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EMPIRICAL ARTICLE

Longitudinal Stability and Cross-Sectional Correlates: Cognition, Stress, and Inflammation in Midlife

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ABSTRACT

To investigate longitudinal relationships among psychological stress, inflammation biomarkers, and cognitive function over a 9-year period using data from the Midlife in the United States (MIDUS) study. Structural Equation Modeling (SEM) was conducted on MIDUS Wave 2 data (M2, $N = 790$), incorporating biomarkers of stress (cortisol, norepinephrine, epinephrine, dopamine), inflammation (interleukin-6, C-reactive protein, fibrinogen, soluble ICAM-1), and cognition (episodic memory, executive function), with follow-up cognitive outcomes from MIDUS Wave 3 (M3). Confirmatory Factor Analysis (CFA) assessed measurement validity, and key SEM assumptions were tested. CFA indicated acceptable model fit. SEM revealed significant cross-sectional associations among stress, inflammation, and cognitive variables at baseline. Baseline cognitive function strongly predicted follow-up cognition 9 years later, indicating high longitudinal stability. However, stress and inflammation biomarkers from M2 did not directly predict M3 cognition. Indirect effects emerged: M2 cognition influenced both M3 executive function and episodic memory through M3 global cognition. Multi-group analysis showed no gender-based differences in model paths. Stress and inflammation biomarkers were associated with cognition cross-sectionally but showed no direct long-term effects. Findings highlight the relative stability and predictive continuity of midlife cognition rather than substantial mean-level change, underscoring midlife as a critical window for sustaining cognitive health.

1 | Introduction

Understanding midlife cognitive aging is crucial as global populations age and adults face rising risks of cognitive decline and health deterioration (Crimmins et al. 2011; Pais et al. 2020; United Nations 2015). Cognitive abilities such as memory, attention, and processing speed typically decline with age (Salthouse 2010), yet evidence from intervention studies indicates that decline is modifiable. Cognitive training and lifestyle interventions have improved performance in community-dwelling older adults, demonstrating the brain's continued capacity for plasticity (Lee et al. 2018; Rebok et al. 2014). Beyond normal aging, biological stress and inflammation are increasingly recognized as key contributors to cognitive variability (Andronie-Cioara et al. 2023; Franks et al. 2023; McEwen 2017; Tao et al. 2018). However, few studies have examined their combined and longitudinal influences during midlife—a critical but underexplored stage in the trajectory of cognitive aging.

1.1 | Stress and Cognition

Stress refers to physiological or psychological demands that challenge homeostasis (James et al. 2023; Selye 1976). Chronic

Summary

- Midlife cognitive function showed high longitudinal stability over a 9-year period.
- Psychological stress and inflammation biomarkers were associated with cognitive function cross-sectionally at baseline.
- Baseline stress and inflammation biomarkers did not directly predict cognitive function 9 years later, suggesting no direct long-term effect.
- Findings underscore midlife as a critical period for sustaining cognitive health, highlighting the relative stability of cognition during this stage.

stress impairs hippocampal function, disrupts neurogenesis, and hinders learning and memory (Kim et al. 2015; Maier and Seligman 2016). The allostatic load framework describes how prolonged exposure to stress hormones such as cortisol produces cumulative wear on body and brain systems (McEwen and Stellar 1993). Elevated cortisol and catecholamine levels are associated with poorer working memory, reduced executive function, and accelerated cognitive aging (Girotti et al. 2018; Juster et al. 2010). Longitudinal studies show that midlife stress predicts greater cognitive decline over subsequent decades (Christensen et al. 2023) and higher risks of incident cognitive impairment across demographic groups (Kulshreshtha et al. 2023). Together, these findings suggest that sustained stress during midlife may initiate processes leading to later-life cognitive vulnerability.

1.2 | Stress and Inflammation

Prolonged stress also disrupts immune balance, producing peripheral and central inflammation. The social signal transduction theory of depression posits that exposure to social threats or chronic stress upregulates inflammatory pathways, increasing cytokine production and promoting behavioral and somatic changes (Slavich and Irwin 2014). Experimental and epidemiological studies have confirmed elevated levels of interleukin-6 (IL-6), C-reactive protein (CRP), and other cytokines under chronic stress conditions (Johnson et al. 2013; Kiecolt-Glaser et al. 2003; McDade et al. 2006). This bidirectional neuroendocrine–immune communication involves the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system, which interact with inflammatory signaling to influence neural function and health (Beurel et al. 2020; Kenney and Ganta 2014). Dysregulated stress-inflammation coupling thus represents a plausible mechanism linking psychological stress to cognitive decline.

1.3 | Inflammation and Cognition

Systemic inflammation contributes to cardiovascular disease, metabolic dysregulation, and cognitive impairment (Yaffe et al. 2004). Pro-inflammatory cytokines interfere with synaptic plasticity and neurogenesis, diminishing cognitive reserve and increasing vulnerability to neural damage (Wilson et al. 2002). Elevated IL-6 and CRP levels are consistently associated with poorer cognitive outcomes (Tao et al. 2018; Yaffe et al. 2004). However, the strength and direction of these associations vary across studies. For instance, Griseta et al. (2023) observed that IL-6 was linked to cognitive impairment cross-sectionally but not longitudinally, indicating that inflammation's cognitive effects may be transient or mediated by other processes. Clarifying these inconsistencies requires long-term, integrative research on inflammatory biomarkers and cognitive change.

1.4 | Midlife Cognition and Longitudinal Change

Midlife represents a transitional stage between the cognitive peaks of early adulthood and the declines of later life (Hughes et al. 2018). Although much research focuses on aging populations, midlife may be the period when subtle cognitive changes first emerge, influencing subsequent aging trajectories. The MIDUS (Midlife in the United States) study offers a rare opportunity to investigate these processes through its large, longitudinal dataset that tracks multiple domains—episodic memory, executive function, and processing speed—across adulthood (Lachman et al. 2014). With its national scope and repeated measurement design, MIDUS allows examination of how midlife cognitive function predicts later outcomes and how physiological factors such as stress and inflammation contribute to these changes over time.

1.5 | Stress, Inflammation, and Cognition Interrelation

Psychoneuroendocrineimmunology (PNEI) research integrates evidence from the nervous, immune, and endocrine systems to explain how chronic stress and inflammation jointly affect brain and cognitive health (Bitzer-Quintero et al. 2022; Bottaccioli 2020; Ravi et al. 2021). Disruption of these regulatory systems can lead to "allostatic overload," a maladaptive physiological state that increases disease and cognitive risk (Guidi et al. 2021; Rohleder 2014) Despite the conceptual progress, longitudinal studies examining these interrelations remain scarce, especially among midlife adults. Identifying whether stress and inflammation act as direct or indirect predictors of long-term cognition requires comprehensive modeling that simultaneously evaluates psychological, biological, and cognitive domains.

1.6 | Research Gap, Study Contribution, and Hypotheses

Few studies have examined how stress, inflammation, and cognition interact longitudinally in midlife. Most existing research is cross-sectional or limited to older adults, constraining insights into the earlier stages of cognitive aging. As shown in Figure 1, the present study addresses this gap using structural equation modeling (SEM) with MIDUS data to test both cross-sectional associations and 9-year longitudinal pathways among stress biomarkers, inflammatory markers, and cognition. The model captures the stability of midlife cognition and explores whether

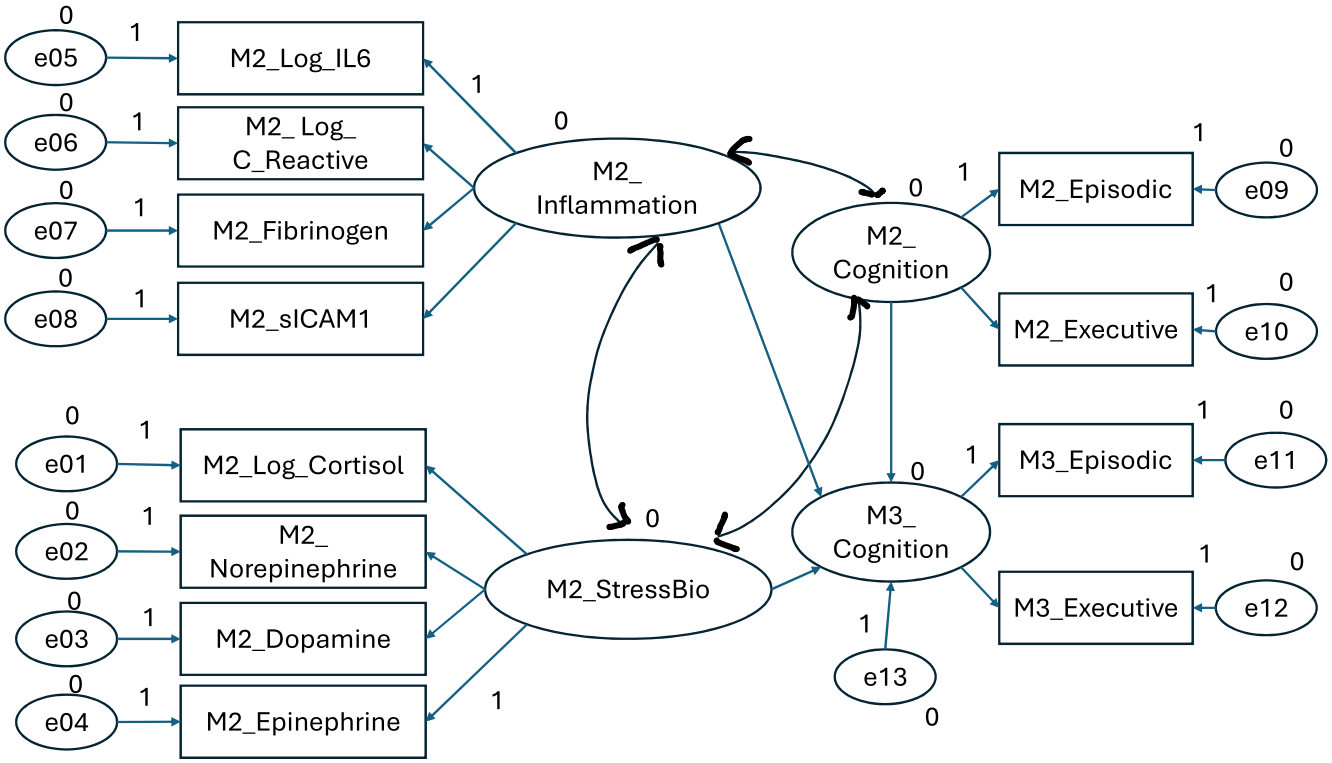

FIGURE 1 | Conceptual model of biomarkers of stress, inflammation, and cognition: Cross-sectional and longitudinal structural equation modeling (SEM).

stress and inflammation exert direct or indirect influences on later cognitive outcomes.

1.7 | Hypotheses

H1. *Stress and inflammation will be positively correlated at baseline.*

H2. *Stress and inflammation will not significantly predict later cognition once baseline cognition is considered.*

H3. *Midlife cognition will predict later cognition, reflecting longitudinal stability.*

H4. *The effect of midlife cognition on later executive and episodic outcomes will be mediated by follow-up global cognition.*

H5. *Structural relationships among stress, inflammation, and cognition will not differ significantly between male and female participants.*

2 | Methods

2.1 | Participants

This study used data from the *Midlife in the United States* (MIDUS 2; Brim et al. 2004), a national longitudinal survey conducted in 2004–2005. The MIDUS project recruited noninstitutionalized, English-speaking adults aged 25–74 years from the 48 contiguous U.S. states through random-digit dialing (RDD) and a national sampling frame. The Wave 2 survey achieved a 70% response rate for the telephone interviews, yielding 4512 respondents. Of these, 1255 individuals participated in the biomarker project, which included overnight clinic visits for biological sample collection.

Approximately 9 years later, a follow-up cognitive assessment (MIDUS 3; $N = 3291$) was conducted through standardized 30-min telephone interviews and self-administered questionnaires. For the present analysis, we merged MIDUS 2 biomarker and cognition data with MIDUS 3 cognitive outcomes, yielding an initial sample of 864 participants. After excluding incomplete cases ($n = 33$) and multivariate outliers based on Mahalanobis distance > 34.53 ($df = 13$, $p < 0.001$), the final analytic sample comprised 790 participants (mean age = 54.17 years, SD = 10.91; 44.8% male, 55.2% female; age range = 34–81). Attrition analyses indicated that participants retained at follow-up were generally healthier and more educated than those lost to follow-up, a common pattern in longitudinal studies of aging.

All MIDUS procedures were approved by institutional review boards at participating centers, and informed consent was obtained from all participants (Hughes et al. 2018).

2.2 | Measures

The measures include biomarkers of stress, inflammatory cytokines, and task-based evaluations of cognitive performance. All biomarker assays were analyzed using standardized laboratory

protocols at the University of Wisconsin–Madison MIDUS Biocore Laboratory, with intra-assay coefficients of variation (CVs) below 10%, indicating high reliability (Dienberg Love et al. 2010).

2.2.1 | Stress Biomarker

2.2.1.1 | Urine Cortisol Adjusted for Creatinine (μg/g). Cortisol is implicated in neurodegeneration and impaired hippocampal neurogenesis, affecting cognitive function (Ouanes and Popp 2019; Sousa and Almeida 2012). To ensure accuracy, cortisol concentration is adjusted for creatinine levels, accounting for variations in urine concentration. This adjustment provides a reliable measure, expressed as micrograms of cortisol per gram of creatinine (μg/g).

2.2.1.2 | Urine Norepinephrine Adjusted for Creatinine (μg/g). Norepinephrine, released during stress to activate "fight or flight" responses (Hussain et al. 2023), is measured in urine samples adjusted for creatinine to correct for urine concentration variability. Results are expressed as micrograms of norepinephrine per gram of creatinine (μg/g).

2.2.1.3 | Urine Epinephrine Adjusted for Creatinine (μg/g). Environmental stressors, such as noise exposure, are linked to increased urine epinephrine levels (Hussain et al. 2023; Wong et al. 2012). Adjusting for creatinine levels ensures accurate measurement of epinephrine relative to kidney function. Results are expressed as micrograms of epinephrine per gram of creatinine (μg/g).

2.2.1.4 | Urine Dopamine Adjusted for Creatinine (μg/g). Dopamine systems contribute to generating the stress response and coping responses to stress (Stanwood 2019). Additionally, dopamine is released alongside epinephrine and norepinephrine during acute stress, supporting adaptive responses and the formation of long-term emotional memories (Ouyang et al. 2012). Adjusting dopamine levels for creatinine compensates for urine concentration variability, ensuring standardized comparisons. Results are expressed as micrograms of dopamine per gram of creatinine (μg/g).

2.3 | Inflammation Biomarkers

2.3.1 | Interleukin-6 (IL-6) (pg/mL)

IL-6 is a cytokine crucial to the immune response, with its production triggered by factors like depression, negative emotions, and stress (Dentino et al. 1999; Kiecolt-Glaser et al. 2003). IL-6 levels are measured in blood serum and expressed in picograms per milliliter (pg/mL).

2.3.2 | C-Reactive Protein (CRP) (μg/mL)

CRP is a key biomarker of inflammation, with elevated levels linked to conditions such as rheumatoid arthritis, cardiovascular diseases, and infections (Du Clos and Mold 2004; Sproston and Ashworth 2018). Blood CRP concentration is analyzed and expressed in micrograms per milliliter (μg/mL).

2.3.3 | Fibrinogen (mg/dL)

Fibrinogen, essential for blood clotting, also serves as an inflammation marker. High levels have been associated with an increased risk of dementia (Lewis and Trempe 2017; Van Oijen et al. 2005). Fibrinogen levels are measured in blood and expressed in milligrams per deciliter (mg/dL).

2.3.4 | Serum Soluble ICAM-1 (sICAM-1) (ng/mL)

Soluble ICAM-1 is involved in neuroinflammatory processes. sICAM-1 has been suggested to reduce Aβ load and improve cognition in animal models of AD (Guha et al. 2022) and a higher level of CSF sICAM-1 is strongly correlated with the higher risk of developing dementia (Janelidze et al. 2018). sICAM-1 levels are measured in blood serum and expressed in nanograms per milliliter (ng/mL).

2.4 | Cognition

Cognition in this study refers to cognitive function, with data collected as part of the MIDUS cognitive study using the *Brief Test of Adult Cognition by Telephone* (BTACT), administered approximately nine years apart during MIDUS 2 and MIDUS 3. The BTACT comprises seven cognitive tests (Hughes et al. 2018; Lachman et al. 2014). Previous studies have established the BTACT's test–retest reliability and construct validity (Lachman et al. 2014). Previous research has demonstrated strong psychometric properties for the BTACT, with test–retest and alternate-form reliability ranging from 0.59 to 0.93 across subtests and 0.84 to 0.87 for the composite score (Lachman et al. 2014). Confirmatory factor analyses indicated two consistently captured factors across both assessments, aligning with prior studies (Farias et al. 2013; Hughes et al. 2018; Jurado and Rosselli 2007; Lachman et al. 2014; Tun and Lachman 2008).

2.4.1 | Episodic Memory

Episodic memory and executive functions are essential cognitive abilities for daily functioning and are particularly vulnerable to decline in neurological disorders such as Alzheimer's disease, as well as in normal aging (Buckner 2004). For measuring episodic memory, participants were tasked with recalling a list of 15 words immediately after hearing them and again following a 12-min delay (Farias et al. 2013; Lachman et al. 2014).

2.4.2 | Executive Function

Executive function was assessed through five tasks: inductive reasoning (Number Series, completing patterns in a series of five numbers), category verbal fluency (number of animal names generated in 60 s), working memory span (backward digit span, the longest sequence recalled in reverse order), processing speed (30-SACT, counting backward from 100 within 30 s), and attention switching and inhibitory control (Stop and Go Switch Task) (Hughes et al. 2018; Lachman et al. 2014).

2.5 | Procedure

Participants first completed structured telephone interviews, followed by self-administered questionnaires and, for the biomarker subsample, an overnight clinic visit at one of three field centers (University of Wisconsin–Madison, UCLA, and Georgetown University). During the clinic stay, fasting blood samples were drawn, and a 12-h urine collection was obtained for catecholamine and cortisol assays (Dienberg Love et al. 2010). Cognitive testing was conducted separately via a standardized 30-min telephone protocol administered by trained interviewers blinded to biomarker results (Tun and Lachman 2008). All samples and data were de-identified and stored following NIH biorepository standards.

2.6 | Statistical Analyses

Multivariate outliers were identified using the Mahalanobis distance method (De Maesschalck et al. 2000; Yan et al. 2018), flagging 41 cases exceeding the critical chi-square value (34.53, df = 13, $\alpha = 0.001$), resulting in a final sample size of 790. Normality was assessed via skewness, kurtosis, and histograms, and natural log-transformed data for IL-6, C-reactive protein, and cortisol were used.

Structural equation modeling (SEM) with *IBM AMOS 27* was employed to examine relationships among stress biomarkers, inflammation biomarkers, and cognition at M2 and their predictive role in M3 cognitive function 9 years later. SEM utilized robust maximum-likelihood estimation, first testing the measurement model for accurate construct representation before evaluating the structural model.

Model fit was evaluated using multiple indices with recommended thresholds—$\chi^2/df < 5.0$, CFI ≥ 0.90, TLI ≥ 0.90, RMSEA ≤ 0.08, and SRMR ≤ 0.08 (Hu and Bentler 1999). These indices jointly ensured acceptable measurement and structural model adequacy. Key variables included stress biomarkers (e.g., cortisol, norepinephrine), inflammation markers (e.g., IL-6, CRP), and cognitive outcomes (episodic memory, executive function). Using 1000 bootstrap samples with bias-corrected confidence intervals, direct and indirect effects were calculated to evaluate bidirectional relationships and the predictive influence of M2 variables on M3 cognitive outcomes, ensuring robust and reliable interpretations.

Convergent and construct validity were further evaluated beyond CFA model fit. Convergent validity was assessed using Composite Reliability (CR) and Average Variance Extracted (AVE), with CR ≥ 0.60 and AVE ≥ 0.50 considered acceptable (Awang 2014; Cheung et al. 2023). Construct validity was supported by model fit indices meeting the recommended thresholds, confirming that the latent variables were well represented by their observed indicators.

Using 1000 bootstrap samples with bias-corrected confidence intervals, direct and indirect effects were calculated to evaluate bidirectional relationships and the predictive influence of M2 variables on M3 cognitive outcomes, ensuring robust and reliable interpretations.

3 | Results

3.1 | Descriptive Statistics and Correlations Among Stress, Inflammation, and Cognition (H1)

Table 1 summarizes demographics and descriptive statistics for M2 stress, inflammation, and cognitive function, and M3 cognitive outcomes ($N = 790$). Correlation values between observed variables are reported in Table 2. Participants were mid-to-late life adults (M = 54.17; SD = 10.912; range = 34–81), with males and females percentage of 44.80% and 55.20%, respectively. The median is reported for log-transformed variables because it provides a more accurate and stable representation of the central tendency for skewed distributions. Note that the MIDUS 3 episodic memory score, standardized using the MIDUS 2 mean and standard deviation, shows a slight decline compared to the baseline, whereas the MIDUS 3 executive functioning score exhibits a relatively larger decline over time.

3.2 | Measurement Model Validation (CFA): Construct and Convergent Validity Check

Before testing the structural model, a confirmatory factor analysis (CFA) is recommended to assess the measurement model's fit (Anderson and Gerbing 1988; Wei et al. 2005). Once an

TABLE 1 | Sociodemographic characteristics, biomarker of stress and inflammation, and cognitive performances, and later cognitive function ($N = 790$).

Sociodemographic/ Variable	Mean (Median)	Standard deviation
Age	54.17	10.912
Gender (Female = 55.20%)	N/A	N/A
Log_Cortisol	(2.5649)	0.74200
Norepinephrine (μg/g)	26.27742	11.116692
Epinephrine (μg/g)	1.92281	1.014833
Dopamin (μg/g)	146.723	54.710
Log_IL6	(0.6392)	0.65307
Log_C_Reactive	(0.1354)	1.06834
Fibrinogen (mg/dL)	333.51	77.109
sICAM-1 (ng/mL)	279.4160	86.87325
M2 episodic memory *Z* score	0.15060	0.881991
M2 executive functioning *Z* score	0.26993	0.858104
M 3 episodic memory *Z* score	0.02405	0.96262
M 3 executive functioning *Z* score	−0.04054	0.67872

Note: M2 and M3 refer to MIDUS study Waves 2 and 3, respectively. Median values are reported for C-reactive protein, cortisol, and IL-6 due to non-normal distributions.

TABLE 2 | Correlation matrix of observed variables.

	1	2	3	4	5	6	7	8	9	10	11	12
1. Cort	1											
2. NorE	0.114**	1										
3. Epi	0.186**	0.446**	1									
4. Dop	0.307**	0.538**	0.366**	1								
5. IL6	−0.142**	0.129**	−0.044	−0.031	1							
6. CRP	−0.086*	0.151**	−0.129**	0.043	0.492**	1						
7. Fibr	0.052	0.192**	0.045	0.091*	0.359**	0.487**	1					
8. ICAM1	0.056	0.133**	0.024	0.065	0.155**	0.169**	0.110**	1				
9. EM	−0.007	−0.025	−0.006	0.113**	−0.057	−0.011	−0.060	−0.099**	1			
10. EF	−0.010	−0.137**	−0.038	−0.029	−0.117**	−0.089*	−0.133**	−0.085*	0.345**	1		
11. EM3	0.002	−0.014	−0.006	0.143**	−0.117**	−0.040	−0.038	−0.066	0.510**	0.309**	1	
12. EF3	−0.023	−0.162**	−0.050	−0.010	−0.126**	−0.085*	−0.113**	−0.060	0.266**	0.759**	0.339**	1

Note: *$p < 0.05$ **$p < 0.01$.

acceptable measurement model is established, the structural model can be tested. The CFA for pooled measurement models is considered efficient and highly recommended (Awang 2014).

Construct validity is achieved when the fitness indexes for a construct meet the required levels, indicating how well the items measure their respective latent constructs. An initial test of the measurement model showed a relatively good fit to the data. All loadings of the measured variables on the latent variables were statistically significant ($p < 0.001$, see Table 3).

Convergent validity was assessed using composite reliability (CR) and average variance extracted (AVE). The CR criterion is typically set at 0.60 (Awang 2014; Haji-Othman and Yusuff 2022) while an AVE value exceeding 0.50 is generally considered acceptable (Cheung et al. 2023). In this study, the CFA model yielded an AVE of 0.441, which statistical testing indicated was not significantly lower than the 0.50 threshold ($z = -1.66$, $p > 0.05$). Additionally, the model satisfied the composite reliability criterion with a CR of 0.655.

The error terms for M2 and M3 episodic memory were correlated based on a modification index value of 156.484, as both variables assessed identical tasks longitudinally within the same cohort. Correlated errors, common when similar instruments are used across time points, arise from shared method variance (Kang and Ahn 2021). The M2 and M3 tests measured immediate and delayed recall of 15 words, reflecting consistent memory strategies and resulting in correlated errors, which were addressed to better capture the underlying construct.

Although Hair et al. (2010) recommended standardized factor loadings of at least 0.5, variables like Cortisol and sICAM-1 on stress and inflammation factors, as well as episodic memory on M2 and M3 cognition factors, were retained for theoretical significance. Their retention was further justified by the measurement model's acceptable fit indices, including CFI, RMSEA, and SRMR (Awang 2014). These indices confirm that the model adequately represents the data, supporting the inclusion of these variables despite factor loadings below the recommended threshold.

3.3 | Structural Model Evaluation: Longitudinal Effects of Stress and Inflammation (H2)

The structural model was evaluated using the maximum-likelihood estimation method in Amos. The Results indicated an acceptable model fit to the data, with $X^2 = 229.987 (p < 0.001)$, CMIN/DF = 4.893 (marginally acceptable), CFI = 0.919, RMSEA = 0.072, and SRMR = 0.067. A CMIN/DF ratio between 2 and 5 is generally considered indicative of acceptable model fit (Marsh and Hocevar 1985). All structural paths were statistically significant ($p < 0.001$), except for the stress biomarker and inflammation to M3 cognition. To evaluate whether the removal of these two paths would negatively impact model fit, we constrained both paths to zero and assessed the resulting model. The modified model (see Figure 2) demonstrated an acceptable fit to the data, with scaled χ^2 (49, $N = 790$) = 232.157, $p < 0.001$, CFI = 0.919, RMSEA = 0.069, and SRMR = 0.058. a corrected scaled chi-square difference test (Satorra and Bentler 2001) comparing the initial model

TABLE 3 | Factor loadings for the measurement model.

Latent variable/Factor	Observed variable	Unstd. loading	SE	*Z* (C.R.)	Std. loading
M3_Cognition	M3_Episodic	0.356	0.035	10.039	0.370
	M3_Executive	0.620	0.029	21.381	0.914
M2_Cognition	M2_Episodic	0.306	0.033	9.294	0.347
	M2_Executive	0.852	0.041	20.771	0.993
M2_Inflammation	M2_Log_IL6	0.402	0.026	15.706	0.616
	M2_Log_C_Reactive	0.843	0.044	19.353	0.789
	M2_Fibrinogen	47.140	3.019	15.617	0.612
	M2_sICAM1	46.706	19.169	3.540	0.221
M2_StressBio	M2_Log_Cortisol	0.198	0.030	6.591	0.267
	M2_Norepinephrine	8.628	0.445	19.376	0.777
	M2_Dopamin	38.122	2.154	17.696	0.697
	M2_Epinephrine	0.560	0.039	14.320	0.553

Note: M2 and M3 refer to the MIDUS study Waves 2 and 3, respectively. Unstd. Loading: Unstandardized Loading; Std. Loading: Standardized Loading.

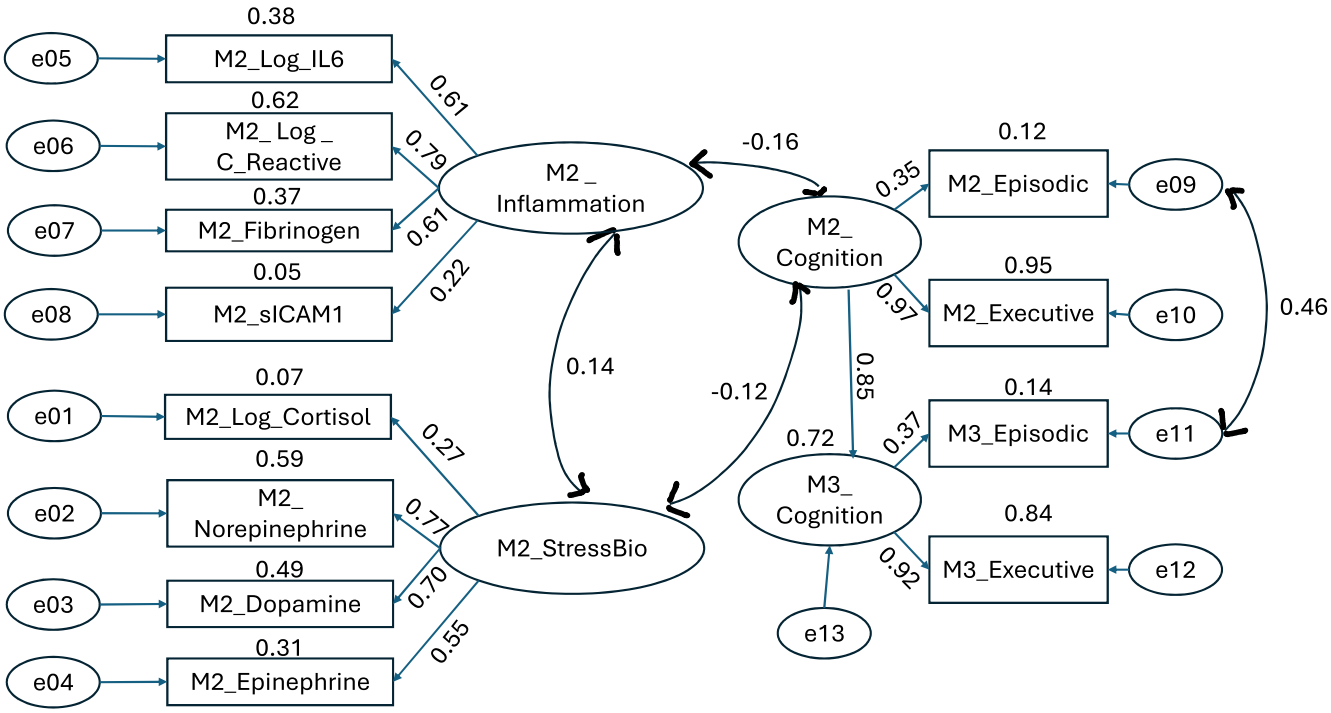

FIGURE 2 | Structural model ($N = 790$) of stress, inflammation, and cognition. All standardized path coefficients are statistically significant at $p < 0.001$.

with the modified version revealed no significant difference in fit between the two models, $\Delta\chi^2$ (2, $N = 790$) = 2.17, $p = 0.34$. These results indicate that the two direct paths, M2 stress and inflammation to M3 cognition, did not significantly contribute to the model's fit. Consequently, the more parsimonious model, with the paths constrained to zero, fits the data equally well as the original model.

To evaluate model robustness, a sensitivity analysis including the 41 cases identified as multivariate outliers by the Mahalanobis distance test was conducted. The reanalysis yielded comparable or slightly improved fit indices ($\chi^2 = 196.74$, df = 49, $p < 0.001$, CFI = 0.932, TLI = 0.909, SRMR = 0.050), indicating that model exclusion criteria did not substantially influence the results.

Additionally, we reviewed the ECVI (Expected Cross-Validation Index) results from the SEM analysis, which is recommended for assessing predictive fit (Kang and Ahn 2021). The ECVI estimates how well the model would perform with a new sample. The ECVI for the default model (0.398) is close to the saturated model (0.228) and much lower than the independence model

(2.994), indicating that the default model fits the data well, though not as perfectly as the saturated model. These results suggest that the default model provides a good fit.

3.4 | Predictive Stability of Midlife Cognition (H3)

The standardized direct effect of midlife cognition at M2 on later cognition at M3 was significant ($\beta = 0.849$, 95% BC CI [0.793, 0.908], $p = 0.013$), indicating strong longitudinal stability. Similarly, the direct effects of M3 cognition on both episodic memory ($\beta = 0.373$, 95% BC CI [0.309, 0.442], $p = 0.010$) and executive function ($\beta = 0.919$, 95% BC CI [0.853, 1.010], $p = 0.015$) were also significant, suggesting that global cognition continues to explain concurrent performance in both domains at follow-up.

3.5 | Indirect Effects of Midlife Cognition via Follow-Up Cognition (H4)

Indirect effects were tested using the bootstrap procedure described by (Shrout and Bolger 2002) and implemented by (Wei et al. 2005). Specifically, 1000 bootstrap samples were generated from the original dataset through random sampling with replacement. Each bootstrap sample was analyzed using structural equation modeling, producing 1000 estimates of each path coefficient. The distribution of these estimates was then used to compute bias-corrected 95% confidence intervals for the indirect effects.

The standardized indirect effect of M2 cognition on M3 episodic memory was $\beta = 0.317$ (95% BC CI [0.267, 0.388], $p < 0.01$), while the indirect effect on M3 executive function was $\beta = 0.780$ (95% BC CI [0.723, 0.845], $p < 0.05$). These results indicate that the influence of midlife cognition on later cognitive domains operates primarily through follow-up global cognition, supporting the mediational pathways:

- M2 Cognition → M3 Cognition → M3 Executive.
- M2 Cognition → M3 Cognition → M3 Episodic.

These findings indicate that follow-up global cognition (M3) mediates the relationship between midlife cognition (M2) and both domain-specific outcomes—executive function and episodic memory—demonstrating the indirect longitudinal stability of cognitive performance.

3.6 | Gender Invariance in Structural Relationships (H5)

We initially examined the regression weights for all paths in both the male and female groups, finding that each was statistically significant at the $p < 0.001$ level. Subsequently, we conducted a multiple group analysis using the structural weights model to investigate whether overall structural differences exist between male and female respondents. The sample was divided into two groups (male: $n = 354$; female: $n = 436$), and we tested for significant differences in the structural model weights between the two groups. To do this, we imposed equality constraints on the structural weights from M2 cognition to M3 cognition across both groups. The model comparison results indicated no significant differences between the male and female groups ($p = 0.985$), suggesting statistical similarity. Additionally, we constrained the structural covariances for the relationship among stress, inflammation, and M2 cognition, and model comparison results also indicated no significant differences ($p = 0.255$), further reinforcing the similarity between the groups.

4 | Discussion

The findings supported most of the proposed hypotheses (H1–H5), offering insight into how midlife biological and cognitive factors shape later cognitive outcomes. This study uniquely integrates physiological (stress and inflammation) and cognitive perspectives within a nine-year longitudinal framework. Using structural equation modeling (SEM) in a large population-based cohort, it provides one of the few comprehensive examinations of how stress–inflammation processes interact with cognitive function over time. This integrative approach extends psychoneuroendocrineimmunology (PNEI) research by linking biological mechanisms with cognitive aging trajectories at the population level.

4.1 | H1: Associations Among Stress, Inflammation, and Cognition

Consistent with psychoneuroendocrineimmunology (PNEI) principles (Bitzer-Quintero et al. 2022; Bottaccioli 2020; Liu et al. 2017), baseline analyses revealed significant positive correlations between stress and inflammatory biomarkers. Specifically, norepinephrine and cortisol were modestly but significantly related to CRP and IL-6 (Table 2), supporting evidence that activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system can promote systemic inflammation (Kiecolt-Glaser et al. 2003; McDade et al. 2006). The small-to-moderate effect sizes suggest that, while stress physiology and inflammatory activation are measurably coupled in midlife, their immediate cognitive consequences remain limited—likely because cognitive reserve and compensatory neuroplasticity continue to buffer against biological strain, allowing middle-aged and younger-old adults to maintain stable performance despite systemic dysregulation (Scarmeas and Stern 2003).

4.2 | H2: Longitudinal Effects of Stress and Inflammation on Later Cognition

Consistent with Hypothesis 2, stress and inflammation did not significantly predict later cognition after controlling for baseline performance, suggesting that long-term cognitive change is primarily determined by prior cognitive capacity. Our findings align with the mixed results in the literature. Griseta et al. (2023) reported cross-sectional associations between elevated IL-6 and poorer cognition, whereas (Leonardo and Fregni 2023) noted that longitudinal data are inconsistent, finding that only some markers (such as IL-6) are associated

with increased risk of cognitive deterioration, while others (such as CRP and TNF-α) are not. These results suggest that transient physiological fluctuations may not accumulate strongly enough to affect cognition over nearly a decade, particularly in generally healthy, community-based adults. Instead, stress and inflammation may exert their influence indirectly through psychoneuroendocrine–immune dysregulation and stress-related behavioral mechanisms (Bottaccioli et al. 2019; Maier and Seligman 2016).

4.3 | H3: Predictive Stability of Midlife Cognition

Supporting Hypothesis 3, midlife cognition (M2) strongly predicted later cognition (M3), confirming longitudinal stability across nearly a decade. This pattern reflects well-established rank-order consistency in adult cognition (Hughes et al. 2018) and suggests that individuals with stronger midlife performance tend to maintain relative advantages over time. The stability likely stems from enduring individual differences in neural efficiency and cognitive reserve (Stern 2012). Given the generally healthy, well-educated MIDUS cohort (Lachman et al. 2014), cognitive trajectories may also reflect protective lifestyle and psychosocial factors that slow decline. Together, these findings emphasize midlife as a pivotal window for sustaining cognitive health and preventing later deterioration.

4.4 | H4: Indirect Effects of Midlife Cognition Through Follow-Up Cognition

Hypothesis 4 was supported. Follow-up cognition (M3) mediated the association between midlife cognition (M2) and both episodic memory and executive function outcomes. This suggests that global cognition functions as a higher-order mechanism through which earlier abilities shape later domain-specific performance. Such mediation likely reflects the top-down integrative role of executive and reasoning processes, which coordinate and sustain other cognitive operations across time (Jurado and Rosselli 2007; Farias et al. 2013). These results are consistent with hierarchical models of adult cognition and prior longitudinal findings showing that midlife cognitive stability predicts later functioning (Lachman et al. 2014; Hughes et al. 2018). Strengthening global cognition in midlife—through cognitive training (Lee et al. 2018; Lee et al. 2024) or multidomain lifestyle interventions (Livingston et al. 2024)—may thus help preserve memory and executive abilities into older age.

4.5 | H5: Gender Invariance in Structural Relationships

Consistent with H5, multigroup SEM analyses revealed no significant gender differences in structural paths among stress, inflammation, and cognition. Despite prior evidence suggesting sex-specific vulnerabilities in stress reactivity and inflammatory responses (Paolillo et al. 2023; Sullivan et al. 2020), the absence of significant group differences indicates that the underlying structural relationships are broadly comparable. While some studies report steeper cognitive decline in women later in life (Karlamangla et al. 2009), these discrepancies may reflect methodological variations in biomarker measurement or sampling intervals rather than true structural divergence.

Although cognitive outcomes were standardized using internally derived Z-scores for within-sample comparability, this approach limits direct clinical interpretability because the scores are not anchored to external normative data. Nevertheless, the modest declines observed—particularly in executive function—align with well-established patterns of cognitive aging characterized by gradual reductions in processing speed and executive control during midlife and early old age (Salthouse 2010; Lachman et al. 2014). Taken together, these findings highlight the relative stability and predictive continuity of midlife cognition rather than substantial mean-level change, underscoring that cognitive performance in midlife serves as a key indicator of later outcomes.

4.6 | Limitations and Future Directions

Although this study advances understanding of stress–inflammation–cognition links, several methodological limitations should be acknowledged. The use of latent constructs strengthened measurement reliability but may have masked biomarker-specific effects, such as the distinct roles of cortisol, norepinephrine, and cytokines. The absence of neuroimaging data limits inferences about the neural substrates underlying these physiological–cognitive associations.

Another limitation involves attrition and selective participation. Although the initial MIDUS cohort was large and nationally representative, the analytic sample ($N = 790$) represents only about 17% of the original cohort, primarily due to selective enrollment in the biomarker project and the exclusion of incomplete or outlier cases. This reduction may bias the sample toward healthier and more educated participants, potentially limiting the generalizability of findings to broader populations.

Future studies should adopt multimodal and longitudinal designs integrating biomarker trajectories, neuroimaging, and psychosocial moderators (e.g., coping, sleep, social support) to clarify mechanisms of cognitive resilience and improve methodological precision. Incorporating retention analyses and representative sampling strategies across future MIDUS waves or comparable cohorts would further strengthen the external validity of physiological–cognitive models.

5 | Conclusion

This study demonstrates the efficacy of a robust SEM model in elucidating the complex relationships among stress biomarkers, inflammation, and cognition. The findings underscore midlife cognitive health as a critical determinant of long-term trajectories, with cognitive performance serving as a central mediator of later outcomes. These results highlight the importance of targeted midlife strategies, such as cognitive training, stress management, and anti-inflammatory approaches, to mitigate cognitive decline and support healthy brain aging (Lachman et al. 2014; Lee et al. 2018; Lee et al. 2024).

Aligned with psychoneuroendocrine–immunology principles, this research integrates psychological, physiological, and cognitive dimensions, addressing the multifaceted nature of cognitive aging. By leveraging longitudinal data and advanced modeling, the study deepens understanding of how stress and inflammation interact with cognition over time. The findings underscore that cognitive aging is not a uniform process but one shaped by both stability and change, offering opportunities for prevention and resilience-building. This study provides a critical foundation for future research to elucidate mechanisms underlying cognitive resilience and decline, paving the way for innovative strategies to promote brain health across the lifespan.

Author Contributions

Pai-Lin Lee: conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft, writing – review and editing. **Chih-Kun Huang:** methodology, writing – review and editing. **Ling-Chun Ou:** methodology, writing – review and editing.

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Ethics Statement

IRB Protocol/Human Subjects Approval Numbers: University of Wisconsin–Madison (2014–2016). MIDUS Biomarker and Cognition Projects: IRB protocol approvals (Protocol Nos. 2014–0813, 2016–1051). Institutional Review Board, University of Wisconsin–Madison.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The dataset supporting the conclusions of this study is publicly available in the Harvard Dataverse repository: Lee (2025).

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