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Original Article

Structural social factors modify the association between Alzheimer's pathology and cognitive function

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ABSTRACT

Background: Social factors have been linked to cognitive decline and risk of dementia. However, our understanding of their impact on cognition in the context of Alzheimer's disease (AD) pathology is still limited.
Objectives: This study examined whether two structural social factors, relationship status (RS) and living situation (LS), modify the association between AD pathology and cognition.
Design: Observational, analysis of existing cohort data.
Setting: Data were obtained from the National Alzheimer's Coordinating Center (NACC) and the Imaging Dementia–Evidence for Amyloid Scanning (IDEAS) study.
Participants: Participants with available data on cognitive performance, AD pathology, and structural social factors.
Measurements: We used the Mini-Mental State Examination (MMSE), a widely used brief screening measure of global cognitive status. For the description of AD, postmortem neuropathology (NACC) reports, or amyloid PET (IDEAS) were used. RS and LS were coded according to the respective datasets. Group comparisons and regression models were used to evaluate interactions between RS or LS with AD pathology on cognition.
Results: Across cohorts, up to 31% of individuals were not in a relationship, and up to 22% lived alone. Individuals in a relationship (RS+) or those who lived with someone (LS+) showed poorer cognitive performance than those not in a relationship (RS-) or living alone (LS-) at comparable levels of AD pathology. Interaction analyses indicated that the association between AD pathology and MMSE differed by LS, with LS+ being associated with slightly lower MMSE scores across pathology levels, an effect primarily driven by participants living with someone who is not a partner. In contrast, within the NACC cohort, RS+ individuals showed overall lower MMSE scores, while the association between AD pathology and MMSE was weaker compared to RS− individuals.
Discussion: LS and RS showed differences in how AD pathology related to global cognitive status. Being in a relationship was linked to a weaker association between AD pathology and global cognitive status, whereas living with someone was associated with a lower global cognitive status at comparable levels of pathology. While the direction of these associations remains unclear, our findings suggest that the relationship between AD pathology and cognitive status may vary across different structural social contexts.

1. Introduction

Lifestyle factors, including social engagement, are increasingly recognized as modifiable determinants of dementia risk and cognitive decline (1). Over 55 million people worldwide are living with dementia, with Alzheimer's disease (AD) being the most common cause (2). The neuropathological characteristics of AD drive progressive cognitive impairment, and can be quantified postmortem via the ABC scoring system for AD-related neuropathology (3) or in vivo using amyloid PET, with the centiloid (CL) scale providing a continuous and standardized measurement across different tracers (4).

Low social participation, infrequent social contacts, and loneliness are linked to a higher incidence of dementia, with effects comparable to those of low education, physical inactivity, and late-life depression (5). Furthermore, small social networks and low social support are associated with an increased risk of dementia, while good social engagement is

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protective (6). Strong social connections, such as regularly interacting with family and friends, are associated with less cognitive decline (7). Both structural social factors (e.g., relationship status (RS), living situation (LS)) and functional aspects of social interactions (e.g., frequency or quality of social connections) appear important (8,9).

However, few studies have examined how structural social factors interact with AD pathology to influence cognitive outcomes (10). Social networks appear to modulate the relationship between AD pathology and cognitive function, with individuals with larger networks showing better cognitive performance than those with smaller networks at similar levels of pathology (11). Neuroimaging has shown that lower cortical thickness is associated with worse global cognition among individuals with smaller social networks (12). However, not all findings are consistent. For example, the ARIC-PET study reported that while social relationships were associated with lower dementia risk, they did not modify the association between amyloid burden and incident dementia (13). Structural social factors, such as RS and LS, contribute to consistent daily social interactions. They are relatively straightforward to define and operationalize, and are commonly assessed as part of demographic data in large cohort studies. The present study aimed to examine whether the association between AD pathology and cognitive status differs according to RS and LS across two large cohorts. Understanding these interactions is relevant for identifying at-risk individuals and developing personalized intervention strategies.

2. Methods

2.1. Data

We analyzed the data from the National Alzheimer's Coordinating Center (NACC) dataset and the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study, which were available in January 2025. Both datasets provide information on AD pathology, cognition, and the structural social factors LS and RS, enabling the joint examination of these factors. The protocols for both studies received approval from the responsible ethics committees. All participants provided written informed consent prior to data collection, which also included consent for access to the data by international research groups upon request.

2.2. Sample descriptions

2.2.1. NACC Uniform Data Set (UDS)

The Uniform Data Set (UDS) was introduced in 2005 to standardize the prospective collection of clinical and neuropathological data from patients and volunteers at Alzheimer's Disease Research Centers (ADRCs) across the US (13). The UDS consists of longitudinal data collected annually, which includes demographics, diagnoses, neuropsychological test results, and clinical ratings. The participants' diagnoses range from cognitively normal to mild cognitive impairment (MCI) to dementia. The dataset includes information on RS and LS. Cognitive assessments include the Mini-Mental State Examination (MMSE). We used data from 46 ADRCs. The neuropathology dataset (NP) includes participants who were followed longitudinally and donated their brains after death for research purposes. This dataset contains the NIA-AA Alzheimer's disease neuropathological change score (ABC score).

2.2.2. IDEAS study

IDEAS is a multisite, longitudinal study that investigated the clinical impact of amyloid PET imaging on the management and health outcomes of individuals with MCI and dementia. Based on the study design, no cognitively unimpaired individuals were included. The study was conducted by the American College of Radiology, with enrollment between 2016 and 2017. Before amyloid PET imaging, referring dementia specialists performed an assessment that included the collection of demographic data, including information on RS and LS, a primary suspected etiological diagnosis of MCI or dementia, the physician's confidence in this diagnosis, brief cognitive screening measures (including the MMSE), and a patient management plan (14). No comprehensive neuropsychological assessment was part of the standardized study protocol. The amyloid PET scan was conducted 30 days after the initial assessment with one of three US Food and Drug Administration (FDA)-approved Aß ligands. Imaging specialists read the scans according to the approved methods for each tracer, categorizing the results as either 'negative' or 'positive' (14). CL values are available for a subset of participants.

2.3. Variables for the analyses

We dichotomized RS into 'not in a relationship' (including widowed, divorced, separated, and never married) and 'in a relationship' (including married and living as married). Similarly, we dichotomized LS into 'living alone' and 'living with someone', where 'living with someone' included individuals living with a spouse or partner, a relative, a friend or caregiver, or in a group setting. Cognition was assessed using the MMSE as a measure of global cognitive status, given its broad availability across both cohorts and its routine use as a brief cognitive screening instrument. While cognitive status for group comparisons was based solely on baseline assessments, all available cognitive data from all study visits were included in the statistical regression models (see below). In the NACC data, AD pathology was assessed post-mortem using the NIA-AA Alzheimer's ABC score. The ABC score summarizes the neuropathology of AD by combining amyloid-β deposition (Thal phase), the stage of neurofibrillary tangles (Braak stage), and the burden of neuritic plaques (CERAD score), resulting in a classification of AD pathology as "none" (ABC 0), "low" (ABC 1) "moderate" (ABC 2), or "high" (ABC 3) (15). In the IDEAS data, AD pathology was assessed in vivo using amyloid PET imaging, and we utilized the Centiloid (CL) scale as a standardized measure of amyloid burden.

2.4. Statistical analysis

Patients were classified based on AD pathology, either according to the ABC neuropathology score (0 = not AD; 1 = low ABC score; 2 = intermediate ABC score; 3 = high ABC score) or by their CL values for amyloid PET. We classified according to Collij et al.: CL < 10 indicated no amyloid pathology; 10-30 CL indicated evolving amyloid pathology; and CL > 30 indicated established amyloid pathology (16). Additionally, amyloid PET visual reads (amyloid positive vs. negative) were available. Analyses were conducted as complete-case analyses, including only participants with available data for all relevant variables. Cognitive performance at baseline was compared between individuals based on their RS and LS within all the pathology-stratified groups, and p-values were corrected for multiple comparisons using the Holm-Bonferroni method. The Mann-Whitney U test was used for the comparison of two groups. In addition, we calculated effect sizes (r) to quantify the extent of the group differences. The results are also displayed as box plots.

Next, we fitted two regression models each to the data of the NACC and IDEAS cohorts (four in total), including linear mixed models and linear models, to assess the interaction effects between RS or LS and AD pathology on global cognitive status. The models varied by the social factor (RS, LS), and the measure of AD pathology (ABC score, amyloid PET). We controlled for the variables age, sex, education, race, PET tracer (if applicable), and time between clinical assessments and autopsy. The participant identifier (ID) was included as a random intercept to account for repeated measurements of cognitive data. The models are described in eTable 1. Since there was only one visit in the IDEAS study before the amyloid PET scan, controlling for a random intercept was not necessary. Correction for multiple comparisons was performed using the Holm–Bonferroni method across both cohorts for each predictor. We utilized the Akaike Information Criterion (AIC) to compare model

performance. Furthermore, as an exploratory step, we fitted one additional model per cohort, combining RS and LS into a single variable (RSLS) to examine the potential influence of overlapping effects between relationship status and living situation. The RSLS variable consisted of four categories: RS-LS- (not in a relationship and living alone), RS+LS- (in a relationship but living alone), RS-LS+ (not in a relationship but living with others), and RS+LS+ (in a relationship and living with others). These analyses were considered secondary.

All analyses were performed using R Statistical Software (R version 4.4.2; 2024-10-31 ucrt) (17). The following R packages were used: dplyr (18), tidyr (19), and haven (20) for data management and preprocessing; Hmisc (21) and FSA (22) for descriptive statistics and exploratory analyses; lme4 (23) and lmerTest (24) for statistical modeling; broom (25), and broom.mixed (26) for model cleaning, interactions (27) for investigating interaction effects; ggplot2 (28), and sjPlot (29) for visualizing results, openxlsx (30) and Matrix (31) for preparing and storing Excel files.

3. Results

3.1. Sample characteristics

We analyzed data from 3,844 participants of the NACC cohort and 8,131 participants of the IDEAS cohort. Table 1 summarizes the demographic and clinical characteristics of the samples, as well as the group comparisons. The median age was 75 (14) years in the NACC cohort, and 76 (10) years in the IDEAS cohort. Across cohorts, 30.5% (NACC) and 27.9% (IDEAS) of participants reported not being in a relationship. Living alone was reported by 22.4% (NACC) and 17.6% (IDEAS). Most participants were both in a relationship and living with someone (68.1% in NACC, 70.8% in IDEAS).

The median MMSE was 27 (7) in the NACC cohort and 26 (6) in the IDEAS cohort. The baseline clinical diagnoses differed between the cohorts. 48.3% of NACC participants and 36.6% of IDEAS participants were diagnosed with dementia. 20.3% of NACC participants, and 63.4% of IDEAS participants were diagnosed with MCI. 28.5% of NACC participants were cognitively unimpaired. AD pathology also varied by cohort. In the NACC cohort, autopsy data revealed a broad range of amyloid and tau pathology, with 46.7% classified as having an ABC score of 3. The mean time between baseline and autopsy was 8 (5) years. Amyloid PET results indicated amyloid positivity in 60.3% of IDEAS participants with a median of 42.4 (83) CL.

3.2. Group comparisons between individuals with different social factors

Table 2 shows the cognitive performance by RS and LS across neuropathological and amyloid PET measures. Individuals in relationships or living with someone generally showed lower MMSE scores than those not in a relationship or living alone. Group differences for RS in the MMSE were observed for ABC scores 0 to 2 ($p < 0.001$) but not for ABC score 3. Effect sizes ranged from 0.15 to 0.21. For LS, this effect was consistent across all ABC scores ($p < 0.001$), with effect sizes ranging

Table 1
Baseline demographics, sample characteristics, and cohort comparison.

		NACC cohort N=3,844	IDEAS cohort N=8,131			
Variable		Median (IQR)	Median (IQR)	Test statistic	p-value*	Effect size
Sex, n (%)	Female	1912 (49.7)	4157 (51.1)	2.0[a]	0.16	0.01
Age (years)		75 (14)	76 (10)	6705987[b]	< 0.001	0.08
Education	Years of education	16 (5)	NA			
	Lower than a high school degree, n (%)	NA	614 (7.56)			
	High school degree, n (%)	NA	2067 (25.4)			
	College or higher education, n (%)	NA	5450 (67.03)			
Ethnicity, n (%)	White	3596 (93.6)	7131 (87.7)	306.7[a]	< 0.001	0.99
	Black or African American	174 (4.5)	244 (3.0)			
	American Indian/ Alaska Native	6 (0.2)	19 (0.2)			
	Native Hawaiian/ Other Pacific Islander	3 (0.1)	8 (0.1)			
	Asian	38 (1.0)	147 (1.8)			
	Other	11 (0.3)	582 (7.2)			
Clinical diagnosis, n (%)	Unimpaired cognition	1095 (28.5)	NA	3421.7[a]	< 0.001	0.54
	Non-amnestic MCI	149 (3.9)	999 (12.3)			
	Amnestic MCI	629 (16.4)	4157 (51.1)			
	Dementia	1856 (48.3)	2975 (36.6)			
MMSE		27 (7)	26 (6)	9982170[b]	< 0.001	0.09
RS, n (%)	Married	2627 (68.3)	5860 (72.1)	10.9[a]	0.01	0.03
	Living as married	46 (1.2)	NA			
	Widowed	693 (18.0)	1438 (17.7)			
	Divorced	320 (8.3)	636 (7.8)			
	Separated	15 (0.4)	NA			
	Never Married	123 (3.2)	197 (2.4)			
LS, n (%)	Living alone	862 (22.4)	1432 (17.6)°	295.6[a]	< 0.001	0.16
	Living with spouse or partner	2587 (67.3)	5750 (70.7)°			
	Living with relative, friend or caretaker	256 (6.7)	1206 (14.8)°			
	Living with group	56 (1.5)	NA			
RSLS (%)	RS-LS-	807 (21.0)	1332 (16.4)	45.1[a]	< 0.001	0.06
	RS+LS-	55 (1.4)	100 (1.2)			
	RS-LS+	364 (9.5)	939 (11.6)			
	RS+LS+	2618 (68.1)	5760 (70.8)			
ABC score, n (%)	0	513 (13.4)	NA			
	1	709 (18.4)	NA			
	2	827 (21.5)	NA			
	3	1795 (46.7)	NA			
Amyloid-PET	Centiloids, CL	NA	42.4 (83)			

Note. Test statistics: χ^2, chi-square test; U, Mann–Whitney U test. Effect sizes: r (Kruskal–Wallis) and Cramér V (chi-square). Superscripts indicate tests ([a], chi-square; [b], Mann–Whitney U). P values were corrected using the Holm–Bonferroni method. ° Duplicate entries for LS were possible in the IDEAS study. Abbreviations: ABC score, NIA-AA Alzheimer disease neuropathologic change score; MMSE, Mini-Mental State Examination; CL, centiloids; LS, living situation; MCI, mild cognitive impairment; PET, positron emission tomography; RS, relationship status; RSLS, combined relationship status and living situation.

Table 2
Group comparisons of cognitive performance by relationship status and living situation.

Cohort	Measurement		MMSE									
			RS, median (IQR)					LS, median (IQR)				
			No relationship	In a relationship	U	p-value*	r	Living alone	Living with someone	U	p-value*	r
NACC	ABC score	0	28 (4)	27 (5)	22159	**<0.001**	0.16	29 (3)	27 (6)	31696	**<0.001**	0.25
		1	29 (3)	28 (4)	42422	**<0.001**	0.15	29 (3)	28 (4)	62048	**<0.001**	0.21
		2	29 (3)	28 (4)	68565	**<0.001**	0.21	29 (2)	28 (5)	99195	**<0.001**	0.28
		3	24 (9)	24 (7)	297090	0.66	0.01	26 (7)	24 (8)	273680	**<0.001**	0.16
IDEAS	CL	<10	27 (6)	27 (5)	764858	0.15	0.03	27 (4)	27 (4)	591206	**0.002**	0.07
		10 - 30	26 (5)	27 (5)	69458	0.62	0.02	27 (5)	26 (5)	62275	**0.003**	0.10
		>30	24 (7)	25 (6)	2258946	**0.008**	0.04	26 (6)	25 (7)	1743028	**<0.001**	0.10

Note. *P values were corrected for multiple comparisons using the Holm–Bonferroni method. Abbreviations: ABC score, NIA-AA Alzheimer disease neuropathologic change score; MMSE, Mini-mental State Examination; CL, centiloids; LS, living situation; RS, relationship status.

from 0.16 to 0.28. In the IDEAS study, LS results were comparable to those in the NACC cohort, but effect sizes were smaller (0.07 to 0.10). For RS in the IDEAS cohort, group differences were only observed for >30 CL with higher MMSE in people in a relationship ($p = 0.003$), but the effect size was small ($r = 0.04$). Fig. 1 presents box plots of the group comparisons.

3.3. Linear mixed model analysis

Models in the NACC cohort included 16,389 observations from 3,826 individuals. In model NACC.RS, both RS and the ABC score were associated with the global cognitive status: individuals in a relationship scored 1.5 points lower on the MMSE ($p < 0.001$) than individuals not in a relationship. Higher ABC scores were associated with a 2.2-point lower MMSE ($p < 0.001$). A significant RS × ABC score interaction ($p < 0.001$) revealed that the negative association between ABC score and MMSE was weaker among individuals in a relationship. Control variables, including education, age, race, and time between visits, were also significant predictors, while sex was not (Table 3 a-b).

In NACC.LS, individuals living with someone had a 1.2-point lower MMSE than those living alone ($p < 0.001$). Higher ABC scores were associated with a 1.5-point lower MMSE ($p < 0.001$). The interaction between LS and ABC score ($p < 0.001$) indicated that the negative association between ABC score and MMSE was stronger among individuals living with someone. Control variables yielded consistent results with Model NACC.RS, but females showed lower MMSE than males ($p = 0.004$).

The model IDEAS.RS showed similar results to model NACC.RS for single predictors, including CL, but RS and the interaction between RS and CL were not significant, indicating that RS did not predict MMSE in this cohort. In IDEAS.LS, individuals living with someone scored 1.19 points lower on the MMSE than those living alone, and LS modified the relationship between CL values and MMSE. The interaction between LS and CL ($p = 0.008$) indicated that the negative association between CL and MMSE was 0.01 stronger per CL among individuals living with someone.

Exploratory analyses of RSLS revealed that in the NACC cohort, compared to individuals without a relationship who lived alone (RS–LS–), those living with someone but not in a relationship (RS–LS+, $p = 0.01$) and those both in a relationship and living with someone (RS+LS+, $p < 0.001$) showed lower MMSE scores. A significant RS–LS+ × ABC score interaction ($p < 0.001$) indicated that the negative association between ABC and global cognitive status was stronger among individuals living with someone but without a relationship. Similar patterns were shown in the IDEAS cohort (eTable 2).

Model comparison based on AIC values showed that models including LS alone performed better than those including RS alone, but the best model fit was observed for the combination of RS and LS in both cohorts. eTable 3 summarizes all model comparisons based on AIC values.

4. Discussion

In this study, we examined the relationship between the structural social factors relationship status and living situation, AD pathology, and global cognitive status across two large cohorts. Across both cohorts, the majority of participants were in a relationship and living with someone, reflecting the composition of the study populations. Consistent with previous research, AD pathology, measured by neuropathology or amyloid PET, was a strong predictor of cognitive performance (32). However, structural social factors modified this association. Individuals in a relationship or living with someone showed poorer global cognitive status at comparable pathology levels than those not in a relationship or living alone.

Across models, structural social factors, AD pathology, and several covariates were associated with the global cognitive status. Patterns diverged between the two structural social factors. Across both cohorts, living with someone was consistently associated with slightly lower MMSE scores, and the association between AD pathology and MMSE performance differed by living situation. Exploratory analyses further indicated that this pattern was primarily driven by participants living with someone who was not a partner (LS+RS–). In the NACC cohort, individuals in a relationship showed lower overall MMSE scores, yet the association between AD pathology and global cognitive status was weaker than in those not in a relationship.

The finding that individuals not in a relationship showed a higher overall global cognitive status may reflect differences in baseline cognitive reserve, as previously reported (33). Independently managing daily responsibilities may be associated with different patterns of cognitive engagement, although such mechanisms cannot be inferred from the present data. At the same time, the weaker association between AD pathology and global cognitive status among individuals with partners aligns with prior research showing that social connections, including partnerships, are associated with slower cognitive decline (7), whereas it may be accelerated by poor social relationships (9,8). Individuals in partnerships engage more frequently in cognitively stimulating activities, including conversational engagement (34,35), which might support compensatory mechanisms.

In contrast, living with someone was associated with lower MMSE scores, and the association between AD pathology and global cognitive status differed by living situation. This pattern may indicate that living with someone reflects emerging dependency in some cases, which often becomes apparent when cognitive symptoms gain functional relevance. This interpretation is supported by the exploratory RSLS analyses, which suggested that the observed effect was driven by individuals living with someone but not in a relationship. This subgroup showed both lower MMSE scores and a stronger association between AD pathology and global cognitive status. One possible explanation is that living with someone who is not a partner may more frequently reflect situations in which impairment has already influenced living arrangements, such as moving in with family members due to cognitive concerns. Furthermore,

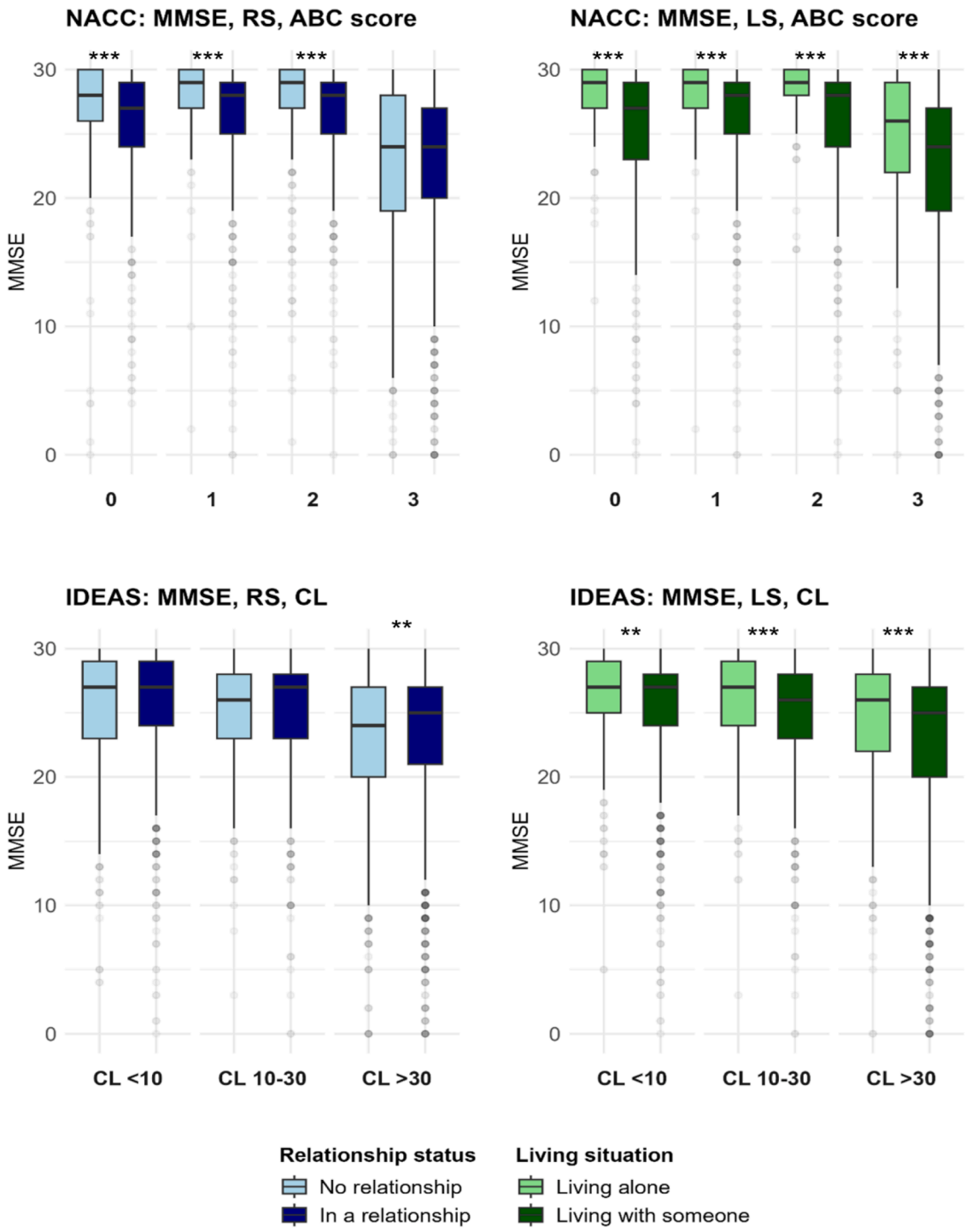

Figure 1. Associations between social factors and cognition across pathology stages and cohorts. Boxplots display cognitive scores by relationship status or living situation, stratified by Alzheimer disease pathology. Asterisks indicate statistical significance ($P < .05$ to $^{**}P < .001$; Mann–Whitney U test). Abbreviations: ABC, NIA-AA Alzheimer disease neuropathologic change score; CL, centiloids; LS, living situation; MMSE, Mini-Mental State Examination; RS, relationship status.

given that the relationship between AD pathology and clinical expression is heterogeneous (36), individuals in this subgroup may also represent cases in which cognitive symptoms are more functionally manifest at comparable levels of pathology. However, the present data do not allow conclusions regarding the directionality or causality of these associations.

The present findings partly align with prior studies reporting that broader social networks are associated with better cognitive performance at similar levels of AD pathology, suggesting that certain aspects of social connectedness may be associated with more favorable cognitive outcomes. At the same time, they differ from the ARIC-PET study by Groechel et al. (2024), which did not observe a modifying effect of social relationships on the association between amyloid burden and incident dementia. Such discrepancies may reflect differences in outcome definitions and the operationalization of social context. While ARIC-PET examined incident dementia as a categorical clinical endpoint, the present study assessed global cognitive status as a continuous measure, potentially capturing subtler variation across disease stages. Moreover,

Table 3a
Linear mixed models for RS and LS in NACC.

Model NACC.RS: MMSE, RS, and ABC score (Linear mixed-effects model with random intercept (ID), fitted by REML)				
Fixed Effects	Estimate (ß)	SE	95% CI	p-value*
(Intercept)	6.87	0.91	[5.08, 8.66]	**<0.001**
RS (ref. RS-)	-1.46	0.25	[-1.96, -0.96]	**<0.001**
ABC score	-2.2	0.11	[-2.43, -1.98]	**<0.001**
Sex (ref. male)	-0.32	0.19	[-0.69, 0.05]	0.18
Education	0.27	0.03	[0.21, 0.33]	**<0.001**
Age	0.16	0.01	[0.14, 0.18]	**<0.001**
Race (ref. white)	-1.03	0.37	[-1.74, -0.31]	**0.005**
Time between baseline and NP	0.78	0.01	[0.75, 0.80]	**<0.001**
RS x ABC score	0.54	0.12	[0.32, 0.77]	**<0.001**
Random Effects	Variance	SD		
Intercept (ID)	25.59	5.06		
Residual (observation)	9.56	3.09		
Observations	16389			
Individuals (ID)	3826			
REML criterion	92465			
Model NACC.LS: MMSE, LS, and ABC score (Linear mixed-effects model with random intercept (ID), fitted by REML)				
Fixed Effects	Estimate (ß)	SE	95% CI	p-value*
(Intercept)	8.11	0.89	[6.37, 9.85]	**<0.001**
LS (LS-)	-1.18	0.23	[-1.63, -0.73]	**<0.001**
ABC score	-1.51	0.12	[-1.74, -1.28]	**<0.001**
Sex (ref. male)	-0.56	0.18	[-0.91, -0.21]	**0.004**
Education	0.26	0.03	[0.21, 0.32]	**<0.001**
Age	0.15	0.01	[0.13, 0.16]	**<0.001**
Race (ref. white)	-1.03	0.36	[-1.73, -0.33]	**0.008**
Time between visits and NP	0.76	0.01	[0.74, 0.79]	**<0.001**
LS x ABC score	-0.32	0.11	[-0.53, -1.05]	**0.007**
Random Effects	Variance	SD		
Intercept (ID)	24.58	4.96		
Residual (observation)	9.51	3.08		
Observations	16389			
Individuals (ID)	3826			
REML criterion	92256.8			

Note.*P values were corrected for multiple comparisons using the Holm–Bonferroni method. Abbreviations: ABC score, NIA-AA Alzheimer disease neuropathologic change score; CI, confidence interval; ID, identifier; LS, living situation; LS−, living alone; MMSE, Mini-Mental State Examination; NP, neuropathology; REML, residual maximum likelihood; RS, relationship status; RS−, not in a relationship; SD, standard deviation; SE, standard error.

Table 3b
Linear mixed models for RS and LS in IDEAS.

Model IDEAS.RS: MMSE, RS, and CL (Linear regression model fitted by ordinary least squares)				
Fixed Effects	Estimate (ß)	SE	95% CI	p-value*
(Intercept)	28.07	0.75	[26.59, 29.55]	**<0.001**
RS (ref. RS-)	-0.05	0.17	[-0.38, 0.28]	0.77
CL	-0.02	0.002	[-0.02, -0.01]	**<0.001**
Sex (ref. male)	-0.02	0.12	[-0.25, 0.20]	0.83
Education	0.74	0.04	[0.66, 0.81]	**<0.001**
Age	-0.08	0.01	[-0.10, -0.06]	**<0.001**
Race (ref. white)	-1.51	0.17	[-1.83, -1.18]	**<0.001**
Amyloid PET tracer	-0.19	0.10	[-0.38, 0.00]	0.06
RS x CL	-0.002	0.003	[-0.01, 0.00]	0.54
Observations	8127			
R^2 / Adjusted R^2	0.1079 / 0.1071			
Model fit	$F(8, 8118) = 122.8$, $p < 0.001$			
Model IDEAS.LS: MMSE, LS, and CL (Linear regression model fitted by ordinary least squares)				
Fixed Effects	Estimate (ß)	SE	95% CI	p-value*
(Intercept)	29.51	0.75	[28.04, 30.97]	**<0.001**
LS (LS+)	-1.11	0.19	[28.04, 30.97]	**<0.001**
CL	-0.01	0.003	[-0.02, -0.01]	**<0.001**
Sex (ref. male)	-0.24	0.11	[-0.46, -0.02]	**0.033**
Education	0.73	0.04	[0.65, 0.80]	**<0.001**
Age	-0.09	0.01	[-0.10, -0.07]	**<0.001**
Race (ref. white)	-1.48	0.16	[-1.80, -1.16]	**<0.001**
Amyloid PET tracer	-0.19	0.10	[-0.38, -0.00]	0.049
LS x CL	-0.01	0.003	[-0.01, -0.00]	**0.008**
Observations	8127			
R^2 / Adjusted R^2	0.1196 / 0.1187			
Model fit	$F(8, 8118) = 137.8$, $p < 0.001$			

Note. *P values were corrected for multiple comparisons using the Holm–Bonferroni method. Abbreviations: CI, confidence interval; CL, centiloids; ID, identifier; LS, living situation; LS+, living with someone; MMSE, Mini-Mental State Examination; RS, relationship status; RS−, not in a relationship; SE, standard error.

most studies examine different aspects of social context. ARIC-PET assessed perceived social support and isolation, whereas our analyses examined structural social factors. These conceptual differences may partly explain divergent findings between studies and may highlight the multidimensional nature of social context.

Furthermore, differences between NACC and IDEAS highlight the importance of study population characteristics, assessment methods, and disease stages for interpreting observed interaction patterns. IDEAS participants were, by design, restricted to individuals with clinician-suspected MCI or dementia and thus represented a more clinically selected cohort, whereas NACC included individuals across a broader and more distributed range of clinical stages, including cognitively unimpaired participants. Although IDEAS exclusively included individuals with MCI or dementia, the wide range of amyloid PET CL values indicates heterogeneity in underlying pathology, suggesting that cognitive impairment in this cohort may not be solely attributable to AD pathology.

Lastly, the cohorts differed in AD pathology assessment. IDEAS measured in vivo amyloid pathology using PET, typically in close temporal proximity to clinical and neuropsychological assessment. In contrast, NACC relied on post-mortem neuropathological evaluation via the ABC score, which incorporates both amyloid and tau pathology and is considered the histopathological reference standard for AD. Post-mortem assessment reflects cumulative end-stage pathology, and the interval between the last clinical evaluation and death may vary, potentially influencing the observed associations between AD pathology and cognition. At the same time, given that tau pathology appears particularly closely linked to cognitive impairment (37), the broader neuropathological characterization in NACC may capture additional aspects of disease burden compared with amyloid PET. These methodological and cohort-specific differences may partly explain why associations involving structural social factors appeared more pronounced in NACC and why a corresponding pattern for relationship status was observed only in this cohort, warranting caution when generalizing findings across cohorts and disease stages.

The strength of this study is the systematic assessment of the interaction between structural social factors and AD pathology on global cognitive status in two large independent cohorts with different measurements of pathology. However, limitations should be considered. First, differences in cohort characteristics and pathology measures, as described above, limit the direct comparability and generalizability of the findings. In addition, the MMSE was used as a measure of cognition due to its broad availability across both cohorts, allowing for comparable analyses and a sufficiently large sample size. Moreover, a comprehensive neuropsychological test battery was not available in the IDEAS cohort, limiting the ability to examine more specific cognitive domains across studies. However, the MMSE represents a screening measure of global cognitive status rather than a detailed assessment of domain-specific cognitive performance. Additionally, potential selection mechanisms may have contributed to the relatively high proportion of participants who were in a relationship and living with someone. Although NACC requires a study partner for participation, and IDEAS does not, the similar distribution of structural social factors across cohorts suggests that this alone does not explain this observation. Individuals with cognitive concerns who have close family members or social support may be more likely to seek medical evaluation, as often observed in routine clinical practice. Consequently, persons without

such support may be underrepresented in clinical and research cohorts, potentially leading to an overrepresentation of socially supported individuals in both samples. Furthermore, AD pathology was assessed cross-sectionally, which limits inferences about temporal relationships between pathology, cognitive status, and social context. Longitudinal studies are needed to further explore whether differences in social context precede changes in cognition and AD pathology or rather reflect consequences of emerging cognitive and functional decline. Finally, the analysis focused solely on structural indicators of social factors, as functional and qualitative dimensions, such as the frequency or quality of social relationships, were not available in the datasets. In this study, RS and LS were operationalized as dichotomous variables reflecting the presence or absence of a partner and living alone or living with someone. This approach was chosen because several original subcategories (e.g., widowed, divorced, separated, married, living as married) may differ administratively but do not necessarily represent clearly distinct social contexts. Similarly, the living situation variable, as assessed in the cohorts, included heterogeneous cohabitation arrangements, with living with relatives, friends, and caregivers grouped within a single response category. This limited the possibility of distinguishing conceptually different forms of cohabitation. Consequently, analyses focused on the broader structural distinction. However, this approach does not capture qualitative differences between relationship types or living arrangements, nor does it account for the duration or stability of these social contexts, as information on how long participants had been in a given relationship or living situation was not available. Such limitations are common in large cohort studies, where social data is typically limited to single structural indicators rather than functional or qualitative dimensions.

Future research should therefore consider subjective and qualitative aspects, such as loneliness, perceived support, and the frequency of social engagement, to better understand social influences on cognition (8, 9). Moreover, these factors should be considered already during the planning and design of large-scale studies, particularly those examining pathological changes at the biomarker level, to allow a more comprehensive assessment and understanding of how social context interacts with disease processes. Future studies should further investigate whether social context primarily reflects consequences of emerging cognitive and functional impairment or whether it plays a more active role in shaping the clinical expression of AD pathology. Addressing this question will require longitudinal study designs with more detailed and multidimensional assessments of social factors, allowing for a clearer differentiation between social exposure, support structures, and care dependency. A more refined understanding of the role of social context across disease stages may ultimately inform the timing and targeting of preventive strategies, depending on whether social factors operate earlier in the disease process or emerge as a consequence of cognitive decline.

Overall, our findings point to a complex pattern of associations between structural social factors, AD pathology, and global cognitive status. RS and LS appeared to reflect different dimensions of social context, with being in a relationship associated with a comparatively weaker association between AD pathology and MMSE performance, whereas living with someone was associated with patterns consistent with greater cognitive impairment at comparable levels of pathology, an effect that appeared to be primarily driven by individuals living with someone who was not a partner. However, the present data do not allow definitive conclusions regarding whether these differences reflect causal mechanisms, consequences of emerging cognitive and functional impairment, or differential roles of relationship status and living situation. At the same time, the findings illustrate the methodological challenges of investigating social–biological interactions within large existing cohort datasets, in which social context is often captured only through relatively coarse structural indicators. Further refinement of social assessments in large-scale studies are therefore necessary to more precisely characterize how social context intersects with AD pathology and cognitive trajectories.

Data access

The Authors declare that they take full responsibility for the data, the analyses and interpretation, and the conduct of the research; that they have full access to all of the data; and that they have the right to publish all data.

Data availability

Data from the National Alzheimer's Coordinating Center is publicly available to investigators through a data request process at https://naccdata.org. Data from the IDEAS (Imaging Dementia—Evidence for Amyloid Scanning) study are available to researchers through the Global Alzheimer's Association Interactive Network (GAAIN) Platform. Both datasets were accessed following their respective data use agreements and institutional guidelines.

Declaration of generative ai and ai-assistes technologies in the wrting process

During the preparation of this work, the authors used Grammarly and ChatGPT to assist with language editing and stylistic improvements in the manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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CRediT authorship contribution statement

Michelle Gerards: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Lena Sannemann:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Frank Jessen:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Frank Jessen reports a relationship with AC Immune that includes: consulting or advisory. Frank Jessen reports a relationship with Biogen that includes: consulting or advisory. Frank Jessen reports a relationship with Danone Nutricia Research that includes: consulting or advisory. Frank Jessen reports a relationship with Eisai that includes: consulting or advisory. Frank Jessen reports a relationship with GE Healthcare that includes: consulting or advisory. Frank Jessen reports a relationship with Grifols that includes: consulting or advisory. Frank Jessen reports a relationship with Janssen that includes: consulting or advisory. Frank Jessen reports a relationship with Lilly that includes: consulting or advisory. Frank Jessen reports a relationship with MSD that includes: consulting or advisory. Frank Jessen reports a relationship with Novo Nordisk that includes: consulting or advisory. Frank Jessen reports a relationship with Roche that includes: consulting or advisory. If there are other authors, they 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.2026.100563.

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