

Mild behavioral impairment is related to frailty in non-dementia older adults: a cross-sectional study

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Research article

Keywords: cognitive impairment, frailty, mild behavioral impairment, neuropsychiatric symptoms

Posted Date: September 18th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-34750/v2>

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Version of Record: A version of this preprint was published on November 27th, 2020. See the published version at <https://doi.org/10.1186/s12877-020-01903-2>.

Abstract

Background: Frailty and cognitive decline are highly prevalent among older adults. However, the relationship between frailty and mild behavioral impairment (MBI), a neurobehavioral syndrome characterized by later-life emergence of sustained neuropsychiatric symptoms, has yet to be elucidated. We aimed to evaluate the associations between mild behavioral impairment and frailty in non-dementia older adults.

Methods: This is a cross-sectional study. A consecutive series of 137 non-dementia older adults in the Anti-Aging Study, recruited from primary care clinics, were enrolled. Frailty was estimated using the Fried phenotype. MBI was evaluated by the Mild Behavioral Impairment Checklist at a cut-off point of >8 (optimizing sensitivity and specificity), which was developed to assess emergent neuropsychiatric symptoms in accordance with the MBI criteria. Cognition was assessed with the Chinese versions of the Montreal Cognitive Assessment (MoCA-BC) and Mini-mental State Examination (MMSE). Multivariate logistic regression was performed to estimate the relationship between MBI and objective cognition with frailty status.

Results: At baseline, 30.7% of the older adults had frailty and 18.2% had MBI (MBI+ status). Multivariate logistic regression analysis demonstrated that compared to MBI- status (without MBI), MBI+ was more likely to have frailty (odds ratio [OR] = 7.44, 95% CI = 1.49-37.21, p = 0.02).

Conclusions: MBI is significantly associated with an increased risk of having frailty before the presence of overt dementia. This association merits further study to identify strategies for the early detection, prevention and therapeutic intervention of frailty.

Background

Frailty is a common geriatric syndrome presenting as a clinical state of decreased physiological reserve, increased vulnerability to death and increased susceptibility to even small stressors(1). It is associated with an increased risk of adverse health-related outcomes, including falls, disability and mortality(2). The prevalence of frailty is 3.9% to 51.4% among community-dwelling people aged 60 years and older, and the incidence increases with age(3). As population aging has become a global phenomenon, frailty has become an emerging public health issue. To date, most definitions have prioritized the physical dimension of frailty syndrome, which involves symptoms and signs such as weight loss, muscle weakness, slower gait speed, and sedentary behavior(4). Frailty has been most commonly operationalised using a phenotypic approach or a deficit accumulation approach(5, 6). One of the most commonly used instrument for research purposes is Fried phenotype, which has been extensively tested for its validity(7, 8).

Frailty that combines a range of diverse deficits, is increasingly recognized as a fundamental determinant of an individual's vulnerability or resilience to stressors(9) and has been linked to impaired cognition(10, 11). Various neurocognitive disorders, including late-life cognitive impairment(12, 13), mild cognitive

impairment (MCI)(14), dementia(15) and Alzheimer's disease (AD)(16, 17), have been shown to be associated with frailty. Researchers have also found that frailty and cognitive decline might share common physiological mechanisms, with greater frailty being associated with worse cognition and a faster rate of cognitive decline(18).

Similar to frailty, neuropsychiatric symptoms (NPS) have been demonstrated to be associated with cognitive decline and have been linked to known dementia biomarkers, thus also suggesting common underlying mechanisms. The Mayo Clinic Study of Aging reported that the presence of NPS (particularly agitation, apathy, anxiety, irritability or depression) increased the risk of developing MCI in cognitively normal older adults(19). More recent evidence from a large sample in the National Alzheimer Coordinating Center dataset demonstrated that in 59% of dementia cases, NPS emerged in advance of cognitive symptoms, including 30% of people who developed AD, reinforcing the notion that later-life onset of NPS can be one of the early markers of dementia(20). To operationalize the assessment of NPS as risk markers for incident cognitive decline and dementia, the International Society to Advance Alzheimer's Research and Treatment developed criteria for mild behavioral impairment. MBI is a validated neurobehavioral syndrome characterized by later-life emergent NPS as an at-risk state for all causes of dementia. Although MBI and MCI can co-occur (MBI can emerge before, in concert with, or after MCI) and both portend a higher risk of dementia, MBI aimed to identify earlier patients with an increased risk of cognitive decline and dementia, but who may or may not have cognitive symptoms(21). As an early manifestation of neurodegeneration, MBI has been connected with known biomarkers for dementia, including amyloid beta in cognitively normal individuals (22), and faster accumulation of neurofilament light in normal cognition and MCI(23). MBI has also been used in machine learning models to predict neurocognitive diagnostic category 40 months later(24). These findings suggested that the early recognition of the NPS that constitute MBI may contribute to earlier detection of dementia, and may represent a clinical entity and premorbid treatment target for intervention strategies to prevent or delay the onset of dementia(25). The Mild behavioral impairment Checklist (MBI-C) is a brief screening instrument developed to capture MBI in accordance with the criteria.

Frailty, as a substantial moderator in the relationship between cognitive decline, Alzheimer's disease and dementia, could be a predictor of cognitive decline over time and influences the clinical expression of dementia(cognitive and functional decline)(17, 28, 29). However, the association between frailty and cognition in pre-dementia has yielded mixed results(30-32). MBI is associated with a significantly faster rate of cognitive decline and progression along the continuum of neurodegenerative pathology than late life psychiatric disorders. The timing of the predictive value of MBI appears to be early in the neuropathologic stage even before cognitive impairment(33). Therefore, it may have significant implications to identify MBI and frailty in preclinical or prodromal patients, since the potential importance of early interventions in these potentially at-risk individuals. So far, the possible association

between frailty and MBI, both independent risk factors for developing dementia appearing early in the disease course, has not been thoroughly investigated. In this cross-sectional study, we aimed to 1) determine the prevalence of frailty and of MBI, 2) replicate prior findings linking frailty to worse objective global cognition, 3) determine the association between MBI and global cognition, and 4) assess the relationships between MBI total and domain scores, and frailty, in non-dementia older adults. We hypothesized that MBI would predict greater frailty burden.

Methods

Participants and Setting

A consecutive series of 185 volunteers aged 60 or older were recruited from the Anti-Aging Study, which investigates health and frailty. Participants were recruited from advertisements in GPs clinics and Medical Management Centers in Guangzhou (the capital of the Guangdong, South-East of China). At eligibility assessment, participants underwent a detailed medical history, record review, and neuropsychological assessment. Participants were excluded with the following: 1) history of neurological and psychiatric diseases (cerebrovascular disease, Parkinson's disease or dementia), 2) head injury with loss of consciousness longer than 5 minutes, and 3) a systemic or terminal illness affecting follow-up participation. At enrollment, participants completed a comprehensive evaluation including but not limited to a physical examination, frailty assessment, medical record and medication review, clinical interview with questionnaires, emotional assessment and a neuropsychological assessment. Participants were excluded here for a cognitive diagnosis other than non-dementia, which were defined in accordance with the MiniMental State Examination (MMSE) cut-off score ≥ 24 (34, 35) (Figure 1 lists exclusion details).

Sociodemographic and Clinical Characteristics

The sociodemographic characteristics analyzed were age, gender and education. Nutritional status was measured and classified based on body mass index (BMI), calculated as weight in kilograms divided by height in meters squared (kg/m^2)(36). To identify polypharmacy and multimorbidity, the participants were asked if they had a physician-determined diagnosis of heart disease, hypertension, stroke, diabetes, cancer, rheumatic disease, lung disease, osteoporosis, neurologic disease, urinary incontinence or fecal incontinence. Polypharmacy has generally been defined as concurrent administration of more than 5 medications and multimorbidity as the presence of >2 chronic diseases(37).

Emotional Assessment

Anxiety and depression were measured by the Generalized Anxiety Disorder 7-item (GAD-7) scale(38) and the 9-item Patient Health Questionnaire (PHQ-9)(39), respectively. The GAD-7 measures the frequency of

each anxious mood item from never (0) to nearly every day (3). A total score of ≥ 10 indicates the presence of an anxiety symptomatology(40). The PHQ-9 measures the frequency of each depressed mood item from not at all (0) to nearly every day (3). The standard cut-off score of 10 or greater maximized the combined sensitivity and specificity in the primary studies(41). We used a GAD-7 score of ≥ 10 and a PHQ-9 score of ≥ 10 as the cut-off points for indicating clinically significant anxiety and depression, respectively(42).

Frailty Assessment

The diagnosis of frailty was based on the Fried phenotype and included five indicators: exhaustion, which was measured by self-report questionnaire based on two items extracted from the Center for Epidemiology Studies Depression (CES-D)(43); unintentional weight loss (≥ 10 pounds or $\geq 5\%$ of body weight in last year); weak grip strength measured by the grip-strength of the dominant hand using a hand grip dynamometer and defined based on established cutoffs by gender and body mass index (BMI); slow walking speed (speeds below an established cutoffs adjusted by recipient sex and height) , which was directly measured by walking time of 15 feet and low energy expenditure (low physical activity in the past two weeks, adjusted by sex), which was estimated using the Minnesota Leisure Time Physical Activity (MLTA) questionnaire (44). Based on these scores, individuals with 0-2 criteria present were categorized into the no-frailty group and those with 3 or more criteria were in the frailty group(45).

Neuropsychiatric and Neuropsychological Assessment

MBI was assessed using the Chinese version of MBI-C developed by Cui(46), a scale developed specifically for functionally independent community-dwelling older adults. The MBI-C(47) includes 34 items in five domains: 1) decreased motivation (apathy), 2) emotional dysregulation (mood and anxiety symptoms), 3) impulse dyscontrol (agitation, aggression, impulsivity), 4) social inappropriateness (impaired social cognition), and 5) abnormal perception or thought content (psychotic symptoms, i.e. hallucinations, delusions). Only symptoms that are characterized by later life onset, representing a change from longstanding patterns of behavior, and that have been present no less than 6 months were assessed as “yes”, and their severity was rated (1 to 3 points)(47). MBI-C domain total scores were calculated by adding the severity scores. MBI+ status was based on a total score >8 , its optimal cut-off point for MBI case detection in a primary care population, with good sensitivity and specificity(27).

As part of the objective cognitive assessment, the participants completed a brief objective cognitive screening tool. The Chinese versions of the Montreal Cognitive Assessment (MoCA-BC)(48) and the Mini-mental State Examination (MMSE)(49) were used to measure cognitive function. The MMSE and the MoCA were administered in a random order to avoid a fatigue effect bias. Potential scores range from 0 to 30, with higher values indicating better cognition. As both the MMSE and MoCA include similar items for orientation and calculation, these items were included only once in the MMSE. The MoCA test contained more attention-executive items than the MMSE. MoCA was sensitive to detect mid cognitive impairment, and MMSE was suited to screen out dementia(50).

Statistical Analysis

Continuous variables were reported as the mean \pm SD, and categorical variables were presented as frequency and percentage. One-way analysis of variance (ANOVA) was performed to determine the differences among the frailty status groups with respect to the continuous variables, and chi-square (χ^2) tests were used to identify the group differences for the categorical variables. The total and domain-specific questionnaire scores for the MBI-C were calculated. The distribution of the scores in MBI-C and the prevalence of MBI diagnosis were determined using frequency and descriptive analyses. A logistic regression model was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between frailty status with age, education, depression, MBI and objective cognition. All analyses were conducted using the statistical analysis software SPSS version 18.0, and a two-sided *P*-value of 0.05 was set as the level of significance.

Results

Participant Characteristics

There were 137 older adults enrolled in this study; the mean age was 69.6 ± 7.6 years, and the age range was 60 to 90 years old. Among these, 94 (68.6%) were female; 21 (15.3%) had a primary school education or lower; 43 (31.4%) had multimorbidity, the presence of more than 2 comorbid conditions; and 27 (19.7%) had polypharmacy (took five or more oral medications daily). Of these enrolled individuals, 31 (22.7%) had depression symptoms, 14 (10.4%) had anxiety symptoms, and the mean BMI was 22.5 ± 3.3 kg/m².

According to the definition, 42 participants were categorized into the frailty group (30.7%); and 95 into the no-frailty group (69.3%). The frailty group showed worse performance on the MMSE (26.7 vs 28.0, $p < 0.05$) and MoCA (25.2 vs 26.1, $p < 0.05$) scores than the no-frailty group. Two groups also presented significant differences in age, education, comorbid conditions >2 , polypharmacy and depression. No significant differences were found with respect to gender, BMI and anxiety symptoms among the two groups (Table 1).

A total of 25 (18.2%) participants were MBI+, and 112 (81.8%) were MBI-. Regarding group composition, the mean age of MBI+ participants (72.2 ± 7.7) was higher than that of MBI- participants (69.5 ± 7.0) ($p < 0.05$). The MBI+ individuals had significantly poorer cognition, with lower MMSE (26.8 vs 27.8, $p < 0.05$) and MoCA (24.7 vs 26.1, $p < 0.05$) scores than the MBI- individuals. No significant differences were found between the MBI+ individuals and MBI- individuals in terms of gender ratio, education level, BMI, comorbid conditions >2 , polypharmacy, or depression and anxiety symptoms ($p > 0.05$) (Table 1).

Table 1 Characteristics of 137 Participants Aged ≥ 60 Years and Stratified by MBI Status and Frailty Status

Variable †	Full Sample (n=137)	MBI Status		Frailty Status			
		MBI- (n=112)	MBI+ (n=25)	P-value	No-frailty (n=95)	Frailty (n=42)	P-value
Age, mean (SD)	69.6 (7.6)	69.0 (7.5)	72.2 (7.7)	.05	67.9(6.9)	73.2 (8.1)	<.001
Female	94 (68.6)	86(76.8)	18 (72.0)	.61	58 (61.1)	36 (85.7)	.07
Education				.34			.01
Primary or lower	21 (15.3)	15 (13.4)	6 (24.0)		10 (10.5)	11 (26.2)	
Completed high school	75 (54.7)	64 (57.1)	11 (44.0)		50 (52.6)	25 (59.5)	
At least some college	41 (29.9)	33 (29.5)	8 (32.0)		35 (36.8)	6 (14.3)	
Comorbid conditions >2	43 (31.4)	37 (33.0)	13 (52.0)	.08	27 (28.4)	23 (54.8)	.01
Polypharmacy	27 (19.7)	22 (19.6)	5 (20.0)	.97	9 (9.5)	18 (42.9)	<.001
BMI, mean (SD)	22.5 (3.3)	22.5 (3.2)	22.7 (3.9)	.75	22.8 (2.8)	21.9 (4.1)	.14
Depression (PHQ-9≥10)	31 (22.7)	26 (23.2)	5 (20.0)	.73	16 (16.8)	15(35.7)	.02
Anxiety (GAD-7≥10)	14 (10.2)	12 (10.7)	2 (8.0)	.69	8 (8.4)	6 (14.3)	.30
MMSE, mean (SD)	27.6 (2.4)	27.8 (2.3)	26.8 (2.9)	.049	28.0 (1.8)	26.7 (3.4)	.01
MoCA, mean (SD)	25.8 (2.5)	26.1 (2.2)	24.7 (3.2)	.009	26.1 (2.2)	25.2 (2.9)	.04

Notes: SD: standard deviation; MBI: mild behavioral impairment; MBI-C: Mild Behavioral Impairment Checklist; BMI: body mass index; Results presented as n (%) unless otherwise noted.. Chi-square tests were used for categorical variables, whereas t-tests were used for continuous variables.

Frailty and Mild Behavioral Impairment

The classification of participants according to the MBI-C was significantly different between participants with and without frailty ($p = 0.038$). The MBI-C composite score was associated with the status of frailty ($p = 0.001$). Of the five MBI domains, the participants with decreased motivation, affective dysregulation and social inappropriateness were more likely to have frailty. No significant differences in impulse dyscontrol and abnormal thought and perception were found in our study (Table 2).

Table 2 Frailty and Cognitive and Behavioural Characteristics

	Frailty (n=42)	No-frailty (n=95)	χ^2/F value	ρ value
MBI, n (%)	12 (28.6)	13 (13.7)	$\chi^2= 4.3$.038
MBI score, mean (SD)	7.3 (5.2)	4.7 (3.6)	F= 5.8	.001
Decreased motivation	2.2 (2.2)	1.3 (1.2)	F= 13.3	.005
Affective dysregulation	1.8 (1.4)	1.3 (1.1)	F= .6	.028
Impulse dyscontrol	2.3 (2.0)	1.6 (1.9)	F= 1.3	.059
Social inappropriateness	0.7 (1.0)	0.4 (.7)	F= 12.5	.041
Psychosis	0.3 (.7)	0.2 (.5)	F= 5.0	.246

MBI: mild behavioral impairment; MBI-C: Mild Behavioral Impairment Checklist.

Multivariate logistic regression analysis indicated that MBI+ status was significantly associated with higher risk of having frailty, with an OR of 3.09 (95% CI = 1.29-9.41; $p = 0.047$) (Table 3). We also evaluated the associations between frailty status with global cognition, depression, education and age and we found that age and depression were significantly related to a higher risk of having frailty ($p < 0.05$), but the association with education, MMSE and MoCA score was not significant ($p > 0.05$) (Table 3).

Table 3. Multivariate logistic regression analysis for the association between frailty status and objective cognition with mild behavioral impairment

	Frailty Status				
	β	Sr	Wal χ^2	ρ value	Odds ratio (95% CI)
Age	-.09	.04	5.28	.022	.91 (.84-.99)
Education	-.69	1.10	.40	.529	.50 (.06-4.3)
Depression	1.62	.51	10.27	.001	5.04 (1.88-13.58)
MoCA	-.13	.15	.73	.392	.88 (.66-1.18)
MMSE	.18	.16	1.21	.272	1.19 (.87-1.64)
MBI	1.13	.57	3.95	.047	3.09 (1.29-9.41)

Abbreviations: CI: confidence intervals

Discussion

To our knowledge, this is the first cross-sectional study to evaluate the relationships between frailty and MBI, and cognition. First, we determined that frailty is common in this population, with a prevalence of 30.7%. Second, MBI was also fairly common, with a prevalence of 18.2%. Third, greater burden of frailty was associated with poorer cognition, measured using the MMSE ($p=.01$) and MoCA ($p=.04$). Fourth, compared to those without MBI, MBI+ status was associated with poorer cognition measured using the MMSE ($p=.049$) and MoCA ($p=.01$) Fifth, MBI+ status predicted higher levels of frailty (OR=3.09; 95% CI=1.29-9.41), and this signal was driven by the MBI domains of decreased motivation, affective/emotional dysregulation and social inappropriateness score ($p<0.05$). These results suggest

that in non-dementia older adults, frailty and MBI are both common and associated with small but significant impairment in global cognition.

While the prevalence of frailty was 30.7% in all participants and 69.3% for no-frailty. The prevalence of frailty in our study was relatively high compared with previous estimates, which ranged from 11% up to 26% in community samples(51-53), and the difference may be attributed to our study design and to the fact that participants came from primary care clinics. Frailty may increase the risk of future cognitive decline and that cognitive impairment may increase the risk of frailty suggesting that cognition and frailty may interact in the cycle of age-related decline(54, 55). Our results indicated that frailty was associated with aging-related cognitive declines at-risk for the preclinical phase of neurocognitive disorders, and consistent with previous studies(11-16). In their seminal study, Solfrizzi and colleagues reported that frail older adults had a higher prevalence of cognitive impairment than those without frailty (77% vs. 54%)(56). Furthermore, components of frailty appeared to be related to pathological findings of AD and vascular dementia, supporting the idea of a possible common biological pathway between frailty and cognitive disorders(57). A previous study found that there was an increase in neurons with cellular senescence and aging of microglia, and therefore, increases in apoptosis, aggregation of protein, mitochondrial dysfunction with increased reactive oxygen species and oxidative damage to proteins and lipids, and accumulation of DNA damage(57). Accordingly, increasing frailty may be an indicator of future cognitive impairment.

The prevalence of MBI (18.2%) in our non-dementia participants was higher than that reported by Creese(33) in the PROTECT study, in which 10% of community-dwelling older adults aged 50 or over (n = 9,931) reported MBI, as captured by the MBI-C. In a clinical sample of Spanish primary care patients who validated the current cut-points, the prevalence was 5.8% in older adults with subjective complaints(27) and 14.2% in MCI(58). These estimates collectively, determined using the MBI-C, are considerably lower than previous prevalence estimated generated using the Neuropsychiatric Inventory (59) which ranged from 28-51% in a community population(60, 61), and 49-85% in a cognitive neurology clinic population(60, 62). These differences may be due to the diagnostic frame of reference of one month of symptoms captured by the Neuropsychiatric Inventory, whereas the MBI-C involves a more rigorous standard of six-month symptom duration and explicit later-life onset of symptoms, in accordance with the MBI criteria. The lower MBI frequency generated using the MBI-C reflects increased diagnostic specificity for MBI, eliminating the inclusion of transient and reactive states, by excluding false positives symptoms.

Neuropsychiatric symptoms are associated with an increased risk of cognitive deficits across the lifespan, and MBI is associated with poorer cognition cross-sectionally(33), also conferring a higher risk of cognitive decline and dementia in comparison to those without MBI(21, 63-66). In agreement with this previous evidence, we also found subtle but significant impairment in global cognition according to lower scores on both the MMSE and MoCA in patients with MBI. Indeed, the MBI-C might have significantly higher discriminatory power than the MMSE when seeking to detect early cognitive decline(47). Considering that MBI reflects the neurobehavioral axis of pre-dementia at-risk states and is a complement

to the neurocognitive risk axis represented by the MCI(67), this complementary approach may increase the yield when using both cognitive and behavioral approaches to screen for early-stage neurocognitive disorders.

In this study, we found that MBI was associated with higher levels of frailty (OR=7.44; 95% CI=1.49-37.21) even after adjustment for many potential confounders, and that this signal was driven by the MBI domains of decreased motivation, affective/emotional dysregulation and social inappropriateness ($p<0.05$). Our findings extend the literature by describing different patterns of association of MBI and its components with frailty, a pattern not previously established. Prior studies of the link between frailty and cognition have focused on individual functional abilities and assessed only global cognitive ability or limited cognitive domains(14, 68). The mechanisms for the association are not clear, but possibly involves abnormalities in biological processes related to aging(69). A growing body of epidemiological evidence indicates that the mechanisms involved in the onset of frailty are also those that promote neurodegeneration, including chronic inflammation(54) and oxidative stress(70). Other clinical polypharmacy and multimorbidity can increase the risk of both frailty and dementia(71, 72).

MBI may serve as a proxy marker for frailty, or potentially a risk factor of frailty. Thus, MBI assessment may provide an approach to identify frailty early or to determine the risk of frailty in advance of completing a clinical assessment. This approach identifies potentially novel opportunities to prevent or delay frailty, age-related cognitive decline and other associated adverse health outcomes. The ease of administration of the MBI-C, which has even been validated for telephone administration with high sensitivity and specificity(27), positions it as a simple and cost-effective tool for detecting those at clinical risk for further assessment and work up.

The limitations of our study include the participant population and the sample size. Lower prevalence of MBI and frailty among participants in communities rather than clinical, hospital, or institutional settings are to be expected, and it is unclear if these results can be generalized. We had a limited sample size in this study, and replication with a larger sample is required. Hence, the clinical utility of the cognitive frailty construct cannot be unequivocally supported by this study, but it should be further investigated in future studies independently undertaken by other investigators in older populations.

Conclusion

In conclusion, our findings provide further evidence that MBI as well as frailty are common among non-dementia older adults, with both reflecting subtle but significant deficits in global cognition. MBI, especially decreased motivation, affective dysregulation and social inappropriateness, is significantly associated with an increased risk of frailty before overt cognitive impairment. The MBI-C used in clinical practice could represent a simple and beneficial instrument for the early indication of potential risk prior to the onset of frailty. Overall, these findings emphasize the importance of assessing physical as well as cognitive and behavioral function in older adults for early interventions, suggesting that the inclusion of

these measures in the assessment of frailty can improve the predictive validity of the phenotype regarding adverse health outcomes.

Abbreviations

MBI:mild behavioral impairment; NPS: neuropsychiatric symptoms; MCI: mild cognitive impairment; AD: Alzheimer's disease; NC: normal cognition; MBI-C: Mild Behavioral Impairment Checklist; FP: the Fried phenotype; MoCA-BC: Chinese versions of the Montreal Cognitive Assessment; MMSE: Mini-mental State Examination; BMI: body mass index; ANOVA: analysis of variance; ORs: odds ratios; CIs: confidence intervals.

Declarations

Acknowledgments

We appreciate the cooperation of the staff of the Guangdong Provincial Hospital of Chinese Medicine.

Funding

The study was supported by the National Key R&D Program of China, No. 2018YFC1705600; Guangdong Provincial Hospital of Chinese Medicine's Scientific and Technological Plan, No. YN2016ZWB07 and Guangdong Research Center for TCM Services and Industrial Development, No.2019YBB06.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SF, ZY and FX conceived and designed the study. SF, XL and TY recruited the participants, collected the data for the manuscript and provided substantial feedback. SF, ZP, ZI and BH analyzed and interpreted the data. SF, ZI, ZY and FX wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Review Board of Guangdong Provincial Hospital of Chinese Medicine Ethics Committee (reference: B2017-168-01) and all the participants provided written informed consent. For some participants recognized as having cognitive impairment and/or severe illness, we obtained proxy consent from a family member or another supportive adult on their behalf.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figures

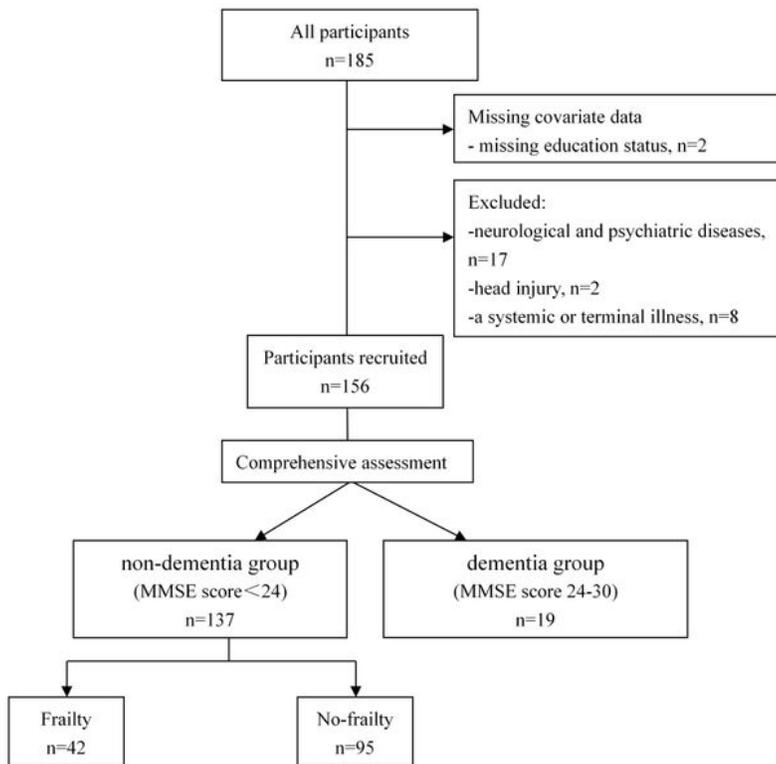


Figure 1 Participant flow chart

Participant inclusion/exclusion criteria. Missing data categories are mutually exclusive. *One participant with missing frailty component (gait speed) and frailty categorical definition not possible.

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Figure 1

Participant flow chart. Participant inclusion/exclusion criteria. Missing data categories are mutually exclusive. (TIF 5.9MB)