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A life course approach to understanding stress exposures and cognitive function among middle-aged and older adults

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ABSTRACT

Background: Many studies have evaluated the stress-cognition association, but few have captured the cumulative nature of stress or distinguished the influences of stressors occurring in childhood versus adulthood. Using a lifecourse approach, we investigated whether cumulative stress exposures are associated with poorer cognitive function and faster cognitive decline.

Methods: We used data from the Midlife Development in the United States Study ($N = 3{,}954$, mean baseline age: 56 years). We fit marginal structural generalized estimating equations models to estimate the difference in baseline cognitive function per *SD* increment in the continuous stressor score, and, separately, between persons in each life course stressor profile and those who did not experience high stress in either childhood or adulthood. We also characterized differences in cognitive decline across levels of stress exposures.

Results: Higher cumulative stress exposure was associated with lower executive function (*difference* per *SD in* continuous stressor score $= -0.12$ *SD* units, 95% CI $= -0.16, -0.08$) and episodic memory (*difference* $= -0.09$ *SD* units, 95% CI $= -0.13, -0.05$). Baseline executive function and episodic memory were lower among those with high stress only in childhood, only in adulthood, and both, than among those without high stress in childhood or adulthood. There was little evidence that rate of change in executive function and episodic memory differed across levels of cumulative stress exposures.

Conclusions: These findings offer support to the hypothesis that stress exposures, accumulated over the life course, worsen cognitive performance, but limited support for the hypothesis that these exposures promote cognitive decline.

1. Introduction

Growing evidence suggests that individuals exposed to high levels of stress face faster cognitive declines and higher risk of mild cognitive impairment in older adulthood, an early stage of dementia (Aggarwal et al., 2014; Korten et al., 2017). These studies shed light on a highly prevalent potential risk factor for dementia that may be amenable to intervention. However, much of this research has used measures of perceived stress, which primarily assess recent perceptions of general stress, typically within the past month. With the restricted time frame and types of questions asked, such measures may not adequately capture stress exposures that have accumulated over the life course (Aggarwal et al., 2014; Korten et al., 2017). Even though stressors from multiple domains often co-occur (Sternthal et al., 2011), of the studies that have considered the cognitive effects of exposure to specific stressors, almost all have considered stress exposure occurring in only one domain (e.g., work stress) (Barnes et al., 2012; Deligkaris et al., 2014).

The stress and health literature has long suggested the importance of considering multiple types of stress exposures. The stress process framework proposed by Pearlin, for example, posits that stressors, whether in the form of an untoward event or a chronic strain associated with a social role, tend to give rise to additional stressors, a process called stress proliferation (Pearlin, 1989; Pearlin et al., 2005). According to this framework, stress proliferation often results in clusters of

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stressors and cumulative adversities that shape health and well-being later in life. Building upon Pearlin's stress proliferation framework, Wheaton further proposed the stress domain hypothesis, which posits that no single source of stress can capture the full impact of stress, and that assessment of the impacts of stress on health outcomes depends on considering multiple key sources of stress over significant periods of time in lives (Wheaton, 1994, 1999). Together, the stress domain hypothesis and the stress proliferation hypothesis suggest that both untoward events and chronic strains shape individuals' stressful experiences, and that, to validly estimate the consequences of these experiences, it is essential to assess constellations of stressors made up of both events and strains. Importantly, both Pearlin and Wheaton advocated the use of a life-course framework to study stress (Pearlin, 2010; Wheaton, 1994). As noted by Pearlin, *"the observation and understanding of stress proliferation are best realized when viewed within a life-course framework"*(Pearlin, 2010).

Given that stress exposures occur at multiple time points during the life course and that even early life exposures appear to influence later health outcomes, incorporating a life course approach into research on stress exposures and cognitive outcomes in middle and older adulthood may facilitate better understanding of the stress-cognition relationship. Epidemiologists and sociologists have proposed different, but not mutually exclusive, conceptual models to explain how exposures across the life course can act to influence health outcomes (Ferraro et al., 2009; Kuh et al., 2003). For example, the accumulation of risk model posits that cumulative exposures across the life course increase the risk of adverse health late in life, regardless of the stage of life when the exposures occur. Prior research using data from the Midlife Development in the United States Study, the Chicago Community Health study, and the Women's Health Study has shown consistent support for the accumulation of risk model (Albert et al., 2017; Cuevas et al., 2019; Slopen et al., 2012). These studies, which typically aggregated multiple domains of acute and chronic stress exposures to create a composite score of cumulative stress exposures, found that higher levels of cumulative stress exposures across the life course were associated with higher odds of smoking, obesity, and cardiovascular diseases (Albert et al., 2017; Cuevas et al., 2019; Slopen et al., 2012). Although the detrimental consequences of cumulative stress exposures have been evaluated in relation to these and other health outcomes, little is known about whether cumulative stress exposures are associated with worse cognitive outcomes.

Separately, the critical period model suggests that exposures at a particular stage in life (e.g., early childhood) lead to long-lasting and irreversible health consequences later in life. For example, a previous study reported that childhood distress was associated with higher cardiometabolic risk later in life, even when adjusting for adulthood stress, indicating that the health consequences of early childhood distress are independent from the effects of stress in other life stages (Winning et al., 2015). Because there has been little distinction between the adverse effects of childhood stressors and adulthood stressors on cognitive outcomes in adulthood, it is unclear whether this critical period model can be used to explain how stress exposures influence cognitive outcomes. Distinguishing the associations of childhood and adulthood stressors with cognitive function, separately and in combination, will add further insight to what is known about the sequelae of these exposures, and, by extension, provide further impetus for the benefits of viewing dementia prevention as a series of life-long interventions, starting early in life, rather than interventions late in life.

Guided by the stress process framework, the stress domain hypothesis, and applying a life course approach to this inquiry, we used data from the Midlife Development in the United States Study (MIDUS) to investigate whether higher life course stress exposures are associated with lower levels of and a faster decline in cognitive function. MIDUS included a rich set of psychosocial measures, allowing us to characterize the relationships between cumulative stress exposures and cognitive function. Our study complements and expands on prior research in MIDUS that has assessed the associations between stressors and cognitive function. For example, Lynch and Lachman used MIDUS2 and MIDUS3 data to assess the relationship between lifetime stressful life events and cognitive function (Lynch and Lachman, 2020). They found that stressful life events predicted faster declines in cognitive function. Stawski et al. used data from the MIDUS daily stressor project (n = 1500) and showed that better cognitive function was associated with healthier profiles of naturally occurring cortisol (Stawski et al., 2011). Other research has used MIDUS data to examine associations between chronic exposure to specific stressors and cognitive function. For example, Munoz et al. used cross-sectional data from three samples including MIDUS to examine neighborhood stress and cognitive function. Their study showed that higher neighborhood stress was associated with lower executive function in MIDUS (Munoz et al., 2015). Grzywacz et al. examined the cross-sectional associations between workplace exposures and cognitive function in MIDUS and found that greater physical strains were associated with poorer episodic memory and executive function (Grzywacz et al., 2016). Lindert et al. assessed the associations between social stress and cognitive declines and showed that daily discrimination had adverse effects on executive function (Lindert et al., 2021). Together, findings of these studies inform our understanding of the stress-cognition association. However, most studies have considered a single type or domain of stress. As older adults tend to experience multiple stress exposures across the life course, considering only one type of stress may underestimate or mischaracterize the total burdens of stress on cognitive function. Additionally, many of these studies included only a single assessment of cognitive function and therefore could not assess associations between stress and cognitive decline.

Building upon prior research on stress and cognitive function, we hypothesized that 1) higher cumulative life course stress exposures would be associated with a lower level of and a faster decline in cognitive function; and 2) individuals who were exposed to high childhood stress would have worse cognitive outcomes later in life, regardless of their levels of adulthood stress exposures. We operationalized cumulative stress exposures by ten different domains of stress exposures, including childhood stress, financial stress, neighborhood stress, work psychological stress, work physical stress, work-family conflict, perceived discrimination, perceived inequality, relationship stress, and stressful life events during adulthood. We created a continuous cumulative stress exposure score, by combining measures of ten stress exposures across the life course and examined its relationship with cognitive function level and rate of cognitive decline. To investigate how stress exposures at specific times during the life course are associated with cognitive function, we created a profile of cumulative stress that characterized both level and timing of exposure to stressors over the life course.

A common practice in estimating the combined effects of stressors in different parts of the life course is to fit a regression model that includes terms for childhood and adulthood stressors, as well as terms for putative sources of confounding in the pre-childhood period (e.g., age, sex, parental education) and adulthood period (e.g., income, working status) (Sternthal et al., 2011). However, using this approach may yield biased estimates of the effects of childhood stressors and any joint effect of these stressors with adulthood stressors. This is, because adulthood confounders may also be affected by childhood stressors, a phenomenon called treatment-confounder feedback (Robins et al., 2000). To address this methodological challenge, we fit marginal structural models to account for potential stressor-confounder feedback.

2. Methods

2.1. Sample population

We used data from MIDUS, a national random digit dial (RDD) sample of non-institutionalized adults. MIDUS began in 1995–1996 (MIDUS1) with a telephone survey followed by mailed self-administered

questionnaires (Barry, 2014). The MIDUS1 sample also included twin pairs and non-twin siblings of the main RDD sample respondents. Of the 7108 MIDUS1 respondents (aged 25–75 years), 4963 were re-interviewed in 2004–2006 (MIDUS2 national sample; 75% of surviving participants). At MIDUS2, to increase the representation of Black Americans, MIDUS investigators recruited 592 new Black participants from Milwaukee, WI. In 2013–2014, the third wave of data (MIDUS3) was collected from 3294 previously enrolled national sample participants, and a second wave of data was collected from 389 Milwaukee participants.

The Cognitive Project began in MIDUS2. It involved separate telephone interviews of MIDUS2 participants (N = 4814; 86% response rate) and continued in MIDUS3 with a follow-up assessment (Hughes et al., 2018). Compared with those who did not participate in the MIDUS cognitive project, individuals who participated in the cognitive project were more likely to be female, White, and have higher education levels and annual household income. MIDUS was approved by the Institutional Review Boards at all participating institutions. Additional details about MIDUS can be found elsewhere (Barry, 2014; Brim et al., 2004; Ryff, 2016).

For the current study, we considered MIDUS2 as the cognitive baseline. From the 5555 individuals who participated in MIDUS2, we excluded those who did not complete the self-administered questionnaires (given at MIDUS2), which contained the stressor questions, and those without complete baseline cognitive function data. Compared with those in our analytic sample, individuals who were excluded were more likely to be Black adults, males, without a college degree, and have lower than $25000 annual income. The analytic sample included 3954 adults (of whom 1350 were twins or siblings; 259 were from the Milwaukee sample). Of these participants, 2517 completed the follow-up cognitive function assessment at MIDUS3 (181 were from the Milwaukee sample). Of those who did not, 480 died prior to the scheduled assessment, and 957 did not complete the assessment for other reasons (see Fig. 1). Compared with those who remained in MIDUS3, those who were lost to follow-up due to death were more likely to be older, male, with lower parental education, lower respondent education, lower household income, not working, had lower cumulative stress exposures, and had lower baseline cognitive function scores. Those who were lost to follow-up due to reasons other than death were more likely to be younger, male, with higher education levels, with lower education, had higher cumulative stress exposures, and had lower baseline cognitive function scores (see Appendix Table 6).

2.2. Measures

2.2.1. Childhood stress exposures

Childhood stress exposures were assessed at MIDUS2 with seven items from the revised Adverse Childhood Experience questionnaire and nine items from the MIDUS stressful life event inventory (see Appendix Table 8) (Turner and Wheaton, 1995). Participants who responded affirmatively to each item indicated their age at the time of the experience. We summed experiences that occurred before age 18 to obtain a

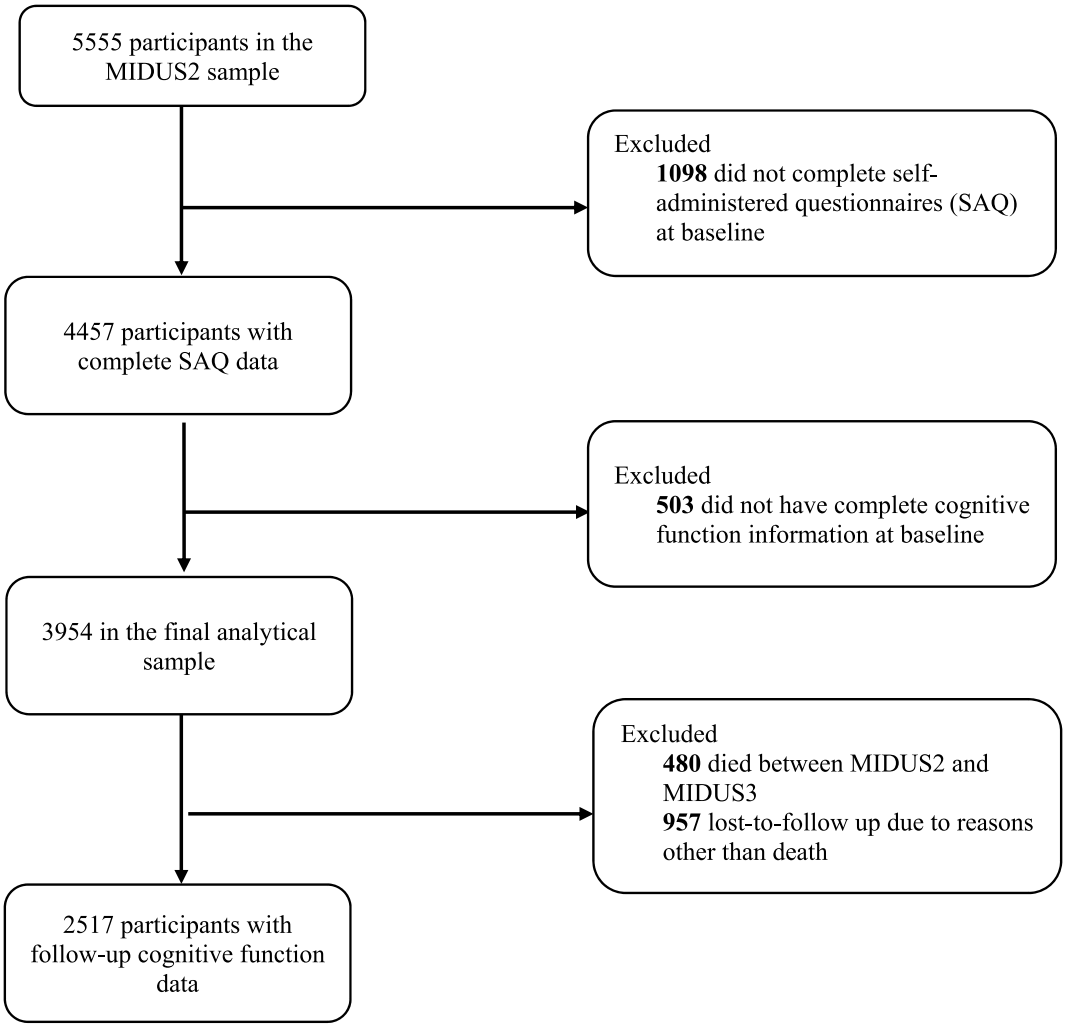

Fig. 1. Flowchart of participant selection, midlife development in the United States study, 2004–2014.

score for childhood stress exposures and transformed the summed score into a z-score. Following previous research (Cuevas et al., 2019), we designated the top quartile of the z-score as "high childhood stress."

2.2.2. Adulthood stress exposures

We measured stress exposures that occurred during adulthood, also assessed at MIDUS2, using questions from nine stressor domains: financial stress, neighborhood stress, work psychological stress, work physical stress, work-family conflict, perceived discrimination, perceived inequality, relationship stress, and stressful life events during adulthood (Chen et al., 2022; Cuevas et al., 2020; Slopen et al., 2012). We used a broad array of measures designed to assess adulthood stress in various domains. Specifically, financial stress was assessed by asking participants if they had enough money to meet their needs and how difficult it was for them to pay their monthly bills. Neighborhood stress was measured using a single scale with four items assessing neighborhood safety, perceived neighborhood support, and perceived neighborhood trust (Keyes, 1998). Work psychological stress was measured by a combination of five separate measures assessing skill discretion, decision authority, job demand, coworker support, and supervisor support (Karasek, 1985). Work physical stress was assessed by combining two measures assessing risk of injury or accident on the job and frequency of job strain. Work-family conflict was assessed by two measures assessing negative work-to-family spillover and negative family-to-work spillover (Grzywacz et al., 2016). Relationship stress was characterized by combining four measures assessing family strain, friend strain, perceived troubles in marriage, and spouse/partner strain (Schuster et al., 1990; Walen and Lachman, 2000). Perceived inequality was derived from three separate measures assessing people's perceptions of inequality across child rearing (e.g., as a family, we have not had the resources to do many fun things together with the children), housing and neighborhood conditions, and work (Ryff et al., 1999). Perceived discrimination was measured by the lifetime discrimination inventory and the well-validated everyday discrimination scale (Williams et al., 1997). Stressful life events in adulthood were assessed by the stressful life event inventory, which includes 20 events that occurred after age 18 (Cohen et al., 1997). A single score was derived for stress exposure in each domain with higher scores indicating higher stress exposure in all domains (see Appendix Table 8). We recomputed the scales such that respondents would have received the lowest value of the scale if a given stressor did not apply to them (e.g., psychosocial work stress did not apply to those not working) (Cuevas et al., 2019; Slopen et al., 2012). To obtain a cumulative stressor score for adulthood stress exposure, we transformed the raw score in each stressor domain into a z-score and summed the standardized scores across the nine domains. We standardized this summed score to facilitate comparisons of the effects of adulthood stress exposures with those of childhood stress exposures. Consistent with "high childhood stress exposures," we designated the top quartile of the z-score as "high adulthood stress exposures."

2.2.3. Life course cumulative stress exposures

We created a life course cumulative stressor score by summing the z-scores of all stressor domains, including childhood stress exposures and the nine domains of adulthood stressor exposures. We standardized the continuous cumulative stressor score, with a higher score indicating a greater level of stressors.

2.2.4. Life course stressor profiles

To characterize exposure to stressors at different points in the life course, we created four mutually exclusive stressor groups: 1) absence of high stressors (i.e., not in the top quartile for stressor exposure in childhood or adulthood) (reference); 2) high-stress exposure in "childhood only"; 3) high-stress exposure in "adulthood only"; 4) persistently high-stress exposure (i.e., high-stress exposure in both childhood and adulthood).

2.2.5. Cognitive function

Cognitive function was measured with the Brief Test of Adult Cognition by Telephone (Tun and Lachman, 2006), which includes seven subtests evaluating: immediate recall, delayed recall, working memory span, verbal fluency, inductive reasoning, processing speed, and attention-switching tasks. Drawing on previous confirmatory factor analyses (Lachman et al., 2014), we characterized cognitive function in two domains: executive function and episodic memory. The MIDUS2 executive function composite score was computed as the mean of standardized scores on working memory, verbal fluency, inductive reasoning, processing speed, and the Stop & Go Switch Task (SGST) assessed at MIDUS2. Notably, the SGST includes both the accuracy and the latency scores. We focused on task switching latency, which was a composite score based on the average reaction time of the switch and non-switch trials. We reverse-coded the score so that a higher score indicated faster reaction times. The episodic memory composite score was computed as the mean of standardized scores on immediate and delayed recalls subtests assessed at MIDUS2. Final MIDUS2 executive function and episodic memory scores were standardized to have a mean of 0 and a standard deviation of 1. To estimate the MIDUS3 executive function score, we first standardized the working memory, verbal fluency, inductive reasoning, processing speed, and attention-switching task subtests based on their raw test scores at MIDUS2. We then took the means of the five domains to obtain the final score for MIDUS3 executive function. In MIDUS3, the SGST values varied by phone type, and therefore we used the score that was corrected for the latency difference in phone type. To calculate the MIDUS3 episodic memory score, we standardized the immediate and delayed recall subtests based on their raw test scores at MIDUS2 and then took the mean score across the two domains to obtain the final MIDUS3 episodic memory score (Hughes et al., 2018).

2.2.6. Covariates

We selected covariates based on their observed and hypothesized relationships with the stress exposures and cognitive outcomes. Covariates included age (years), sex (male, female), self-identified race/ethnicity (White, Black, others), father's or mother's highest education level (less than high school, high school or GED, some college, college or more), respondent's education (less than high school, high school or GED, some college, college or more), current annual household income ($<$\$25,000, \$25,000–44,999, \$45,000–69,999, $\geq$\$70,000), presence of chronic conditions (yes, no), currently working (yes, no), currently married (yes, no), and having any children (yes, no). All covariates were assessed at MIDUS2 except for parents' education in the national sample, which was assessed at MIDUS1.

2.2.7. Statistical analyses

We first checked monotonicity in the relation between cumulative stressor scores and cognitive function by evaluating the relationship using tertiles of cumulative stress exposures. Compared with those in the lowest tertile of cumulative stressors, those in the 2nd tertile of stressors had markedly lower executive function and episodic memory scores, on average. Both cognitive scores were lower still among those in the highest tertile of stressors, providing some evidence of monotonicity in the relationship (see Appendix Table 1). We fit marginal structural generalized estimating equations (GEE) models to estimate the difference in baseline cognitive function score per SD unit increment in the continuous stressor score. Following prior work in MIDUS (Nishimi et al., 2021; Slopen et al., 2016), we accounted for twin and sibling clustering ($n = 1350$) by including "family ID" in the repeated statement of the GEE models. We conducted separate analyses for each cognitive score, i.e., executive function and episodic memory. We then fit marginal structural GEE models to examine the differences in baseline cognitive function score per SD between persons in each life course stressor profile and the reference group comprising those who did not experience high-stress exposure in either childhood or adulthood. To

Table 1
Baseline characteristics by tertile of the cumulative stress exposure score (N = 3954), midlife development in the United States study, 2004–2014[a].

Characteristic	All participants (*N* = 3954)	Tertile of Cumulative Stress Exposure Score		
		Lowest (*N* = 1318)	Middle (*N* = 1318)	Highest (*N* = 1318)
Age group, *N* (%)				
- ≥ 65 years old	1081 (27.3)	651 (49.4)	302 (22.9)	127 (9.6)
- < 65 years old	2873 (72.7)	667 (50.6)	1016(77.1)	1191 (90.4)
Gender, *N* (%)				
- Female	2226 (56.3)	782 (59.3)	700 (53.1)	744 (56.4)
- Male	1728 (43.7)	536 (40.7)	618 (46.9)	574 (43.6)
Race, *N* (%)				
- White	3423 (86.6)	1224 (92.9)	1166(88.5)	1033 (78.4)
- Black	396 (10.0)	65 (4.9)	99 (7.5)	232 (17.6)
- Others	135 (3.4)	29 (2.2)	53 (4.0)	53 (4.0)
Father's or mother's highest levels of education, *N* (%)				
- Less than High school	1104 (27.9)	414 (31.4)	344 (26.1)	347 (26.3)
- High school or GED	1408 (35.6)	423 (32.1)	462 (35.1)	523 (39.7)
- Some college	384 (9.7)	131 (9.9)	121 (9.2)	133 (10.1)
- College or more	1057 (26.7)	350 (26.6)	392 (29.7)	316 (24.0)
Participant's education level, *N* (%)				
- Less than High school	255 (6.4)	67 (5.2)	78 (5.8)	110 (8.3)
- High school or GED	1084 (27.4)	358 (27.2)	337 (25.6)	388 (29.4)
- Some college	849 (29.0)	254 (25.9)	282 (29.1)	313 (23.7)
- College or more	1767 (37.1)	639 (41.8)	621 (39.5)	507 (38.5)
Adulthood household income, *N* (%)				
- Less than $25,000	900 (22.8)	347 (26.3)	251 (19.0)	302 (22.9)
- $25,000 to $44,999	732 (18.5)	250 (19.0)	219 (16.6)	263 (20.0)
- $45,000 to $69,999	780 (19.7)	221 (16.8)	273 (20.7)	286 (21.7)
- More than $70,000	1543 (39.0)	500 (37.9)	575 (43.6)	467 (35.4)
Currently working, *N* (%)				
- Yes	2564 (64.9)	520 (39.5)	973 (73.8)	1071 (81.3)
- No	1390 (35.2)	798 (60.5)	345 (26.3)	247 (18.7)
Currently married, *N* (%)				
- Yes	2872 (72.6)	974 (73.9)	992 (75.3)	906 (68.7)
- No	1082 (27.4)	344 (26.1)	326 (24.7)	412 (31.3)
Has 1+ child, *N* (%)				
- Yes	3464 (87.6)	1160 (88.1)	1153 (87.5)	1151 (87.3)
- No	490 (12.4)	158 (11.9)	165 (12.5)	167 (12.7)
Presence of chronic conditions, *N* (%)				
- Yes	3100 (78.4)	1020 (77.4)	1003 (76.1)	1076 (81.6)
- No	854 (21.6)	298 (22.6)	315 (23.9)	242 (18.4)

Abbreviation: GED: General Educational Diploma; *SD*: Standard Deviation.
[a] Results were generated from 20 imputed datasets.

Table 2
Adjusted Mean Difference in Baseline Cognitive Function Score per SD unit Increment in Cumulative Stress Exposure, and Per Year in Baseline Age, in the Midlife Development in the United States Study[a].

	Executive Function Score		Episodic Memory Score	
	Difference, SD units (95% CI)		*Difference, SD units* (95% CI)	
All Participants (N=3954)				
Per SD in Cumulative Stress Exposure	−0.12	−0.16, −0.08	−0.09	−0.13, −0.05
Per year in Baseline age	−0.03	−0.04, −0.03	−0.03	−0.03, −0.02
Workers only (N=2564)				
Per SD in Cumulative Stress Exposure	−0.10	−0.14,-0.05	−0.06	−0.11,-0.01
Per year in Baseline age	−0.03	−0.033,-0.026	−0.02	−0.024,-0.016

Abbreviation: CI: confidence interval; SD: standard deviation.
[a] Multiple imputation results are summarized from 20 imputed data sets.[b] Estimates are from marginal structural models and were additionally adjusted for childhood confounders including age, gender, race/ethnicity status, and parent's education levels. Stabilized inverse probability of treatment weights were included to adjust for "stressor-confounder" feedback.

provide context for the magnitude of the cognitive function differences by stress level, we ran a separate model to estimate the differences in each cognitive score per year in age, adjusting for sex and race/ethnicity.

To estimate corresponding differences in rates of change in cognition, we extended these analyses to GEE models for repeated measures. Specifically, we regressed each cognition score on the cumulative stress exposure variable(s), covariates, time (years since baseline, continuous), cross products of cumulative stress exposures with time, and the cross-products of covariates with time. The coefficient of interest was the cross-product term between stress exposures and time, the mean difference in rate of change in cognitive function per year, per SD unit increase in stress exposure measure. We did not assess the associations between lifecourse stress profiles and changes in cognitive function because the numbers in some strata were too small (e.g., n = 10) after stratification by age.

Several potential confounders of the associations of adulthood stress exposures (e.g., education, income) with cognitive outcomes are plausibly affected by childhood stress exposures (see the directed acyclic graph in Fig. 2). Including these covariates as terms in the regression models could induce collider bias and/or mask associations of childhood stress exposures on cognitive function. Thus, we calculated inverse probability-of-treatment weights to mitigate confounding of the estimated adult stressor effects in the context of "stressor-confounder feedback" (Hernán et al., 2004; Naimi et al., 2014; Robins et al., 2000). Additionally, to account for potential bias introduced by lost-to-follow-up, we used inverse probability-of-survival weights to separately account for attrition due to death and due to other reasons in longitudinal models of change (See Appendix for detail information regarding inverse probability weights).

Missing data. Data missingness ranged from 0.05% (perceived inequality) to 14% (childhood stressors) of participants; most variables were missing for <5% of participants. We addressed missing stress exposure and covariates with multiple imputation.

Secondary and sensitivity analyses. To probe the extent to which specific stress domains might drive the association of aggregate cumulative stressor score with levels of cognitive function, we fit separate models for each stressor domain in relation to cognitive scores. Since the definition of high vs. low stress was specific to this study sample, we calculated and presented the means and standard errors of individual stress domains across the four lifecourse stress profiles (see Appendix Tables 3 and 4). Additionally, to evaluate the robustness of the results under a broader definition of "high-stress exposure," we reran our analyses designating high-stress exposure as the top tertile (instead of the top quartile) of each stressor domain. Because change in cognitive function is sensitive to age (Murman, 2015), we stratified these analyses on stressors and cognitive changes by baseline age (<65 years old, ≥ 65 years old). As prior research suggests that the association between stressors and changes in cognitive function may differ between men and women (Munro et al., 2019), we also assessed the associations between stressors and cognitive changes by gender. In constructing work-related stress scores, we assigned the lowest scores for non-workers. Although this approach has been widely used in prior research (Lantz et al., 2005; Slopen et al., 2012), it may not accurately capture the effect of work stress since the sociodemographic profiles of non-workers may differ from that of those who have actually experienced the lowest levels of work-related stress, and also reasons for not working may vary in ways

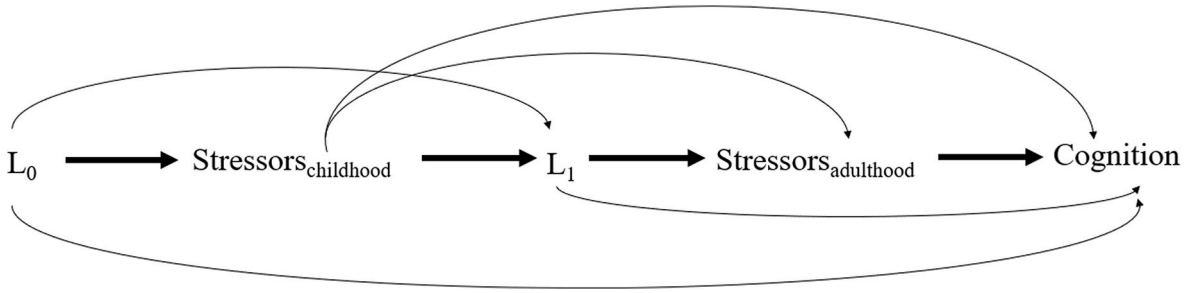

Fig. 2. Directed Acyclic Graph showing the hypothesized causal relationships between childhood stress exposures, adulthood stress exposures, cognitive function, and confounders in the Midlife Development in the United States Study, 2004–2014. L_0: Age, gender, and race/ethnicity status. L_1: Education, income, parental status, spousal status, working status, whether had chronic conditions or not.

Table 3
Adjusted Mean Difference in Baseline Cognitive Function score, by Life-course Stressor Profile, in the Midlife in the United States Study[a].

Childhood Stress Exposure[b]	Adulthood Stress Exposure[b]	*N*	Executive Function Score[c]		Episodic Memory Score[c]	
			Difference, SD units	95% CI	*Difference, SD units*	95% CI
All Participants (N=3954)						
Lower	Lower	2491	0, Ref		0, Ref	
High	Lower	475	−0.22	−0.31, −0.12	−0.17	−0.27, −0.07
Lower	High	696	−0.13	−0.21, −0.05	−0.13	−0.22, −0.05
High	High	292	−0.34	−0.46, −0.22	−0.21	−0.33, −0.08
Workers only (N=2564)						
Lower	Lower	1489				
High	Lower	247	−0.17	−0.30,-0.04	−0.14	−0.27,-0.02
Lower	High	589	−0.09	−0.19,0.02	−0.08	−0.20.0.04
High	High	239	−0.38	,-0.52,-0.23	−0.14	−0.31,0.04

Abbreviation: CI: confidence interval; SD: standard deviation.

[a] Multiple imputation results are from 20 imputed data sets. Generalized estimating equations (with normal distribution and identity link) were used to estimate the associations of cumulative stressor profiles with cognitive function, adjusting for clustering by sibling status.

[b] We designated the top quartile of the z-score of childhood and adulthood stress exposures as "high stress," and the lowest and the 2nd quartile of the z-score of childhood and adulthood stress exposures as "lower stress."

[c] Estimates are from marginal structural models and were additionally adjusted for childhood confounders included age, gender, race/ethnicity status, and parent's education levels. Stabilized inverse probability of treatment weights were included to adjust for "stressor-confounder" feedback.

Table 4
Adjusted mean differences in changes in cognitive function, by baseline cumulative stress exposures score, in the midlife development in the United States study, 2004–2014[a].

	Mean differences in changes in executive function scores	Mean differences in changes in episodic memory scores
	Difference, SD units, (95% CI)	*Difference, SD units, (95% CI)*
All Participants (*N* = 2517)	0.004 (−0.0004,0.01)	−0.00002(-0.01,0.01)
Workers only (*N* = 1754)	0.003 (−0.01,0.01)	0.01 (−0.01,0.03)

Abbreviation: CI: confidence interval.

[a] Multiple imputation results were summarized from 20 imputed data sets. Models included age, race/ethnicity status, parent's education, cumulative stress exposures, time, the cross-products of time with stress, and the cross-products of time with covariates. Stabilized inverse probability of weights were included to account for "stressor-confounder" feedback, lost to follow up due to death, and lost to follow up due to other reasons.

that also affect stress levels and health. In a sensitivity analysis, we restricted the sample to those who were working and reran the primary analyses to check whether this approach influenced the results All analyses were performed in SAS, Version 9.4.

3. Results

At baseline, participants were 28–84 years old (mean (*SD*), 56 (12)); approximately one-third were 65 years or older (Table 1). Compared with individuals in the lower two tertiles of the cumulative stress score, those in the highest tertile were more likely to be younger, Black, working, and unmarried; they were also more likely to have a high school degree or lower, have no children, and have chronic conditions. Both MIDUS2 executive function and episodic memory scores were standardized to have a mean of 0 and a standard deviation of 1. At MIDUS3, the average executive function and episodic memory scores were −0.16 (*SD* 0.76) and −0.03 (*SD* 0.98), respectively. The average change in executive function between MIDUS2 and MIDUS3 was −0.32 (*SD* 0.60), and the average change in episodic memory was −0.14 (*SD* 0.94).

Table 2 presents the associations between *continuous* cumulative stress exposures and levels of cognitive function in the full analytical sample and among working adults only. In results from the marginal structural models, a 1-*SD* higher cumulative stress exposure score corresponded to a baseline executive function score that was a mean 0.12 *SD* lower (95% CI, −0.16 to −0.08) and an episodic memory score that was 0.09 *SD* lower (95% CI, −0.13 to −0.05), on average. To place the magnitude of these differences in context, executive function and episodic memory scores were both 0.03 SD lower per year in baseline age. Among working adults only, a 1-*SD* higher cumulative stress exposure score corresponded to a baseline executive function score that was a mean 0.10 *SD* lower (95% CI, −0.14 to −0.05) and an episodic memory score that was 0.06 *SD* lower (95% CI, −0.11 to −0.01).

Table 3 shows the associations between four categorical lifecourse stressor profiles and levels of cognitive function in the full analytical

sample and among working adults only. Relative to the mean executive function scores among respondents who did not experience high-stress exposure in either childhood or adulthood, the mean score was 0.22 *SD* units lower (95% CI, −0.31 to −0.12) among those with high-stress exposures only in childhood, 0.13 *SD* units lower (95% CI, −0.21 to −0.05) among those with high-stress exposures only in adulthood, and 0.34 *SD* units lower among those with persistently high-stress exposures (95% CI, −0.46 to −0.22). The corresponding differences in episodic memory score were similar to executive function, although the difference in episodic memory scores for those with persistently high stress was less pronounced than differences in executive function. The patterns of the associations of lifecourse profiles with executive function and episodic memory were similar among workers.

Regarding the associations between cumulative stress exposures and the rate of cognitive change, we found little evidence that cumulative stress exposure levels were associated with the rate of cognitive change in the full sample or among workers only (Table 4).

3.1. Secondary and sensitivity analyses

Higher stress in several specific domains—particularly, financial stress, childhood stress, neighborhood stress, perceived discrimination, and relationship stress–was associated with lower executive function scores. Similarly, financial stress, neighborhood stress, perceived inequality, and childhood stress were associated with lower levels of episodic memory (see Appendix Figs. 1–2). When using the highest tertile (rather than quartile) as the cut-off defining high versus low stress, the results were similar for executive function, with scores being lower among those with high stress only in childhood or adulthood, and lowest among those with persistently high stress. For episodic memory, results were largely similar except that those with high stress only in childhood (rather than those with high stress in childhood and adulthood) had the lowest scores when compared with individuals in other stress profiles (see Appendix Table 2). Additionally, we found no evidence of age and gender differences in the associations between cumulative stressors and changes in cognitive function (see Appendix Table 5).

4. Discussion

In this large, longitudinal cohort of middle-aged and older adults, we found strong inverse associations between cumulative exposure to stressors over the life course and cognitive function. Additionally, high-stress exposures only in childhood were associated with lower levels of cognitive function later in life. However, there is little evidence that changes in cognitive function over an average of 9 years of follow-up differed across levels of cumulative exposure to stressors.

The inverse associations demonstrated between stressor exposures and cognitive performance in the current study are consistent with most previous research on stress and cognitive aging (Aggarwal et al., 2014; Munoz et al., 2015; Turner et al., 2017), and they provide some evidence to the accumulation of risk model. Our study adds critical detail to the literature by including a more comprehensive assessment of stressors occurring throughout the life course. The findings suggest that cumulative stress exposures have strong impacts on cognitive function and highlight the importance for considering multiple domains of stress exposures when understanding differences in cognitive function at the population level. A variety of mechanisms could underlie the associations between cumulative stressor exposures and cognition. Exposures to stressors across the lifecourse may decrease gray matter and white matter volumes in the hippocampus, a brain region that is crucial for learning and memory (Gianaros et al., 2007). Stress exposures may activate biological stress responses via the hypothalamic-pituitary-adrenal axis, the system responsible for the release of glucocorticoids, including cortisol (Frodl and O'Keane, 2013). As individuals with cognitive impairment have been found to secrete more cortisol than normal older adults (Arsenault-Lapierre et al., 2010; Csernansky et al., 2006; Lind et al., 2007; Marin et al., 2011), it is possible that cumulative stress exposures are linked to cognitive function through elevated cortisol. Exposure to stressors, especially during childhood, may influence educational attainment and employment opportunities in adulthood and reduce one's likelihood of engaging in cognitively stimulating activities, factors that have been found to be closely linked to cognitive function in late adulthood (Montez and Hayward, 2014). Stress exposures may also lead to unhealthy behaviors (e.g., physical inactivity, smoking) or induce biobehavioral responses (e.g., insomnia and sleep apnea) that, in turn, lead to poor cognitive functioning and dementia (Blondell et al., 2014; Rusanen et al., 2011; Yaffe et al., 2014). Identifying the mechanisms underlying cumulative stress exposures and cognitive function would be an important avenue for future research. Such knowledge will help evaluate whether intervening on these stress exposures has the potential to promote cognitive health at the population level.

Our findings also suggest that even in the absence of high adulthood stress exposure, respondents with a history of high exposure to childhood stressors had poorer cognitive function than those without high-stress exposure across the life course. These findings are broadly consistent with previous research on cardiometabolic risk which found that childhood distress was associated with higher cardiometabolic risk in adulthood event after accounting for adulthood distress (Winning et al., 2015). While our childhood stress measure includes 16 items that capture several stressful events, it was less comprehensive than the adulthood stress measures. Our findings on childhood stress and cognitive function may have been even stronger if more stress experiences in childhood have been measured. Together, these findings provide some evidence to the critical period model and suggest that the deleterious impact of childhood stress exposures on adult health could be long-lasting and enduring.

In our sensitivity analysis, work psychological stress and work family conflicts appear to have weaker associations with cognitive function, particularly episodic memory, than other stress domains. It is worth noting that individually, some stress domains may have weaker associations with cognitive outcomes than others, but they may still exert strong impacts on cognitive function when they co-occur with other stress domains. A recurring question in this literature is whether one should assign weights to specific stress domains to create the cumulative stress score. Although weighing the relative importance of multiple stressors seems promising, it is difficult to do so empirically in a way that is generalizable across age and sociodemographic groups. Prior research on cumulative risk factors and developmental outcomes has suggested that unitary weights are more robust predictors than weighted scores (Evans et al., 2013; Slopen et al., 2018; Wainer, 1976). Further investigation is needed into the predictive performance of different operations of cumulative stress concerning cognitive outcomes.

In contrast with prior research, we found little evidence of an association between cumulative stress exposures and rate of cognitive change. Our study included stress exposures occurring across the life course, but it may be that recent stress exposures affect cognitive decline with more potency than remote or enduring stressful experiences. Indeed, a recent study using data from MIDUS data showed that those who were first exposed to traumatic events later in life had greater decline in executive function than those whose first traumatic events occurred earlier in life (Lynch and Lachman, 2020). Likewise, a study using data from the Baltimore Epidemiologic Catchment Area Follow-up Study found that stressful life events occurring within the last year, but not those occurring prior to the past year, were associated with greater verbal memory decline over approximately 11 years among women but not men (Munro et al., 2019). Unfortunately, we did not know the exact timing of exposure to many of the chronic stressors (e.g., financial stress) assessed in our study. Therefore, we could not distinguish roles of recent from those of stressful experiences occurring well before the MIDUS assessment period, beyond separating out those exposures occurring in

childhood. Taken together with findings from other work (Lynch and Lachman, 2020), our findings may suggest that it is important for future research to consider timing when constructing the cumulative stress metric and to evaluate the timing of cumulative stress exposures, including both untoward events and chronic stressors, and their relationships with cognitive declines. The null associations of stress exposure with cognitive decline may also suggest that the stress exposures we measured affect cognitive performance or, in the case of childhood exposures, the developmental processes leading to peak adult performance but not late-life neurodegeneration or decompensation, which is more relevant to cognitive decline and dementia.

4.1. Limitations

Our study has several limitations. First, childhood stress exposures were retrospectively reported and might have been subject to faulty recall. However, research on twins participating in MIDUS has found moderate-to high-sibling agreement on the self-reported childhood stressor indicators, suggesting retrospective recall bias of the childhood stress exposures may be minimal (Gruenewald et al., 2012). Second, cognitive function status at the time of recall might affect the report of stress exposures. If, for example, those who were with poorer cognitive performance at baseline were less likely to recall stress exposures, then our estimate of the stress-cognition association might have been underestimated. Third, although we included a broad range of potential confounders, unmeasured confounding is likely as in any observational study. Importantly, we did not have information about early life cognitive function, which may have affected both exposure to stressors and later cognitive function. Additionally, our definitions of "high--stress" exposure are specific to this sample. However, concerns about such specificity are somewhat mitigated by findings in sensitivity analyses that found largely similar results using a different cut-off point.

Further, despite nine years of follow-up, the average change in cognitive score was small, particularly among the younger group, which potentially limited our statistical power to detect factors that affect rate of change. The use of only two waves of cognitive data presents additional methodological challenges, as we were unable to characterize more detailed cognitive trajectories and evaluate their relationship with cumulative stress exposures. Although we have calculated inverse probability weights to account for bias from loss-to-follow-up, there might have been selection bias resulting from differential participation. It is important to recognize those with poorer cognitive function or who have experienced high-stress exposures may be less likely to participate in studies like MIDUS or may have been excluded from our sample due to missing SAQ data. Lastly, while our stress measures are more comprehensive than many other previous studies, they might have failed to capture some important stress exposures (e.g., caregiver stress) that could potentially affect the cognitive function of middle-aged and older adults. Additionally, most stress exposure measures in MIDUS did not assess stress appraisals and thus we were not able to assess the extent to which participants experienced any given stress exposure as actually being stressful and then evaluating how much actual stress experienced cumulatively over the life course influenced cognitive function in late life (Brown et al., 2020; Morris et al., 2021). It would be helpful for future research to also consider stress appraisals in their measures of cumulative stress exposures.

5. Conclusions

In conclusion, higher cumulative exposure to stressors across the life course was strongly associated with lower levels of cognitive function. We found little evidence that cumulative stress exposures are associated with changes in cognitive function in this study sample. Our study advances the literature with its assessment of stress exposure in multiple domains. This allowed a more comprehensive assessment of stressor exposure across the life course and how such exposure may be associated with cognitive function. In particular, information on childhood and adulthood stressors allowed us to investigate how stressors at different times in the life course independently and cumulatively influence cognition. By using marginal structural models, our study was able to account for stressor-confounder feedback that could potentially bias estimates of the association between stressor exposure and cognitive outcomes. Our findings may suggest the value of further investigation when more assessments of cognitive function data are available or with older samples. For future research, it would be useful to collect more detailed information on when stressors occurred to determine whether proximity plays a role in the associations between stress and cognitive decline.

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Author contributions

Ruijia Chen: Conceptualization, Methodology, Writing, David R Williams: Supervision; Conceptualization; Writing – original draft preparation. Kristen Nishimi: Writing- Reviewing and Editing, Code Review, Natalie Slopen: Writing- Reviewing and Editing, Laura Kubzansky: Supervision; Methodology; Conceptualization; Writing-Reviewing and Editing, Jennifer Weuve: Supervision; Methodology; Conceptualization; Writing- Reviewing and Editing.

Declaration of competing interest

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

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2022.115448.

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