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Biopsychosocial contexts influence adult cognitive function concurrently and longitudinally

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ABSTRACT

Background: Cognitive aging is a complex process that impacts human behavior. Identifying the factors that preserve cognitive functioning is a public health priority, given that 20% of the US population will be at least 65 years old in the next decade. Biopsychosocial determinants of cognitive decline across the lifespan are often examined as ecological factors that independently moderate cognitive aging, despite the known complexity surrounding these relationships.

Objective: We aimed to address this gap by exploring the synergistic and simultaneous relationship between risk and protective factors on cognitive functioning.

Method: Using the MIDUS study datasets, we examined the relationships among physiological markers, friendship quality, and global cognition functioning, concurrently and longitudinally over ten years. Our participants included 929 healthy (417 men, 512 women) adults (average age at Time 1: 54.6 ± 11.6 years). Exploratory analyses examining the effects of racial minority status were also conducted.

Results: Cross-sectionally, age, and friendship quality moderated the relationship between vagally-mediated heart rate variability (vm-HRV) and cognition such that younger adults with greater friendship quality had a negative relationship between vm-HRV and cognitive performance; our unexpected finding suggests the heart-brain relationship is sensitive to the biopsychosocial environment. Longitudinally, higher IL-6 levels at Time 1 predicted poorer cognitive performance a decade later, but only among those with greater levels of friendship quality, especially for white-identifying individuals.

Conclusions: The relationships among physiological risk factors, social protective factors and cognitive functioning appear to be temporally different during mid-adulthood. Given many of the whole sample findings were not replicated within the racial minority subgroup, we suggest that these relationships should be examined in a larger and more diverse racial minority sample to determine whether this study lacked the power necessary to detect a relationship or if the relationships are in fact different by racial minority sub-group. In addition, future research should overcome the study's reliance on healthy adults and self-report measures of friendship quality by including adults with pre-existing cognitive impairments, and employing more real-time measures of friendship quality, such as daily diary or ecological momentary assessment.

1. Introduction

Social relationships are vital to health. Decades of biopsychosocial research on cognition across the lifespan have revealed the significance of social health on quality of life, especially among older adults (Abbott et al., 2021; Zahodne et al., 2021). For example, social support is a key mediator between risk and mortality (Berkman and Glass, 2000) and having a larger social network size can help diverse older adults maintain overall cognition (Sharifian et al., 2019). While meta-analyses have shown the buffering strength of diverse social activities, such as volunteering and religious activities, on cognition in ethnically-diverse older adults (Guiney and Machado, 2018; Kraal et al., 2019), the field would benefit from integrating empirical models that explore the synergistic relationships between physiological risk and protective social

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factors and their effects on concurrent and longitudinal cognitive functioning. This approach moves beyond the traditional exploration of siloed models, allowing for a more comprehensive understanding of the interconnected web.

1.1. Social connection

Many researchers have adapted the Berkman conceptual model for social support, which differentiates social networks from social support, highlighting their indirect relationship and contributions to optimizing health outcomes (Berkman and Glass, 2000). Social networks are the links between an individual and others, similar to that between nodes, and are often examined quantitatively (Can and Alatas, 2019). Social support encompasses the level of integration within one's network or community, involves the provision of instrumental or emotional resources, and can be a life-long determinant of health outcomes depending on the structure and function of the relationships (Uchino, 2006). However, due to the multi-faceted and dynamic nature of social relationships, pinpointing the exact mechanism by which social support affects cognition remains challenging.

To address this challenge, the life course health perspective offers a useful framework conceptualizing the complex and adaptative influences of social support on aging due to the growing evidence that factors such as friendships can impact one's physiological and psychological health years later (Davis et al., 2016; Zahodne et al., 2019). Friendship quality, as indicated by self-reported levels of emotional and instrumental assistance from non-related persons (Levine et al., 2015), is one aspect of a broader social support construct. Because of the lifelong and transcultural aspects of friendship, friendship quality, including self-report ratings of the readiness and accessibility to friends during distressful times, how often participants contact their friends and their overall level of satisfaction with their friendships, may be an optimal proxy for social support (Sharifian et al., 2020). Few have explored the perception of the quality of friendship as a proxy for social support utilizing large epidemiological data.

Strong friendships across the lifespan may help to strengthen resiliency against the adverse effects of stress on the cardiovascular and nervous systems by strengthening neural networks related to reward processing and mentalizing (Güroğlu, 2022), strengthening the hippocampal learning and memory-associated neural patterns (Kelly et al., 2017) and improving cognitive reserve through supportive listening (Salinas et al., 2021). More broadly, the cognitive reserve hypothesis refers to a common phenomenon where vast discrepancies are observed between brain pathology and clinical and neuropsychological presentations, suggesting there are modifying lifestyle factors, such as educational attainment, that buffer the relationship between brain pathology and function despite age-related pathology (Stern et al., 2019; Xu et al., 2019).

1.2. Physiological pathways underlying benefits of friendships

While the exact physiological mechanisms by which social support attenuates the neuro-inflammatory aging process are unknown, investigating the effects of friendships on the heart-brain and body-brain axes of cognitive functioning can shed light on this relationship. Given that positive and supportive friendships are hypothesized stress buffers and stress adversely alters the body, the protective effects of friendship quality on cognition may be related to inflammatory and neurovisceral health markers. The two main hypotheses, the neurovisceral and social support stress buffer hypotheses, may explain the complementary processes and provide insight into how social health modifies brain and body health.

The neurovisceral integration hypothesis postulates that the connection between the heart and brain, as mediated by the vagus nerve and measured by the heart's beat-to-beat fluctuations, heart rate variability (HRV), is integral for monitoring the influence of physiological indicators on brain functioning. As a measure of neurocardiac flexibility, higher levels of vagally-mediated HRV (vm-HRV) appear to indicate greater ability to adapt to one's environmental demands and is a consistent biomarker of heart-brain health (de Oliveira Matos et al., 2020). Notably, in a study on healthy adult males, those with higher vm-HRV performed more accurately and faster on two randomly presented cognitive tests than those with lower vm-HRV (Hansen et al., 2003). These findings highlight the importance of exploring the physiological and neuropsychological intersections of cognitive functioning.

Perhaps the mechanism by which social support, a known cognitive reserve factor (Chan et al., 2018), improves neuronal health is by protecting against chronic inflammation, a known risk factor for neuronal cell death, neuroinflammation, and exacerbated cognitive aging (Chang et al., 2019). Chronically elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6) have been associated with poorer cognitive functioning, especially during the acute infection phases (Heringa et al., 2014). Furthermore, pro-inflammatory cytokines in the nervous system can cross the blood-brain barrier and lead to brain atrophy and neuronal injury, especially in medial temporal structures critical for learning and memory (Lin et al., 2018). As such, social support may preserve cognitive health for older adults with elevated cytokine levels or poor neurocardiac health due to the inflammatory process of aging. Vm-HRV and pro-inflammatory cytokines, often associated (Cooper et al., 2015), may be useful peripheral biomarkers to predict cognitive decline.

Thus, future research may benefit from examining the interplay between physiological risk, as measured by vm-HRV, CRP, and IL-6 for instance, with the protective element of strong friendships and exploring how the dynamic relationship between physiological risk and protective friendships intersect with cognition. This approach aligns with previous studies on the effects of social relationships on cognition, while also incorporating a novel focus on examining the interplay between risk and protective factors to enhance our understanding of the intricate relationships between physiological risk, social relationships, and cognition, thereby contributing to a more comprehensive and ecologically valid body of knowledge.

1.3. Objectives

This study examined the potential moderating benefit of friendship quality on cognitive aging in the context of physiological risk indicators-namely, vm-HRV, IL-6, and CRP, using the large nationally representative data set, Midlife in the United States (MIDUS), of middle-aged cognitively healthy American adults. The conceptual model is

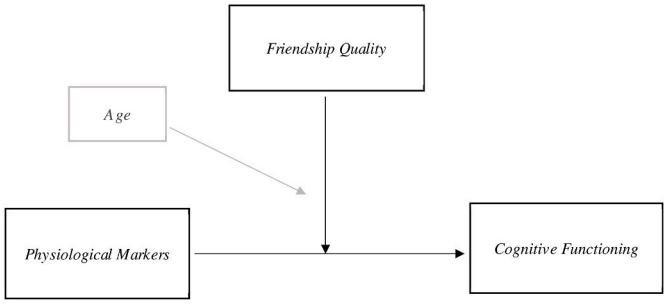

Fig. 1. Proposed model of friendship quality moderating the relationship between physiological markers and cognitive functioning.
Note. Given age is highly predictive of cognitive functioning, age was entered as a moderator in concurrent analyses as age may contextually shift the relationship among physiological markers, friendship quality, and cognitive functioning simultaneously. However, in the longitudinal analyses, age was entered as a covariate because cognitive functioning at time 1 was also included as covariate. Age was not expected to moderate the relationship among physiological markers, friendship quality, and cognitive functioning decline. The gray color highlights how age was incorporated into the model depending on the type of analysis, concurrent or longitudinal.

presented in Fig. 1. The goals of this study are two-fold: (a) explore the concurrent buffering effects and (b) investigate the longitudinal benefits of friendship quality on the neurovisceral and inflammatory risks for cognitive decline. In addition, exploratory analyses on how racial minority status may affect the outcomes were conducted.

2. Methods

2.1. Study data

Data for these analyses came from the second (M2) and third wave (M3) of the Midlife in the United States Study (MIDUS), which were collected between 2004-09 and 2013-17, respectively. MIDUS study has multiple longitudinal projects designed to examine various biopsychosocial factors on healthy aging (Karlamangla et al., 2014). M2 data was aggregated from multiple projects, including a phone survey (main (Ryff et al., 2021) + Milwaukee sub-study (Ryff et al., 2022a)), cognitive phone testing (Ryff and Lachman, 2023a,b), and biomarker study (Ryff et al., 2022b). The biomarker study involved a comprehensive two-day clinic-based biobehavioral assessment. Participants were recruited from those who completed the phone survey and were generally healthy enough to travel to a data collection center. At M3, only the phone cognitive testing data were used in this current study. Additional details about the MIDUS data collection methods, project designs, and participant attrition rates are delineated elsewhere (Dienberg Love et al., 2010; Hughes et al., 2018).

2.2. Participants

At M2, the present study utilized data from participants with complete data across all three projects; thus, the starting sample was 1052 participants, 43.1 % male, 83.2 % White, and 54.4 ± 11.5 years old. Participants (n = 123) were removed for the following reasons: incomplete cognitive data (n = 36), missing all three biomarkers of interest (n = 2), incomplete survey data on friendship quality questions (n = 6), missing covariate data (n = 3), potential acute infection as indexed by serum CRP values over 20 mg/L (n = 12), and those with a body mass index over 40 kg/m^2 (n = 64). Thus, the final M2 sample included 929 participants, 44.9 % male, 85.6 % White, and 54.6 ± 11.6 years old. Due to attrition at M3, the longitudinal analyses include 757 participants, 43.7 % male, 86.4 % White, and 62.7 ± 10.7 years old. Given that some participants were missing some biomarker data, the sample sizes varied slightly by biomarker analysis in the following manner: at M2 and M3, respectively, vm-HRV sample was 929 and 757, CRP sample was 921 and 751, and IL-6 sample was 925 and 755.

2.3. Biological markers

2.3.1. Vagally-mediated heart rate variability

The biomarker procedure was administered on the second day of the laboratory clinic visit. To maintain consistency, meals were standardized, and caffeine was not served during the participants' stay. Resting HRV was collected using a standardized procedure across all participants. The psychophysiological procedure collected seated resting baseline HRV data for 11 min. The root mean squared successive beat-to-beat variation differences (RMSSD) at rest was used to estimate vm-HRV, given it is considered a proxy for vagal or parasympathetic activity (Kimhy et al., 2013; Shaffer and Ginsberg, 2017; Williams et al., 2019). All HRV data flagged as scoreable or better were retained in the analyses, and the natural log-transformed RMSSD values were used as done in previous publications (Karlamangla et al., 2014).

2.3.2. Systemic inflammation

C-reactive protein (CRP) and IL-6 levels were assessed from a morning fasting blood draw on day 2. CRP was quantified by BNI nephelometer (Dade Behring Inc., Deerfield., IL) (Cooper et al., 2015), while IL-6 was assayed via enzyme-linked immunosorbent assay (ELISA; Karlamangla et al., 2014; Sartori et al., 2012; Simen et al., 2011). The positively skewed CRP and IL-6 values were natural-log transformed to facilitate statistical analyses and interpretations as done in prior studies (Cooper et al., 2015).

2.4. Friendship quality

A friendship quality composite score (i.e., quality + contact frequency) was estimated using a 4-item friendship quality scale and 1-item frequency of friend contact on a scale from 1 ″several times a day" to 8 ″never or hardly ever." The quality items included questions like "How much do your friends really care about you" and were reverse-coded when necessary. The four quality items were averaged, providing a score between 1 and 4, with higher scores meaning greater quality. The frequency item was reversed coded and divided by 2 resulting in values ranging from 0.5 to 4 with higher levels meaning more friend contact. The two sub-scores were multiplied to calculate the combined effect of friend quality and contact frequency, creating a final composite score ranging from 0.5 to 16. A higher total score indicated greater levels of quality friendship. Friendship quality composite score had an acceptable internal consistency for the present study sample (Cronbach's $\alpha = .88$).

2.5. Global cognition

Global cognition was measured using the Brief Test of Adult Cognition by Telephone (BTACT), a well-validated telephone measure of many cognitive functions, including working memory and information processing. BTACT was administered at both M2 and M3 time points. Previous studies have found no significant differences between telephone and in-person assessments of these tests (Lachman et al., 2014). Studies have found these tests to be strong measures of cognitive ability because of their ease of administration, strong evidence of construct validity, and reliability in another study using the MIDUS dataset (Gurnani et al., 2015). The BTACT composite scores, consisting of the average of the standardized values of the sub-tests, were transformed into Z-scores for analysis (Lachman et al., 2014). Higher values indicate better cognitive functioning.

2.6. Control variables

Sex, education, and racial minority status were used as covariates because various studies have associated these variables with influencing the relationship between cognition and age (Hughes et al., 2018; Lachman et al., 2014). Cardiovascular-related medication use (yes = 1 and no = 0) was added as a covariate for the vm-HRV analyses due; this dichotomous variable was used because 65 % of the sample did not report using a cardiovascular-related medication. For IL-6 and CRP analyses, anti-hypertensive, cholesterol-controlling, antidepressant, and anti-inflammatory (e.g., steroids, non-steroidal anti-inflammatory drugs) medication use was totaled; this variable was added as a covariate due to their potential influence on immune function (Friedman and Herd, 2010). Education was measured on a scale from 1, indicating "no school/some grade school", to 12, indicating "Ph.D., Ed.D., MD, DDS, LLB, LLD, JD or other professional degree". Racial minority status was coded as a binary variable (0 = White and 1 = Minority). Sex was measured as a binary variable (0 = Male and 1 = Female).

2.7. Analyses

Statistical analyses were conducted using the PROCESS Macro (version 3.5) and SPSS Statistics software (version 26). All tests are two-tailed and set at a significance level of $\alpha = 0.05$. Racial minority status, sex, medication use, and education level were control variables for the cross-sectional analyses. Except for sex, racial minority status and cardiovascular medication use, all variables were analyzed as continuous.

All continuous predictor variables were automatically mean-centered using the PROCESS Macro prior to analysis to aid the results interpretation and generate estimates to examine the interactions (Hayes, 2017).

To test our proposed moderated moderation model at M2, separate three-way interactions were conducted using PROCESS model 3 such that cognitive functioning was the dependent variable and the physiological risk factor was the primary predictor variable, while the friendship quality composite score and age were inputted as the moderating variables. Any significant 2-way interactions were further explored. To examine whether M2 biomarkers and friendship quality and their interaction were related to M3 cognitive function, separate 2-way interactions were examined using PROCESS model 1 while controlling for covariates from cross-sectional analyses plus M3 age and M2 cognitive functioning.

3. Results

3.1. Sample characteristics and key variable correlations

As expected, M2 and M3 cognitive function were highly associated. In addition, poorer M2 and M3 cognitive functioning was related to identifying as a racial minority, use of cardiovascular or inflammation-related medications, elevated systemic inflammation, and being older, while better M2 and M3 cognitive functioning was linked to higher education. M2 cognitive functioning was positively associated with friendship quality. Higher vm-HRV at M2 was related to greater M3 cognitive function. The sample characteristics (mean, frequencies, and zero-order correlations) of the study variables are represented in Table 1. Given the strong relationship between racial minority status and cognitive functioning at M2 and M3 (r = −0.29 and r = −0.26, respectively), analyses were conducted with the overall sample and repeated by racial minority status. The racial minority sub-group (n = 134) was comprised of those who identified as Black/African American (n = 115), Native American/Indian (n = 6), Asian American (n = 2) or other (n = 11).

3.2. Concurrent moderated moderation among age, biological markers, and friendship quality on global cognition

Higher friendship quality remained a significant predictor of better cognitive function across models. See Table 2 for the detailed statistical model summaries for all biological marker analyses. For the whole sample, vm-HRV, friendship quality, and age interacted to predict concurrent global cognition ($\Delta R^2 = 0.003$, $F(1, 917) = 4.27$, $p = .039$, 95 % CI [0.0001, 0.0036]). Tests of the conditional interactions demonstrate that vm-HRV and friendship quality interaction was significant for younger individuals (β = −.03, $p = .04$), but not older individuals (β = 0.01, $p = .40$). Simple slopes revealed that among younger adults with higher friendship quality, as their vm-HRV increased, their cognition functioning decreased (β = −.16, $p = .03$, 95 % CI [-0.31, −0.01]), but not for those with poorer friendship quality (β = 0.06, $p = .45$, 95 % CI [-0.10, 0.23]; see Fig. 2). All 2-way interactions were insignificant.

For the whole sample, only the CRP by age interaction significantly predicted cognitive functioning ($\Delta R^2 = 0.003$, $F(1, 912) = 4.57$, $p = .033$, 95 % CI [0.0003, 0.0081]). Simple slopes revealed that among younger adults, as CRP increased, cognition functioning decreased (β = −0.07, $p = .02$, 95 % CI [-0.13, −0.01]), but not for older adults (β = 0.03, $p = .47$, 95 % CI [-0.04, 0.09]; see Fig. 3). All other 2-way interactions and the 3-way interaction were not significant. For the whole sample analysis utilizing IL-6 as the biological marker, no 2- or 3- way interactions were significant.

In sub-group analyses for vm-HRV and CRP, the White results mirrored the overall group, ($\Delta R^2 = 0.003$, $F(1, 784) = 3.65$, $p = .056$, 95 % CI [-0.000, 0.004]) and ($\Delta R^2 = 0.004$, $F(1, 781) = 4.69$, $p = .031$, 95 % CI [0.0004, 0.0089]), respectively, while the racial minority results did not ($\Delta R^2 = 0.004$, $F(1, 123) = 0.70$, $p = .40$, 95 % CI [-0.003, 0.006]) and ($\Delta R^2 = 0.001$, $F(1, 126) = 0.29$, $p = .88$, 95 % CI [-0.011, 0.009]), respectively. For the IL-6 analyses, both sub-groups' results mirrored the overall group with no statistically significant findings. In addition, higher friendship quality was only a significant predictor of better cognitive function for the White sub-sample, not the racial minority sub-sample. For detailed summaries of the sub-group analyses, see Supplemental Tables 1 and 2

3.3. Longitudinal relationships among biological markers and friendship quality on global cognition over time

For the whole sample, as expected, M2 cognitive functioning was a strong predictor of M3 cognitive functioning; such that neither M2 vm-HRV nor M2 CRP as main effects or their interactions with M2 friendship quality significantly predicted M3 cognitive functioning. See Table 3 for the detailed statistical model summaries for all biological marker analyses. The analyses by racial minority sub-sample mirrored the whole group analyses. For detailed summaries of the sub-group analyses, see Supplemental Tables 3 and 4

However, for the overall sample, M2 IL-6 and M2 friendship quality interacted to predict M3 cognitive functioning, over and above M2 cognitive functioning at the trend level ($\Delta R^2 = 0.002$, $F(1, 745) = 3.84$, $p = .050$, 95 % CI [-0.022, 0.000]). In the sub-group analyses, this interaction reached significance for White sub-sample ($\Delta R^2 = 0.003$, $F(1, 643) = 5.07$, $p = .02$, 95 % CI [-0.027, −0.002]), but not the racial minority sub-sample ($\Delta R^2 = 0.001$, $F(1, 94) = 0.119$, $p = .73$, 95 % CI

Table 1
Descriptive statistics and zero-order correlations among study variables.

Variables	M/n	SD/%	1	2	3	4	5	6	7	8	9	10	11
1. M2 Sex (female)	512	55.1 %	–										
2. M2 Racial Minority (yes)	134	14.4 %	.08*	–									
3. M2 Education	7.6	2.5	−.07*	−.15***	–								
4. M2 CV Med Use (yes)	324	34.9 %	−.02	.04	−.06†	–							
5. M2 Inflam Med Use (#)	2.2	1.7	.03	−.02	−.02	.53***	–						
6. M2 Age (years)	54.6	11.6	−.03	−.07*	−.08*	.36**	.30***	–					
7. M2 RMSSD (msec)[d]	22.02	16.72	.01	.13***	−.03	−.06†	−.17***	−.20***	–				
8. M2 CRP (mg/L)[a,d]	2.2	2.5	.14***	.09**	−.10**	.13***	.14***	.03	−.11***	–			
9. M2 IL-6 (pg/mL)[b,d]	2.7	2.7	.04	.15***	−.10**	.23***	−.13***	.20***	−.13**	.46***	–		
10. M2 Friendship Quality	9.8	3.7	.13***	−.02	.09**	.04	−.01	.05†	.01	.03	.02	–	
11. M2 BTACT	.14	.93	.01	−.29***	.38***	−.24***	−.17***	−.39***	.02	−.10**	−.19***	.08*	–
12. M3 BTACT[c]	.05	.67	−.01	−.26***	.38***	−.22***	−.16***	−.42***	.08*	−.13***	−.15***	.05	.79***

Note. $N = 929$, unless otherwise noted. [a] $N = 921$, [b] $N = 925$, [c] $N = 757$. †$p < .10$ *$p < .05$, **$p < .01$, ***p < .001. M2 = MIDUS Wave 2 data collection; CV Med = cardiovascular medication use; Inflam Med = number of inflammation-altering medications; RMSSD = root-mean squared of successive differences of R–R intervals; msec = millisecond; CRP=C-reactive protein; mg/L = milligrams per liter; IL-6 = interleukin-6; pg/ml = picograms per milliliter; BTACT = Brief Test of Adult Cognition by Telephone Z-score; M3 = MIDUS Wave 3 data collection. [d] Raw scores were provided for interpretation, but natural log-transformed data were used in analyses. RMSSD was used as the index for vagally-mediated heart rate variability (vm-HRV).

Table 2
Summary of the analyses examining the 3-way interaction (PROCESS macro model 3) among biological markers, friendship quality, and age on concurrent cognitive functioning.

Variable	Biological Marker					
	vm-HRV (n = 929)		CRP (n = 921)		IL-6 (n = 925)	
	β	[LLCI, ULCI]	*β*	[LLCI, ULCI]	*β*	[LLCI, ULCI]
Sex (female)	.056	[-.043, .155]	.073	[-.027, .173]	.061	[-.038, .161]
Racial Minority Status (yes)	−.701***	[-.842, −.559]	−.717***	[-.859, −.574]	−.708***	[-.851, −.564]
M2 Education	.115***	[.095, .135]	.117***	[.096, .137]	.115***	[.095, .135]
M2 Med Use[a]	−.177**	[-.287, −.067]	−.036*	[-.065, −.007]	−.037*	[-.066, −.008]
Biomarker	−.015	[-.094, .065]	−.024	[-.070, .022]	−.057	[-.129, .016]
Friendship Quality (Friend Qual)	.020**	[.006, .033]	.015*	[.002, .029]	.016*	[.003, .030]
Biomarker X Friend Qual	−.009	[-.030, .012]	−.000	[-.013, .012]	−.015	[-.035, .005]
Age	−.029***	[-.033, −.024]	−.029***	[-.034, −.025]	−.028***	[-.033, −.024]
Biomarker X Age	.003	[-.003, .010]	.004*	[.000, .008]	−.003	[-.009, .004]
Friend Qual X Age	.001	[-.001, .002]	.001	[-.000, .002]	.001	[-.000, .002]
Biomarker X Friend Qual X Age	.002*	[.000, .004]	−.000	[-.001, .001]	−.001	[-.002, .001]
	ΔR^2 =	.003*	ΔR^2 =	.000	ΔR^2 =	.000

Note. *p < .05, **p < .01, ***p < .001. vm-HRV = vagal-mediated heart rate variability; CRP=C-reactive protein; IL-6 = interleukin-6; M2 = MIDUS Wave 2 data collection; Med Use = medication use; β = beta coefficient; LLCI = lower limit of 95% confidence interval; ULCI = upper limit of 95% confidence interval. [a] For the vm-HRV analyses, cardiovascular medication use (yes = 1 or no = 0) was controlled for, while for the CRP and IL-6 analyses, total number of medications used that are known to potentially influence systemic inflammation was controlled for.

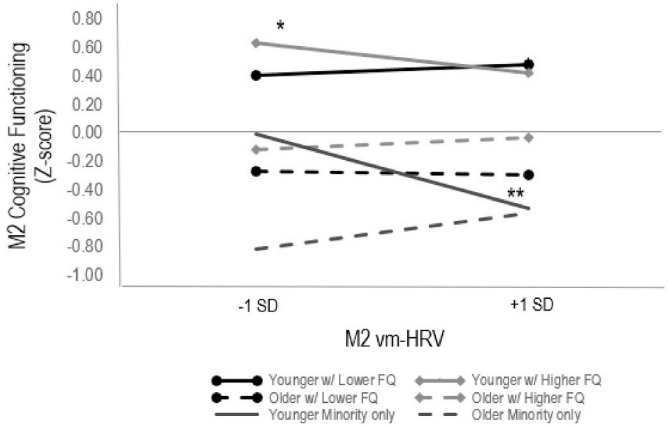

Fig. 2. Simple Slopes Showing a 3-Way Interaction among vm-HRV, Friendship Quality (FQ), and Age for Overall Sample on Concurrent Cognitive Functioning as well as a 2-Way Interaction between vm-HRV and Age on Concurrent Cognitive Functioning for the Racial Minority Sub-group Only.
Note. *$p < .05$, **$p < .01$. Using PROCESS macro model 3, the 3-way interaction for the overall sample significantly predicted cognitive functioning when controlling for racial minority status, gender, education, and cardiovascular medication use. For the line representing younger adults with higher friendship quality, vm-HRV was negatively associated with cognitive functioning (β = −.164, $p = .03$). The other 3 lines' slopes indicating varying levels of friendship quality by age were not different than 0. The analyses were repeated by racial minority status. The White sub-sample analysis mirrored the overall sample findings; however, the racial minority sub-sample revealed a significant vm-HRV by age interaction, instead of a 3-way interaction with friendship quality. For the line indicating the younger racial minority sub-sample, vm-HRV was negatively associated with cognitive functioning (β = −.383, $p = .008$), while the slope of the line representing their older counterparts was not different than 0. vm-HRV = vagally mediated-heart rate variability, M2 = MIDUS wave 2 data collection, FQ = Friendship quality, SD = standard deviation.

[-0.032, 0.023]). Simple slopes revealed that among White individuals with greater friendship quality, as their IL-6 increased, their cognition functioning decreased (β = −0.070, $p = .047$, 95 % CI [-0.138, −0.001]), but not for those with poorer friendship quality (β = 0.036, $p = .25$, 95 % CI [-0.025, 0.097]; see Fig. 4).

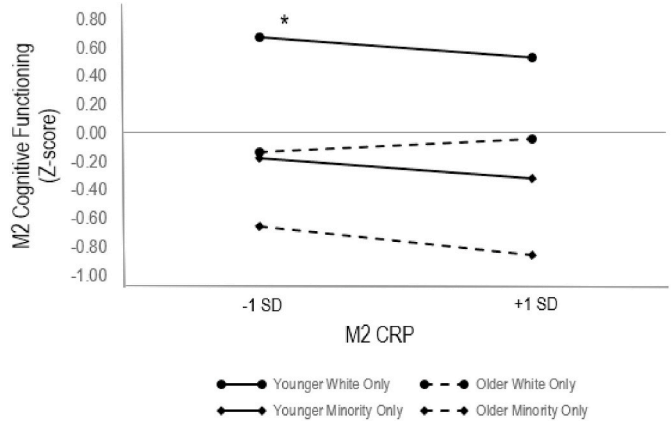

Fig. 3. Simple slopes Showing a 2-way interaction between CRP and age on concurrent cognitive functioning by racial minority status.
Note. *$p < .05$. Using PROCESS macro model 1, the 2-way interaction for the overall sample significantly predicted cognitive functioning when controlling for racial minority status, gender, education, and inflammation-related medication use. When further investigating the 2-way interaction by racial minority status, the interaction was only significant for the White sub-sample, not the racial minority sub-sample. For the line representing younger white adults, CRP was negatively associated with cognitive functioning (β = −.066, $p = .049$). The other 3 lines' slopes were not different than 0. CRP=C-reactive protein, M2 = MIDUS wave 2 data collection, SD = standard deviation.

4. Discussion

This study expands upon prior literature by examining the differential effects of protective and risk factors on global cognition and highlighting the nuanced interplay between physiological and psychosocial factors in cognitive health. Consistent with prior literature examining the MIDUS sample, we found that as age increased, global cognition decreased concurrently and longitudinally (Agrigoroaei and Lachman, 2011; Hughes et al., 2018). Yet, the decrease in global cognitive functioning was differentially affected by separate protective and risk factors.

Greater friendship quality was related to better cognitive function when controlling for known confounds (see Table 2). Our cross-sectional results demonstrate the interactive effects among age, vm-HRV, and friendship quality on global cognition as well as age and CRP levels; these observed biomarker effects on concurrent cognitive function

Table 3
Summary of the analyses examining the 2-way interaction (PROCESS macro model 1) among biological markers and friendship quality on cognitive functioning over time.

Variable	Biological Marker					
	vm-HRV (n = 757)		CRP (n = 751)		IL-6 (n = 755)	
	ß	[LLCI, ULCI]	*ß*	[LLCI, ULCI]	*ß*	[LLCI, ULCI]
M2 Cognitive Functioning	.488***	[.451, .524]	.488***	[.451, .524]	.485***	[.448, .521]
Sex (female)	.003	[-.054, .059]	.009	[-.048, .066]	.005	[-.052, .062]
Racial Minority Status (yes)	−.117**	[-.202, −.031]	−.120**	[-.206, −.034]	−.115**	[-.201, −.028]
M2 Education	.029***	[.016, .041]	.027***	[.015, .039]	.029***	[.017, .042]
M2 Med Use[a]	−.010	[-.073, .053]	−.011	[-.028, .005]	−.014	[-.030, .003]
M3 Age	−.013***	[-.016, −.010]	−.012***	[-.015, −.009]	−.012***	[-.015, −.010]
Biomarker	.025	[-.022, .071]	−.022	[-.048, .005]	−.006	[-.048, .036]
Friendship Quality	.000	[-.008, .008]	.000	[-.007, .008]	.000	[-.007, .008]
Biomarker X Friendship Quality	−.004	[-.016, .008]	−.001	[-.008, .006]	−.011†	[-.023, .000]
	ΔR^2 =	.000	ΔR^2 =	.000	ΔR^2 =	.002†

Note. †p = .05, *p < .05, **p < .01, ***p < .001. vm-HRV = vagal-mediated heart rate variability; CRP=C-reactive protein; IL-6 = interleukin-6; M2 = MIDUS Wave 2 data collection; M3 = MIDUS Wave 3 data collection; Med Use = medication use; ß = beta coefficient; LLCI = lower limit of 95% confidence interval; ULCI = upper limit of 95% confidence interval. [a] For the vm-HRV analyses, cardiovascular medication use (yes = 1 or no = 0) was controlled for, while for the CRP and IL-6 analyses, total number of medications used that are known to potentially influence systemic inflammation was controlled for.

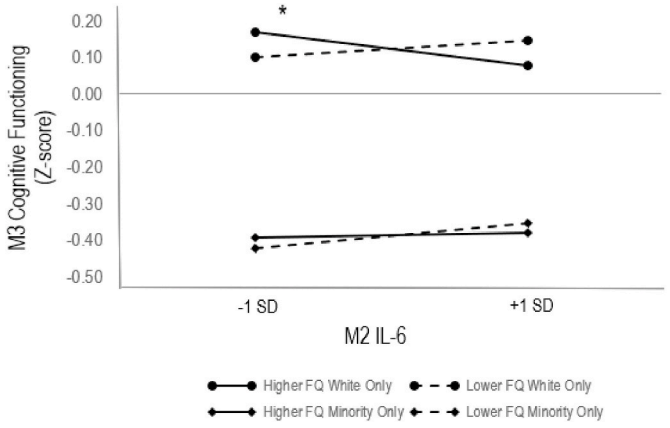

Fig. 4. Simple slopes Showing a 2-way interaction between IL-6 and friendship quality (FQ) on cognitive functioning a decade later by racial minority status. *Note.* *$p < .05$. Using PROCESS macro model 1, the 2-way interaction for the overall sample predicted M3 cognitive functioning when controlling for M2 cognitive functioning, M3 age, minority status, gender, education, and inflammation-related medication use. When further investigating the 2-way interaction by racial sub-group, the interaction was only significant for the White sub-sample, not the racial minority sub-sample. For the line representing white individuals with higher friendship quality, higher M2 IL-6 predicted poorer M3 cognitive functioning ($\beta = -0.069$, $p = .047$). The other 3 lines' slopes were not different than 0. IL-6 = Interleukin-6, M3 = MIDUS wave 3 data collection, M2 = MIDUS wave 2 data collection, SD = standard deviation.

appear only for young adults. Uniquely, M2 friendship quality and M2 IL-6 levels interacted to predict M3 global cognition over and above M2 cognitive functioning.

4.1. Predicting future cognitive functioning

IL-6 interacted with friendship quality to significantly predict future, not concurrent, cognitive functioning over and above prior cognitive functioning and age. Specifically, higher IL-6 levels predicted cognitive function decline a decade later for those with greater friendship quality, as expected, but not in their counterparts with lower friendship quality. Although the expected relationship between IL-6 and cognitive function was observed, it was observed unexpectedly in those with greater friendship support (see Fig. 4). Specifically, perhaps chronic elevations in IL-6 create a physiological vulnerability that allows for a greater benefit from the protective effects of social support. Another way to think about this finding in this sample is that the context of having better friendship quality afforded the opportunity to observe the negative effect of IL-6 on cognitive functioning over time, suggesting that prior data exhibiting this negative relationship (Puterman et al., 2014) may happen to have included sample populations who on average had higher friendship quality. Furthermore, the finding was carried by the White/Caucasian sub-sample.

These context-dependent findings highlight the need to further understand the lived experience more completely. For example, among those with poorer friendship quality, other factors, such as greater perceived stress, chronic stress, or chronic physical health conditions, may better explain cognitive decline over time than systemic inflammation levels. Other studies have pointed to the role of genetic markers, such as APOε4 alleles, as a moderator of the relationship between IL-6 and global cognition such that those with the allele may have a stronger negative relationship (Windham et al., 2014). While it remains unknown if the effects of IL-6 on cognition are direct or indirect, our findings suggest the latter and that moderating factors, such as psychosocial influences, are necessary to incorporate in future cognitive aging research.

4.2. Context influences concurrent cognition findings

In line with prior research, baseline CRP and IL-6 negatively correlated with concurrent and longitudinal global cognition levels, supporting the role of systemic inflammation as a negative predictor of cognition. Further, vm-HRV was positively associated with global cognition longitudinally (see Table 1). While prior cross-sectional studies have found similar associations, they argued for their utility as broad indicators of allostatic load, a negative predictor of cognition across the lifespan, regardless of age (Karlamangla et al., 2014; Kimhy et al., 2013).

However, in the present analyses, age was a significant moderator or contextual variable on how the concurrent biological and psychosocial factors influenced global cognition. For the overall sample, higher friendship quality only buffered the effect of lower vm-HRV on cognitive functioning among younger adults (see Fig. 2). Furthermore, higher CRP levels were only related to poorer cognitive functioning for younger adults (see Fig. 3). In this sample, these neurovisceral and inflammatory markers were not related to cognitive function among older adults, suggesting that monitoring biomarkers among mid-life adults may be particularly informative for understanding cognitive health outcomes.

Unexpectedly, vm-HRV was negatively related to global cognition levels concurrently in particular psychosocial contexts. This relationship existed within the overall sample, among younger adults with greater

friendship quality, and uniquely within the racial minority sub-group, regardless of friendship quality (see Fig. 2). These findings provide partial evidence that stronger friendship quality may preserve cognitive functioning in the context of lower vm-HRV for some populations but not all.

Through a dysregulated body lens, this finding may indicate that an individual experiencing chronic stress or at an increased physiological risk for chronic disease development, especially White individuals, may cognitively benefit by maintaining stronger friendships and suggest that the relationship between vm-HRV and cognition is sensitive to the bio-psychosocial environment. However, these findings starkly contrast prior evidence linking greater vm-HRV and parasympathetic activation with better cognitive performance in cognitively normal older adults (Forte et al., 2019; Magnon et al., 2022). The overall sample results, that the White only sample mirrored, indicate that stronger friendship quality is only protective during times of distress (i.e., lower vm-HRV) but not when the body is functioning well (i.e., higher vm-HRV). This benefit of social support in a high-stress context has replicated previous findings in samples that are mostly from European/Caucasian descent (Gerteis and Schwerdtfeger, 2016).

The traditional framing of vm-HRV as a positive marker of neurovisceral functioning (Tiwari et al., 2021) may be an oversimplification of a more nuanced index. For example, several studies found positive relationships between vm-HRV and perceived discrimination (Kemp et al., 2016; Rosati et al., 2021; Shaffer and Ginsberg, 2017), but not necessarily linked to better health outcomes. This relationship led Hill et al. (2015) to coin the term *cardiovascular conundrum,* describing the repeated findings that Black/African-American samples in the US have greater vm-HRV than White/Caucasian-American samples and, yet, they are still at greater risk of developing and have higher prevalence rates of cardiovascular diseases.

Similar to the negative relationship in the current data, higher vm-HRV was related in greater left ventricle hypertrophy, a negative health outcome, within a Black/African-American sample (Hill et al., 2017). Hence, vm-HRV may be more a marker of emotion regulation and connected with the flexibility needed to navigate regular perceived discrimination as seen in sexual or racial minority samples (Rosati et al., 2021), not a global marker of better physiological functioning. We encourage future studies to replicate and explore this potential racial difference, given this secondary data analysis was not designed to look at racial differences and that 15% of the racial minority sub-sample did not identify as Black/African-American.

Further, our construct of friendship quality, which assessed perceptions of care, understanding, and reliance from friends, does not differentiate between reliance on friendship quality during times of high or low stress. As such, in a context of chronic stress resulting in greater reliance on friends and higher friendship quality among the younger adults overall, greater vm-HRV may reflect continuous neurovisceral adjustments to cumulative stressors (Fig. 2). In this case, the inflammatory effects of chronic stress may indicate a more stable dysfunctional state than the momentary adjustments between the brain and heart and demonstrate the expected negative relationship with cognitive functioning, which is consistent with what we found (Figs. 3 and 4).

As expected, higher CRP levels were associated with poorer concurrent cognitive functioning (see Fig. 3). However, this relationship was only statistically significant for younger adults, suggesting that systemic inflammation levels may not be a useful proxy for understanding cognitive functioning for older adults. Upon splitting the sample by racial minority status, the overall finding appears to be carried by the White identifying sample; however, both (younger and older) lines representing racial minority sample have a slight negative slope. Thus, it is unclear if the lack of relationship between CRP and cognitive function among the racial minority sub-sample is due to power – small effect and small sample size – or whether the relationship does exists. Future studies should be designed to answer this question.

Our results add to the literature by providing evidence for a nuanced and dynamic relationship between physiological risk and social protective factors on cognitive functioning. For instance, prior authors have opined on the increased cognitive demand necessary for maintaining friendships and friend-based dialogues and conversations, such as memory, planning, inhibition, and processing speed (Kelly et al., 2017). Regularly using cognitive skills to maintain friendships may prime the brain to efficiently use remaining neuroanatomical resources that are not yet affected by neuroinflammation (Peng et al., 2022). That is, friendships may offer a form of regular cognitive exercise useful for optimizing cognitive health and can offset inflammation-mediated neuronal decay. Thus, quality friendships may protect the brain's functioning in the context of a stressed body, as purported by the cognitive reserve hypothesis (Stern et al., 2019).

Similar to studies on the role of overall social support on health, our data align with previous findings on the positive associations between friendship quality, specifically, and cognition (Table 2). One recent study examined friendship through network size among African-Americans and found that older adults with more friends and not more family members, in their social networks had better cognition (Sharifian et al., 2019). Moreover, among older Chinese adults, when examining both the quantitative and qualitative aspects of friendships, quantitative structural aspects of friendships maintained specific aspects of cognition and friendship quality had a protective benefit on global cognition (Li and Dong, 2018). Qualitative studies have described how rural older adults in the US incorporate social health and regular social interactions as central to their overall well-being (Bacsu et al., 2014).

Our findings contribute to the existing literature by highlighting the complex interrelationships between myriad external and internal factors on cognitive functioning. The study provides novel insights into the interactive effects of age, physiological risk factors, and friendship quality on global cognition. With the intention to improve the ecological validity of the cognitive research landscape by considering the various health-promoting and health-limiting factors that simultaneously and dynamically influence cognitive outcomes, this study uniquely utilizes cross-sectional and longitudinal data within a complex moderation model.

4.3. Limitations

Although the current study examined cross-sectional and longitudinal associations, some limitations should be noted. One, participants in multi-wave longitudinal studies tend to be healthier than their population counterparts, which limits their generalizability (Agrigoroaei and Lachman, 2011). The presence of this limiting factor has implications for how the results should be interpreted. It may be that, among individuals with clinically significant levels of physiological risk who were automatically excluded from the MIDUS study (e.g., elevated blood pressure levels), friend support may not buffer cognitive decline concurrently or longitudinally. Second, the items measuring friendship quality were not rigorously assessed for standardization and reliability; however, they were used in previous research to assess friendship in the MIDUS sample (Sharifian et al., 2020). Future studies may benefit from utilizing validated and reliable social support measures that tease apart types, like given versus received support.

Furthermore, understanding the mechanism(s) through which friendship quality or social support influences cognitive functioning may require ecological momentary assessment or daily diary study designs Campbell et al., 2020; Ma et al., 2023; Neff et al., 2021). Third, these preliminary findings were analyzed from a secondary dataset, which was not designed with these analyses specifically in mind. Although large nationally representative epidemiological datasets can provide useful macro-level data on cross-sectional and longitudinal relationships, researchers are subject to the design of the original data collectors.

Last, friendship is a challenging construct to qualify across the lifespan. Health may have a confounding impact on friendship, such that health is needed to maintain friendship, and friendship, also, is

necessary for maintaining health. In addition, the loss of friendships over time was not measured in this study and friendship losses can be stressful, given that the friendship once existed. Qualitative studies have found that as people age, the meaning of friendships and their durability evolve over time and that older adults report their friendships to be more meaningful as they age (Sharifian et al., 2020; Zahodne et al., 2021). Thus, a friendship scale that measures the ongoing role and importance of friendship across the lifespan may benefit from including statements about the dynamic influence of friendships and perhaps the strain due to the loss of friendships. Our friendship quality measure only inquired into the supportive aspects of friendships and the frequency of contact.

4.4. Conclusion

In order to gain a more comprehensive and clinically useful understanding of the complex processes involved in aging, it is crucial to employ models that explore the dynamic relationships between risk and protective factors simultaneously. This approach allows for a more holistic analysis of concurrent and longitudinal relationships between physiological risk and social protective factors on cognitive functioning, as opposed to studying these factors in isolation. While previous research has examined various aspects of social relationships (Agrigoroaei and Lachman, 2011), physiological risk (Karlamangla et al., 2014), and inflammation (Bradburn et al., 2017) on cognition, this study presents a novel contribution by exploring the concurrent and longitudinal relationships as a whole using the large MIDUS dataset sample. Multiple factors interacted to predict global cognition at one-time point and across 10 years.

To the authors' knowledge, this is the first study to explore the concurrent and longitudinal relationships between physiological risk and psychosocial protective factors in the MIDUS dataset. In support of many existing hypotheses on cognitive functioning and social stress buffers, friendship quality was a strong protector of cognitive functioning, especially when considering neurovisceral health and systemic inflammatory markers. These findings highlight the importance of integrating physiological and psychosocial data when investigating cognitive aging. It is premature to intervene directly at the biological level to stimulate the desired long-term cognitive effects. Yet, these findings support broad recommendations for improving cognitive health through whole-body health interventions before old age. The novelty of this study lies in its holistic and integrative examination of these relationships within the context of the cognitively healthy and diverse epidemiological dataset. These findings align with existing hypotheses on the biopsychosocial determinants of cognitive health and the importance of social stress buffers, supporting the need for comprehensive approaches that explore internal and external dynamic influences on cognitive aging.

CRediT authorship contribution statement

Ameanté Payen: Conceptualization, Formal analysis, Writing – original draft. **James R. Bateman:** Writing – review & editing. **Michael J. Persin:** Conceptualization, Writing – review & editing. **Jeanette M. Bennett:** Conceptualization, Formal analysis, Software, Supervision, Writing – review & editing.

Declaration of competing interest

All authors have no conflicts of interest or financial disclosures to report in regards to the creation of this manuscript. The authors received no funding to draft this manuscript.

Data availability

MIDUS data are publicly available except the Milwaukee sub-study. An additional confidentiality agreement to access the Milwaukee sub-study is required by researchers, stating the data would not be shared outside the research team. However, all data can be accessed via ICPSR; the studies used are listed in the Acknowledgements.

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Appendix A. Supplementary data

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