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Original Article

Living arrangements and cognitive resilience in aging: unraveling distinct pathways through plasma biomarkers

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ABSTRACT

Background: Global aging and changing family structures necessitate identifying modifiable factors for cognitive health. While social isolation is a known risk, the protective role of specific living arrangements and their interplay with neurobiology is unclear.
Objectives: This study aimed to: (1) examine the longitudinal association between living arrangements and cognitive function in older adults, and (2) investigate the potential moderating roles of plasma Alzheimer's disease (AD) biomarkers in this relationship.
Methods: Using data from the Hubei Memory and Aging Cohort Study, we followed 3403 older adults aged 65 years and above with different living arrangements. Participants underwent standardized cognitive assessments and plasma biomarker measurements, including amyloid-beta (Abeta) 40, Abeta 42, glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), phosphorylated tau (p-tau) 181, and p-tau 217. Linear mixed-effects models were employed to analyze cognitive trajectories.
Results: Compared to older adults living separately from their families, those in two specific living arrangements, living with a spouse only or in multigenerational living, demonstrated significantly better cognitive performance across multiple domains. These protective associations proved robust even after comprehensive adjustment for plasma AD biomarkers. Importantly, we found that higher plasma GFAP levels significantly attenuated the cognitive benefits conferred by favorable living arrangements. In a separate, distinct pathway, higher plasma Abeta40 levels were independently associated with better-preserved language function over time.
Conclusions: Favorable living arrangements may benefit cognitive health through pathways independent of typical AD pathology. Incorporating living arrangements and plasma biomarkers, particularly GFAP, could enhance risk assessment and targeted interventions for cognitive decline in older adults.

1. Introduction

The global number of dementia cases is surging, projected to rise from 57.4 million in 2019 to 152.8 million by 2050 [1]. This trend stems not only from increased human longevity but is also closely linked to social transformations such as declining fertility rates, accelerated

Abbreviations: AD, Alzheimer's disease; Abeta, Amyloid-beta; ANCOVA, analysis of covariance; CI, confidence interval; EDTA, ethylenediaminetetraacetic acid; GFAP, glial fibrillary acidic protein; GDS-15, 15-item Geriatric Depression Scale; HMACS, Hubei Memory and Aging Cohort Study; L-BFGS-B, Limited-memory Broyden–Fletcher–Goldfarb–Shanno algorithm with Box constraints; NfL, neurofilament light chain; p-tau, phosphorylated tau; SD, standard deviation.

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urbanization, and the dissolution of multigenerational family structures [2]. These changes have led to smaller average household sizes and heightened social isolation among older adults, resulting in a continuous rise in caregiving burden and mortality risk within the aging population [3]. In response to these escalating challenges, there is an urgent need to develop integrated policies that combine family support, dementia screening, and long-term care systems to mitigate the pressures arising from demographic shifts and social change.

Social isolation has been established as a significant predictor of cognitive decline and dementia risk [4]. Evidence indicated it promoted dementia onset and progression through several mechanisms: limited cognitive reserve accumulation, heightened chronic stress responses, systemic inflammation, and reduced engagement in health-promoting behaviors [5–7]. Within this framework, living arrangements serve as a key objective indicator of social isolation levels among older adults. Living alone not only exacerbated health vulnerability in older adults but also correlated with diminished social interaction and emotional support. This living arrangement typically involved multiple overlapping challenges, including financial pressures and inadequate care resources, particularly when family support is unavailable [8–10]. Contemporary social transformations, with young adults increasingly relocating for education or employment, have resulted in growing numbers of "left-behind" older adults. Consequently, more older individuals face living situations marked by solitude or family separation. As household sizes continue to shrink and solo-living rates rise among older populations [11–15], a thorough investigation into how living arrangements affect cognitive trajectories becomes crucial. Such research possesses substantial theoretical and practical importance for formulating targeted public health policies and proactive social support systems.

However, two major limitations existed in previous research. First, most studies oversimplified the classification of living arrangements among older adults by predominantly using a simple binary variable (living alone versus not living alone) for analysis [16,17]. This approach failed to capture potential differential cognitive effects across specific living arrangements, particularly between the increasingly common living with a spouse only pattern in East Asia and traditional multigeneration living, whose comparative cognitive implications remained inadequately explored. Second, researchers over-relied on global cognitive scores (e.g., the Mini-Mental State Examination or Preclinical Alzheimer Cognitive Composite) as primary outcome measures [18–21]. This comprehensive assessment approach could mask subtle trajectories of decline in specific cognitive domains, such as episodic memory, executive function, or information processing speed.

Beyond methodological limitations, core Alzheimer's disease (AD) biomarkers might play key mediating or moderating roles in the complex relationship between living arrangements and cognitive performance. Research on the amyloid-beta (Abeta) pathway indicated that psychosocial stressors could promote Abeta pathological deposition in the brain. Stressors such as bereavement or living alone were found to operate through multiple pathways, including unhealthy lifestyle habits, enhanced chronic psychological stress responses, and exacerbated financial strain [19,22,23]. These mechanisms collectively contributed to accelerated cognitive decline. Phosphorylated tau (p-tau) represents a key mechanistic candidate linking psychosocial stressors to AD pathology, as experimental studies indicate that chronic stress and social isolation can promote tau hyperphosphorylation and aggregation [24,25].

Meanwhile, glial fibrillary acidic protein (GFAP), a marker of neuroinflammation, might link peripheral stress signals to central amyloid burden through microglial activation mechanisms [26]. Neurofilament light chain (NfL), a sensitive indicator of axonal injury, could improve the detection of related pathologies such as sporadic cerebral amyloid angiopathy [27]. These AD biomarkers may play central roles in the relationship between living environment and cognitive performance. However, limited epidemiological evidence had yet to systematically clarify the complex interactions between household living arrangements characteristics and the multiple neuropathological processes underlying cognitive decline.

This longitudinal study investigated how living arrangements affect cognitive function in older adults and examined the potential involvement of plasma AD biomarkers in this relationship. By tracking older adults with different living arrangements and measuring plasma Abeta and other AD-related biomarkers, we examined how living arrangements influence cognitive health through multiple pathways. Initial analyses indicated that both living with a spouse only and multigeneration living showed protective effects across several cognitive domains compared to those living separately from family. Plasma GFAP levels also appeared to moderate the relationship between living arrangements and cognitive changes. These preliminary findings support further exploration of living-arrangement-based plasma biomarker profiling for assessing cognitive decline risk.

2. Materials and methods

2.1. Study design and participants

This study was conducted based on the Hubei Memory and Aging Cohort Study (HMACS), a community-based prospective study registered as ChiCTR1800019164. The cohort was launched in 2016 and completed baseline data collection in 2018. HMACS aimed to systematically investigate the dynamic relationships between aging, cognitive trajectories, and various social, familial, clinical, lifestyle, psychosocial, and environmental factors [28–36]. The overall design, assessment procedures, and baseline characteristics of the cohort have been previously detailed [37]. All participants underwent standardized on-site evaluations covering demographic characteristics, lifestyle factors, medical history, and a comprehensive neuropsychological test battery.

The inclusion criterion for this analysis was completion of at least one cognitive follow-up assessment. Exclusion criteria encompassed participants who had relocated, died, developed severe cognition-impairing illnesses, or had missing data on living arrangements or key cognitive measures. The final analytical sample comprised 3403 participants, among whom 649 had completed AD biomarker measurements at baseline. The study protocol received approval from the Ethics Committee of Wuhan University of Science and Technology (Approval No. 201,845). All participants provided written informed consent before enrollment.

2.2. Living arrangements assessment

Living arrangements information was collected through a baseline questionnaire. Participants selected their current living arrangements from five options: (1) living alone, (2) residing in a nursing institution, (3) living with friends or caregivers, (4) living with a spouse only, and (5) multigeneration living. Guided by evidence that social support from family is qualitatively distinct from non-kin support [38,39], and given the limited sample residing in nursing institutions or with friends/caregivers (n = 23, 0.6 % of the total sample), this study focuses on kinship-based co-residence. Therefore, living arrangements were consolidated into three mutually exclusive categories: living separately from family (encompassing living alone, in a nursing institution, or with friends/caregivers), living with a spouse only, and multigenerational living.

2.3. Plasma AD biomarkers assessment

EDTA-anticoagulated plasma samples were collected at baseline. The samples were aliquoted into polypropylene tubes, rapidly frozen, and stored at −80 °C in Wuhan University of Science and Technology. For analysis, the samples were transported on dry ice to Shanghai Kangli Medical Laboratory Co., Ltd. for batch testing. Plasma concentrations of

Abeta 40, Abeta 42, GFAP, NfL, p-tau181, and p-tau217 were quantified using the Simoa® HD-X Analyzer from Quanterix (Billerica, MA, USA). The following assay kits were employed: the Simoa® Neurology 4-Plex E Advantage Kit (Cat#: 103,670, Lot#: 503,940) for Abeta 40, Abeta 42, GFAP, and NfL; the Simoa® pTau-181 Advantage V2 Kit (Cat#: 103,714, Lot#: 503,732) for p-tau181; and the ALZpath Simoa® p-Tau 217 v2 Assay Kit (Cat#: 104,371, Lot#: MAB231122) for p-tau217.

2.4. Domain-specific cognitive assessment

All participants underwent standardized face-to-face cognitive assessments at both baseline and follow-up visits. These evaluations were administered by clinical neuropsychologists or systematically trained physicians. The assessment battery covered five core cognitive domains: (1) memory, assessed using the Auditory Verbal Learning Test; (2) language, evaluated with the Animal Verbal Fluency Test; (3) visuospatial function, measured by the Clock Drawing Test; (4) executive function, examined through the Trail Making Test Part B; and (5) attention, tested using the Digit Span Test. The raw scores from each cognitive domain were first converted to z-scores based on baseline population data. Subsequently, a global cognition z-score was derived by calculating the arithmetic mean of the five-domain z-scores. The detailed standardization procedures and computational methods are described in the supplementary material.

2.5. Covariates

All covariate data were collected at the baseline assessment. The covariates encompassed three categories: (1) Demographic characteristics: including age, sex (male/female), residence (urban/rural), and years of education; (2) Socioeconomic indicators: covering individual monthly income ($\leq$ 3000 RMB or $>$ 3000 RMB) and social network size (categorized as ≤ 2 or > 2 frequently contacted relatives/friends); (3) Mental health indicators: assessed using the 15-item Geriatric Depression Scale (GDS-15) score. Detailed assessment methods, operational definitions, and classification criteria for all covariates are provided in the methodology section of the supplementary material.

2.6. Statistical analysis

In the baseline analysis, continuous variables were presented as mean $\pm$ standard deviation. Group comparisons for these variables were performed using analysis of covariance (ANCOVA), followed by Bonferroni-adjusted post hoc tests based on estimated marginal means. Categorical variables were summarized as counts (percentages). Group differences were assessed using chi-square tests, with Bonferroni-adjusted pairwise z-tests applied for post hoc comparisons when necessary. Prior to regression analyses, missing data in covariates (0.2 %−12 % missing rate) were handled using multiple imputation to generate five complete datasets for subsequent analyses. All cognitive domain scores were standardized by conversion to z-scores. To better meet model assumptions of normality, the original concentrations of plasma Abeta40, Abeta42, GFAP, NfL, p-tau181, and p-tau217 underwent log10 transformation [40].

For the cross-sectional analysis, multiple linear regression models were employed to assess the association between living arrangements and cognitive functions at baseline. All analyses were adjusted for the covariates listed in Section 2.5.

For longitudinal analysis, linear mixed-effects models were employed. The fixed effects included baseline living arrangements, follow-up time, and their interaction term. Random effects incorporated subject-specific intercepts and slopes for follow-up time [19,41]. Model parameters were estimated using the maximum likelihood method. The optimization procedure was performed with the R function optim() using the Limited-memory Broyden–Fletcher–Goldfarb–Shanno algorithm with Box constraints (L-BFGS-B) algorithm. To explore potential heterogeneity, stratified analyses were conducted by sex and residence location.

In the subgroup with baseline plasma AD biomarker data, we conducted additional analyses using linear mixed-effects models. Each biomarker's baseline levels and its interaction with follow-up time were sequentially incorporated into the models. This model evaluated how living arrangements and time, both independently and interactively, affected cognitive function, with adjustment for biomarker main effects. To further investigate the complex relationships among living arrangements, biomarker levels, and time, we constructed additional models that included three-way interaction terms (living arrangements $\times$ biomarker $\times$ follow-up time). All models controlled for the interaction between baseline age and follow-up time to account for the potential influence of age on cognitive decline trajectories.

Sensitivity analyses were performed using complete-case data without imputing covariates. To directly compare the cognitive trajectories between living with a spouse only and multigeneration living, the reference group was switched to the living with a spouse only category in subsequent linear mixed-effects models. All statistical analyses were conducted using R software (version 4.4.1). Results were reported as β coefficients with 95 % confidence intervals (CI), and a p-value < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of participants

The study included 3403 participants with a mean age of 70.9 $\pm$ 5.43 years, 44.4 % of whom were male. Baseline demographic characteristics stratified by living arrangements are summarized in Table 1. Compared with the reference group (living separately from family, $n = 628$), both the living with a spouse only and multigeneration living groups exhibited more favorable baseline profiles. These included longer education duration, a higher proportion of urban residence, higher monthly income, larger social networks, and lower GDS-15 scores. Regarding cognitive functions, both the living with a spouse only and multigeneration living groups demonstrated higher global cognition and exhibited superior performance in specific domains, including language, attention, and memory (all $p < 0.001$).

3.2. Associations between living arrangements and cognitive subdomains

Covariate-adjusted multiple linear regression analyses revealed significant associations between living arrangements and baseline cognitive function. Compared with the reference group (living separately from family), the living with a spouse only group demonstrated superior language function ($\beta = 0.087$, 95 % CI: 0.004–0.169). The multigeneration living group showed higher functional levels across multiple cognitive domains, including global cognition ($\beta = 0.204$, 95 % CI: 0.105–0.304), language function ($\beta = 0.280$, 95 % CI: 0.175–0.384), and memory ($\beta = 0.141$, 95 % CI: 0.019–0.264). (Figure S1, supplementary material)

Covariate-adjusted linear mixed-effects models revealed that living arrangements significantly influenced cognitive trajectories during follow-up. Compared to the reference group (living separately from family), the living with a spouse only group demonstrated more favorable maintenance or improvement trends in multiple cognitive domains: global cognition ($\beta = 0.035$, 95 % CI: 0.012–0.058), attention ($\beta = 0.028$, 95 % CI: 0.004–0.051), language function ($\beta = 0.034$, 95 % CI: 0.009–0.058), and visuospatial function ($\beta = 0.039$, 95 % CI: 0.003–0.075) (Fig. 1). The multigeneration living group showed better preservation in attention ($\beta = 0.033$, 95 % CI: 0.005–0.061) and visuospatial function ($\beta = 0.081$, 95 % CI: 0.038–0.123) (Fig. 1). Additionally, older baseline age was significantly associated with faster cognitive decline. Specifically, each additional year of age was associated with an accelerated decline in cognitive z-scores of −0.005 for

Table 1
Basic characteristics of study participants.

	All (N = 3403)	Baseline living arrangements			p-Value[†]
		Living separately from family (N = 628)	Living with a spouse only (N = 2234)	Multigenerational living (N = 541)	
Demographic characteristics					
Age, years, mean (SD)	70.9 (5.43)	72.4 (5.99)	70.6 (5.13)	70.7 (5.68)	<0.001[ab]
Sex, male, n (%)	1511 (44.4 %)	266 (42.4 %)	1055 (47.2 %)	190 (35.1 %)	<0.05[abc]
Education, years, mean (SD)	6.66 (5.37)	4.02 (4.63)	7.49 (5.32)	6.29 (5.36)	<0.001[abc]
Residence, urban, n (%)	1605 (47.2 %)	126 (20.1 %)	1244 (55.7 %)	235 (43.4 %)	<0.001[abc]
Socioeconomic indicators					
Personal income levels, n (%)					<0.001[abc]
≤ 3000 CNY/month	2090 (61.4 %)	513 (81.7 %)	1226 (54.9 %)	351 (64.9 %)	
> 3000 CNY/month	1313 (38.6 %)	115 (18.3 %)	1008 (45.1 %)	190 (35.1 %)	
Social network size, n (%)					<0.001[ab]
≤ 2 friends	1549 (45.5 %)	384 (61.1 %)	926 (41.5 %)	239 (44.2 %)	
> 2 friends	1854 (54.5 %)	244 (38.9 %)	1308 (58.5 %)	302 (55.8 %)	
GDS-15, mean (SD)	1.38 (1.74)	1.64 (1.87)	1.27 (1.69)	1.49 (1.73)	<0.05[ac]
Baseline cognitive functions[*]					
Global cognition	0.02 (1.06)	−0.40 (1.01)	0.12 (1.03)	0.11 (1.12)	<0.001[ab]
Language	0.00 (1.02)	−0.39 (1.00)	0.07 (0.99)	0.14 (1.05)	<0.001[ab]
Attention	0.02 (0.97)	−0.25 (0.97)	0.09 (0.98)	0.08 (0.90)	<0.001[ab]
Executive function	0.18 (0.99)	0.32 (0.97)	0.14 (0.98)	0.18 (1.06)	0.012[a]
Visuospatial function	−0.15 (1.04)	−0.33 (1.06)	−0.06 (1.01)	−0.23 (1.08)	<0.05[ac]
Memory	−0.06 (0.96)	−0.28 (0.91)	−0.03 (0.93)	0.06 (1.05)	<0.001[ab]
Follow-up years, mean (SD)	2.69 (1.67)	2.65 (1.69)	2.71 (1.59)	2.65 (1.93)	0.652

Abbreviations: SD, standard deviation; GDS-15, the 15-item geriatric depression scale score.

[†] Welch and post hoc Games-Howell test were used to test the difference of continuous variables, while chi-square and post hoc z test (Bonferroni method for adjusting multiple comparisons) were adopted to compare the difference of categorical variables among participants of living separately from family, living with a spouse only, and multigenerational living. The superscripts a, b, and c indicated the significant difference of post hoc analyses between living separately from family and living with a spouse only (a), living separately from family and multigenerational living (b), and living with a spouse only and multigenerational living (c).

[*] The number of available data in six baseline cognitive functions was: global cognition (n = 3403), language (n = 3353), attention (n = 2265), executive function (n = 1323), visuospatial function (n = 1728), and memory (n = 1938).

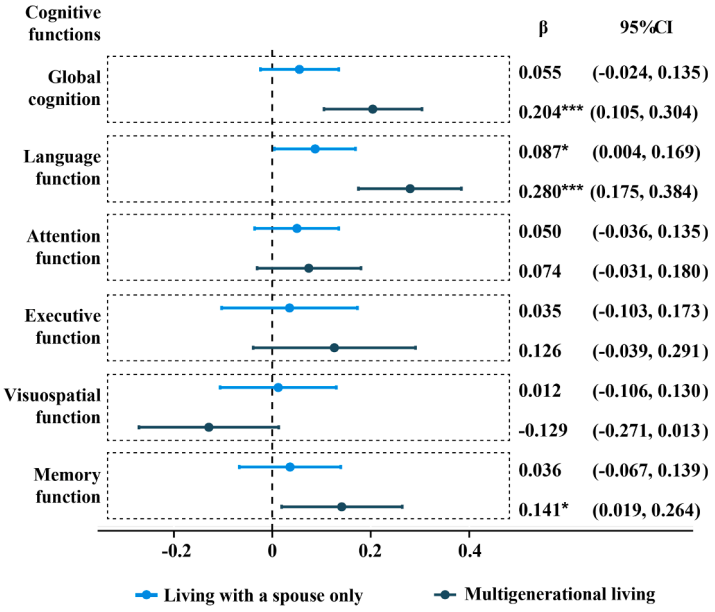

Fig. 1. Association of living arrangements with cognitive function change over time. The reference group was living separately from family × Time. The data were analyzed using a mixed linear model. Domain-specific cognition was standardized using population-normative z-scores. All models were adjusted for age, sex, residence (urban/rural), years of education, income levels, social network size, and the 15-item geriatric depression scale score.

global cognition (95 % CI: −0.007 to −0.003), −0.005 for language function (95 % CI: −0.007 to −0.003), −0.002 for visuospatial function (95 % CI: −0.004 to 0.000), and −0.006 for memory (95 % CI: −0.008 to −0.003) (Table S1, supplementary material).

3.3. Stratified analysis

Stratified analyses by sex and residence were conducted using linear mixed-effects models to examine associations between living arrangements and longitudinal cognitive function, with results presented in Fig. 2. Among males, main effect analyses showed that compared with the reference group (living separately from family), the living with a spouse only group demonstrated significantly better language function (β = 0.174, 95 % CI: 0.055–0.292). The multigeneration living group exhibited higher levels across multiple cognitive domains, including global cognition (β = 0.241, 95 % CI: 0.111–0.370), attention (β =

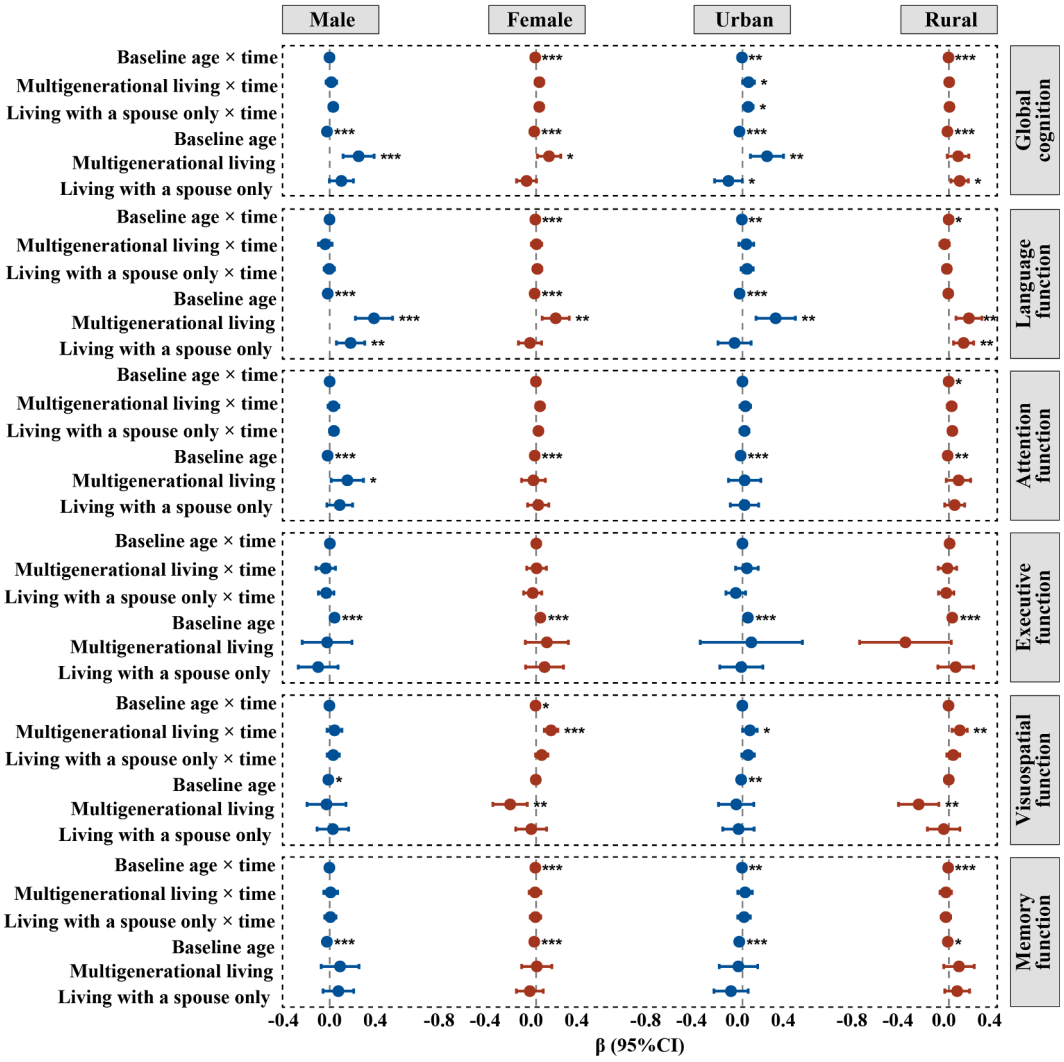

Fig. 2. Association of living arrangements with longitudinal cognitive functions in stratified analysis by sex and residence. Abbreviations: CI, confidence interval. The reference group was living separately from family (× Time). The data were analyzed using a mixed linear model. Domain-specific cognition was standardized using population-normative z-scores. All models were adjusted for, sex, residence (urban/rural), years of education, income levels, social network size, and the 15-item geriatric depression scale score. "*" means $p < 0.05$, "**" means $p < 0.01$, "***" means $p < 0.001$.

0.174, 95 % CI: 0.012–0.282), and language function (β = 0.365, 95 % CI: 0.214–0.525). However, no statistically significant interactions between living arrangements and time were observed in males. Among females, main effect analyses indicated that the multigeneration living group showed significant advantages in global cognition (β = 0.107, 95 % CI: 0.010–0.205) and language function (β = 0.163, 95 % CI: 0.050–0.276) compared with the reference group. Furthermore, the interaction between multigeneration living and follow-up time revealed a significant improving trend in visuospatial function among females (β = 0.124, 95 % CI: 0.067–0.181).

Among urban residents, longitudinal analyses revealed that compared with the reference group (living separately from family), the living with a spouse only group showed an improving trend in global cognition (β = 0.035, 95 % CI: 0.012–0.058). The multigeneration living group also demonstrated positive trends in global cognition (β = 0.050, 95 % CI: 0.000–0.100) and visuospatial function (β = 0.061, 95 % CI: 0.000–0.122), although the lower confidence limits approaching zero suggested limited strength of these associations. Among rural residents, the multigeneration living group showed a similar positive trend in visuospatial function (β = 0.061, 95 % CI: 0.000–0.122). The lower confidence limit similarly approached zero, indicating this association was at the boundary of statistical significance.

3.4. To explore the regulatory role of plasma AD biomarkers between living arrangements and cognitive functions

Figure S2 (supplementary material) shows the plasma AD biomarker profiles of participants across different baseline living arrangements groups. Compared with the reference group (living separately from family), both the living with a spouse only and multigeneration living groups had significantly lower plasma Abeta40 and Abeta42 concentrations (all $p < 0.05$). In linear mixed-effects models that further incorporated baseline AD biomarkers and their interactions with follow-up time, the multigeneration living group maintained significantly improved trends in global cognition and language function ($p < 0.001$). After additional adjustment for baseline plasma p-tau217 levels, this group also showed significant improvement in visuospatial function (β = 0.148, 95 % CI: 0.024–0.272). Furthermore, the interaction between higher Abeta40 levels (compared to lower levels) and follow-up time was positively associated with language function during follow-up (β = 0.136, 95 % CI: 0.046–0.225). This Abeta40-by-time interaction, illustrating the differential cognitive trajectories between Abeta40 low and high groups, is specifically visualized in Figure S3 (supplementary material). The overall trends from the longitudinal models are summarized in Fig. 3.

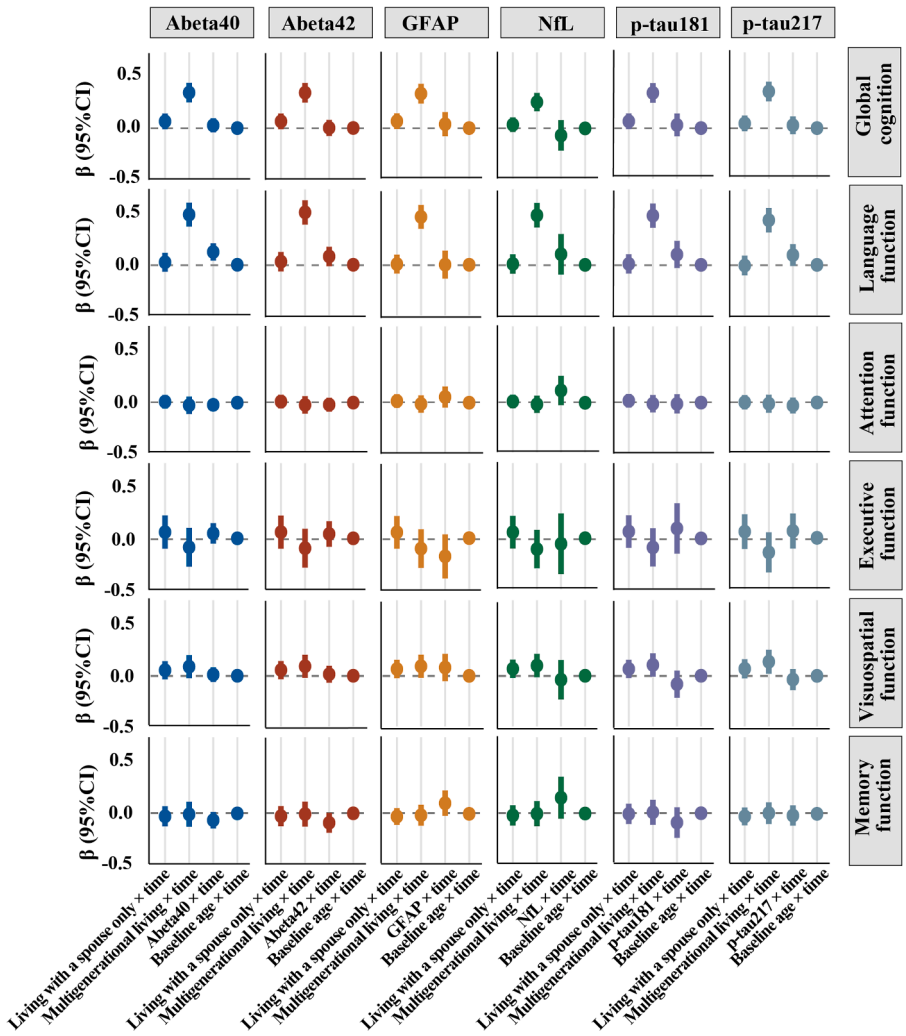

Fig. 3. Association of living arrangements with longitudinal cognitive functions after adjusting plasma Abeta40, Abeta42, GFAP, NfL, p-tau181, and p-tau217 in turn. Abbreviations: CI, confidence interval; Abeta, amyloid-beta; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; p-tau, phosphorylated tau. The reference group was living separately from family × Time. The data were analyzed using a mixed linear model. Domain-specific cognition was standardized using population-normative z-scores. All models were adjusted for sex, residence (urban/rural), years of education, income levels, social network size, and the 15-item geriatric depression scale score.

To further investigate the potential moderating role of baseline plasma AD biomarkers in the relationship between living arrangements and cognitive function, we constructed linear mixed-effects models incorporating three-way interaction terms (living arrangements × biomarker × follow-up time). These models examined whether biomarkers moderated the association between living arrangements and cognitive trajectories. The analyses revealed that GFAP levels significantly moderated the association between living arrangements and cognitive changes, as multigeneration living participants with high baseline GFAP showed accelerated decline in global cognition (β = −0.534, 95 % CI: −0.863 to −0.205), language (β = −0.499, 95 % CI: −0.896 to −0.102), and attention (β = −0.376, 95 % CI: −0.666 to −0.086) compared to the reference group (low GFAP and living separately from family). A similar moderating pattern was observed in the living with a spouse only group. Higher GFAP levels also demonstrated a significant negative moderating effect on language function decline in this group (β = −0.445, 95 % CI: −0.803 to −0.087). These findings suggest that GFAP, as a key neuroinflammation marker, may diminish the cognitive protection associated with specific living arrangements. In contrast, none of the other plasma AD biomarkers, including Abeta40, Abeta42, NfL, p-tau181, and p-tau217, showed statistically significant moderating effects in comparable models (Table 2).

The reference group was living separately from family × AD biomarker × Time. The data were analyzed using a mixed linear model. Domain-specific cognition was standardized using population-normative z-scores. All models were adjusted for, sex, residence (urban/rural), years of education, income levels, social network size, and the 15-item geriatric depression scale score. "*" means $p < 0.05$, "**" means $p < 0.01$, "***" means $p < 0.001$.

3.5. Sensitivity analysis

Sensitivity analyses based on the unimputed dataset confirmed the robustness of our primary findings (Table S2, supplementary material). In the complete-case dataset, both the living with a spouse only and multigeneration living groups demonstrated consistent improvement trends in global cognition, attention, and visuospatial function compared to the reference group (living separately from family). To further compare cognitive trajectories between different living arrangements, we redefined the reference group as living with a spouse only in additional linear mixed-effects models (Table S3, supplementary material). The results showed that compared to living with a spouse only, the multigeneration living group exhibited a more pronounced improvement in visuospatial function (β = 0.037, 95 % CI:

Table 2
Association of the interaction of living arrangements and AD biomarkers with longitudinal cognitive functions.

Interaction items	β Estimate (95 % CI)		
Living with a spouse only (living arrangements 2, LA2)			
	Global cognition	Language function	Attention function
LA2 × Abeta40 × Time	−0.026 (−0.21, 0.158)	0.077 (−0.16, 0.314)	−0.031 (−0.189, 0.128)
LA2 × Abeta42 × Time	−0.028 (−0.237, 0.18)	−0.023 (−0.285, 0.24)	0.025 (−0.155, 0.205)
LA2 × GFAP × Time	−0.063 (−0.357, 0.23)	−0.445 (−0.803, −0.087)*	−0.084 (−0.342, 0.175)
LA2 × NfL × Time	0.042 (−0.355, 0.438)	0.145 (−0.06, 0.351)	0.019 (−0.169, 0.207)
LA2 × *p*-tau181 × Time	−0.025 (−0.277, 0.226)	−0.163 (−0.471, 0.144)	0.102 (−0.112, 0.317)
LA2 × *p*-tau217 × Time	0.068 (−0.125, 0.261)	0.048 (−0.15, 0.246)	0.098 (−0.092, 0.289)
LA2 × Abeta40 × Time	−0.026 (−0.21, 0.158)	0.077 (−0.16, 0.314)	−0.031 (−0.189, 0.128)
	Executive function	Visuospatial function	Memory function
LA2 × Abeta40 × Time	−0.054 (−0.388, 0.28)	−0.049 (−0.247, 0.15)	−0.126 (−0.35, 0.097)
LA2 × Abeta42 × Time	−0.185 (−0.569, 0.2)	0.049 (−0.181, 0.279)	−0.114 (−0.376, 0.147)
LA2 × GFAP × Time	0.263 (−0.538, 1.063)	0.042 (−0.337, 0.422)	0.163 (−0.226, 0.552)
LA2 × NfL × Time	−0.09 (−0.391, 0.211)	0.07 (−0.142, 0.282)	0.222 (−0.039, 0.483)
LA2 × *p*-tau181 × Time	0.231 (−0.473, 0.935)	−0.036 (−0.35, 0.278)	−0.14 (−0.482, 0.203)
LA2 × *p*-tau217 × Time	−0.006 (−0.486, 0.473)	−0.051 (−0.304, 0.202)	−0.18 (−0.419, 0.059)
LA2 × Abeta40 × Time	−0.054 (−0.388, 0.28)	−0.049 (−0.247, 0.15)	−0.126 (−0.35, 0.097)
Multigenerational living (living arrangements 3, LA3)			
	Global cognition	Language function	Attention function
LA3 × Abeta40 × Time	0.002 (−0.218, 0.222)	0.071 (−0.209, 0.351)	−0.076 (−0.267, 0.115)
LA3 × Abeta42 × Time	0.023 (−0.214, 0.26)	−0.04 (−0.333, 0.253)	−0.043 (−0.246, 0.16)
LA3 × GFAP × Time	−0.534 (−0.863, −0.205)**	−0.499 (−0.896, −0.102)*	−0.376 (−0.666, −0.086)*
LA3 × NfL × Time	0.2 (−0.273, 0.672)	−0.137 (−0.706, 0.432)	−0.02 (−0.44, 0.401)
LA3 × *p*-tau181 × Time	0.291 (−0.076, 0.657)	0.334 (−0.112, 0.78)	−0.076 (−0.399, 0.246)
LA3 × *p*-tau217 × Time	0.148 (−0.119, 0.415)	0.086 (−0.196, 0.368)	0.067 (−0.192, 0.326)
	Executive function	Visuospatial function	Memory function
LA3 × Abeta40 × Time	−0.005 (−0.387, 0.377)	−0.031 (−0.279, 0.218)	0.029 (−0.247, 0.305)
LA3 × Abeta42 × Time	−0.009 (−0.447, 0.43)	0.045 (−0.235, 0.325)	0.041 (−0.269, 0.351)
LA3 × GFAP × Time	0.155 (−0.665, 0.974)	−0.084 (−0.481, 0.313)	−0.09 (−0.508, 0.328)
LA3 × NfL × Time	−0.284 (−1.449, 0.882)	0.097 (−0.485, 0.68)	−0.052 (−0.683, 0.579)
LA3 × *p*-tau181 × Time	0.903 (−0.029, 1.834)	−0.183 (−0.672, 0.305)	−0.132 (−0.648, 0.384)
LA3 × *p*-tau217 × Time	0.004 (−0.646, 0.654)	0.015 (−0.37, 0.4)	0.072 (−0.26, 0.404)

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; Abeta, amyloid-beta; GFAP, glial fibrillary acidic protein; NfL neurofilament light chain; p-tau, phosphorylated tau.

0.004–0.071), which may suggest a relative advantage of multigeneration living in specific cognitive domains.

4. Discussion

This community-based longitudinal study of older adults demonstrated that living with a spouse or in multigenerational households may confer positive effects on cognitive health. Importantly, while the association with multigenerational living remained significant after adjusting for baseline AD biomarkers, we cannot fully rule out residual confounding from unmeasured pathology. Notably, neuroinflammatory processes reflected by higher GFAP levels potentially attenuated these protective effects. These findings suggested that screening for plasma AD biomarkers, particularly GFAP, among older adults with disadvantaged living arrangements could help identify individuals at high risk for cognitive decline and guide targeted interventions.

This study's primary innovation was its integrated analysis of longitudinal data on living arrangements, plasma AD biomarkers, and specific cognitive domains. This multidimensional framework expanded current research approaches in the field. After adjusting for demographic characteristics and multiple AD biomarkers, the multigeneration living group maintained significantly improved trajectories in both global cognition and language function. These findings suggested this living arrangement's protective effects might operate independently of typical AD pathology. Regular social engagement and varied daily activities may provide neuroprotection through sustained cognitive activation and enhanced cognitive reserve [17,42,43]. Even after adjusting for demographic characteristics and multiple AD biomarkers, the statistically significant association between multigenerational living and cognitive outcomes should be interpreted with caution. The groups exhibiting this protective pattern were generally younger, more educated, more likely to reside in urban areas, wealthier, and had lower cognitive function at baseline. Furthermore, the limitation of relying on a single time point for biomarker assessment means we cannot fully rule out the possibility that the observed protective effect is partly driven by background AD pathology. Future studies incorporating repeated biomarker measurements are needed to definitively disentangle the temporal dynamics between the social environment, AD pathology, and cognitive decline. We also found that the interaction between baseline plasma Abeta40 levels and follow-up time positively correlated with language function. This aligns with the view that plasma Abeta40 concentrations may reflect brain-to-periphery Abeta clearance efficiency [44–46]. Higher plasma Abeta40 levels could indicate better clearance pathway function, supporting its potential dual roles across different disease stages.

Further analyses examined whether plasma AD biomarkers moderated the relationship between living arrangements and cognition. Higher GFAP levels were consistently associated with accelerated cognitive decline in both the living with a spouse only and multigeneration living groups, suggesting that neuroinflammation may undermine the protective cognitive effects of favorable living environments [47]. This offers a pathophysiological basis for varying cognitive trajectories among individuals with similar living arrangements. Notably, GFAP demonstrated specificity in this moderating role, which may stem from its sensitivity to astrocyte activation and neuroinflammatory responses to environmental stressors via neuroimmune

pathways [48]. In contrast, Abeta and tau primarily track AD-specific pathology accumulation, whose interactions with environmental factors appear more indirect or require extended observation to detect. The associated mechanistic hypothesis was depicted in Figure S4. Future larger-scale studies should validate these biomarker-specific roles. Our findings highlight the importance of considering neuroinflammatory arrangements when assessing how living environments affect cognitive health. Biomarker-guided approaches could improve targeted prevention for at-risk older adults.

Compared with the reference group (living separately from family), both living with a spouse only and multigeneration living groups demonstrated significant improvements in global cognition, language, and attention. These results not only confirmed the protective effect of favorable living environments on cognitive function but also suggested heterogeneous responses across cognitive domains to different living arrangements. This heterogeneity might stem from distinct neural circuit dependencies and domain-specific decline trajectories [49]. Additionally, older age was significantly associated with faster decline rates across all cognitive domains. This finding further supported the pathophysiological hypothesis that accumulated vascular pathologies and neuroinflammation jointly promote cognitive aging [50–52].

In the sex-stratified analyses, although male participants demonstrated cognition-related advantages associated with living arrangements at baseline, these benefits did not show significant changes over the follow-up period. This pattern contrasted markedly with the cognitive trajectories observed in females. Male cognitive function appeared to be more strongly influenced by early-life cumulative factors such as career experiences and social arrangements [53,54], with current living arrangements exerting relatively limited moderating effects. In contrast, females demonstrated greater adaptability in social relationships [55] and were able to continuously obtain cognitive support through family interactions. These gendered patterns are consistent with prior literature suggesting that women's cognitive resilience may be sustained through broader social networks, even when marital status alone shows a stronger protective effect for men [56]. Consequently, the multigeneration living environment not only provided baseline advantages but also produced sustained positive effects on visuospatial function in females. These differences likely reflect fundamental distinctions in psychosocial characteristics and environmental interaction patterns between sexes.

Regarding residence, urban-rural differences significantly influenced the association between living arrangements and cognitive function. Among urban residents, both living with a spouse only and multigeneration living demonstrated cognitive protective trends. This likely benefited from well-developed community services, healthcare resources, and cultural facilities in urban areas [57,58], which created synergistic effects with family support. In contrast, a notable pattern emerged among rural residents in visuospatial function: the multigenerational living group started with a lower adjusted baseline score but improved more over time. This pattern suggests that multigenerational households may include individuals with higher initial cognitive needs, which aligns with cross-sectional analyses showing no baseline advantage. Given the relative scarcity of public resources and medical services in rural areas [59,60], the daily social interactions, practical assistance, and structured routines provided by such households likely serve as a crucial compensatory resource. Consequently, multigenerational living demonstrates a significant protective effect in slowing cognitive decline. These disparities highlighted how regional development imbalances substantially affect cognitive health in older adults. They indicated that intervention strategies should incorporate regional characteristics to effectively integrate family support with public services. Future studies with larger samples are needed to specifically examine the emotional and social support needs of rural older adults in such living arrangements.

Several limitations should be considered in this study. First, the relatively short follow-up period (mean 2.69 years) and limited number of cognitive assessments (mean 2.5 times) may have been insufficient to fully capture the long-term effects of living arrangements on cognitive trajectories. Second, the failure to include potential confounding factors such as family relationship quality and caregiver burden might have led to some overestimation of the protective effects of living arrangements. Additionally, the lack of longitudinal biomarker data restricted the exploration of dynamic changes in underlying mechanisms like neuroinflammation. Future studies should extend follow-up duration, increase assessment frequency, and incorporate multidimensional social environment indicators to more comprehensively elucidate the complex relationship between living arrangements and cognitive health.

5. Conclusions

This study demonstrated that living with family members buffered against cognitive decline. Notably, higher plasma Abeta40 levels were associated with improved language function, whereas higher GFAP levels attenuated the cognitive benefits of favorable living environments. These findings indicated that the clinical interpretation of AD biomarkers should be considered in the context of an individual's living environment. Accordingly, we recommend incorporating living arrangements into risk assessment systems during community-based health screenings for older adults. Individuals living alone with higher GFAP levels should be prioritized for interventions. Furthermore, differentiated cognitive intervention strategies should be developed for older adults with different living arrangements.

Declaration of generative AI and AI-assisted technologies in the writing process

AI-assisted technologies were used to assist with grammar editing.

Institutional review board statement

This study received approval from the Wuhan University of Science and Technology Ethics Committee (approval code: 201,845). All participants provided written informed consent.

CRediT authorship contribution statement

Yuanyuan Peng: Writing – original draft, Visualization, Validation, Software, Investigation, Formal analysis, Data curation. **Heqianxi Dong:** Validation, Investigation, Formal analysis. **Yu Luo:** Investigation. **Wen Zhou:** Investigation. **Lu Liu:** Investigation. **Ming Chen:** Investigation. **Na Liu:** Investigation. **Jiwen Che:** Investigation. **Feifei Hu:** Investigation. **Yifeng Cheng:** Supervision, Resources, Investigation, Funding acquisition. **Xinyan Xie:** Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Yan Zeng:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100536.

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