Cumulative stress exposure and cognitive function among older adults: The moderating role of a healthy lifestyle

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Abstract

Objectives: Although chronic stress is a risk factor for poor age-related cognitive health, there is limited research that has examined how cumulative stress across the lifespan impacts cognitive aging. There may also be resilience factors that minimize the effects of cumulative stress on cognitive health. Engaging in a healthy lifestyle is protective against cognitive decline and may therefore interact with cumulative stress to buffer the stress-cognition relationship. The objective of the current study was to examine the moderating role of a healthy lifestyle, comprised of physical activity, social engagement, and sleep quality, in the relationship between cumulative stress exposure and baseline and change in cognitive performance (global cognition, episodic memory, executive function) over 9 years among 1297 older adults in the MIDUS cohort (M_{age} = 69.0±6.4, 57.8% female). Method: Cumulative stress exposure and healthy lifestyle behaviours were indexed using self-reported questionnaires at baseline, and cognitive function was assessed using a battery of standardized neuropsychological tests at baseline and follow-up. Results: Controlling for age, sex, education, race, marital status, employment status, hypertension, diabetes, and depression, higher cumulative stress exposure was associated with poorer baseline performance and slower decline over time in global cognition and executive function, but not episodic memory. A healthy lifestyle did not significantly moderate the relationship between cumulative stress and cognitive function. Exploratory analyses showed a significant cumulative stress-cognition relationship among females only. Discussion: This study lends support for a lifespan model of cognitive aging and suggests that the cognitive health consequences of stress extend beyond immediate timescales.

Keywords*:* stress, lifestyle, cognitive aging, life course, brain health

Introduction

With an aging population on the rise, understanding the factors that facilitate healthy cognitive aging and reduce the risk of dementia is an urgent public health priority. In the absence of an effective disease-modifying treatment for dementia, research has largely shifted towards risk factor management, with the intention of delaying the onset of cognitive deterioration (Rockwood et al., 2020). A substantial body of work suggests that cognitive aging trajectories are largely explained by the interaction between modifiable risk and protective factors over the life course (Livingston et al., 2020). Psychological stress is one such modifiable risk factor for age-related cognitive decline that warrants attention due to its high prevalence rates and potential for intervention (Franks et al., 2022).

Decades of prior research have shown that high levels of chronic stress exert detrimental effects on brain health (Lupien et al., 2009), especially among older adults who are particularly vulnerable to the effects of stress on cognition (Sapolsky, 1999). Most studies to date have assessed perceptions of stress within the previous month, with mixed findings reported (e.g., Solder et al., 2021; Turner et al., 2017). This restricted time frame neglects stressful experiences accrued throughout the life span, which fails to capture the chronic and cumulative nature of stress that is central to its effects on health (Shields & Slavich, 2017). Understanding how psychological stress impacts cognitive aging may be better conceptualized using a life course perspective. Indeed, multiple stressors accumulate and cluster over the lifespan such that, as the severity and duration of stressors increase, there is cumulative wear and tear on the brain and body (Ben-Shlomo & Kuh, 2002), leading to negative health consequences, including an increased risk for age-related cognitive decline and impairments (D'Amico et al., 2020a). Moreover, both acute and chronic stress exposures across multiple life domains should be assessed when measuring cumulative stress across the lifespan, as no single stressor can capture the full impact of stress on health (Pearlin et al., 2005; Wheaton, 1994). Taking a life course approach is especially important when examining the antecedents of cognitive health as factors that enhance or diminish cognitive resilience accumulate over different periods across the lifespan (Livingston et al., 2020). Mixed findings have been reported, however, on the association between cumulative life stress and cognitive function suggesting that there may be individual difference factors that influence the relationship between stress and cognition. For example, Peavy et al. (2009) found that a greater number of stressful life events were associated with greater age-related cognitive decline, while Senft Miller et al. (2021) did not find a relationship between cumulative stress exposure and cognitive function.

Not all individuals are equally impacted by the same exposures to stress (Lupien et al., 2018), implying that there may be protective factors rendering some individuals better able to withstand the degenerative effects of stress on the brain. Additionally, the effects of stress on cognitive function may be malleable, evidenced by the brain's ability to adapt to environmental changes (McEwen & Morrison, 2013). It is therefore important to examine factors that may interact with stress to minimize its negative impact on cognition. Engaging in a healthy lifestyle may be a protective mechanism through which the negative effects of stress on cognitive aging can be attenuated.

A large and growing body of literature provides considerable evidence that healthy lifestyle behaviours, such as physical activity, social engagement, and getting good quality sleep, are modifiable factors that reduce the risk of age-related cognitive decline (Livingston et al., 2020). Considering the cumulative and combined effect of multiple healthy lifestyle behaviours on cognitive health, as opposed to individual behaviours in isolation, may be more practical as healthy lifestyle parameters often cluster and act synergistically to benefit cognitive function (Rabel et al., 2019). Engaging in healthy lifestyle behaviours confers cognitive benefits, in part, by enhancing cognitive reserve, or the ability to remain cognitively intact despite the presence of risk factors (Stern et al., 2019). Further, physical activity, social engagement, and good sleep hygiene are coping behaviours that have all been shown to reduce feelings of stress (Churchill et al., 2022). A healthy lifestyle may be a plausible explanation for the individual differences seen in the stress-cognition relationship, such that engaging in a healthy lifestyle may buffer the association between cumulative stress exposure and cognitive function among older adults (Lupien et al., 2018). To date, however, no studies have directly evaluated the moderating role of a healthy lifestyle in this relationship.

The current study examined the moderating effect of a healthy lifestyle on the association between cumulative stress over the lifespan and cognitive functioning in later adulthood. Specifically, this study examined whether a healthy lifestyle indicator score, including physical activity, social engagement, and sleep quality, moderates the association between greater cumulative stress exposure and cognitive function in domains of episodic memory, executive functioning and global cognition, at baseline and over 9 years among older adults. It was hypothesized that a higher healthy lifestyle indicator score would buffer the negative association between cumulative stress exposure and cognition at baseline and over time. Sex-stratified models were also conducted to explore whether the aforementioned associations differ by sex. Additional models were conducted to explore the moderating effect of individual components of the healthy lifestyle indicator score.

Methods

Participants

Data for this study was drawn from the second and third waves of the National Survey of Midlife in the United States (MIDUS), a longitudinal cohort study designed to investigate the biopsychosocial factors associated with physical, mental, and cognitive health in middle-age and older adulthood (Radler & Ryff, 2010). For the current study, MIDUSII was considered the baseline. From the 5,555 individuals who participated in MIDUSII, 1,089 were removed for not having completed the questionnaires pertaining to stress exposures across the lifespan and lifestyle behaviours. A total of 3,045 individuals were then excluded from analyses for meeting the following self-reported *a priori* exclusion criteria at MIDUSII: age less than 60, diagnosis of a neurological disorder, Parkinson’s disease, a history of stroke, a history of a serious head injury, and/or having previously undergone chemotherapy or radiation treatment. Participants were then removed if they were missing information on age, sex, and/or educational attainment (*n* = 2). Participants were also excluded from the final analytical sample if they did not participate in the MIDUSII Cognitive Project or were missing all baseline cognitive assessments (*n* = 113). This resulted in a final analytical sample of 1,297. Of these participants, 806 completed the follow-up cognitive assessment at MIDUSIII (mean follow-up time: 9.2 $\pm$ 0.5 years). Those who were lost to follow-up were more likely to be older, male, have less than at least some post-secondary education, have higher levels of baseline cumulative stress exposure, have lower baseline healthy lifestyle adherence, and have poorer baseline global cognition, episodic memory, and executive function performance (see Supplementary Table 1). Supplementary Figure 1 provides a flowchart of the study sample.

MIDUS data collection was reviewed and approved by the Education and Social/Behavioural Sciences and the Health Sciences Institutional Review Boards at the University of Wisconsin-Madison. Ethics approval for secondary data analysis was approved by Toronto Metropolitan University's Research Ethics Board (REB 2021–385).

Measures

Sociodemographic and Health-related Information. The following self-reported variables were collected at baseline: age; sex (male or female); highest level of education attained; race self-identified as Black/African American, White, or other; marital status (married or not married); employment status (currently working or not currently working); diagnosis of diabetes, hypertension, and depression (yes/no); perceived socioeconomic status indexed using the MacArthur Scale of Subjective Social Status (Adler et al., 2000); and informal caregiving status (yes/no). Participants were also asked if they currently smoke cigarettes regularly (yes/no), their frequency of alcohol intake within the previous month ranging from 0 (*never*) to 5 (*everyday*), and their self-reported memory abilities compared to others of their same age on a scale ranging from 1 (*poor*) to 5 (*excellent*).

Cumulative Stress Exposure. Following previous MIDUS research (Chen et al., 2022), cumulative stress exposure was indexed using the following 10 stress domains assessed via self-reported questionnaires at MIDUSII: childhood stress, adulthood stress, financial stress, relationship stress, work-family conflict, neighbourhood stress, work-related psychological stress, work-related physical stress, perceived inequality, and perceived discrimination. Higher scores on each domain sub-score indicate higher levels of stress, except for work-related physical stress and work-family conflict, where lower scores are indicative of greater stress. Accordingly, sub-scores for work-related physical stress and work-family conflict were multiplied by -1 so that higher scores on all stress domains indicate higher levels of stress. For the domains that were not applicable to a given participant (e.g., occupational stress for individuals who were unemployed, marital stress for single individuals, and child-related measures for participants without children), the lowest possible value on the item was assigned. The total cumulative stress exposure score was calculated by standardizing each of the 10 stress domain sub-scores into a Z-score and summing the Z-scores, with higher total scores representing more cumulative stress exposure across the lifespan. See Supplementary Material for additional details on the measure items and scoring algorithm used to create the cumulative stress exposure composite score.

Healthy Lifestyle Indicator Score. Physical activity, social engagement, and sleep quality were assessed via self-reported questionnaires at MIDUSII. Total scores for both physical activity and social engagement were calculated using methods derived from previous MIDUS studies (Cotter & Lachman, 2020; Tun et al., 2013). Total sleep quality was assessed using the Jenkins Sleep Questionnaire (JSQ; Jenkins et al., 1988). Further details on each questionnaire and individual lifestyle behaviour scoring method are included in the Supplementary Material. To create the moderating variable, each of the three lifestyle behaviour scores was converted into a Z-score and summed to create a total healthy lifestyle indicator score, with higher scores representing greater adherence to a healthy lifestyle.

Cognitive Function. Cognitive function was assessed at MIDUSII and MIDUSIII using the Brief Test of Adult Cognition by Telephone (BTACT; Tun & Lachman, 2006), a battery of neurocognitive tasks designed to measure seven areas of cognitive functioning that are sensitive to aging. These tasks included the Rey Auditory-Verbal Learning Test to assess immediate and delayed episodic memory; and the backward digit span (working memory span), the category fluency test (verbal fluency), the number series completion task (inductive reasoning), the backwards counting task (speed of processing), and the Stop and Go Switch Task (attention switching) to assess executive function. For a detailed description of the test battery administration, see Tun and Lachman (2006). The BTACT has demonstrated good convergent validity compared to the in-person version among participants in the MIDUS sample (Lachman et al., 2014). The Supplementary Material includes scoring details for global cognition, episodic memory, and executive function composite scores at baseline and follow-up.

Statistical Analyses

All analyses were performed using R (R Core Team, 2023). A nominal Type I error rate of $\alpha = .05$ was used as a threshold for statistical significance in all analyses (i.e., $p < .05$). Missing responses for cumulative stress exposure (0.1%-15.0% missing) and healthy lifestyle behaviour (0.5%-15.5% missing) items were imputed using maximum likelihood multiple imputations with 5 imputations and 10 iterations using the "mice" package (van Buuren et al., 2021). All analyses were conducted using the pooled imputed dataset.

A total of three primary linear mixed-effects models were conducted using the "lme4" package in R (Bates et al., 2022) to examine the moderating effect of the healthy lifestyle indicator score on the relationship between cumulative stress exposure and cognitive function over time. The robust Kenward-

Roger estimation (Kenward & Roger, 1997) was used for more precise standard errors. Time was coded linearly as 0 = baseline and 1 = follow-up. Each model was analyzed with cumulative stress exposure (CSE) as the independent variable, the healthy lifestyle indicator (HLI) as the moderating variable, and either global cognition, episodic memory, or executive function composite score as the dependent variable. Cumulative stress, the healthy lifestyle indicator, and all covariates were entered as fixed effect factors and participant-specific intercepts were specified as the random effect. All models were adjusted *a priori* for age, sex, and educational attainment. Fully adjusted models included additional covariates of race (White or not White), marital status, employment status, depression, hypertension, and diabetes due to their known influence on psychological stress, lifestyle behaviours, and cognitive function (Jin et al., 2023; Moheet et al., 2016). All variables were standardized to Z-scores before being added into the models. R^2 model fit statistics for mixed models (Rights & Sterba, 2019) were derived separately for each imputed dataset and then averaged across all imputed datasets for a total pooled R^2 statistic for each model.

Data were disaggregated by sex to explore whether the moderating role of a healthy lifestyle indicator in the relationship between cumulative stress exposure and cognitive change differs between males and females. To explore whether the moderating role of a healthy lifestyle may be driven by specific lifestyle behaviours, each individual moderating lifestyle behaviour (i.e., physical activity, social engagement, and sleep quality) was explored independently.

Results

Participant Characteristics

A full summary of participant sociodemographic and health-related characteristics, including descriptive information about cumulative stress exposure, healthy lifestyle behaviours, and standardized baseline cognitive performance scores are shown in Table 1. Briefly, participants were, on average, 69±6.4 years of age and 57.8% of the sample was female. The majority of the sample self-identified as White (89.1%), 57.5% had at least some post-secondary education, and perceived socioeconomic position was moderate with a mean score of 4.1±3.1 out of a possible score of 10. Fifteen percent of the sample reported a diagnosis of diabetes, 45.3% reported a diagnosis of hypertension, and 13.5% reported a diagnosis of depression. See Supplementary Table 2 for the bivariate correlations between the sociodemographic and health-related variables, CSE, HLI score and its components, and cognitive function composite scores at baseline.

Moderation Models

Global cognition. In the partially adjusted model controlling for age, sex, and education, greater CSE was associated with poorer baseline global cognition (B = -0.20, 95% CI [-0.25, -0.14]), and lower decline over time (B = 0.08, 95% CI [0.02, 0.14]). The HLI score was not significantly associated with baseline cognition (B = 0.02, 95% CI [-0.10, 0.14]) or change over time (B = 0.03, 95% CI [-0.09, 0.14]). Moderation analyses were not statistically significant for baseline performance (B = -0.01, 95% CI [-0.04, 0.02]) or global cognition over time (B = -0.006, 95% CI [-0.04, 0.03]). Results were similar in the fully adjusted model. See Table 2 for all model estimates.

Episodic memory. In the partially adjusted model, greater CSE was associated with poorer baseline episodic memory (*B* = -0.05, 95% CI [-0.08, -0.03]), but not with change in episodic memory (*B* = 0.006, 95% CI [-0.03, 0.04]). The HLI score was not significantly associated with baseline episodic memory (*B* = 0.02, 95% CI [-0.10, 0.14]) or change in episodic memory (*B* = 0.04, 95% CI [-0.04, 0.11]). No statistical evidence was found in the CSE × HLI interaction for episodic memory at baseline (*B* = 0.001, 95% CI [-0.01, 0.01]) or change in episodic memory (*B* = -0.003, 95% CI [-0.02, 0.02]). Results were similar in the fully adjusted model. See Table 2 for all model estimates.

Executive function. In the partially adjusted model, greater CSE was associated with poorer baseline executive function (*B* = -0.14, 95% CI [-0.19, -0.10]) and less decline over time (*B* = 0.08, 95% CI [0.04, 0.12]). HLI was not significantly associated with baseline (*B* = 0.001, 95% CI [-0.09, 0.09]) or change in executive function (*B* = -0.006, 95% CI [-0.09, 0.08]). No statistically significant CSE × HLI interaction was found for baseline executive function (*B* = -0.01, 95% CI [-0.03, 0.009]) or change in executive function over time (*B* = 0.001, 95% CI [-0.02, 0.03]). Results were similar in the fully adjusted model. See Table 2 for all model estimates.

Exploratory Analyses

When stratifying the fully adjusted primary models by sex, CSE was associated with baseline global cognition (*B* = -0.16, 95% CI [-0.23, -0.09]), episodic memory (*B* = -0.05, 95% CI [-0.08, -0.01]), and executive function (*B* = -0.11, 95% CI [-0.17, -0.06]) among females but not males. Among females only, lower levels of baseline CSE were associated with faster rates of decline in global cognition decline (*B* = 0.10, 95% CI [0.03, 0.18]) and executive function (*B* = 0.09, 95% CI [0.04, 0.14]). No statistically significant associations were found between the HLI score and baseline cognition or cognitive change among males or females in any cognitive domain. Similarly, no significant CSE × HLI interaction was found on baseline cognition or change in cognition among males or females. See Supplementary Table 3 for all sex-stratified model estimates. Figure 1a-c displays change in cognition (a. global cognition, b. episodic memory, c. executive function) at low, moderate, and high levels of CSE among males and females.

In exploring the moderating effect of individual lifestyle behaviours in the relationship between CSE and cognitive function, higher levels of social engagement were associated with higher baseline global cognition (*B* = 0.34, 95% CI [0.14, 0.54]), episodic memory (*B* = 0.13, 95% CI [0.04, 0.23]), and executive function (*B* = 0.21, 95% CI [0.06, 0.35]). Better sleep quality was associated with lower baseline executive function scores (*B* = -0.19, 95% CI [-0.34, -0.04]). Physical activity, social engagement, and sleep quality were not significantly associated with cognitive change over time, nor moderated the association between CSE and baseline cognition or change in cognition over time. See Supplementary Tables 4, 5, and 6 for the model estimates with physical activity, social engagement, and sleep quality as the moderator, respectively.

Discussion

The purpose of the current study was to examine if engagement in multiple healthy lifestyle behaviours (physical activity, social engagement, and sleep quality) moderated the relationship between stress exposure accumulated over the life course and cognitive function among older adults in the MIDUS cohort. As expected, greater cumulative stress exposure was associated with poorer cognitive performance at baseline. However, greater cumulative stress exposure was associated with less decline in global cognition and executive function over time. Finally, the results did not support the hypothesized moderating effect of a healthy lifestyle indicator score on the association between cumulative stress exposure and cognition. Exploratory analyses provided some support for the importance of disaggregating data by sex and stimulate discussion for the use of a healthy lifestyle indicator score.

The association found between higher levels of cumulative stress exposure and poorer cognitive performance is consistent with prior research showing a relationship between psychological stress and cognitive function among older adults (Peavy et al., 2009), as well as theoretical conjectures pertaining to the effects of accumulation of risk over time on health outcomes (Ben-Shlomo & Kuh, 2002). This study adds to the extant body of work by highlighting the need to consider a constellation of stressful exposures across the life course when examining the stress-cognition relationship. There are a number of mechanisms that may explain the association between higher levels of stress across the lifespan and poorer cognitive performance in older adulthood. In particular, chronically elevated glucocorticoids (i.e., cortisol) released by the hypothalamic-pituitary-adrenal (HPA) axis in response to perceived threats may exert neurotoxic effects on the brain regions most sensitive to age-related changes, including the hippocampus and prefrontal cortex, which are crucial structures that regulate learning and memory and executive functioning (Lupien et al., 2009). Dysregulation of the HPA axis stemming from repeated exposure to chronic stressors over time may further disrupt the functioning of other physiological systems including the cardiometabolic and immune systems, leading to allostatic overload (McEwen, 1998), and eventually adverse health outcomes, including poor cognitive functioning (D'Amico et al., 2020a). Future research is needed to delineate the biopsychosocial mechanisms through which cumulative stress across the lifespan leads to poor cognitive health outcomes in later life.

While the association between cumulative life stress exposure and cognition functioning was statistically significant, the effect sizes were relatively small. Although it is plausible that cumulative stress exposure may account for a small proportion of the variance in age-related cognitive performance, the exposure-based framing of the items that contributed to the calculated composite score may provide an alternative explanation. More specifically, items of the composite score reflected stressor exposure (i.e., whether a discrete event occurred) without considering the degree to which exposure to the event was perceived as stressful. According to the Transactional Model of Stress

(Lazarus & Folkman,1984), the degree to which one experiences distress is determined by the extent to which the stressor is evaluated as exceeding one's ability to cope. Measurements of stress that account for subjective appraisals of stress may be stronger predictors of cognitive health outcomes compared to count- or exposure-based measures as they are more sensitive to individual differences in stress appraisals (Hayman et al., 2014). Further research is needed to explore the relative associations between appraisal- versus exposure-based measures of stress and cognitive health.

Although episodic memory declined across the 9-year study period, no association was found with cumulative stress exposure. This is surprising given that episodic memory relies heavily on the functioning of the hippocampus, a glucocorticoid-dense structure that is particularly vulnerable to the neurotoxic effects of chronically high levels of circulating stress hormones (Sapolsky, 1999). However, change in episodic memory over time was relatively small compared to the other cognitive outcomes, possibly leading to less of an ability to detect an effect of stress on episodic memory. Unexpectedly, greater cumulative stress was associated with slower declines in global cognition and executive function over the 9-year follow-up period. Although counterintuitive to what one might expect based on the literature and the study hypotheses, it may be surmised that participants reporting higher cumulative stress displayed a floor effect in cognitive change over time as their cognitive scores were lower at baseline. Moreover, recent findings from the MIDUS study found that higher cumulative stress exposure was not associated with cognitive decline among the entire MIDUS cohort aged 25+ (Chen et al., 2022), suggesting that the nature of the cumulative stress-cognition relationship may be age-dependent. It is also possible that individuals experiencing a greater number of stressful events throughout the lifespan have accrued adaptive coping mechanisms that enhance their resilience to the effects of stress. Indeed, previous research has shown that moderate levels of cumulative lifetime adversity are associated with more favourable health outcomes by building effective coping resources to manage stress (Seery et al., 2010). As these interpretations are simple conjectures, future research is needed to understand the role of stress across the lifespan as a protective mechanism for age-related cognitive decline.

A healthy lifestyle composite comprised of physical activity, social engagement, and sleep quality was not associated with baseline or change in cognition after controlling for potential confounders. This is contrasted with a number of studies showing that higher engagement in a combination of multiple healthy lifestyle behaviours is associated with better cognitive performance (Anastasiou et al., 2018; Mamalaki et al., 2021) and less cognitive decline (Weng et al., 2018) among older adults. One possible explanation for these null findings is that previous studies typically include dietary pattern intake and nutrition as components of an overall healthy lifestyle, while the current study did not. Adherence to a healthy dietary pattern high in fruits, vegetables, lean meats, and healthy fats, and low in processed meats and refined sugars is a key lifestyle behaviour that is associated with more favourable cognitive health outcomes (Loughrey et al., 2017) via health-promoting anti-inflammatory and antioxidant pathways (Féart et al., 2010) and reduction in chronic disease associated with cognitive impairment and neurodegeneration (e.g., diabetes, hypertension, and hypercholesterinaemia; Noce et al., 2021). Dietary intake also acts synergistically with other lifestyle behaviours, including physical activity and social engagement to confer cognitive benefits (Fiocco et al., 2012; Parrott et al., 2021). Further, a previous cross-sectional study reported that adherence to a Mediterranean diet moderates the association between perceived stress and cognition in older adults (D’Amico et al., 2020b).

The moderating role of a healthy lifestyle in the association between cumulative stress exposure and cognition was not supported in the current study. As noted above, the exclusion of dietary intake from the composite lifestyle score may have minimized the sensitivity of the moderating variable. Although dietary intake was not available in the core MIDUS study, the healthy lifestyle composite score encompassed three important lifestyle behaviours. Exploratory analyses showed that greater social engagement was associated with better cognitive functioning at baseline, while better sleep score associated with poorer cognitive performance. This may suggest that the contradictive association between social engagement and sleep diluted the sensitivity of the healthy lifestyle indicator score. It may be possible that poorer sleep quality was associated with better cognitive performance as older adults with better executive functioning are more cognizant of problemed sleep.

Exploratory analyses provided support for possible effect modification by sex in the cumulative stress-cognition relationship. Specifically, the current study found that greater cumulative stress exposure was associated with baseline cognition and cognitive trajectory only in females. This sex-specific association may have diluted effect estimates stemming from the full-sample analytical models and is contrary to a recent study showing a relationship between higher levels of perceived stress and poorer cognitive function among males, but not females (Paolillo et al., 2022). The study, however, did not measure cumulative stress exposure, but indexed perceptions of stress within the previous month. It may be postulated that, although males may be more sensitive to stress experienced within proximal timeframes, females may be more sensitive to the longer-term effects of stress with aging (Wolfova et al., 2021). This sex difference may be due to more stressful experiences across the lifespan reported among females in the current study.

Previous research also suggests that females may be more vulnerable to the biological embedding and proliferation of stress in early life and its impact on age-related cognitive health outcomes (D'Amico et al., 2022). It is important to note that greater levels of cumulative stress exposure were associated with less cognitive decline among females, which, as previously mentioned, may be due to floor effects in cognitive decline or an accrual of coping mechanisms over time that enhance resilience to stress. Although the current sex-specific analyses were exploratory, requiring future hypothesis-driven investigation, this study supports the need for sex- and gender-based analyses in cognitive aging research to better inform individualized recommendations for cultivating healthy brain aging.

Although this study is novel and leverages the data-rich MIDUS study, several limitations must be addressed. First, cumulative stress exposure was measured using retrospective self-reported questionnaires, which likely entailed recall bias, especially when reflecting on experiences in early life. Similarly, lifestyle behaviors were self-reported, which may have resulted in a biased estimate of engagement in healthy behaviours. Furthermore, it is possible that adherence to a healthy lifestyle may change over the lifespan, and that these lifestyle changes may differentially associate with cognitive functioning in later life (Livingston et al., 2020; Middleton et al., 2010). Measures in the current study were limited to engagement in lifestyle factors in the past week or month, failing to capture life course changes in lifestyle behaviors. The study sample was also relatively healthy, racially homogenous, and cognitively high functioning, which limits generalizability of the findings to more racially diverse groups with a broader range of functional abilities. This adds to the growing need for population-based cohort studies to prioritize participant recruitment among marginalized groups who are not typically included in research studies. Furthermore, there was significant attrition bias over the 9-year span, such that those who were lost to follow up were more likely to be older, male, have lower educational attainment, and have greater cumulative stress exposure, a lower healthy lifestyle index score, and poorer baseline cognitive function. As such, results should be interpreted with caution as the cognitive trajectories reported in the current study may reflect those who are healthier at baseline. Finally, although the 9-year follow-up time is a strength of the study, having only two time points precludes the detection of possible non-linear changes in cognition over time, such that the pattern of cognitive decline may differ as a function of baseline cumulative stress exposure and/or healthy lifestyle behaviours.

Despite these limitations, the current results contribute to the existing body of work highlighting the need to consider stressful exposures across the lifespan as important risk factors for age-related cognitive decline. Indeed, the current study lends support for a lifespan model of cognitive aging and suggests that the cognitive health consequences of stress extend beyond immediate timescales. Although no modulating effects of a healthy lifestyle were found in the current study, future research is needed to understand whether lifestyle behaviours or other resilience factors may offset the insidious effects of stress on cognitive health in order to cultivate and promote a healthy aging population.

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Conflicts of Interest

None to disclose.

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Table 1. *Participant sociodemographic and health-related characteristics (n = 1,297*).

Table 2. *Linear mixed-effect model estimates predicting baseline and 9-year change in cognition.*

Figure 1a-c. Change in global cognition over time at low, moderate, and high levels of cumulative stress exposure among males and females for a) global cognition, b) episodic memory, and c) executive function. (CSE = cumulative stress exposure; SD = standard deviation) *Note*: The plots were derived from the model estimates for one of the imputed datasets which was virtually identical to the pooled results.

Table 1. *Participant sociodemographic and health-related characteristics (n = 1,297)*.

	Mean ± SD or % (n)
Age in years at baseline	69.0 ± 6.4
Sex (% female)	57.8 (750)
Race (%)	
Black and/or African American	7.6 (98)
White	89.1 (1,151)
Other	3.3 (43)
Educational attainment (%)	
Less than high school	9.7 (125)
High school (or equivalent)	32.9 (427)
Some college	20.8 (269)
College diploma or associate degree	6.3 (82)
Bachelor's degree	13.9 (180)
Some graduate school	3.4 (44)
Master's degree	9.1 (118)
Doctoral or professional degree	4.0 (52)
Marital status (% married)	65.6 (851)
Employment status (% employed)	33.6 (432)
Diabetes (% yes)	15.2 (197)
Hypertension (% yes)	45.3 (587)
Depression (% yes)	13.5 (175)
Perceived socioeconomic position	4.1 ± 3.1
Self-reported memory abilities (%)	
Poor	0.8 (10)
Fair	9.2 (118)
Average	32.8 (420)
Good	45.2 (580)
Excellent	12.0 (154)
Current smoking (% yes)	13.6 (134)
Alcohol intake	
Everyday	8.0 (94)
5-6 days/week	4.7 (55)
3-4 days/week	7.0 (83)
1-2 days/week	12.3 (145)
< 1 day/week	23.2 (274)
Never	44.8 (528)
Caregiver status (% yes)	12.7 (164)
	Z-score range
CSE	-9.32 – 24.13
Childhood stress	-0.73 – 11.74
Adulthood stress	-1.28 – 9.89
Financial stress	-1.24 – 2.48

Work-related psychological stress	-2.78 – 3.22
Work-related physical stress	-2.86 – 1.08
Neighbourhood stress	-0.95 – 6.43
Work-family conflict	-3.44 – 1.74
Relationship stress	-0.91 – 7.91
Perceived inequality	-1.41 – 5.54
Perceived discrimination	-0.66 – 6.58
HLI	-6.50 – 4.71
Physical activity	-1.71 – 1.06
Social engagement	-3.35 – 3.68
Sleep quality	-2.89 – 1.65
MIDUSII global cognition composite	-16.57 – 14.30
MIDUSII episodic memory composite	-3.58 – 7.40
MIDUSII executive function composite	-15.12 – 10.16

Notes. CSE = cumulative stress exposure; HLI = healthy lifestyle indicator; SD = standard deviation

Table 2. *Linear mixed-effect model estimates predicting baseline and 9-year change in cognition.*

	Partially adjusted models [a]				Fully adjusted models [b]			
	B	*SE*	*p*-value	95% CI	*B*	*SE*	*p*-value	95% CI
Global cognition		R^2 = 0.26				R^2 = 0.30		
CSE	-0.20	0.03	**< 0.001**	**-0.25, -0.14**	-0.14	0.03	**< 0.001**	**-0.20, -0.09**
HLI	0.02	0.06	0.73	-0.10, 0.14	0.02	0.06	0.76	-0.10, 0.13
Time	-1.47	0.11	**< 0.001**	**-1.68, -1.27**	-1.50	0.11	**< 0.001**	**-1.70, -1.29**
CSE × HLI	-0.01	0.01	0.43	-0.04, 0.02	-0.006	0.01	0.64	-0.03, 0.02
CSE × Time	0.08	0.03	**0.008**	**0.02, 0.14**	0.08	0.03	**0.009**	**0.02, 0.14**
HLI × Time	0.03	0.06	0.66	-0.09, 0.14	0.03	0.06	0.61	-0.09, 0.15
CSE × HLI × Time	-0.006	0.02	0.74	-0.04, 0.03	-0.008	0.02	0.65	-0.04, 0.03
Episodic memory		R^2 = 0.18				R^2 = 0.18		
CSE	-0.05	0.01	**< 0.001**	**-0.08, -0.03**	-0.04	0.01	**< 0.001**	**-0.07, -0.02**
HLI	0.02	0.03	0.49	-0.04, 0.07	0.02	0.03	0.47	-0.03, 0.08
Time	-0.44	0.06	**< 0.001**	**-0.56, -0.31**	-0.44	0.06	**< 0.001**	**-0.56, -0.31**
CSE × HLI	0.001	0.007	0.93	-0.01, 0.01	0.001	0.007	0.93	-0.01, 0.01
CSE × Time	0.006	0.03	0.74	-0.03, 0.04	0.008	0.03	0.67	-0.03, 0.04
HLI × Time	0.04	0.04	0.32	-0.04, 0.11	0.04	0.04	0.31	-0.03, 0.11
CSE × HLI × Time	-0.003	0.01	0.76	-0.02, 0.02	-0.003	0.01	0.75	-0.02, 0.02
Executive function		R^2 = 0.25				R^2 = 0.30		
CSE	-0.14	0.02	**< 0.001**	**-0.19, -0.10**	-0.10	0.02	**< 0.001**	**-0.14, -0.06**
HLI	0.001	0.05	0.98	-0.09, 0.09	-0.002	0.04	0.96	-0.09, 0.08
Time	-1.02	0.07	**< 0.001**	**-1.16, -0.87**	-1.04	0.07	**< 0.001**	**-1.19, -0.90**

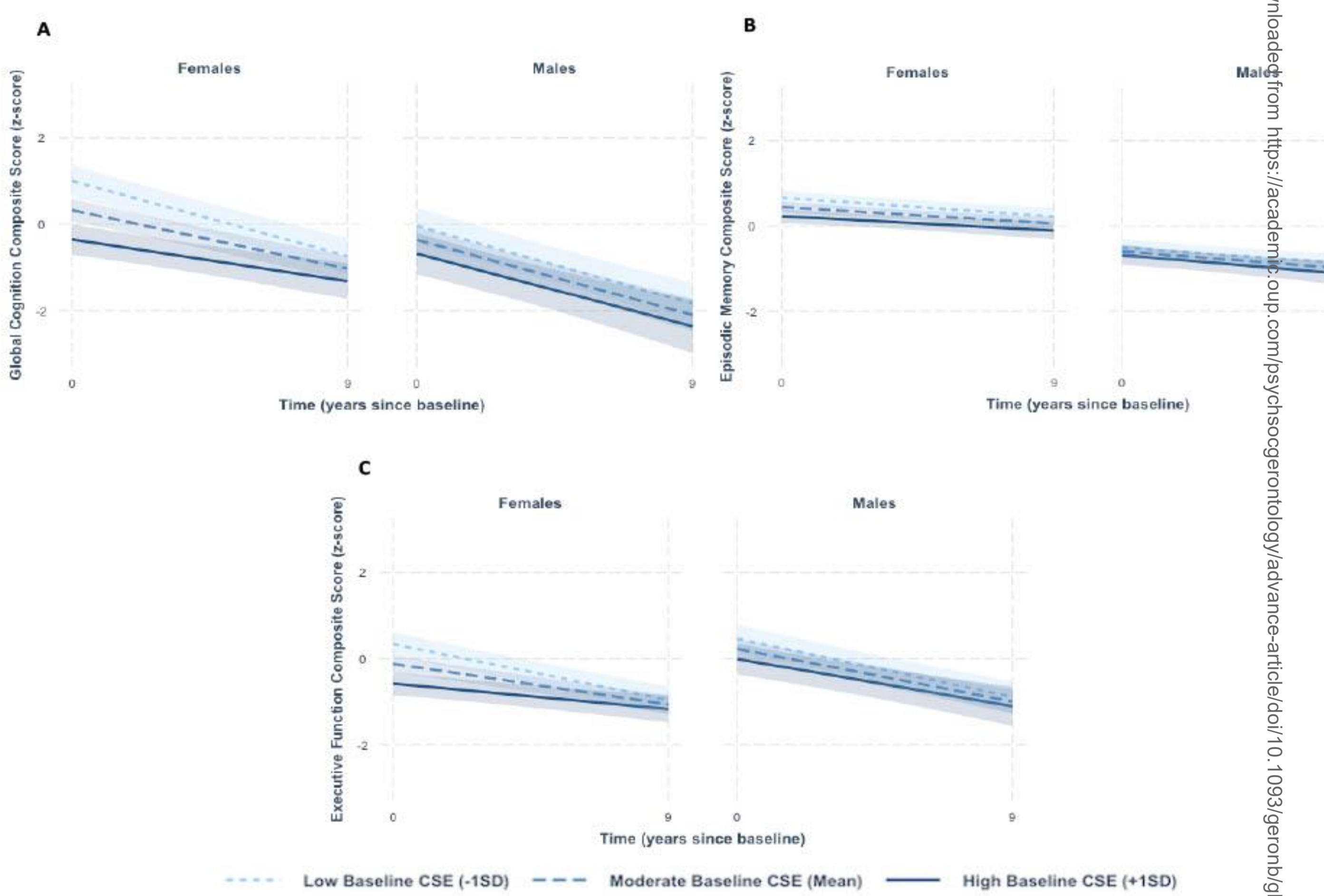
CSE × HLI	-0.01	0.01	0.27	-0.03, 0.009	-0.007	0.01	0.50	-0.03, 0.01
CSE × Time	0.08	0.02	**< 0.001**	**0.04, 0.12**	0.08	0.02	**< 0.001**	**0.03, 0.12**
HLI × Time	-0.006	0.04	0.88	-0.09, 0.08	-0.003	0.04	0.94	-0.09, 0.08
CSE × HLI × Time	0.001	0.01	0.93	-0.02, 0.03	-0.001	0.01	0.95	-0.03, 0.02

Notes. B = unstandardized regression coefficient; CI = confidence interval; CSE = cumulative stress exposure; HLI = healthy lifestyle indicator; SE = standard error

[a] Adjusted for age, sex, and educational attainment

[b] Adjusted for age, sex, educational attainment, race, marital status, employment status, depression, hypertension, and diabetes

Figure 1


A
Females
Males
Global Cognition Composite Score (z-score)
Time (years since baseline)
B
Females
Episodic Memory Composite Score (z-score)
Time (years since baseline)
C
Females
Males
Executive Function Composite Score (z-score)
Time (years since baseline)
Low Baseline CSE (-1SD)
Moderate Baseline CSE (Mean)
High Baseline CSE (+1SD)

Supplementary Material

Methods

Measures

Cumulative Stress Exposure. Childhood stress was measured by reporting whether 16 different events occurred before age 18 (yes = 1, no = 0), resulting in a summed score ranging from 0 to 16. Adulthood stressful life events were measured by indicating whether 20 different events from the Stressful Life Events Inventory (Turner & Wheaton, 1997) occurred after age 18 (yes = 1, no = 0), resulting in a summed score ranging from 0 to 20. Financial stress was assessed by summing responses from two items asking participants a) if they currently have enough money for their needs, and b) how difficult it is for them to pay their monthly bills, for a total score ranging from 2 to 7. Relationship stress was evaluated by combining four measures assessing a) family strain (four items), b) friend strain (four items), c) marital risk (five items), and d) spouse/partner strain (12 items). Items from each measure were summed to create a total relationship stress score ranging from 19 to 100. Work-family conflict indexed negative work-to-family spillover (four items) and negative family-to-work spillover (four items), with item scores summed to create a total score ranging from 8 to 40. Neighbourhood stress was derived by summing four items measuring neighbourhood safety, perceived neighbour support, and perceived neighbour trust, with total scores ranging from 4 to 20. Work-related psychological stress was indexed by combining five measures assessing a) skill discretion (three items), b) decision authority (six items), c) job demands (four items), d) co-worker support (two items), and e) supervisor support (three items). Items from each measure were summed to create a total work-related psychological stress score ranging from 19 to 95. Work-related physical stress included 10 items pertaining to the risk of injury or accident on the job (one item) and frequency of job strain (nine items), with total scores ranging from 10 to 49. Perceived inequality was derived from separate measures assessing individual's perceptions of inequality across a) child rearing (six items), b) housing and neighbourhood conditions (six items), and c) work (six items), with scores on all 18 items summed to create a total score ranging from 18 to 72. Perceived discrimination was measured by summing 10 items on the lifestyle discrimination inventory and nine items on the everyday discrimination scale, with total scores ranging from 9 to 46.

Physical Activity. Physical activity was assessed via self-report at MIDUSII by asking participants to indicate how often per week, on average, they engage in 12 moderate (e.g., slow/light swimming, brisk walking) and vigorous (e.g., running, lifting heavy objects) physical activities during the summer and winter months at home, work, and in leisure settings from 1 (*never*) to 6 (*several times a week or more*). Using the scoring method from Cotter and Lachman (2020), a total moderative physical activity sub-score was created by averaging the participant's highest moderate physical activity score in the summer months with the highest moderate physical activity score in the winter months. The same procedure was used to create a vigorous physical activity sub-score. The highest of the moderate or vigorous physical activity sub-scores was used as a measure of overall physical activity, resulting in a total score ranging from 1 to 6, with a higher score representing greater levels of physical activity.

Social Engagement. Engagement in social activities was assessed at MIDUSII using 10 items pertaining to frequency of contact with friends and family, volunteer work, attending gatherings, and attending educational lectures/courses. Two items assessed frequency of contact with friends and family was assessed with responses ranging from 1 (*never or hardly ever*) to 8 (*several times per day*). Volunteer work was assessed by asking participants how many hours per month they engage in volunteer work at hospitals/long-term care facilities, school/youth programs, political causes, and other work (yes = 1, no = 0). Attending gatherings was assessed by asking participants how many times per month they attend social/sport, professional/union, or other gatherings (yes = 1, no = 0). Frequency of attending educational lectures/courses was measured with a single item with responses ranging from 1 (*never*) to 6 (*daily*). The total score was calculated by summing the scores for each of the 10 items, resulting in a total score ranging from 8 to 29 with higher scores indicating higher levels of social engagement.

Sleep Quality. Sleep quality was assessed at MIDUSII using the Jenkins Sleep Questionnaire (JSQ; Jenkins et al., 1988), a four-item measure widely used to measure subjective sleep quality. The scale is comprised of four items indicating the frequency of trouble falling asleep, waking during the night, waking too early, and feeling unrested during the day on a 5-point Likert scale from 1 (*almost always/4+ times per week*) to 5 (*never/0 times*). A total score was calculated by summing the responses for each item, yielding a total score ranging from 4 to 20, with higher scores indicating better subjective sleep quality. The JSQ has demonstrated good reliability and validity, with a Cronbach's alpha of 0.80 (Juhola et al., 2021).

Cognitive Function. Raw scores for each of the seven BTACT tasks at MIDUSII were first standardized to z-scores to facilitate interpretable comparison across all tests. Z-scores for the Stop and Go Switch task latency score were first multiplied by -1 so that higher scores indicate better cognitive performance. A global cognitive composite score was derived by summing the z-scores for each task. Based on previously reported exploratory and confirmatory factor analyses of the BTACT item scores (Lachman et al., 2014), episodic memory and executive function composite scores were also calculated. The episodic memory score was calculated by summing the z-scores for immediate and delayed word list recall. The executive function score was calculated by summing the z-scores for working memory, verbal fluency, inductive reasoning, processing speed, and attention switching. Higher total scores on the composite scores indicate better global cognitive performance, episodic memory, and executive function. For participants who were missing scores for less than half of the cognitive tasks in a given domain (i.e., missing 3 or fewer scores out of 7 for global cognition, missing 1 out of 2 scores for episodic memory, and missing 2 or fewer scores out of 5 for executive function) the composite scores were still calculated with the scores available. The composite score with the missing data was not calculated for participants who were missing scores for more than half of the cognitive tasks in a given domain. The same procedure was used to calculate the global cognition, episodic memory, and executive function composite scores at MIDUSIII. Individual task scores were standardized to the mean and standard deviation of the raw task scores at baseline.

Statistical Analyses

In the linear mixed-effects models, parameter estimates for CSE represent the association between stress exposure and baseline cognitive function, and parameter estimates for CSE × Time represent the association between stress exposure and rate of cognitive change over time. Similarly, parameter estimates for HLI represent the association between a healthy lifestyle and baseline cognitive function, and parameter estimates for HLI × Time represent the association between a healthy lifestyle and the rate of cognitive change over time. Positive estimates indicate that greater cumulative stress exposure and a greater healthy lifestyle are associated with better baseline cognitive scores and less cognitive decline at follow-up. Effect-modification of the relationship between cumulative stress exposure and cognitive function by healthy lifestyle was interpreted by estimates pertaining to baseline cognitive score (CSE × HLI) and estimates pertaining to rate of change over time (CSE × HLI × Time).

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Supplementary Table 1. *Differences in sociodemographic information and key variables of interest between those who did and did not complete the Cognitive Project at MIDUSIII follow up.*

	Completed MIDUSIII Cognitive Project (n = 806)	Did not complete MIDUSIII Cognitive Project (n = 491)	*p*-value
Age	67.5 ± 5.6	71.5 ± 6.8	**< 0.001**
Sex (% female)	57.8	52.2	**0.002**
Educational attainment (% with at least some post-secondary education)	57.5	49.8	**< 0.001**
CSE	-0.29 ± 3.69	0.52 ± 4.04	**< 0.001**
HLI	0.24 ± 1.81	-0.14 ± 1.72	**< 0.001**
MIDUSII global cognition composite	1.02 ± 4.21	-1.68 ± 4.21	**< 0.001**
MIDUSII episodic memory composite	0.33 ± 1.81	-0.56 ± 1.77	**< 0.001**
MIDUSII executive function composite	0.68 ± 3.25	-1.13 ± 3.28	**< 0.001**

Notes. *B* = unstandardized regression coefficient; CSE = cumulative stress exposure; HLI = healthy lifestyle indicator
p-value derived by independent samples *t*-test for continuous variables and χ^2 for categorical variables. Data presented as mean ± standard deviation unless otherwise specified

Supplementary Table 2. *Standardized bivariate correlations between the study variables of interest.*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Age (1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sex (2)	-0.01	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Education (3)	**-0.07**	**0.17**	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Race (4)	-0.05	-0.05	**-0.08**	-	-	-	-	-	-	-	-	-	-	-	-	-
Marital status (5)	**-0.14**	**0.28**	0.05	**-0.17**	-	-	-	-	-	-	-	-	-	-	-	-
Employment status (6)	**-0.35**	**0.08**	**0.09**	-0.03	0.03	-	-	-	-	-	-	-	-	-	-	-
Diabetes (7)	0.02	**0.08**	**-0.07**	**0.07**	-0.01	**-0.09**	-	-	-	-	-	-	-	-	-	-
Hypertension (8)	**0.08**	-0.05	**-0.08**	**0.08**	-0.04	**-0.10**	**0.20**	-	-	-	-	-	-	-	-	-
Depression (9)	-0.04	**-0.10**	-0.05	0.0001	**-0.12**	**-0.06**	**0.06**	0.04	-	-	-	-	-	-	-	-
CSE (10)	0.05	**-0.11**	**-0.19**	**0.26**	**-0.10**	0.03	0.05	0.04	**0.12**	-	-	-	-	-	-	-
HLI (11)	-0.03	0.04	**0.20**	0.02	0.001	0.05	-0.04	**-0.06**	**-0.16**	**-0.16**	-	-	-	-	-	-
Physical activity (12)	-0.03	0.01	0.03	**0.06**	-0.02	0.03	-0.01	-0.02	-0.02	-0.01	**0.59**	-	-	-	-	-
Social engagement (13)	-0.01	**-0.07**	**0.23**	-0.03	0.01	-0.0003	-0.01	-0.03	**-0.07**	**-0.15**	**0.61**	0.05	-	-	-	-
Sleep (14)	-0.005	**0.14**	**0.09**	0.01	0.01	0.05	**-0.06**	**-0.06**	**-0.19**	**-0.12**	**0.56**	-0.01	-0.003	-	-	-
Baseline GC (15)	**-0.32**	0.02	**0.36**	**-0.22**	**0.13**	**0.20**	**-0.11**	**-0.11**	**-0.07**	**-0.23**	**0.10**	-0.01	**0.17**	0.01	-	-
Baseline EM (16)	**-0.26**	**-0.23**	**0.16**	**-0.10**	0.01	**0.13**	**-0.09**	-0.01	0.02	**-0.12**	**0.06**	-0.04	**0.14**	0.01	**0.70**	-
Baseline EF (17)	**-0.28**	**0.14**	**0.39**	**-0.24**	**0.16**	**0.19**	**-0.09**	**-0.13**	**-0.10**	**-0.24**	**0.10**	0.004	**0.15**	0.01	**0.92**	**0.37**

Notes. CSE = cumulative stress exposure; EF = executive function; EM = episodic memory; GC = global cognition; HLI = healthy lifestyle indicator

Bolded correlation statistics are statistically significant at $p < 0.05$

Supplementary Table 3. *Linear mixed-effect model estimates predicting baseline and 9-year change in cognition stratified by sex.*

	Females (n = 750)				Males (n = 547)			
	B	*SE*	*p*-value	95% CI	*B*	*SE*	*p*-value	95% CI
Global cognition		R^2 = 0.30				R^2 = 0.29		
CSE	-0.16	0.04	**< 0.001**	**-0.23, -0.09**	-0.10	0.05	0.05	-0.20, 0.001
HLI	0.003	0.08	0.97	-0.15, 0.16	0.03	0.09	0.70	-0.14, 0.21
Time	-1.36	0.14	**< 0.001**	**-1.63, -1.09**	-1.76	0.17	**< 0.001**	**-2.08, -1.43**
CSE × HLI	-0.01	0.02	0.49	-0.05, 0.02	0.004	0.03	0.86	-0.05, 0.06
CSE × Time	0.10	0.04	**0.006**	**0.03, 0.18**	0.01	0.05	0.83	-0.09, 0.12
HLI × Time	0.07	0.08	0.38	-0.08, 0.22	-0.03	0.10	0.73	-0.23, 0.16
CSE × HLI × Time	-0.008	0.02	0.71	-0.05, 0.03	-0.01	0.03	0.71	-0.08, 0.05
Episodic memory		R^2 = 0.16				R^2 = 0.12		
CSE	-0.05	0.02	**0.006**	**-0.08, -0.01**	-0.03	0.02	0.15	-0.08, 0.01
HLI	0.009	0.04	0.82	-0.07, 0.09	0.02	0.04	0.56	-0.05, 0.10
Time	-0.41	0.08	**< 0.001**	**-0.58, -0.25**	-0.47	0.10	**< 0.001**	**-0.66, -0.28**
CSE × HLI	0.003	0.009	0.70	-0.01, 0.02	-0.006	0.01	0.59	-0.03, 0.02
CSE × Time	0.01	0.02	0.52	-0.03, 0.06	-0.01	0.03	0.70	-0.07, 0.05
HLI × Time	0.05	0.05	0.30	-0.04, 0.15	0.03	0.06	0.59	-0.08, 0.05
CSE × HLI × Time	-0.007	0.01	0.55	-0.03, 0.02	0.008	0.02	0.65	-0.03, 0.04
Executive function		R^2 = 0.28				R^2 = 0.29		
CSE	-0.11	0.03	**< 0.001**	**-0.17, -0.06**	-0.07	0.04	0.08	-0.14, 0.008
HLI	-0.007	0.06	0.91	-0.12, 0.11	0.01	0.07	0.86	-0.12, 0.15
Time	-0.94	0.09	**< 0.001**	**-1.13, -0.75**	-1.24	0.12	**< 0.001**	**-1.48, -1.00**
CSE × HLI	-0.02	0.01	0.22	-0.04, 0.009	0.01	0.02	0.59	-0.03, 0.05
CSE × Time	0.09	0.03	**< 0.001**	**0.04, 0.14**	0.03	0.04	0.45	-0.05, 0.11
HLI × Time	0.02	0.05	0.68	-0.08, 0.13	-0.05	0.07	0.47	-0.20, 0.09
CSE × HLI × Time	0.002	0.01	0.89	-0.03, 0.03	-0.01	0.03	0.65	-0.06, 0.04

Notes. B = unstandardized regression coefficient; CI = confidence interval; CSE = cumulative stress exposure; HLI = healthy lifestyle indicator; SE = standard error

All models adjusted for age, educational attainment, race, marital status, employment status, depression, hypertension, and diabetes

Supplementary Table 4. *Associations between cumulative stress exposure, physical activity, baseline cognition, and cognitive change over 9 years.*

	B	*SE*	*p*-value	95% CI
Global cognition		$R^2 = 0.30$		
CSE	-0.10	0.02	**0.005**	**-0.13, -0.06**
Physical activity	-0.02	0.07	0.76	-0.17, 0.12
Time	-1.05	0.07	**< 0.001**	**-1.19, -0.90**
CSE × Physical activity	0.005	0.02	0.78	-0.03, 0.04
CSE × Time	0.07	0.02	**< 0.001**	**0.03, 0.12**
Physical activity × Time	0.04	0.07	0.56	-0.10, 0.19
CSE × Physical activity × Time	0.005	0.02	0.80	-0.03, 0.04
Episodic memory		$R^2 = 0.19$		
CSE	-0.04	0.01	**0.001**	**-0.07, -0.02**
Physical activity	-0.09	0.05	0.05	-0.19, 0.002
Time	-0.43	0.06	**< 0.001**	**-0.55, -0.31**
CSE × Physical activity	0.02	0.01	0.17	-0.007, 0.04
CSE × Time	0.002	0.02	0.92	-0.03, 0.04
Physical activity × Time	-0.01	0.06	0.84	-0.14, 0.11
CSE × Physical activity × Time	0.02	0.02	0.22	-0.01, 0.05
Executive function		$R^2 = 0.29$		
CSE	-0.10	0.02	**< 0.001**	**-0.14, -0.06**
Physical activity	-0.02	0.07	0.76	-0.17, 0.12
Time	-1.05	0.07	**< 0.001**	**-1.19, -0.90**
CSE × Physical activity	0.005	0.02	0.78	-0.03, 0.04
CSE × Time	0.07	0.02	**< 0.001**	**0.03, 0.12**
Physical activity × Time	0.04	0.07	0.56	-0.10, 0.19
CSE × Physical activity × Time	0.005	0.02	0.80	-0.03, 0.05

Notes. B = unstandardized regression coefficient; CI = confidence interval; CSE = cumulative stress exposure; SE = standard error

All models adjusted for age, sex, educational attainment, race, marital status, employment status, depression, hypertension, and diabetes

Supplementary Table 5. *Associations between cumulative stress exposure, social engagement, baseline cognition, and cognitive change over 9 years.*

	B	*SE*	*p*-value	95% CI
Global cognition		R^2 = 0.30		
CSE	-0.13	0.03	**< 0.001**	**-0.19, -0.07**
Social engagement	0.34	0.10	**< 0.001**	**0.14, 0.54**
Time	-1.50	0.11	**< 0.001**	**-1.71, -1.29**
CSE × Social engagement	-0.02	0.02	0.50	-0.06, 0.03
CSE × Time	0.08	0.03	**0.01**	**0.02, 0.14**
Social engagement × Time	0.02	0.10	0.85	-0.18, 0.22
CSE × Social engagement × Time	-0.01	0.03	0.73	-0.06, 0.05
Episodic memory		R^2 = 0.19		
CSE	-0.04	0.01	**0.003**	**-0.07, -0.01**
Social engagement	0.13	0.05	**0.006**	**0.04, 0.23**
Time	-0.45	0.06	**< 0.001**	**-0.57, -0.32**
CSE × Social engagement	-0.01	0.01	0.23	-0.04, 0.009
CSE × Time	0.01	0.02	0.58	-0.03, 0.04
Social engagement × Time	0.09	0.06	0.16	-0.03, 0.20
CSE × Social engagement × Time	-0.002	0.02	0.88	-0.03, 0.03
Executive function		R^2 = 0.30		
CSE	-0.09	0.02	**< 0.001**	**-0.13, -0.05**
Social engagement	0.21	0.08	**0.007**	**0.06, 0.35**
Time	-1.03	0.08	**< 0.001**	**-1.18, -0.89**
CSE × Social engagement	-0.003	0.02	0.88	-0.04, 0.03
CSE × Time	0.07	0.02	**< 0.001**	**0.03, 0.12**
Social engagement × Time	-0.07	0.07	0.32	-0.21, 0.07
CSE × Social engagement × Time	-0.005	0.02	0.80	-0.04, 0.03

Notes. B = unstandardized regression coefficient; CI = confidence interval; CSE = cumulative stress exposure; SE = standard error

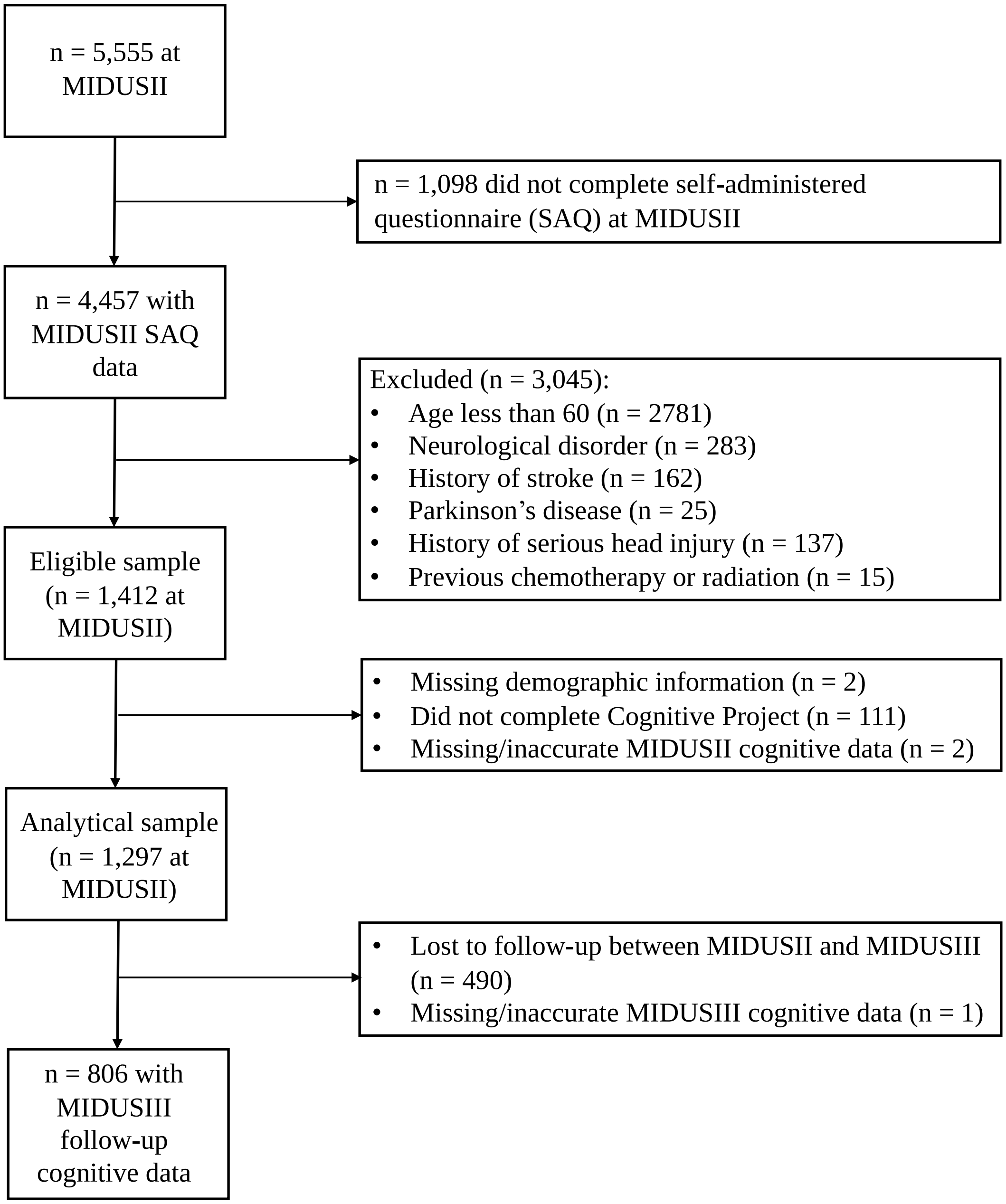
All models adjusted for age, sex, educational attainment, race, marital status, employment status, depression, hypertension, and diabetes

Supplementary Table 6. *Associations between cumulative stress exposure, sleep quality, baseline cognition, and cognitive change over 9 years.*

	B	*SE*	*p*-value	95% CI
Global cognition		R^2 = 0.30		
CSE	-0.15	0.03	**< 0.001**	**-0.21, -0.09**
Sleep quality	-0.16	0.10	0.11	-0.36, 0.04
Time	-1.50	0.10	**< 0.001**	**-1.70, -1.29**
CSE × Sleep quality	0.02	0.02	0.37	-0.07, 0.03
CSE × Time	0.08	0.03	**0.01**	**0.02, 0.14**
Sleep quality × Time	0.04	0.11	0.74	-0.18, 0.25
CSE × Sleep quality × Time	-0.04	0.03	0.21	-0.10, 0.02
Episodic memory		R^2 = 0.18		
CSE	-0.04	0.01	**0.002**	**-0.07, -0.02**
Sleep quality	0.03	0.05	0.56	-0.07, 0.12
Time	-0.43	0.06	**< 0.001**	**-0.56, -0.31**
CSE × Sleep quality	0.001	0.01	0.91	-0.02, 0.02
CSE × Time	0.005	0.02	0.76	-0.03, 0.04
Sleep quality × Time	0.03	0.06	0.63	-0.09, 0.16
CSE × Sleep quality × Time	-0.03	0.02	0.10	-0.06, 0.006
Executive function		R^2 = 0.30		
CSE	-0.11	0.02	**< 0.001**	**-0.15, -0.06**
Sleep quality	-0.19	0.08	**0.01**	**-0.34, -0.04**
Time	-1.04	0.07	**< 0.001**	**-1.19, -0.90**
CSE × Sleep quality	-0.02	0.02	0.20	-0.06, 0.01
CSE × Time	0.08	0.02	**< 0.001**	**0.04, 0.12**
Sleep quality × Time	0.02	0.08	0.82	-0.13, 0.17
CSE × Sleep quality × Time	-0.002	0.02	0.94	-0.04, 0.04

Notes. B = unstandardized regression coefficient; CI = confidence interval; CSE = cumulative stress exposure; SE = standard error

All models adjusted for age, sex, educational attainment, race, marital status, employment status, depression, hypertension, and diabetes



Supplementary Figure 1. Flowchart of participant selection for the current study sample.