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

Shaoyi Fan
Guangzhou University of Chinese Medicine
Ximin Liang
Guangzhou University of Chinese Medicine
Tianchan Yun
Guangzhou University of Chinese Medicine
Zhong Pei
Sun Yat-sen University First Affiliated Hospital
Bin Hu
University of Calgary Cumming School of Medicine
Zahinoor Ismail
University of Calgary
Zhimin Yang
Guangdong Hospital of Traditional Chinese Medicine
Fuping Xu (xufuping163@163.com)
Guangdong Hospital of Traditional Chinese Medicine

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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 cognitively normal older adults.

Methods: This is a cross-sectional study. A consecutive series of 137 cognitively normal older adults in the Anti-Aging study, recruited from primary care clinics, were enrolled. Frailty was estimated using the original 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, 30.6% of the older adults had frailty, 35.0% had prefrailty 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, p = 0.02). The frailty and MBI categories were both significantly associated with both MMSE and MoCA-BC score ($p<0.05$).

Conclusions: Both frailty and MBI status are related to higher risk of cognitive impairment. MBI is significantly associated with an increased risk of having frailty before overt cognitive impairment. This association merits further study to identify strategies to 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 is most commonly measured using the Fried phenotype (FP)(4), which was considered appropriate for older adults who are less likely to have cognitive decline.

Frailty is increasingly recognized as a fundamental determinant of an individual’s vulnerability or resilience to stressors(5) and has been linked to impaired cognition(6). Various neurocognitive disorders

including late-life cognitive impairment(7, 8), mild cognitive impairment (MCI)(9), dementia(10) and Alzheimer's disease (AD)(11) have shown associations 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(12).

Similar to frailty, neuropsychiatric symptoms (NPS) have demonstrated associations 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(13). 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(14). 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 incident cognitive decline and dementia(15). As an early manifestation of neurodegeneration, MBI has been connected with known biomarkers for dementia including amyloid beta in cognitive normals(16), and faster accumulation of neurofilament light in normal cognition and MCI(17). MBI has also been used in machine learning models to predict neurocognitive diagnostic category 40 months later(18). 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(19). The Mild behavioral impairment Checklist (MBI-C) is the brief screening instrument developed to capture MBI in accordance with the criteria(20, 21).

Identifying at-risk populations earlier in the process of declining health has significant implications for maintaining health, and estimating the prevalence of MBI and frailty in cognitively normal older adults could be helpful when developing interventions to promote healthy aging. In addition, the possible association between MBI and frailty - both independent risk factors for dementia appearing early in the disease course - should also be further 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 relationship between MBI total and domain scores, and frailty, in cognitively normal older adults. We hypothesized that MBI would predict greater frailty burden.

Methods

Participants and Setting

A consecutive series of 185 cognitively normal subjects 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. Exclusion criteria included the following: 1) history of neurological and psychiatric diseases (cerebrovascular disease, Parkinson's disease, depression or dementia); 2) head injury with loss of consciousness longer than 5 minutes; 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 normal cognition (NC). (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)(22). 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(23).

Emotional Assessment

Anxiety and depression were measured by the Generalized Anxiety Disorder 7-item (GAD-7) scale(24) and the 9-item Patient Health Questionnaire (PHQ-9)(25), 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(26). 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 combined sensitivity and specificity in the primary studies(27). 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(28).

Frailty Assessment

The diagnosis of frailty was based on the original Fried phenotype and included five indicators: exhaustion, unintentional weight loss, weak grip strength, slow walking speed and low energy expenditure (physically inactive)(4). Based on these scores, individuals with 0 criteria present were categorized into the non-frailty or robust group, those with 1 to 2 frailty criteria were in the prefrailty group, and those with 3 or more criteria were in the frailty group(29).

Neuropsychiatric and Neuropsychological Assessment

MBI was assessed using the Chinese version of MBI-C developed by Cui(30), a scale developed specifically for functionally independent community-dwelling older adults. The MBI-C(31) 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 through content (psychotic symptoms, i.e. hallucinations, delusions). Only symptoms that are characterized by later life onset, representing a change from longstanding patterns of behaviour, and have been present no less than 6 months were assessed as “yes”, and their severity was rated (1 to 3 points)(31). 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 a good sensitivity and specificity(20).

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)(32) and the Mini-mental State Examination (MMSE)(33) were used as screening tests for cognitive impairment. 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 standard cutoffs indicative of cognitive impairment vary across populations, and a recent review of screening measures in the older population suggested a cut-off of <26 for the MoCA(32) and <24 for the MMSE(33).

Statistical Analysis

Continuous variables were reported as the mean ± 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, 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, and 14 (10.4%) had anxiety symptoms, and the mean BMI was 22.5 ± 3.3 kg/m^2. According to the definition, 42 participants were categorized into the frailty group (30.7%), 48 into the prefrailty group (35.0%), and 47 into the robust group (34.3%). The frailty group showed worse performance on the MMSE (26.7 vs 27.6 vs 28.3, $p < 0.05$) and MoCA (25.2 vs 25.7 vs 26.6, $p < 0.05$) scores than prefrailty and robust group. Besides, the groups also presented significant differences in age, education and polypharmacy. No significant differences were found with respect to gender, BMI, comorbid conditions >2, depression and anxiety symptoms among the three 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, 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	Robust (n=47)	Prefrailty (n=48)	Frailty (n=42)	*P*-value
Age, mean (SD)	69.6 (7.6)	69.0 (7.5)	72.2 (7.7)	.05	66.6 (5.5)	69.3(7.8) *	73.2 (8.1) Δ	<.001
Female	94 (68.6)	86(76.8)	18 (72.0)	.61	35 (74.5)	33 (68.8)	36 (85.7)	.17
Education				.34				.01
Primary or lower	21 (15.3)	15 (13.4)	6 (24.0)		2 (4.3)	8 (16.7)	11 (26.2)	
Completed high school	75 (54.7)	64 (57.1)	11 (44.0)		26 (55.3)	24 (50.0)	25 (59.5)	
At least some college	41 (29.9)	33 (29.5)	8 (32.0)		19 (40.4)	16 (33.3)	6 (14.3)	
Comorbid conditions >2	43 (31.4)	37 (33.0)	13 (52.0)	.08	11 (23.4)	16 (33.3)	23 (54.8)	.08
Polypharmacy	27 (19.7)	22 (19.6)	5 (20.0)	.97	4 (8.5)	5 (10.4)	18 (42.9)	<.001
BMI, mean (SD)	22.5 (3.3)	22.5 (3.2)	22.7 (3.9)	.75	22.8 (2.3)	22.8 (3.3)	21.9 (4.1)	.34
Depression (PHQ-9≥10)	31 (22.7)	26 (23.2)	5 (20.0)	.73	6 (12.8)	10 (20.8)	15(35.7) Δ	.33
Anxiety (GAD-7≥10)	14 (10.2)	12 (10.7)	2 (8.0)	.69	4 (8.5)	4 (8.3)	6 (14.3)	.58
MMSE, mean (SD)	27.6 (2.4)	27.8 (2.3)	26.8 (2.9)	.049	28.3 (1.5)	27.6 (2.0)	26.7 (3.4)[c]	.01
MoCA, mean (SD)	25.8 (2.5)	26.1 (2.2)	24.7 (3.2)	.009	26.6 (1.5)	25.7 (2.6)	25.2 (2.9)[c]	.02

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. *P < 0.05, compared to robust group; ΔP < 0.05, compared to prefrail group. Chi-square tests were used for categorical variables, whereas t-tests were used for continuous variables. [c] Kruskal-Wallis test,

Frailty and Mild Behavioral Impairment

The MBI-C composite score was associated with the status of frailty (p = 0.001). Of the five MBI domains, the participants with affective dysregulation and impulse dyscontrol were more likely to have frailty. No significant differences were found in decreased motivation, social inappropriateness and abnormal thought and perception in our study (Table 2).

Table 2 Frailty and Cognitive and Behavioural Characteristics

	Robust (n=47)	Prefrailty (n=48)	Frailty (n=42)	χ2/F/Z value	ρ value
MBI, n (%)	2 (4.3)	11 (22.9)	12 (28.6)	χ2= 9.9	.007
MBI score, median (QR)	4 (2,5)	5 (3,8)	6 (3,9)	Z= 13.7	.001
Decreased motivation	1 (0,2)	2 (0,2)	2 (0,3)	Z= 5.0	.081
Affective dysregulation	1 (0,2)	1 (0,2)	2 (1,2)	Z= 6.4	.041
Impulse dyscontrol	1 (0,2)	1 (1,3)	2 (1,3)	Z= 10.1	.006
Social inappropriateness	0 (0,0)	0 (0,1)	0 (0,1)	Z= 4.9	.088
Psychosis	0 (0,0)	0 (0,0)	0 (0,0)	Z= 4.6	.102
MMSE, mean (SD)	28.3 (1.5)	27.6 (2.0)	26.7 (3.4)c	F= 4.8	.009
MoCA, mean (SD)	26.6 (1.5)	25.7 (2.6)	25.2 (2.9)c	F= 3.8	.024

[c] Kruskal-Wallis test,

Multivariate logistic regression analysis indicated that MBI+ status was significantly associated with higher risk of having frailty, with an OR of 7.44 (95% CI = 1.49-37.21; p = 0.02) (Table 3). We also evaluated the associations between frailty status with global cognition and age, we found that age was significantly related to higher risk of having frailty (OR = 0.90; 95% CI = 0.82- 0.97; p = 0.01), but the association with 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 χ2	ρ value	Odds ratio (95% CI)
Age	-.11	.04	6.90	.01	.90 (.82-.97)
MoCA	-.06	.18	.11	.74	.94 (.67-1.33)
MMSE	.10	.18	.31	.58	1.11 (.78-1.56)
MBI	2.01	0.82	5.97	0.02	7.44 (1.49-37.21)

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=.02). 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=7.44; 95% CI=1.49-37.21), and this signal was driven by the MBI domains of affective/emotional dysregulation and impulse dyscontrol score (p<0.05). These results suggest that in cognitively normal older adults, frailty and MBI both are common and associated with small but significant impairment in global cognition.

While the prevalence of frailty was 30.7% in all participants, the prevalence was 35.0% for pre-frailty and 34.3% for robust. The prevalence of frailty in our study was relatively high compared with previous estimates, which ranged from 11% up to 26% in community samples(34-36), which may be attributed to our study design and that participants came from primary care clinics. Frailty and cognitive impairment are distinguishable facets of aging that interact in the cycle of age-related decline. Our results indicated that in cognitively normal older adults, frailty status was associated with aging-related cognitive declines at-risk for the preclinical phase of cognitive disorders, and consistent with previous studies(7-11). 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%)(37). 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(38). A previous study found that there was an increase in of neurons with cellular senescence and aging of microglia, and therefore, an increase in apoptosis, aggregation of protein, mitochondrial dysfunction with increased reactive oxygen species and oxidative damage to proteins and lipids, and accumulation of DNA damage(38). Accordingly, increasing frailty may be an indicator of future cognitive decline and impairment.

The prevalence of MBI (18.2%) in our cognitively normal participants was higher than that reported by Creese(39) 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 cognitive normal older adults with subjective complaints(20) and 14.2% in MCI(40). These estimates collectively, determined using the MBI-C, are considerably lower than previous prevalence estimated generated using the Neuropsychiatric Inventory (41) which ranged from 28-51% in a community population(42, 43), and 49-85% in a cognitive neurology clinic population(42, 44). 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(39), also conferring a higher risk of cognitive decline and dementia in comparison to those without MBI(15, 45-48). In agreement with this previous evidence, we also found subtle but significant impairment in global cognition according to lower score of both 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(31). MBI represents the neurobehavioral axis of pre-dementia risk states and is a complement to the neurocognitive risk axis represented by MCI(49). This complementary approach may increase the yield when using both cognitive and behavioural approaches to screen for early stage neurocognitive disorders.

The association between MBI and frailty may be of particular relevance to preclinical cognitive impairment. In this study, we found that MBI was associated with higher levels of frailty (OR=7.44; 95% CI=1.49-37.21), and that this signal was driven by the MBI domains of affective/emotional dysregulation(50) and impulse dyscontrol(51) ($p<0.05$). Our findings extend the literature by describing different patterns of associations 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(9, 52). The mechanisms for the association is not clear, but possibly involves abnormalities in biological processes related to aging(53). 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(55). Other clinical polypharmacy and multimorbidity can increase the risk of both frailty and dementia(56, 57).

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 determine of risk for 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 adverse health outcomes. The ease of administration of the MBI-C, which has even been validated for telephone administration with high sensitivity and specifificity[(20)],

positions it as a simple and cost-effective tool for detecting those at clinical risk for further assessment and work up.

Limitations of our study include the participant population and the sample size. A lower prevalence of MBI and frailty among participants in communities rather than clinical, hospital, or institutional settings is 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 cognitively unimpaired older adults, both reflecting subtle but significant deficits in global cognition. MBI, especially affective dysregulation and impulse dyscontrol, is significantly associated with an increased risk for 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 behavioural 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

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Availability of data and materials

The datasets used and/or analysed 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 interpret 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 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

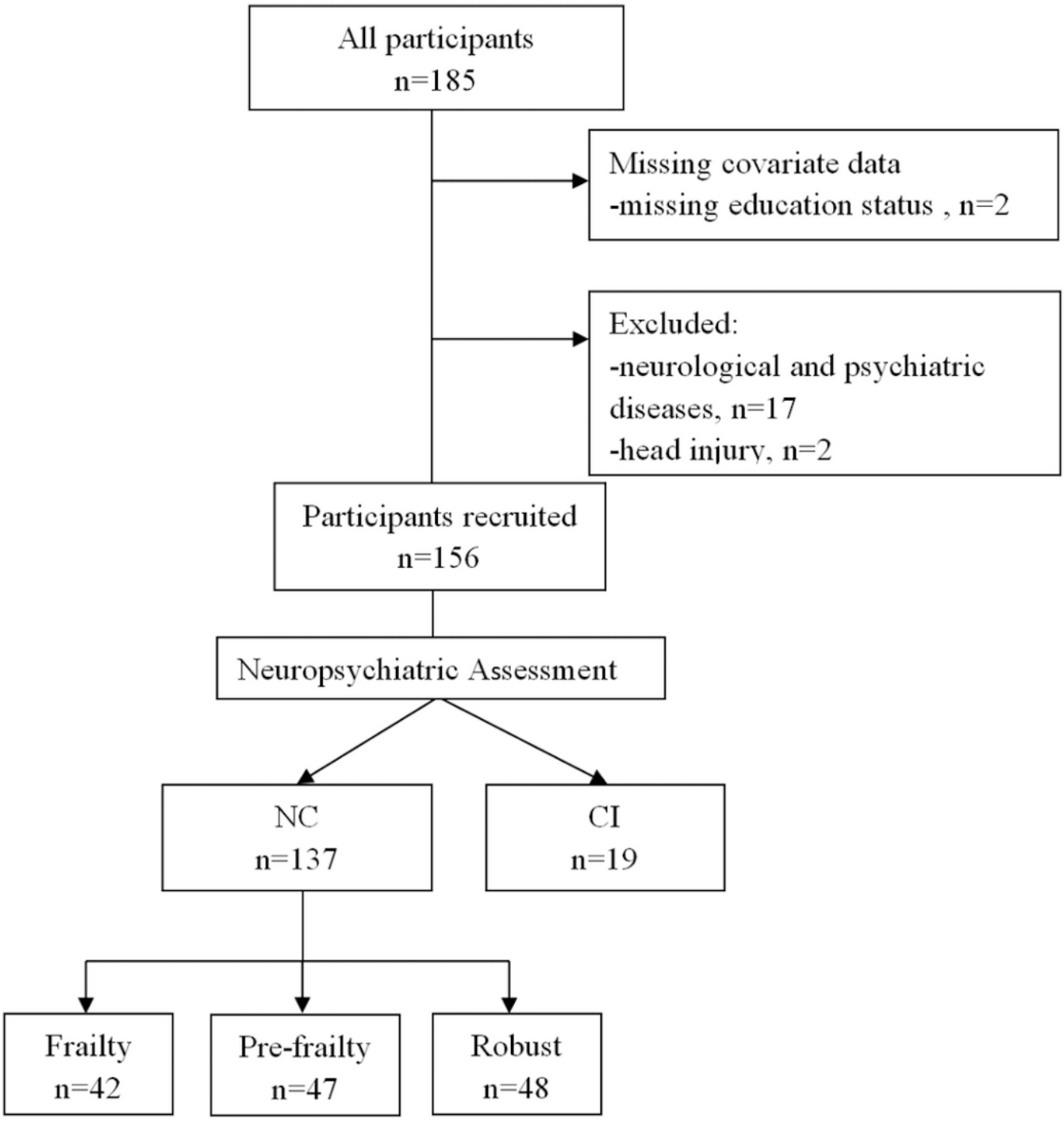

Figure 1

Participant flow chart. Participant inclusion/exclusion criteria. Missing data categories are mutually exclusive. NC: normal cognition; CI: cognitive impairment.