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ORIGINAL RESEARCH

Traditional Chinese Medicine Constitution and Cognitive Frailty in Older Adults: Prediction Models and Sleep-Quality Mediation Pathway from a Multicenter Study in China

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Purpose: To investigate the predictive value of Traditional Chinese Medicine Constitution (TCMC) in cognitive frailty (CF) among older adults and explore its potential influencing pathways.

Patients and Methods: From 2021 to 2023, a total of 905 older participants were recruited from three geographic regions in China: Southwest (Sichuan), East (Shanghai), and North (Beijing). A multidimensional survey (including TCMC assessment) was conducted. Prediction models were developed using nomogram and C5.0 decision tree algorithms. Internal and external validations were performed. The KHB method was applied for mediation analysis.

Results: Logistic regression identified Qi-stagnation constitution (QSC) and Qi-deficiency constitution (QDC) as important risk factors for CF ($P < 0.01$). Both the C5.0 decision tree model and Nomogram model based on TCMC demonstrated strong predictive performance (AUC=0.824 and 0.812, respectively). External validation indicated superior extrapolability of the C5.0 model (AUC=0.810 vs 0.772). Mediation analysis revealed that sleep quality partially mediated the association between QSC and CF ($P < 0.05$), with a mediation proportion of 22.7%.

Conclusion: QSC and QDC were identified as modifiable risk factors for CF. Prediction models based on TCMC demonstrated strong predictive performance and generalizability. Furthermore, QSC may worsen CF progression through its detrimental effects on sleep quality, identifying its clinical applicability as both a risk stratification factor and a prevention focus for CF.

Keywords: cognitive frailty, Traditional Chinese Medicine Constitution, prediction model, mediation effects analysis

Introduction

With the accelerated aging of the global population, the prevention and management of age-related syndromes have become a public health priority. In this context, Cognitive Frailty (CF), a non-dementia syndrome characterized by the co-occurrence of physical frailty and cognitive impairment, is gaining increasing clinical significance.[1] According to World Health Organization projections, the global population aged 60 and above will double by 2050, a trend that will substantially expand the at-risk population for CF, positioning it as a critical target in healthy aging strategies. A unique feature of CF is its dual nature. On one hand, research confirms its role as a precursor to dementia and functional decline; on the other hand, its potential reversibility offers a valuable window for intervention.[2,3] Effective treatments for dementia remain limited. As CF represents a critical window for early intervention, current research focuses on its modifiable factors - including physical frailty components, cognitive impairment drivers, and their dynamic interactions. Targeting these factors may not only mitigate CF progression but also potentially delay or even prevent dementia onset.[4]

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Current CF screening faces significant limitations, relying either on time-intensive clinical assessments (eg, Fried Frailty Phenotype combined with MoCA and CDR scales requiring specialized administration) or risk prediction models with constrained clinical utility. Only 31.8% of existing models have undergone external validation, risking overfitting, while many incorporate complex biomarkers (eg, SNPs, protein markers) or opaque machine learning algorithms (25% of models). While these approaches demonstrate promising theoretical efficacy (AUC 0.86–0.88), their clinical adoption in community or primary care settings remains challenging due to limited interpretability, operational complexity, and restricted generalizability (eg, being primarily validated in chronic disease subgroups).[5,6] To address these gaps, we developed a dual-model system combining interpretable nomograms for individualized risk assessment in community, senior residence, and outpatient settings with optimized machine learning algorithms for efficient population screening.

The concept of Traditional Chinese Medicine Constitution (TCMC) was proposed by Wang Qi in 1994 and has been widely used in the prevention, management, and treatment of diseases.[7] The theory of TCMC posits that body constitution represents inherent and relatively stable characteristics in an individual's morphological structure and physiological functions. Contemporary TCM classifies constitutions into balanced type (healthy state) and eight imbalanced types. The relationship between TCMC and health is akin to soil and plants: balanced constitution is fertile soil, while imbalanced constitutions resemble nutrient-deficient soil. The unbalanced constitutions exhibit disease-specific correlations and can guide precision medicine approaches. Constitution-based regulation (eg, through environmental regulation, lifestyle modification, psychological adjustment, and TCM therapies) may enhance internal homeostasis, thereby conferring both disease-preventive and health-promoting effects.

However, current evidence remains insufficient to establish associations between constitutional types and CF, substantially limiting the clinical utility of constitutional theory in CF screening and intervention. Moreover, extant research has consistently demonstrated an inverse correlation between imbalanced TCMC and sleep quality.[8–11] Separately, the role of sleep disturbances as precipitating factors for CF is also well-established.[12–14] Nevertheless, whether constitutional deviations influence CF progression partially through sleep quality-mediated pathways remains mechanistically undefined.

Building upon the constitution as a modifiable personalized determinant, this study aims to: (1) investigate the potential of TCMC as an independent predictive factor for CF risk stratification; and (2) elucidate the underlying mechanistic pathways, with particular emphasis on evaluating the hypothesized mediating role of sleep quality.

Materials and Methods

Study Design

This multicenter observational study was conducted in three phases. First, from 2021 to 2022, we recruited 478 older adults from Sichuan Province in southwestern China. After applying exclusion criteria (>10% missing questionnaire data [n=49], severe audiovisual impairment [n=2], or Alzheimer's disease diagnosis [n=1]), 426 eligible participants were included as the primary study cohort and stratified into cognitive frailty (CF, n=120) and non-CF (n=306) groups. Second, using this primary cohort from Sichuan, we developed predictive models for CF using both Nomogram and C5.0 boosted decision tree algorithms, with TCMC as the primary predictor. Third, we externally validated these models in independent cohorts from Beijing (Northern China, n=255; 2022–2023) and Shanghai (Eastern China, n=224; 2021–2023). Finally, we employed the KHB method to examine sleep quality as a potential mediator between TCMC and CF, thereby elucidating its predictive value and potential influencing pathways. The research flowchart is shown in Figure 1.

Participants

The study enrolled participants meeting the following inclusion criteria: aged 60 years or older, capable of independent daily living and communication (Barthel Index [BI] score ≥75), willing to provide written informed consent, and able to comply with study procedures and follow-up requirements. Exclusion criteria comprised: (1) diagnosed dementia of any type; (2) severe visual or hearing impairment precluding study participation; (3) severe systemic diseases including cardiac, cerebral, renal, hepatic or other major organ dysfunction; (4) acute neurological impairment or ongoing

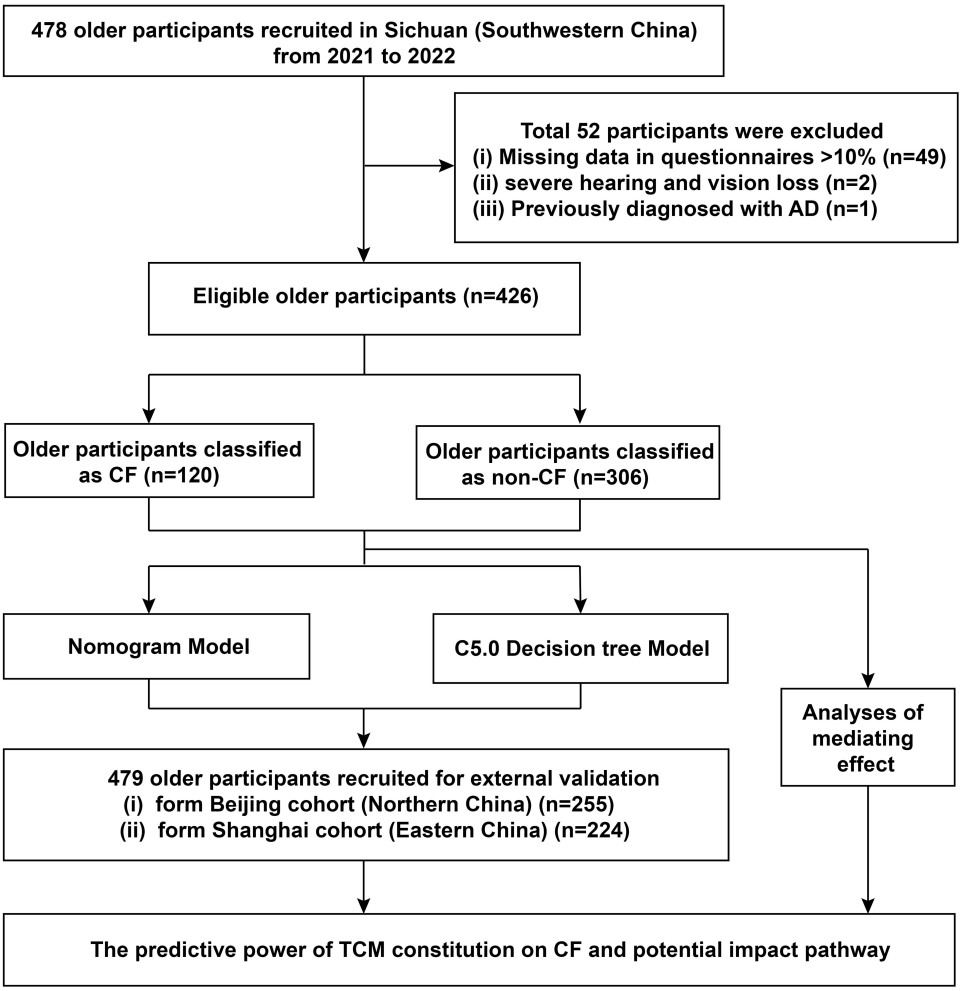

Figure 1 Study flowchart.

cardiovascular events; and (5) severe neuropsychiatric disorders such as major depression or schizophrenia. These criteria ensured the selection of cognitively evaluable participants without significant multimorbidity that might confound cognitive frailty assessment.

Variables and Measurement

The data were collected by strictly trained investigators using structured questionnaires and standardized procedures.

Demographic Characteristics, Clinical Factors, and Multimorbidity

The assessed variables included: age (from birth date), sex, education, residence (1=home, 2=senior residence), living arrangement (1=alone, 2=cohabiting), social support (number of close friends providing substantial help; 1=none, 2=1-2, 3=3-5, 4=≥6), smartphone usage (1=daily, 2=no), visual impairment (vision condition including wearing classes; 1=normal, can read books; 2=mild, can watch TV; 3=moderate, blur; 4=severe, light perception or blind), hearing impairment (1=normal; 2=mild, requires slowed speech or raised volume to hear clearly; 3=moderate, mostly inaudible; 4=severe, completely inaudible), masticatory function (1=no difficulty, 2=mild, 3=moderate, 4=severe), living ability (Barthel Index, BI; Instrumental Activities of Daily Living Scale, IADL), sleep quality (Pittsburgh Sleep Quality Index, PSQI), anxiety (Generalized Anxiety Disorder-7 items Scale, GAD-7), depression (Patient Health Questionnaire-9, PHQ-9), nutritional status (Mini Nutritional Assessment Short Form, MNA-SF), and multimorbidity (≥2 chronic diseases; 1=yes, 2=no).

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Physical examinations included measurements of dominant-hand grip strength, waist circumference, and body height, all obtained using calibrated instruments. Grip strength was assessed with a handgrip dynamometer; participants were instructed to exert maximal voluntary force, and the highest value from at least two trials was recorded. Measurements were recorded in kilograms (kg) for grip strength and centimeters (cm) for waist circumference and height. The waist-to-height ratio (WtHR) was calculated by dividing waist circumference by height.

Cognitive Frailty

Based on the international consensus by International Academy on Nutrition and Aging (I.A.N.A) and the International Association of Gerontology and Geriatrics (I.A.G.G), the diagnostic criteria for CF must simultaneously fulfill the following conditions: 1) Presence of physical frailty or pre-frailty screened by the FRAIL scale; 2) Presence of mild cognitive impairment by Montreal Cognitive Assessment (MoCA) Changsha version score of <22 and Clinical Dementia Rating (CDR) scale score of 0.5; 3) Exclusion of concurrent Alzheimer's disease or other dementias. All three conditions were required for a definitive CF diagnosis.[1]

Traditional Chinese Medicine Constitution (TCMC)

The TCMC was assessed based on the TCM constitution scale for geriatrics.[15] The scale includes 33 items, and each item is scored from 1 to 5 points. There are 9 constitutions with its corresponding items: Balanced constitution (Type A: *items1, 2, 4, 5, 13)*, Qi-deficiency constitution (Type B, *items 2, 3, 4, 14*), Yang-deficiency constitution (Type C: *items 11, 12, 13, 29)*, Yin-deficiency constitution (Type D, *items 10, 21, 26, 31*), Phlegm-dampness constitution (Type E: *items 9, 16, 28, 32)*, Damp-heat constitution (Type F: *items 23, 25, 27, 30)*, Blood-stasis constitution (Type G: *items 19, 22, 24, 33)*, Qi-stagnation constitution (Type H: *items 5, 6, 7, 8*), Inherited-special constitution (Type I: *items 15, 17, 18, 20)*. Detailed scoring criteria and classification rules for each TCMC are provided in the Supplementary Material.

Statistical Analysis

Descriptive Statistical Analysis

Statistical analyses were performed using SPSS 25.0 software, including descriptive statistics and binary logistic regression. Continuous variables with normal distribution were presented as mean ± standard deviation, while non-normally distributed data were expressed as median (interquartile range). Categorical variables were reported as counts (percentages). The significance level α was set at 0.05.

Data normality and homogeneity of variance were assessed using the Kolmogorov–Smirnov test. Between-group comparisons were conducted using *t*-tests for normally distributed data or the Mann–Whitney U nonparametric test for non-normally distributed data. Categorical variables were compared using Chi-square tests, with Yates' continuity correction applied when at least one expected frequency was between 1 and 5, and Fisher's exact test used when any expected frequency was less than 1.

Binary Logistic Regression and the Nomogram

The binary logistic regression model was developed using the Forward-Conditional method, with multinomial variables converted to dummy variables. The final model was validated through the Omnibus and Hosmer-Lemeshow tests. The validated model was subsequently transformed into a clinically applicable nomogram (M_{nomo}) using R software (version 2.2.2), which represents the predictive model for CF in older adults through weighted scoring of significant predictors.

Machine Learning Model Establishment

The decision tree model for CF diagnosis prediction (M_{tree}) was constructed using the C5.0 algorithm in SPSS Modeler 18.0 visual data mining software. CF was designated as the marker variable, with statistically significant variables from logistic regression analysis and clinically relevant input variables being incorporated into model development. The study cohort was randomly partitioned into training (70%) and testing (30%) sets using a fixed random seed to ensure reproducibility. To enhance predictive performance, we implemented a boosting ensemble algorithm combining multiple decision trees (15 iterations) for classification, with model robustness optimized through 10-fold cross-validation to address data partitioning challenges in limited sample sizes. The algorithm incorporated expert configuration with three

key safeguards: (1) pruning severity set at 75% with a minimum of 2 records per sub-branch, (2) global pruning to prevent overfitting, and (3) a clinical reality-informed misclassification cost matrix (false-positive cost = 1.0; false-negative cost = 2.0) to guide pruning decisions. This comprehensive approach balanced statistical rigor with clinical applicability throughout model development.

Model Evaluation and Comparison

M_{nomo} was evaluated using receiver operating characteristic (ROC) curves, the area under the curve (AUC), decision curve analysis (DCA), and calibration curves. M_{tree} was assessed with confusion matrices, ROC curves, and AUC. Ultimately, the performance of the two models was compared based on their confusion matrices, ROC curves, and AUC values.

Mediation Effect Analysis

In this part, based on prior evidence,[16] we analyzed mediation pathways using the Karlson-Holm-Breen (KHB) method, which addresses scaling limitations in logistic regression when decomposing direct and indirect effects. CF served as the binary outcome variable, with Qi-stagnation constitution scores (continuous; higher values indicating stronger constitutional tendency) as the independent variable and PSQI scores (higher values reflecting poorer sleep quality) as the

Table 1 Characteristics of the Sample According to the Presence of Cognitive Frailty (n = 426)

Characteristics	Stratification	All (n=426)	CF (n=120)	Non-CF (n=306)	Statistic Value	*P* value
Age [year, n (%)]	60-69	93 (21.8)	17 (14.2)	76 (24.8)	29.688	<0.001
	70-79	158 (37.1)	29 (24.2)	129 (42.2)		
	80-89	153 (35.9)	66(55.0)	87 (28.4)		
	≥90	22 (5.2)	8(6.7)	14(4.6)		
Sex n (%)	Male	155 (36.4)	29 (24.2)	129 (42.2)	9.355	0.002
	Female	271 (63.6)	66(55.0)	87 (28.4)		
Education n (%)	Illiterate	35 (8.2)	8(6.7)	14(4.6)	30.352	<0.001
	Primary school	79 (18.5)	21 (17.5)	58 (19.0)		
	Middle school	121 (28.4)	36 (30.0)	85 (27.8)		
	High school	131 (30.8)	30 (25.0)	101 (33.0)		
	College	60 (14.1)	10 (8.3)	50 (16.3)		
Residence n (%)	Home	223 (52.3)	38 (31.7)	185 (60.5)	28.643	<0.001
	Senior residence	203 (47.7)	82 (68.3)	121 (39.5)		
Living arrangement n (%)	Live alone	397 (93.2)	113 (94.2)	284 (92.5)	0.25	0.617
	With others	29 (6.8)	7 (5.8)	22 (7.2)		
Social support n (%)	None	19 (4.5)	10 (8.3)	9 (2.9)	16.371	0.001
	1-2 friends	98 (23.0)	37 (30.8)	61 (19.9)		
	3-5 friends	137 (32.2)	37 (30.8)	100 (32.7)		
	6 or more friends	139 (32.6)	26 (21.7)	113 (36.9)		
	Not available	33 (7.7)	10(8.3)	23(7.5)		

(*Continued*)

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Table 1 (Continued).

Characteristics	Stratification	All (n=426)	CF (n=120)	Non-CF (n=306)	Statistic Value	*P* value
Smartphone usage n (%)	No	179 (42.0)	81 (67.5)	98 (32.0)	44.522	<0.001
	Yes	247 (58.0)	39 (32.5)	208 (68.0)		
Visual impairment n (%)	No	272 (63.8)	66 (55.0)	206 (67.3)	11.285	0.004
	Mild	121 (28.4)	37 (30.8)	84 (27.5)		
	Moderate	33 (7.7)	17 (14.2)	16 (5.2)		
Hearing impairment n (%)	No	301 (70.7)	74 (61.7)	227 (74.2)	8.324	0.016
	Mild	107 (25.1)	37 (30.8)	70 (22.9)		
	Moderate	18 (4.2)	9 (7.5)	9 (2.9)		
Masticatory function n (%)	Normal	238 (55.9)	58 (54.7)	180 (63.2)	–	0.150#
	Mild impairment	107 (25.1)	30 (28.3)	77 (27.0)		
	Moderate impairment	38 (8.9)	16 (15.1)	22 (7.7)		
	Severe impairment	8 (1.9)	2 (1.9)	6 (2.1)		
ADL n (%)	Independent	372 (87.3)	83 (69.2)	289 (94.4)	–	<0.001#
	Slight dependency	52 (12.2)	35 (29.2)	17 (5.6)		
	Moderate dependency	2 (0.5)	2 (1.7)	0 (0.0)		
IADL n (%)	Independent	243 (57.0)	39 (32.5)	24 (66.7)	–	<0.001#
	Mild dependency	148 (34.7)	61 (50.8)	87 (28.4)		
	Moderate dependency	34 (8.0)	19 (15.8)	15 (4.9)		
	Severe dependency	1 (0.2)	1 (0.8)	0 (0.0)		
PSQI n (%)	Good sleep quality	249 (58.5)	60 (50.0)	189 (61.8)	4.912	0.027
	Poor sleep quality	177 (41.5)	60 (50.0)	117 (38.2)		
GAD-7 n (%)	Non-anxiety	398 (93.4)	106 (88.3)	292 (95.4)	–	0.032#
	Mild Anxiety	21 (4.9)	10 (8.3)	11 (3.6)		
	Moderate Anxiety	5 (1.2)	3 (2.5)	2 (0.7)		
	Severe Anxiety	2 (0.5)	1 (0.8)	1 (0.3)		
PHQ-9 n (%)	Non-depression	379 (89.0)	98 (81.7)	281 (91.8)	–	0.002#
	Mild depression	38 (8.9)	15 (12.5)	23 (7.5)		
	Moderate depression	6 (1.4)	4 (3.3)	2 (0.7)		
	Severe depression	3 (0.7)	3 (2.5)	0 (0.0)		

(*Continued*)

Table 1 (Continued).

Characteristics	Stratification	All (n=426)	CF (n=120)	Non-CF (n=306)	Statistic Value	*P* value
MNA-SF n (%)	Non-risk	362 (85.0)	96(80.0)	266(86.9)	–	0.005[#]
	At risk	60 (14.1)	20(16.7)	40(13.1)		
	Malnourished	4 (0.9)	4(3.3)	0(0.0)		
Multimorbidity	No	130 (30.5)	24 (20.0)	106 (34.6)	8.713	0.003
	Yes	296 (69.5)	96 (80.0)	200 (65.4)		
Grip strength [kg, M(P_{25}, P_{75})]	Male	25.7 (20.3,34.6)	21.8 (17.7, 24.5)	27.2 (20.7, 35.1)	−2.949	0.003
	Female	17.6 (14.0,21.2)	15.9 (12.4, 18.6)	18.9 (14.8, 22.2)	−4.304	<0.001
WtHR) M (P_{25}, P_{75})	Male	0.55 (0.51,0.58)	0.55 (0.52, 0.60)	0.55 (0.51, 0.58)	−1.019	0.308
	Female	0.58 (0.52,0.62)	0.59 (0.56, 0.65)	0.56 (0.51,0.61)	−4.025	<0.001

Notes: [#]Fisher's exact probability method.
Abbreviations: CF, cognitive frailty; ADL, activities of daily living; IADL, instrumental activities of daily living; PSQI, Pittsburgh Sleep Quality Index; GAD-7, Generalized Anxiety Disorder-7 Items Scale; PHQ-9, Patient Health Questionnaire-9; MNA-SF, Mini Nutritional Assessment Short Form; WtHR, waist-to-height ratio.

mediator in the hypothesized pathways. The KHB approach was specifically chosen to overcome comparability issues in nested logistic models, enabling accurate effect decomposition while accounting for the binary nature of CF.[17,18] This analytical strategy builds upon established mediation frameworks while addressing the unique requirements of binary health outcomes.

Results

Preliminary Statistics and Demographic Characteristics

This study first included 426 older adults aged ≥60 years in Sichuan, excluding 49 people with >10% missing data completion, two people with severely impaired hearing and vision, and one person who had been definitively diagnosed with Alzheimer's disease, including 155 (36.4%) males and 271 (63.6%) females, with a mean age of (76.92±7.89) years.

Results of Cognitive Frailty Analysis and Univariate Analysis

As revealed in Table 1, 28.2% of the 426 research participants (120 instances) had cognitive frailty. Comparison of intergroup factor variability between the cognitive frailty group (CF group) and the non-cognitive frailty group (NCF group) indicated that cognitive frailty was associated with age, gender, education, residence, social support, smartphone usage, and visual or hearing impairment ($P < 0.01$). In terms of geriatric syndromes, participants in the CF group had higher rates of ADL or IADL disability, poor sleep quality, depression, anxiety, nutritional risk, and suffering from multimorbidity than the NCF group ($P < 0.05$). Given the physiological differences in body measurements between men and women, we performed gender-stratified analyses, which showed that in the CF group, grip strength decreased in both males and females, but only females showed an increase in waist-to-height ratio ($P < 0.01$).

Notably, the CF group exhibited a significantly higher proportion of imbalanced TCM constitutions compared to the NCF group ($P < 0.001$). This was reflected in both the lower prevalence of balanced constitution ($P < 0.05$) and the higher frequencies of Qi-deficiency (QDC), Yin-deficiency, phlegm-dampness, and Qi-stagnation (QSC) constitutions (all $P < 0.05$). These findings suggest that a balanced constitution may confer protection against CF, whereas imbalanced constitutions (eg, Qi-deficiency, Yin-deficiency, phlegm-dampness, and Qi-stagnation) may predispose individuals to CF development (Table 2).

Binary Logistic Regression Analysis of Independent Risk Factors for Cognitive Frailty

The binary logistic regression analysis identified six significant independent predictors that remained in the final model after adjusting for potential confounders (Table 3 and Figure 2). The model demonstrated excellent overall performance, with a significant omnibus test ($P < 0.001$) and a non-significant Hosmer-Lemeshow test ($P = 0.460$), indicating good model fit to the data.

Logistic regression identified a range of independent risk factors for CF, with QSC showing a particularly strong association (OR=14.37, 95% CI: 2.37–87.32, P=0.004). Other significant risk factors included ADL dependence, IADL dependence, and moderate or severe depression. Meanwhile, higher education level and smartphone usage were identified as independent protective factors. In addition to the above independent influences, it is noteworthy that QDC (OR=4.48, 95% CI: 1.35–14.90, P=0.015) and grip strength remained significant in the M2 after adjustments for common geriatric syndromes, grip strength, age, gender, and education level, which suggests that QDC and grip strength also have a meaningful effect on CF.

Given that senior residence may be closely associated with functional measures, we conducted a sensitivity analysis based on Model 3 (the comprehensive model) by including senior residence as a covariate while removing ADL and IADL to assess potential overadjustment. As shown in Table S1, the significant association between QSC and CF remained robust (aOR = 11, p = 0.009), indicating that the key finding from our primary models is stable and not biased by overadjustment.

Table 2 TCMC of the Sample According to the Presence of Cognitive Frailty (n = 426)

TCMC	Stratification	All (n=426)	CF (n=120)	Non-CF (n=306)	Statistic Value	*P* value
Balanced constitution n (%)	No	273 (64.1)	95 (79.2)	178 (58.2)	16.511	<0.001
	Yes	153 (35.9)	25 (20.8)	128 (41.8)		
Qi-deficiency n (%)	No	410 (96.2)	110 (91.7)	300 (98.0)	8.001[a]	0.005
	Yes	16 (3.8)	10 (8.3)	6 (2.0)		
Yang-deficiency n (%)	No	362 (85)	89 (82.5)	263 (85.9)	0.803	0.370
	Yes	64 (15)	21 (17.5)	43 (14.1)		
Yin-deficiency n (%)	No	353 (82.9)	90 (75.0)	263 (85.9)	7.275	0.007
	Yes	73 (17.1)	30 (25.0)	43 (14.1)		
Phlegm-dampness n (%)	No	304 (71.4)	77 (64.2)	227 (74.2)	4.232	0.040
	Yes	122 (28.6)	43 (35.8)	79(25.8)		
Damp-heat n (%)	No	420 (98.6)	119(99.2)	301(98.4)	0.030[a]	0.862
	Yes	6 (1.4)	1(0.8)	5(1.6)		
Blood-stasis n (%)	No	413 (96.9)	116(96.7)	297(97.1)	0.000	>0.999
	Yes	13 (3.1)	4(3.3)	9(2.9)		
Qi-stagnation n (%)	No	419 (98.4)	115 (95.8)	304 (99.3)	4.588[a]	0.032
	Yes	7 (1.6)	5 (4.2)	2 (0.7)		
Inherited-special n (%)	No	419 (98.4)	119 (99.2)	300 (98.0)	0.160[a]	0.689
	Yes	7 (1.6)	1 (0.8)	6 (2.0)		

Note: [a]Yates correction χ^2 value.

Abbreviations: TCMC, Traditional Chinese Medicine Constitution; CF, cognitive frailty.

Table 3 Association of CF with TCMC and Other Variables (n = 426)

Variables	M1		M2		M3	
	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value
QSC	12.81 (2.16~75.87)	0.005	12.37 (2.04~74.90)	0.006	14.37 (2.37~87.32)	0.004
QDC	4.54 (1.39~14.84)	0.012	4.48 (1.35~14.90)	0.015	–	–
ADL dependence	5.96 (3.05~11.65)	<0.001	6.61 (3.29~13.28)	<0.001	6.79 (3.28~14.05)	<0.001
Mild IADL dependence	2.43 (1.39~4.27)	0.002	2.44 (1.38~4.32)	0.002	2.39 (1.38~4.14)	0.002
Moderate or severe IADL dependence	3.19 (1.32~7.70)	0.010	2.92 (1.19~7.12)	0.019	2.54 (1.05~6.19)	0.040
Mild depression	1.64 (0.75~3.61)	0.220	1.59 (0.71~3.56)	0.264	1.53 (0.69~3.41)	0.300
Moderate or severe depression	9.39 (1.57~55.98)	0.014	8.65 (1.49~50.12)	0.016	11.32 (2.04~62.79)	0.006
Grip strength	1.98 (1.13~3.48)	0.017	1.99 (1.12~3.54)	0.019	–	–
Education level	/	/	0.67 (0.53~0.83)	<0.001	0.72 (0.57~0.90)	0.005
Smartphone usage	/	/	/	/	0.30 (0.18~0.52)	<0.001

Note: Model 1 (Basic functional model): Adjusted for basic functional indicators including ADL, IADL, PSQI, GAD-7, PHQ-9, MNA-SF, and grip strength. Model 2 (Demographic-adjusted model): Built upon Model 1 with additional adjustment for fundamental demographic factors (age, sex, and education level). Model 3 (Comprehensive model): Extended from Model 2 by further adjusting for lifestyle and health-related factors (residence, smartphone use, social support, visual impairment, hearing impairment, and multimorbidity).

Abbreviations: CF, cognitive frailty; TCMC, Traditional Chinese Medicine Constitution; aOR, adjusted odds ratio; QSC, Qi-stagnation constitution; QDC, Qi-deficiency constitution; ADL, activities of daily living; IADL, instrumental activities of daily living.

Construction and Evaluation of Prediction Models for Cognitive Frailty

The Nomogram Prediction Model

In order to evaluate the predictive potential of TCMC in CF, we constructed a Nomogram graph prediction model (M_{nomo}) based on the results of logistic regression analysis with QDC, ADL, IADL, depression, education, and smartphone usage as predictors (Figure 3a). We also converted the graphical results of the nomogram model into a scale for easier clinical application (Table 4). The nomogram plot more visually shows the important role of QSC in the above indicators, followed by moderate or severe depression and ADL dependence.

The M_{nomo} was validated using receiver operating characteristic (ROC) curve analysis, decision curve analysis (DCA) curve, and calibration curve assessment. The results showed an AUC (area under curve) of 0.812 (95% CI: 0.767–0.858) for the ROC, which indicated that the M_{nomo} had good discrimination, and the prediction was accurate and statistically significant ($P < 0.001$; Figure 3b). Furthermore, the DCA curve revealed good clinical utility across a wide threshold range, showing favorable net clinical benefit (Figure 3c). The calibration curve similarly confirmed that the model was well calibrated (Figure 3d).

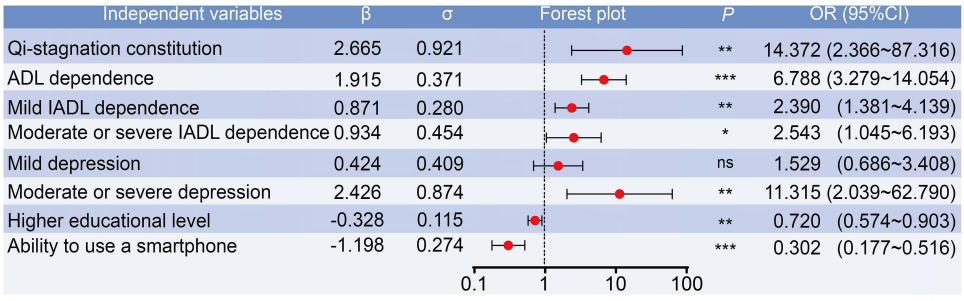

Figure 2 Forest plot for the logistic regression analysis showing the independent influences of cognitive frailty (CF). *P<0.05, **P<0.01, ***P<0.001. ns, not significant.

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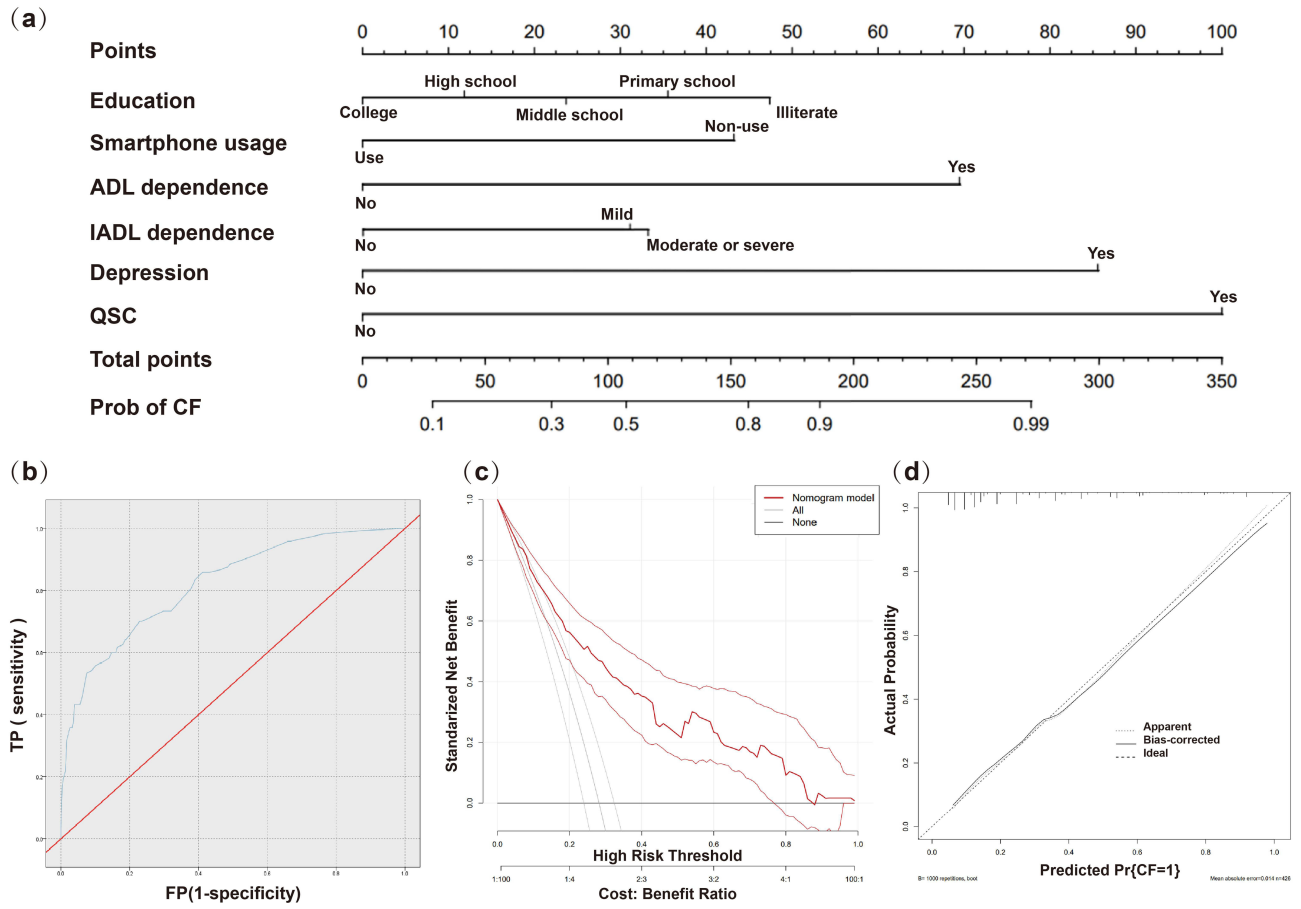

Figure 3 Nomogram for cognitive frailty prediction (**a**) and its validation through ROC curve (**b**), decision curve analysis (**c**), and calibration plot (**d**).

The C5.0 Integrated Decision Tree Model

We used the C5.0 integrated decision tree algorithm in machine learning for predictive model construction. We selected variables for modeling based on stepwise regression results, existing literature, and our clinical observations.[19,20] Consequently, QDC and

Table 4 A Nomogram-Based Scale for CF Prediction

Scoring Items	Options	Scores
QSC	Yes	100
	No	0
Education	Illiterate	48
	Primary school	36
	Middle school	24
	High school	12
	College	0
Smartphone usage	No	45
	Yes	0

(*Continued*)

Table 4 (Continued).

Scoring Items	Options	Scores
ADL	<100	72
	100	0
IADL	≤5	35
	6-7	33
	8	0
PHQ-9	≥10	91
	<10	0

Notes: 1.Score Calculation: Sum all item scores according to the selected options (eg, QSC "yes"=100 + Education "Primary school"=36 +.); 2.Probability Interpretation: Scores are non-linear predictors (e.g, 108→50%, 157→80%, 186→90% reflects accelerating risk); 3. Example: A score of 191 (eg, QSC "yes"=100 + PHQ-9 "≥10"=91 + others=0) → more than 90% likelihood of cognitive frailty.

Abbreviations: CF, cognitive frailty; QSC, Qi-stagnation constitution; ADL, activities of daily living; IADL, instrumental activities of daily living; PHQ-9, Patient Health Questionnaire-9.

grip strength, both of which were significant variables in the M2 model, were included. In total, eight predictor variables were used in this section. We divided the 426 study cases from Sichuan (SC) into a train set (SCtrain) and a test set (SCtest) according to the ratio of 7:3, and the results of SCtest were used as the internal validation of the model. After iteration, a total of 15 rule sets were generated. The final protective result was judged by the algorithm synthesizing the results of these rule sets.

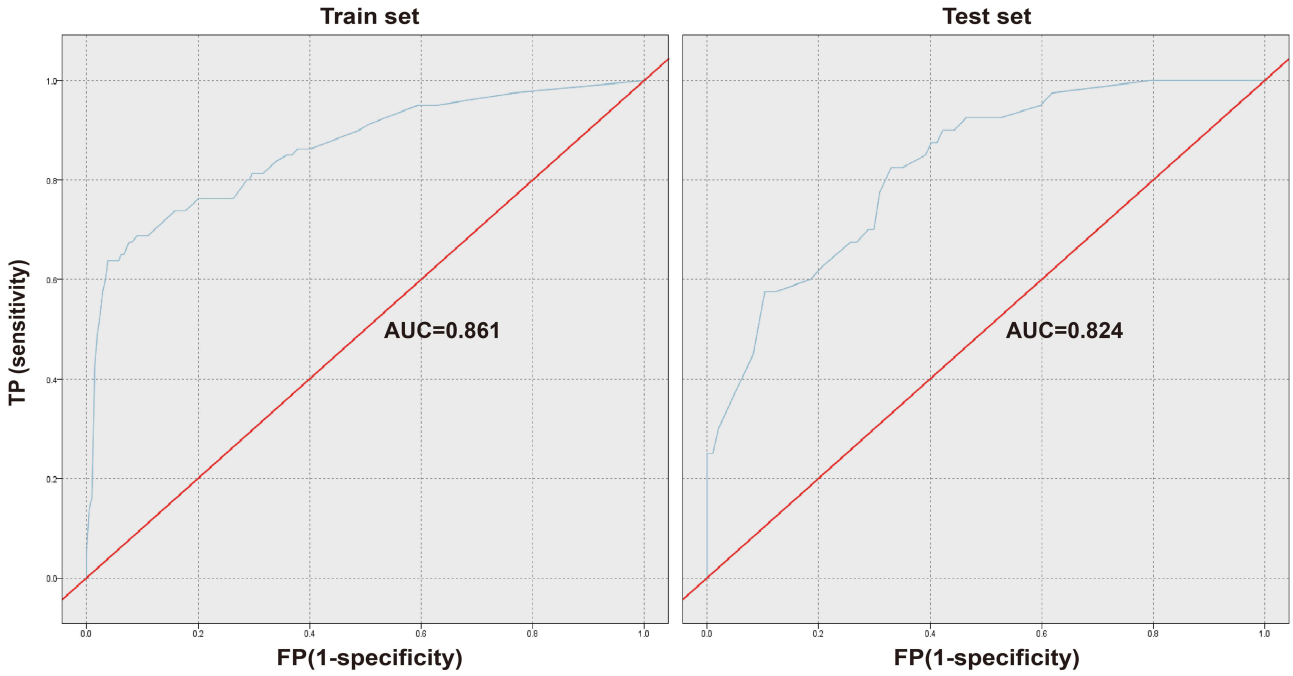

Figure 4 Receiver operating characteristic (ROC) curve of the C5.0 integrated decision tree model (Mtree) for cognitive frailty prediction.

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Table 5 Internal and External Validation Results for Each Model

Evaluation Indicators	M_{tree}				M_{nomo}		
	SC_{train}	SC_{test}	SH	BJ	SC_{all}	SH	BJ
ACC, %	85.47	80.29	75.89	70.59	78.64	72.77	59.22
Sensitivity (TPR/Recall), %	65.00	57.50	65.00	45.45	49.17	70.00	63.64
Specificity (TNR), %	93.30	89.69	76.96	74.32	90.20	73.04	58.56
Precision (PPV), %	78.79	69.70	21.67	20.83	66.29	20.29	18.58
NPV, %	87.44	83.65	95.73	90.16	81.90	96.13	91.55
AUC	0.861	0.824	0.810	0.719	0.812	0.772	0.713

Abbreviations: SC, Sichuan; SH, Shanghai; BJ, Beijing; ACC, accuracy; TPR, true positive rate; TNR, true negative rate; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

Table 6 Baseline Comparison of Internal and External Validation Among Different Areas

Characteristics	Stratification	Sichuan (n=426)	Beijing (n=255)	Shanghai (n=224)	*P* value
Age n (%)	60-69	92 (21.6)	110 (43.1)	148 (66.1)	<0.001
	70-79	159 (37.3)	80 (31.4)	66 (29.5)	
	80-89	153 (35.9)	65 (25.5)	10 (4.5)	
	≥90	22 (5.2)	0 (0.0)	0 (0.0)	
Sex n (%)	Male	155 (36.4)	113 (44.3)	99 (44.2)	0.055
	Female	271 (63.6)	142 (55.7)	125 (55.8)	
Education n (%)	Illiterate	35 (8.2)	1 (0.4)	11 (4.9)	<0.001
	Primary school	79 (18.5)	11 (4.9)	43 (19.2)	
	Middle school	121 (28.4)	64 (25.1)	73 (32.6)	
	High school	131 (30.8)	94 (36.9)	70 (31.3)	
	College or above	60 (14.1)	85 (33.3)	27 (12.1)	
Living n (%)	Live alone	29 (6.8)	13 (5.1)	18 (8.0)	0.427
	Cohabit	397 (93.2)	242 (94.9)	206 (92.0)	
Smartphone usage n (%)	No	179 (42.0)	223 (87.5)	180 (80.4)	<0.001
	Yes	247 (58.0)	32 (12.5)	44 (19.6)	
Smoking n (%)	No	324 (80.8)	198 (77.6)	177 (79.0)	0.613
	Yes	77 (19.2)	57 (22.4)	47 (21.0)	
Drinking n (%)	No	325 (81.0)	209 (82.0)	193 (86.2)	0.257
	Yes	76 (19.0)	46 (18.0)	31 (13.8)	

Finally, the C5.0 integrated decision tree model (M_{tree}) was evaluated by ROC and confusion matrix for comparison with M_{nomo}. The M_{tree} showed an AUC of 0.824 in the internal validation of the SCtest (Figure 4), which is slightly higher than the M_{nomo} (0.812). Similarly, the M_{tree} showed higher accuracy (ACC), sensitivity, precision, and NPV

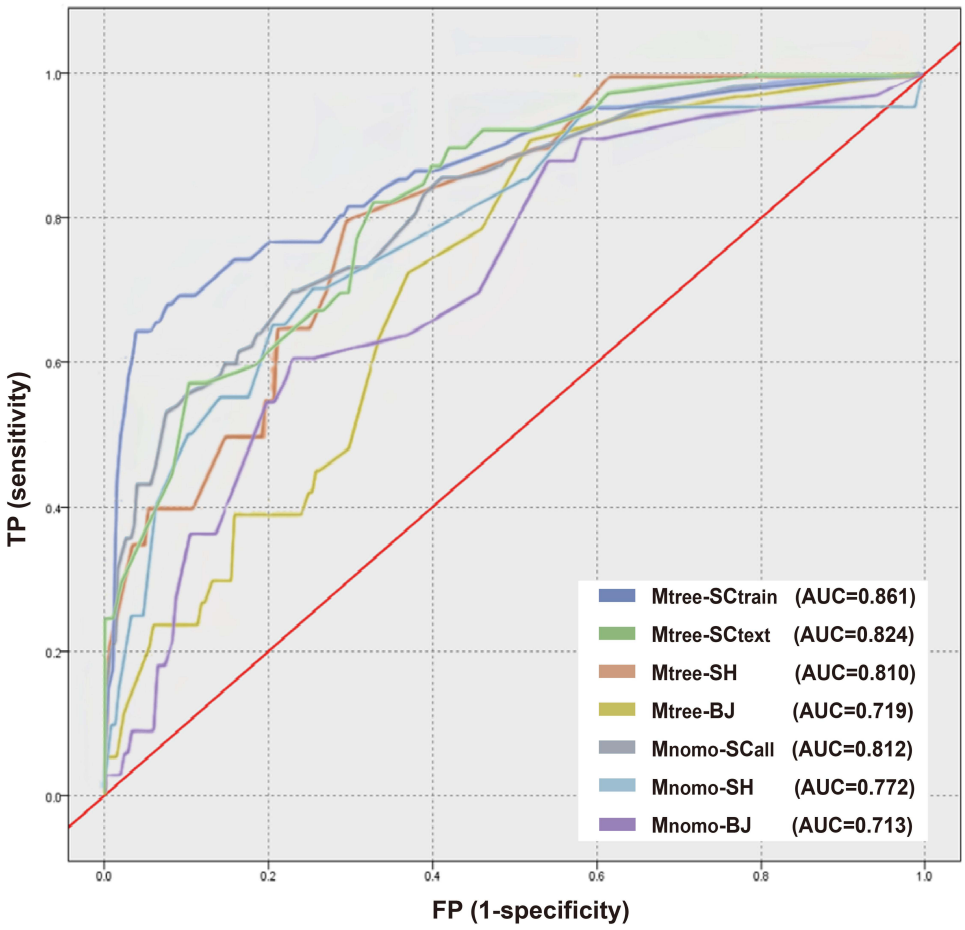

Figure 5 Comparison of ROC curves for internal and external validation of nomogram (M_{nomo}) and decision tree (M_{tree}) models.

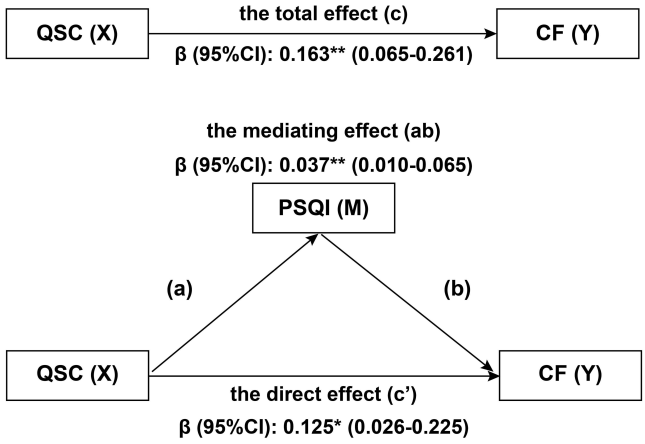

Figure 6 Mediation effect of sleep quality on the association between Qi-stagnation constitution (QSC) and cognitive frailty (CF). The mediating effect (ab) was significant (ab = 0.037, 95% CI [0.010, 0.065]), accounting for 22.7% of the total effect. The direct (c' = 0.125) and total (c = 0.163) effects were also significant, consistent with partial mediation. *P < 0.05, **P < 0.01.
Abbreviation: CI, confidence interval.

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(Negative Predictive Value) than the M_{nomo}, and only the specificity was slightly lower than the M_{nomo} (Table 5). Therefore, it can be determined that the M_{tree} outperformed the M_{nomo} in terms of predictive performance.

External Validation of Predictive Models of CF

Next, we collected a total of 479 older adults in the eastern (Shanghai, SH) and northern (Beijing, BJ) regions of China, as the external validation to evaluate the extrapolation performance of the two models constructed in the previous section. A comparison of the baseline situation of older adults in the three sites is shown in Table 6, which reveals differences in age, education, and smartphone usage among these seniors. AUC and a confusion matrix were used for predictive performance evaluation. The results showed that both the tree M_{tree} and M_{nomo} achieved an AUC greater than 0.7 in the two external validation sets. Among them, the M_{tree} achieved an AUC of 0.810 for the SH, which is the best result in the external validation sets. For the M_{tree}, the ACC in both validation sets were higher than 70% (75.89% in SH, 70.59% in BJ). For the M_{nomo}, the ACC in SH is also higher than 70%, while that in BJ is only 59.22%. It can be seen that both models have good extrapolation in external validation sets, while combining all the metrics, the M_{tree} had better extrapolation performance (Table 5 and Figure 5).

Analysis of the Mediating Effects Between TCMC and CF

Based on the regression results and TCMC theory, we constructed a mediated effects model using the KHB method with QSC (score) as the independent variable, sleep quality (PSQI score) as the mediator variable, and CF (binary variable as yes or no) as the dependent variable. The results showed that the total effect of QSC on CF was 0.163 (95% CI: 0.065–0.261, P=0.001), and the direct effect was 0.125 (95% CI: 0.026–0.225, P=0.013). And the mediating effect of sleep quality between QSC and CF was 0.037 (95% CI: 0.010–0.065, P=0.008<0.01). The mediation effect ratio for sleep quality was 22.7% (0.037/0.163), suggesting that QSC may contribute to the development of CF by reducing sleep quality in older adults (Figure 6).

Discussion

With the accelerating global aging process, CF has emerged as a major challenge in older adult health management. This was a multicenter study that elaborated the epidemiological evidence relationship between TCMC and CF at the level of influential factors, predictive value, and impact pathway. This study employed dual validation through both nomogram and machine learning-based clinical prediction models, first revealing that QSC serves as a robust predictor of CF, with cross-regional applicability confirmed by external validation. Our findings demonstrated that sleep quality mediates 22.7% of the effect pathway, indicating that QSC not only directly impacts CF but also indirectly influences CF occurrence through the mediating effect of sleep quality. These results provide clinically actionable early prevention perspectives and tools for CF screening and intervention.

Our results support QSC as an independent risk factor for CF, aligning with TCM theory that constitution represents the soil of disease onset. It has been demonstrated by preceding studies that TCMC plays a pivotal role in the genesis and progression of chronic diseases from a variety of vantage points. In the context of disease associations, significant correlations were identified between Yin-deficient constitution and sarcopenia, Yang-deficient/phlegm-dampness/blood-stasis constitution and mild cognitive impairment, and phlegm-dampness constitution and metabolism-related fatty liver.[21–23] In terms of predictive value, similar to our results, QSC not only predicted cognitive decline and physical frailty in older adults, but was also strongly associated with migraine, depression, psychological disorders mediated by childhood trauma.[24–29] Intervention studies have further demonstrated that TCMC modification (eg, improving damp-heat constitution) may improve health outcomes through mechanisms such as regulating intestinal flora.[30] The present study revealed the important roles of TCMC and QDC in CF, which not only supports the theory of TCMC as the basis of disease susceptibility, but also provides new ideas for early intervention in CF. Further exploration is warranted into the clinical application value of TCMC in cognitive health management in forthcoming studies.

This study developed two different predictive models for CF: the first model (M_{nomo}) incorporated six key predictors (QSC, depression, ADL/IADL dependency, education level, and smartphone usage), while the ML model (M_{tree}) additionally combined QDC and grip strength as significant contributing factors. The models constructed in this study

demonstrate methodological rigor and practical advantages. In contrast to the models reviewed by Ren et al, where only 18.1% underwent external validation, our approach employed a rigorous validation process based on a multicenter sample (external validation n = 479).[6]

M_{tree} exhibited robust performance in the Shanghai validation cohort (AUC = 0.810), approaching the mean AUC of externally validated models reported (pooled AUC = 0.841).[6] Critically, both models achieved AUCs exceeding the clinical utility threshold (AUC > 0.70) in external cohorts from both geographical regions.[31] This multi-center, multi-region validation strategy effectively addresses the prevalent issue of limited generalizability in previous research.[32]

Technically, this study innovatively established a dual-model system adaptable to diverse application scenarios, where M_{tree} is ideal for high-throughput screening scenarios, whereas M_{nomo} is optimized for rapid assessment in routine clinical or institutional settings. This "precision screening and rapid assessment" architecture offers a promising solution to the research-practice gap highlighted by Ren, providing customizable solutions for settings with varying resources. In addition, whereas previous studies primarily focused on community-dwelling older adults or specific clinical populations (like individuals with renal disease or hypertension), incorporating high-risk institutionalized older adults into our predictive model ensures greater applicability.

While existing research predominantly relies on nomograms with only limited adoption of machine learning (ML) models, our findings corroborate the superior performance of ML approaches over traditional models. The M_{tree} model demonstrated enhanced adaptability to regional heterogeneity, leveraging ML algorithms to effectively capture complex data patterns intrinsic to diverse populations. In contrast, M_{nomo} provides efficient assessment comparable to community screening tools through minimal routine indicators, but innovatively integrates TCMC.

Furthermore, our study identified QSC, QDC, and smartphone usage behavior as important key predictors of risk stratification for CF. This not only confirms Bai's assertion about the value of nontraditional factors, but also does not rely exclusively on basic demographics and other burdensome comprehensive assessments of aging.[33] Our findings support Rivan's claims for multidimensional interventions and establish an assessment paradigm that is responsive to the digital health needs of aging populations.[34]

This study further explored the mechanism by which QSC influences the occurrence of CF through sleep quality. People with QSC are not only at high risk of CF, but they may also have poorer sleep quality and be more likely to experience it. QSC is a TCMC state characterized by introversion, emotional instability, depression, vulnerability, sensitivity, and suspicion due to long-term emotional distress and stagnation of Qi. Common manifestations of QSC include: a melancholic outlook, boredom and unhappiness, fullness and pain in the chest and hypochondrium, frequent sighing and hiccups, or a foreign body sensation between the pharynx, or breast distension and pain, poor sleep, and loss of appetite. Previous studies have shown that QSC is the main TCMC constitution for physical frailty, as well as an important risk factor for mild cognitive impairment (MCI).[35,36] Clinical and basic research has revealed that QSC patients exhibit reduced cerebral oxygen metabolism and that QSC-induced cellular peroxidation and free radical accumulation can impair learning and memory functions.[37,38] Furthermore, TCM formulas have been shown to improve cognitive scores by addressing these pathologies.[39] Moreover, chronic stress-induced persistent activation of the hypothalamic-pituitary-adrenal (HPA) axis, exacerbated systemic inflammation, neurotransmitter imbalances, and concomitant adverse lifestyle factors (eg, sedentary behavior and social isolation) may collectively contribute to the progression of CF through both direct and indirect pathways.[40–45]

Our study demonstrated a negative correlation between QSC and sleep quality, with QSC individuals exhibiting poorer sleep quality - a finding consistent with both QSC characteristics and prior research.[8–11] Furthermore, we found sleep quality to be significantly associated with CF, corroborating existing evidence.[12–14] Sleep quality, primarily determined by subjective perception (including sleep duration and satisfaction), was assessed using the PSQI, evaluating seven components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, hypnotic medication use, and daytime dysfunction.[46] Existing evidence suggests two potential biological pathways linking impaired sleep quality to CF: (1) compromised insulin metabolism leading to reduced cerebral glucose utilization efficiency, and (2) oxidative stress-induced neuronal damage.[47–50]

This study provides important tools and targets for the early identification and clinical intervention of CF. We have developed two risk prediction models: a simplified clinical assessment model for rapid screening of high-risk individuals

in medical institutions, and a large-scale screening model offering efficient solutions for community-based early detection. Building upon previous research, we particularly emphasized the clinical application value of TCM constitutions as a modifiable factor in our predictive model. Compared to non-modifiable factors like age or education level, constitutions such as Qi-stagnation can be improved through TCM interventions and lifestyle adjustments, demonstrating greater clinical applicability.

The proposed targeted interventions include:

- Environmental regulation: Maintaining quiet living spaces free from excessive noise.
- Lifestyle modification: Balancing activity and rest while increasing outdoor exposure to nature.
- Psychological adjustment: Proactively participating in social and recreational activities while cultivating hobbies.
- TCM therapies: Utilizing traditional approaches including medicinal teas, herbal cuisine, foot baths, moxibustion, and acupoint massage.

We recommend that primary healthcare institutions integrate constitution assessment into routine check-ups and implement stepped management for QSC/QDC individuals: initial lifestyle and psychological interventions, supplemented by TCM external therapies for suboptimal responders, and herbal medication for refractory cases. Communities could leverage public health platforms to establish comprehensive intervention systems incorporating environment optimization, exercise guidance, social engagement promotion, and TCM healthcare. This integrated model, combining modern screening techniques with traditional regimen methods, offers a TCM-characterized solution for CF prevention and management.

This study has several notable strengths. First, we employed a comprehensive analytical approach by combining traditional regression methods with nomogram visualization and machine learning (decision tree model) for predictive model construction. The consistent demonstration of TCM constitutions' predictive value for CF across multiple modeling approaches enhances the robustness and generalizability of our findings. Second, our multicenter design incorporated internal and external validation across northern, eastern, and southwestern China, ensuring good geographical representativeness and clinical applicability of the prediction models.

Several limitations should be acknowledged. First, the cross-sectional design restricts causal inferences between identified risk factors and CF outcomes-future prospective cohort studies are needed to verify these temporal relationships. Second, while our models showed good performance in the derivation and validation cohorts, there is still a need for further optimized model calibration using independent populations to further extend clinical utility. Third, our study has limitations in the measurement of certain variables. Specifically, the assessment of multimorbidity was based on a single self-report question rather than a validated index. While practical, this approach does not capture the severity of conditions and may have led to an underestimation of the true burden. Additionally, some potentially influential factors, like detailed socioeconomic status or dietary patterns, were not included due to data availability. Future studies should incorporate validated comorbidity index, such as the Charlson Comorbidity Index, and explore these missing variables to provide a more comprehensive understanding of the factors influencing cognitive frailty.

Despite these limitations, our study provides valuable evidence for CF prediction by innovatively integrating TCM with modern analytical approaches. The multicenter design and dual-model strategy (clinical-friendly vs population-screening) offer flexible implementation pathways for different healthcare settings.

Conclusion

This study demonstrated that QSC and QDC served as modifiable risk factors for CF. The predictive model incorporating TCMC exhibited satisfactory discriminative ability and generalizability. QSC may contribute to CF both directly and indirectly through poorer sleep quality. These findings highlight the dual utility of TCMC: (1) as a screening indicator for early CF detection, and (2) as a modifiable target for non-pharmacological interventions. The established models provided practical tools for implementing precision prevention strategies in clinical practice.

Abbreviations

ACC, accuracy; ADL, activities of daily living; AUC, area under the curve; BI, Barthel Index; BJ, Beijing; CDR, Clinical Dementia Rating scale; CF, cognitive frailty; DCA, decision curve analysis; GAD-7, Generalized Anxiety Disorder-7 items Scale; HPA, hypothalamic-pituitary-adrenal; IADL, instrumental activities of daily living; I.A.G.G., International Association of Gerontology and Geriatrics; I.A.N.A., International Academy on Nutrition and Aging; KHB, Karlson-Holm-Breen method; MCI, mild cognitive impairment; ML, machine learning; MNA-SF, Mini Nutritional Assessment Short Form; MoCA, Montreal Cognitive Assessment; NPV, negative predictive value; PHQ-9, Patient Health Questionnaire-9; PPV, positive predictive value; PSQI, Pittsburgh Sleep Quality Index; QDC, Qi-deficiency constitution; QSC, Qi-stagnation constitution; ROC, receiver operating characteristic curves; SC, Sichuan; SH, Shanghai; SNPs, single nucleotide polymorphisms; TCM, Traditional Chinese Medicine; TCMC, Traditional Chinese Medicine Constitution; TNR, true negative rate; TPR, true positive rate; WtHR, waist-to-height ratio.

Ethics Approval and Consent to Participate

The study protocol received ethical approval from the Ethics Committee of the Hospital of Chengdu University of Traditional Chinese Medicine (Approval No. 2021KL-055). Prior to study commencement, all participants provided written informed consent. The investigation was conducted in full compliance with both the ethical guidelines established by the reviewing institutional board and the principles outlined in the Declaration of Helsinki. All study procedures, including data collection and analysis, strictly adhered to institutional ethical standards for human subjects research, ensuring participant confidentiality and welfare throughout the study duration.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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