FFP and Local Muscle Thickness and Muscle Quality

There was no correlation between FFP and anterior ulnar muscle thickness and muscle quality (**Figures 2A,D**), however, it was negatively correlated with muscle thickness and muscle quality of the lower limbs, especially vastus lateralis muscle. As shown in **Figure 2**, with the increase of FFP, the thickness of vastus lateralis muscle decreased ($R = -0.367$, $P < 0.0001$) and the gray value increased ($R = 0.413$, $p < 0.0001$) (**Figures 2B,E**). There was only weak correlation between FFP and anterior tibial muscle (thickness: $R = -0.192$, $p = 0.041$; gray value: $R = 0.190$, $p = 0.045$) (**Figures 2C,F**).

Multiple Logistics Regression Analysis of FFP, Local Muscle Thickness and Muscle Quality

Given the significant relationships between age, sex, BMI, glucose, Vitamin D, thyroid function and lipid metabolism and frailty, with FFP as the dependent variable and meaningful variables of univariate analysis as independent variables, multivariate logistics regression analysis was conducted (**Table 3**). The results indicated that FFP was positively associated with the gray value (Vastus lateralis muscle:$\beta = 0.158$, $p = 0.021$;Anterior Tibialis muscle:$\beta = 0.107$, $p = 0.042$) in the prefrailty stage, while positively associated with gray value (Vastus lateralis muscle:$\beta = 0.457$, $p < 0.001$; Anterior tibialis muscle: $\beta = 0.220$, $p = 0.037$) and inversely associated with muscle thickness (Vastus lateralis muscle:$\beta = -0.973$, $p = 0.031$; Anterior tibialis muscle: $\beta = -4.551$, $p = 0.004$) in the frailty stage. However, no correlation was found between FFP and muscle thickness and quality of anterior ulnar muscle. Moreover, in the frailty stage, FFP was positively associated with age ($\beta = 0.164$, $p = 0.019$) and negatively correlated with vitamin D ($\beta = -0.231$, $p = 0.036$) and FT3 ($\beta = -0.342$, $p = 0.023$).

TABLE 2 | Local muscle thickness and muscle quality in control group, Prefrailty group and Frailty group.

	Normal	Prefrailty	Frailty
Anterior ulnar muscle			
MT(cm)	3.44 ± 0.11	3.52 ± 0.55	3.13 ± 0.39
Grayscale value	21.05 ± 2.83	19.57 ± 4.05	22.90 ± 4.43$^{\#}$
Vastus lateralis muscle			
MT(cm)	1.55 ± 0.36	1.59 ± 0.36	1.28 ± 0.32$^{**\#\#}$
Grayscale value	25.11 ± 5.40	27.30 ± 3.50*	30.52 ± 6.37$^{**\#\#}$
Anterior Tibialis muscle			
MT(cm)	2.62 ± 0.27	2.56 ± 0.36	2.42 ± 0.38$^{**\#\#}$
Grayscale value	29.53 ± 3.92	28.47 ± 5.95	31.14 ± 3.58$^{**\#\#}$

*compared with normal; $^{\#}$compared with prefrailty. MT, muscle thickness *$P < 0.05$; **and $^{\#\#}P < 0.01$.

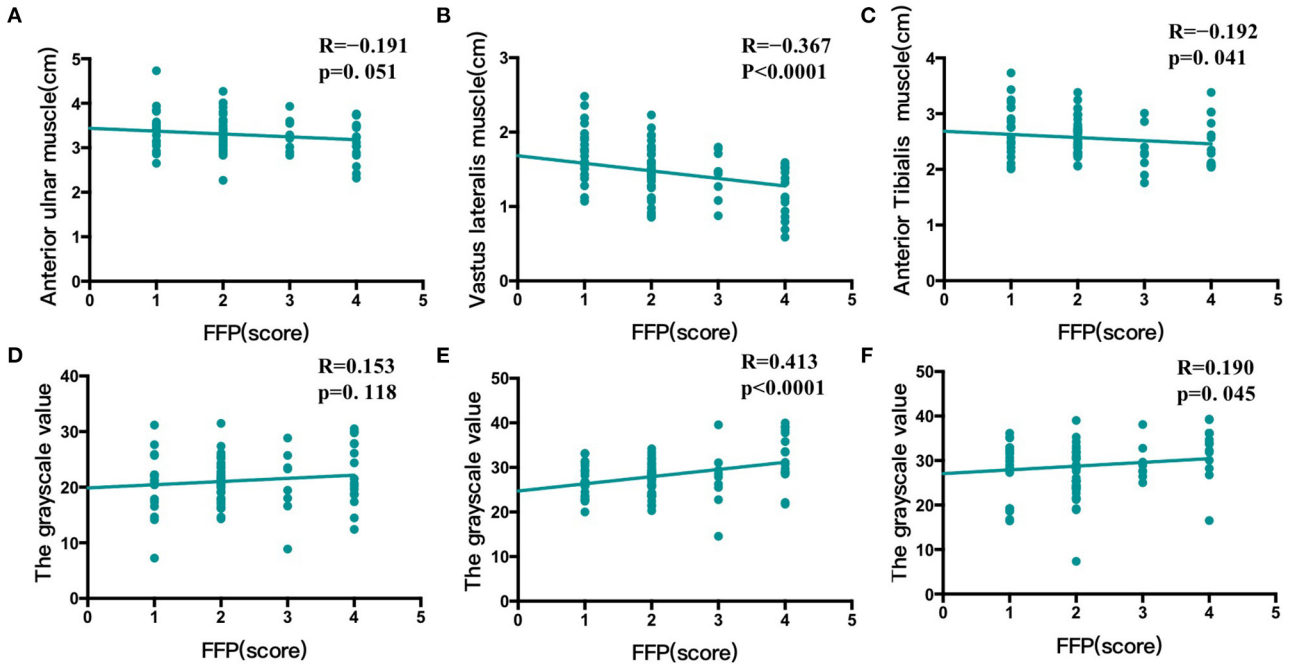

FIGURE 2 | Correlation between FFP and muscle thickness and quality of anterior ulnar muscle, vastus lateralis muscle and anterior tibialis muscle. **(A)** There was no correlation between fried frailty phenotype (FFP) and the thickness of anterior ulnar muscle **(B)** FFP was negatively correlated with the thickness of vastus lateralis muscle **(C)** FFP was negatively correlated with the thickness of anterior tibialis muscle **(D)** There was no correlation between FFP and the gray value of anterior ulnar muscle **(E)** FFP was positively correlated with the gray value of vastus lateralis muscle **(F)** FFP was positively correlated with the gray value of anterior tibialis muscle.

DISCUSSION

In our study, ultrasonic measurements of the thickness and grayscale of the anterior ulnar muscle of the upper extremity and the vastus lateralis and anterior tibialis muscle of the lower extremity were performed on people over 65 years of age.

Participants in the prefrailty group had a higher grayscale value of the vastus lateralis muscle, indicating the deterioration of muscle quality. At the frailty stage, the muscle thickness and quality of the vastus lateralis muscle and the anterior tibialis muscle decreased significantly compared with the normal and the prefrailty group.

Pearson's correlation analysis showed no correlation between FFP and anterior ulnar muscle thickness and quality, however, it was negatively correlated with muscle thickness and quality of the lower limbs. These results suggested that the FFP is closely related to the thickness and quality of lower limb muscles, especially vastus lateralis muscle.

The use of ultrasound technology has gradually extended from the initial cardiovascular diseases to musculoskeletal diseases in recent years. With the development of muscle ultrasound, it has been known that sarcopenia declines at inconsistent rates in different areas of the body. With aging, the abdominal muscles decline first, followed by the lower limbs, and finally the upper limbs. The muscle decline rate of the lower limbs is faster than that of the upper limbs; Sometimes the upper limb muscle mass of the elderly will even increase due to compensation. Considering that the nutritional status of the elderly people included in this study is basically normal, the degree of sarcopenia may not be serious. These may be the reason why there was no correlation between the anterior ulnar muscle and FFP and weak relation between anterior tibialis muscle and FFP (15). Longitudinal studies of follow-up and animal models may be needed to explore the deeper factors such as gene and mitochondrial function and so on in the future. Also, it has been reported that local muscle changes can improve the diagnosis of sarcopenia compared with systemic muscle (16). As we all know, sarcopenia is the core of frailty. Thus, the analysis of muscle changes in different parts of the body can not only detect sarcopenia in the early stage but also exercise the local muscles with a specific aim to improve the local muscle function, which is of great significance to improve frailty, prevent disability, maintain the health of the elderly and improve the quality of life.

At present, the muscle thickness measured by ultrasound has a good correlation with the muscle mass measured by dual-energy X-ray absorption as the gold standard (17, 18). More importantly, the advantage of ultrasound lies not only in the evaluation of muscle mass in various parts of the body but also in the accurate detection of muscle quality (19). Muscle quality, defined as muscle unit cross-sectional area of muscle strength, is closely related to muscle function and is becoming a prominent factor affecting physiological function in the elderly (20). With aging, muscle fibers become thinner, connective tissue increases, lipid droplets infiltrate, extracellular water increases, and protein breakdown increases. These changes suggest poor muscle quality. MRI and CT have been used to assess muscle

TABLE 3 | Multivariate logistics regression analysis of the effects of muscle thickness and muscle quality of Anterior ulnar muscle, Vastus lateralis muscle and Anterior Tibialis muscle on FFP.

	Frailty				Prefrailty			
	β	Wardχ^2	*p*-value	OR(95%CI)	β	Wardχ^2	*p*-value	OR(95%CI)
Age	0.164	5.493	**0.019**	1.179 (1.027, 1.352)	0.052	1.467	0.226	1.054 (0.968, 1.146)
BMI	0.032	0.056	0.814	1.033 (0.791, 1.347)	−0.055	0.431	0.511	0.946 (0.802, 1.116)
HbA1c	0.683	2.432	0.119	1.980 (0.839, 4.670)	0.485	2.549	0.110	1.623 (0.896, 2.943)
Glucose	−0.632	3.361	0.067	0.532 (0.271, 1.045)	−0.498	3.630	0.057	0.608 (0.364, 1.014)
VD	−0.231	4.380	**0.036**	0.971 (0.929, 1.015)	−0.027	1.704	0.192	0.974 (0.949, 0.998)
FT3	−0.342	0.182	**0.023**	0.711 (0.148, 3.414)	−0.262	0.728	0.394	0.769 (0.421, 1.405)
Depression	0.105	1.405	0.236	1.111 (0.934, 1.321)	0.066	1.435	0.231	1.068 (0.959, 1.190)
Anterior ulnar muscle								
MT	0.716	0.240	0.624	2.046 (0.116, 35.985)	0.138	0.044	0.834	1.148 (0.316, 4.164)
Grayscale value	0.074	0.341	0.559	1.077 (0.839, 1.383)	−0.068	1.017	0.313	0.934 (0.819, 1.066)
Vastus lateralis muscle								
MT	−0.973	0.296	**0.031**	0.378 (0.011, 12.555)	1.348	1.872	0.171	3.851 (558, 26.575)
Grayscale value	0.457	15.233	**0.000**	1.580 (1.256, 1.988)	0.158	5.344	**0.021**	1.171 (1.024, 1.340)
Anterior Tibialis muscle								
MT	−4.551	8.084	**0.004**	0.011 (0.000, 0.243)	−1.700	4.143	0.062	0.183 (0.036, 0.939)
Grayscale value	0.220	4.328	**0.037**	1.246 (1.013, 1.532)	0.107	3.470	**0.042**	1.113 (0.994, 1.246)

Fried Frailty Phenotype (FFP) as the dependent variable and meaningful variables of univariate analysis as independent variables. Adjustment for age, BMI, HbA1c, Glucose, VD, FT3 and Depression; β standardized coefficient. Bold values are statistically significant ($p < 0.05$).

quality by determining fat infiltration into muscle and utilizing muscle attenuation (21). Echo-intensity measured by ultrasound can indicate lipid droplets infiltration and fibrosis in non-contractile tissues (22). Based on this information, the muscle quality was judged. The greater the value of ultrasonic echo intensity, the worse the muscle quality was suggested. Muscle quality is closely related to muscle strength and function and is a reliable indicator for early reflection of sarcopenia. In recent years, more and more studies have confirmed that the muscle thickness measured by ultrasound is closely related to muscle mass and strength, and it shows potential as a screening tool for frailty in older adults (23). Furthermore, in this study, we found that muscle thickness of the upper limb was not associated with FFP, while muscle thickness and quality of the vastus lateralis muscle were closely associated with FFP, and the muscle quality has deteriorated in the stage of prefrailty, which is earlier than the change of muscle thickness.

The pathogenesis of frailty is complicated, including genes and races, decreased exercise of the elderly, decreased protein intake and synthesis, changes in hormone levels, immunity, cell apoptosis and changes in the microenvironment, impaired mitochondrial function, and mental and psychological factors (24–27). Therefore, we have also conducted some clinical indicators, depression and frailty studies, then we found that in the frailty stage, blood glucose increased, vitamin D, FT3 levels significantly decreased, and depression scores increased, but had nothing to do with lipid. These results suggested that vitamin D supplementation is necessary for the elderly, thyroxine supplementation is necessary for patients with hypothyroidism, and psychological counseling is carried out to relieve depression.

There were certain limitations to this study. For example, since the better physical function is associated with improvement of frailty, we believe that being able to add physical activity is beneficial to analyze the risk factors for frailty. We will acquire data on activity levels, such as with the International Physical Activity Questionnaire (IPAQ). Second, due to the relatively high sample size, we got a small correlation between FFP and muscle thickness and quality of anterior tibialis muscle, more evidence will be needed to confirm this correlation. Finally, another limitation was the lack of interventions and follow-up due to their time-consuming nature. These shortcomings merit further study.

In conclusion, our study demonstrated that muscle quality has deteriorated in the stage of prefrailty, which is earlier than the decrease of muscle thickness. Moreover, FFP was closely related to local muscle thickness and quality, especially vastus lateralis muscle of the lower limbs. Together, our findings highlight the significance and practicability of ultrasound examination of local muscle with frailty assessment.

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

The studies involving human participants were reviewed and approved by Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (No. 2019-SR-481). The

patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SL, LL, and HS: conceived the study, analyzed the data, and wrote the manuscript. XC, SC, SZ, and WL: subject recruitment and data collections. RL and GD: helped develop the design, gave critical input on interpretation of the results, and critically revised the manuscript draft. All authors contributed to the writing of the final manuscript draft and approved the version to be published.

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Risk Factors for the Onset of Frozen Shoulder in Middle-Aged and Elderly Subjects Within 1 Year of Discharge From a Hospitalization That Involved Intravenous Infusion: A Prospective Cohort Study

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Aim: To investigate the incidence of frozen shoulder and risk factors for the onset of frozen shoulder in middle-aged and elderly subjects within 1 year of discharge from a hospitalization that involved intravenous infusion in Zhangjiagang Second People's Hospital.

Methods: A total of 1,900 subjects who were discharged from a hospitalization that involved intravenous infusion in the hospital between May 2020 and September 2020 met the inclusion criteria for this study: 950 subjects had a mean daily duration of intravenous infusion $\leq$2 h (low exposure) and 950 subjects had a mean daily duration of intravenous infusion $\geq$3 h (high exposure). Subjects were followed up by telephone at 6 months $\pm$ 1 week and 12 months $\pm$ 1 week after discharge the incidence of frozen shoulder.

Results: The cumulative incidence rate of frozen shoulder within 1 year of discharge was 5.2%. Multivariate logistic regression analysis revealed the risk of frozen shoulder was higher in subjects with a mean daily duration of intravenous infusion $\geq$3 h compared to $\leq$2 h (OR = 3.082, 95% CI 1.919–4.949, $P < 0.001$); subjects hospitalized for 11–30 days had a higher risk of frozen shoulder compared to those hospitalized for 10 days or less (OR = 6.836, 95%CI 4.363–10.709, $P < 0.001$); subjects who were overweight/obese (BMI $\geq$ 25 kg/m^2) had a higher risk of frozen shoulder compared to those of normal weight (BMI 18.5–24.9 kg/m^2) (OR = 2.166, 95%CI 1.376–3.410, $P = 0.001$); subjects in the 56–70-year-old age group had a higher risk of developing frozen shoulder compared to those in the 40–55-year-old age group (OR = 1.977, 95%CI 1.154–3.387, $P = 0.013$); diabetes increased the risk of frozen shoulder (OR = 3.009, 95%CI 1.826–4.959, $P < 0.001$). The 71–85 years old age group and hypertension were statistically significant in univariate analysis but not in multivariate analysis ($P > 0.05$).

Conclusion: Compared with middle-aged and elderly in the general population, middle-aged and elderly subjects who received intravenous infusion during a hospitalization

had a higher cumulative incidence rate of frozen shoulder within 1 year after discharge. Independent risk factors for the onset of frozen shoulder included mean daily duration of intravenous infusion ≥3 h, length of hospital stay 11–30 days, BMI ≥ 25 kg/m^2, age 56–70 years, and diabetes.

Keywords: frozen shoulder, hospitalized patients, intravenous fluid, risk factors, cohort study

INTRODUCTION

Frozen shoulder is a common clinical disorder. In addition to pain, frozen shoulder can cause a gradual reduction in the range of motion of the shoulder joint, which seriously impacts all areas of an affected individual's work and life. Globally, the incidence of frozen shoulder is estimated at 2–5% (1). In 1934, Codman introduced the term "frozen shoulder" (2). In 1945, Neviaser named the condition "adhesive capsulitis" (3). In 2011, the American Society of Shoulder and Elbow Surgeons (ASES) (4) defined frozen shoulder as: "a morbid state of the shoulder joint in which both active and passive mobility of the shoulder joint are limited. Except for the possibility of osteopenia or calcific tendinitis, there is no obvious change in the glenohumeral joint on X-ray."

Frozen shoulder is a self-limiting condition. The course of disease is generally between 2 and 3 years, but 50–70% of patients will have varying degrees of shoulder pain and limited mobility for a longer period of time (5, 6). Common interventions for frozen shoulder include physical therapy, acupuncture, manipulation, orally administered medications, local steroid injection, manual release under anesthesia, and arthroscopic capsular release (7). These approaches may be successful in the short-term; however, symptoms such as shoulder pain and limited mobility gradually worsen with time (1, 8). There is no cure for frozen shoulder, as there is no recognized effective treatment; therefore, research should focus on identifying risk factors for frozen shoulder, which will broaden knowledge about prevention and treatment and reduce the incidence of frozen shoulder.

The etiology of the frozen shoulder has not been fully understood. The Upper Limb Committee of the International Society of Arthroscopy, Knee Surgery and Orthopedic Sports Medicine (ISAKOS) classify frozen shoulder as primary (idiopathic) or secondary (shoulder trauma [fracture, dislocation, and soft tissue injury]; non-traumatic osteoarthritis, rotator cuff injury, calcific tendinitis, prolonged immobilization of the shoulder joint after surgery, injury to the cervical spine or brachial plexus) (6, 9, 10). Risk factors for primary frozen shoulder include diabetes, Dupuytren's contracture, thyroid disease, myocardial infarction, and Parkinson's disease (1). In other studies, the incidence of frozen shoulder has been associated with occupational factors, whereby individuals working at high altitudes, handling heavy objects and performing manual labor are more likely to suffer from frozen shoulder (11).

In our acupuncture department, we treat a large number of patients with frozen shoulder each year. While obtaining routine medical history from our patients, we found that some patients had been hospitalized and received intravenous infusion prior to experience frozen shoulder, and they had shoulder pain and limited mobility for some time after discharge without obvious predisposing factors. A previous report identified prolonged post-operative intravenous infusion as a risk factor for frozen shoulder in patients who underwent neurosurgery (12). Previously, in a preliminary study that included small sample size, we found that the duration of intravenous infusion in inpatients was associated with the incidence of frozen shoulder. The objective of the present study was to investigate the incidence of frozen shoulder and risk factors for the onset of frozen shoulder in middle-aged and elderly subjects within 1 year of discharge from a hospitalization that involved intravenous infusion in the Zhangjiagang Second People's Hospital. Findings should contribute to the development of strategies to prevent the onset of frozen shoulder after hospitalization with intravenous infusion.

MATERIALS AND METHODS

Study Design

This single-center, prospective cohort study was conducted in compliance with the Declaration of Helsinki (13). The research protocol was reviewed by the Ethics Committee of Zhangjiagang Second People's Hospital (approval number: ZEY−2020007), and was registered in the Chinese Clinical Trial Registry, ChiCTR (http://www.chictr.org.cn; registration number: ChiCTR2000031862). In this study, the exposure was intravenous infusion, which uses the principles of atmospheric pressure and hydrostatic pressure to infuse a large amount of sterile fluid, electrolytes, and/or drugs into the body. The outcome was incidence of frozen shoulder. The mean daily duration of intravenous infusion was calculated as total duration of intravenous infusion during hospitalization divided by the number of hospitalization days. According to our previous unpublished study, subjects were stratified based on mean daily duration of intravenous infusion as high exposure (mean daily duration of intravenous infusion ≥3 h) or low exposure (mean daily duration of intravenous infusion ≤2 h).

Sample Size Calculation

PASS 11 software was used to estimate the sample size according to the relative risk (RR) of the outcome of the two groups of subjects that underwent intravenous infusion. We conducted a preliminary study in middle-aged and elderly subjects who were discharged from a hospitalization that involved intravenous infusion. Findings showed that the incidence of frozen shoulder was 6.7% in the high-exposure group and 3.3% in the low-exposure group, with an RR of 2.03. The present study included an equal number of subjects in the low and high exposure groups.

With $\alpha = 0.05$ and power 1-$\beta = 0.9$, the effective sample size for each group was calculated as $n = 862$. Based on clinical experience, we expected a 10% drop-out rate; therefore, the effective sample size for each group was calculated as $n = 950$.

Study Subjects

Subjects who were discharged from a hospitalization that involved intravenous infusion in the Second People's Hospital of Zhangjiagang City, Jiangsu Province, China between May 2020 and September 2020 were eligible for this study. Inclusion criteria were: (1) subjects discharged from a hospitalization that involved intravenous infusion; (2) subjects aged 40–85 years; (3) subjects hospitalized for 1–30 days; (4) subjects signed an informed consent form upon discharge and agreed to post-discharge follow up. Exclusion criteria were: (1) subjects aged <40 years or >85 years; (2) subjects hospitalized for >30 days; (3) subjects admitted to hospital due to trauma-induced shoulder pain and dysfunction, such as shoulder sprain, fracture, dislocation, rupture of the supraspinatus tendon, etc. (4) subjects who had frozen shoulder before admission and had recovered, or had frozen shoulder at admission and during hospitalization; (5) subjects who had undergone craniocerebral or other neurosurgical procedures before admission or during hospitalization, or suffered from intracranial lesions etc., and had poor recovery after discharge, resulting in decreased muscle strength of the neck and shoulder (muscle strength ≤ grade 4), causing limited activity of the shoulder joint; (6) subjects who underwent surgery on the shoulder, neck, chest, and other parts that would later lead to stiffness and adhesion of the soft tissue around the shoulder joint; (7) subjects with mental disorders, such as dementia, psychiatric diagnosis, and intellectual retardation etc, or who could not clearly express themselves for other reasons; (8) subjects who were unwilling to sign the informed consent form or expressly stated that they would not comply with follow-up.

Outcome Measure

The primary endpoint was the incidence of frozen shoulder within 1 year of discharge from a hospitalization that involved intravenous infusion. The secondary endpoint was the identification of risk factors for the onset of frozen shoulder following discharge from a hospitalization that involved intravenous infusion.

Data Collection

We included subjects in order of discharge until we met the required sample size for each group. During the period we included a total of 1,900 subjects meeting the criteria. There were 950 cases in each group of exposure group and control group. The hospital records of included subjects were reviewed. Demographic characteristics (gender, age, body mass index [BMI], education, work status) and clinical characteristics (diabetes, hypertension, surgery, length of stay, mean daily duration of intravenous infusion) were recorded.

Follow-up was calculated from the day of hospital discharge. Subjects were followed-up by telephone at 6 months ± 1 week and 12 months ± 1 week after hospital discharge by specially trained staff. Subjects were asked whether they had shoulder pain and limited mobility. Subjects who reported shoulder pain and limitation of activities were asked whether there were any predisposing factors such as shoulder joint trauma or central and peripheral nerve injury. Subjects with no predisposing factors were instructed to attend the hospital for a follow-up visit, where frozen shoulder was diagnosed based on criteria reported in the literature (9, 14, 15). If a subject clearly stated that there were no predisposing factors and they refused to come to the hospital for examination, shoulder pain, and limited activity were considered unrelated to frozen shoulder, and follow-up ended.

At the follow-up hospital visit, an experienced orthopedic surgeon asked the subjects about their medical history and conducted a physical examination. X-ray, MRI, or other examinations may have been performed to exclude other joint and soft tissue disorders such as acromioclavicular arthritis, rheumatoid arthritis, septic arthritis, supraspinatus tendonitis, subacromial bursitis or biceps long head tendonitis; bone structural abnormalities such as osteonecrosis, primary and metastatic tumors or Paget's disease; neck lesions such as cervical spondylosis or thoracic outlet syndrome; or shoulder pain caused by visceral lesions such as upper lung tumor, esophagitis, myocardial infarction, digestive tract ulcers, or cholecystitis. This procedure screened out subjects who did not meet the diagnostic criteria for frozen shoulder, those with frozen shoulder were included in the analysis.

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 software. Multiple imputation was used to handle missing data (16). Categorical variables were reported as number of cases (%) and compared with the χ^2 test. Rate difference and corresponding 95% confidence intervals (95% CIs) were calculated with the Wilson method. The associations between relevant risk factors and the onset of frozen shoulder were explored with binary logistic regression analysis. The dependent variable, frozen shoulder, was binary (not occur = 0; occur = 1), and the independent variables were binary or ordered multi-category. Binary variables were: mean daily duration of intravenous infusion (≤2 h = 0; ≥3 h = 1), gender (male = 0; female = 1), work status (no = 0; yes = 1), hypertension (no = 0; yes = 1), diabetes (no = 0; yes = 1), surgical history (no = 0; yes = 1), and length of hospital stay (≤10 days = 0, 11–30 days = 1). Ordered multi-category variables were: age (40–55 years = 1; 56–70 years = 2; 71–85 years = 3), BMI (18.5–24.9 kg/m^2 = 1; <18.5 kg/m^2 = 2; ≥25 kg/m^2 = 3), and education (primary school and below = 1; middle school = 2; university and above = 3). Potential risk factors were identified with univariate analysis. Factors with $P < 0.05$ were recruited into multivariate logistic regression analysis. Odds ratios (OR) with 95% CIs were calculated. $P < 0.05$ was considered statistically significant.

RESULTS

Study Subjects

A total of 5,201 consecutive subjects who were discharged from the Second People's Hospital of Zhangjiagang City, Jiangsu Province, China between May 1, 2020 and September 25, 2020

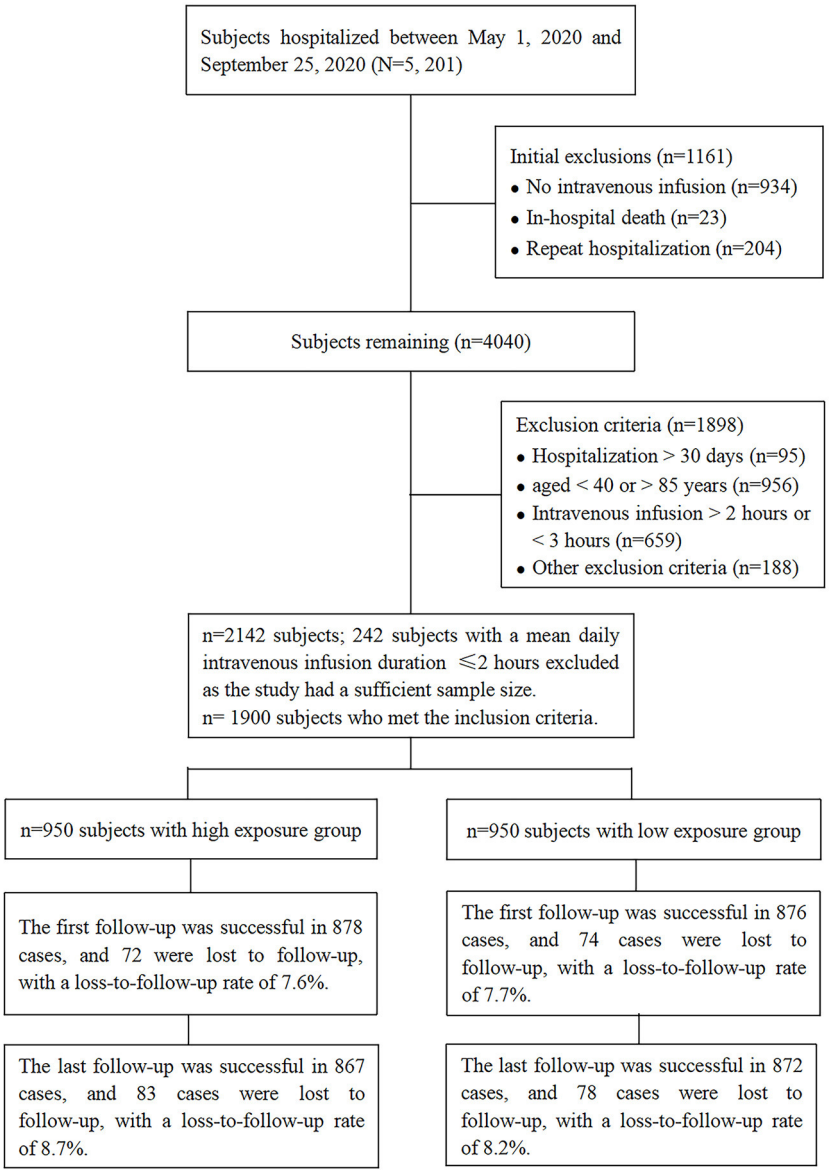

FIGURE 1 | Study flow chart.

were screened to determine their eligibility for inclusion in this study. Among these, 4,267 subjects received an intravenous infusion, and 2,125 patients were excluded as they met the study's predefined exclusion criteria. Subjects were recruited until the required sample size for each group was met. Among eligible subjects, 242 subjects were excluded after the sample size for the low exposure group was met. Finally, the study included 1,900 subjects: 950 subjects with a mean daily duration of intravenous infusion ≤2 h (low exposure) and 950 subjects with a mean daily duration of intravenous infusion ≥3 h (high exposure). Overall, 78 (8.2%) subjects with a mean daily duration of intravenous infusion ≤2 h (low exposure) and 83 (8.7%) subjects with a mean daily duration of intravenous infusion ≥3 h (high exposure) were lost to follow-up, with no significant difference in lost to follow-up rates between subjects with low and high exposure to intravenous infusion (RD = 0.005, 95% CI −0.020–0.031, P = 0.680) (**Figure 1**). Subjects' baseline demographic and clinical characteristics stratified by mean daily duration of intravenous infusion are summarized in **Figure 2**.

Incidence of Frozen Shoulder

During follow-up, a total of 98 subjects had frozen shoulders, for a cumulative incidence rate of 5.2%: 31 subjects with a mean daily duration of intravenous infusion ≤2 h were diagnosed with frozen shoulder, for a cumulative incidence rate of 3.3%; 67 subjects with a mean daily duration of intravenous infusion ≥3 h

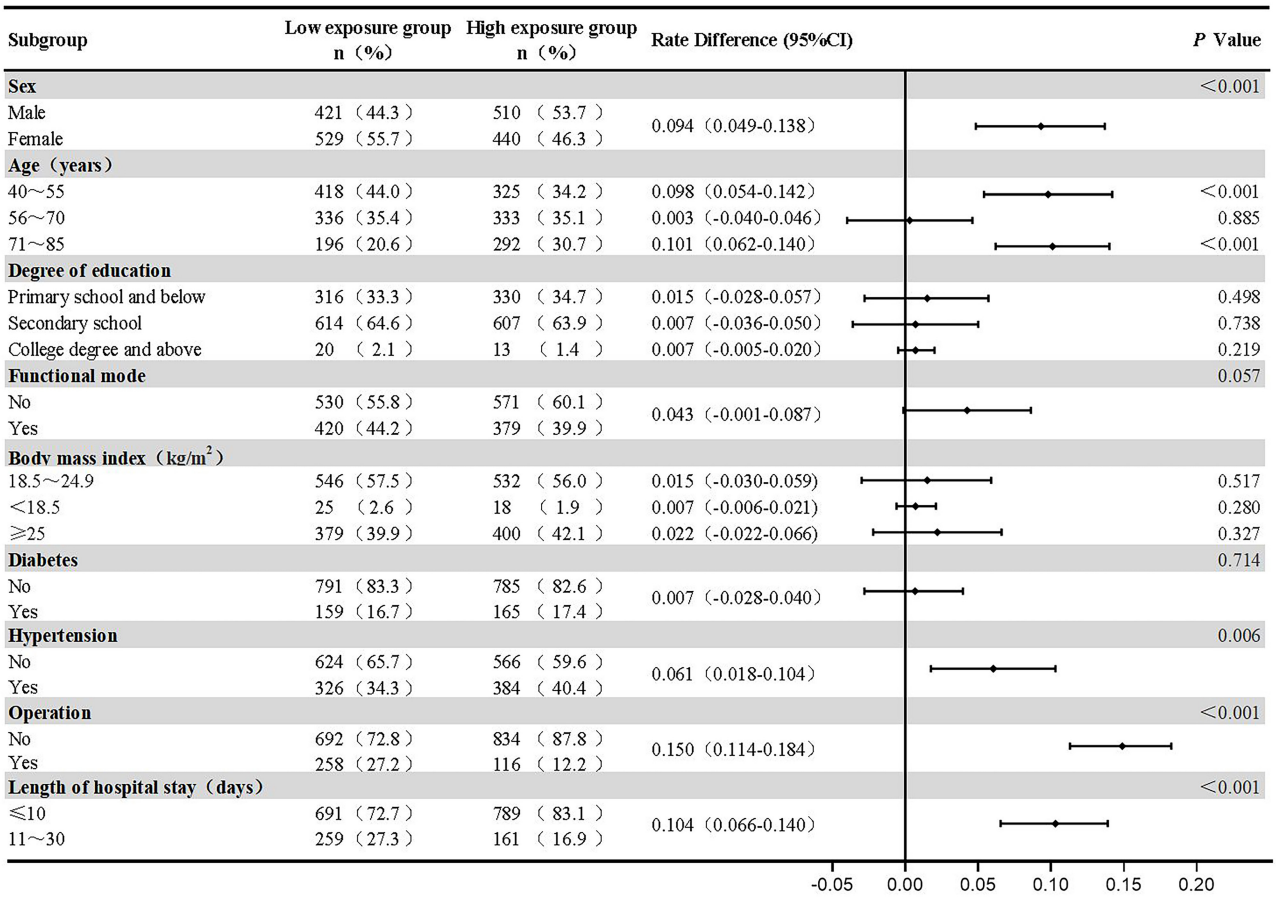

FIGURE 2 | Subjects' baseline demographic and clinical characteristics stratified by mean daily duration of intravenous infusion.

were diagnosed with frozen shoulder, for a cumulative incidence rate of 7.1% (RR = 2.15).

At the first follow-up, 79 subjects reported shoulder pain (n = 29, mean daily duration of intravenous infusion ≤2 h; n = 50 mean daily duration of intravenous infusion ≥3 h), and 65 subjects were diagnosed with frozen shoulder (n = 20, mean daily duration of intravenous infusion ≤2 h; n = 45 mean daily duration of intravenous infusion ≥3 h), for an incidence rate of 3.4%, and accounting for 66.3% of the cumulative cases.

At the last follow-up, 64 subjects reported shoulder pain (n = 23, mean daily duration of intravenous infusion ≤2 h; n = 41 mean daily duration of intravenous infusion ≥3 h), and 33 subjects were diagnosed with frozen shoulder (n = 11, mean daily duration of intravenous infusion ≤2 h; n = 22 mean daily duration of intravenous infusion ≥3 h), accounting for 33.7% of the cumulative cases.

Univariate Analysis

Univariate analysis revealed significant associations between mean daily duration of intravenous infusion, length of hospital stay, BMI, age, diabetes, and hypertension and the onset of frozen shoulder ($P < 0.05$). There were no significant associations between subjects' gender, education, work status, and surgery and the onset of frozen shoulder (**Figure 3**).

Multivariate Analysis

Multivariate analysis revealed longer mean daily duration of intravenous infusion, longer length of hospital stay, BMI ≥ 25 kg/m^2, age 56–70 years, and diabetes were independent risk factors for the onset of frozen shoulder in middle-aged and elderly subjects within 1 year of discharge from a hospitalization that involved intravenous infusion.

The Hosmer-Lemeshow goodness of fit index for the multivariate logistic regression model was good (P = 0.426). The model could correctly classify 95.2% of the predicted values. The model sensitivity was 6.1%, specificity was 100%, positive predictive value was 100%, and negative predictive value was 95.1%.

Multivariate logistic regression analysis revealed the risk of frozen shoulder was higher in subjects with a mean daily duration of intravenous infusion ≥3 h compared to ≤2 h (OR = 3.082, 95% CI 1.919–4.949, $P < 0.001$); subjects hospitalized for 11–30 days had a higher risk of frozen shoulder compared to those hospitalized for 10 days or less (OR = 6.836, 95%CI 4.363–10.709,

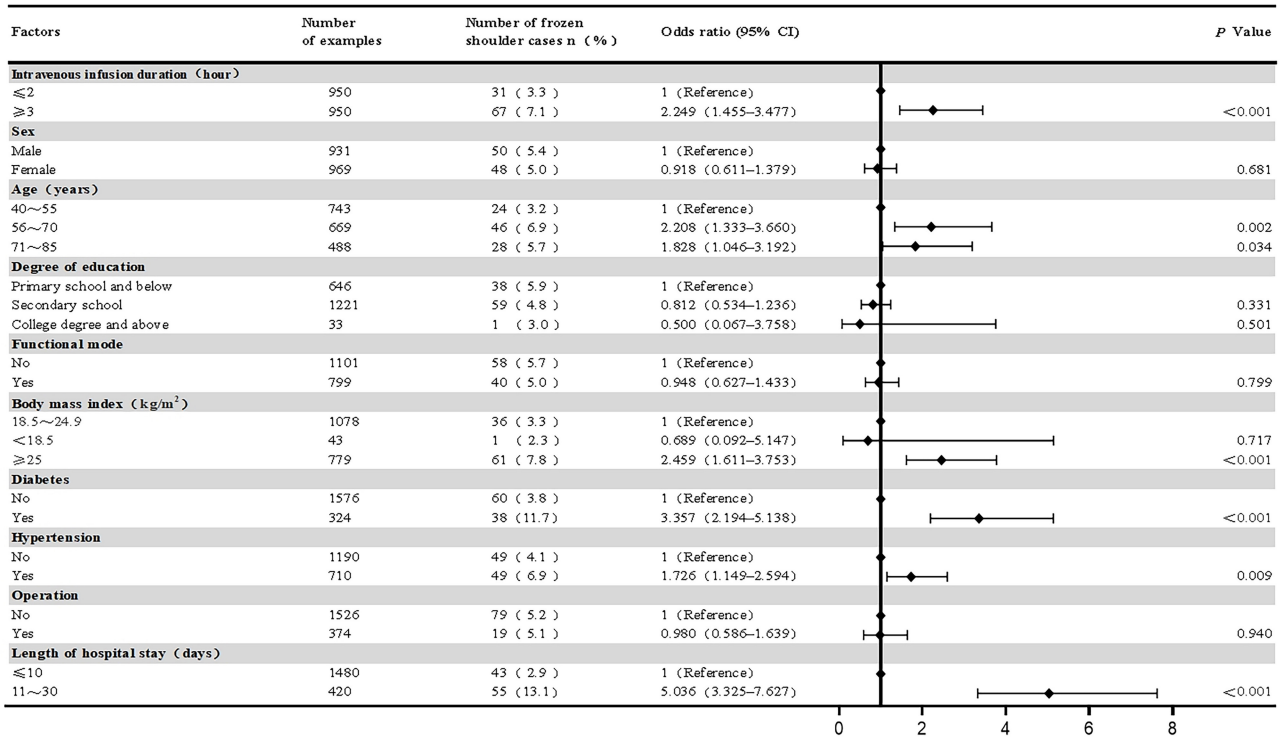

FIGURE 3 | Univariate binary logistic regression analysis on the risk of frozen shoulder in study subjects.

$P < 0.001$); subjects who were overweight/ obese (BMI $\geq$ 25 kg/m^2) had a higher risk of frozen shoulder compared to those of normal weight (BMI 18.5–24.9 kg/m^2) (OR = 2.166, 95%CI 1.376–3.410, $P = 0.001$); subjects in the 56–70-year-old age group had a higher risk of developing frozen shoulder compared to those in the 40–55-year-old age group (OR = 1.977, 95% CI 1.154–3.387, $P = 0.013$); diabetes increased the risk of frozen shoulder (OR = 3.009, 95% CI 1.826–4.959, $P < 0.001$). The 71–85 years old age group and hypertension were statistically significant in univariate analysis but not in multivariate analysis ($P > 0.05$) (**Figure 4**).

DISCUSSION

This study investigated the incidence of frozen shoulder and risk factors for the onset of frozen shoulder in middle-aged and elderly subjects within 1 year of discharge from a hospitalization that involved intravenous infusion. Findings showed the cumulative incidence rate of frozen shoulder within 1 year of discharge was 5.2%, with frozen shoulder within 6 months of discharge accounting for 66.3% of the cumulative cases. Independent risk factors for the onset of frozen shoulder in middle-aged and elderly subjects who were discharged from a hospitalization that involved intravenous infusion included mean daily duration of intravenous infusion $\geq$3 h, length of hospital stay 11–30 days, BMI $\geq$ 25 kg/m^2, age 56–70 years, and diabetes.

The incidence of frozen shoulder among the middle-aged and elderly subjects included in this study was higher than previously reported for the general population. In Europe and the US, frozen shoulder affects an estimated 2% of the general population, with a cumulative incidence of 2.4 cases per 1,000 person-years (17); in the UK, the annual incidence of frozen shoulder in the general population is ∼1.4 per 1,000 individuals (18); and in the US, the 1-year prevalence of frozen shoulder in individuals aged >65 years is 0.35% (19). In China, intravenous infusion is the most common mode of administration of medications, nutrients and fluids in inpatients; in 2016, 93.1% of inpatients in urban hospitals in China received intravenous medication administration (20). Complications associated with establishing an intravenous route for administering therapy (infiltration, hematoma, air embolism, phlebitis, extravascular drug administration, intraarterial injection) have been well-documented (21); however, reports on the long-term sequelae of intravenous infusion are scarce.

In the present study, mean daily duration of intravenous infusion and length of hospital stay were independent risk factors for the onset of frozen shoulder in middle-aged and elderly subjects within 1 year of discharge from a hospitalization that involved intravenous infusion. Patients must temporarily limit upper extremity activities during intravenous infusion. A long duration of intravenous infusion and prolonged hospital stay will cause substantial limitations on upper extremity activities, increasing the incidence of frozen shoulder. A study in patients

Factors	Number of examples	Number of frozen shoulder cases n (%)	Odds ratio (95% CI)	*P* Value
Intravenous infusion duration (hour)				
≤2	950	31 (3.3)	1 (Reference)	
≥3	950	67 (7.1)	3.082 (1.919–4.949)	<0.001
Age (years)				
40∼55	743	24 (3.2)	1 (Reference)	
56∼70	669	46 (6.9)	1.977 (1.154–3.387)	0.013
71∼85	488	28 (5.7)	1.276 (0.696–2.339)	0.431
Body mass index (kg/m^2)				
18.5∼24.9	1078	36 (3.3)	1 (Reference)	
<18.5	43	1 (2.3)	0.740 (0.095–5.740)	0.773
≥25	779	61 (7.8)	2.166 (1.376–3.410)	0.001
Diabetes				
No	1576	60 (3.8)	1 (Reference)	
Yes	324	38 (11.7)	3.009 (1.826–4.959)	<0.001
Hypertension				
No	1190	49 (4.1)	1 (Reference)	
Yes	710	49 (6.9)	0.958 (0.594–1.547)	0.862
Length of hospital stay (days)				
≤10	1480	43 (2.9)	1 (Reference)	
11∼30	420	55 (13.1)	6.836 (4.363–10.709)	<0.001

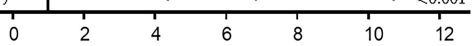

FIGURE 4 | Multivariate binary logistic regression analysis on the risk of frozen shoulder in study subjects.

who had surgical treatment for sub-arachnoid hemorrhage reported the incidence of frozen shoulder at 6 months of follow-up was 25.3%, and the development of frozen shoulder was associated with duration of post-operative intravenous infusion (12). Consistent with this, patients undergoing breast surgery and elderly patients with predisposed joint disease develop frozen shoulder following long periods of immobilization (22). The ISAKOS Upper Limb Committee proposed that joint capsule contracture after long-term immobilization of the shoulder joint and muscle tension around the shoulder joint can cause frozen shoulder (9).

Accumulating evidence suggests that diabetes and hypertension are risk factors for the onset of frozen shoulder (1, 23, 24). Specifically, frozen shoulder occurs 2–5 times more frequently in individuals with diabetes compared to those without (25, 26). In the present study, middle-aged and elderly subjects with diabetes had an increased risk of developing frozen shoulder within 1 year of discharge from a hospitalization that involved intravenous infusion, with an OR of 3.009. There was a significant association between hypertension and the onset of frozen shoulder on univariate analysis ($P = 0.009$); however, hypertension was not an independent risk factor for frozen shoulder on multivariate analysis ($P = 0.862$). Evidence suggests that the incidence of hypertension increases with age and in subjects with diabetes, implying an interaction between hypertension and age and diabetes. Accordingly, we performed *ad-hoc* analyses. Consistency testing of our data using SPSS 21.0 software showed that the OR values for hypertension and frozen shoulder in subjects aged 40–55, 56–70, and 71–85 years, were 1.775, 1.711, and 1.144, and the incidence of frozen shoulder tended to decrease with increasing age, indicating that age was an effect modifier for hypertension. The OR values for hypertension and frozen shoulder in subjects with no diabetes or diabetes were 1.445 and 0.856, respectively, which indicated that the pathogenesis of hypertension on frozen shoulder was affected by diabetes.

Some studies showed no association between obesity and the incidence of frozen shoulder (27, 28). Other reports suggested that the incidence of frozen shoulder was higher in obese people (23, 26), with one report showing obesity was a risk factor for frozen shoulder in individuals in Shanghai, China (29). Our study implied that overweight and obese subjects were more likely to develop frozen shoulder than subjects of normal-weight.

Many studies (17, 30) have shown that frozen shoulder is more common in individuals aged between 40 and 70 years (31, 32). To maximize the number of cases of frozen shoulder, and match the number of independent variables in this study, we included middle-aged and elderly subjects aged 40–85 years. Brun et al. (33) indicated that the peak age of onset of frozen shoulder was 56 years old. Saito et al. (32) reported that the mean age of onset of frozen shoulder was 58 years. In the present study, subjects aged 56–70 years were most likely to develop frozen shoulder within 1 year of discharge from a hospitalization that involved intravenous infusion.

Previous studies showed frozen shoulder is more common in women than men, with women comprising an estimated 58.0–60.9% of subjects with frozen shoulder (34, 35). Rawat et al. (36) found 68.75% of subjects with frozen shoulder were women. In the present study, there was no significant difference in the proportion of males and females suffering from frozen shoulder (RD = 0.004, 95%CI −0.016–0.025, $P = 0.681$). This may be because our study was limited to a specific

population of subjects that received intravenous infusion during a hospitalization, gender-specific differences in the onset of frozen shoulder have been influenced by the effect of intravenous infusion or other confounders.

STUDY LIMITATIONS

(1) This study only analyzed subjects receiving inpatient intravenous infusion in a single center and the study sample was limited by conditions, which affected the extrapolation of the study results. (2) The sample size was small and the incidence of frozen shoulder in the study population was low, resulting in a relatively small number of total cases. (3) The baseline characteristics of subjects with a mean daily duration of intravenous infusion $\leq$2 h (low exposure) and a mean daily duration of intravenous infusion $\geq$3 h (high exposure) were not matched using propensity scores; therefore, our findings may have been influenced by cofounders. (4) Our analyses did not consider mean daily durations of intravenous infusion between 2 and 3 h.

CONCLUSION

Compared with middle-aged and elderly subjects in the general population, middle-aged, and elderly subjects who received intravenous infusion during a hospitalization had a higher cumulative incidence rate of frozen shoulder within 1 year after discharge, and most incidences of frozen shoulder occurred within 6 months after discharge. Risk factors for the onset of frozen shoulder in middle-aged and elderly subjects discharged from a hospitalization that involved intravenous infusion were mean daily duration of intravenous infusion $\geq$3 h, length of hospital stay 11–30 days, BMI $\geq$ 25 kg/m^2, age 56–70 years, and diabetes. In middle-aged and elderly subjects that undergo intravenous infusion during hospitalization, the incidence of frozen shoulder after discharge may be reduced by accurate identification of these risk factors and timely intervention with appropriate functional exercises.

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: Clinical trial public platform management (http://www.medresman.org.cn).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Zhangjiagang Second People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YC is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. WC conceived and designed the study and wrote the manuscript. JC performed the statistical analysis. JP and YF carried out the literature search and data collection. WC and JC conducted an investigation. YC and JC revised the manuscript. All authors contributed to the article and approved the submitted version.

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Cognitive Frailty as a Predictor of Mortality in Older Adults: A Longitudinal Study in Peru

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Objective: To evaluate the role of cognitive frailty and its components as risk factors of mortality in older adults of the *Centro Médico Naval* (CEMENA) in Callao, Peru during 2010-2015.

Methods: We performed a secondary analysis of data from a prospective cohort that included older adults (60 years and older) treated at the CEMENA Geriatrics service between 2010–2015. Frailty was defined as the presence of three or more criteria of the modified Fried Phenotype. Cognitive impairment was assessed using the Peruvian version of the Mini Mental State Examination (MMSE), considering a score <21 as cognitive impairment. Cognitive frailty was defined as the coexistence of both. In addition, we included sociodemographic characteristics, medical and personal history, as well as the functional evaluation of each participant.

Results: We included 1,390 older adults (mean follow-up: 2.2 years), with a mean age of 78.5 ± 8.6 years and 59.6% (n = 828) were male. Cognitive frailty was identified in 11.3% (n = 157) and 9.9% (n = 138) died during follow-up. We found that cognitive frailty in older adults (aHR = 3.57; 95%CI: 2.33–5.49), as well as its components, such as sedentary behavior and cognitive impairment (aHR = 7.05; 95%CI: 4.46–11.13), weakness and cognitive impairment (aHR = 6.99; 95%CI: 4.41–11.06), and exhaustion and cognitive impairment (aHR = 4.51; 95%CI: 3.11–6.54) were associated with a higher risk of mortality.

Conclusion: Cognitive frailty and its components were associated with a higher risk of mortality in older adults. It is necessary to develop longitudinal studies with a longer follow-up and that allow evaluating the effect of interventions in this vulnerable group of patients to limit adverse health outcomes, including increased mortality.

Keywords: cognitive frailty, cognitive impairment, frailty, mortality, older adult, aging

INTRODUCTION

During aging, the presence of multiple subclinical comorbidities and stressors can exacerbate the decrease in physiological reserves in various systems, causing homeostatic imbalance or frailty (1). Frailty results in the inability to perform basic activities of daily living (2), neurocognitive disorders (3) and an increased risk of mortality (4). In addition, frailty can increase the risk of future cognitive decline and vice versa (5–8). Cognitive impairment prevalence varies from 12.05 to 33.7% in frail older adults (9–11), with frailty being associated with poorer cognitive performance (12), and the coexistence of the two inducing a higher risk of adverse outcomes such as dementia, disability, hospitalizations, and death (13).

Coexistence of frailty and cognitive impairment is common and its prevalence in older adults varies from 10.3 to 42.8% (14–16), and therefore, a syndrome encompassing both (17) was defined as cognitive frailty in 2013. This syndrome excludes the presence of Alzheimer's disease and other dementias (18). Cognitive frailty refers to brain frailty that may be associated with neuropathological changes related to Alzheimer's disease or other neurodegenerative conditions (19). This is a potentially reversible clinical entity with an important goal of secondary prevention in the asymptomatic or early stage of dementia (20). Likewise, it predisposes older adults to more complex and serious outcomes (18), increasing the risk of dementia and all-cause mortality by approximately 4.01 and 3.4 fold, respectively (21, 22), being greater than the risk attributed to each syndrome separately (frailty and cognitive impairment increase in 1.8 and 1.3 mortality risk fold, respectively) (14).

Cognitive frailty as a risk factor for mortality has been described in systematic reviews (21, 23) and previous studies conducted in Asian countries (22, 24–26) and Europe (9), but the number of studies in in Latin American older adults is fewer (27, 28). Health systems in Latin America are fragmented and do not provide quality care to all population groups (29). In Peru, the situation is similar, with poverty limiting access to health services to older adults, who represent a vulnerable population due to the high prevalence of geriatric syndromes and the risk of adverse outcomes (30). It is important to identify early cognitive frailty because it is a reversible condition prior to dementia, so we could avoid adverse outcomes by acting promptly and it would be beneficial in the Peruvian context. For this reason, the objective of this study was to evaluate the role of cognitive frailty and its components as risk factors of mortality in older adults in Peru during the period from 2010 to 2015.

MATERIALS AND METHODS

Study Design, Population, and Sample

We performed a secondary analysis of data from a prospective cohort that included 1891 older adults (60 years and over) enrolled in the Geriatrics Service of the *Centro Médico Naval* (CEMENA) "Cirujano Mayor Santiago Távara" during the period 2010–2015. The primary objective was to evaluate the prevalence and factors associated with frailty in older adults from CEMENA. In addition, other studies have been carried out with this database (31–34). The primary study included all the participants evaluated in the CEMENA Geriatrics Service from 2010 to 2015. For the secondary data analysis, we excluded participants with no record of the variables of interest.

Participants were enrolled in 2010 and followed annually until 2015. Likewise, a new group of older adults was enrolled annually and followed until 2015. We did not perform any additional measurement of baseline measurements, only mortality was assessed during follow-up. The mean follow-up was 2.2 years. Participants were chosen using non-probabilistic convenience sampling. A total of 1891 individuals were enrolled in the database and 501 were excluded for not having the variables of interest. Thus, 1390 older adults were finally analyzed. A statistical power of 100% was calculated for the final sample size based on a hazard ratio (HR) of 3.0 reported by Feng L. et al. (25).

Variables

Outcome Variable: Mortality

Mortality was defined as death by all causes in the elderly registered by the CEMENA Epidemiological Surveillance Office during the follow-up period.

Exposure Variables

Frailty

We evaluated frailty using the modified Fried Phenotype, which consists of five criteria. (1) Exhaustion: defined using the following questions from the geriatric depression scale (35, 36): (a) Do you feel full of energy?; (b) Do you feel that you cannot go on?; (c) Do you feel that everything you do is an effort? Exhaustion was considered with two or more positive responses (37); (2) Weight loss: defined as a positive response to the following question taken from the Edmonton questionnaire (38): "Have you recently lost enough weight that your clothes are too loose?; (3) Weakness: defined as the recording of grip strength $<$16 kg in women and $<$27 kg in older men using a dynamometer (39); (4) Sedentary behavior: evaluated by the application of the Physical Activity Scale for the Elderly (PASE) and was considered positive with a score $<$64 in men and $<$52 in women (40, 41); and (5) Slow gait speed: defined as a walking speed $<$0.8 m/s or in cases in which the participant could not complete the four meter walk (39). The highest time recorded in each participant was considered. Frailty was defined as an older adult with three or more criteria.

Cognitive Impairment

We used the Peruvian version of the Mini Mental State Examination (MMSE), which is divided into five sections and has a maximum score of 30 points, with a higher score being interpreted as better cognitive performance. A score $<$21 points was considered as cognitive impairment (42).

Cognitive Frailty

Cognitive frailty is defined by the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics as the simultaneous presence of frailty (according to the phenotypic model) and cognitive impairment, excluding neurodegenerative causes or definite

dementia (18). The term was coined in view of extensive evidence highlighting the association between these two geriatric syndromes.

Other Variables

Sociodemographic Characteristics

We collected the following sociodemographic characteristics: sex (male, female), age (60–70 years, 71–80 and ≥81), marital status (single, married/cohabiting, divorced/widowed), educational level (≤11 years or >11) and whether the participant lived alone (yes, no).

Medical and Personal History

We created a variable that included the following comorbidities: high blood pressure, type 2 diabetes mellitus, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, arterial insufficiency, history of depression, urinary incontinence, and overweight or obesity according to the body mass index. In addition, by self-reporting we evaluated the history of tobacco consumption (no, yes) and alcohol consumption (no, yes), hospitalizations in the last year (no, yes), the number of prescribed medications and falls in the last year (no, yes). We obtained these variables from the participant's medical records.

Functional Evaluation

We evaluated functional dependence in basic activities of daily living (BADL) using the Barthel index, which evaluates 10 activities and has a maximum score of 100. We defined disability as a score <100 (43).

Statistical Analysis

We used the statistical package STATA® v17.0 (StataCorp, TX, USA) to perform the analysis. We did not have follow-up loss of the participants. Descriptive results corresponding to the qualitative variables are described using absolute and relative frequencies, while the quantitative variables are shown using measures of central tendency and dispersion. We performed the bivariate analysis using Pearson's chi-square test to compare the covariates of interest and the exposure variables (cognitive frailty, frailty, and cognitive impairment) and outcomes. In addition, we used the Student's *t*-test or the Mann-Whitney *U*-test to evaluate the differences between the numerical covariates and the exposure and outcome variables. We performed crude and adjusted Cox regression models to assess the association between cognitive frailty and all-cause mortality in the study sample. In addition, we evaluated the association between the components of cognitive frailty and the incidence of mortality in the study participants. The adjusted model included the following variables: sex, age, educational level, comorbidities, history of tobacco use, history of alcohol use, number of drugs prescribed, functional dependence for BADL and falls in the last year. We chose these variables using the classical confusion criteria and the description of their association in the literature (44–48). Crude (cHR) and adjusted (aHR) hazard ratios with their 95% confidence intervals (95%CI) were calculated. Likewise, a Kaplan-Meier curve was constructed to evaluate the survival of the participants according to the presence or absence of cognitive frailty and they were compared using the Log-rank test.

Ethical Aspects

This secondary analysis was reviewed and approved by the institutional research ethics committee of the Universidad Científica del Sur, in Lima, Peru (151-2021-PREB15). Since this study involved analysis of secondary data, no additional measurement was performed in the participants. In addition, the primary study was approved by the CEMENA ethics committee, and the participants signed informed consent prior to entering the study.

RESULTS

General Characteristics of the Sample and Bivariate Analysis According to the Exposure Variables

The cohort study enrolled 1,891 older adults, and we excluded 501 due to not having the variables of interest for this secondary data analysis (**Figure 1**). Then, we analyzed 1,390 older adults with a mean age of 78.5 ± 8.6 years and 59.6% ($n = 828$) were male. In addition, 78.9% ($n = 1,097$) studied for more than 11 years, the median number of years of retirement was 21 (interquartile range [IQR]: 12–28), 84.6% ($n = 1,176$) did not live alone and 30.9% ($n = 430$) had 3 or more comorbidities. On the other hand, we found that 73.2% ($n = 1,017$) had a history of tobacco consumption, 61.6% ($n = 856$) had functional dependence for BADL, 51.1% ($n = 711$) had been hospitalized during the previous year and the median number of medications prescribed was 3 (IQR: 2–6). It was found that 11.3% ($n = 157$) of the participants had cognitive frailty, 24.0% ($n = 333$) were frail while 18.9% ($n = 263$) had cognitive impairment, and the incidence of mortality was 9.9% ($n = 138$). In addition, we found a greater percentage of male older adults (73.9 vs. 57.8%; $p < 0.001$), higher mean of age (80.4 vs. 78.2 years; $p = 0.003$), less median years of retirement (16 vs. 22; $p = 0.030$), and a higher median of drugs prescribed (8 vs. 3; $p < 0.001$) in cognitive frailty group compared with the non-exposed group (**Table 1**).

Bivariate Analysis According to Mortality in the Study Sample

The group with cognitive frailty presented a higher incidence of mortality compared to those without this condition (50.3 vs. 4.8%; $p < 0.001$). In addition, mortality was higher in frail participants (27.0 vs. 4.5%; $p < 0.001$) or those with cognitive impairment (45.2 vs. 1.7%; $p < 0.001$) compared to individuals without these conditions. However, there were no statistically significant differences in relation to mortality and sex, marital status, educational level, military rank, years of retirement, living alone, comorbidities, body mass index, history of consumption of alcohol, hospitalizations in the last year and self-reported weight loss (**Table 2**).

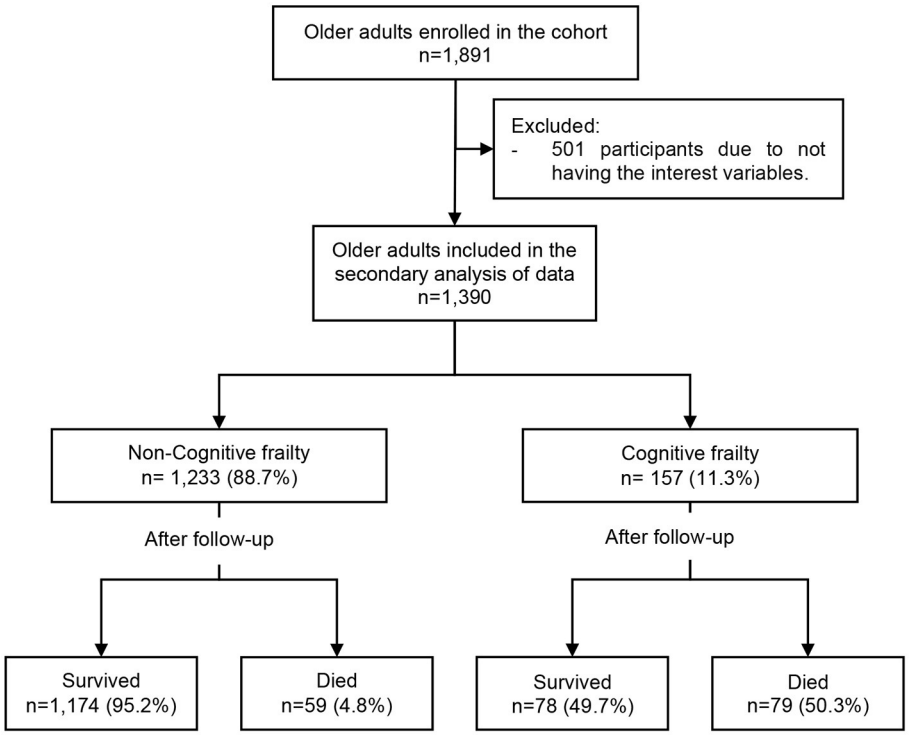

FIGURE 1 | Flowchart of the sample selection.

Cognitive Frailty as a Risk Factor for Mortality in Older Adults

The adjusted Cox regression analysis showed that cognitive frailty (aHR = 3.57; 95%CI: 2.33–5.49; $p < 0.001$) was a risk factor for mortality in older adults. In addition, we evaluated the association of the components of cognitive frailty, finding that exhaustion and cognitive impairment (aHR = 4.51; 95%CI: 3.11–6.54; $p < 0.001$), weight loss and cognitive impairment (aHR = 1.68; 95%CI: 1.06–2.67; $p = 0.027$), weakness and cognitive impairment (aHR = 6.99; 95%CI: 4.41–11.06; $p < 0.001$), sedentary behavior and cognitive impairment (aHR = 7.05; 95%CI: 4.46–11.13; $p < 0.001$), slow gait speed and cognitive impairment (aHR = 2.61; 95%CI: 1.76–3.85; $p < 0.001$) were associated with a higher risk of mortality (**Table 3**). In addition, the group of patients with cognitive frailty presented a lower survival ($p < 0.001$) (**Figure 2**). The mean survival of cognitive frailty group was 1.6 years (median: 1.4), while in the non-exposed group the mean survival was 2.3 years (median: 1.7).

DISCUSSION

The present study evaluated 1,390 older adults, among whom two out of 10 were frail, two out of 10 had cognitive impairment, and one out of 10 had cognitive frailty. In addition, the latter was associated with a 3.57-fold increase in the risk of mortality. When evaluating the components of cognitive frailty, we found a higher incidence of mortality in older adults with a sedentary behavior, weakness, and exhaustion. Likewise, six out of 10 had disability in BADL or at least one fall in the last year and nine out of 10 had at least one comorbidity.

Our findings indicate the need for timely identification of cognitive frailty in primary care in order to reduce adverse outcomes. This is very important in our country due to the high prevalence of frailty (17.5 to 23.3%) and cognitive impairment (18.2 to 36.67%) described in several studies (49–54).

The prevalence of frailty, cognitive impairment, and cognitive frailty in the present study was 24, 18.9, and 11.3%, respectively. These prevalences are lower than those reported in previous studies in China, although the frequency of cognitive impairment was higher in one of these studies (48, 55). Likewise, a South Korean study reported a higher prevalence of cognitive impairment, but a lower frequency of frailty (14). On the other hand, a systematic review found a prevalence of cognitive frailty ranging from 2.5 to 50% in cohort studies using different operational definitions (23).

We found that cognitive frailty was associated with an increased risk of mortality in older Peruvian adults. This finding is similar to what has been described in China (48, 55), South Korea (14) and France (9). However, these studies were heterogeneous in relation to follow-up time, sample size, age of the older adults, and the instruments used to measure frailty and cognitive impairment. Mortality risk assessment according to each component of cognitive frailty was not reported by any of the previous studies. Likewise, only one previous study used the modified version of the Fried phenotype (14). It should be

TABLE 1 | Descriptive and bivariate analyses according to exposure variables (n = 1,390).

Variables	*n*	%	Cognitive frailty		*P* value	Frailty		*P* value	Cognitive impairment		*P* value
			No 88.7% (*n* = 1,233)	Yes 11.3% (*n* = 157)		No 76.0% (*n* = 1,057)	Yes 24.0% (*n* = 333)		No 81.1% (*n* = 1,127)	Yes 18.9% (*n* = 263)	
Sex					<0.001			<0.001			0.457
Female	562	40.4	521 (42.2)	41 (26.1)		473 (44.8)	89 (26.7)		461 (40.9)	101 (38.4)	
Male	828	59.6	712 (57.8)	116 (73.9)		584 (55.3)	244 (73.3)		666 (59.1)	162 (61.6)	
Age	78.5 ± 8.6		78.2 ± 8.5	80.4 ± 8.8	0.003	77.3 ± 8.1	82.1 ± 9.0	<0.001	78.2 ± 8.6	79.7 ± 8.4	0.008
60–70 years old	221	15.9	205 (16.6)	16 (10.2)	0.074	193 (18.3)	28 (8.4)	<0.001	193 (17.1)	28 (10.6)	0.016
71–80 years old	623	44.8	553 (44.9)	70 (44.6)		497 (47.0)	126 (37.8)		506 (44.9)	117 (44.5)	
≥81 years old	546	39.3	475 (38.5)	71 (45.2)		367 (34.7)	179 (53.8)		428 (38.0)	118 (44.9)	
Marital status					0.377			0.863			0.115
Single	39	2.8	37 (3.0)	2 (1.3)		31 (2.9)	8 (2.4)		36 (3.2)	3 (1.1)	
Married/Cohabitating	1,098	79.0	975 (79.1)	123 (78.3)		835 (79.0)	263 (79.0)		881 (78.2)	217 (82.5)	
Divorced/Widower	253	18.2	221 (17.9)	32 (20.4)		191 (18.1)	62 (18.6)		210 (18.6)	43 (16.4)	
Educational level					0.984			0.048			0.271
≤11 years	293	21.1	260 (21.1)	33 (21.0)		210 (19.9)	83 (24.9)		231 (20.5)	62 (23.6)	
>11 years	1,097	78.9	973 (78.9)	124 (79.0)		847 (80.1)	250 (75.1)		896 (79.5)	201 (76.4)	
Military rank					0.104			0.121			0.003
Subaltern	721	51.9	638 (51.7)	83 (52.9)		533 (50.4)	188 (56.5)		581 (51.6)	140 (53.2)	
Officer	135	9.7	127 (10.3)	8 (5.1)		109 (10.3)	26 (7.8)		124 (11.0)	11 (4.2)	
Civilian	534	38.4	468 (38.0)	66 (42.0)		415 (39.3)	119 (35.7)		422 (37.4)	112 (42.6)	
Years of retirement	21	(122–8)	22 (13–28)	16 (10–28)	0.030	21 (14–28)	19 (92–9)	0.528	22 (13–28)	17 (92–8)	0.036
Living alone					0.327			0.359			0.923
No	1,176	84.6	1,039 (84.3)	137 (87.3)		889 (84.1)	287 (86.2)		954 (84.7)	222 (84.4)	
Yes	214	15.4	194 (15.7)	20 (12.7)		168 (15.9)	46 (13.8)		173 (15.3)	41 (15.6)	
Comorbidities	2	(1–3)	2 (1–3)	2 (1–2)	0.165	2 (1–3)	2 (1–3)	0.002	2 (1–3)	2 (13–)	0.068
0	121	8.7	111 (9.0)	10 (6.4)	0.056	89 (8.4)	32 (9.6)	0.020	102 (9.1)	19 (7.2)	0.038
1	400	28.8	344 (27.9)	56 (35.7)		285 (27.0)	115 (34.5)		307 (27.2)	93 (35.4)	
2	439	31.6	385 (31.2)	54 (34.4)		338 (32.0)	101 (30.3)		356 (31.6)	83 (31.6)	
≥3	430	30.9	393 (31.9)	37 (23.6)		345 (32.6)	85 (25.5)		362 (32.1)	68 (25.8)	
BMI[a]	26.1 ± 5.7		26.2 ± 5.6	25.3 ± 6.3	0.094	26.2 ± 5.6	25.7 ± 5.8	0.204	26.4 ± 5.5	24.7 ± 6.1	<0.001
History of tobacco consumption					0.352			0.005			0.145
No	373	26.8	326 (26.4)	47 (29.9)		264 (25.0)	109 (32.7)		293 (26.0)	80 (30.4)	
Yes	1,017	73.2	907 (73.6)	110 (70.1)		793 (75.0)	224 (67.3)		834 (74.0)	183 (69.6)	
History of alcohol consumption					0.511			0.298			0.023
No	769	55.3	686 (55.6)	83 (52.9)		593 (56.1)	176 (52.9)		640 (56.8)	129 (49.1)	
Yes	621	44.7	547 (44.4)	74 (47.1)		464 (43.9)	157 (47.1)		487 (43.2)	134 (50.9)	
Functional dependance in BADL[b]					0.203			0.444			0.401

(Continued)

TABLE 1 | Continued

Variables	*n*	%	Cognitive frailty		*P* value	Frailty		*P* value	Cognitive impairment		*P* value
			No 88.7% (*n* = 1,233)	Yes 11.3% (*n* = 157)		No 76.0% (*n* = 1,057)	Yes 24.0% (*n* = 333)		No 81.1% (*n* = 1,127)	Yes 18.9% (*n* = 263)	
No	534	38.4	481 (39.0)	53 (33.8)		412 (39.0)	122 (36.6)		427 (37.9)	107 (40.7)	
Yes	856	61.6	752 (61.0)	104 (66.2)		645 (61.0)	211 (63.4)		700 (62.1)	156 (59.3)	
Hospitalizations in the last year					0.070			0.001			0.729
No	679	48.9	613 (49.7)	66 (42.0)		544 (51.5)	135 (40.5)		548 (48.6)	131 (49.8)	
Yes	711	51.1	620 (50.3)	91 (58.0)		513 (48.5)	198 (59.5)		579 (51.4)	132 (50.2)	
Number of drugs prescribed	3 (2–6)		3 (2–4)	8 (7–9)	<0.001	3 (2–4)	6 (3–8)	<0.001	3 (2–4)	8 (6–8)	<0.001
Exhaustion					<0.001			<0.001			<0.001
No	1,075	77.3	1,021 (82.8)	54 (34.4)		916 (86.7)	159 (47.8)		939 (83.3)	136 (51.7)	
Yes	315	22.7	212 (17.2)	103 (65.6)		141 (13.3)	174 (52.2)		188 (16.7)	127 (48.3)	
Weight loss					<0.001			<0.001			0.020
No	915	65.8	840 (68.1)	75 (47.8)		795 (75.2)	120 (36.0)		758 (67.3)	157 (59.7)	
Yes	475	34.2	393 (31.9)	82 (52.2)		262 (24.8)	213 (64.0)		369 (32.7)	106 (40.3)	
Weakness					<0.001			<0.001			<0.001
No	945	68.0	925 (75.0)	20 (12.7)		872 (82.5)	73 (21.9)		848 (75.2)	97 (36.9)	
Yes	445	32.0	308 (25.0)	137 (87.3)		185 (17.5)	260 (78.1)		279 (24.8)	166 (63.1)	
Sedentary behavior					<0.001			<0.001			<0.001
No	762	54.8	762 (61.8)	0 (0)		717 (67.8)	45 (13.5)		710 (63.0)	52 (19.8)	
Yes	628	45.2	471 (38.2)	157 (100)		340 (32.2)	288 (86.5)		417 (37.0)	211 (80.2)	
Slow gait speed					<0.001			<0.001			<0.001
No	954	68.6	908 (73.6)	46 (29.3)		855 (80.9)	99 (29.7)		834 (74.0)	120 (45.6)	
Yes	436	31.4	325 (26.4)	111 (70.7)		202 (19.1)	234 (70.3)		293 (26.0)	143 (54.4)	
Falls in the last year					0.094			<0.001			0.888
No	555	39.9	502 (40.7)	53 (33.8)		455 (43.1)	100 (30.0)		451 (40.0)	104 (39.5)	
Yes	835	60.1	731 (59.3)	104 (66.2)		602 (56.9)	233 (70.0)		676 (60.0)	159 (60.5)	
Mortality					<0.001			<0.001			<0.001
No	1,252	90.1	1,174 (95.2)	78 (49.7)		1,009 (95.5)	243 (73.0)		1,108 (98.3)	144 (54.8)	
Yes	138	9.9	59 (4.8)	79 (50.3)		48 (4.5)	90 (27.0)		19 (1.7)	119 (45.2)	

[a]*Body mass index;* [b]*Basic activities of daily life.*

TABLE 2 | Descriptive and bivariate analyses of the study variables based on all-cause mortality (n = 1,390).

Variables	Mortality		*P* value
	No 90.1% (n = 1,252)	Yes 9.9% (n = 138)	
Cognitive frailty			<0.001
No	1,174 (95.2)	59 (4.8)	
Yes	78 (49.7)	79 (50.3)	
Frailty			<0.001
No	1,009 (95.5)	48 (4.5)	
Yes	243 (73.0)	90 (27.0)	
Cognitive impairment			<0.001
No	1,108 (98.3)	19 (1.7)	
Yes	144 (54.8)	119 (45.2)	
Sex			0.214
Female	513 (91.3)	49 (8.7)	
Male	739 (89.3)	89 (10.7)	
Age	78.3 ± 8.6	80.2 ± 8.4	0.012
60–70 years old	206 (93.2)	15 (6.8)	0.078
71–80 years old	565 (90.7)	58 (9.3)	
≥81 years old	481 (88.1)	65 (11.9)	
Marital status			0.138
Single	36 (92.3)	3 (7.7)	
Married/Cohabitating	980 (89.2)	118 (10.8)	
Divorced/Widower	236 (93.3)	17 (6.7)	
Educational level			0.119
≤11 years	271 (92.5)	22 (7.5)	
>11 years	981 (89.4)	116 (10.6)	
Military rank			0.126
Subaltern	649 (90.0)	72 (10.0)	
Officer	128 (94.8)	7 (5.2)	
Civilian	475 (89.0)	59 (11.0)	
Years of retirement	21 (13–28)	19 (10–29)	0.825
Living alone			0.153
No	1,065 (90.6)	111 (9.4)	
Yes	187 (87.4)	27 (12.6)	
Comorbidities	2 (1–3)	2 (1–2)	0.064
0	111 (91.7)	10 (8.3)	0.066
1	350 (87.5)	50 (12.5)	
2	392 (89.3)	47 (10.7)	
≥3	399 (92.8)	31 (7.2)	
BMI[a]	26.2 ± 5.6	25.2 ± 6.7	0.054
History of tobacco consumption			0.042
No	346 (92.8)	27 (7.2)	
Yes	906 (89.1)	111 (10.9)	
History of alcohol consumption			0.510
No	689 (89.6)	80 (10.4)	
Yes	563 (90.7)	58 (9.3)	
Functional dependance in BADL[b]			<0.001
No	444 (83.2)	90 (16.8)	
Yes	808 (94.4)	48 (5.6)	
Hospitalizations in the last year			0.941
No	612 (90.1)	67 (9.9)	
Yes	640 (90.0)	71 (10.0)	
Number of drugs prescribed	3 (2–4)	8 (7–9)	<0.001
Exhaustion			<0.001
No	1,017 (94.6)	58 (5.4)	
Yes	235 (74.6)	80 (25.4)	
Weight loss			0.269
No	830 (90.7)	85 (9.3)	
Yes	422 (88.8)	53 (11.2)	
Weakness			<0.001
No	900 (95.2)	45 (4.8)	
Yes	352 (79.1)	93 (20.9)	
Sedentary behavior			<0.001
No	735 (96.5)	27 (3.5)	
Yes	517 (82.3)	111 (17.7)	
Slow gait speed			<0.001
No	892 (93.5)	62 (6.5)	
Yes	360 (82.6)	76 (17.4)	
Falls in the last year			0.010
No	514 (92.6)	41 (7.4)	
Yes	738 (88.4)	97 (11.6)	

(Continued)

TABLE 2 | Continued

[a]Body mass index; [b]Basic activities of daily life.

noted that few studies has evaluated this association of interest in Latin American countries (27, 28, 44). One study evaluated the association of interest in older Mexican adults residing in the United States, using pre-frailty instead of frailty for the definition of cognitive frailty (44). Two previous studies conducted in older adults from Brazil evaluated the role of cognitive frailty as a predictor of mortality. One of them estimated the incidence of mortality, disability and falls (28) after 1 year of follow-up, while the other only evaluated mortality, but after 10 years (27). Both evaluated frailty by accumulation of deficits (one using the FRAIL questionnaire and the other using the Frailty Index), while we used the Fried phenotype. Both quantified mortality risk not only for older adults with cognitive frailty, but also for prefrail participants with cognitive impairment, however, we explored each component of cognitive frailty. The identification of accessible markers that, added to frailty, could increase the risk of mortality in older adults could be useful in Peru, whose health system is fragmented and does not allow rapid access to appointments, medications, or periodic control (56).

Several studies have described a lower degree of physical activity in older adults with a decrease in brain mass (57, 58). Likewise, a reduction of muscle strength and physical performance has been associated with cognitive deterioration (59). On the other hand, both syndromes share multiple risk

TABLE 3 | Cox regression models to evaluate the association between the cognitive frailty phenotype and the risk of mortality in the study sample.

	Crude			Adjusted		
Exposure variables	**cHR**	**95%CI**	***P* value**	**aHR[a]**	**95%CI**	***P* value**
Cognitive frailty						
No	Reference	–	–	Reference	–	–
Yes	12.61	8.98–17.71	<0.001	3.57	2.33–5.49	<0.001
Cognitive frailty phenotype components						
Exhaustion + cognitive impairment						
No	Reference	–	–	Reference	–	–
Yes	12.54	8.95–17.57	<0.001	4.51	3.11–6.54	<0.001
Weight loss + cognitive impairment						
No	Reference	–	–	Reference	–	–
Yes	5.80	4.00–8.41	<0.001	1.68	1.06–2.67	0.027
Weakness + cognitive impairment						
No	Reference	–	–	Reference	–	–
Yes	14.23	10.09–20.06	<0.001	6.99	4.41–11.06	<0.001
Sedentary behavior + cognitive impairment						
No	Reference		–	Reference	–	–
Yes	19.58	13.35–28.71	<0.001	7.05	4.46–11.13	<0.001
Slow gait speed + cognitive impairment						
No	Reference	–	–	Reference	–	–
Yes	10.74	7.67–15.04	<0.001	2.61	1.76–3.85	<0.001

[a]*Adjusted for: sex, age, educational level, comorbidities, history of tobacco consumption, history of alcohol consumption, number of drugs prescribed, functional dependence in BADL and falls in the last year.*

aHR: adjusted hazard ratio; cHR: crude hazard ratio; CI: confidence interval.

factors such as advanced age itself (60), cardiovascular disease, mental disorders and lifestyles (61–63).

The presence of an inflammatory state mediated by cytokines in aging has been identified as an etiological factor in cognitive decline. It is known that increased concentrations of interleukins, specifically IL-6, favor memory decline. In addition, some infectious or proinflammatory processes, such as cancer, which are more frequent in the elderly, can lead to an increase in interleukins and subsequent inflammatory processes that can degrade cognitive capacity in the long term (64–66). Furthermore, chronic inflammation has been associated with poor physical performance and decreased muscle mass, as part of immunosenescence or inflammaging (7). In addition, previous studies have described cancer as a risk factor for frailty (67), both increasing the occurrence of adverse outcomes (68).

Reduced testosterone and other androgen hormones may be implicated in the development of frailty and cognitive impairment. Testosterone could have a protective effect on cognition due to its role in promoting hippocampal synaptic plasticity and amyloid beta protein regulation (69). In addition, the decrease in testosterone levels due to aging is associated with a decrease in muscle mass, and therefore, with frailty (70). In addition, the role of insulin resistance has been described as a possible risk factor for the development of both conditions (71).

Other factors related to the development of cognitive frailty are vascular damage (72), vitamin D deficiency (73) and malnutrition (74). Nutrition is linked to cognitive impairment and frailty through sarcopenia, and oxidative stress may have an important role. Previous studies have described that Mediterranean diet (a diet high in antioxidants), was associated with less frailty and cognitive impairment (75, 76). In addition, nutrition could also be associated with frailty due to changes in behavior produced by cognitive impairment, which would affect the ability to eat (or remember to) or to accomplish a healthy eating plan (77). These pathophysiological pathways that respond to the multifactorial origin of cognitive frailty may be related to

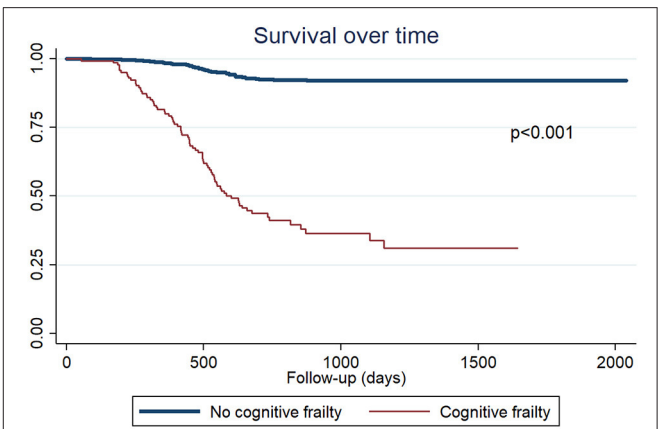

FIGURE 2 | Kaplan-Meier survival curves according to the cognitive frailty phenotype.

the increased risk of mortality evidenced in our study. This is due to a higher prevalence of comorbidities, less ability to maintain healthy lifestyles due to cognitive impairment and the consequent detriment to physical performance (78, 79).

Although the global prevalence of frailty varies significantly depending on the operational definition used and the characteristics of the population studied (4–59%) (80), we can affirm that it is a relevant syndrome among older adults. In Latin America, it is estimated that one in five elderly people is frail (81), with a prevalence of frailty of 24% in our study of the Peruvian population, thereby demonstrating the need to adapt health services to a population with greater demands.

While the prevalence of cognitive frailty is low and variable, ranging from 1 to 5% due to operational difficulties (60), it has been consistently identified as a risk factor for disability, morbidity and mortality in the elderly. However, due to its potential reversibility, it has been considered a possible intervention target to improve the quality of life in this population group.

Interventions aimed at addressing cognitive frailty include the promotion of exercise, a healthy diet, smoking cessation, psychological sessions, improvement of the social environment, and the control of variables such as weight, cholesterol, diabetes mellitus, and blood pressure (82–84). Interventions applied at various stages (pre-frailty, frailty and cognitive frailty) can help delay the development of frailty and improve the patient's adaptation to the physiological decrease in reserves (5, 7, 40, 82, 83, 85).

Although there is no consensus as to the best method for detecting cognitive frailty (86), our study found that two practical instruments available in daily clinical practice, such as the modified Fried phenotype and the MMSE, can predict a 3-fold higher risk of a mortality risk in patients with compared to those without cognitive frailty. This is especially useful in the context of the first level of care in countries with few available resources, such as Latin America.

Finally, this is the first study to describe an association between cognitive impairment and each component alone of the modified Fried phenotype and a higher risk of mortality (from 1.68 to 7.05 times higher depending on the component). This can have relevant implications due to the underdiagnosis of pre-frail states, in which only one or two criteria are present. Our findings highlight the importance of intervention in this group of patients to limit adverse health outcomes, including increased mortality.

This study has limitations: (1) The patients included did not have the same follow-up time, which could affect the incidence of mortality; (2) We included only older adults treated at CEMENA, which provides medical care to retired seafarers and their families, and thus, our findings may not be representative of the general population; (3) We did not exclude older adults with dementia in primary study data collection, because we did not evaluate them using the DSM-5 (gold standard); (4) We were unable to collect variables related to the type of medication received and the state of control of chronic diseases, which could affect the incidence of mortality; and (5) We did not collect the history of cancer as a variable, which could increase the risk of frailty and cognitive impairment in the study sample. Despite these limitations, our study is one of the first cohorts in Latin America which allowed evaluation of the role of cognitive frailty and its components as predictors of mortality in older adults. Our results allow us to identify cognitive frailty and its components as useful and practical markers in the first levels of healthcare. In the Peruvian context, these findings could be very important because they would allow the identification of risk groups in whom healthcare should be prioritized to avoid adverse outcomes. This would avoid the increase in the burden of the health system and would allow better care for older Peruvian adults.

In conclusion, our study found that cognitive frailty and its components are risk factors for mortality in older adults. Cognitive impairment associated with each component of the modified Fried phenotype was independently associated with an increased risk of mortality, with sedentary behavior, weakness, and exhaustion being of note. It is necessary to develop longitudinal studies with a longer follow-up time that allow evaluating the effect of interventions in this vulnerable group of patients to limit adverse health outcomes, including increased 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 Institutional Research Ethics Committee of the Universidad Científica del Sur, in Lima, Peru (151-2021-PREB15). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DV-T-Y, LS-T, SC-R, DU-P, FR-C, and JP participated in concept design and supervising the study. DU-P and FR-C conducted the statistical analysis. All the authors participated in manuscript writing, editing, final revision, and have read and agreed on the submitted manuscript, and also participated in this research and contributed to the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Muscle Ultrasound as Imaging Domain of Frailty

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Introduction: Frailty is a geriatric syndrome, a clinical state of vulnerability for developing dependency and/or death. Due to its multidimensional nature, Comprehensive Geriatric Assessment (CGA) constitutes the best strategy to evaluate frailty in older patients. Accumulation of deficits model synthesizes the global assessment of geriatric domains in the Frailty Index (FI) score. Muscle Ultrasound (MUS) has been employed to evaluate muscle mass wasting as tool to assess sarcopenia in late life. The present study aims to evaluate the association between CGA-based FI and MUS measures in a population of hospitalized older adults.

Methods: Patients aged ≥65 years underwent CGA for the evaluation of the domains of health and functional status, psycho-cognition, nutritional status, socio-environmental condition. Following standard procedure, a CGA-based FI was elaborated, taking into account 38 multidimensional items. Muscle thicknesses (MT) of rectus femoris plus vastus intermedius were measured through MUS axial cross-section. Multivariable regression analysis was employed to determine factors associated with FI.

Results: The study population consisted of 136 older patients, 87 men (63.9%), with median age of 74 (70–81) years, FI of 0.3 (0.21–0.46), and MT of rectus femoris plus vastus intermedius 29.27 (23.08–35.7) mm. At multivariable regression analysis, FI resulted significantly and independently associated with age and MT.

Conclusion: Muscle thicknesses of rectus femoris plus vastus intermedius, measured through MUS, resulted to be significantly related to FI in a population of hospitalized older patients. In the CGA-based assessment of frailty, MUS may constitute an additional imaging domain.

Keywords: frailty, ultrasound, geriatric domain, muscle thickness, Comprehensive Geriatric Assessment

INTRODUCTION

Frailty is a multifactorial geriatric syndrome with multiple causes and contributors, constituting the most complex expression of population aging (1). It represents a clinical state of increased vulnerability for developing dependency and/or death, due to poor homeostatic response after a stressor event, which derives from the decline in many physiological systems during the aging process. The result is a particularly susceptible substrate, on which even minor stressor events may trigger a relevant alteration in health status (2).

In the last decades, several definitions of frailty have been proposed and multiple instruments have been developed for its assessment for both clinical and scientific purposes. Although several scores have been proposed for frailty assessment, the gold standard tool has not been identified yet, thus the selection of a specific frailty instrument depends on the clinical setting, the study purpose, and the geriatric domains of interest (3). In this regard, it is important to underline that the enormous heterogeneity of the geriatric population represents a relevant difficulty in defining a single universal tool to identify frailty.

A growing piece of scientific research has focused on muscle ultrasound (MUS) to evaluate muscle mass wasting in older populations, assessing both muscle quantity and quality (4). MUS has been shown to constitute a reliable tool for the measurement of muscle size in young and old subjects, with consistent results across different body sites. Importantly, the highest intra- and inter-rater reliability has been found for large muscle groups, such as the musculus quadriceps, probably because the evaluation of smaller muscles might be complicated by limited spatial ultrasound resolution (5, 6). In this scenario, MUS has been proposed as a potential tool to assess sarcopenia in geriatric populations, including in the community setting.

Fried's frailty phenotype shows close overlap with sarcopenia, which constitutes a key contributor to frailty, facilitating the development of disability and being responsible for several adverse outcomes. Indeed, sarcopenic patients suffer increased vulnerability, negative adaptation to external stressors, and disability for basic activities of daily living (BADL) (7). Nevertheless, multidimensional frailty refers to the broader concept of complex geriatric syndrome accounting for physical, functional, mental, and social issues. Accordingly, sarcopenia should be considered as a biological substrate of physical frailty, a relevant subset of general frailty, whose assessment requires adequate diagnostic tools to reflect its multiple dimensions, such as cumulative decline in multiple body systems or functions (8).

Therefore, the central hypothesis of the present study is that MUS may constitute an additional "imaging" domain of multidimensional frailty, and to this aim, we explored the association between frailty and MUS measures in a population of hospitalized older patients.

METHODS

Study Population

The participants have been recruited among patients aged ≥65 years referred to the Geriatric division of Department of Translational Medical Sciences of the University of Naples "Federico II". The specific procedures of the study, described below, were performed at the resolution of the acute clinical condition that led to hospital admission. Exclusion criteria were: cachexia, extreme obesity, dialysis-dependent kidney failure and/or end-stage organ failure, central and peripheral nervous system diseases, myositis and diseases inducing muscular atrophy, major surgery on the lower limbs, and the presence of scars at the measurement sites.

All patients underwent medical history collection, clinical examination, and evaluation of the main demographic/clinical factors. The results of the main biochemical blood tests were also registered. All participants were carefully informed and signed a written consent to participate in this study. The research protocol was reviewed and approved by the Local Ethics Committee (124/17) and was conducted in compliance with the ethical principles stated in the Declaration of Helsinki.

Frailty Assessment

All patients underwent Comprehensive Geriatric Assessment (CGA), with the evaluation of the domains of health and functional status, nutrition, psycho-cognition, and socio-environmental condition. A CGA-based Frailty Index (FI) was created following a standard procedure as proposed by the Rockwood's research group (9), taking into account a total of 38 multidimensional health deficits, such as comorbidities, laboratory and diagnostic data, and symptoms and signs of diseases (**Tables 1**, **2**). The presence of deficits in these items was ascertained by trained physicians, each deficit was awarded 1 point if present or 0 in its absence. FI for a single participant resulted by the ratio between his/her cumulative points and the total number of evaluated items, thus this ranged between 0 and 1. A cut-off of 0.25 was used to define an individual as frail.

Muscle Ultrasound

The participants were assessed in a supine position, with the knees resting in extension for 30 min. The rectus femoris and vastus intermedius of dominant thigh of each patient were assessed at mid-point between greater trochanter and proximal border of patella, following proposed standards (10). A linear array probe of an ultrasound diagnostic apparatus (MyLab^{TM} Twice – Ultrasound Systems Esaote) was positioned perpendicular to the midpoint of the dorsal thigh to record the axial image. Ultrasound gel was applied both on the probe and the thigh to not make the two surfaces in direct contact, thus minimizing pressure on the soft tissue. Once the image was captured, thicknesses of subcutaneous fat, rectus femoris muscle, and vastus intermedius muscle were measured through axial cross-section (11). Muscle Thickness (MT) was defined as the mean value of three measurements of the sum of the distance between the anterior fascia and the posterior fascia of the rectus femoris and the vastus intermedius muscles (**Figure 1**).

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (*SD*) or median and interquartile range (IQR) and compared using Student's *t*-test or the Mann–Whitney *U*-test.

TABLE 1 | Health variables and cut-points for the frailty index – adapted from (9).

List of variables included in the frailty index	Cut point
Help bathing	Yes = 1, No = 0
Help dressing	Yes = 1, No = 0
Help getting in/out of chair	Yes = 1, No = 0
Help walking around house	Yes = 1, No = 0
Help eating	Yes = 1, No = 0
Help grooming	Yes = 1, No = 0
Help using toilet	Yes = 1, No = 0
Help up/down stairs	Yes = 1, No = 0
Help lifting 10 lbs	Yes = 1, No = 0
Help shopping	Yes = 1, No = 0
Help with housework	Yes = 1, No = 0
Help with meal preparations	Yes = 1, No = 0
Help taking medication	Yes = 1, No = 0
Help with finances	Yes = 1, No = 0
Lost more than 10 lbs in last year	Yes = 1, No = 0
Self rating of health	Poor = 1, Fair = 0.75, Good = 0.5, V. Good = 0.25, Excellent = 0
How health has changed in last year	Worse = 1, Better/Same = 0
Stayed in bed at least half the day due to health (in last month)	Yes = 1, No = 0
Cut down on usual activity (in last month)	Yes = 1, No = 0
Walk outside	<3 days = 1, ≤3 days = 0
Feel everything is an effort	Most of time = 1, Some time = 0.5, Rarely = 0
Feel depressed	Most of time = 1, Some time = 0.5, Rarely = 0
Feel happy	Most of time = 0, Some time = 0.5, Rarely = 1
Feel lonely	Most of time = 1, Some time = 0.5, Rarely = 0
Have trouble getting going	Most of time = 1, Some time = 0.5, Rarely = 0
High blood pressure	Yes = 1, Suspect = 0.5, No = 0
Heart attack	Yes = 1, Suspect = 0.5, No = 0
Chronic heart failure	Yes = 1, Suspect = 0.5, No = 0
Stroke	Yes = 1, Suspect = 0.5, No = 0
Cancer	Yes = 1, Suspect = 0.5, No = 0
Diabetes	Yes = 1, Suspect = 0.5, No = 0
Arthritis	Yes = 1, Suspect = 0.5, No = 0
Chronic lung disease	Yes = 1, Suspect = 0.5, No = 0
Mini mental state examination	<10 = 1, 11–17 = 0.75, 18–20 = 0.5, 20–24 = 0.25, >24 = 0
Body mass index	See **Table 2**
Grip strength	See **Table 2**
Usual pace	See **Table 2**
Rapid pace	See **Table 2**

TABLE 2 | Deficit cut-off values for continuous variables by sex – adapted from (9).

Variable	Deficit for men	Deficit for women
Body mass index (BMI)	<18.5, ≥30 as a deficit	<18.5, ≥30 as a deficit
	25–<30 as a "half deficit"	25–<30 as a "half deficit"
Grip strength (kg)	For BMI ≤ 24, GS ≤ 29	For BMI ≤ 23, GS ≤ 17
	For BMI 24.1–28, GS ≤ 30	For BMI 23.1–26, GS ≤ 17.3
	For BMI > 28, GS ≤ 32	For BMI 26.1–29, GS ≤ 18
		For BMI > 29, GS ≤ 21
Rapid pace walk (s)	>10	>10
Usual pace walk (s)	>16	>16

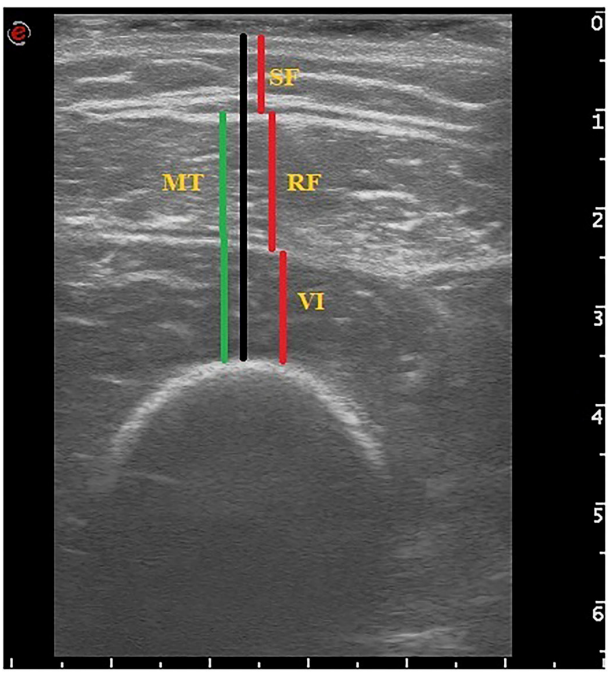

FIGURE 1 | Representative image of muscle ultrasound. Muscle thickness (MT) was defined as the mean value of three measurements of the sum of the distance between the anterior fascia and the posterior fascia of the rectus femoris (RF) and the vastus intermedius (VI) muscles. SF, subcutaneous fat.

The Normal distribution was assessed using the Shapiro–Wilk test. The categorical variables were expressed as a percentage and compared using Pearson's χ^2 test. Descriptive comparisons between groups were conducted according to gender and frailty status. The multivariable regression analysis was used to identify factors associated with continuous dependent variable FI. Parsimonious selection criteria were used to avoid overfitting bias. The analysis considered: age, gender, and BMI as independent variables. An alternative model was developed with subcutaneous fat thickness as an independent factor, instead of BMI. The regression model was employed to determine the impact of the MUS parameters on FI. All analyses were performed using the STATA statistical software (STATA version 17; StataCorp LLC, College Station, TX, USA), and a p-value < 0.05 was considered as the statistical significance threshold.

TABLE 3 | Characteristics of the overall population and of subgroup according to frailty status.

Characteristics	Overall population ($n = 136$)	Frail FI ≥0.25 ($n = 91$)	Non frail FI <0.25 ($n = 45$)	Sig.
Age (years)	74 (70–81)	76 (71–82)	73 (69–76)	0.007
Gender (male) *n* (%)	87 (63.9)	53 (58.2)	34 (75.6)	0.041
BMI (kg/m^2)	26.01 ± 4.51	25.82 ± 5.08	26.38 ± 3.06	0.433
Hemoglobin (g/dl)	11.99 ± 2.43	11.81 ± 2.25	12.35 ± 2.73	0.263
eGFR (ml/min/1.73 m^2)	65 (47–82)	64 (45–81)	66 (47–86)	0.476
Serum protein (g/dl)	6.47 ± 0.75	6.43 ± 0.76	6.59 ± 0.73	0.344
MMSE (/30)	25 (21.7–27)	24.3 (20.8–26.2)	26.7 (24.7–29)	<0.001
BADL (/6)	6 (5-6)	5 (4-6)	6 (5-6)	<0.001
IADL (/8)	7 (4-8)	6 (3-8)	8 (7-8)	<0.001
POMA (/28)	24.5 (16-27)	21 (12-26)	27 (25-28)	<0.001
SPPB (/12)	5.85 ± 3.5	4.68 ± 3.21	8.22 ± 2.83	<0.001
MNA (/30)	22 (19–24.5)	20.5 (17.5–23)	24 (23-26)	<0.001
CIRS (*n*)	3.76 ± 1.96	3.90 ± 1.84	3.47 ± 2.18	0.254
Chronic drugs (*n*)	6.71 ± 2.85	6.64 ± 2.85	6.87 ± 2.86	0.661
PASE (*n*)	80 (37.85–125)	55 (20-110)	116 (81–151)	<0.001
Social support score (/17)	6.47 ± 2.72	7.25 ± 2.52	4.89 ± 2.42	<0.001
Grip strength (kg)	24.15 ± 9.93	23.4 ± 10.46	26.67 ± 8.19	0.441
FI (/1)	0.3 (0.21–0.46)	0.4 (0.33–0.56)	0.18 (0.11–0.21)	<0.001
Rectus femoris (mm)	17.01 ± 4.65	16.1 ± 4.37	18.85 ± 4.37	0.002
Vastus intermedius (mm)	12.3 (9.1–16.05)	10.9 (8.36–15.4)	13.96 (11.6–17.5)	0.002
MT (mm)	29.27 (23.08–35.7)	26.4 (21.9–33)	33.4 (26.8–38.5)	<0.001
Subcutaneous fat (mm)	11.4 (8.16–18.05)	11.7 (8.13–18.8)	10.8 (8.4–15.1)	0.533

BADL, basic activity of daily living; BMI, body mass index; CIRS, cumulative illness rating scale; eGFR, estimated glomerular filtration rate (according to CKD-EPI formula); FI, frailty index; IADL, instrumental activity of daily living; MMSE, mini mental state examination; MNA, mini nutritional assessment; MT, muscle thickness (vastus intermedius plus rectus femoris); PASE, physical activity scale for the elderly; POMA, Tinetti's Performance Oriented Mobility Assessment; SD, standard deviation; SPPB, short performance physical battery.

RESULTS

The study population consisted of 136 older patients, 87 men (63.9%), with median age of 74 (70–81) years and mean BMI of 26.01 ± 4.51 kg/m^2. The overall sample presented MT of rectus femoris plus vastus intermedius of 29.27 (23.08–35.7) mm, and FI of 0.3 (0.21–0.46). Dividing the population according to the predetermined FI cut-off, 91 (66.9%) subjects were "frail" (FI ≥ 0.25) and 45 "non-frail." Characteristics of the overall study population and of subgroups divided according to the frailty status are reported in **Table 3**.

At univariate analysis, frail subjects resulted to be significantly older than non-frail ones [76 (71–82) vs. 73 (69–76) years, respectively, $p = 0.007$] and less predominantly male (58.2 vs. 75.6% $p = 0.041$). Of note, no other relevant differences emerged between the two groups in terms of BMI, kidney function, hemoglobin, and serum protein levels. As expected, frail patients presented worse scores in the great majority of tests and tools included in the CGA, compared to non-frail ones. While subcutaneous fat thickness did not statistically differ between the two groups, frail patients presented significantly lower thickness values of all examined muscles compared to non-frail ones, in particular MTs of rectus femoris plus vastus intermedius were 33.4 (26.8–38.5) and 26.4 (21.9–33) mm, respectively ($p < 0.001$). After stratification according to gender, the groups did not differ for age and BMI, but female participants showed higher subcutaneous fat thickness assessed through ultrasound, worse scores at physical performance tests (POMA, SPPB, and Grip Strength), and significantly higher FI [0.26 (0.2–0.42) vs. 0.38 (0.25–0.51), $p = 0.012$] (**Supplementary Table S2**). Consistently, all MUS thickness were significantly greater in male patients than counterparts [MT of rectus femoris plus vastus intermedius: 32.7 (24.6–37.9) mm and 25.0 (20.9–29.6) mm, respectively ($p < 0.001$)]. MT values stratified according to gender and frailty status are shown in **Figure 2**.

The multivariable regression analysis included as independent variables the binary predictor gender and the continuous predictors age, BMI, and MT of vastus intermedius plus rectus femoris (**Table 4** and **Supplementary Table S1**). Importantly, the final model revealed that frailty was significantly and independently associated with age and MT ($p < 0.01$), while no relevant association emerged with BMI and gender. Notably, the contribution of MT to the overall R2 of the employed model was remarkable and superior to chronological age (55.07 vs. 44.93%, respectively). Similar results were obtained by replacing the independent variable BMI with subcutaneous fat (not shown).

DISCUSSION

The main result of the present study is represented by the identification of a significant association between frailty, assessed through accumulation of deficits model, and MT of vastus intermedius and rectus femoris, measured using MUS, in a

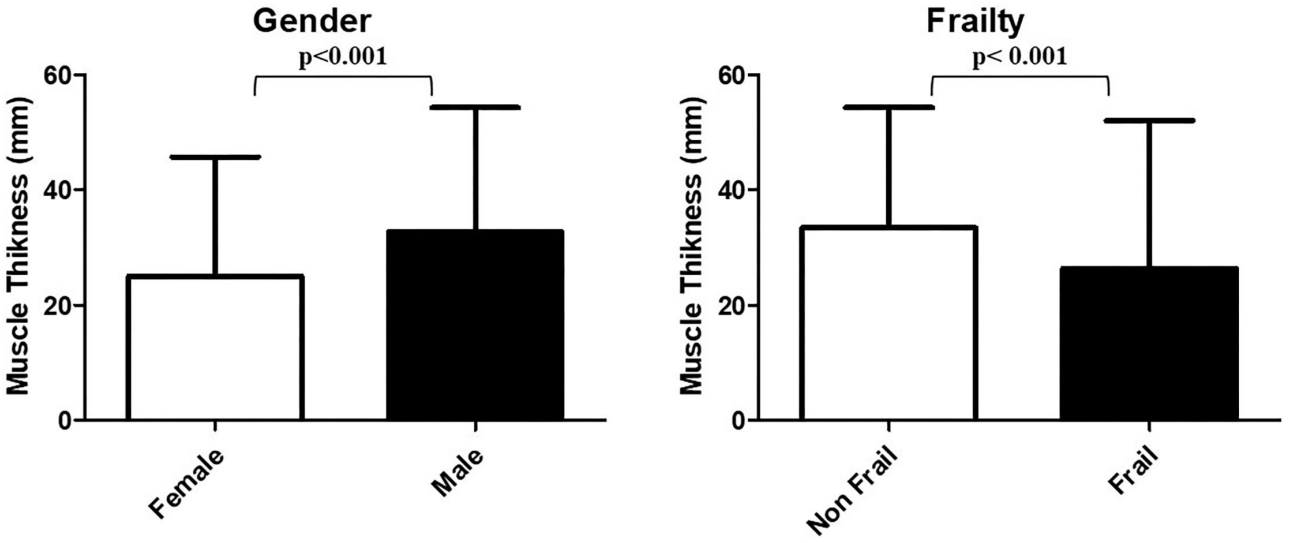

FIGURE 2 | MT values stratified according to gender and frailty status. The *p*-values correspond to the Mann–Whitney *U*-test.

population of older patients. To the best of our knowledge, this is the first study demonstrating a role of bedside MUS as marker of frailty evaluated through the CGA-based FI.

Along with the increasing interest of scientific community on sarcopenia, MUS has been proposed as valuable potential diagnostic tool to perform estimation of muscle mass. Compared to the current gold standard [Dual-energy X-ray absorptiometry (DXA), Computed Tomography (CT), Magnetic Resonance Imaging (MRI)], MUS represents a promising portable, accessible, cheap, cost-effective, and non-invasive imaging tool, particularly suitable for assessing older adults (12). Bioelectrical impedance analysis (BIA), which is also applicable bedside, is dependent on hydration status thus resulting less accuracy in specific clinical cases, as peripheral edema.

Several previous studies reported MT measurements of lower extremities, obtained through MUS, to be positively correlated with muscle strength and sarcopenia in older subjects (13). The reliability and validity of MUS in quantifying muscle size have been confirmed by the analysis of several studies of comparison with DXA (14), CT (15), MRI (5), especially in large muscle groups, as femoral quadriceps, whereas this ultrasound based technique may result challenging in the assessment of small muscles, probably caused by limited spatial resolution (5). The main problem with the use of MUS in the evaluation of muscle in the older patient is the little consistency, due to the lack of standardization in the adopted protocols, as emerged from literature search (4). Accordingly, the SARCUS working group has recently provided indications for an ultrasound protocol in the skeletal muscle assessment (10) from which the MUS method of the present study has been derived.

Frailty is a geriatric syndrome widely investigated in landmark studies through several valid models of assessment. Irrespective of the adopted tools, frailty has been associated with adverse health outcomes in different settings of care, thus increasing the scientific interest of geriatric research. Progressively more clinical decision processes are considering frailty status when selecting people to the most appropriate procedure (e.g., aortic valve replacement) or drug treatment (16). Among the multitude of instruments employed in geriatric medicine to measure frailty, FI seems to be the most suitable one to evaluate outcomes. Indeed, it is strongly associated with the risk of death and it may be considered an estimation of biological aging, which is more precisely correlated with morbidity and mortality than chronological age (17). Moreover, FI allows an accurate evaluation of physiologic reserve, that is known to exert an extremely important role in the response to stressors (18).

Following these premises, the aim of the present study was to evaluate whether the measurements of MT, obtained through an imaging technique increasingly employed in clinical research for sarcopenia assessment (which represents a physical substrate of frailty), were correlated with frailty, assessed through validated instruments of CGA, in a population of hospitalized older adults. The central hypothesis was that MUS may constitute an additional imaging tool of the geriatric multidimensional CGA-based approach.

TABLE 4 | Regression analysis for frailty index.

Variables	FI R^2: 0.16			
	Coeff.	SE	Sig.	Partial contribution to R^2 (%)
Age	0.005	0.002	0.01	44.93
MT	−0.005	0.002	0.01	55.07
Gender	−0.031	0.032	0.333	–
BMI	0.001	0.003	0.753	–

BMI, body mass index; FI, Frailty index; MT, muscle thickness (vastus intermedius plus rectus femoris).

The MUS values of MT of vastus intermedius plus rectus femoris came out to be significantly and independently correlated to FI in the study population, as emerged both at univariate and multivariable analyses. Importantly, the results of the latter analyses were corrected for potential confounding factors, such as BMI, gender, and age, aiming to avoid that such biological and anthropometric measures could influence the result and consequently condition MT impact on frailty. Furthermore, taking into account of the redistribution of body adiposity with age (19), we have also performed additional regression analyses introducing subcutaneous fat, instead of BMI, as independent variable, obtaining comparable results. Indeed, in both models, MT of vastus intermedius and rectus femoris remained independently correlated to the FI, as well as the chronological age, thus suggesting a potential role of MUS as instrumental domain of CGA. Of note, the final model has included MT and age, whose partial contribution to the global R2 was, respectively, 55.07 and 44.93%. This result is particularly interesting because it supports the robust contribution of MUS measures to explain the variability of the multifactorial CGA-based FI observed in the study population of older subjects, even when corrected by chronological age, which is an intrinsic characteristic of aging. Our results are in line with consolidated evidence indicating that female participants in clinical studies are frailer than male ones (20). We also confirmed the previous results showing that MT values of vastus intermedius plus rectus femoris obtained through MUS are significantly higher in male participants, while female individuals show the greater subcutaneous fat thickness (11).

Previous studies have focused on MUS as measure of frailty, with a specific interest on muscle strength and sarcopenia. The research group of Miron-Mombiela has demonstrated both MT and echo intensity of quadriceps to be correlated with grip strength in a subpopulation of adult outpatients aged 60 years and older. Moreover, the authors reported these measures to constitute imaging biomarkers of frailty, assessed according to Fried's criteria (21). A very elegant study by Narici and collaborators recently proposed the ultrasound sarcopenic index (USI) as novel imaging marker of reduced muscle mass associated with sarcopenia, independent of sex, body mass, and height that can impact on muscle sizes and architectural values. The authors calculated USI as the ratio between vastus lateralis muscle fascicle length and thickness, and reported that the greatest differences, compared to young controls, were found for the "mobility impaired elderly" and "sedentary elderly" groups (22). Another study, analyzing bedside MUS as a tool for sarcopenia assessment, has reported rectus femoris cross-sectional area to provide a prediction of adverse outcomes, as well as frailty diagnosed by FI, in the surgical intensive care unit (23).

Besides these pieces of literature that are consistent with the findings of the present study, our results are not in line with the previous evidence reported by Madden and collaborators, which performed point-of-care MUS of vastus medialis to test for association between MT and frailty in older adults. The authors detected only a weak correlation of MUS measurements with frailty, assessed through the Frailty Phenotype and the Clinical Frailty Scale (CFS), a 9-point judgment-based measure of frailty (24). Otherwise, it is important to mention that there are many and relevant differences in the applied protocols, including differences in the examined muscles. Although a gold standard methodology for MUS has not yet been established, also with regard to the anatomical muscles to be analyzed, we chose to measure the rectus femoris and the vastus intermedius MT based on the previous reports (11), because this approach offered the possibility of combining the measurements of two contiguous components of the same muscle group. Furthermore, from the pioneering studies on MUS by the research group of Abe, it has been developed the concept of "site-specific sarcopenia" to highlight that the age-related decline in muscle mass does not homogeneously proceed in all anatomic regions (25). Accordingly, it has been suggested that the muscle mass decline of rectus femoris seems to precede the one of other muscle groups (4, 26). Another main distinction between the two studies regards frailty assessment. Although the correlation between the two scales has been demonstrated to subsist, the CFS and the CGA-based FI present several relevant differences. As suggested by some authors, CFS is a valid instrument for initial frailty assessment, but it owns some limitations, in particular, in patients with dementia (27). Further, FI constitutes a more discriminative instrument compared to CFS, which is burdened by the rater subjectivity of clinical judgment (28).

Thus, taking into account the multifactorial nature of FI and considering the great heterogeneity which characterizes older subjects, the promising results of the present study allow to speculate on the potential role of MUS in detecting phenotypic characteristics of aging other than those canonically captured by the consolidated CGA tools.

LIMITATIONS

The study participants were recruited from a single geriatric medicine clinic, a population that tends to be frailer than the general population, due to multiple chronic illnesses. No control group was included in the protocol. The sample size calculation is burdened by the lack of evidence and reference values in the method and by the specificity of the population in question. Larger studies are needed to confirm our findings, even considering MT controlled by definite physical indicators which may affect its measures, not yet established by the scientific community. Even though the comparison with sarcopenia was not an aim of the present research, the lack of ascertained diagnosis of muscle mass decline does not allow a comparison between the MT measurements and the result of other reference methods.

CONCLUSION

Frailty is a multifactorial geriatric syndrome; CGA-based tools are valid instruments for its diagnosis and management. MUS measures of MT of vastus intermedius plus rectus femoris resulted to be significantly correlated to FI in a population of hospitalized older patients, independently from other considered covariates. Further studies are needed to confirm this association

and determine the clinical impact of these findings, aiming at defining MUS as an additional imaging domain of frailty.

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

The studies involving human participants were reviewed and approved by Comitato Etico per le attività biomediche - Università degli Studi di Napoli Federico II. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LB and GR conceived this study. LB, FP, and CR extracted the data. LB, DV, and KK designed and performed the statistical analyses. LB, LF, FR, IS, GG, and GF wrote the first draft of the manuscript. NF and GR reviewed and modified the final manuscript. All authors read, critically reviewed, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.922345/full#supplementary-material

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The Clinical Frailty Scale (CFS) employment in the frailty assessment of patients suffering from Non-Communicable Diseases (NCDs): A systematic review

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Background: The Clinical Frailty Scale (CFS) is a well-established tool that has been widely employed to assess patients' frailty status and to predict clinical outcomes in the acute phase of a disease, but more information is needed to define the implications that this tool have when dealing with Non-Communicable Diseases (NCDs).

Methods: An electronic literature search was performed on PubMed, Scopus, EMBASE, Web of Science, and EBSCO databases to identify studies employing the CFS to assess frailty in patients with NCDs.

Findings: After database searching, article suitability evaluation, and studies' quality assessment, 43 studies were included in the systematic review. Researches were conducted mostly in Japan (37.5%), and half of the studies were focused on cardiovascular diseases (46.42%), followed by cancer (25.00%), and diabetes (10.71%). Simplicity (39.29%), efficacy (37.5%), and rapidity (16.07%) were the CFS characteristics mostly appreciated by the authors of the studies. The CFS-related results indicated that its scores were associated with patients' clinical outcomes (33.92%), with the presence of the disease (12.5%) and, with clinical decision making (10.71%). Furthermore, CFS resulted as a predictor of life expectancy in 23 studies (41.07%), clinical outcomes in 12 studies (21.43%), and hospital admissions/readmissions in 6 studies (10.71%).

Discussion: CFS was found to be a well-established and useful tool to assess frailty in NCDs, too. It resulted to be related to the most important

disease-related clinical characteristics and, thus, it should be always considered as an important step in the multidisciplinary evaluation of frail and chronic patients.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/display_record.asp? PROSPERO 2021, ID: CRD42021224214.

KEYWORDS

frailty, Clinical Frailty Scale, Non-Communicable Diseases, chronic diseases, systematic review

Introduction

It is well known that one of the most compelling challenges of our time is population aging (1). In recent years, as to the World Health Organization report on aging (1), the number of people aged 65 years or over is progressively increased: it is estimated that for the year 2050 the population over 60 years old will double, reaching almost 22% of the total one. In parallel, the number of people aged 80 years or over is growing even faster, and it is expected to triple by 2050 (2). Aging is often associated with chronicity and multimorbidity and their prevalence increases in people aged 65 years and older (3, 4).

Elderly people often are affected by Non-Communicable Diseases (NCDs), also defined as chronic diseases. It is estimated that each year NCDs are responsible for 71% of all deaths (5). The NCDs can be clustered into four main categories: Cardiovascular, Chronic respiratory diseases, Cancer, and Diabetes. Cardiovascular diseases are responsible for most NCDs deaths, followed by cancers, respiratory diseases, and diabetes (5). Furthermore, old age and chronicity are often associated with frailty syndrome.

Despite the importance and the interest toward frailty, there is no agreement on the definition (6). In fact, according to the literature, two theoretical paradigms try to define frailty: the biomedical and bio-psycho-social paradigms. As to the biomedical paradigm, frailty is considered a biological syndrome in which there is an important reduction in the functional reserves and a diminished resistance to stressors. These features result in a cumulative impairment of the multiple physiological systems that cause a state of increased vulnerability and adverse consequences (7). Conversely, the bio-psycho-social paradigm defines frailty as a dynamic state that affects an individual that loses one or more functional domains (physical, psychological, and social) due to the influence of different variables that increase the risk of adverse health outcomes (8). Despite the differences between the two considered paradigms, it is possible to underline a common conclusion: frailty is associated with the loss of different functional domains, which leads to an increased vulnerability to adverse events such as risk of falls, hospitalization, disability, and mortality (9). Anyhow, it is universally recognized that frailty is a clinical condition that can impair several areas (e.g., general health and operative risk) (10) and, according to the criteria established by Fried, its prevalence is around 10% in ≥65 and between 25–50% in over 85 years old (11). Moreover, in a recent systematic review and meta-analysis, the prevalence data collected from 62 countries and territories showed that the pooled prevalence in studies using physical frailty measures was 12% (95% CI = 11–13%; n = 178), compared with 24% (95% CI = 22–26%; n = 71) for the deficit accumulation model (those using the Frailty Index, FI) (12).

The overall result of the interaction between the aging process and clinical conditions is the progressive deterioration of the homeostatic balance, so it follows that a deteriorated homeostasis may result in an increased difficulty in coping with stressors (10). People affected by frailty syndrome are more susceptible to health status changes following a minor stress event than non-frail people.

Rockwood et al. proposed an operational definition of frailty with the Frailty Index (FI), by counting the number of deficits accumulated over time, within an extensive list (13, 14). This definition was based on the idea that frailty is a state of chaotic disorganization of physiological systems that can be estimated by evaluating certain indexes such as functional status, diseases, physical and cognitive deficits, psychosocial risk factors, and geriatric syndromes. Furthermore, in 2005, Rockwood et al. described a different approach in frailty evaluation, which was embedded in the Clinical Frailty Scale (CFS), a screening tool based on clinical judgment (14).

CFS, originally developed in Canada, is entirely based on clinical judgment, fast and easy to use, and it has proven to be an effective instrument for frailty assessment (1= Very Fit; 2= Well; 3= Managing Well; 4= Vulnerable; 5= Mildly Frail; 6= Moderately Frail; 7= Severely frail; 8= Very severely Frail; 9= Terminally Ill) (13–16).

According to the scientific literature, the use of CFS in frailty assessment has been widely used to predict patients' outcomes in the acute phase of the disease (16–18). Few studies tried to understand the impact of frailty on rehabilitation outcomes, for example, Holland and colleagues (18) by focusing on pulmonary rehabilitation and Pandey and colleagues (17) on heart failure patients.

More information is needed to define the implications of frailty syndrome, not only in the acute phase of a disease but also in the presence of chronic disease, therefore, this systematic review aims to evaluate the use of CFS for frailty assessment, with a specific focus on chronic and non-communicable diseases.

Methods

The systematic review was registered on the PROSPERO database that was previously searched for similar reviews in order to avoid duplication: "The Clinical Frailty Scale (CFS) employment in the frailty assessment of patients suffering from Non-Communicable Diseases (NCDs): a systematic review" (PROSPERO 2021 CRD42021224214).

Data were reported according to the international PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (19) and, a meta-analysis was not conducted due to the wide heterogeneity of the methodologies (20, 21) adopted by the studies considered, so we have conducted a narrative synthesis.

Search strategy

An electronic literature search was performed on PubMedMedline through Pubmed, Scopus, EMBASE, Web of Science, and EBSCO databases, considering all the publications until December 2021, to describe how CFS is employed with patients suffering from chronic conditions (Appendix a). Different combinations of keywords, including *Clinical Frailty Scale, noncommunicable (or non-communicable) disease/s, chronic disease/s, heart disease/s, cardiovascular disease/s, heart failure, coronary heart disease, hypertension, stroke, cancer, diabetes, chronic obstructive pulmonary disease (or COPD), chronic respiratory disease/s, chronic lung disease/s,* and *asthma*, were entered and applied in the title and abstract sections.

A support from the Microsoft Office^{TM} pack was used: after the Comma-Separated Values (CSV) files were downloaded from the online databases, the organization functions of Microsoft Excel were used to unify all the results in a single sheet and to remove all the duplicated records.

After the electronic search was completed, two reviewers (AS, LR) independently performed the screening of the records retrieved and subsequently, after a full text analysis, they identified the eligible papers. Doubts and concerns about inclusion and exclusion criteria were discussed by all researchers through a triangulation process (NG, MV, AS, LR, AP).

Inclusion and exclusion criteria

Studies were considered suitable for inclusion if written in English, published in peer-reviewed journals, and where the CFS was employed to screen patients' frailty. There were no limits concerning patients' age, sample size, type of disease/s, and settings where the studies were performed.

Articles that did not deal with frailty, meeting abstract, books/book chapters, comment/editorial, protocol/design, reviews, and meta-analysis, were excluded.

Data extraction

Information collected through the full-text analysis was extracted by two independent reviewers (NG, MV) and it was organized in a synoptic table, according to the following categories: [A] Characteristics of the study: first author, year of study, nation of the study, nation ranking according to the Human Development Index (HDI) (22), study design, study setting, and professional figures involved; [B] Characteristics of the participants: sample size, mean age, and type of disease/s; [C] CFS-related characteristics: reason/s for CFS utilization, time at which CFS was used (e.g., during outpatient or inpatient visits, retrospectively based on clinical records), study authors' comment on CFS, and CFS related results; [D] Other eventual frailty indexes employed and other eventual outcomes considered (e.g., clinical, functional, and psychological outcomes).

The quality of each study was assessed by two independent reviewers (NG, MV) with the Newcastle Ottawa Scale (NOS) (23). In particular, two adapted versions were used, one for cohort and case-control studies, and one for cross-sectional studies. Using these scales, each study was judged on eight or ten items, categorized into three groups: the selection of the study groups, the comparability of the groups, and frailty-related outcomes. As to cohort and case-control studies, stars are awarded for each quality item, and the highest quality studies are awarded up to nine stars. A study is considered of good quality if there are 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain. Concerning cross-sectional studies, each study is judged on a 10-point scale and divided into four groups: very good studies (9–10 points), good studies (7–8 points), satisfactory studies (5–6 points), and unsatisfactory studies (0–4 points).

Results

After database searching and duplication removal, 969 records were found. Following the title/abstract screening, 236

suitable articles were found and after the full-text reading, 58 studies were considered for quality assessment. Most of the excluded records were not focused on chronic disease/s ($n = 63$), did not include CFS ($n = 47$) or had no focus on CFS ($n = 37$) (Figure 1).

Most studies were of good quality as assessed by the Newcastle-Ottawa Scale (NOS), both for cohort and case-control studies (mean 7.33 ± 0.81), and cross-sectional studies (mean 7.71 ± 0.71). Two articles were excluded as they were judged "fair" quality, particularly in the methodological description of their studies, and they could affect the reliability of the results: for this reason, 56 studies were included and analyzed in the present review.

The information collected is represented in a synoptic table (Appendix a) (24–79). Most of the studies were observational studies (67.86%), followed by retrospective studies (32.14%). The total number of patients in the included studies was 20,497 and the sample sizes varied widely, ranging from 20 patients to 2,588 patients, with most of the studies including more than 100 patients (87.5%) (mean age range: from 42.9 ± 9.4 to 87.4 ± 4.96). Most of the studies were conducted in a hospital (85.71% inpatients and 10.71% outpatients), one study was performed both in inpatient and outpatient settings (1.79%), and only one in a community-dwelling center (1.79%). In all of the studies, CFS was used to assess frailty and for statistical analysis, and in almost half of the studies, it was employed for sample stratification (46.43%) too. In the considered studies, besides CFS, these outcomes were evaluated too: 35.71% functional measures (basic and instrumental activities of daily living, mobility, gait speed, etc.), 23.21% psychological status (anxiety, depression), and 17.86% cognitive functioning. Almost in all of the studies, a physician assessed the CFS score (82.14%), in six cases it was assessed by a nurse (10.71%), in two cases alternatively by a physician or a nurse (3.57%), in one case by an occupational therapist (1.97%), and in one study the patients performed a CFS self-assessment (1.97%). In 10 studies (17.86%), in addition to the CFS, other frailty indexes were employed: the Fried frailty criteria (53, 55, 58, 62), Sarcopenia (44, 45), Frailty index (51, 53), CKD Frailty Index Lab (67), Liver frailty index (55), PARTNER frailty scale (53), Derby frailty scale (51, 52), and Acute frailty (51, 52).

Tables 1a,1b summarize the results concerning the nations of the studies, the type of disease/s, data used for CFS compilation, the CFS evaluation timing, the authors' comment on CFS, and the CFS related results. Tables 1a,1b show that studies were conducted mostly in Japan (37.5%), and almost half of the studies were focused on cardiovascular diseases (46.42%). The other chronic diseases that have been found most frequently were cancer (25.00%) and diabetes (10.71%). In many studies clinical judgement (41.07%), ADL (28.57%), functional capacity status (19.64%), comorbidities (14.29%) and mobility (14.29%) data were used for CFS compilation. The evaluation timing of CFS was: during inpatient clinical visits (19.64%), in the preoperative phase (28.57%), at patients' admission (16.07%), on clinical records of hospitalized patients (10.71%), and retrospectively on clinical records (10.71%). Simplicity (39.29%), efficacy (37.5%), and rapidity (16.07%) were the major authors' comments on CFS. The CFS-related results indicated that CFS was associated with clinical outcomes (33.92%), with the presence of the disease (12.5%), and with clinical decision-making (10.71%). Furthermore, CFS resulted a good predictor of life expectancy (41.07%) and clinical outcomes (21.43%).

Discussion

This systematic review was focused on the CFS utilization in patients suffering from chronic diseases (or NCDs), its dissemination in the different nations, the clinical data used to complete it, and the evaluation timing. Moreover, specific attention was dedicated to investigating the CFS characteristics concerning its usability, reliability, and efficacy in predicting disease-related outcomes.

Although CFS is a well-established tool and used worldwide, most of the included studies were conducted in Japan. In a recent scoping review, it was reported that most of the studies were conducted in Canada (80). This inconsistency with the results of the present study could be explained by the specific focus on NCDs, while in the Church and colleagues' review were considered also critical illnesses. Additionally, the elderly population in Japan amounts to more than 30% of the total population (1) and this might explain the dedicated attention to this topic.

In recent years, the number of studies that provided a CFS evaluation is considerably increased, underlining specific attention dedicated to frailty syndrome in different clinical settings and diseases (80). Most of the included studies involved patients affected by chronic cardiovascular diseases (46.42%) and by different types of cancer (25.00%). This prevalence could be due to the impact that these clinical conditions have on mortality since, as highlighted in the WHO report, these diseases account for most of NCDs deaths per year (5).

Frailty is largely considered a geriatric syndrome, but many studies highlight that frailty syndrome has a notable impact on the younger population as well (81). In the present review, five studies (36, 55, 56, 58, 64) considered a sample size of patients with a mean age of <65 years. Although chronic conditions are often associated with the elderly population, scientific evidence shows that NCDs are responsible for 15 million deaths per year in people aged 30–69 years (5). Furthermore, it has been shown that, even though absolute mortality in relation to frailty was higher with increasing age, the relative risk of mortality in relation to frailty was highest for younger people (81). Therefore,

TABLE 1a Main features of the studies included ($n = 56$).

Nation	HDI° (Ranking)	*n* (%)	Disease/s	*n* (%)	Data considered for CFS evaluation	*n* (%)*
Japan	0.919 (19)	21 (37.5)	Cardiovascular disease[a]	26 (46.42)	Clinical judgement	23 (41.07)
UK	0.932 (13)	11 (19.64)	Cancer	14 (25.00)	ADL	16 (28.57)
Canada	0.929 (16)	5 (8.93)	Diabetes	6 (10.71)	Functional capacity status	11 (19.64)
Poland	0.880 (35)	4 (7.14)	Chronic kidney disease	4 (7.14)	Comorbidities	8 (14.29)
Italy	0.892 (29)	3 (5.36)	Cirrhosis	2 (3.57)	Mobility	8 (14.29)
China	0.761 (85)	2 (3.57)	Chronic lung disease	1 (1.79)	Cognitive functions	2 (3.57)
Argentina	0.845 (46)	1 (1.79)	End-stage kidney disease	1 (1.79)	Exhaustion	2 (3.57)
Australia	0.944 (8)	1 (1.79)	End-stage renal disease	1 (1.79)	IADL	2 (3.57)
Germany	0.947 (6)	1 (1.79)			Inactivity	2 (3.57)
Greece	0.888 (32)	1 (1.79)			Preadmission life history	2 (3.57)
Pakistan	0.557 (154)	1 (1.79)			Social support	2 (3.57)
Slovakia	0.860 (39)	1 (1.79)			Symptoms	2 (3.57)
Spain	0.904 (25)	1 (1.79)			Clinical records	1 (1.79)
Sweden	0.945 (7)	1 (1.79)			Comparison to peers	1 (1.79)
Taiwan	n.a. (n.a.)	1 (1.79)			Description of general appearance	1 (1.79)
USA	0.926 (17)	1 (1.79)			Medical examination	1 (1.79)
					Patients' perspective	1 (1.79)
					Psychological distress	1 (1.79)

°HDI index is based on 3 dimensions: a) Life expectance at birth; b) Expected years of schooling and mean years of schooling; c) Gross National Income per capita (United Nations Development Programme, http://hdr.undp.org/en. Accessed on January 2021).
*Refers to the absolute frequency and percentage of each single category retrieved in the included studies (for further details see Appendix b).
[a]Including: Heart Failure 17.86%, Atrial Fibrillation 8.93%, Aortic Valve Stenosis 7.14%, Coronary Artery Disease 3.57%, Peripheral Artery Disease 3.57%, N-STEMI 1.79%, STEMI 1.79%, Stroke 1.79%.

TABLE 1b Main features of the studies included ($n = 56$).

CFS evaluation timing	n (%)*	Authors' comment on CFS (n=34)§	*n* (%)*	Study outcomes involving CFS△	*n* (%)*
Preoperative	16 (28.57)	Simplicity	22 (39.29)	Associated with clinical outcomes	19 (33.92)
Inpatient clinical visits	11 (19.64)	Efficacy (Reliability)	21 (37.5)	Associated with the disease	7 (12.5)
Admission	9 (16.07)	Rapidity	9 (16.07)	Associated with clinical decision making	6 (10.71)
Clinical records of hospitalized patients	6 (10.71)	Subjectivity	4 (7.14)	Associated with socio-demographic characteristics	5 (8.93)
Retrospectively on clinical records	6 (10.71)	Lacking	2 (3.57)	Associated with hospital readmission	1 (1.79)
Outpatient clinical visits	3 (5.36)	Inexpensive	1 (1.72)	Associated with quality of life	1 (1.79)
Discharge	2 (3.57)			Predictor of life expectancy	23 (41.07)
6 months after discharge	1 (1.79)			Predictor of clinical outcomes	12 (21.43)
Home clinical visits	1 (1.79)			Predictor of hospitalization/hospital readmission	6 (10.71)
Initiation of dialysis	1 (1.79)			Predictor of quality of life	1 (1.79)
Postoperative	1 (1.79)			Clinical variables predictors of frailty	2 (3.57)
Not specified	1 (1.79)			Disease predictor of frailty	1 (1.79)
				Socio-demographic characteristics predictors of frailty	1 (1.79)
				CFS not significant	5 (8.93)

*Refers to the absolute frequency and percentage of each single category retrieved in the included studies (for further details see Appendix b).
§Clustered categories according to authors' comments on CFS (for further details see Appendix b).
△Clustered according to the CFS-related results (for further details see Appendix b).

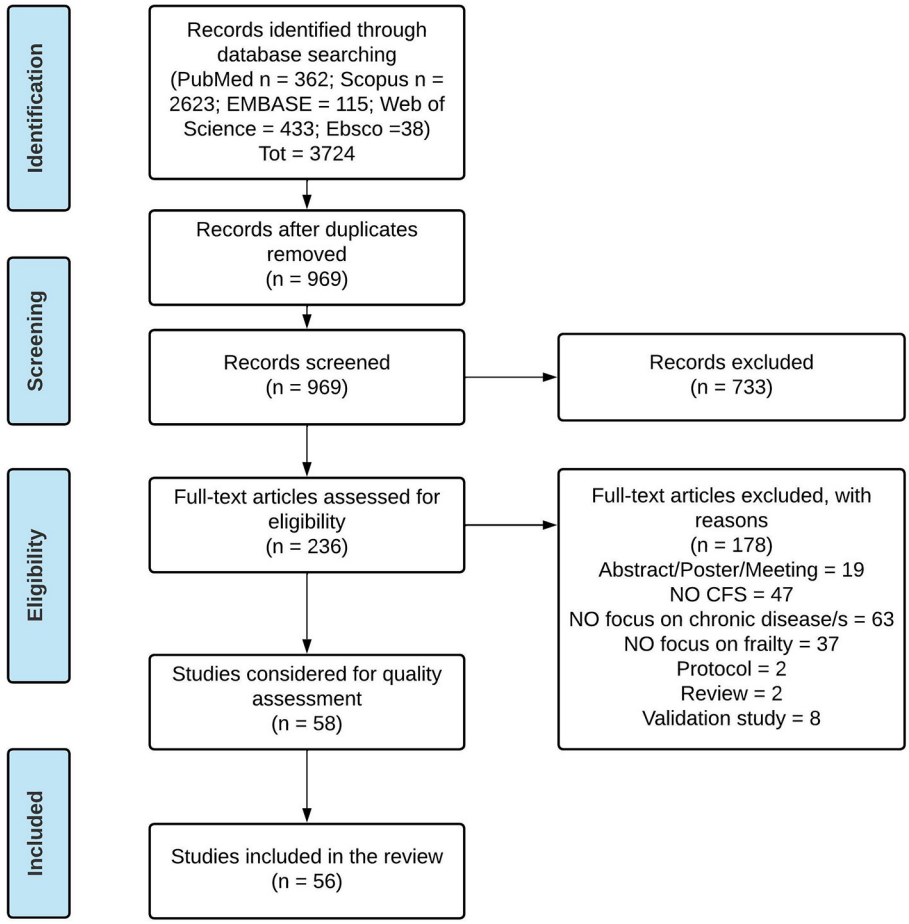

FIGURE 1
PRISMA Flow Diagram of the systematic review.

efforts to identify, manage, and prevent frailty should include middle-aged individuals with multimorbidity, in whom frailty is significantly associated with mortality, even after adjustment for the number of long-term conditions, sociodemographic characteristics, and lifestyle (82).

All the studies were conducted with an observational or retrospective design. There are no studies in which is described a specific intervention for disease-related frailty and it could be interesting to evaluate the CFS reliability in pre and post-study designs. Indeed, in a recent scoping review, the authors found only few studies conducted in rehabilitation settings (80). Among these, different types and timing of rehabilitation were taken into account, for example, pre-operatory (83, 84) or post-acute rehabilitation (85, 86), and none was focused on NCDs or on chronic diseases. Moreover, a meta-analysis performed by Attwell and Vassallo found only three studies focused on COPD frail patients' rehabilitation (87). This data is consistent with our results since no articles were found about NCDs rehabilitation and it highlights a lack of studies focused on the use of CFS in NCDs rehabilitation. Therefore, specific attention should be given to deepening and shedding light on this topic.

Even though CFS is based on clinical judgment, in six studies (10.71%), the CFS score has been attributed retrospectively based on patients' medical records. This scoring method was reported to be reliable, provided that the charts (medical records, nurse records, etc.,) contain all the elements required to assign a CFS score (88). Also, evidence reports a consistency between CFS scores attributed considering medical records and CFS scores attributed through interviews with patients or their families (89). Moreover, CFS should be administered by medical doctors, but, despite this, ten studies included in this review show that CFS is not always administered by physicians (42, 46, 55–57, 59, 68, 70, 75, 77). This is made possible by the multidimensionality of this tool because it relies on data other than clinical judgment.

In a recent study, the results obtained with the CFS were compared with those obtained with the Edmonton Frail Scale (EFS) (90). The findings of this study imply that the CFS is a valid measurement tool for frailty in critically ill patients, compared with a multidimensional and more comprehensive tool. Similarly, Ritt and colleagues (91), compared this instrument with the Frailty Index, finding that the predictive accuracy of mortality was similar between the two instruments, but the CFS score was even able to predict unplanned hospital admission. Moreover, CFS was found to be an easy-to-use tool and had high inter-rater reliability in addition to a good prognostic value (92). Also in the present review, most of the included studies (82.14%) used only CFS to evaluate frailty. This data is supported by existing literature that reports a high degree of effectiveness of the CFS as a screening instrument (93). Besides, these data may be consistent with this review's results related to the observations on CFS, since most authors commented that it was a simple (Simplicity, 39.29%), reliable (Efficacy, 37.5%), and fast (Rapidity, 16.07%) instrument for frailty assessment.

As for CFS-related results, different studies find associations between CFS score and the disease taken into account, and, conversely, one study finds that the presence of the disease is a predictor of CFS score. These results are supported by the literature, since it was found that chronic diseases contribute to the frailty status development (10) and, in addition, another study suggests a bidirectional association between frailty and the disease, specifically in presence of multimorbidity (94). Same results were found concerning CFS and clinical outcomes: in most of the studies, CFS was found to be associated with or a predictor of patients' clinical outcomes. Literature supports these findings both when it deals with frailty, evaluated with different frailty indexes (95, 96), and when frailty is evaluated specifically with CFS (80). Our results are consistent with the aforementioned studies although they were not focused specifically on chronic diseases.

Moreover, CFS was found to be associated with clinical decision-making, as well. This result is in line with recent literature that outlines the importance of taking into account frailty when dealing with chronic diseases (97, 98). Indeed, frailty is a syndrome that could interact with therapeutic prescriptions for other diseases, worsening the clinical condition, or, on the other side, its course could be accelerated by the implementation of disease-related clinical practices (97, 98).

Socio-demographic characteristics were found to be associated with CFS in different studies. This result is in line with previous literature since frailty is a syndrome that affects particularly older people (99). Moreover, in a recent study, it was found that people with worsening economic conditions over time simultaneously experience a rapid increase in the frailty symptoms (100).

In several articles frailty resulted to be associated with or a predictor of mortality and rehospitalizations. A recent meta-analysis conducted on Chronic Heart Failure (CHF) found that frailty is a significant predictor of all-cause mortality and CHF-related hospitalizations (95). Similar findings are reported in a systematic review on Chronic Kidney Disease and on End-Stage Renal Disease, which suggests that frailty is an independent risk factor of overall mortality in patients affected by these diseases (101). Moreover, Church and colleagues report that several outcomes are associated with CFS score, such as mortality, length of hospitalization, readmissions, and also institutionalizations (80).

Even though different studies focus on the relationship between frailty and quality of life, only one study in this systematic review finds this result. In literature, frailty is associated with worse quality of life in patients affected by different diseases, such as breast and prostate cancer (96, 102), or in cardiovascular diseases (103, 104). Uchmanowicz and colleagues underline that all the areas forming the construct of quality of life (physical, psychological, social, and environmental) are negatively affected by frailty status (103).

In this systematic review, an eventual limitation lies in the labels assigned to group the findings of the included studies, which were created arbitrarily to provide an immediate understanding. Nevertheless, this procedure was conducted by a triangulation process between the reviewers (NG, MV, AS, LR), and supervised by all the authors, to guarantee the best level of objectivity.

On the other side, as far as we know, this is the first systematic review specifically focused on the use of CFS in NCDs, and it could provide useful information both for a further investigation through a meta-analysis and for clinical practice.

Conclusions

This systematic review provides a specific focus on the utilization of CFS in patients suffering from NCDs that adds useful information in the field of frailty assessment. Indeed, CFS seems to be an easy-to-use and reliable instrument to assess frailty in this kind of disease, it resulted to be associated with a variety of disease-related characteristics, and it is a good predictor of clinical outcomes, life expectancy, hospitalizations, and quality of life. Further research is needed to corroborate these findings, particularly related to CFS predictivity in clinical settings, in order to support a routine assessment of frailty in NCDs patients with this tool. This kind of assessment might be provided also in rehabilitation settings since it provides an overview of patients' frailty status and adds useful information that could be implemented in the tailored rehabilitation program and subsequent intervention.

Data availability statement

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

Author contributions

Conceptualization and methodology: NG, MV, SSB, and AP. Investigation: AS and LR. Data curation: NG, MV, AS, and LR. Supervision: SSB and PB. Writing—original draft: NG, MV, AS, and LR. Writing—review and editing: PB and AP. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.967952/full#supplementary-material

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Presbyopia: An outstanding and global opportunity for early detection of pre-frailty and frailty states

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Introduction

According to the World Population Prospects 2022 of the United Nations, the world's population will rise over the next decades (e.g., by 6.3 and 21% from 2022 to 2030 and 2050, respectively) (1). Likewise, the population of older persons is increasing (1). Indeed, the United Nations expects that the share of the global population aged 65 years and above will rise by 6% between 2022 and 2050 (1). Consequently, age-related diseases, including eye ones, are expected to be very prevalent (2–4). For this reason, population aging is a crucial demographic issue with a growing global impact on all socioeconomic areas (4). This fact has provoked different global initiatives like the one declared by the United Nations in 2020, called the Decade of Healthy Aging 2021–2030, whose aim is to promote and maintain the wellbeing of older adults (5). In this context, the Lancet Global Health Commission on Global Eye Health argues that eye health should be part of such strategies focused on achieving universal healthy aging (6). Indeed, vision impairment and blindness affect multiple functional domains (physical, cognitive, psychological, social) and overall quality of life and wellbeing (6). Now, 510 million people have impaired vision, and 43.3 million are blind (7). Among these people, older adults present with a moderate/severe vision impairment and blindness prevalence of 112 cases and 18.5 cases per 1,000 people, respectively (7). Age-related eye diseases (e.g., cataracts, glaucoma, age-related macular degeneration, and diabetic retinopathy) are the leading global causes of visual impairment and blindness (6, 8). Hence, as the population ages, an increase in those numbers is expected, and by 2050 866 million and 61.0 million people will have moderate/severe vision impairment and be blind, respectively (7). Consequently, this global eye health initiative urges, like healthy aging initiatives, an in-depth understanding of the aging process and its associated diseases for preventing or delaying age-related eye conditions (6, 9).

Age-related eye changes: Presbyopia

The aging process involves a progressive decline of all organ-specific functions, including eye ones. Like the rest of the body, the eye undergoes age-triggered changes that alter its structures, impairing its physiological functions [(10) review eye changes critical for the onset of age-related eye diseases]. One of these impaired functions is the accommodation process. This process, which allows focusing on near objects, occurs by the harmonized action of the ciliary muscle and the zonule fibers which hold the lens in place. Aging triggers changes in these structures involved in accommodation, leading to the gradual inability of the eye to focus (11, 12). This physiological event called presbyopia starts to express itself at around 40 years and affects 100% of the population by age 50 (13, 14). The tell-tale symptom of presbyopia is blurred vision while reading, sewing, using a mobile phone, tablet, computer, or doing anything that requires intermediate and near vision (5). Furthermore, presbyopia may present with eyestrain and headaches after reading or doing close-up work (5). Therefore, it negatively impacts the individuals' quality of life, urging them to seek a solution from an eye specialist (15–17).

Frailty and eye

Frailty is an age-related syndrome that implies changes at all physiological levels, leading to a state of vulnerability, which could facilitate age-related disease onsets (18). A recent systematic review has shown that the overall prevalence of frailty and pre-frailty among individuals aged 50 years and older varies between 12–24% and 46–49%, respectively (19). Likewise, another systematic review has revealed that the incidence of frailty and pre-frailty among older adults is 43.4 and 150.6 new cases per 1,000 person-years, respectively (20).

Several recent studies have identified pre-frailty/frailty signs in middle-aged adults (40–50 years old) (21–23). Even more notable is that this frailty/pre-frailty condition is associated with multimorbidity and mortality in UK older/middle-aged participants of a prospective analysis (22). So, early detection of this condition could allow rapid implantation of measures that prevent or delay these poor health outcomes (22). Unfortunately, its multiple signs and symptoms (often non-specific) and the limited knowledge of its underlying molecular mechanisms (mainly in middle-aged adults) have hindered its early diagnosis (18).

The World Health Organization (WHO) has introduced the concept of intrinsic capacity (IC) (i.e., the combination of all the individual's physical and mental capacities) as a crucial component of healthy aging (24). It has also provided recommendations and tools to manage IC decline at the community level and primary care level, assuring integrated care for older adults (ICOPE) (25, 26).

According to the WHO ICOPE guidelines, vision is a critical component of IC (26). A simple eye chart permits the measurement of visual capacity, and distance acuity worse than 6/18 implies moderate vision impairment that needs further diagnostic assessment (26).

In one US study with 2,705 older adults, individuals with near vision impairment were more likely to be pre-frail and frail than those without visual loss (27). This result suggests an association between vision impairment, which promotes IC decline, and frailty (27). In this sense, some prospective studies have found that IC decline overlaps with frailty syndrome and can predict poor health outcomes in older adults (28–30).

Another UK prospective study with 493,737 middle-aged adults and older adults showed that individuals with glaucoma had a high prevalence of pre-frailty and frailty conditions (41.2 and 5%, respectively) (22). Equally, Wang et al. have found in a prospective China population-based study that this disease is associated with 10-year mortality (31).

The previously mentioned study by Hanlon et al. of middle-aged and older adults also revealed that patients with diabetes presented higher pre-frailty and frailty prevalence (54.8 and 13%, respectively) than glaucomatous ones (22). Besides, a systematic review has proved an association between diabetic retinopathy (DR, a major microvascular diabetes complication) and poor psychosocial functioning, affecting the quality of life of these patients (8, 32, 33). Likewise, a retrospective cohort study with 477 participants found that both frailty and diabetic microvascular complications can predict adverse clinical outcomes (e.g., emergency hospitalizations, institutionalization in a long-term care facility, falls, fractures, and death) in diabetic older adults (34).

Although the prevalence of pre-frailty/frailty in individuals with age-related macular degeneration (AMD) is yet unknown, Zhu et al. have suggested in a prospective study that late AMD is a biomarker of frailty syndrome (35). These authors argued that the poor survival observed in late AMD participants could be due to age- and frailty-related systemic comorbidities that coexist and share underlying molecular mechanisms with AMD (35). Moreover, several prospective studies have demonstrated that patients with AMD present a higher risk of falls and fear of falling, which leads to a decreased quality of life and disability (36–38). This fear of falling also has been observed in glaucomatous patients using the same validated questionnaire (the University of Illinois at Chicago Fear of Falling Questionnaire) (39). Some systematic reviews have also demonstrated an association between the fear of falling and poor quality of life with frailty (40, 41). Therefore, all these data seem to connect AMD and frailty.

A prospective study performed with age-related cataract patients found that they have poor survival rates, suggesting that cataracts, the most important cause of visual impairment and blindness, are also a biomarker of frailty (42). This study confirmed a previous cohort study that had shown

the association between age-related cataracts and some measures of frailty independent of visual acuity and systemic comorbidities (43).

Villani et al. have built an ocular surface frailty index (OSFI) and tested *via* a longitudinal study its capacity to identify frail-ocular surfaces among patients who underwent cataract surgery (44). Consequently, these authors propose OSFI as a tool to predict patients with a high risk of post-surgical development of dry eye disease (DED) (44). This disease is also an age-related condition of the ocular surface that represents a growing problem with a substantial negative impact on the quality of life and global economy (45, 46).

To support this subsection, we searched in PubMed for the combination of the words: "frailty" and "eye" or one of the four age-related eye diseases leading causes of visual impairment/blindness: "cataracts", "glaucoma", "age-related macular degeneration", and "diabetic retinopathy". As we only aimed to summarize knowledge concerning this subsection's topic, among all articles found, we selected those most recent and focused on our point of view.

Eye as a source of diagnostic biomarkers

The eye and especially the tear film have become, in recent years, the target for researchers of being an outstanding source of biomarkers for the diagnosis of both ocular and systemic diseases such as dry eye, Sjogren's syndrome, keratoconus, cancer, and COVID-19 (47–52). The main reason for this is that tears are the most accessible corporal fluid, and collecting them is easier, faster, and less invasive than the collection methods of other fluids (53).

Tear film covers the external ocular surface and consists of an inner mucous/aqueous and an external lipid phase, presenting a great diversity of macromolecules that undergo measurable changes in pathological conditions (54–58). Among these conditions are age-related diseases, including eye diseases. So, tears have provided several potential biomarkers for cataracts, glaucoma, AMD, DR, Alzheimer's, and Parkinson's diseases (57, 59–63). Conversely, the presence of specific frailty biomarkers in tears is unknown.

Discussion

Age is a driving factor for frailty and age-related diseases, sharing underlying molecular mechanisms (64–66). According to the population aging and life expectancy prospects, these conditions, including eye-related ones, will be very prevalent (1, 2, 64). Age-related eye diseases are the world leading causes of visual impairment and blindness (6, 8). Hence, as the population ages, a growing number of visually impaired and blind people is expected, which will have an enormous humanistic and economic impact (8). These visual problems decrease the IC and quality of life of those affected by it and are associated with frailty syndrome (6–8, 27). Moreover, age-related eye diseases coexist with pre-frailty/frailty syndrome and are potential biomarkers of frailty and predictors of poor health outcomes (8, 22, 31, 34, 35, 42). These data reflect the crucial role of visual performance in achieving healthy aging (6). In this context, future studies should explore the validity of including new visual function-related tests in primary care for the integrated attention of older adults (6, 37, 39–41, 67). Indeed, some vision experts claim to perform the contrast sensitivity test to evaluate the fear of falling (a marker of poor quality of life, disability, and frailty) because it is a better predictor of this fear than the visual acuity test (37). Moreover, a recent cross-sectional study has found that poor contrast sensitivity is associated with frailty (68). Likewise, the older adults' health programs could include questionnaires to measure fear of falling and quality of life previously validated in patients with age-related eye diseases (37, 39, 67).

The pivotal role of visual performance in achieving healthy aging also urges research in the diagnosis and treatment of age-related eye disorders fields to implement new global preventive and therapeutic strategies against those diseases (6).

Frailty syndrome, a geriatrician's high-priority theme, has become an emerging target of gerontologists. They have found that this disorder that predisposes a person to age-related disease onsets is present in older and middle-aged adults and is associated with mortality, particularly in individuals with multi-morbidity (18, 21–23, 69). Given that a rapid intervention can reverse the condition, thus preventing its poor health outcome, gerontologists recommend screening frailty biomarkers in middle-aged adults (from the fourth decade of life onwards) (21–23, 69).

In this life period, presbyopia can also occur. This physiological process gradually reduces the ability of the eye to focus at different distances, impacting individuals without and with refractive errors (e.g., myopia, hyperopia, or astigmatism) who start to feel presbyopia symptoms from 40–50 years (12, 14). Because of these presbyopic symptoms, the entire population of middle-aged adults will visit eye care professionals seeking a solution. Probably, no other biomedical professionals attend to the whole population of middle-aged adults. This fact is remarkable because, as we have commented above, screening frailty biomarkers in middle-aged adults is critical for timely interventions to prevent age-related diseases and mortality.

Some data support the concept of age-related eye diseases as biomarkers of frailty phenotype and predictors of poor health outcomes (8, 22, 27, 31, 34, 35, 42, 67). Equally, data back the concept of the eye and its tear as a source of diagnostic biomarkers of ocular and systemic diseases, including age-related ones (57, 59–63). Thus, it would not be surprising that tears would contain frailty biomarkers. As any eye practitioner can easily

collect tears, screening for frailty biomarkers from tears of presbyopic subjects may represent an outstanding opportunity for early detection of pre-frailty and frailty states, allowing timely intervention and thus preventing poor clinical outcomes.

Molecular mechanisms of frailty could also arise at the eye level, as occur with aging and age-related diseases (65). Indeed, a systematic review has revealed recently that frailty mechanisms occur in oral tissues (70). In this sense, the prospective study of Villani et al. has suggested the existence of frailty underlying mechanisms at the ocular surface of individuals who undergo cataract surgery (44). Thus, a future screening of frailty biomarkers from tears of presbyopic subjects could be a simple method of studying possible ocular surface frailty mechanisms and how they could link to the processes that occur in the rest of the eye and body. The understanding of these mechanisms could provide new biomarkers, helping delay age-related diseases onsets, including eye ones.

In summary, this article aims to show that theoretically, it is possible to perform a simple and large-scale frailty screening of middle-aged adults' tears, taking advantage of the unavoidable visit of presbyopic individuals to eye care professionals looking for a solution to their symptoms. The previous search for frailty biomarkers taken from tears of presbyopic people would allow this screening and thus timely interventions, delaying age-related diseases onsets and mortality.

We have confidence in the value of the tears of presbyopic people as an easy means to identify frail/pre-frail individuals, validate frailty biomarkers candidates, and study local frailty molecular mechanisms, which will provide new biomarkers.

Author contributions

AC, DM-C, and JR-A contributed to the research conception. AC, JR-A, and IM-A contributed to the literature review. AC and JR-A contributed to the manuscript writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Heart rate variability: A biomarker of frailty in older adults?

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Frailty is a state of critical loss of physiological complexity resulting in greater vulnerability to stressors and has been characterized as a debility syndrome in the older adult. Changes in functional capacity and the cardiovascular system during aging are the most significant and relevant for this population, including the clinically healthy. In this sense, this review aims to investigate methods to monitor the performance of older adults, such as heart rate variability and verify how it can be related to frailty. It contributes to understanding that the changes in heart variability can be a marker for frailty in older adults.

KEYWORDS

frailty, older adults, heart rate variability, autonomic control, wearable device (WD)

Introduction

The World Health Organization (WHO) established the period from 2021 to 2030 as the "Decade of healthy aging." However, the COVID-19 pandemic demonstrated inequality in the aging process and the lack of public policies for this segment of the population, raising the importance of developing studies to alleviate the decline of intrinsic capacity associated with aging (1). The intrinsic capacity of older adults can be evaluated through performance measures, however, it remains a challenge to validate such measures in this population (2). Understanding the mechanism of vulnerability to stressors in frail older adults can become useful for the creation of preventive measures and improvement of quality of life and resistance to stressors (3). In this sense, this review aims to investigate methods to monitor the performance of older adults, such as heart rate variability and verify how it can be related to frailty.

TABLE 1 Frailty assessment.

Tools	Components
FRAIL scale (6)	Fatigue, resistance, ambulation, illness, loss of weight
Frailty phenotype (7)	Weight loss, low physical activity, exhaustion, slowness, weakness
Study of Osteoporotic Fractures frailty criteria (8)	Weight loss, exhaustion, unable to rise from a chair five times
Multidimensional Prognostic Index (9)	Comorbidity, nutrition, cognition, polypharmacy, pressure score risk,living status, activities of daily living (ADL), instrumental activities of daily living (IAD) Basic activities of daily living (ADLs), instrumental ADLs, chronic medical conditions that require drugs, exercise, and appearing fitter compared with patients of similar age.
Clinical Frailty Scale (10)	

Frailty assessment

Frailty is a state of critical loss of physiological complexity resulting in greater vulnerability to stressors. This has been characterized as a debility syndrome in the elderly in which there is decreased strength, low physical activity, energy depletion and unintentional weight loss (4). In turn, frail older adults become more likely to develop health complications and a high risk of important adverse outcomes. They may also have accelerated functional decline, physical disability, low ability to recover and mortality (4).

As frailty develops in older adults, it often leads to a decline in general health, characterizing a dynamic state in which it can improve or worsen over time (5). For frailty assessment, different tools can be used but only a few of them divide the classification into pre-frailty, frailty and robust which allows us to apply preventive measures (Table 1), The most frequent tool is the frailty phenotype proposed by Fried et al. (7). The Fried Phenotype Criteria is determined by the presence of five measurable components, namely: (1) weakness measured by handgrip strength in the dominant hand; (2) slow gait; (3) unintentional weight loss greater than or equal to 4.5 kg or greater than 5% of body weight in the previous year; (4) report of exhaustion, assessed by self-report of fatigue, indicated by two questions on the Depression Scale of the Center for Epidemiological Studies, and (5) low level of physical activity (7). To be considered a frailty syndrome according to this index, three out of the five criteria must be present, in a way that those who present one or two criteria are considered pre-frail and those who do not obtain any are considered non-frail or robust (7). According to the theory of Fried et al. (7), frailty is based on a reduction in the activity of anabolic hormonal axes, the installation of sarcopenia and the presence of a chronic inflammatory state (Figure 1).

However, although the Fried phenotype is the most used tool to assess frailty, specially in patients with some heart disease (11), there are some challenges to be overcome. The Fried phenotype measuring can be complicated and relatively time-intensive and mainly focuses on physical impairments disregarding other domains such as cognitive dysfunction, which are common in older patients (12). In this sense, new methodology where combine physical and cognitive impairment evaluation should be consider for frailty assessment.

Cardiovascular disease and frailty

Several studies have demonstrated the possible association between cardiovascular disease (CVD) and frailty (13–15). However, literature is limited to be sure if frailty can be a cardiovascular risk factor or vice versa. Many hypotheses are based on common risk factors to identify this association. Franceschi et al. (16), and Ferruci and Fabbri (17) suggested that the inflammatory process leads the cardiovascular diseases (CVD) and frailty. Furthermore, oxidative stress (18) and dysfunction in coagulation (13) are present in CVD and frailty. Even with all these associations, other mechanisms should be addressed, such as the activity of the autonomic system in frailty older adults. It is well documented that during the aging process there is a change in cardiovascular control, causing a decrease in vagal tone and an increase in sympathetic tone. These changes contribute to the occurrence of cardiovascular events, being one of the main causes of death in older adults (19).

Heart rate variability methods of analysis

It is worth noting that parasympathetic activation is lower in older adults compared to younger individuals. There is evidence that even if the myocardium does not respond with an expected intensity concerning the increase in heart rate and contraction force, sympathetic modulation may be increased. In turn, these are some reasons why older adults have a higher cardiovascular risk, as changes in the autonomic balance can have serious consequences on health (20). Since de heart rate is modulated by sympathetic and parasympathetic system, Heart Rate Variability (HRV) can be considered a cardiac autonomic control marker (21). HRV is the quantitative measurement of minimal changes in heartbeats, which provides the regulation of the autonomic nervous system and reflects the system's ability to react to stressors. This index has gained prominence among the various cardiac health measurement indices (22, 23). In addition to the ability to coordinate between the sympathetic and parasympathetic nervous systems, HRV also acts as an indicator

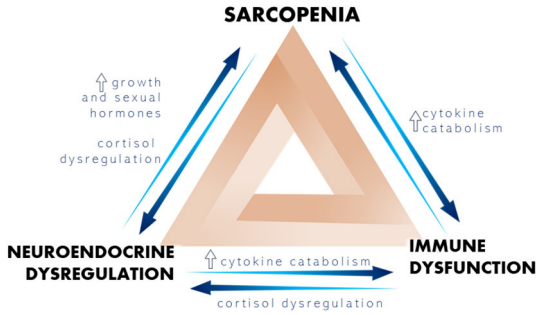

FIGURE 1
Representation of the most important physiological changes that trigger frailty.

of other aspects directly linked to autonomic function, such as self-regulatory capacity, and psychological and physiological stress (23). HRV can be measured using an electrocardiogram (ECG) exam or a 24-h Holter monitor. Recent advances in technology, such as mobile apps, smartwatches, and other devices allow for less invasive and discreet assessments, without affecting the accuracy of the procedure (24).

The HRV calculation can be obtained through linear methods and two categories of measures have been used: time and frequency domain. The time domain, such as the R-R intervals (R-Ri), translate fluctuations in the duration of the cardiac cycle from statistical means. The statistical indices in the time domain include: SDNN (standard deviation of all R-Ri), SDANN standard deviation of the means of normal R-Ri every 5 min), rMSSD (square root of the mean square of the differences between adjacent normal R-Ri in a time interval) and pNN50 (percentage of R-Ri with duration difference >50 ms). The SDNN and SDANN represent the sympathetic and parasympathetic activities, but do not allow distinguishing when changes in HRV are due to increased sympathetic tone or withdrawal of vagal tone. The rMSSD and pNN50 indices represent parasympathetic activity (25).

Another linear method of analysis is the frequency domain, such analysis shows fundamental oscillatory components of the HRV, namely: High Frequency–HF (0.15 to 0.4 Hz corresponding to respiratory modulation, indicating vagal action under the heart); Low Frequency–LF (0.04–0.15 Hz, joint vagal and sympathetic action on the heart, with sympathetic predominance) and Very Low Frequency components–VLF, which seems to be related to the renin angiotensin aldosterone system, thermoregulation and peripheral vasomotor tone (25). For the selection of the appropriate index, the duration of the record and the quality of the data must be considered, carefully so as not to affect the results (23).

Time and frequency domain are measures which reflect the magnitude of heart rate fluctuation, and their decreases

TABLE 2 Methods of HRV measure.

Method	Components
Linear	
Time	• Standard deviation of all NN intervals total variability (SDNN) • Square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD) • Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording (NN50 count) • NN50 count divided by the total number of all NN interval(pNN50)
Frequency	• Power in low frequency range (≤0.04 Hz) (LF) • Power in high frequency range (0.15–0.4 Hz) (HF) • LF power in normalized units LF/(Total Power–VLF) × 100 (LF nu) • HF power in normalized units HF/(Total Power–VLF) × 100 (HF nu) • Ratio LF /HF (LF/HF)
Nolinear	
Poincaré plot	• Area of the ellipse which represents total HRV (S) • Poincaré plot standard deviation perpendicular the line of identity (SD) • Poincaré plot standard deviation along the line of identity (SD2) • SD1/SD2 % Ratio of SD1-to-SD2
Deceleration capacity (DC)	• Detrended fluctuation analysis, which describes short-term (DFA α1) Fluctuations • Detrended fluctuation analysis, which describes long-term fluctuations (DFA α2) • Correlation dimension, which estimates the minimum number of variables required to construct a model of system dynamics (D2)
Fractal scaling exponents	• Approximate entropy, which measures the regularity and complexity of a time series (ApEn) • Sample entropy, which measures the regularity and complexity of a time series (SampEn)

are associated with increased risk for cardiovascular disease. However, it has been shown that not all information carried by R-R intervals variability can be explained by linear method (26). Therefore, the nonlinear measures of HRV, can better capture the tiny but physiologically important changes in HRV and be associated with the development of cardiovascular disease as well (27). Nonlinear measures quantify properties of heart rate dynamics, caused by complex interplays between vagal and sympathetic regulations as response patterns and self-correlations (28) i.e., quantify the unpredictability of a time series. Some categories of nonlinear measures have been used: deceleration capacity (DC), estimating ability to decelerate heart rate on specific time scales, Poincaré plot, plotting every R–R

interval against the prior interval, creating a scatter plot and fractal scaling exponents, assessing fractal organization of heart rate regulation based on chaos theory (28, 29). In Table 2 we summarize the linear and nonlinear measures of HRV.

Evidence link between heart rate variability and frailty

Changes in functional capacity and the cardiovascular system during aging are the most significant and relevant for older adults (30). A systematic review conducted by Afilalo et al. (31) found that frailty increased 2 to 3-fold the risk of vascular disease. Additionally, other studies reported that increased frailty was correlated with increased cardiovascular risk and decreased survival (32–34).

Previous studies carried out with older women pointed out a correlation between HRV and frailty. Chaves et al. (3) used the non-linear measure of HRV [(ApEn) and Varadhan et al. (4) performed it through logarithmic transformation (SDNN, VLF, LF, and LF/HF)], demonstrated that decreases in HRV was associated with an increased risk of frailty. Katayama et al. (35) also found results similar to those mentioned previously, where differences in cardiac activity were found between frail and non-frail older women, which reinforced the theory of the influence of frailty on HRV, using linear (SD, RMSSD and LF/HF Ratio) and non-linear measurement (SampEn).

Another observational study showed that low HRV is related to physical frailty, indicating that this measure can add relevant information to assess physical functioning and identify individuals with a greater possibility of physical decline (23). Toosizadeh et al. (36), evaluated the HRV (RMSSD, HR mean and RR intervals) of older adults during gait, reporting the non-frail had a greater variety of HR concerning the frail and pre-frail. It is estimated that this difference is due to the lack of cardiovascular reserve and the impairment of the autonomic nervous system by the elderly in a situation of frailty or at the beginning of it. More recently, the same group carried out another study comparing the relationship between frailty and HRV variation during the performance of a functional task in older adults. This study showed that the recovery time of HR after the task was 47% lower in pre-frail/frail participants compared to non-frail, suggesting a strong association between the dynamics between HRV and frailty (37).

There is a link between low HRV and cognitive impairment, that acts as a biomarker due to autonomic dysfunction caused by dysregulation in cerebral perfusion. External factors such as cardiovascular risks are considered responsible for the association between HRV and frailty (38, 39). In addition, HRV may reflect an early manifestation of brain damage and future cardiovascular events. These events lead to cognitive decline through the cardiovascular regulatory processes in the brain and cognition regulatory processes located, especially, in the prefrontal cortex.

Reduced parasympathetic activity at rest has been related to worse performance on cognitive exercises, confirming the predictions of the "neurovisceral integration" model, which suggests that HRV can regulate the functional integrity of the central nervous system (40). Higher activities of prefrontal brain structures increase HRV, while underactivity reduces HRV. The predominantly vagal control of the heart allows flexible and rapid responses to environmental demands, promoting effective executive performance. Therefore, higher HRV is related to better cognitive performance, while low HRV has been associated with cognitive impairment and is considered an early biomarker of cognitive deterioration (40).

Therefore, we suggest that HRV measure can be used as a potential marker for frailty because it helps to understand the changes in cardiac autonomic modulation. Moreover, with the dates from HRV evaluation we can elaborate a strategy for prevent frailty and CVD. The idea of new methodologies with easy access to the population to assess HRV has been increasingly emerging.

Methods to monitor the performance of the older adults

The changes in heart rate variability can be used as a marker for frailty and could be assessed using proper tools to monitor the heart rate variability in the older adult population. A systematic review by Parvaneh et al. (41) showed that frail compared to non-frail older adults present a reduction in the complexity of HR dynamics, reduced HRV, and reduced HR changes in response to daily activities (e.g., postural transitions from lying to standing). More recently, another systematic review revealed beneficial effects of monitoring HRV in healthy older adults during different exercise interventions (42). In this sense, wearable devices are non-invasive tools that present advantages such as low cost and high benefits.

The HR monitor RS800CX Polar Electro has been used successfully to measure the cardiac autonomic modulation in non-frail, pre-frail and frail elderly women (35). In addition, the use of Polar RS800 chest belt has also been reported in studies examining the effects of endurance training on various parameters of HRV in sedentary seniors (39, 43), and in a study of an exergaming-based dance training to improve HRV in healthy older adults (44). The Heart Rate Monitor Polar RS800 (45), Polar H7 Heart Rate Sensor (46) and Polar V800 Monitor (47) are one of the most well-established brands in HR monitoring, with Polar H7/H10 HR sensors having been validated both at rest and during exercise. The Polar V800 Monitor has been validated in detecting R-R intervals in the older adult population under mental stress or dual-task considerations (47).

Although the available evidence of wearable smart technologies to monitor HRV in older adults is still scarce, we believe those devices could be used for monitoring frailty in older adults. Long-term HRV monitoring is recommended to reduce artifacts produced by sensor disconnection or motion. On top of that, advanced signal processing such as nonlinear quantifications are considered more sensitive to aging-related problems such as frailty, and could therefore be used to minimize eventual erratic rhythms (41).

Conclusion

Heart rate variability can be used as a potential marker for frailty because it helps to understand the changes in cardiac autonomic modulation. Using proper tools to monitor the heart rate variability would be ideal for the older adult population. In this sense, resources such as wearable devices are non-invasive and present advantages such as low cost and high benefit, representing an excellent tool to analyze the daily cardiac performance of the older adult population, thus making it possible to make a detailed monitoring.

Author contributions

FA, VR, and RP conceived the design and concept. FA, VR, AL, JA, AF, DF, DM, IC, LO, and RP wrote the manuscript. All authors contributed to the editing and revision of the manuscript and approved the submission.

Conflict of interest

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

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A positive association between hunger in childhood and frailty in old age: Findings from the Chinese longitudinal healthy longevity survey

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Background: Childhood hunger not only directly affects the physical and mental health of children and adolescents but also has a long-term negative effect on later health outcomes. In this cross-sectional study, we used a nationally representative Chinese sample to examine the relationship between hunger in childhood and frailty in older adults.

Materials and methods: The data were obtained from the 2018 Chinese Longitudinal Healthy Longevity Survey. The frailty index with 44 health deficits was used to identify frailty. Childhood hunger was measured by the question "Did you often go to bed hungry as a child?" Insurance status was categorized as New Rural Cooperative Medical Scheme (NRCMS), Urban Basic Medical Insurance Scheme (UBMIS), others, and no insurance. Multivariate logistic regression analysis was performed to estimate the adjusted relationship between childhood hunger and frailty.

Results: A total of 7,342 older people aged 65 years and older were analyzed in this study. Older people who experienced childhood hunger were more likely to have frailty than those who did not (OR = 1.13, 95% CI: 1.02–1.26), after adjustment for sociodemographic characteristics, family/social support, socioeconomic status, insurance status, and health behaviors. The association of childhood hunger with frailty was found in the 65–79 years group (OR = 1.21, 95% CI: 1.03–1.43), women (OR = 1.25, 95% CI: 1.08–1.45), individuals with rural residence (OR = 1.16, 95% CI: 1.03–1.31), agricultural work (OR = 1.16, 95% CI: 1.00–1.34), financial dependence (OR = 1.18, 95% CI: 1.02–1.37), and those participating in NRCMS (OR = 1.35, 95% CI: 1.16–1.56). Participants with hunger in childhood who were 80 years or older (OR = 0.80, 95% CI: 0.65–0.98) had lower odds of frailty. NRCMS (OR = 1.42, 95% CI: 1.02–1.98) showed increased odds of childhood hunger-related frailty.

Conclusion: Exposure to hunger during childhood is linked to frailty among older adults, and age, financial support, and insurance status may mediate this relationship. Targeted interventions and policies to address frailty in older adults should be implemented.

KEYWORDS

childhood, China, frailty, hunger, older people

Introduction

Frailty is a modern geriatric syndrome among older adults and is one of the most serious global public health challenges we will face in the next century (1). It reflects a multifactorial syndrome that includes physical, psychological, and social deficits that accumulate during the aging process, loss of reserves, and decreased resistance to stress and is linked with a high risk of adverse health-related outcomes, such as decreased functional capacity, falls, delirium, hospitalization, and death (2). Research (3) shows that frailty is reversible, and health promotion, nutrition, and physical and social support interventions can be used to treat and delay frailty.

China experienced the Great Leap Forward Famine in 1959–1961. Most Chinese people aged over 65 years today have experienced famine in their early life (4). Early life food deprivation has been found to be an important risk factor of negative health outcomes (5) and increase the risk of developing obesity, diabetes, hypertension, and other diseases in adulthood (6). Childhood experiences of hunger are common among older people, and understanding the impact of hunger on individuals can be particularly enlightening (7). There is growing evidence that traumatic events in childhood may have an impact on health throughout the life course (7).

The link between childhood conditions and health in later life might be explained by the theory of cumulative disadvantage/advantage, which places individual trajectories under the context of structural factors that might ameliorate or exacerbate previous disadvantages/advantages, and further influences individual health in later life and population-level inequality (8). The three aspects of the cumulative disadvantage/advantage hypothesis can be tested in the context of frailty as follows. First, to examine the relationship between childhood hunger and frailty by age, sex, and residence. Second, to examine the role of adulthood socioeconomic conditions (e.g., education, occupation, and financial support) in the association between childhood hunger and frailty at older age. Third, to evaluate the role of insurance status in the association between child hunger and frailty. Relating factors in the life course to frailty will increase our understanding of the social origins of frailty (9). Therefore, this study aimed to evaluate the association between childhood hunger and frailty in older people and to determine the roles of sociodemographic characteristics and socioeconomic status in this association.

Abbreviations: CLHLS, Chinese Longitudinal Healthy Longevity Survey; GLIM, Global Leadership Initiative on Malnutrition; FI, Frailty Index; OR, Odds Ratio; CI, Confidence Intervals; NRCMS, New Rural Cooperative Medical Scheme; UBMIS, Urban Basic Medical Insurance Scheme; BMI, body mass index.

Materials and methods

Study sample

Data for the present study were obtained from the seventh wave of the Chinese Longitudinal Healthy Longevity Survey (CLHLS) in 2018, which was conducted by Peking University and the Chinese Center for Disease Control and Prevention. The CLHLS is a nationally representative survey that aims to understand the health status of older adults and related biological, behavioral, and social factors in China. A multi-stage disproportionate and targeted random sampling was adopted. Approximately 50% of counties/districts were randomly selected from 23 out of the 31 provinces of mainland China, in which all centenarians who volunteered to participate were interviewed. For each centenarian interviewee, one non-agenarian, one octogenarian, and three participants aged 65–79 years were matched nearby in the same street, village, or town. All information was obtained in participants' homes through face-to-face interviews using internationally compatible questionnaires by trained investigators. The CLHLS study was approved by the Research Ethics Committee of Peking University (IRB00001052-13074), and all participants provided written informed consent.

A total of 15,874 participants were interviewed in the 2018 CLHLS survey. Among them, the proportion of the senior population ($\geq$ 80 years old) was 65.7%. The inclusion criteria were as follows: (1) participant aged 65 years old or above; (2) complete information on frailty index and childhood hunger was collected. After excluding 8,524 participants due to missing

data on key variables (6,830 with missing frailty data, and 1,694 with missing childhood hunger information), 7,342 participants aged 65 years or above finished the survey and had complete information on the frailty index and childhood hunger. Moreover, 5,700 had complete covariates data, and 1,642 had missing data on covariates (137 with missing residence, 64 with missing marriage, 127 with missing living arrangements, 118 with missing education, 131 with missing occupation, 609 with missing financial support, 175 with missing insurance status, 66 with missing smoking, 74 with missing drinking, 88 with missing exercise, 79 with missing social and leisure activity index, 152 with missing dietary patterns, and 246 with missing nutritional status). The samples having answers of "I don't know/have no idea" in key variables were excluded in this study. Missing data were mainly due to no answer to key variables. To control bias from missing data, we managed missing data using multiple imputations, which is a relatively flexible and general purpose approach to dealing with missing data (10). Finally, a total of 7,342 participants were analyzed in this study (**Figure 1**). The missing participants were more likely to be female, aged 80 years or above, illiterate, have other marital statuses, living with household members, financially dependent on others, non-smokers, non-drinkers, performing no exercise, and have a low Body Mass Index (BMI).

Frailty index

The frailty index (FI) is a mathematical model based on the accumulation of deficits, which can include any symptom, sign, disease, laboratory abnormality, or disability (11). Following the standard procedure proposed by Searle et al., we constructed the FI using 44 health deficits, including daily life events, chronic illness, and psychological functioning (**Table 1**). Although different numbers of deficits were used to construct each FI, the pattern of frailty with age remained consistent as long as the major domains of health, such as activities of daily living, were included (12). The deficits in the present study were comparable with those of other studies (12), with a Cronbach's alpha of 0.868. Each deficit variable was dichotomized or multicut and

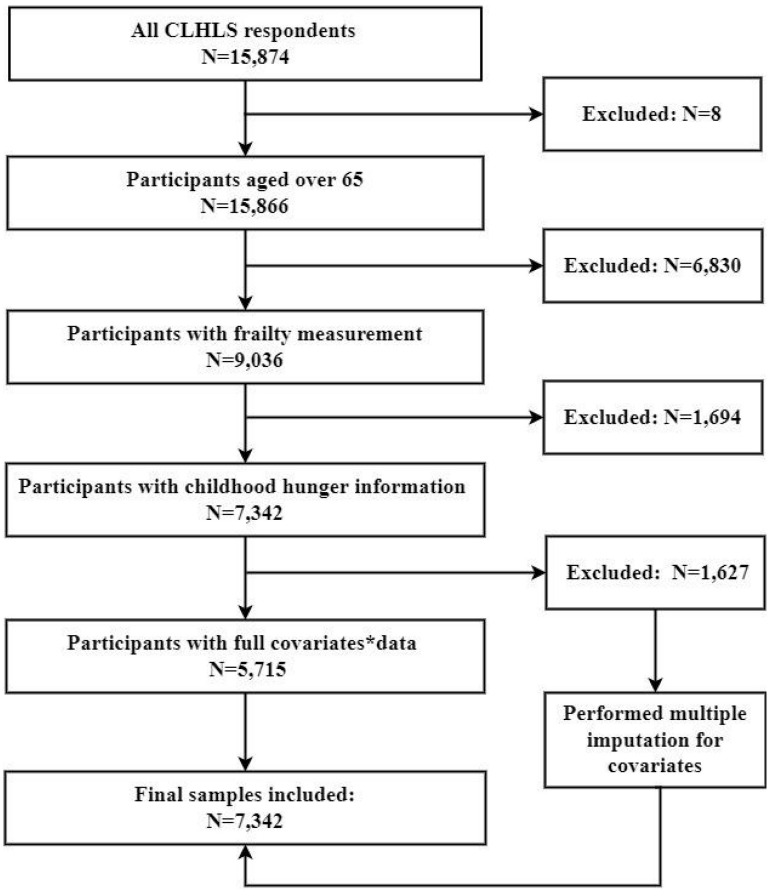

FIGURE 1
Flowchart on the sample selection and exclusion. *Covariates: residence, marriage, living arrangements, education, occupation, smoking, drinking, exercise, social and leisure activity index, dietary pattern, and nutrition status, financial support, insurance status.

TABLE 1 Variables for constructing frailty index in the 2018 waves of Chinese Longitudinal Healthy Longevity Survey.

Number	Variables	Values
1	Feel useless with age	Never = 0; seldom = 0.25; sometimes = 0.5; often = 0.75; always = 1
2	Feel lonely and isolated	Never = 0; seldom = 0.25; sometimes = 0.5; often = 0.75; always = 1
3	Feel fearful or anxious	Never = 0; seldom = 0.25; sometimes = 0.5; often = 0.75; always = 1
4	Keep my belongings neat and clean	Always = 0; often = 0.25; sometimes = 0.5; seldom = 0.75; never = 1
5	Self-reported health	Very good = 0; good = 0.25; so so = 0.5; bad = 0.75; very bad = 1
6	Do you feel any change in your health since	Much better = 0; slightly better = 0.25; almost the same = 0.5;
	The last year?	Slightly worse = 0.75; much worse = 1
7	Make own decision	Always = 0; often = 0.25; sometimes = 0.5; seldom = 0.75; never = 1
8	Bathing	Without assistance = 0; partial assistance = 0.5; need assistance = 1
9	Dressing	Without assistance = 0; partial assistance = 0.5; need assistance = 1
10	Toileting	Without assistance = 0; partial assistance = 0.5; need assistance = 1
11	Transferring	Without assistance = 0; partial assistance = 0.5; need assistance = 1
12	Continence	Without assistance = 0; partial assistance = 0.5; need assistance = 1
13	Feeding	Without assistance = 0; partial assistance = 0.5; need assistance = 1
14	Able to go outside to visit neighbors?	Yes = 0; a little difficult = 0.5; not able to do so = 1
15	Able to go shopping by yourself?	Yes = 0; a little difficult = 0.5; not able to do so = 1
16	Able to make food by yourself?	Yes = 0; a little difficult = 0.5; not able to do so = 1
17	Able to wash clothes by yourself?	Yes = 0; a little difficult = 0.5; not able to do so = 1
18	Able to walk 1 km?	Yes = 0; a little difficult = 0.5; not able to do so = 1
19	Able to carry 5-kg weight?	Yes = 0; a little difficult = 0.5; not able to do so = 1
20	Able to crouch and stand for three times?	Yes = 0; a little difficult = 0.5; not able to do so = 1
21	Able to take public transport?	Yes = 0; a little difficult = 0.5; not able to do so = 1
22	Visual function	Can see and distinguish the break in the circle = 0; can see but not
		Distinguish the break in the circle = 0.33; cannot see = 0.67; blind = 1
23	Hand behind neck	Both = 0; right = 0.5; left = 0.5; neither = 1
24	Hand behind lower back	Both = 0; right = 0.5; left = 0.5; neither = 1
25	Raise arms upright	Both = 0; right = 0.5; left = 0.5; neither = 1
26	Able to stand up from sitting in a chair	Yes, without using hands = 0; yes, using hands = 0.5; no = 1
27	Able to pick up a book from the floor	Yes, without using hands = 0; yes, using hands = 0.5; no = 1
28	Of times suffering from serious illness	Not applicable = 0; one serious illness = l; two or more serious
	In the past 2 years	Illnesses = 2
29	Suffering from hypertension?	No = 0; yes = 1
30	Suffering from diabetes?	No = 0; yes = 1
31	Suffering from heart disease?	No = 0; yes = 1
32	Suffering from stroke or cardiovascular disease?	No = 0; yes = 1
33	Suffering from bronchitis, emphysema,	No = 0; yes = 1
	Pneumonia, and asthma?	
34	Suffering from tuberculosis?	No = 0; yes = 1
35	Suffering from cataract?	No = 0; yes = 1
36	Suffering from cancer?	No = 0; yes = 1
37	Suffering from glaucoma?	No = 0; yes = 1
38	Suffering from gastric or duodenal ulcer?	No = 0; yes = 1
39	Suffering from Parkinson's disease?	No = 0; yes = 1
40	Suffering from bedsore?	No = 0; yes = 1
41	Suffering from arthritis?	No = 0; yes = 1
42	Suffering from dementia?	No = 0; yes = 1
43	Was interviewee able to hear?	Yes, without hearing aid = 0; yes, but needs hearing aid = 0.33;
		Partly, despite using hearing aid = 0.67; no = 1
44	The health of interviewee rated	Surprisingly healthy = 0; relatively healthy = 0.33; moderately
	By interviewer	ill = 0.67; very ill = 1

mapped to the 0–1 interval (e.g., routine task-bathing, with "no assistance" coded as 0, "partial assistance" coded as 0.5, and "need assistance" coded as 1) to indicate its severity. The sum of all deficits (n = 44) was then used to calculate the FI, which ranged from 0 to 1. We divided the FI score into three levels of variables: non-frail (FI $\leq$ 0.10), pre-frail (0.10 < FI $\leq$ 0.21), and frail (FI > 0.21) (13).

Childhood hunger

Childhood hunger was measured by the question "Did you often go to bed hungry as a child?" The responses included "yes" or "no."

Explanatory variables

Sociodemographic characteristics included age (age 65–79 vs. age 80 +), sex (male vs. female), and residence (rural vs. urban). Family/social support included marriage and living arrangements. Marriage was divided into married and other (including separated, divorced, widowed, and unmarried). Living arrangements were classified as follows: living alone, living with household members, and living in an institution. Socioeconomic status included education, occupation, and financial support. Education was divided into illiterate, primary school, junior high school, and high school and above. Occupations before 60 years old were allocated into two categories: agricultural work, which was coded as 0, and non-agricultural work, which was coded as 1. Financial support included financial dependence (coded as 0) and financial independence (coded as 1). Participants' financial independence included work and retirement wages, and financial dependence included participants' financial dependence on other family members. Insurance status was categorized into the New Rural Cooperative Medical Scheme (NRCMS), Urban Basic Medical Insurance Scheme (UBMIS) (including urban resident basic medical insurance and urban employee basic medical insurance), others (including commercial medical insurance and public free medical services), and no insurance.

Health behaviors included smoking (yes or no), drinking per day (liang) (including 0, 0 < –1, 1 < –2, and > 2), exercise (yes or no), social and leisure activity index, dietary patterns, and nutritional status. The social and leisure activity scores were calculated for eight activity types (whether a respondent gardened, practiced Tai Chi, participated in square dancing, kept poultry or pets, read, played Mahjong or cards, listened to the radio or watched TV, and participated in community social activities). We scored each activity 1 for "never," 2 for "sometimes," and 3 for "almost every day." Scores ranged from 8 to 24, with 14 or less being defined as a low social and leisure activity level, and higher scores indicating more leisure activities. Dietary patterns were classified as unfavorable, intermediate, or favorable through a simplified healthy eating index based on the frequency of intake of five food groups: fish, vegetables, fruits, tea, and bean products, which have been shown to be associated with frailty. The intake scores for these five food groups were summed and divided into three categories: unfavorable: 0–4; intermediate: 5–6; favorable: 7–10. BMI reflects nutritional status. According to the Global Leadership Initiative on Malnutrition (GLIM) criteria (14), the BMI cut-off for malnutrition risk is < 18.5 kg/m^2 if the participant is aged < 70 years, and < 20 kg/m^2 if the participant is aged $\geq$ 70 years; or else, the participant is identified as normal BMI.

Statistical analysis

Multiple imputation was used to adjust for selection bias and information loss. In the multiple imputation strategy, 50 iterations were used to impute missing data, and five imputed datasets were generated using predictive mean matching. The results were pooled over all five sets using Rubin's rules. We present the descriptive statistics, and the results are expressed as the number of categorical variables (proportions). The relationship between childhood hunger and sociodemographic characteristics, family/social support, socioeconomic status, insurance status, and health behaviors was analyzed using chi-square tests, and the same process was applied to frailty. Covariates with three or more classifications were analyzed for their differences using a chi-square test of partitioning. Bonferroni correction was used for multiple comparisons. P < 0.017 was considered statistically significant for a two-way comparison between the 3 groups and P < 0.008 was considered statistically significant for a two-way comparison between the 4 groups. Mean and standard deviation (SD) were used to describe age. We evaluated multicollinearity among covariates, and the largest variance inflation factor was < 2, suggesting no multicollinearity biases in the models. The relationship between childhood hunger and frailty was evaluated by ordinal logistic regression analysis. Subgroup analyses were then conducted by stratifying variables. Finally, we explored whether age, financial support, and insurance status were potential moderators of this relationship, and we added an interaction term to test for a moderating effect. All statistical analyses were conducted with SPSS 26.0. A p-value of < 0.05 was considered statistically significant.

Results

As shown in **Table 2**, the sample was composed of 7,342 participants, comprising 3,420 males (46.6%) and 3,922 females (53.4%). The mean age of the study group was 82.99 (SD = 11.4)

TABLE 2 Association of baseline characteristics with childhood hunger and frailty; data are expressed as number (prevalence) [n (%)].

Characteristics	Total n (%)	Childhood hunger n (%)	χ^2	Frailty n (%)	χ^2
Total	7,342	5,170 (70.42)		2,150 (29.28)	
*Age group (*years)			13.211***		1437.747***
65–79	3,089 (42.07)	2,105 (68.15)		253 (8.19)	
80 +	4,253 (57.93)	3,065 (72.07)		1,897 (44.60)	
Sex			6.374*		192.327***
Female	3,922 (53.42)	2,811 (71.67)		1,377 (35.11)	
Male	3,420 (46.58)	2,359 (68.98)		773 (22.60)	
Residence			517.174***		17.609***
Rural	6,085 (82.88)	4,620 (75.92)		1,720 (28.27)	
Urban	1,257 (17.12)	550 (43.76)		430 (34.18)	
Marital status			14.425***		761.973***
Married	3,375 (45.97)	2,302 (68.22)		508 (15.04)	
Others	3,967 (54.03)	2,868 (72.28)		1,642 (41.40)	
Living arrangement			16.685***		182.672***
With household member(s) (1)	6,123 (83.39)	4,348 (71.02)		1,884 (30.76)	
In an institution (2)	197 (2.69)	114 (57.85)[a]		106 (53.90)[a]	
Alone (3)	1,022 (13.92)	708 (69.25)[b]		160 (15.66)[ab]	
Education			607.065***		514.832***
High school and above (1)	1,273 (17.34)	568 (44.64)		267 (20.97)	
Junior high school (2)	1,130 (15.39)	752 (66.54)[a]		193 (17.09)	
Primary school (3)	1,766 (24.05)	1,259 (71.30)[ab]		400 (22.68)[b]	
Illiterate (4)	3,173 (43.22)	2,591 (81.65)[abc]		1,290 (40.64)[abc]	
Occupation			463.701***		13.535**
Agricultural work	4,492 (61.19)	3,574 (79.55)		1,253 (27.89)	
Non-agricultural work	2,850 (38.81)	1,596 (56.01)		897 (31.49)	
Financial support			390.197***		201.103***
Financial dependence	4,296 (58.52)	3,406 (79.28)		1,462 (34.02)	
Financial independence	3,046 (41.48)	1,764 (57.92)		688 (22.60)	
Insurance status			499.079***		49.934***
NRCMS (1)	4,429 (60.32)	3,539 (79.90)		1,189 (26.84)	
UBMIS (2)	1,888 (25.71)	1,015 (53.77)[a]		581 (30.76)[a]	
Others (3)	229 (3.12)	125 (54.71)[a]		80 (35.08)[a]	
No (4)	796 (10.85)	491 (61.63)[ab]		300 (37.72)[ab]	
Smoking			5.186*		148.532***
Yes	1,212 (16.51)	887 (73.14)		201 (16.58)	
No	6,130 (83.49)	4,283 (69.88)		1,949 (31.80)	
Drinking per day (liang)			1.358		125.001***
0 (1)	5,309 (72.30)	3,718 (70.04)		1,710 (32.21)	
0 < −1 (2)	641 (8.73)	457 (71.34)		172 (26.82)[a]	
1 < −2 (3)	618 (8.43)	443 (71.68)		131 (21.21)[a]	
>2 (4)	774 (10.54)	552 (71.25)		137 (17.72)[ab]	
Exercise			41.657***		452.748***
Yes	2,623 (35.72)	1,726 (65.80)		402 (15.32)	
No	4,719 (64.28)	3,444 (72.98)		1,748 (37.04)	
Social and leisure activity level			58.064***		387.330***
High	1,248 (17.00)	767 (61.45)		119 (9.55)	
Low	6,094 (83.00)	4,403 (72.25)		2,031 (33.33)	

(Continued)

TABLE 2 (Continued)

Characteristics	Total n (%)	Childhood hunger n (%)	χ^2	Frailty n (%)	χ^2
Dietary pattern			197.711***		159.645***
Unfavorable (1)	2,828 (38.52)	2,207 (78.04)		998 (35.31)	
Intermediate (2)	3,161 (43.05)	2,192 (69.35)[a]		841 (26.61)[a]	
Favorable (3)	1,353 (18.43)	771 (56.99)[ab]		311 (22.95)[ab]	
BMI			33.582***		146.387***
Low BMI	1,855 (25.27)	1,405 (75.72)		730 (39.36)	
Normal BMI	5,487 (74.73)	3,765 (68.62)		1,420 (25.88)	

UBMIS represents urban basic medical insurance scheme, NRCMS represents new rural cooperative medical scheme, Others represents commercial medical insurance and public free medical services, BMI represents body mass index.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

[a] represents significant difference in childhood hunger or frailty compared with the group (1); [b] represents significant difference in childhood hunger or frailty compared with the group (2); [c] represents significant difference in childhood hunger or frailty compared with the group (3).

years. Of these participants, 42.1% were aged 65–79 years, 57.9% were aged ≥ 80 years, 46.0% were married, 82.9% resided in rural areas, 17.3% had high school and above, 61.2% did agricultural work, and 58.5% were financially dependent on others. A total of 1,888 (25.7%) were covered by UBMIS, 4,429 (60.3%) were covered by NRCMS, 229 (3.1%) were others, and 796 (10.9%) were not covered.

Overall, the prevalence of childhood hunger was 70.4%, with 68.2% in the 65–79 years group and 72.1% in the ≥ 80 years group (Table 2). Hunger in childhood was more likely to be experienced by individuals with the following characteristics: female, residents of rural areas, other marital statuses, living with household members, illiterate, had been an agricultural worker, financial dependence on others, having NRCMS, smoking, performing no exercise, low social and leisure activity levels, unfavorable dietary patterns, and low BMI. There were no significant differences between childhood hunger and drinking.

Table 2 also shows the prevalence of frailty according to participants' characteristics. Of the 7,342 eligible participants, 2,465 (33.6%) were non-frail, 2,727 (37.1%) were pre-frail and 2,150 (29.3%) were frail. Participants with frailty symptoms were likely to have the following characteristics: older, female, living in urban areas, other marital statuses, living in an institution, illiterate, non-agricultural work, financial dependence on others, without insurance, non-smokers, non-drinkers, performing no exercise, low social and leisure activity levels, unfavorable dietary patterns, and low BMI.

As shown in Table 3, older adults who experienced childhood hunger were more likely to have frailty than those who did not (OR = 1.15, 95% CI: 1.05–1.26) in the crude model. Further adjustment for sociodemographic characteristics, family/social support, socioeconomic status, insurance status, and health behaviors did not affect the relationship (OR = 1.13, 95% CI: 1.02–1.26). Considering differences in age, sex, residence, socioeconomic status, and insurance status in relation to frailty, *post hoc* analyses stratified by age, sex, residence, socioeconomic status, and insurance status were conducted. In the final model, the association of childhood hunger with frailty was found in the 65–79 years group (OR = 1.21, 95% CI: 1.03–1.43), women (OR = 1.25, 95% CI: 1.08–1.45), rural residents (OR = 1.16, 95% CI: 1.03–1.31), agricultural work (OR = 1.16, 95% CI: 1.00–1.34), those with financial dependence (OR = 1.18, 95% CI: 1.02–1.37), and NRCMS (OR = 1.35, 95% CI: 1.16–1.56). In the crude model, childhood hunger was significantly associated with lower odds of frailty in high school and above and financial independence. However, in the final model, the difference was small and not statistically significant.

Given that age, financial support, and insurance status could mediate the relationship of childhood hunger with frailty, we tested the interaction between childhood hunger and age, financial support, and insurance status (Table 4). The results showed that the effects of childhood hunger on frailty were partially mediated by age, financial support, and insurance status. The 80 years or older group (OR = 3.61, 95% CI: 3.22–4.04) were significantly associated with higher odds of frailty. Participants with hunger in childhood who were 80 years or older (OR = 0.80, 95% CI: 0.65–0.98) had a lower odds ratio of frailty. NRCMS (OR = 0.66, 95% CI: 0.56–0.77) was significantly associated with lower odds of frailty. However, NRCMS (OR = 1.42, 95% CI: 1.02–1.98) showed an increased odds ratio of childhood hunger-related frailty.

Discussion

This study used a large, nationally representative sample of older Chinese individuals to evaluate the association between childhood hunger and frailty in old age. The findings showed that older adults who often experienced hunger as children had a significantly higher risk of frailty, especially those with low socioeconomic status, suggesting that more light should be shed on policies or interventions to end children and adolescents'

TABLE 3 The association of childhood hunger and frailty stratified by age, sex, residence, socioeconomic status, insurance status.

Characteristics	Crude model OR (95% CI)	Final model OR (95% CI)
Childhood hunger	1.15 (1.05, 1.26)**	1.13 (1.02, 1.26)*
Stratified by age *group*		
65–79	1.15 (0.99, 1.33)	1.21 (1.03, 1.43)*
80 +	1.04 (0.91, 1.18)	1.05 (0.92, 1.21)
Stratified by *sex*		
Female	1.27 (1.12, 1.45)***	1.25 (1.08, 1.45)**
Male	0.98 (0.86, 1.12)	1.03 (0.88, 1.20)
Stratified by *residence*		
Urban	1.03 (0.84, 1.26)	1.11 (0.87, 1.41)
Rural	1.28 (1.14, 1.43)***	1.16 (1.03, 1.31)*
Stratified by *education*		
High school and above	0.64 (0.52, 0.79)***	1.01 (0.79, 1.29)
Junior high school	1.02 (0.81, 1.28)	1.22 (0.94, 1.59)
Primary school	0.82 (0.68, 1.00)	1.15 (0.93, 1.42)
Illiterate	1.14 (0.96, 1.35)	1.14 (0.95, 1.37)
Stratified by *occupation*		
Agricultural work	1.37 (1.20, 1.57)***	1.16 (1.00, 1.34)*
Non-agricultural work	1.03 (0.89, 1.18)	1.17 (0.99, 1.37)
Stratified by *financial support*		
Financial dependence	1.28 (1.11, 1.47)**	1.18 (1.02, 1.37)*
Financial independence	0.77 (0.67, 0.88)***	1.11 (0.94, 1.30)
Stratified by *insurance status*		
NRCMS	1.52 (1.33, 1.75)***	1.35 (1.16, 1.56)***
UBMIS	0.97 (0.82, 1.15)	0.99 (0.82, 1.20)
Others	0.89 (0.55, 1.44)	1.37 (0.73, 2.55)
No	1.11 (0.84, 1.45)	0.93 (0.68, 1.28)

OR represents the odds ratio, 95% CI represents 95% confidence intervals, UBMIS represents urban basic medical insurance scheme, NRCMS represents new rural cooperative medical scheme, Others represents commercial medical insurance and public free medical services.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

The final model is adjusted for age, sex, residence, marital status, living arrangement, education, occupation, financial support, insurance status, smoking, drinking per day, exercise, social and leisure activity index, dietary pattern, and BMI.

TABLE 4 Effect of the interaction between childhood hunger and age, and insurance status on frailty.

Characteristics	Crude model OR (95% CI)	Final model OR (95% CI)
Childhood hunger	1.15 (1.05, 1.26)**	1.13 (1.02, 1.26)*
Age group (Ref. = *65–79 years*)		
80 +	5.95 (5.40, 6.55)***	3.61 (3.22, 4.04)***
Childhood hunger × Age group		0.80 (0.65, 0.98)*
Insurance status (Ref. = *No*)		
NRCMS	0.67 (0.58, 0.77)***	0.66 (0.56, 0.77)***
UBMIS	0.78 (0.67, 0.91)**	1.07 (0.90, 1.27)
Others	0.79 (0.60, 1.04)	1.05 (0.78, 1.42)
Childhood hunger × Insurance status		
NRCMS		1.42 (1.02, 1.98)*
UBMIS		0.91 (0.65, 1.28)
Others		1.06 (0.59, 1.91)

OR represents the odds ratio, 95% CI represents 95% confidence intervals, Ref. represents reference, UBMIS represents urban basic medical insurance scheme, NRCMS represents new rural cooperative medical scheme, Others represents commercial medical insurance and public free medical services.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Multiple logistic regression analysis was applied to estimate the OR and 95% CI for frailty. The final model is adjusted for age, sex, residence, marital status, living arrangement, education, occupation, financial support, insurance status, smoking, drinking per day, exercise, social and leisure activity index, dietary pattern, and BMI.

hunger in consideration of the socioeconomic status, providing a better understanding of the determinants of healthy longevity.

Previous studies (5) explored the relationship between food deprivation in early life and risk of frailty in older Chinese adults aged 45 years and above using the data from the China Health and Retirement Longitudinal study, and showed that exposure to food deprivation in childhood was also significantly associated with frailty. Experiencing prolonged hunger and poor health and growing up in a family with poor socioeconomic conditions can have a strong and lasting impact on later health (15). Our findings suggested that older adults who experienced childhood hunger were more likely to experience frailty than those who did not. People who experience malnutrition in their early years are at a higher risk of subsequently developing metabolic syndrome in a nutrient-rich environment due to metabolic maladjustment (6). Exposure to hunger early in life was found to increase the probability of being overweight and depressed in old age (4). Our findings suggested that nutrition is closely related to frailty syndrome, and all frailty criteria are more or less influenced by poor dietary habits. Studies have shown an association between frailty and specific components of the diet, including protein and energy intake, as well as the intake of specific micronutrients (16). This evidence indicates that nutritional status in early life is closely linked to health conditions in old age. Thus, improving nutritional status early in life should be prioritized to control the increasing trend of chronic non-communicable diseases (17).

Our findings suggested that older adults who were hungry in childhood, females, rural residents, agricultural workers, those with NRCMS, and those who were financially dependent had a higher odds ratio of frailty, which is consistent with earlier studies (18). Generally, the prevalence of frailty increased with the increase of age. The aging process and longevity have a direct impact on frailty status; thus, frailty is more prevalent in older people (19). However, our findings also showed that people who were 80 years or older and experienced hunger in childhood had a lower odds ratio of frailty. A potential reason for this finding relates to survivor bias, as individuals who were 80 years or older may already have died if they had a poor health status and from a low socioeconomic status (20).

Our findings indicated that women who experienced childhood hunger had an aggravated possibility of frailty.

A previous study reported that childhood hunger has a stronger effect on physical health outcomes in women than in men (21). The discrepancy may be associated with the noticeable gender difference to pro-male bias in the Chinese culture (4). The apparent increase in the prevalence of frailty with age among women may be in part a result of frail women outliving frail men (22). This survival advantage in women is often linked to a higher prevalence of disability and poor health status (22). Additionally, women are also more prone to developing psychosocial disorders associated with frailty due to their lifetime stressors, poverty, and loneliness at the end of life (23).

Our findings showed that rural residence was significantly associated with childhood hunger. Rural residents had a significantly higher risk of malnutrition than urban residents (18), and differences in frailty and life expectancy were found between rural and urban older adults. Urban residents may have an advantageous educational system compared to rural residents, which may influence individual health outcomes (24). Rural residence with low levels of education might increase the risk of frailty in older adults. This finding may reflect the impacts of regional differences in socioeconomic and environmental attributes or access to health care between two populations (25). Our analysis found that having UBMIS as the main payment method was effective in alleviating healthcare costs for older Chinese individuals compared to out-of-pocket spending. Our findings showed that participants who experienced hunger in childhood and with UBMIS had a lower odds ratio of frailty. However, NRCMS showed an increased odds ratio of childhood hunger-related frailty. Previous studies have reported that the actual reimbursement rate for UBMIS enrollees was higher than that for NRCMS enrollees in China (26). The NRCMS has the weakest financial security, which is consistent with other scholars' studies. The NRCMS covers a greater proportion of the rural population, who are also the most vulnerable group for non-communicable diseases (27). In China, the rural population has more restricted access to health services and a heavier financial burden than urban residents (28). Higher income individuals are reimbursed more frequently than lower income individuals, who are less healthy, and inequalities in welfare exacerbated health inequities (29). There is a gap between nominal and actual reimbursement rates, and the NRCMS has not significantly reduced this gap (30).

Previous studies interviewed 13,185 individuals aged 65–99 years and found that childhood experiences of hunger affect socioeconomic status in adult life, which, in turn, can affect health outcomes in older adults (31). Our findings showed that high educational level and financial independence may reduce the probability of childhood hunger-mediated frailty in older age. Education builds an individual's knowledge and skills, determines future attitudes and behaviors, and helps people achieve a better occupational class and higher economic status (32). Although education and income do not directly affect the pathophysiology of frailty, they may interfere with the lifestyle of the individual and influence the development of frailty (33). Thus, education is also a good social predictor of frailty, and reflects childhood circumstances and attained adult socioeconomic status (34). Our findings also identified that financial dependence was significantly associated with both childhood hunger and frailty, and older adults with childhood hunger who were financially dependent on others had a higher odds ratio of frailty. Poor financial security is one of the most important risk factors of frailty in old age (35). Older people with a low income might choose to live alone, which can lead to an increased risk of developing frailty because they may be less likely to have the ability to meet their daily needs (36).

As older people become frailer, their level of physical activity decreases, and this lowered physical activity in turn provokes a vicious cycle, which can make the frail older people become frailer (37). Our findings suggested that participants with frailty symptoms were likely to have no exercise and low social and leisure activity levels. Social participation in older people directly increases social interactions, which has the potential to result in decreased cognitive decline and decreased risk of having depression; moreover, it also increases physical activities, which decreases the risk of developing frailty (38).

Our study showed that high prevalence of frailty was associated with low BMI. Being underweight or obese can increase the risk of frailty and sarcopenia (39). Healthy nutrition may alleviate the risk of being obese or underweight, further decreasing the risk of frailty (40). Older people with normal BMI had a relatively low prevalence of frailty in our study. In fact, in addition to the population, the setting also seems to determine the relationship between BMI and adverse outcomes in older adults (41). A lower BMI would be more favorable in community dwelling older adults in terms of frailty or functionality (42), but the opposite was reported to be true for nursing home residents (43). Maintaining a healthy BMI in older adults is important for maintaining healthy nutritional status and skeletal muscle mass (44). Notably, non-smokers and non-drinkers were more likely to be frail in our study. It is possibly explained by abstainer/quitter bias; for example, people might have been advised not to smoke or drink because of poor health (45).

Strengths and limitations

This study investigated the relationship of childhood conditions with the aging process and health status in older adults in the context of socioeconomic status based on a large representative sample of centenarians in China, providing a

better understanding of the determinants of healthy longevity. Our research has several limitations. First, frailty index represents the cumulative deficit model and has been criticized for being a disease checklist rather than an assessment tool for physiological reserves. This study adopted a more detailed definition of frailty index using 44 health deficits as top studies constructing a frailty index (13); actually, there are appropriate and useful tools for identifying "true frailty," e.g., Fried frailty scale (46) and SARC-F questionnaire (47). Second, this study determined the nutritional status of older people according to the GLIM criteria. However, it does not take gender difference into account, since it is well known that female gender is associated with higher fat mass than male. Third, differences in demographic characteristics, social support, socioeconomic status, and health behaviors between the missing participants and study participants may have influenced our results. Finally, frailty status might change over time, and we could not explore the impact of relevant risk factors on the frailty trajectory. More longitudinal studies are needed to identify the determinants of frailty progression or remission in older adults.

Conclusion

Exposure to hunger during childhood is linked to frailty among older adults, and age, financial support, and insurance status may mediate this relationship. In early life, nutrition-targeted interventions and policies should be implemented to address hunger, and universal access to education should be promoted to reduce the socioeconomic status gap that accumulates in old age. In old age, socio-economically relevant strategies to control medical expenses for older people and to improve the reimbursement rate for NRCMS are beneficial in reducing inequality in frailty.

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: https://opendata.pku.edu.cn/dataverse/CHADS.

Author contributions

TG and HL conceived the study. TG and SH analyzed the data. GM, QS, and MZ helped in interpreting the data. TG wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

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Conflict of interest

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

Publisher's note

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