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RESEARCH ARTICLE

Physical and biopsychosocial frailty, cognitive phenotypes, and plasma biomarkers for Alzheimer's disease in Chinese older adults: A population-based study

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Abstract

INTRODUCTION: We sought to examine the associations of physical frailty (PF) and biopsychological frailty (BF) with dementia and mild cognitive impairment (MCI) among Chinese older adults and further to explore neuropathological mechanisms underlying the associations.

METHODS: This population-based cross-sectional study included 5149 participants in the MIND-China baseline examination (2018); of these, we measured plasma amyloid-β (Aβ), neurofilament light chain (NfL), and total tau in 1371 persons and phosphorylated tau 217 (p-tau217) and glial fibrillary acidic protein (GFAP) in 3387 persons.

RESULTS: PF and BF were significantly associated with increased likelihoods of dementia, Alzheimer's disease (AD), vascular dementia (VaD), and MCI. PF was significantly correlated with increased plasma p-tau217, GFAP, and NfL, and reduced Aβ42/Aβ40 ratio; BF was related to higher plasma total tau and NfL and lower Aβ42/Aβ40 ratio. PF in combination with demographics performed excellent in differentiating dementia from non-dementia (area under the curve [AUC] = 0.83).

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DISCUSSION: PF and BF are potential clinical biomarkers for dementia and MCI in older adults. Alzheimer's pathology, neuroinflammation, and neurodegeneration may underlie their associations.

KEYWORDS
dementia, frailty, mild cognitive impairment, plasma biomarkers, population-based study

Highlights

- Physical (PF) and biopsychosocial frailty (BF) were strongly associated with dementia and mild cognitive impairment (MCI) in rural Chinese older adults.
- Frailty, especially PF, was associated with increased plasma phosphorylated tau 217 (p-tau217), glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL) and a reduced plasma amyloid-β (Aβ)42/Aβ40 ratio.
- Alzheimer's pathology, neuroinflammation, and neurodegeneration may underlie the associations of frailty with dementia.
- PF, in combination with demographic factors, performed excellent (area under the curve [AUC] = 0.83) in differentiating dementia from non-dementia in rural older adults.

1 | BACKGROUND

In the past half a century, China has experienced rapid population aging, with people aged ≥65 years accounting for 14.2% of the nation's population.[1] As a result, China has the world's largest population of people with dementia, with approximately 15 million older adults living with dementia.[2] Thus, dementia has emerged as an urgent public health concern in China. Given that there is a lack of curative treatments for dementia, identifying modifiable risk factors for preventive interventions could be an alternative strategy to deal with the huge challenge of the disease.

Frailty is characterized by reduced reserve capacities to maintain homeostasis in multiple physiological systems.[3,4] Thus, frailty represents a crucial condition that is associated with several adverse health outcomes such as disability, delirium, falls, hospitalization, and mortality.[5,6] In the past decades, several operational definitions of frailty have been proposed, which can be summarized into three major conceptual models.[7] The physical frailty (PF) model defines frailty according to five physical components: involuntary weight loss, exhaustion, low grip strength, slow gait speed, and low physical activity.[8] However, this model neglects other important domains such as cognition, psychosocial factors, and nutrition. The deficit accumulation model assesses frailty using a continuous score based on symptoms, signs, disabilities, and diseases.[9] The biopsychosocial frailty (BF) model expands the concept of frailty to include both physical and psychosocial domains, which overcomes the limitations of the PF phenotype.[10,11] Previous studies have linked frailty with dementia,[12,13] but the association may vary depending on frailty phenotypes (e.g., PF and BF). Indeed, a systematic review and meta-analysis found that BF, but not PF, was associated with an increased risk of Alzheimer's disease (AD).[14] In addition, the relationship between frailty and mild cognitive impairment (MCI) has been under-explored in community-dwelling older adults. Of note, most of the studies in the current literature have been conducted among high-income countries. It is important to investigate the association between frailty phenotypes and cognitive outcomes across ethnically, geographically, and socio-culturally diverse older populations.

Moreover, the neuropathological mechanisms linking PF and BF with cognitive outcomes remain poorly understood. Evaluating the associations between frailty and AD-related plasma biomarkers may provide deeper insight into the mechanisms underlying the association of frailty with dementia. This becomes possible in the population-based studies, because in the past few years, highly sensitive plasma biomarkers for Alzheimer's pathologies, neuroinflammation, and neurodegeneration have been identified.[15] For instance, plasma phosphorylated tau at threonine 217 (p-tau217) has been strongly associated with brain amyloid and tau pathology,[16,17] and the diagnostic accuracy of plasma p-tau217 for AD was comparable to cerebrospinal fluid (CSF) p-tau217 in the head-to-head studies.[18] A few population-based studies have so far examined the relationships of frailty with plasma AD-related biomarkers. A community-based study of men found that a higher frailty index at mid- and late-life was associated with increased plasma β-amyloid (Aβ)40, Aβ42, and neurofilament light chain (NfL) in old age.[19] By contrast, data from the French Multidomain Alzheimer Preventive Trial showed no association of PF with plasma Aβ42/Aβ40 ratio or NfL.[20–22] However, population-based studies have not yet explored the associations of frailty with newly identified reliable plasma biomarkers for AD pathology or neuroinflammation such as p-tau217 and glial fibrillary acidic protein (GFAP).[23,24] Therefore, exploring the associations of PF and BF with these plasma

biomarkers among ethnically, socioeconomically, and culturally diverse populations such as rural Chinese older adults will not only increase our understanding of the mechanisms underlying the frailty-cognition relationships but also bridge the knowledge gap.

Therefore, in this population-based study of rural-dwelling Chinese older adults, we aimed (1) to examine the associations of PF and BF with cognitive phenotypes (e.g., dementia, MCI, and subtypes), (2) to evaluate the relationships of PF and BF with plasma biomarkers for AD-related pathology, and (3) to assess the utility of frailty for the detection of dementia.

RESEARCH IN CONTEXT

1. **Systematic review**: We searched PubMed for relevant literature. Current evidence has linked frailty with dementia and cognitive impairment in older adults. However, population-based data regarding the relationships of frailty with cognitive phenotypes in Chinese older populations remain limited, and very few studies have explored the neuropathological mechanisms underlying their associations.
2. **Interpretation**: Physical frailty (PF) and biopsychological frailty (BF) were associated with increased likelihoods of dementia, Alzheimer's disease (AD), vascular dementia (VaD), mild cognitive impairment (MCI), and amnestic MCI (aMCI) in a rural-dwelling Chinese older population. Furthermore, PF was associated with plasma biomarkers for Alzheimer's pathology, neuroinflammation, and neurodegeneration. This suggests that frailty and the dementia syndrome in older adults may share common neuropathological pathways.
3. **Future directions**: Prospective cohort studies are warranted to clarify the causal relationship of frailty with cognitive phenotypes as well as the underlying mechanisms. Furthermore, given that frailty is a modifiable syndrome, further studies may assess whether early detection and optimal management of frailty might help delay dementia onset.

2 | METHODS

2.1 | Study design and participants

This population-based cross-sectional study used data from the 2018 baseline assessments of the Multimodal Interventions to Delay Dementia and Disability in rural China (MIND-China),[25] a participating project of the World-Wide FINGERS Network.[26] Briefly, MIND-China targeted individuals who were aged ≥60 years by the end of 2017 and living in 52 villages of Yanlou Town, Yanggu County, western Shandong province. Between March and September 2018, 5765 participants (74.9% of all eligible people) undertook the baseline examination for MIND-China. Of these, we excluded 616 participants due to missing data on the diagnosis of dementia status ($n = 49$) or PF status ($n = 567$), leaving 5149 individuals for analyzing the association between frailty and dementia (analytical sample 1). Of these, we further excluded 271 participants due to prevalent dementia ($n = 169$) and insufficient information to determine cognitive function ($n = 102$), leading to 4878 persons for analyzing the association of frailty with MCI (analytical sample 2).

Of the 5149 participants in the analytical sample 1, 1371 individuals had available data on plasma Aβ40, Aβ42, total tau (t-tau), and NfL. This biomarker subsample was chosen using the cluster (village)-based sampling method, involving 1265 dementia-free participants from 18 villages that were randomly selected from the 52 villages, plus 106 individuals who were diagnosed with AD from all the 52 villages in Yanlou Town. In addition, 3387 individuals had available data on plasma p-tau217 and GFAP. This biomarker subsample consisted of individuals who had data on plasma Aβ40, Aβ42, t-tau, and NfL plus dementia-free participants from additional 14 villages that were randomly selected from the remaining 34 villages, as well as those who were diagnosed with non-AD dementia from all the 52 villages. These two biomarker subsamples were used for the analysis involving different plasma AD-related biomarkers (analytical sample 3). Figure 1 shows the flowchart of the study participants.

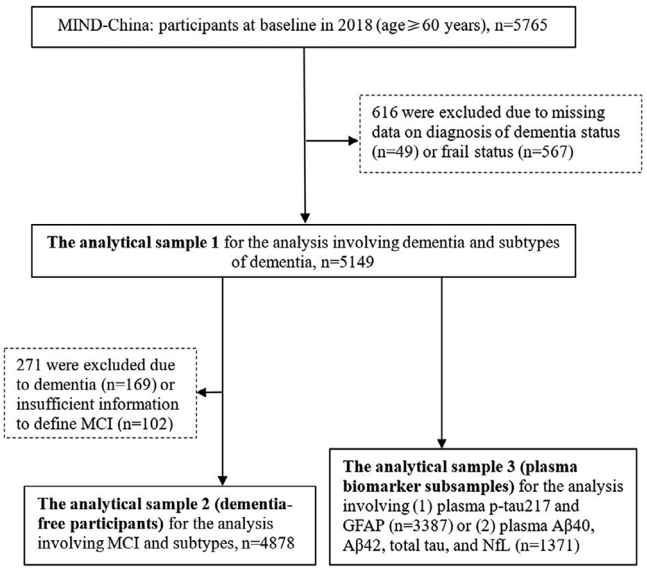

FIGURE 1 Flowchart of study participants. Aβ, amyloid-β; GFAP, glial fibrillary acidic protein; MIND-China, Multimodal Interventions to Delay Dementia and Disability in Rural China; MCI, mild cognitive impairment; NfL, neurofilament light chain; p-tau217, phosphorylated tau at threonine 217.

2.2 | Data collection and definitions

From March to September 2018, data were collected by trained medical staff via face-to-face interviews, clinical evaluations,

neuropsychological assessments, and laboratory testing, as previously reported.[25] The data included demographic characteristics (e.g., age, sex, and education), lifestyle factors (e.g., smoking, drinking alcohol, and physical activity), medical history (e.g., hypertension, diabetes, dyslipidemia, coronary heart disease [CHD], stroke, and depressive symptoms), and apolipoprotein E (*APOE*) genotype. The 15-item Geriatric Depression Scale (GDS-15) was employed to assess depressive symptoms, and a total GDS-15 score ≥ 5 was considered to indicate depressive symptoms.[27] Data collection and the definitions and classifications of all other covariates have been published previously.[28]

2.3 | Definitions of physical and BF

PF was defined following the criteria that were in accordance with those used in the United States Cardiovascular Health Study (CHS),[8] with some modifications. The CHS criteria for defining PF have been used with some modifications in previous studies, such as the French Three-City Study and MOBILIZE Boston Study.[29–31] Specifically, the five criteria used to define PF in MIND-China were assessed as follows: (1) weight loss was defined as body mass index (BMI) under 21 kg/m^2.[29] This threshold was used in the Mini Nutritional Assessment[32] and was associated with increased mortality[33]; (2) exhaustion was assessed by a response "no" to the question: "Do you feel full of energy?" [30]; (3) weakness was assessed using the sit-to-stand test time, which was proved to be a good proxy for measuring handgrip strength.[31,34] After adjusting for sex and BMI, individuals in the highest quintile were classified as weakness; (4) slowness was assessed using the 4-m walk test, adjusting for sex and height. Individuals in the highest quintile were classified as slow [31]; (5) low physical activity was identified as participating in sports for fewer than an hour or in leisure activities for fewer than 3.5 h each week.[29] Table S1 shows details of the original CHS criteria, the modified criteria used in the French Three-City Study, and our modified criteria for defining PF in MIND-China. Participants were considered to have frailty if they met three or more out of the five criteria, prefrailty if they fulfilled one or two criteria, and robust if none of the five criteria was met. Individuals were considered to have BF if they met the criteria for PF and responded "yes" to at least one of the following two questions derived from the GDS-15 scale: "Do you feel that your life is empty?" and "Do you often feel helpless?".[30,35]

2.4 | Diagnosis of dementia and MCI

Following the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, dementia was clinically diagnosed through a three-step procedure, as described elsewhere.[36] Dementia was further categorized into AD based on the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria for probable AD dementia[37] and vascular dementia (VaD) based on the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for probable VaD.[38] Dementia cases that could not be categorized as AD or VaD were classified as other types of dementia.

Among participants who were free of dementia, MCI was diagnosed by integrating information from the interviews, clinical examinations, and comprehensive cognitive evaluations following the Petersen's criteria, operationalized in the same way as used in the Mayo Clinic Study of Aging, as previously described.[28] MCI was further categorized into amnestic MCI (aMCI) when the memory domain was impaired, or non-amnestic MCI (non-aMCI) when the memory domain was not affected.[28]

2.5 | Measurement of plasma biomarkers

After an overnight fast, peripheral blood samples were collected into ethylenediaminetetraacetic acid (EDTA)-coated vacutainers, followed by centrifugation to obtain plasma. Then, the plasma samples were stored at −80°C for further analysis. Plasma Aβ40, Aβ42, t-tau, NfL, p-tau217, and GFAP were measured using a single-molecule array (Simoa) on the HD-X platform (Quanterix Corp, MA, USA).[39] We used the Human Neurology 3-Plex A assay (N3PA) Kit to measure Aβ40, Aβ42, and t-tau, the NF-light advantage kit for NfL, the ACC pTau217 Assay for p-tau217, and the GFAP Simoa Discovery Assay Kit for GFAP. Two quality control (QC) plasma samples were run in duplicate on each plate for each analyte. The intra-assay and inter-assay coefficients of variability were both controlled within 15%.

2.6 | Statistical analysis

Characteristics of study participants by frailty status were compared using the chi-squared test for categorical variables and Kruskal–Wallis H test for continuous variables. We used logistic regression models to examine the odds ratio (OR) and 95% confidence interval (CI) of dementia, MCI, and its subtypes associated with frailty. We initially categorized frailty status into robust, prefrail, and frail groups. Because there were too few people with dementia in the robust group, we combined robust and prefrail groups together as non-frail group in the analysis that involved the outcome of dementia. General linear regression models were used to estimate the associations of frailty with plasma AD-related biomarkers. Prior to the data analysis, plasma p-tau217, GFAP, and NfL concentrations were log-transformed owing to skewed distributions. We reported the main results from two models: Model 1 was adjusted for age, sex, and education. Model 2 was additionally adjusted for smoking, alcohol drinking, hypertension, diabetes, hyperlipidemia, CHD, stroke, and *APOE* genotype, and when examining the association between PF and cognitive phenotypes, for the presence of depressive symptoms. Statistical interactions of frailty with age groups (< 70 vs. ≥70 years), sex, education (no schooling vs. any schooling), or *APOE* ε4 allele (carriers vs. non-carriers) on the likelihood of cognitive outcomes were assessed by simultaneously entering the independent variables and their cross-product term into the same

model. Stratified analysis was conducted when a statistical interaction was identified (*P* for interaction < 0.05). To assess the utility of frailty in differentiating dementia from non-dementia, we calculated sensitivity and specificity and used the area under the receiver operating characteristic (ROC) curve (AUC) to assess the accuracy of frailty for the detection of dementia.[40] The ROC analyses were performed separately by age, sex, education, frailty, and combinations of these factors. Predictive ROC models were compared using the DeLong test.

ROC analysis was performed using the partial ROC (pROC) package in the R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). All other analyses were performed using Stata, version 15.1 (Stata Corp., College Station, TX, USA). Two-tailed $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of study participants ($n = 5149$)

The mean age of the 5149 participants was 70.41 (SD = 5.47) years (age range: 60–93 years), 57.18% were females, and 38.76% had no formal school education. Of these, PF was defined in 583 (11.32%) persons and prefrailty in 3075 (59.72%) individuals. Compared with robust participants, people with frailty were older and more likely to have CHD and stroke, and both frail and prefrail participants were more likely to be female, less educated, less likely to drink alcohol, and had a lower prevalence of hypertension and a higher prevalence of depressive symptoms ($p < 0.05$) (Table 1).

3.2 | Associations of physical and BF with dementia and its subtypes ($n = 5149$)

In the multivariable-adjusted model, PF (vs. non-frailty) was significantly associated with increased likelihoods of all-cause dementia (OR: 4.73; 95% CI: 3.28-6.81), AD (3.99; 2.60-6.14), and VaD (9.94; 4.75-20.77). BF had analogous associations with all-cause dementia, AD, and VaD (Table 2). There was no statistical interaction of either PF or BF with demographics and *APOE* genotype on the likelihood of dementia or subtypes (*p* for all interactions > 0.05).

3.3 | Associations of physical and BF with MCI and its subtypes ($n = 4878$)

Among dementia-free participants ($n = 4878$), prefrailty and frailty were significantly associated with the multivariable-adjusted OR (95% CI) of 1.41 (1.20–1.65) and 2.21 (1.73–2.83), respectively, for MCI; the associations were statistically evident with aMCI (prefrailty: 1.43; 1.21-1.70; frailty: 2.35; 1.81–3.04), but not evident with naMCI in the multivariable-adjusted model (Table 3). BF had analogous associations with increased likelihoods of MCI and aMCI, but not with naMCI in the multivariable-adjusted model (Table 3, Model 2). We detected a statistical interaction of PF and BF with education on the likelihood of MCI (*p* for interaction = 0.021 and 0.015, respectively). Further analysis stratified by educational levels (no schooling vs. any schooling education) suggested that the association between frailty (PF and BF) and MCI was stronger among individuals with schooling education than those without, with the multivariable-adjusted OR of MCI in people with any schooling education versus those without education being 3.04 versus 1.70 for having PF and 4.26 versus 1.67 for having BP (Table S2). There were no statistical interactions of frailty status with age, sex, and *APOE* genotype on the likelihood of MCI (*p* for all interactions > 0.05).

3.4 | Associations of physical and BF with plasma biomarkers

In the subsamples of plasma biomarkers, PF was significantly associated with higher plasma p-tau217 (multivariable-adjusted β-coefficient: 0.07; 95% CI: 0.01-0.13), GFAP (0.05; 0.00-0.10; $p = 0.049$), and NfL (0.16; 0.06-0.26), and a lower Aβ42/Aβ40 ratio (−3.99; −7.41 - −0.58), but not with plasma t-tau in the multivariable-adjusted models; prefrailty was significantly associated with higher plasma p-tau217 (multivariable-adjusted β-coefficient: 0.05; 95% CI: 0.01-0.09) and GFAP (0.04; 0.01-0.07), but not with plasma Aβ42/Aβ40 ratio, t-tau, and NfL (Table 4). BF was significantly associated with higher plasma t-tau (0.30; 0.01-0.60) and NfL (0.18; 0.03-0.33), and a lower Aβ42/Aβ40 ratio (−5.46; −10.41 to −0.52), but not with plasma p-tau217 and GFAP in the multivariable-adjusted model (Table 4).

3.5 | Discriminative ability of physical and BF for dementia ($n = 5149$)

The discriminative performance of frailty alone and in combination with demographic factors for dementia were assessed in three models using AUC: frailty alone in model 1, demographic-based model that included age, sex, and education in model 2, and frailty in combination with demographic factors in model 3. The AUC for discriminating all-cause dementia from non-dementia was 0.72 (95% CI: 0.69-0.76) for PF alone, 0.76 (0.73-0.80) for demographic factors alone, and 0.83 (0.80-0.87) for the combination of PF and demographic factors (Figure 2, Table S3). The AUC was significantly improved when adding the PF to the demographic-based model using the logistic regression model ($p < 0.05$, Delong's tests), with the sensitivity being increased from 0.65 to 0.76 and the specificity being increased from 0.73 to 0.79. Similarly, the AUC for discriminating all-cause dementia from non-dementia was 0.62 (0.58-0.65) for BF alone, 0.75 (0.71-0.79) for demographic factors alone, and 0.80 (0.76-0.84) for the combination of BF and demographic factors (Figure 2, Table S3). The AUC was significantly improved when adding the BF to the demographic-based model using the logistic regression model ($p < 0.05$, Delong's tests), with the sensitivity being slightly decreased from 0.67 to 0.64, but the specificity being increased from 0.70 to 0.84. Similar results were

TABLE 1 Characteristics of the study participants by physical frailty

Characteristics[a]	Total sample ($n = 5149$)	Physical frailty		
		Robust ($n = 1491$)	Prefrail ($n = 3075$)	Frail ($n = 583$)
Age (years), mean (SD)	70.41 (5.47)	69.94 (4.80)	70.10 (5.34)	73.27 (6.73)*
Female sex, *n* (%)	2944 (57.18)	801 (53.72)	1793 (58.31)*	350 (60.03)*
Education, *n* (%)				
Illiterate	1996(38.76)	481(32.26)	1219(39.64)	296(50.77)
Primary school	2206(42.84)	657(44.06)	1321(42.96)	228(39.11)
Middle school or above	947(18.39)	353(23.68)	535(17.40)*	59(10.12)*
Current smoking, *n* (%)	1107(21.50)	336(22.55)	652(21.20)	119(20.41)
Current alcohol drinking, *n* (%)	1519(29.72)	543(36.57)	856(28.08)*	120(20.76)*
Hypertension, *n* (%)	3406(66.69)	1034(70.05)	1997(65.48)*	375(64.54)*
Hyperlipoidemia, *n* (%)	1247(24.22)	362(24.28)	728(23.67)	157(26.93)
Diabetes, *n* (%)	733(14.24)	235(15.76)	405(13.17)	93(15.95)
Coronary heart diseases, *n* (%)	1081(20.99)	277(18.58)	637(20.72)	167(28.64)*
Stroke, *n* (%)	764(16.18)	180(13.26)	438(15.64)	146(25.84)*
APOE ε4 allele, *n* (%)	800(15.92)	220(15.11)	485(16.16)	95(16.73)
Depressive symptoms, *n* (%)	475(9.34)	40(2.68)	272(8.92)*	163(29.85)*

[a]The number of participants with missing values was 1 for smoking, 38 for alcohol drinking, 42 for hypertension, 427 for stroke, 124 for *APOE* genotype, and 62 for depressive symptoms. In subsequent analyses, categorical variables with missing values were replaced with a dummy variable.
Abbreviations: *APOE*, apolipoprotein E gene; SD, standard deviation.
*$p < 0.05$ was for the test of comparison with the robust group.

obtained for differentiating AD or VaD from non-dementia (Figure 2, Table S3).

4 | DISCUSSION

In this large-scale, population-based cross-sectional study of rural-dwelling older adults in China, we found strong associations of both PF and BF with dementia, AD, VaD, MCI, and aMCI. We further revealed that frailty phenotypes, particularly PF, were associated with plasma biomarkers for AD pathology (e.g., a reduced Aβ42/Aβ40 ratio and increased p-tau217), neuroinflammation (e.g., increased GFAP), and neurodegeneration (e.g., increased t-tau and NfL), suggesting potential neuropathological pathways underlying the relationship between frailty and cognitive phenotypes. Additionally, PF in combination with demographic factors showed strong discriminative abilities for distinguishing dementia from non-dementia (AUC = 0.83), highlighting the potential of frailty as a clinical marker for dementia.

The findings of strong associations of PF and BF with dementia and its subtypes among rural-dwelling Chinese older adults were aligned with the reports from previous cross-sectional studies.[12,35] Notably, we observed that PF appeared to have a stronger association with VaD than with AD. This may be due partly to the fact that cardiovascular risk factors (e.g., diabetes and obesity), which are known to predispose frailty,[41] also cause vascular damage in the brain, thus, strengthening its association with VaD.[42] These findings underscore the importance of incorporating frailty assessment into dementia risk evaluation and highlight the potential of multidomain interventions to target cardiovascular risk factors for risk reduction and prevention of dementia.

In addition, we found that both PF and BF were associated with MCI, and aMCI in particular, but their associations with an increased likelihood of naMCI were not statistically evident when adjusting for multiple potential confounders, partly due to the limited statistical power because the overall prevalence of naMCI was only 3.98%. Our findings were in good agreement with some but not all previous population-based studies that examine the associations of frailty with MCI and subtypes of MCI among older adults. For instance, the cross-sectional data from the Obu Study of Health Promotion for the Elderly (OSHPE) (age ≥65 years) in Japan found that PF was associated with a 2-fold increased likelihood of MCI when adjusting for age, sex, and education.[43] The population-based Italian PRoject on the Epidemiology of Alzheimer's disease (IPREA) (age ≥ 65 years) showed that BF was associated with MCI, especially with naMCI, but not with aMCI[30]; the lack of association of BF with aMCI in the IPREA study might be attributable to the limited statistical power because aMCI accounted for only 2.93% of dementia-free individuals in the study sample. Further large-scale population-based prospective cohort studies are warranted to clarify the longitudinal association of different frailty phenotypes with subtypes of MCI in the general older population settings. Notably, we also found that prefrailty was associated with an increased likelihood of MCI, which was in line with a previous

TABLE 2 Odds ratios (95% confidence intervals) of all-cause dementia, Alzheimer's disease, and vascular dementia associated with physical and biopsychosocial frailty ($n = 5149$)

Frailty phenotypes	No. of subjects	All-cause dementia			Alzheimer's disease			Vascular dementia		
		n	Modal 1[a]	Modal 2[a]	*n*	Modal 1[a]	Modal 2[a]	*n*	Modal 1[a]	Modal 2[a]
Physical frailty										
No	4566	77	1.00(reference)	1.00(reference)	58	1.00(reference)	1.00(reference)	15	1.00(reference)	1.00(reference)
Yes	583	92	7.91(5.64–11.08)†	4.73(3.28–6.81)†	59	5.89(3.93–8.82)†	3.99(2.60–6.14)†	30	17.14(8.97–32.73)†	9.94(4.75–20.77)†
Biopsychosocial frailty[b]										
No	4913	112	1.00(reference)	1.00(reference)	80	1.00(reference)	1.00(reference)	28	1.00(reference)	1.00(reference)
Yes	171	39	11.83(7.72–18.14)†	9.79(6.27–15.28)†	23	9.70(5.74–16.39)†	9.33(5.45–15.96)†	14	16.68(8.51–32.70)†	9.82(4.61–20.91)†

[a]Data were odds ratio (95% confidence interval). Model 1 was adjusted for age, sex, and education; Model 2 was further adjusted for smoking, drinking alcohol, hypertension, hyperlipidemia, diabetes, coronary heart disease, stroke, and apolipoprotein E (*APOE*) genotype, and when examining the association with physical frailty, for the presence of depressive symptoms.
[b]Data on biopsychosocial frailty were missing in 65 participants.
*$p < 0.05$; †$p < 0.01$.

TABLE 3 Odds ratios (95% confidence intervals) of mild cognitive impairment and its subtypes associated with physical and biopsychosocial frailty among dementia-free participants ($n = 4878$)

Frailty phenotypes	No. of subjects	MCI			aMCI			naMCI		
		n	Modal 1[a]	Modal 2[a]	*n*	Modal 1[a]	Modal 2[a]	*n*	Modal 1[a]	Modal 2[a]
Physical frailty										
Robust	1480	283	1.00(reference)	1.00(reference)	236	1.00(reference)	1.00(reference)	47	1.00(reference)	1.00(reference)
Prefrail	2948	796	1.48(1.27–1.73)†	1.41(1.20–1.65)†	675	1.51(1.28–1.78)†	1.43(1.21–1.70)†	121	1.35(0.95–1.91)	1.26(0.89–1.80)
Frail	450	190	2.59(2.05–3.28)†	2.21(1.73–2.83)†	164	2.65(2.07–3.39)†	2.35(1.81–3.04)†	26	2.30(1.39–3.80)†	1.58(0.92–2.71)
p for trend			<0.01	<0.01		<0.01	<0.01		<0.01	0.09
Biopsychosocial frailty[b]										
No	4730	1194	1.00(reference)	1.00(reference)	1010	1.00(reference)	1.00(reference)	184	1.00(reference)	1.00(reference)
Yes	132	66	2.78(1.95–3.98)†	2.72(1.90–3.91)†	57	2.83(1.95–4.10)†	2.89(1.99–4.20)†	9	2.52(1.23–5.17)*	1.99(0.95–4.18)

Abbreviations: aMCI, amnestic mild cognitive impairment; MCI, mild cognitive impairment; naMCI, non-amnestic mild cognitive impairment.
[a]Data were odds ratio (95% confidence interval). Model 1 was adjusted for age, sex, and education; Model 2 was further adjusted for smoking, drinking alcohol, hypertension, hyperlipidemia, diabetes, coronary heart disease, stroke, and apolipoprotein E (*APOE*) genotype, and when examining the association with physical frailty, for the presence of depressive symptoms.
[b]Data on biopsychosocial frailty were missing in 16 participants.
*$p < 0.05$; †$p < 0.01$.

TABLE 4 Associations of physical and biopsychosocial frailty with Alzheimer's disease-related plasma biomarkers

		β-coefficient (95% confidence interval), plasma biomarkers	
Frailty phenotypes	**No. of subjects**	**Modal 1[a]**	**Modal 2[a]**
Plasma p-tau217 (ln)			
Physical frailty (*n* = 3387)			
Robust	954	0.00 (reference)	0.00 (reference)
Prefrail	2037	0.05(0.02–0.09)†	0.05(0.01–0.09)†
Frail	396	0.08(0.03–0.14)†	0.07(0.01–0.13)*
p for trend		<0.01	<0.01
Biopsychosocial frailty (*n* = 3342)			
No	3231	0.00 (reference)	0.00 (reference)
Yes	111	0.04(−0.05–0.13)	0.04(−0.05–0.13)
Plasma GFAP (ln)			
Physical frailty (*n* = 3387)			
Robust	954	0.00 (reference)	0.00 (reference)
Prefrail	2037	0.05(0.02–0.08)†	0.04(0.01–0.07)†
Frail	396	0.08(0.03–0.13)†	0.05(0.00–0.10)*
p for trend		<0.01	<0.01
Biopsychosocial frailty (*n* = 3342)			
No	3231	0.00 (reference)	0.00 (reference)
Yes	111	0.07(−0.01–0.14)	0.05(−0.02–0.13)
Plasma Aβ42/Aβ40 ratio (×1000)			
Physical frailty (*n* = 1371)			
Robust	465	0.00 (reference)	0.00 (reference)
Prefrail	775	−0.02(−1.91–1.86)	−0.11(−1.98–1.76)
Frail	131	−3.56(−6.82–−0.31)*	−3.99(−7.41–−0.58)*
p for trend		0.13	0.12
Biopsychosocial frailty (*n* = 1363)			
No	1320	0.00 (reference)	0.00 (reference)
Yes	43	−4.57(−9.57–0.44)	−5.46(−10.41–−0.52)*
Plasma total tau			
Physical frailty (*n* = 1371)			
Robust	465	0.00 (reference)	0.00 (reference)
Prefrail	775	0.01(−0.10–0.12)	0.01(−0.10–0.12)
Frail	131	0.19(−0.00–0.38)	0.20(−0.00–0.41)
p for trend		0.16	0.18
Biopsychosocial frailty (*n* = 1363)			
No	1320	0.00 (reference)	0.00 (reference)
Yes	43	0.30(0.00–0.60)*	0.30(0.01–0.60)*
Plasma NfL (ln)			
Physical frailty (*n* = 1370)			
Robust	465	0.00 (reference)	0.00 (reference)
Prefrail	774	0.04(−0.02–0.10)	0.03(−0.03–0.09)
Frail	131	0.20(0.10–0.30)†	0.16(0.06–0.26)†
p for trend		<0.01	0.01

(Continues)

TABLE 4 (Continued)

Frailty phenotypes	No. of subjects	β-coefficient (95% confidence interval), plasma biomarkers	
		Modal 1[a]	Modal 2[a]
Biopsychosocial frailty ($n = 1362$)			
No	1319	0.00 (reference)	0.00 (reference)
Yes	43	0.19(0.04–0.35)*	0.18(0.03–0.33)*

Abbreviations: Aβ, amyloid-β; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; p-tau217, phosphorylated tau at threonine 217.
[a]Model 1 was adjusted for age, sex, and education; Model 2 was further adjusted for smoking, drinking alcohol, hypertension, hyperlipidemia, diabetes, coronary heart disease, stroke, and apolipoprotein E (*APOE*) genotype, and when examining the association with physical frailty, for the presence of depressive symptoms.
*$p < 0.05$; †$p < 0.01$.

report of urban-dwelling Chinese older adults showing that prefrailty was associated with poor performance in global cognitive function.[44] Taken together, these studies indicate that prefrailty might be an early clinical marker for cognitive impairment even at pre-dementia stage in older adults.

The neuropathological mechanisms underlying the associations of frailty with cognitive phenotypes are not fully understood. To shed light on the potential mechanisms, we further investigated the associations of PF and BF with multiple AD-related plasma biomarkers in the subsamples. We found that frailty was associated with a lower Aβ42/Aβ40 ratio and higher plasma p-tau217, GFAP, NfL, and t-tau, plasma biomarkers that were correlated with AD-related pathology in central nervous system.[24,45] This is in line with the reports from previous amyloid PET studies showing that PF was associated with brain Aβ deposition.[46,47] The Alzheimer's Disease Neuroimaging Initiative 2 (ADNI-2) study also supported an association of frailty with lower CSF Aβ42[48]. Data from a subsample of 375 community-dwelling older adults (age ≥ 60 years) derived from the West China Health and Aging Trend study showed that PF was associated with higher plasma p-tau181, but not with plasma Aβ42, Aβ40, NfL, or t-tau that were measured using the enzyme-linked immunosorbent assay.[49] The discrepant findings across studies may be partially attributable to variations in the methods of defining frailty and measurement of plasma biomarkers, the study settings, demographic characteristics of the study samples, and a relatively small sample of the previous studies. Frailty is known to be associated with pathophysiological changes in multiple body systems such as endocrine dysregulation, immune dysfunction, metabolic imbalance, and oxidative stress,[11] which may perturb Aβ metabolism, exacerbate tau phosphorylation, enhance inflammation, and accelerate neurodegeneration.[50] In addition, data from the Vietnam Era Twin Registry cohort study showed that frailty at midlife was associated with increased plasma Aβ42, Aβ40, and NfL in late life.[19] Taken together, these findings indicate that frailty, dementia, and MCI in older adults may share the common neuropathological basis of AD (Aβ and tau), neuroinflammation, and neurodegeneration in the brain.

We further evaluated the utility of PF and BF in distinguishing all-cause dementia, AD, and VaD from non-dementia among older adults. We found that PF alone was already useful for the detection of dementia or main subtypes of dementia and that adding demographic factors to PF could further improve the accuracy for the detection of individuals with dementia, AD, and VaD, with AUC ranging from 0.83 to 0.85. BF appears to be less powerful than PF in detecting dementia, likely due to limited statistical power. Taken together, frailty, in combination with demographic factors, appears to be a useful tool for the detection of dementia among older people living in remote rural areas.

Our community-based study engaged rural-dwelling older adults in China who had limited formal education, relatively low socioeconomic position, and distinct lifestyles from urban residents, a sociodemographic group that has been substantially underrepresented in dementia and frailty research.[51] Thus, findings from our study could bridge the knowledge gap regarding the relationships of frailty phenotypes and cognitive outcomes among ethnically, geographically, and socioeconomically diverse older populations. Furthermore, we were able to explore the potential neuropathological pathways underlying the associations of frailty with cognitive outcomes by integrating clinical and neuropsychological data with data of highly sensitive plasma biomarkers for brain pathology assessed using the state-of-the-art Quanterix Simoa technology, and notably, this is the first large-scale population-based study that links frailty phenotypes with increased plasma p-tau217 and GFAP in older adults. However, our study does have limitations. First, the cross-sectional design of the study did not allow us to make any inference on the direction of the observed association. Furthermore, our study sample was derived only from one rural region in western Shandong province, which should be kept in mind when generalizing our research findings to other older populations.

In conclusion, this population-based study of rural-dwelling older adults in China showed evidence supporting the strong cross-sectional associations of frailty phenotypes with dementia and MCI as well as with plasma biomarkers for AD pathology, astrogliosis, and neurodegeneration. Frailty in combination with demographic factors has the potential to differentiate dementia from non-dementia in older adults. These findings suggest that frailty may be a clinical marker for dementia, even at the pre-dementia stage (i.e., MCI), which underscores the importance of incorporating the assessment of frailty with the evaluation of dementia risk in clinical practice (e.g., geriatric care and clinical geriatrics). In addition, our study reveals that Alzheimer's pathology, neuroinflammation, and neurodegeneration are the underlying pathways linking frailty to cognitive phenotypes in older adults. Future

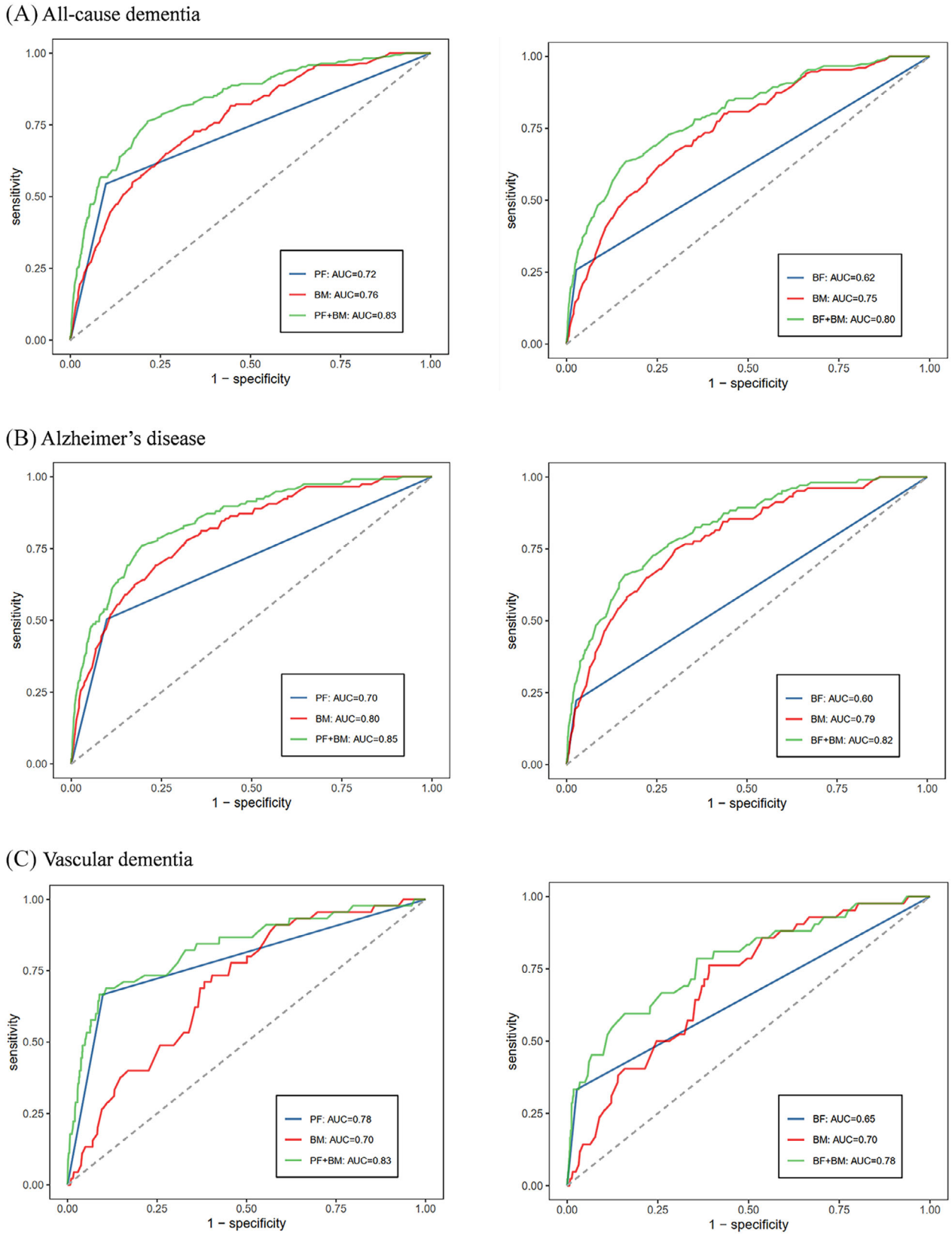

FIGURE 2 The receiver operating characteristic curves for physical frailty and biopsychosocial frailty to discriminate all-cause dementia (A), Alzheimer's disease (B), and vascular dementia (C) from non-dementia. AUC, area under curve; BF, biopsychosocial frailty; BM, demographic-based model; PF, physical frailty.

longitudinal studies may help elucidate the potential causal relationship of frailty with cognitive phenotypes as well as the underlying mechanisms. Furthermore, given that frailty is a modifiable syndrome, further studies are warranted to assess whether early detection and preventive and therapeutic interventions might help delay onset of the dementia syndrome.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Written informed consent was obtained from all participants or, in the case of cognitively impaired persons, from an informant (usually a guardian or a family member).

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SUPPORTING INFORMATION

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