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Health Disparities in Cognitive Impairment and Dementia: Role of Social Strain, Depression, and C-Reactive Protein

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Abstract

We investigated the association of social strain from friends, depression, and systemic inflammation (C-Reactive Protein [CRP]) with cognitive impairment without dementia (CIND) and dementia among 9,262 participants (age ≥ 65). We analyzed data from the Health Retirement Study (HRS), performing Chi-squared and logistic regression analyses. Measures included the 27-point HRS cognition scale, social strain scale, Center for Epidemiological Studies Depression scale, and dried-blood CRP levels. Black and Hispanic participants had a significantly increased dementia risk (OR = 2.69 and OR = 2.54). Black participants also had a high risk of CIND (OR = 2.80), but no association of Hispanic participants with CIND. Increased social strain from friends and depression were significantly associated with CIND (OR = 1.50 and OR = 1.44) and dementia (OR = 1.57 and OR = 1.78). Elevated CRP levels were only linked to CIND risk (OR = 1.03), not dementia. Early detection and interventions targeting social strain, depression, and CRP levels may help promote cognitive functioning in older adults.

Keywords

dementia, cognitive impairment, disparities, social strain, depression, systemic inflammation

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What This Paper Adds

- There is a significant variation in cognitive impairment and dementia risk between racial and ethnic groups.
- Social strain from friends is an important indicator of cognitive impairment and dementia.
- Older adults with elevated CRP levels have a high risk of cognitive impairment.

Applications of Study Findings

- Studies integrating biological, psychological, and social factors are essential for unraveling the mechanisms underlying cognitive decline.
- To gain a comprehensive understanding of cognitive health, future research should incorporate multiple components of social life and their interrelationships.
- Continued research and advanced study designs are necessary to further our understanding of the risk factors associated with dementia, especially within racial and ethnic groups.

There is a growing recognition of the contribution of social strain, depression, and systemic inflammation to the risk of Alzheimer's disease and related dementias (ADRD). Levels of social support and social strain in

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relationships have been found to influence loneliness and social isolation in later life (Chen & Feeley, 2013). Approximately 24% of community-dwelling older adults in the United States are socially isolated (Cudjoe et al., 2020). Notably, social strain has consistently been linked to an increased risk of cognitive impairment and dementia (Khondoker et al., 2017; Liao et al., 2018; Meister & Zahodne, 2022). In the context of later life, social strain refers to the perception of negative social interactions received from one's social network. Existing research supports the independent effects of social strain (Meister & Zahodne, 2022), late-life depression (Muhammad & Meher, 2021), and systemic inflammation (Fernandes et al., 2020) on the increased risk of ADRD. However, there is limited evidence in describing the collective association of social strain, depression, and systemic inflammation with the risk of ADRD in racial and ethnic variations.

ADRD is a neurodegenerative and progressive disorder affecting cognition, thinking, language, and functioning, leading to loss of independence in severe stages (Alzheimer's Association, 2023; Li et al., 2023). In addition to advanced age and lower education level, racial and ethnic disparities are major risk factors for ADRD (Alzheimer's Association, 2023; Luth & Prigerson, 2022). The estimated 60% variation in dementia incidence between racial and ethnic groups highlights the significance of research into ethnic and racial disparities (Wright et al., 2021). Findings from a population-based study revealed that non-Hispanic Blacks (19%) and Hispanics (14%) have disproportionately higher rates of Alzheimer's Disease than Whites (Rajan et al., 2021). Similarly, the incidence of dementia was highest for Blacks, intermediate for Hispanics, American Indians, and Native Alaskans, and lowest for Asian Americans (Mayeda et al., 2016).

Our study is guided by the National Institute on Aging Health Disparities Framework (Hill et al., 2015), emphasizing the importance of understanding the multidimensional mechanisms of risk factors contributing to health disparities among racial and ethnic groups. By incorporating multiple indicators of cognitive aging at various levels, we aimed to expand our knowledge of the relationship between modifiable risk factors and the risk of cognitive impairment and dementia. This approach allows us to gain a more nuanced understanding of how these factors impact the development and progression of ADRD, ultimately contributing to efforts to reduce health disparities.

The association of social support with cognitive impairment or dementia has been examined in multiple studies, but the results were mixed. A systematic review of 22 population-based studies revealed a significant positive association between perceived positive social support and cognitive functioning (Costa-Cordella et al., 2021). Conversely, a longitudinal study found no significant association between global cognitive function and overall perceived support over time (Du et al., 2023). Although researchers found a positive association between social support from children and cognitive alterations, differences in positive family support were inversely related to cognitive function changes (Du et al., 2023).

The protective role of social support has been examined widely; however, only a few studies concentrated on the effects of social strain on cognitive functioning in older adults, sometimes within social isolation. Results from the English Longitudinal Study of Ageing (ELSA) indicated that social strain from spouses, children, and other immediate family members increased the risk of dementia. In contrast, social support from children significantly reduced the risk of dementia (Khondoker et al., 2017). Meister and Zahodne (2022) examined the association of social support and social strain with the domains of cognition. They found that social strain from peers was inversely associated with all domains except episodic memory. Nonetheless, positive family support was negatively related to episodic memory, executive function, and language (Meister & Zahodne, 2022). Additionally, a systematic review of 19 longitudinal cohort studies revealed that poor social connectedness has a strong correlation with incident dementia, and the strength of this association is comparable to other well-known risk factors for dementia, such as lower educational attainment, physical inactivity, and late-life depression (Kuiper et al., 2015). The magnitude of the effects of social strain on the risk of cognitive impairment or dementia seems to be stronger and more consistent than that of social support.

Late-life depression commonly occurs in older adults and is associated with a reduced quality of life and progression along the ADRD spectrum. Late-life depression is depression that first appears between the ages of 60 and 65 (Aziz & Steffens, 2017). Researchers argued that depression could have been an important marker for the increased risk of conversion to dementia among patients with mild cognitive impairment (MCI), especially amnestic MCI (Aziz & Steffens, 2017). Some other researchers found that high levels of depressive symptoms may be a predictor of clinical symptoms onset among cognitively intact individuals and useful in identifying persons at risk for Alzheimer's disease (AD).

Chan et al. (2019) investigated 300 cognitively normal people (Average Age: 57.4 years) for 20 years. Higher baseline depression scores were linked to MCI development within 7 years from the baseline, but no significant association between depression scores and clinical symptoms of cognitive impairment after 7 years (Chan et al., 2019). A meta-analysis of 57 studies examined the prevalence of depression among cognitively impaired persons and found that the depression rate in MCI patients was 25% in population studies and 40% in clinical studies, which was substantially different (Ismail

et al., 2017). Another meta-analysis of 23 cohort studies demonstrated that older adults with late-life depression had an increased risk for all-cause dementia, vascular dementia, and AD (Diniz et al., 2013).

Systemic inflammation is another important risk factor for ADRD and is associated with depression and social support (Kim & Thomas, 2019). The immune system plays a significant role in brain aging, as systemic inflammation has been linked to the etiology and pathogenesis of dementia, causing structural and functional alterations in the aging brain (Fernandes et al., 2020). A recent meta-analysis showed that elevated pro-inflammatory cytokines levels were associated with a higher risk of developing subsequent cognitive decline (Feng et al., 2023), while findings from the Sacramento Area Latino Study of Aging suggested no association of inflammatory cytokines with incident dementia (Stebbins et al., 2021). Another study examined the association of pro-inflammatory biomarkers with cognitive decline in 3,031 Black and White participants and found a significant correlation between higher levels of Interleukin-6 (IL-6) and C-Reactive Protein (CRP) and cognitive decline, regardless of race variances (Yaffe et al., 2003). In contrast, a study conducted on the cohort of MCI patients in a dementia clinic revealed that patients with reduced CRP levels appear to develop dementia more rapidly, indicating that CRP may provide information regarding conversion risk in patients with MCI (Fernandes et al., 2020).

This study examined the association of social strain from friends, depression, and systemic inflammation with cognitive impairment without dementia (CIND) and dementia among ethnically and racially diverse older adults aged 65 and above. We hypothesized that higher levels of social strain, depressive symptoms, and systemic inflammation raise the risk of cognitive impairment and dementia, and Black and Hispanic participants experience cognitive impairment and dementia at significantly higher rates than White and non-Hispanic participants. Our research questions were:

1) How do social strain, depression, and CRP levels associate with CIND and dementia in racial groups?
2) How do social strain, depression, and CRP levels associate with CIND and dementia in ethnic groups?

By examining the social, psychological, and biological risk factors, this study has the potential to reveal first-level evidence toward more complex research designs to elucidate deeper mechanisms among risk factors on the continuum of ADRD from cognitive impairment to dementia. Furthermore, by building separate models with ethnicity and race, this study also captures the variances in the relationship between social strain, depression, systemic inflammation, and ADRD in ethnic and racial groups.

Methods

Data and Sample

We used datasets from the Health and Retirement Study (HRS) in this cross-sectional study. HRS is a nationally representative longitudinal survey conducted in the United States, comprising a cohort of approximately 20,000 adults aged 50 and older. The Institute for Social Research at the University of Michigan has conducted the study to collect data on participants' health, functional status, cognitive status, and social environment every 2 years since 1992, using a probability sampling method with oversampling of Blacks, Hispanics, and residents of Florida (Sonnega et al., 2014).

We analyzed a sample of 9,262 participants aged 65 or older who completed Wave 13 of the HRS survey during 2016 to 2017. Wave 13 was selected as it was the most recent one to collect dried blood biomarker samples. We utilized three datasets for our analyses: RAND HRS Longitudinal File 2020, Gateway Harmonized HRS Version C, and 2016 Biomarker Data.

Measures

Our demographic variables included age, gender (female, male), race (White, Black, Other race), education (less than high school [HS], HS graduate, and more than HS).

We measured cognitive status with the validated HRS 27-point cognition scale. The cutoff values were defined as 0 to 6 for dementia, 7 to 11 for cognitive impairment without dementia (CIND), and 12 to 27 for normal cognition. These cutoffs were validated against the Aging, Demographics, and Memory Study, where a comprehensive neuropsychiatric evaluation was conducted (Crimmins et al., 2011).

Social strain from friends is measured with the perceived social strain scale (Walen & Lachman, 2000). Questions on the scale include: *How often do they make too many demands on you? How much do they criticize you? How much do they let you down when you are counting on them? How much do they get on your nerves?* with response options ranging from *1* (*a lot), 2 (some), 3 (a little)*, or *4 (not at all)*. Each response was reverse coded so that a higher score indicated a higher perception of social strain. The average of the coded responses is used as an index of perceived social strain from friends, with an established internal consistency, Cronbach's $\alpha = .74$.

Late-life depression is measured with the validated Center for Epidemiologic Studies Depression (CES-D) scale (Wei et al., 2022). The 8-item CES-D scale includes *feeling depressed, feeling everything was an effort, restless sleep, happiness, loneliness, sadness, unable to get going*, and *enjoying life*. The total score ranges from 0 to 8, with a score of 4 points or higher classified as depression.

Table 1. Participants Characteristics Stratified by Cognitive Status in the Health and Retirement Study (2016–2017).

Characteristic	Total sample *N* = 9,262	Dementia *N* = 586	Cognitive impairment *N* = 1,968	Normal cognition *N* = 6,708	*p*-Value
Social strain (friends), mean (*SD*)	1.62 (0.43)	1.70 (0.47)	1.70 (0.49)	1.60 (0.41)	<.0001
Depression, *n* (%)					
Depressed	1,257 (13.57)	158 (26.96)	386 (19.62)	713 (10.63)	<.0001
Not depressed	8,004 (86.43)	428 (73.04)	1,581 (80.38)	5,995 (80.37)	
C-reactive protein (CRP), mean (*SD*)	3.57 (4.39)	4.20 (5.15)	3.83 (4.75)	3.44 (4.21)	0.012
Race, *n* (%)					
White/Caucasian	7,207 (77.88)	341 (58.19)	1,346 (68.46)	5,520 (82.36)	<.0001
Black/African American	1,521 (16.44)	188 (32.08)	486 (24.72)	847 (12.64)	
Other	526 (5.68)	57 (9.73)	134 (6.82)	335 (5.00)	
Ethnicity, *n* (%)					
Hispanic	1,017 (10.99)	136 (23.25)	301 (15.31)	580 (8.64)	<.0001
Non-Hispanic	8,240(89.01)	449 (76.75)	1,665 (84.69)	6,126 (91.35)	
Age, mean (*SD*)	75.53([7.43)	80.01 (8.30)	78.07 (7.81)	74.40 (6.88)	<.0001
Gender, *n* (%)					
Female	5,528 (59.68)	358 (61.09)	1,147 (58.28)	4,023 (59.97)	0.313
Male	3,734 (40.32)	228 (38.91)	821 (41.72)	2,685 (40.03)	
Education, *n* (%)					
Less than high school	1,883 (20.38)	342 (58.36)	711 (36.15)	830 (12.41)	<.0001
High school	3,010 (32.58)	149 (25.43)	686 (34.88)	2,175 (32.53)	
More than high school	4,346 (47.04)	95 (16.21)	570 (28.98)	3,681 (55.06)	

Note. Other race includes American Indian, Alaska Native, Asian, or other race and ethnicity.

The high-sensitivity C-Reactive Protein (CRP) from the dried blood spot (DBS) was used as an index of systemic inflammation. Blood samples were taken and prepared by trained HRS research technicians and shipped to the University of Vermont to be assayed. The HRS team adjusted CRP values based on plasma-based CRP concentrations in a similarly aged and nationally representative sample, the National Health and Nutrition Examination Survey (Crimmins et al., 2017). We standardized the CRP levels to adjust for differences in variances across measures.

Statistical Analysis

To compare baseline characteristics across cognitive statuses, we conducted chi-squared tests for categorical variables and *t*-tests for continuous variables. The supplemental analysis included a skewness test, revealing a moderate level of skewness in our data. Considering our large sample size and leveraging the central limit theorem's support (Kwak & Kim, 2017), we remain confident that the observed skewness is unlikely to impact the accuracy of our t-tests. Multivariate logistic regression was then utilized to model the association between social strain, depression, and CRP with CIND or dementia in two separate analyses. One analysis adjusted for race, while the other adjusted for ethnicity, enabling the assessment of disparities while mitigating potential multicollinearity. A nested model-building strategy was employed to fit the data: (1) adjustment for social strain, age, gender, education, and race or ethnicity; (2) additional adjustment for depression; and (3) final adjustment including CRP. All statistical analyses were performed using SAS 9.4.

Results

Participants' characteristics by cognition status are shown in Table 1. The sample included 9,262 older adults with a mean age of 75.53 years (*SD* = 7.43). More than half of the participants were female (59.68%), White (77.88%), and had more than a high school education (47.04%). Across the participants, 72.42% had normal cognition, 21.25% had cognitive impairment without dementia (CIND), and 6.33% had dementia. The proportions of Black and Hispanic participants in the group with dementia and CIND were higher than in the normal cognition group. Depression rates were noticeably higher in the dementia and CIND groups than in the normal cognition group. The pattern of CRP levels has a similar trend with higher means in dementia and CIND groups compared to the normal cognition group.

Our unadjusted model revealed a significant association between social strain from friends with CIND (OR = 1.68, 95% CI [1.37, 2.06]) and dementia (OR = 1.64, 95% CI [1.10, 2.47]). Additionally, having depressive symptoms was linked with a higher risk of CIND (OR = 2.05, 95% CI [1.79, 2.35]) and dementia (OR = 3.10, 95%, CI [2.55, 3.79]). A significant correlation between elevated CRP levels and CIND (OR = 1.02, 95% CI [1.00, 1.04]) and dementia (OR = 1.04, 95% CI [1.01, 1.07]) was also found. Table 2 shows the adjusted

Table 2. Race Adjusted Association of Social Strain, Depression, and CRP With Cognitive Impairment and Dementia in the Health and Retirement Study (2016–2017).

	Model 1 *OR* [95% CI]		Model 2 *OR* [95% CI]		Model 3 *OR* [95% CI]	
Variable	CIND	Dementia	CIND	Dementia	CIND	Dementia
Social strain (friends)	1.57 [1.26, 1.96]***	1.40 [0.93, 2.10]	1.52 [1.22, 1.89]***	1.32 [0.88, 2.00]	1.50 [1.18, 1.91]***	1.57 [1.01, 2.42]*
Race (ref: White]						
Black	3.16 [2.45, 4.09]***	3.44 [2.13, 5.53]***	3.14 [2.43, 4.05]***	3.40 [2.11, 5.47]***	2.80 [2.10, 3.73]***	2.69 [1.56, 4.64]***
Other	1.99 [1.27, 3.14]**	3.02 [1.42, 6.42]**	1.96 [1.25, 3.10]**	2.93 [1.38, 6.26]**	1.77 [1.07, 2.94]*	2.83 [1.26, 6.37]*
Age	1.08 [1.06, 1.10]***	1.10 [1.07, 1.13]***	1.08 [1.06, 1.10]***	1.10 [1.07, 1.13]***	1.08 [1.07, 1.10]***	1.11 [1.07, 1.14]***
Gender (ref: female)						
Male	1.11 [0.91, 1.36]	1.41 [0.95, 2.09]	1.14 [0.93, 1.40]	1.49 [0.99, 2.21]	1.16 [0.93, 1.44]	1.38 [0.89, 2.13]
Education (ref: HS)						
>HS	0.50 [0.40, 0.63]***	0.41 [0.23, 0.71]***	0.50 [0.40, 0.63]***	0.41 [0.23, 0.71]***	0.48 [0.37, 0.61]***	0.28 [0.15, 0.53]***
<HS	2.04 [1.58, 2.64]***	5.05 [3.19, 8.00]***	1.98 [1.53, 2.56]***	4.82 [3.03, 7.66]***	1.97 [1.50, 2.60]***	4.12 [2.54, 6.70]***
Depression						
Depressed			1.43 [1.07, 1.92]*	1.67 [1.00, 2.80]*	1.44 [1.05, 1.98]*	1.78 [1.02, 3.09]*
C-reactive protein (CRP)					1.02 [0.10, 1.05]	1.01 [0.97, 1.06]

Note. Other race includes American Indian, Alaska Native, Asian, or other race and ethnicity. Model 1: adjusted for social strain + demographics. Model 2: adjusted for social strain + demographics + depression. Model 3: adjusted for social strain + demographics + depression + CRP. CIND = cognitive impairment without dementia; HS = high school; Non-Hisp. = non-Hispanic.
*$p < .05$. **$p < .01$. ***$p < .001$.

models with race variations. Model 1 showed that the effect of social strain from friends (adjusted for race and other demographics) on CIND and dementia was significant. The association persisted after further adjustment for depression (Model 2) and CRP levels (Model 3).

The full model (Model 3) analysis showed that Black participants and participants in other race category were 2.80 times and 1.77 times more likely to have CIND than Whites. Similarly, the likelihood of having dementia was 2.69 times higher in Black participants and 2.83 times higher in participants belong to other races category compared to White participants. There was also a significant association of social strain from friends with CIND and dementia. Furthermore, participants with depression had increased odds of having CIND (44%) and dementia (78%) compared to participants without depression. We did not observe any significant association of CRP with CIND or dementia in the fully adjusted model. Age and having less than high school education significantly increased the odds of having CIND and dementia, whereas participants who had college education were 52% less likely to have CIND and 72% less likely to have dementia. The association of gender with CIND and dementia was not significant across the models.

Table 3 shows adjusted models with ethnicity variations. Results of the fully adjusted model (Model 3) revealed that ethnicity was significantly associated with the risk of dementia, indicating that Hispanic participants were 2.54 times more likely to have dementia compared to non-Hispanic participants. However, there was no significant association between ethnicity and CIND. Higher level of social strain from friends was significantly associated with the risk of CIND and dementia. Participants with depression were 48% more likely to have CIND and 76% more likely to have dementia than their counterparts without depression. Furthermore, higher levels of CRP were significantly associated with CIND, but we did not observe any significant association between CRP levels and dementia. Age and education level—less than high school significantly increased the likelihood of having CIND and dementia. In contrast, college-educated participants were less likely to have CIND and dementia. The association of gender with CIND or dementia was not significant (Table 3).

Discussion

In this nationally representative sample of community-dwelling older adults, we used datasets from the 2016 wave of Health and Retirement Study (HRS) to examine the collective association of social strain from friends, depression, and C-Reactive Protein (CRP) levels. Our findings revealed significant disparities in the risk of dementia among different racial and ethnic groups. Specifically, Black and Hispanic participants had a higher risk of dementia compared to White participants, while the risk of cognitive impairment without dementia (CIND) was associated only with Black participants. These results align with previous research showing that Blacks are about twice as likely (Manly et al., 2022; Weuve et al., 2018) while Hispanics are 1.5 times more likely than Whites to have Alzheimer's or another kind of dementia (Samper-Ternent et al., 2012). However, we did not confirm the findings of the Northern Manhattan study, which reported higher cognitive impairment and dementia rates for Hispanics compared to Whites and Blacks (Wright et al., 2021). This discrepancy might be attributed to differences in covariates included in the studies, as Wright and associates adjusted their analyses with vascular risk and brain imaging factors.

The results on the effect of social strain from friends are consistent with evidence from the literature. The associations of social strain with CIND and dementia in the current study were similar to the findings of the English Longitudinal Study of Ageing, which indicated a 31% higher risk of dementia among individuals with high levels of social strain (Khondoker et al., 2017). Meister and Zahodne (2022) also found that higher social strain from friends is associated with reductions in various cognitive domains, including executive function, learning, and processing speed, except episodic memory. In their age-stratified model, social strain-cognition relationships were strongest for individuals older than 74 (Meister & Zahodne, 2022). Moreover, a meta-analysis revealed significant positive associations between high emotional support from friends and family members and cognition compared to other types of support. In contrast, poor social connectedness with friends was linked to an increased risk of dementia (Costa-Cordella et al., 2021). These findings suggest that chronic stress and anxiety resulting from social strain may have detrimental effects on brain health and cognition (Meister & Zahodne, 2022), as well as the increased risk of depression among people with poor social relationships (Shim et al., 2012).

Depression was significantly associated with CIND and dementia in the current study, and the rates were similar in the race and ethnicity adjusted models. The trend is supported by previous research, indicating that the risk of depression differs across cognition trajectories, and that depression may be a risk factor and prodrome of dementia (Aziz & Steffens, 2017). Our findings on the depression-dementia association align with those of a large meta-analysis, which reported an odds ratio of 1.85 for all-cause dementia and 1.64 for Alzheimer's dementia (Diniz et al., 2013). However, we could not confirm the findings of the Longitudinal Ageing Study in India (LASI), which indicated a lower risk of CIND compared to our cohort (Muhammad & Meher, 2021). It is hypothesized that recurrent depressive episodes might accelerate the aging process by shifting allostatic processes into dysfunctional states, increasing allostatic load via the hypothalamic-pituitary-adrenal axis and inflammatory processes. In turn, this process may speed

Table 3. Ethnicity Adjusted Association of Social Strain, Depression, and CRP With Cognitive Impairment and Dementia in the Health and Retirement Study (2016–2017).

	Model 1 *OR* [95% CI]		Model 2 *OR* [95% CI]		Model 3 *OR* [95% CI]	
Variable	CIND	Dementia	CIND	Dementia	CIND	Dementia
Social strain (friends)	1.63 [1.31, 2.02]***	1.41 [0.93, 2.12]	1.57 [1.26, 1.95]***	1.33 [0.88, 2.02]	1.53 [1.21, 1.94]***	1.56 [1.01, 2.42]*
Ethnicity (ref: non-Hisp)						
Hispanic	1.21 [0.87, 1.70]	2.04 [1.22, 3.41]**	1.19 [0.85, 1.67]	1.98 [.18, 3.32]**	1.30 [0.80, 1.87]	2.54 [1.47, 4.41]***
Age	1.07 [1.05, 1.08]***	1.09 [1.06, 1.12]***	1.07 [1.05, 1.08]***	1.09 [1.06, 1.12]***	1.07 [1.06, 1.09]***	1.10 [1.07, 1.14]***
Gender (ref: female)						
Male	1.07 [0.88, 1.31]	1.37 [0.93, 2.02]	1.11 [0.91, 1.35]	1.45 [0.98, 2.15]	1.13 [0.91, 1.41]	1.37 [0.89, 2.11]
Education (ref: HS)						
>HS	0.51 [0.41, 0.64]***	0.42 [0.24, 0.75]**	0.51 [0.41, 0.64]***	0.42 [0.24, 0.73]**	0.47 [0.37, 0.60]***	0.28 [0.15, 0.53]***
<HS	2.19 [1.70, 2.84]***	4.94 [3.08, 7.93]***	2.12 [1.64, 2.75]***	4.72 [2.93, 7.60]***	2.04 [1.54, 2.70]***	3.65 [2.20, 6.04]***
Depression						
Depressed			1.48 [1.11, 1.97]**	1.69 [1.01, 2.83]*	1.48 [1.08, 2.02]*	1.76 [1.01, 3.08]*
C-reactive protein (CRP)					1.03 [1.01, 1.06]**	1.02 [0.98, 1.07

Note. Model 1: adjusted for social strain + demographics. Model 2: adjusted for social strain + demographics + depression. Model 3: adjusted for social strain + demographics + depression + CRP. CIND = cognitive impairment without dementia; HS = high school; Non-Hisp. = non-Hispanic.
*$p < .05$. **$p < .01$. ***$p < .001$.

up the path of biological aging, leading to increased brain atrophy and cognitive deterioration over time (Szymkowicz et al., 2023).

Inflammatory markers have been found to be useful in predicting and monitoring the progression of cognitive decline and dementia. CRP, one of many inflammatory biomarkers, is a well-known indicator of systemic inflammation and is frequently used in research studies and clinical settings (Darweesh et al., 2018). Higher CRP levels have been linked to brain inflammation, which impairs cognition by directly harming cerebral brain microvascular endothelial cells and increasing blood-brain barrier permeability (Feng et al., 2023). While our race or ethnicity adjusted full models did not reveal a significant association between CRP and dementia, we observed a significant association between elevated CRP levels and CIND in the ethnicity adjusted model. This finding is consistent with the report from Yang et al. (2015), indicating a significant relationship between higher CRP levels and cognitive decline among individuals who are not at the dementia stage (Yang et al., 2015).

A meta-analysis of 22 studies also showed that elevated pro-inflammatory cytokines levels, including CRP, Interleukin-6, and tumor necrosis factor-α, were associated with a 14% increased risk of developing cognitive impairment (Feng et al., 2023). However, our findings conflict with those of a clinical study conducted in a dementia clinic, which suggested that lower CRP levels in patients with mild cognitive impairment are associated with a more rapid progression to dementia (Fernandes et al., 2020). It should be noted that the Fernandes and associates focused only on individuals in the prodromal stage of Alzheimer's disease, and therefore, their observations may not be generalizable to other stages of cognitive impairment. In our study, the mean CRP level was significantly higher in the dementia group compared to the CIND and normal cognition group, which led us to anticipate a stronger association between CRP and dementia. However, our regression results did not reveal a significant association between CRP and the risk of dementia. We assumed that unobserved associations between CRP and other predictors might be accounted for the relationship between CRP and dementia risk. Future studies should provide a more careful investigation of the interaction effects of CRP with other predictors across different stages of Alzheimer's disease and related dementias. Nonetheless, the small but significant association between CRP and CIND in our study supports the argument that the relationship between CRP and the risk of Alzheimer's disease and related dementias varies with the stages and severity of the disease (Fernandes et al., 2020).

Study Limitations and Recommendations

Our study findings align with previous research on social strain from friends. However, we could not explore the strain from family members due to the potential impact of participants living alone or lacking a spouse/partner or children on results. Furthermore, our study did not address other aspects of social relationships, such as social support, loneliness, and lack of connectedness within the social network. For comprehensive insights into cognitive health, future research should incorporate multiple measures of social relationships to cover various components of social life and their associations. Regarding the relationship between systemic inflammation and cognitive impairment or dementia, our report relied solely on CRP levels. To gain a broader understanding, future studies should include other inflammatory markers.

We analyzed the correlation between social strain from friends, depression, and systemic inflammation in cognitive impairment without dementia and dementia stages. However, we did not explore changes in these predictors over time in relation to different cognitive stages. Longitudinal studies could offer valuable information on how these predictors influence ADRD progression. Lastly, our study did not examine the interaction effects of race and ethnicity with other variables. Exploring the moderating effects of race and ethnicity could provide specific evidence on the biological, psychological, and social mechanisms of ADRD for different racial and ethnic groups, which would contribute to a better understanding of the disease and its impact on diverse populations.

Implications

Our study highlights the significance of social strain, depression, and systemic inflammation as modifiable factors that profoundly impact the well-being of individuals across their lifespan. These factors have been consistently linked to various health outcomes, including cardiovascular disease, physical health, and cognition. By focusing on multi-level investigations, as recommended by the National Institute on Aging Health Disparities Framework, we gain valuable insights into the potential risk and protective pathways in the cognitive trajectories of older adults.

The findings of our study have practical implications for practitioners and policymakers involved in the care of older adults. Screening for perceived and functional social deficits, depression, and systemic inflammation in clinical settings can be a valuable tool for identifying individuals at risk and implementing appropriate interventions to maintain their physical and mental health. However, it is crucial to move beyond interventions targeting individual factors and adopt a holistic approach that considers the complex interplay between psychosocial and biological aspects of well-being. Such comprehensive interventions have the potential to improve social well-being and support individuals at different cognitive stages.

Moreover, our study underscores the need for continued research and advanced study designs to deepen our understanding of the risk factors associated with dementia, particularly in different racial and ethnic groups. Given the high and increasing diversity among older adults in the United States, it is vital to ensure adequate representation of these groups in research, including clinical studies. Understanding the specific differences among racial and ethnic groups can contribute to more effective and tailored interventions, reducing health disparities in dementia care.

In summary, this study emphasizes the importance of addressing social strain, depression, and systemic inflammation as key risk factors in promoting the cognitive well-being of older adults. By adopting a comprehensive approach and considering the unique needs of diverse populations, we can develop targeted interventions and policies that positively impact cognitive health and reduce the burden of dementia.

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