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Independent and Combined Effects of Frailty and Depressive Symptoms on Cognitive Decline in Chinese Middle-aged and Older Adults

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Research Article

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Independent and Combined Effects of Frailty and Depressive Symptoms on Cognitive Decline in Chinese Middle-aged and Older Adults

Abstract

Objective: To investigate the independent and combined effects of physical frailty and depressive symptoms on cognitive decline in middle-aged and older adults in China, and further examine whether these two factors have additive or synergistic effects, aiming to provide epidemiological evidence for early identification and integrated interventions in high-risk populations for dementia.

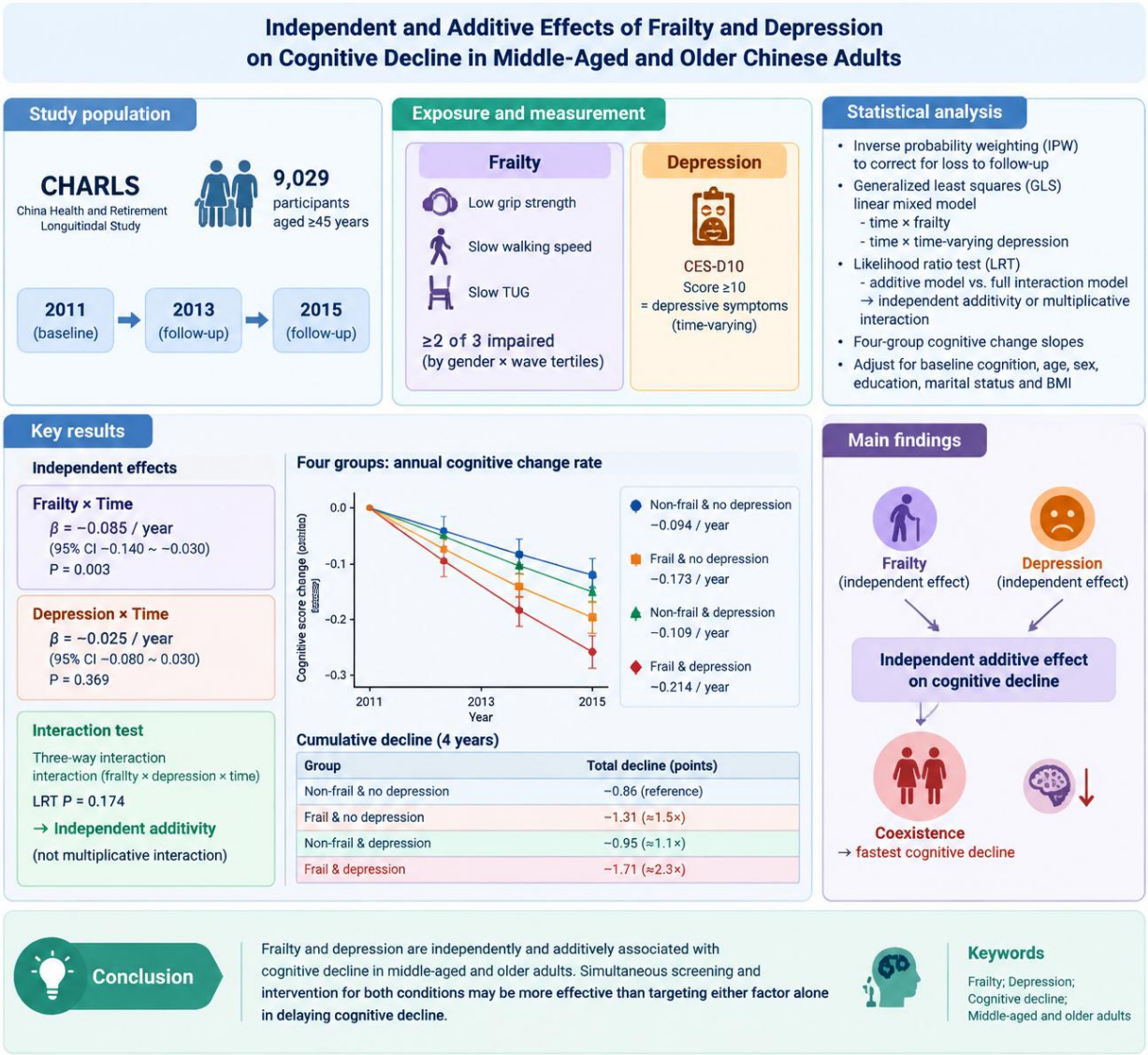
Method: Based on the baseline data from the China Health and Retirement Longitudinal Study (CHARLS) in 2011, and two follow-up waves in 2013 and 2015, a total of 9,029 middle-aged and older adults aged ≥45 were included. Frailty was defined as meeting at least two out of three criteria for physical function impairment—low grip strength, slow gait speed, and slow timed up and go (TUG) test—each criterion categorized by gender-specific tertiles within each wave. Depression was assessed using the CES-D10 scale, with a total score ≥10 indicating depressive symptoms (time-varying). To correct for attrition bias, inverse probability weighting (IPW) was applied, and a generalized least squares (GLS) linear mixed model was constructed to examine the interaction terms of time × frailty and time × time-varying depression. An additive model versus a full interaction model likelihood ratio test (LRT) was used to determine whether the effects were independent (additive) or multiplicative. The four combinations of cognitive change slopes were calculated based on model coefficient combinations. Adjustments were made for baseline cognition, age, sex, education, marital status, and BMI.

Results: Time × frailty was significantly associated with accelerated cognitive decline (β = −0.085 per year, 95% CI −0.140 to −0.030, P = 0.003); time × time-varying depression showed a consistent but non-significant trend (β = −0.025 per year, 95% CI −0.080 to 0.030, P = 0.369). The three-way interaction term was not significant (LRT P = 0.174), supporting additive rather than multiplicative effects. The mean annual rates of cognitive change across the four groups were as follows: non-frail without depression, −0.094 points/year; frail without depression, −0.173 points/year; non-frail with depression, −0.109 points/year; and frail with depression, −0.214 points/year (cumulative over 4 years ≈ −0.86 points, approximately 2.3 times higher than the non-frail without depression group). Sensitivity analyses (removing abnormal coding, excluding

TUG components) yielded robust conclusions.

Conclusion: Frailty and depression have independent additive effects on cognitive decline in middle-aged and older adults, with those experiencing both conditions showing the fastest cognitive decline. Simultaneously screening for and intervening on both frailty and depression may be more effective in delaying cognitive decline than targeting either factor alone.

Keywords: frailty; depression; cognitive decline; middle-aged and older adults



Research Background

Dementia has become a major public health challenge globally and in China. Based on large-scale surveys of individuals aged 60 and above in China, it is estimated that approximately

15.07 million people suffer from dementia, with a prevalence rate of about 6.0%, including around 9.83 million cases of Alzheimer's disease. The disease burden has continued to rise in recent years [1]. According to the "China Alzheimer's Disease Report," the overall prevalence of all types of dementia in China reaches 8.8%, with nearly 17 million patients suffering from Alzheimer's disease and other dementias—accounting for about 30% of global AD cases and exceeding the global average prevalence [2]. Meanwhile, the prevalence of mild cognitive impairment stands at 20.8%, affecting nearly 40 million high-risk individuals, many of whom progress to dementia each year, forming a substantial preclinical population. Meta-analyses further reveal that dementia prevalence among older Chinese adults increases significantly with age: 2.5% for those aged 60–69, rising to 6.1% for ages 70–79, and reaching as high as 17.0% for those aged 80 and above; women and individuals with lower educational levels show notably higher rates [3]. The economic burden is equally staggering, with the total annual cost of dementia care in China approaching 2.89 trillion yuan, over 60% of which is borne by families. Given this severe situation, shifting prevention efforts forward and identifying modifiable risk factors have become central strategies in dementia control and prevention [4][6][7].

The 2024 update report from the Lancet Commission on Dementia Prevention and Intervention indicates that approximately 45% of global dementia cases can be attributed to 14 modifiable risk factors, adding untreated vision impairment and high levels of low-density lipoprotein cholesterol to the previous 12 factors [5]. Among these modifiable factors, frailty and depression are receiving increasing attention due to their high prevalence, identifiability, and potential for intervention. Frailty is a common clinical condition in older adults characterized by reduced physiological reserves across multiple systems and diminished capacity to withstand stressors [8]. The frailty phenotype proposed by Fried et al. operationalizes this concept through five criteria: unintentional weight loss, fatigue, low physical activity, slow gait speed, and reduced grip strength, with grip strength and gait speed being the most widely used objective components [10][11]. In Chinese community-dwelling older adults, the prevalence of frailty and pre-frailty is approximately 39.88%, and an adapted frailty phenotype based on Chinese population characteristics has been developed, with recommended cutoff points of grip strength <28 kg for men and <18 kg for women, and gait speed <1.0 m/s.

Previous studies have indicated that frailty is significantly associated with cognitive decline

and an increased risk of dementia. A longitudinal cohort study from the Alzheimer's Disease Neuroimaging Initiative database found that the risk of Alzheimer's disease (AD) was 67.7% higher in the frail group compared to the non-frail group, and 61.8% higher compared to the pre-frail group. Moreover, the greater the degree of frailty, the faster the cognitive decline and the more pronounced the atrophy in both whole brain and hippocampal regions [12][13][14]. The impact of frailty on cognition is partially mediated by total brain volume and hippocampal volume [9]. Mechanistically, frailty may promote cognitive decline through pathways such as chronic low-grade inflammation, vascular damage, and neuroendocrine dysregulation.

Depression is also an important modifiable risk factor for dementia. Epidemiological evidence shows that depression is not only associated with lower baseline cognitive levels but also predicts accelerated subsequent cognitive decline and the onset of dementia [15]. A multinational comparative study based on CHARLS data indicates that depressive symptoms are an independent risk factor for dementia in England, the United States, and China. The prevalence of depressive symptoms among older adults in China ranges from approximately 20% to 40%, yet detection and intervention rates at the primary care level remain low [17]. The 10-item CES-D short form is widely used for screening depressive symptoms in older populations, with a cutoff score of ≥10 demonstrating good sensitivity and specificity [16].

It is noteworthy that frailty and depression are highly comorbid clinically and mechanistically interrelated. Meta-analyses have shown a bidirectional interaction between the two. Shared pathophysiological mechanisms include elevated levels of pro-inflammatory cytokines, dysregulation of the hypothalamic-pituitary-adrenal axis, and reduced gray matter volume in specific brain regions [18]. Using a 10-year trajectory model from the Health and Retirement Study, it was found that compared to individuals who remained robust and depression-free, those with worsening frailty combined with incident depression, as well as those with severe frailty and persistent depression, exhibited significantly accelerated cognitive decline, with dementia risks increased by 81% and 86%, respectively [20]. Another study based on CHARLS data from 2011 to 2018 indicated that depressive symptoms increase the risk of rapid cognitive decline among frail individuals [19]. Furthermore, research estimates that frailty and depression together may account for approximately 17% of dementia risk.

However, previous studies have mostly examined the relationship between frailty or

depression and cognition separately, with few assessing their combined effects simultaneously. Moreover, most studies used baseline exposure to predict outcomes without considering changes in exposure over time [21][22]. From a preventive perspective, clarifying whether these two factors act independently in an additive manner or interact multiplicatively is directly relevant: if additive, joint screening and concurrent interventions could yield cumulative benefits; if multiplicative interaction exists, targeted interventions for high-risk subgroups would be particularly critical [23]. Based on this, our study uses three waves of longitudinal data from CHARLS (2011–2015), applying time-varying exposure and drop-out weighting methods, to systematically evaluate the independent additive effects of frailty and depression on cognitive decline among middle-aged and older adults, providing evidence-based support for primary prevention of dementia.

Research Methodology

Study population

The data were obtained from the China Health and Retirement Longitudinal Study (CHARLS). CHARLS is a nationwide longitudinal survey targeting Chinese residents aged 45 and older, designed to generate a high-quality, representative, and publicly accessible micro-database providing comprehensive information on the health, economic, and social status of middle-aged and older adults. The study participants were selected using a multi-stage probability-proportional-to-size (PPS) sampling technique across 28 provinces in China, ensuring that the sample is representative of the national population aged 45 and above.[24] This study used the 2011 baseline survey of CHARLS as the starting point and incorporated follow-up data from 2013 and 2015 for longitudinal analysis. Inclusion criteria included: (1) age ≥45 years; (2) completion of at least two physical function assessments—grip strength, walking speed, and timed up-and-go test (TUG)—at the 2011 baseline, enabling construction of a frailty composite indicator; (3) completion of cognitive function assessment and full depressive symptom evaluation at the 2011 baseline; and (4) completion of at least one cognitive function measurement during follow-up. Exclusion criteria included: (1) missing key covariate information such as age, gender, education level, marital status, or BMI at baseline; and (2) absence of any cognitive function measurement records during follow-up. After merging data from three waves, a total of 24,954 respondents (57,405 observations, including 17,705 from 2011) were initially included. Following data cleaning and variable selection, 9,029 participants (18,354 observations) were ultimately retained for longitudinal analysis, of whom 8,961 had complete baseline data from 2011. The screening process is illustrated in Figure 1. Among them, 4,328 were non-frail without depressive symptoms, 1,663 were frail without depressive symptoms, 1,737 were non-frail with depressive symptoms, and 1,233 were frail with depressive symptoms. All participants provided informed consent, and the CHARLS research protocol has been approved by the Ethics Committee of Peking University.

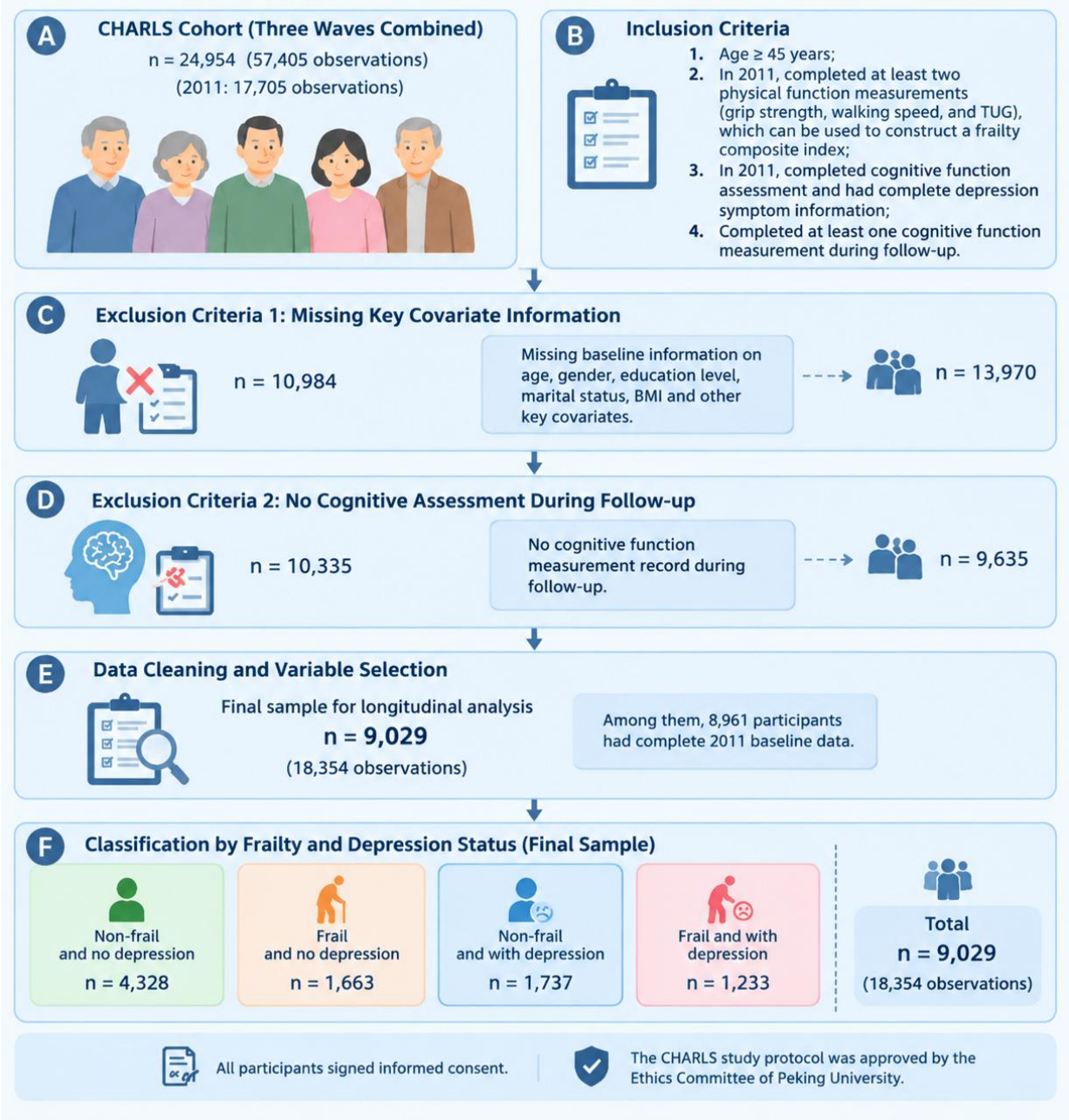


Figure 1, Process Screening Diagram

Frailty

Frailty was constructed based on physical function impairment, comprising three objective components: (1) low grip strength: the average of two measurements from each hand (kg), defined as impaired if below the third quartile within sex-by-wave groups; (2) slow gait speed: the mean time to walk 2.5 m (s), averaged over two trials, defined as impaired if above the third quartile

within sex-by-wave groups; (3) slow TUG: time for the timed up and go test, defined as impaired if above the third quartile within groups. The number of impaired components (0–3) was calculated only when at least two components had valid measurements; frailty was defined as having ≥2 impaired components. Frailty was considered a time-varying exposure, meaning it was re-evaluated in each wave based on current measurements.

Depression

Depression was assessed using the 10-item short form of the Center for Epidemiologic Studies Depression Scale (CES-D-10). The scale includes 10 items, each scored from 0 to 3 based on the frequency of symptoms experienced in the past week. Two positively worded items—"I feel hopeful about the future" and "I am happy"—were reverse-scored (3 minus the original score) before being summed with the other items. Total scores range from 0 to 30, with higher scores indicating more severe depressive symptoms. Scoring requires responses to all 10 items; if any item is missing, the total score is considered missing (no imputation performed). A total score of 10 or higher was defined as presence of depressive symptoms (coded as 1), while a score below 10 indicated absence of depressive symptoms (coded as 0). In sensitivity analyses, continuous CES-D scores were also used (with risk increment corresponding to every 5-point increase).

Cognitive Function Outcomes

A 31-point comprehensive cognitive score was constructed using the cognitive module of the CHARLS questionnaire, consisting of five dimensions: orientation (0–5 points, year, month, day, weekday, season), calculation (0–5 points, serial subtraction of 7 from 100), figure drawing (0–1 point), immediate word recall (0–10 points), and delayed word recall (0–10 points). Cognitive scores across the three waves were calculated using a unified algorithm, with higher scores indicating better cognitive function. The total cognitive score in 2011 served as the baseline cognitive level.

Covariate

The baseline covariates included in this study were age, gender, education level, marital status, body mass index (BMI), physical activity, alcohol consumption, and smoking status, all derived from the 2011 CHARLS baseline questionnaire. Age was calculated as 2011 minus year of birth; for sensitivity analysis, it was categorized into <60 years, 60–69 years, and ≥70 years. Gender was classified as female or male. Education level was categorized as primary school or below, junior high school, and senior high school or above; based on the education attainment question, individuals who were illiterate, had not completed primary school, or had only completed primary school were coded as "primary school or below," those who had completed junior high school were coded as "junior high school," and those with senior high school, vocational school, or college education and above were grouped together as "senior high school or

above." Marital status was categorized as married or other; individuals currently married and living with their spouse, or married but separated due to work or other reasons, were coded as "married," while those who were divorced, widowed, unmarried, or never married were collectively coded as "other."

Body Mass Index (BMI, kg/m²): Calculated from self-reported height and weight (BMI = weight / height²), categorized according to World Health Organization (WHO) standards: underweight (BMI < 18.5), normal (18.5 ≤ BMI < 24.0), overweight (24.0 ≤ BMI < 28.0), and obese (BMI ≥ 28.0). In the main analysis, BMI was treated as a continuous variable; in subgroup analyses, it was dichotomized into <24.0 and ≥24.0. Extreme values—height <100 cm or >250 cm, or weight <20 kg or >200 kg—were considered measurement errors and set as missing.Physical activity (no, yes): Assessed based on frequency of participation in vigorous physical activities (e.g., farming, exercise), moderate-intensity activities, and walking. Respondents were recoded as "yes" if they selected "more than once per week" or "daily" for any of these activities (corresponding items in CHARLS assigned as "yes"). If all three categories (vigorous, moderate, and walking) were answered "no/never," the response was coded as "no." Alcohol consumption (no, yes): Self-reported based on the question "Have you consumed alcohol in the past year?" Responses of "yes" were coded as "yes," and "no" as "no." Smoking status (no, yes): Self-reported based on the question "Are you currently smoking?" Responses of "yes" were coded as "yes," and "no" as "no." Missing data handling: For age and education level, missing values were imputed by carrying forward the most recent available value across waves using individual ID (values from 2013/2015 waves imputed into 2011). Other covariates were not imputed; the main analysis was conducted on the complete-case sample, with inverse probability weighting (IPW) applied to adjust for loss-to-follow-up selection bias.

Statistical Analysis

Continuous baseline characteristics were described using means (standard deviations), an d categorical variables were described using frequencies (percentages). Between-group compar isons were conducted using independent samples t-tests and χ^2 tests, with a two-sided α level of 0.05. Statistical analyses were performed using R 4.4.1 software. Longitudinal data from t hree waves (2011, 2013, and 2015) were integrated by linking the three waves via individual identifiers (ID) to create a longitudinal dataset. The objective cognitive function total score (0–31 points, composed of five domains: orientation, calculation, drawing, immediate word re call, and delayed word recall) was calculated. A total of 7,503 participants were included in t he analysis who were aged ≥45 at baseline, had complete assessments for frailty indicators a nd depressive symptoms, and had available baseline cognitive function scores. Frailty was def ined as impairment in at least two of three physical function measures: grip strength, walking speed, and the timed up-and-go test (TUG). Thresholds for impaired performance were deter mined based on gender-specific tertiles for each survey wave. Depressive symptoms were trea ted as a time-varying variable, defined as CES-D-10 scores ≥10 at each assessment time poin t. Longitudinal cognitive trajectories were modeled using generalized least squares (GLS) reg ression within the nlme package, with inverse probability weighting (IPW) applied to correct for attrition bias. Adjustments were made for baseline cognitive function, age, sex, education level, marital status, and body mass index (BMI). Interaction terms time×frailty and time×dep _t were included to assess the independent contributions of frailty and depression to annual c ognitive decline. To determine whether the effects of frailty and depression on cognitive decli

ne were additive or multiplicative, we compared a full interaction model including the third-order term time×frailty×dep_t with an additive model using likelihood ratio tests (LRT). The third-order interaction was not statistically significant (P > 0.05), supporting an additive effect. Annual average rates of cognitive change were estimated for four groups—non-frail without depression, frail without depression, non-frail with depression, and frail with depression—using linear combinations of model coefficients. Adjusted predicted cognitive trajectories for these four groups were plotted. Sensitivity analyses included: (1) re-running the main analysis after treating abnormal response codes (999) as missing values and recalculating cognitive scores; (2) refitting the model using only participants with ≥2 cognitive assessments; and (3) testing robustness by changing the frailty threshold to ≥1 impaired measure. Minor missing data for age and education level were imputed across waves using the most recent available value per individual ID. Participants with missing values for other key covariates were excluded.

Result

Baseline characteristics

A total of 9,029 participants were included in the longitudinal analysis (18,354 observations), of whom 8,961 had complete baseline data from 2011 (Table 1). The mean age of participants was 57.7 ± 9.0 years, with 60.2% under 60 years old; 49.3% were female; 38.9% had at least a high school education; and 90.1% were married or cohabiting. The prevalence of baseline depressive symptoms (CES-D-10 ≥ 10) was 33.1%, and the prevalence of frailty (≥ 2 impaired physical function domains) was 32.3%.

Based on the 2011 baseline, participants were divided into four groups: non-frail without depression (n=4328), frail without depression (n=1663), non-frail with depression (n=1737), and frail with depression (n=1233). Baseline characteristics differed significantly among the four groups (all P<0.001): the frail with depression group had the highest mean age (63.0±8.7 years), the highest proportion aged ≥70 years (22.7%), the lowest educational level (only 20.2% with high school or higher education), the lowest baseline cognitive score (13.7±4.2 points), the weakest grip strength (22.2±7.6 kg), the slowest gait speed (4.8 s), the highest prevalence of chronic pain (57.4%), and the shortest nighttime sleep duration (6.0 h). In contrast, the non-frail without depression group exhibited the best cognitive function (17.2±4.3 points) and physical performance (grip strength 35.7±8.6 kg, gait speed 3.4 s, and only 18.7% with chronic pain). Detailed information is shown in Table 1.

Variable	Overall	Non-frail and non-depressed	Frailty without depression	Non-frail with depression	Frailty + Depression	P-value
Sample size n	8961	4328	1663	1737	1233	
Age (years)	57.7 ± 9.0	55.0 ± 7.8	63.6 ± 9.1	55.3 ± 7.7	63.0 ± 8.7	<0.001
Age <60 years, n(%)	60.2 (5394)	74.4 (3221)	30.7 (510)	72.5 (1259)	32.8 (404)	<0.001
Age 60–69 years, n(%)	28.5 (2554)	20.6 (891)	42.9 (713)	23.1 (401)	44.5 (549)	<0.001

Variable	Overall	Non-frail and non-depressed	Frailty without depression	Non-frail with depression	Frailty + Depression	P-value
Age ≥70 years, n(%)	11.3 (1013)	5.0 (216)	26.5 (440)	4.4 (77)	22.7 (280)	<0.001
Female, n(%)	49.3 (4414)	46.1 (1996)	41.7 (694)	61.2 (1063)	53.6 (661)	<0.001
Education: Primary school and below, n(%)	36.4 (3261)	27.5 (1189)	41.7 (693)	41.9 (727)	52.9 (652)	<0.001
Education: Junior high school, n(%)	24.7 (2214)	23.3 (1007)	27.0 (449)	24.5 (426)	26.9 (332)	0.005
Education: High school or above, n(%)	38.9 (3486)	49.3 (2132)	31.3 (521)	33.6 (584)	20.2 (249)	<0.001
Married, n(%)	90.1 (8073)	94.3 (4082)	86.7 (1442)	88.8 (1543)	81.6 (1006)	<0.001
BMI(kg/m²)	23.7 ± 3.8	24.3 ± 3.7	23.0 ± 4.0	23.7 ± 3.6	22.7 ± 3.8	<0.001
BMI < 18.5, n(%)	5.3 (475)	2.6 (113)	8.8 (146)	4.5 (78)	11.2 (138)	<0.001
BMI 18.5–23.9, n(%)	52.4 (4693)	48.3 (2092)	56.7 (943)	54.1 (940)	58.2 (718)	<0.001
BMI 24–27.9, n(%)	30.4 (2725)	35.0 (1515)	25.2 (419)	29.9 (520)	22.0 (271)	<0.001
BMI≥28, n(%)	11.9 (1068)	14.0 (608)	9.3 (155)	11.5 (199)	8.6 (106)	<0.001
Baseline cognitive total score (0–31)	16.1 ± 4.5	17.2 ± 4.3	15.8 ± 4.5	15.2 ± 4.3	13.7 ± 4.2	<0.001
Number of chronic diseases	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	2.0 (1.0, 3.0)	<0.001
Chronic pain, n(%)	30.6 (2740)	18.7 (809)	20.7 (345)	50.6 (879)	57.4 (707)	<0.001
Number of pain sites	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.0 (0.0, 4.0)	1.0 (0.0, 4.0)	<0.001
Sleep duration (h)	7.0 (5.0, 8.0)	7.0 (6.0, 8.0)	7.0 (6.0, 8.0)	6.0 (5.0, 7.0)	6.0 (4.0, 7.0)	<0.001
Smoking, n(%)	41.8 (3746)	43.0 (1859)	45.8 (762)	35.6 (618)	41.1 (507)	<0.001
Drinking, n(%)	26.5 (2375)	30.1 (1303)	26.0 (432)	22.4 (389)	20.4 (251)	<0.001
Regular physical activity, n(%)	91.1 (3542)	92.9 (1763)	87.2 (611)	92.1 (687)	88.6 (481)	<0.001
Systolic blood pressure (mmHg)	130.1 ± 38.7	129.0 ± 36.2	132.7 ± 29.7	129.1 ± 48.6	132.1 ± 41.8	0.001

Variable	Overall	Non-frail and non-depressed	Frailty without depression	Non-frail with depression	Frailty + Depression	P-value
Diastolic blood pressure (mmHg)	75.6 ± 12.1	76.4 ± 11.8	75.0 ± 12.3	75.2 ± 12.3	74.5 ± 12.2	<0.001
Average grip strength (kg)	31.1 ± 9.9	35.7 ± 8.6	24.3 ± 8.1	32.7 ± 7.9	22.2 ± 7.6	<0.001
Pace (steps per 2.5 meters)	3.9 (3.2, 5.0)	3.4 (2.8, 3.9)	4.7 (3.5, 6.1)	3.6 (3.1, 4.1)	4.8 (3.8, 6.3)	<0.001
Depressive symptoms, n(%)	33.1 (2970)	0.0 (0)	0.0 (0)	100.0 (1737)	100.0 (1233)	<0.001
Frailty, n(%)	32.3 (2896)	0.0 (0)	100.0 (1663)	0.0 (0)	100.0 (1233)	<0.001
≥2 cognitive assessments, n(%)	80.8 (7242)	85.2 (3688)	75.6 (1258)	82.6 (1435)	69.8 (861)	<0.001

Table 1. Baseline characteristics by baseline frailty and depression status in 2011

Independent Effects of Frailty and Depression on Cognitive Decline

After adjusting for baseline cognition, age, sex, education, marital status, and BMI (Table 2): the interaction between time and frailty was significantly associated with accelerated cognitive decline (β = −0.085 per year, 95% CI −0.140 to −0.030, P = 0.003), indicating that individuals with frailty experienced an additional annual cognitive decline of 0.085 points compared to non-frail individuals (approximately 0.34 points over 4 years). The interaction between time and time-varying depression showed a consistent but non-significant trend (β = −0.025 per year, 95% CI −0.080 to 0.030, P = 0.369); the main effect of time was −0.092 per year (95% CI −0.124 to −0.060, P < 0.001). Time-varying depression was significantly negatively correlated with total cognitive score (β = −0.511, P < 0.001), indicating lower overall cognitive levels among depressed individuals. Each additional year of age was associated with a 0.018-point decline in cognition; higher education level (middle school: β = 0.671; high school or above: β = 1.257, both P < 0.001) and being married (β = 0.186, P = 0.016) were protective factors. The direction and magnitude of effects of each variable on cognitive performance are shown in Figure 2. The 95% confidence interval for the time × frailty interaction lies entirely to the left of the null line (β = −0.085, 95% CI −0.140 to −0.030),

suggesting that frailty independently and significantly accelerates cognitive decline. The confidence interval for the time × time-varying depression interaction crosses the null line (β = −0.025, 95% CI −0.080 to 0.030), indicating a consistent but non-significant effect of depression on the rate of decline. The confidence interval for the main effect of time-varying depression is far from the null line (β = −0.511, 95% CI −0.638 to −0.384), indicating that depression significantly reduces cognitive levels. These findings are consistent with the results presented in Table 2.

Variable	β	SE	t	P value	95% CI
Intercept	5.451	0.261	20.85	<0.001	(4.939, 5.964)
Time (per year)	−0.092	0.017	−5.59	<0.001	(−0.124, −0.060)
Frailty	0.001	0.069	0.02	0.983	(−0.133, 0.136)
Time-varying depression	−0.511	0.065	−7.90	<0.001	(−0.638, −0.384)
Baseline cognition	0.672	0.005	123.48	<0.001	(0.661, 0.683)
Age	−0.018	0.003	−6.23	<0.001	(−0.024, −0.012)
Female (ref. male)	0.130	0.044	2.93	0.003	(0.043, 0.217)
Education: junior high school (ref. primary school or below)	0.671	0.060	11.16	<0.001	(0.553, 0.789)
Education: senior high school or above	1.257	0.058	21.76	<0.001	(1.144, 1.370)
Married	0.186	0.077	2.40	0.016	(0.034, 0.338)
BMI	0.015	0.006	2.67	0.007	(0.004, 0.026)
Time × frailty	−0.085	0.028	−3.02	**0.003**	(−0.140, −0.030)
Time × time-varying depression	−0.025	0.028	−0.90	0.369	(−0.080, 0.030)

Table 2 Longitudinal model coefficient estimates. Note: GLS model, IPW weighting, adjusted for baseline cognition, age, sex, education, marital status, and BMI; time unit is every 2 years (2011→2013→2015).

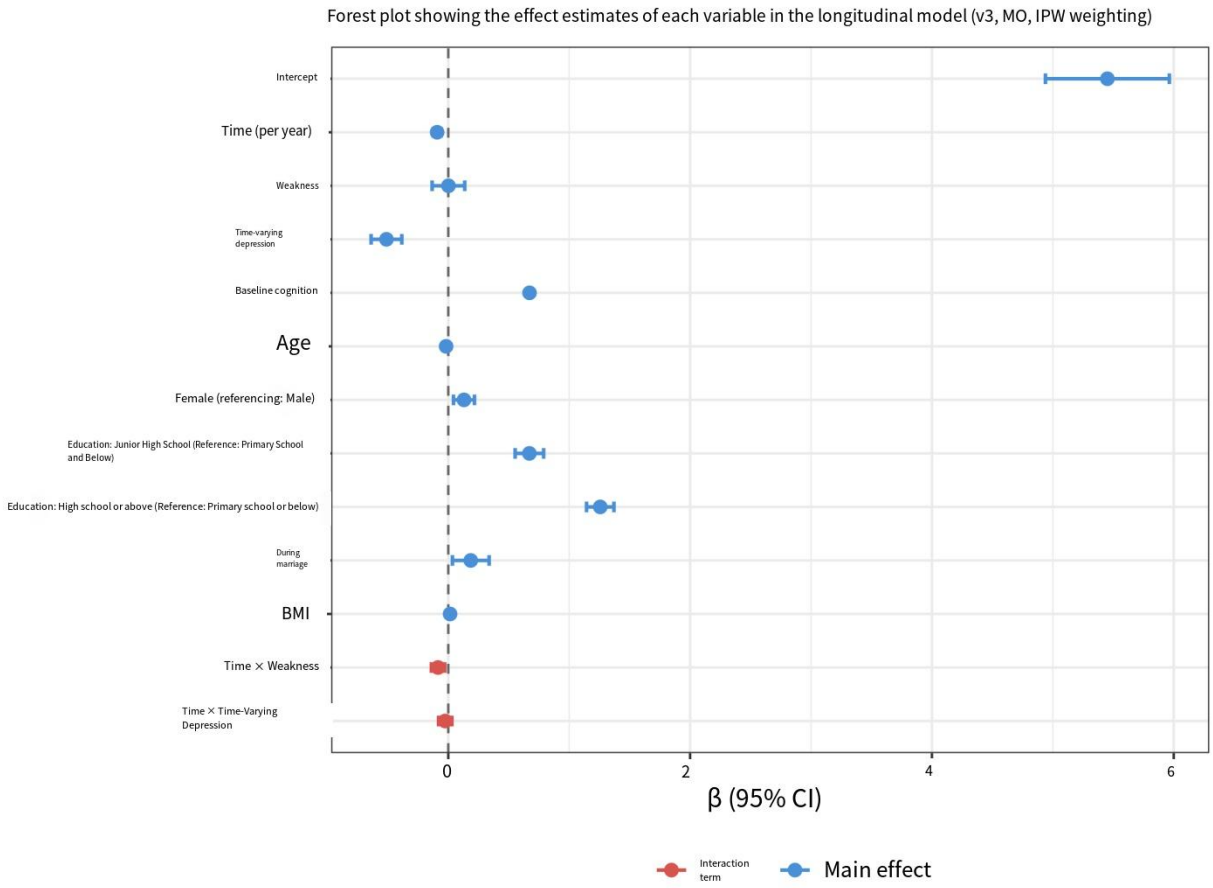


Figure 2 Forest plot of estimated effects for variables in the longitudinal model (M0, IPW weighted)

Independent additive test

In the full interaction model, the three-way interaction term for time × frailty × depression had a coefficient $\beta = -0.026$ ($P = 0.665$); the likelihood ratio test between M0 and M1 indicated that the three-way interaction was not significant (LRT $P = 0.174 > 0.05$). Considering the time × frailty ($P = 0.003$) and time × time-varying depression interactions (with consistent direction), no evidence of multiplicative interaction was found, supporting an independent additive relationship between frailty and depression on cognitive decline.

Four cognitive trajectories

The four annual average cognitive decline rates calculated based on the M1 group combination (Table 3, Figure 2) were as follows: non-frail without depression −0.094 points/year (cumulative

over 4 years: −0.38 points), frail without depression −0.173 points/year (−0.69 points), non-frail with depression −0.109 points/year (−0.44 points), and frail with depression −0.214 points/year (cumulative over 4 years: −0.86 points), approximately 2.3 times higher than the non-frail without depression group. Frailty alone contributed an additional acceleration of about 0.079 points/year, while depression alone added approximately 0.015 points/year (not significant). When both conditions coexisted, the combined additional acceleration was about 0.120 points/year, consistent with the expectation of additive effects (Figure 3).

Group	Annual average change (per year)	Every two years (Points)	Cumulative change over 4 years (Points, 2011–2015)
Non-frail + No depression	−0.094	−0.19	−0.38
Frailty + No Depression	−0.173	−0.35	−0.69
Non-frail + with depression	−0.109	−0.22	−0.44
Frailty + depression	**−0.214**	**−0.43**	**−0.86**

Table 3. Four groups of cognitive change slopes (M1 coefficient combinations). Note: Negative values indicate cognitive decline; annual average change equals the model slope β (time unit in years); change every 2 years = 2β; cumulative change over 4 years = 4β.

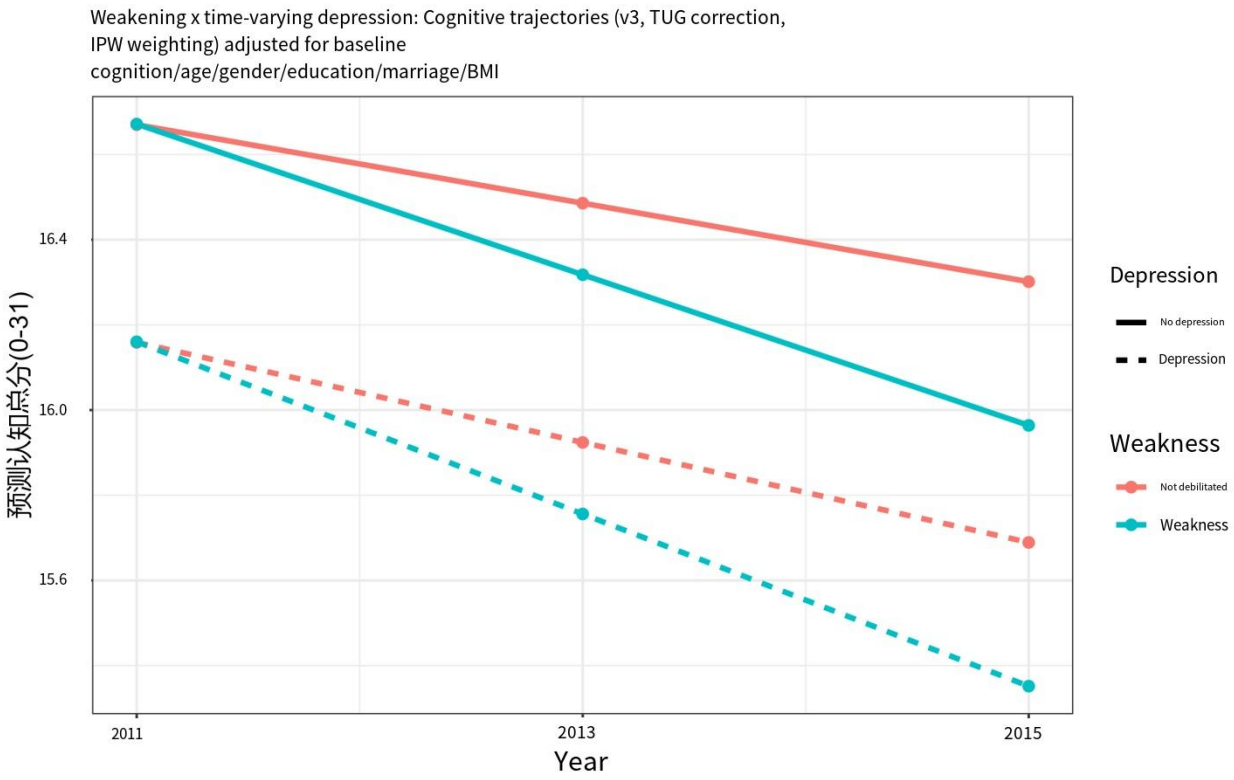


Figure 3 Cognitive trajectories across four groups of frailty and depression (v3, IPW weighted)

Sensitivity analysis

Sensitivity analysis results are shown in Table 4. Excluding only clearly abnormal codes (sensitivity A): time × frailty β = −0.085 (P = 0.002), time × time-varying depression β = −0.025 (P = 0.366), three-way interaction P = 0.177; conclusions remain unchanged. Excluding TUG components (sensitivity B, 6,687 observations, 3,485 individuals): time × frailty β = −0.140 (P = 0.032), with a stronger effect; time × time-varying depression β = −0.060, consistent in direction but not significant (P = 0.188); three-way interaction P = 0.303, and the conclusion of independent additive effects remains unaffected.

Analysis Scope	**time_frailty**	**time_dep_t**	**Third-order interaction p_ML**	**Conclusion**
Main Analysis (Thesis Scope)	−0.085 (p=0.003)	−0.025 (p=0.369)	0.174	Independent superposition is established
Sensitivity A:	−0.085	−0.025	0.177	Independent addition holds

Analysis Scope	time_frailty	time_dep_t	Third-order interaction p_ML	Conclusion
Only clear > 100 error codes	(p=0.002)	(p=0.366)		(robust)
Sensitivity B: Exclude TUG component	−0.140 (p=0.032)	−0.060 (p=0.188)	0.303	Frailty was significantly associated; depression showed a consistent but non-significant trend.

Table 4. Sensitivity analysis results. Note: Sensitivity A excludes only clearly abnormal codes for grip strength, gait speed, and blood pressure >100; Sensitivity B removes the TUG component and defines frailty solely by impaired grip strength and gait speed (only participants with both measures included, resulting in a smaller sample); p for three-way interaction is the p-value from the maximum likelihood likelihood ratio test.

Discussion

This study systematically evaluated the independent and combined effects of physical fra ilty and depressive symptoms on cognitive decline among middle-aged and older adults in Ch ina, using three waves of prospective cohort data from the China Health and Retirement Lon gitudinal Study (CHARLS) between 2011 and 2015 [25], within a framework that accounts f or time-varying exposures and inverse probability weighting to correct for attrition bias [27][2 8]. Three main findings emerged: first, frailty independently and significantly accelerates cog nitive decline, with frail individuals experiencing an additional annual decline of approximatel y 0.085 points in cognitive scores compared to non-frail individuals [26]; second, time-varyin g depression showed a significant negative correlation with total cognitive scores, indicating l ower overall cognitive levels among depressed individuals, although its additional effect on th e rate of cognitive decline was consistent in direction but not statistically significant; third, th e three-way interaction term was not significant, supporting an additive rather than multiplicat ive interaction between frailty and depression—individuals with both conditions experienced t he fastest cognitive decline [29][30], with a cumulative decline of about 0.86 points over four years, roughly 2.3 times greater than that observed in the non-frail, non-depressed group. Th ese results were generally robust across sensitivity analyses, including exclusion of abnormal coding and removal of the TUG component. Prior studies have mostly examined the relations hip between frailty or depression and cognitive function separately, or predicted outcomes bas ed solely on baseline exposure, with few assessing their joint effects while accounting for tim e-varying exposures [32][34]. Other studies based on CHARLS data from 2011 to 2018 also reported that depressive symptoms increase the risk of rapid cognitive decline among frail ind ividuals [33][31]. Building on these findings, this study further utilized longitudinal data from three waves, incorporating time-varying frailty and depression exposures, and employed likel

ihood ratio tests comparing additive and full interaction models to distinguish between additive and multiplicative interactions. The results support an additive model. This finding aligns with the broader framework of the Lancet Commission on Dementia Prevention, Intervention, and Care, which identifies frailty and depression as modifiable risk factors, and provides stronger epidemiological evidence for "joint screening and joint intervention" [36][38]. Notably, the interaction term between time and time-varying depression was not statistically significant, whereas the main effect of time-varying depression remained significantly negative [37]. This suggests that depression may primarily be associated with lower overall cognitive levels rather than a significant change in the slope of cognitive decline during the four-year follow-up period [39][40]. Possible reasons include relatively short follow-up duration, limited magnitude of cognitive changes, the use of self-reported CES-D-10 scale with fluctuating symptom levels over time, and insufficient statistical power [41][42]. Additionally, the impact of depression on the rate of cognitive decline might only become fully apparent after a longer latency period. Therefore, the contribution of depression in the joint effect should not be dismissed lightly. In this study, the group combining frailty and depression exhibited the fastest cognitive decline, and the additional decline matched expectations under an additive model, confirming that depression remains a significant contributing factor in the joint risk profile.

Frailty and depression are highly comorbid clinically and share multiple pathophysiological mechanisms. [43] Chronic low-grade inflammation, hypothalamic-pituitary-adrenal axis dysregulation, vascular endothelial dysfunction, neuroendocrine disturbances, white matter lesions, and hippocampal atrophy may all contribute simultaneously to the development of both frailty and depression, further accelerating cognitive decline. Frailty reflects diminished physiological reserves across multiple systems and reduced stress resilience, [45][46] leading to inadequate cerebral perfusion, neuroinflammation, and neurodegenerative changes; [44] depression, on the other hand, may impair brain regions involved in cognition through elevated cortisol levels, reduced neurotrophic factors, and imbalances in monoaminergic systems. [48][49] When co-occurring, multi-system damage may accumulate, thereby hastening cognitive decline. This study did not detect a significant multiplicative interaction, suggesting that the combined effect of frailty and depression on cognitive decline follows a pattern more consistent with independent additive effects. This could imply that the two conditions act through partially independent or partially overlapping pathways, [47] without reaching the level of biological synergy; alternatively, it may be due to limitations in follow-up duration, measurement error, and statistical power, leaving room for long-term synergistic effects. Future research incorporating inflammatory biomarkers, neuroimaging, and genetic susceptibility may help further elucidate the underlying mechanistic pathways behind this additive pattern[35].

From a preventive standpoint, clarifying that frailty and depression have independent additive effects has direct implications. [50] If the two conditions interact multiplicatively, intervention efforts should focus on high-risk subgroups; if they are independently additive, combined screening and simultaneous interventions could yield cumulative benefits. The findings of this study support the latter: in middle-aged and older populations, jointly assessing physical frailty and depressive symptoms, identifying individuals at high risk for both, and implementing integrated interventions may be more effective than targeting either condition alone in delaying cognitive decline. Specifically, primary healthcare services could incorporate simple tools such as grip strength, gait speed, chair stand test, and CES-D-10 into elderly health management to identify and closely monitor individuals with coexisting frailty and depression. Interventions might include resistance training, aerobic exercise, nutritional support, chronic disease management, psychotherapy, and, when necessary, antidepressant medication, complemented by cognitive training and social support. Given that both frailty and depression are identifiable and amenable to intervention, integrating them into primary prevention strategies for dementia holds strong feasibility and significant public health value. [52][53]

The strengths of this study include: three-wave prospective cohort data from a nationally representative sample of middle-aged and older adults; the use of time-varying frailty and time-varying depression exposure, which more closely reflects real-world exposure trajectories; [51] construction of a composite frailty variable using objective physical function measures; adjustment for loss-to-follow-up selection bias using inverse probability weighting (IPW); assessment of independent additive effects and multiplicative interactions through additive models and full interaction models; and multiple sensitivity analyses to verify the robustness of the findings.

This study also has several limitations. [54][55]First, the follow-up period was four years, during which cognitive changes were relatively small, potentially underestimating long-term effects; the impact of depression on the rate of cognitive decline may also have been insufficiently captured due to inadequate follow-up duration. Second, cognitive function was assessed using a 31-point composite score that covers orientation, calculation, drawing, and word recall, but it has limited sensitivity to early subtle cognitive changes and may be influenced by factors such as education and culture. Third, frailty was defined based solely on three physical performance measures—grip strength, gait speed, and TUG test—excluding components from the Fried phenotype such as weight loss, fatigue, and low physical activity, which may result

in an incomplete assessment of frailty. Fourth, depression was measured using the CES-D-10 self-report scale, which cannot replace clinical diagnosis and may be affected by transient emotional fluctuations due to its time-varying nature. Fifth, observational studies are inherently limited in controlling for residual confounding; unadjusted potential factors such as antidepressant use, APOE genotype, inflammatory markers, and comorbidity severity require cautious interpretation when making causal inferences. Sixth, although inverse probability weighting (IPW) was used to adjust for attrition, sample exclusions and dropouts could still introduce selection bias. Seventh, frailty and depression may have a bidirectional relationship, and cognitive decline might also influence frailty and depression in return; future research should employ more sophisticated causal inference methods to verify these associations.

In summary, this study demonstrates that physical frailty and depressive symptoms have independent additive effects on cognitive decline in middle-aged and older adults in China, with the fastest cognitive decline observed among individuals experiencing both conditions. This finding suggests that in the early identification and intervention of individuals at high risk for dementia, both frailty and depression should be addressed simultaneously rather than focusing on a single factor alone. Future research could extend follow-up periods, incorporate more objective biological and neuroimaging markers, and conduct randomized controlled trials of combined interventions to further evaluate whether addressing both frailty and depression together can more effectively delay cognitive decline, thereby providing higher-quality evidence for primary prevention of dementia.

Conflict of interest

The author states that there is no competing economic interest.

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Data Availability Statement

Support this conclusion the raw data can be publicly available in the repository: from the original queue CHARLS (https://charls.pku.edu.cn/). The processed dataset (including a subset of the CHARLS data used for statistical analysis) and the analysis code will be provided by the corresponding author (Kai Wang) at reasonable request without any reservation.

Availability of data and materials

China health and retirement longitudinal study (CHARLS) data from Beijing university open data platform (https://opendata.pku.edu.cn/CHARLS, study number 2025-042).

Ethical approval and participation consent

Studies involving human subjects are approved by the following institutional ethics committees:

CHARLS: Peking University Institutional Review Board (IRB00001052-11015);

All studies were conducted in accordance with local legislation, institutional requirements and the principles of the Declaration of Helsinki. All subjects provided written informed con sent at the time of enrollment.

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