ORIGINAL ARTICLE

The Mediating Role of Cardiometabolic Dysregulation on the Relation Between Adverse Childhood Experiences and Adult Cognition

Sheyla Moliner, BA, Jamie M. Quinn, PhD, and Julia Sheffler, PhD

ABSTRACT

Objective: Adverse childhood experiences (ACEs) are uncontrollable stressful events during early life that predispose adults to adverse health outcomes, such as impaired cognitive functioning. However, little is known about the factors indirectly impacting this relation. Biological dysregulation may be one pathway that can help explain the relations between ACEs and later cognition. The current study examined the mediating role of cardiometabolic dysregulation on the relation between ACEs and cognition.

Methods: Our study gathered data from 1053 participants using three waves of the Midlife in the United States longitudinal study. Linear regression analyses and bootstrapped mediation analyses were performed to analyze the direct and indirect associations of cardiometabolic dysregulation on ACEs and cognition.

Results: Our results showed a significant linear relationship between ACEs and cardiometabolic dysregulation ($b = 0.152$, standard error [SE] = 0.056, $p = .007$), and a significant indirect association, such that cardiometabolic dysregulation mediated the relation between ACEs and cognitive status at wave II ($b = -0.007$, SE = 0.004, $p = .044$) and cognitive status at wave III ($b = -0.006$, SE = 0.003, p .042). There was no significant direct or indirect relation when cognitive change was the outcome variable.

Conclusions: The present study identifies a combined biological pathway that connects ACEs to cognition in late life. These findings supports the need to empirically determine biological mechanism that can be used to develop targeted clinical interventions to prevent the progression of chronic cognitive impairment.

Key words: MIDUS, cardiometabolic, biomarkers, dysregulation, ACEs, cognition.

INTRODUCTION

Sixty-six percent of the US population has reported enduring at least one adverse childhood experience (ACE) before the age of 18 years (1). The injurious effects of ACEs begin to arise when children are exposed to prolonged or frequent distressing events, such as emotional, physical, and/or sexual abuse, neglect, financial strain, loss of a parent, and/or household dysfunction in the form of parental divorce or household substance abuse (2). Research shows that ACEs can lead to the development of a toxic stress response, which in turn can affect an individual's physiology at a cellular level (3), resulting in chronic cognitive impairments in later life, specifically in the domains of fluid cognition and episodic memory (4). However, relatively little research has examined potential biological pathways linking ACEs and cognition in adults.

One cluster of risk factors that can potentially explain the relations between ACEs and cognitive impairment is disruptions in cardiometabolic biomarkers, namely, fasting glucose, triglycerides, low-density lipoproteins, and high-density lipoproteins levels (5). ACEs may influence these biomarkers through their impact on glucocorticoid dysregulation related to toxic stress (6). Glucocorticoids are secreted by the adrenal cortex when the hypothalamus perceives stress; once released, glucocorticoids produce a multitude of effects throughout the body, with the goal of restoring homeostasis (6). One of the effects of glucocorticoids is to use negative feedback on the axis that modulates its release, the hypothalamic-pituitary-adrenal axis (HPA axis) (6). Individuals who have experienced frequent ACEs may have chronically increased glucocorticoid levels due to a dysregulated HPA axis (3,5,6). A sustained elevation of tissue glucocorticoids and circulating corticosterone contribute to the progression of insulin resistance, increased blood glucose, blood pressure, triglyceride levels, and inflammatory responses (5). Thus, early-life stress may exacerbate cardiometabolic dysregulation in midlife and late life through disruption of the neuroendocrine system.

These chronic biological alterations associated with ACEs may be primary contributors to cognitive impairment in individuals with high ACEs. Various studies examining the effects of cardiovascular and metabolic biological dysfunction on cognitive impairment in middle-aged and older adults have shown a significant association. For example, the rate of cognitive decline in older adults without dementia was positively associated with a greater

ACEs = adverse childhood experiences, **BTACT** = Brief Test of Adult Cognition by Telephone, **HPA axis** = hypothalamic-pituitary-adrenal axis, **MIDUS** = Midlife in the United States study, **SAQ** = self-administered questionnaire

From the Florida State University College of Medicine (Moliner, Sheffler); Florida State University (Quinn); and Florida Center for Reading Research (Quinn), Tallahassee, Florida.

Address correspondence to Sheyla Moliner, BA, Florida State University College of Medicine, Tallahassee 2010 Levy Ave, Tallahassee, FL 32310. E-mail: sm20jg@fsu.edu

Received for publication October 5, 2021; revision received February 27, 2022.

DOI: 10.1097/PSY.0000000000001093

severity of periventricular white matter lesions (7). Periventricular white matter lesions are areas of small vascular vessel damage in the periventricular white matter of the cortex commonly caused by insult secondary to atherosclerosis, arteriosclerosis, lipohyalinosis, and hypertension (7,8). Borderline diabetes was found to increase the risk of dementia and Alzheimer's disease; however, this hazard risk multiplied when participants also had severe systolic hypertension (9). Similarly, a longitudinal study that examined 1938 postmenopausal women found that the risk of cognitive impairment or dementia amplified with every 1% increase in glycosylated hemoglobin (10). Thus, research strongly indicates that cardiometabolic dysregulation is associated with cognitive impairment in middle-aged and older adulthood.

The current study examined if cardiometabolic dysregulation mediates the relation between ACEs and cognitive status and/or cognitive change in middle-aged and older adults using multiple waves of data from the Midlife in the United States (MIDUS) study. Understanding this gap in the literature is especially important because these pathways may help clarify targets for interventions and preventions in high-risk middle-aged and older adults. Our study examined the following hypotheses: a) higher number of ACEs will be associated with more significant cardiometabolic dysregulation in mid and older adulthood, b) higher ACEs will be associated with greater change in cognitive status across a 10-year span and/or impairment of cognitive status across adulthood, and c) cardiometabolic dysregulation will mediate the association between ACEs and cognitive status.

METHODS

Data were obtained from waves I to III of the MIDUS Study of Health and Well-Being publicly accessible data sets. MIDUS is a longitudinal, multidisciplinary study that assesses the impact of behavioral and biopsychosocial influences on physical and mental health outcomes of aging adults in the form of surveys, evaluations of daily stress diaries, cognitive evaluations, and biological, neuroscience assessments. The ACE variable and relevant covariates were collected from wave I (1995–1996), cardiometabolic biomarkers were drawn from the wave II biological protocol study (2004–2009), and cognitive data were drawn from waves II (~2004) and III (~2013).

Participants

MIDUS wave I collected survey data via telephone interviews and self-administered questionnaires (SAQs) from 7108 noninstitutionalized US residents (aged 25–74 years). Participants who completed wave I were qualified to participate in wave II, approximately 10 years later. All participants from wave I were eligible to participate in the biomarker project; however, biomarker data were collected from 1054 respondents (aged 35–85 years) in 2004 to 2009. Individuals who participated in the biological protocol study traveled to eligible General Clinical Research Centers for a 2-day itinerary of biological data collection in the form of fasting blood, 12-hour urine, and saliva specimens, as well as physical examinations and medical history evaluations (11). Additional information of the protocol description, measures, and sample characteristics can be found in a prior article (11). The cognitive status projects collected data from 4206 participants in 2004 to 2006 (wave II) and from 2387 in 2013 to 2017 (wave III) using a standardized telephone cognitive assessment. Participants at wave III were 42 to 92 years old.

Measures

Adverse Childhood Experiences

Using the Childhood Trauma Questionnaire and the SAQ in wave I and wave II, a count variable was created using reported ACEs in the categories of a) emotional, b) physical, and c) severe physical abuse; d) financial strain during childhood; e) divorce or separation of parents; f) death of a parent; g) parental substance abuse; and h) sexual assault. Parental substance abuse and sexual assault categories were the only variables obtained from wave II. Participants who reported an ACE category as often, sometimes, or rarely were coded as yes (1) for experiencing an event, and never as no (0) for not experiencing that event in one of the categories described previously. Because of positive skewness with few values present greater than 4, the count variable for ACEs was winsorized at 4 (range, 0–4 or more).

Biological Measures

Biomarker data were collected from wave II of the MIDUS biological protocol study. To determine cardiometabolic dysregulation, biological markers including systolic blood pressure, diastolic blood pressure, body mass index, total cholesterol, high-density lipoproteins, total cholesterol/high-density lipoprotein ratio, triglycerides, low-density lipoproteins, glycosylated hemoglobin, fasting glucose, and insulin resistances were recoded into three cardiometabolic risk categories: high risk (1 point), moderate risk (0.5 points), and low risk (0 points). See Table 1 for biomarker cut points. These cardiometabolic risk categories were based on recommended clinical cutoff values using National Health and Nutrition Examination Survey data and nationally recommended cut points (12–15). A count variable (0–11) was created using the biomarkers mentioned previously, with 0 indicating an individual who had low-risk for all biomarker categories listed and 11 indicating an individual who had a cumulative high-risk score for all biomarker categories.

Cognitive Status

Cognitive status was assessed using the Brief Test of Adult Cognition by Telephone (BTACT) total score in waves II and III. The BTACT is a cognitive battery designed for the evaluation of cognitive aging through the telephone administration of multiple assessments measuring immediate and delayed recall, inductive reasoning, category fluency, processing speed, working memory, executive function, and attention switching (16). MIDUS wave II and III data sets calculated each participant's BTACT component scores by averaging the standardized mean *z* scores of all tests using the main national MIDUS 2 sample (16). Using the BTACT total score in waves II and

TABLE 1. Biomarker Cut Points Based on Clinically Recommended Values

Biological Markers	High-Risk	Moderate-Risk	Low-Risk
Cardiovascular			
SBP, mm Hg	≥150	120 to 149	<120
DBP, mm Hg	≥90	80 to 89	<80
BMI, kg/m^2	≥30	25 to <30	18 to < 25
Total cholesterol, mg/dl	≥240	200 to 239	<200
HDL cholesterol, mg/dl	<40	40 to 59	>60
Total cholesterol/HDL ratio	≥6	5 to <6	<5
Triglycerides, mg/dl	>200	150 to 199	<150
LDL cholesterol, mg/dl	>160	130 to 159	<70
Metabolic: glucose metabolism			
Glycosylated hemoglobin, %	≥6.5	5.7 to <6.5	<5.7
Fasting glucose, mg/dl	>126	100 to 126	<100
Insulin resistances[a]	>5	3 to 5	<2

SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

[a] Insulin resistance was calculated using the homeostatic model assessment of insulin resistance (HOMAIR). HOMAIR = glucose (G0) × insulin (I0)/405.

III allowed us to evaluate changes in cognition from midlife to older age, as well as cognitive status.

Covariates

Covariates included were age, education (grade school to some high school, 1; GED to graduated high school, 2; some college and no bachelor's degree, 3; graduated college to professional degree, 4), sex (male, 1; female, 2), income (<$25,000, $25,000–$75,000, >$75,000), and race (non-White, 0; White, 1). Cognitive outcomes from MIDUS II were included as a predictive variable in our analyses to examine change in cognitive status across a 10-year span. See Table 2 for full sample demographics.

Statistical Analysis

Four linear regression models were fit to assess the relation between ACEs and cardiometabolic dysregulation using the biomarker count variables as the dependent variables and to determine the relations between ACEs and cognitive status and between ACEs and cognitive change across 10 years using the wave II and wave III BTACT variables. Next, four multiple mediation analysis models using bootstrapped standard errors (ESs) and confidence intervals (CIs) were run to determine the indirect association of ACEs on adult cognition (i.e., cognitive status at wave II and wave II and cognitive change) through cardiometabolic dysregulation. Analyses were completed in IBM SPSS 26.0 and Mplus version 8.4 (17,18).

TABLE 2. Sample Demographics for All Participants in MIDUS II (n = 1053)

Variables	M (SD) (Min–Max) or n (%)
Sex	
Male	477 (45.8%)
Female	576 (54.7%)
Age, y	**55.26 (11.79) (34–84)**
Race	
Non-White	63 (6.0%)
White	960 (91.2%)
Education level	
Grade school to some high school	38 (3.6%)
GED to graduated high school	251 (23.8%)
Some college (no bachelor's degree)	300 (28.5)
Graduated college to professional degree	463 (44.0%)
Household total income, $	**76,691 (60,435.55) (0–300,000)**
<25,000	166 (15.8%)
25,000–75,000	450 (42.7%)
>75,000	415 (39.4%)
ACE count	**2.73 (1.09) (0–4)**
0	49 (4.7%)
1	95 (9.0%)
2	228 (21.7%)
3	339 (37.9%)
4+	282 (26.8%)
Biomarker scores	
Cardiometabolic dysregulation score	**3.17 (1.88) (0–9)**
Cognitive status score	
BTACT II (n = 983)	**0.14 (0.92) (−2.37–3.05)**
BTACT III (n = 850)	**0.08 (0.66) (−2.18–2.03)**
Cognitive change difference score	
BTACT Δ (n = 797)	**0.17 (p < .001)**

MIDUS = Midlife in the United States study; M (SD) = mean (standard deviation); Min = minimum; Max = maximum; GED = General Education Diploma; ACE = adverse childhood experience; Brief Test of Adult Cognition by Telephone.

Bolded values are expressed as mean (standard deviation) (range of values).
[a] The cognitive change difference score represents a mean difference score between BTACT II and BTACT III.

Missing Data

The Little test of missing completely at random showed that missing data could be considered missing completely at random ($\chi^2(88) = 100.89$, $p = .16$) for the purposes of our data modeling using full-information maximum likelihood estimation in Mplus 8.4. Therefore, all information was used in the model, and no cases were dropped listwise. An investigation of the differences at wave I for those participants who stayed in the complete study and those who dropped out after wave I showed that there were significant differences in income ($F(1,1029) = 31.40$, $p < .001$), age ($F(1,1051) = 66.84$, $p < .001$), education ($F(1,1050) = 11.76$, $p = .001$), and BTACT ($F(1,981) = 69.61$, $p < .001$). There were no significant differences in participants who stayed versus those who left the study on measures of cardiometabolic dysregulation scores ($p = .132$), sex ($p = .156$), and race ($p = .818$).

RESULTS

Demographics

Descriptive statistics for the MIDUS wave II sample are displayed in Table 2. The initial cohort for this study contained 1053 participants who completed wave I and the biological protocol study at wave II. At wave II (2004–2009), the average (standard deviation [SD]) age of participants was 55 (11.8) years, and by wave III (2013), the average (SD) age increased to 63.49 (10.87) years. The sample was predominately White (91.2%) and female (54.7%), with participants having higher educational attainment (44% graduated college or have a professional degree) and higher household income (mean [SD] = $76,691 [$60,435.55]) than the national average (19,20). The majority of participants in wave II reported experiencing more than one ACE (86.4%) and had an average (SD) cardiometabolic dysregulation score of 3.17 (1.88). Participants who completed wave I, the biological protocol at wave II, and the BTACT at wave II (n = 983) had an average (SD) BTACT II score of 0.14 (0.92). Those who completed wave I, the biological protocol at wave II, and the BTACT at wave III (n = 850) had an average (SD) BTACT III score of 0.08 (0.66).

Finalizing Our Models

In our initial analysis, the covariates age, sex, race, income, and education were controlled for to examine the direct relation between ACEs and cardiometabolic dysregulation along with cognitive status. In addition, the said covariates were also used to assess the indirect associations of cardiometabolic dysregulation on ACEs and cognition. Because of our results suggesting nonsignificant findings for all pathways involving cognition as the outcome variable, we were concerned of the possible masking effects of one or more of our covariates. Based on prior research, an overall nonsignificant relation between early life socioeconomic adversity and physiological dysregulation in adulthood occurs because of education's mediating role (21). Similarly, using MIDUS data sets and mediational analyses, Liu and Lachman (22) found an indirect association

via higher educational attainment on aging cognition, specifically on episodic memory and executive functioning.

To confirm whether education had a mediating effect on our results, we examined the indirect associations of education on the relation between ACEs and cognitive status, cognitive change, and cardiometabolic dysregulation. Our results showed significant indirect associations through education for BTACT II ($b = -0.030$, SE = 0.009, $p = .001$), BTACT III ($b = -0.033$, SE = 0.010, $p = .001$), cognitive change ($b = -0.005$, SE = 0.002, $p = .025$), and cardiometabolic dysregulation ($b = 0.015$, SE = 0.005, $p = .006$), while controlling for age, sex, race, and income. Given this significant indirect effect, education was removed as a covariate and used the covariates age, sex, race, and income in our final analysis.

Model Results

Linear Regression Models

Consistent with our first hypothesis, we found that an increase in the frequency of ACEs predicts greater cardiometabolic dysregulation ($b = 0.152$, SE = 0.056, $p = .007$) in adulthood. Hypothesis 2 was not supported. A separate linear regression model showed that the association between ACEs and cognitive change across a 10-year span was not statistically significant ($p = .213$; Table 3); however, a higher frequency of ACEs was associated with lower BTACT scores at time II ($b = -0.053$, SE = 0.026, $p = .046$) and time III ($b = -0.047$, SE = 0.020, $p = .022$).

Mediation Models

Finally, we used mediation models to examine the direct and indirect associations of cardiometabolic dysregulation score on the relation between ACEs and cognitive status, including the covariates age, sex, race, and income (Table 4; Figures 1, 2). The total association model demonstrated that ACEs were significantly associated with BTACT II ($b = -0.053$, SE = 0.025, $p = .033$) and BTACT III ($b = -0.048$, SE = 0.022, $p = .030$). The direct association between ACEs and BTACT II ($b = -0.045$, SE = 0.025, $p = .065$) and BTACT III ($b = -0.042$, SE = 0.022, $p = .060$) was not significant. There was a weak but significant negative indirect association through cardiometabolic dysregulation for both BTACT II ($b = -0.007$, SE = 0.004, $p = .044$) and BTACT III ($b = -0.006$, SE = 0.003, $p = .042$). No significant total ($b = -0.018$, SE = 0.015, $p = .22$), direct ($b = -0.017$, SE = 0.002, $p = .26$), or indirect ($b = -0.002$, SE = 0.001, $p = .24$) associations were observed for cognitive change. The final mediation model accounted for 65.7% of the variance in cognitive change over a 10-year span.

DISCUSSION

The role of ACEs on both physiological and mental health has been an area of increasing research interest for the past several decades. Although various studies have shown the direct associations of ACEs on adverse health outcomes, few have explored the relation between ACEs and the indirect mechanisms predisposing adults to worsening physiological function, and subsequent disease. Our study is one of the first to examine how specific biological systems, such as cardiometabolic health, indirectly impact adult cognitive status and cognitive change using longitudinal data from a large sample of middle-aged and older adults. We found that ACEs were associated with worse cardiometabolic functioning, and cardiometabolic functioning indirectly accounted for a small proportion of the association between ACEs and cognitive status in adulthood.

Consistent with our first hypothesis, a greater frequency of ACEs was significantly associated with the severity of an individual's cardiometabolic dysregulation. The alterations on the structure and function of biological and neuroendocrine systems as a consequence of frequent or severe ACEs have been postulated to be the result of dysfunctional glucocorticoid receptor stimulation (4). Specifically, as a normal consequence of stress, the glucocorticoid receptor signaling pathway stimulates the production of multiple cardiometabolic biomarkers such as glucose, triglycerides, and elevated blood pressure (5,6). The overstimulation and consequent dysregulation of glucocorticoid hormones throughout the body predispose individuals to cardiovascular and metabolic dysregulation.

With ACEs having such a prominent negative impact on adverse health outcomes via biological pathways, it is of clinical and public health importance to determine which pathways result in disease and ultimately how they can be modified to prevent

TABLE 3. Linear Regression Models of ACEs and Covariates on CM Dysregulation, Cognitive Status, and Cognitive Change

	CM Dysregulation			Cognitive Status II			Cognitive Status III			Cognitive Change		
	b	*β*	SE	*b*	*β*	SE	*b*	*β*	SE	*b*	*β*	SE
ACEs	0.152	0.084	0.056**	−0.053	−0.059	0.026*	−0.047	−0.072	0.020*	−0.018	−0.028	0.015
Age	0.002	0.015	0.005	−0.030	−0.389	0.002***	−0.027	−0.430	0.002***	−0.013	−0.204	0.001***
Sex	−0.949	−0.253	0.116***	0.038	0.021	0.054	0.012	0.009	0.042	−0.008	−0.006	0.030
Race	−0.259	−0.031	0.252	0.413	0.102	0.119***	0.370	0.125	0.091***	0.155	0.053	0.066*
Income	−0.204	−0.078	0.083	0.206	0.161	0.039***	0.133	0.140	0.030***	0.045	0.047	0.022*
BTACT II										0.503	0.678	0.018***
R^2		8.00%	0.016***		21.6%	0.024***		23.5%	0.026***		62.8%	0.021***

ACEs = adverse childhood experiences; CM = cardiometabolic; SE = standard error, which is reported based on the unstandardized *b* coefficients; Cognitive Status II = BTACT II score; Cognitive Status III = BTACT III score, CM = Cardiometabolic; BTACT = Brief Test of Adult Cognition by Telephone.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

TABLE 4. Mediation Models of ACEs and Covariates on Cardiometabolic Dysregulation, Cognitive Status, and Cognitive Change

	Cognitive Status II			Cognitive Status III			Cognitive Change		
	b	*β*	SE	*b*	*β*	SE	*b*	*β*	SE
CMD on									
ACEs	0.152	0.084	0.054**	0.152	0.084	0.054**	0.138	0.076	0.053**
Age	0.002	0.015	0.005	0.002	0.015	0.005	−0.005	−0.032	0.005
Sex	−0.949	−0.253	0.116***	−0.949	−0.253	0.116***	−0.900	−0.241	0.122***
Race	−0.259	−0.031	0.284	−0.259	−0.031	0.284	−0.218	−0.026	0.306
Income	−0.204	−0.078	0.089*	−0.204	−0.078	0.089*	−0.156	−0.060	0.090
BTACT II							−0.234	−0.115	0.070**
Cognitive outcome on									
ACEs	−0.045	−0.051	0.025	−0.042	−0.064	0.022	−0.017	−0.025	0.015
Age	−0.030	−0.389	0.002***	−0.026	−0.457	0.002***	−0.013	−0.217	0.001***
Sex	−0.006	−0.003	0.056	−0.026	−0.019	0.039	−0.018	−0.013	0.031
Race	0.398	0.098	0.123**	0.352	0.118	0.078***	0.151	0.050	0.069*
Income	0.196	0.153	0.038***	0.125	0.132	0.035***	0.043	0.045	0.023
CMD	−0.048	−0.098	0.014**	−0.039	−0.108	0.012**	−0.012	−0.032	0.008
BTACT II							0.499	0.671	0.018***
Model R^2		22.4%	0.024***		28.0%	0.028***		65.7%	0.022***

ACEs = adverse childhood experiences; Cognitive Status II = BTACT II score; Cognitive Status III = BTACT III score; SE = standard error; CMD = cardiometabolic dysregulation; BTACT = Brief Test of Adult Cognition by Telephone.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

disease. It should be noted that a recent study found that ACEs were associated with an increased risk of poor health outcomes in adulthood; however, solely using ACE screenings was not an effective tool for preventing adverse health outcomes (23). The current study, for example, examined a combined cardiometabolic indicator with ACEs and cognition, which may further support the necessity for administering multiple system screening tools alongside ACE screening tools in clinical practice.

Second, we assessed whether the frequency of ACEs was associated with impaired cognitive health. Our findings suggested that there was a relevant relation between those with a greater ACE count and impairment of cognitive status across adulthood. These findings propose that ACEs have an adverse effect on cognitive health, which is accordant with existing literature. In particular, prior literature has established ACEs as a predictive risk factor for the development of impairment in working memory and cognitive control beginning in childhood (24) and persisting in adulthood (25). Notably, however, our findings showed that ACEs were not associated with change in cognitive status over time. These findings are consistent with prior studies that have found that chronic early-life stressors negatively affect the levels of peak cognitive status, but not cognitive change in midlife (25,26). These findings may be the result of individual variability in cognitive protective factors throughout an individual's life that decrease the risk of cognitive change and dementia in late life, such as higher parental socioeconomic status and individual levels of educational attainment (27).

Our findings demonstrate that cardiometabolic dysregulation weakly mediates the relation between ACEs and cognitive status

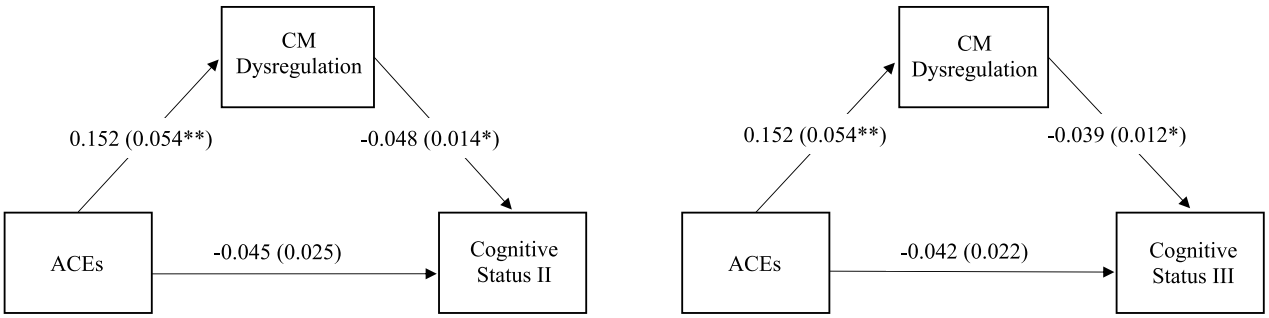

FIGURE 1. Mediation models for cognitive status ($n = 994$). Coefficients and standard errors displayed. The association between ACEs and cognitive status at two time points mediated by cardiometabolic dysregulation. * $p \leq .05$, ** $p \leq .01$, *** $p \leq .00$. Total association of ACEs on cognitive status at BTACT II ($b = -0.053$, SE = 0.025, $p = .033$) and BTACT III ($b = -0.048$, SE = 0.022, $p = .030$). Indirect association of cardiometabolic dysregulation on cognitive status at BTACT II ($b = -0.007$, SE = 0.004, $p = .044$) and BTACT III ($b = -0.006$, SE = 0.003, $p = .042$). Age, sex, age, and income were included in the model as covariates. ACEs = adverse childhood experiences; BTACT = Brief Test of Adult Cognition by Telephone; CM = cardiometabolic.

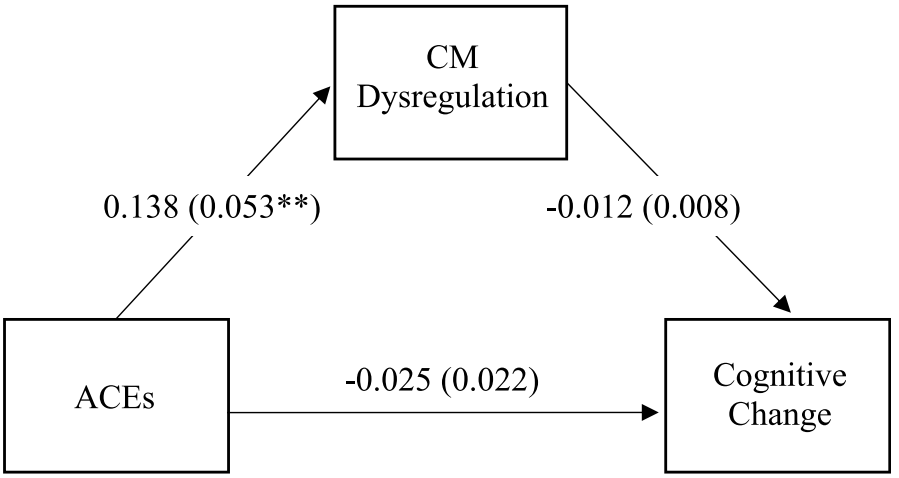

FIGURE 2. Mediation model for cognitive change across a 10-year span (n = 930). Coefficients and standard errors displayed. The association between ACEs and cognitive change mediated by cardiometabolic dysregulation. * $p \leq .05$, ** $p \leq .01$, *** $p \leq .00$. The total association of ACEs on cognitive change ($b = -0.018$, SE = 0.015, $p = .22$). Indirect association of cardiometabolic dysregulation on cognitive change ($b = -0.002$, SE = 0.001, $p = .24$). Age, sex, age, and income were included in the model as covariates. ACEs = adverse childhood experiences; CM = cardiometabolic.

across adulthood. These results indicate that a cumulative effect of cardiovascular and metabolic dysregulation is sufficient to impair cognitive status in those who have experienced frequent childhood stressors. One mechanism that may explain why ACEs alter the developing physiology of the brain relates to glucocorticoid neurotoxicity. Berens and et al. (5) explain that early-life elevations in glucocorticoids mediate the impaired growth and destruction of neurons via oxidative stress. Our study provides an additional hypothesis explaining the mechanism between ACEs and impaired cognition to be the consequence of aggregated cardiometabolic dysregulation in childhood.

To explain, numerous studies have demonstrated that increased levels of cardiometabolic biomarkers, such as glucose, glycosylated hemoglobin, cholesterol, and elevated blood pressure, elicit impaired cognitive functioning in middle-aged and older adults via vascular damage in distinct brain regions (7–10). Therefore, it is possible that children who have experienced frequent ACEs have elevated levels of glucocorticoids and thus increased levels of the said cardiometabolic biomarkers that damage small vascular vessels in the brain, and subsequently contribute to neuronal damage. Our findings posit that elevated cardiometabolic biomarkers in the central nervous system may be one etiological pathway that predisposes individuals to cognitive impairments via pervasive modifications in brain structures during early life. However, our study indirectly accounted for a small proportion of the association between ACEs and cognitive status, and future research studies should continue to evaluate additional mediators that strengthen this association.

It is important to note that our study used cardiometabolic biomarker scores from middle-aged and older adults, not children. Nevertheless, prior research has established that the effects of ACEs on the overstimulation of the stress response and consequent glucocorticoid dysregulation via a resistant HPA axis persist throughout adulthood (5). Therefore, our findings suggest that individuals with higher ACE counts are at risk for developing cardiometabolic dysregulation, which may adversely alter brain development in early life resulting in impaired cognitive status throughout adulthood.

Limitations

Limitations related to the data collection methods and the assessments used should be acknowledged. To begin, the Childhood Trauma Questionnaire and SAQ survey questions asked in wave I, specifically those pertaining to ACEs, overlook various socioeconomic and racially specific ACEs, such as community violence exposure, living in an unsafe neighborhood, and experiencing discrimination (3). As a consequence, future studies should expand the category of ACEs to include additional social determinants of health. Furthermore, although random sampling was used to recruit adults residing in the United States, the initial MIDUS sample demographic was not representative of the American population. Rather, the MIDUS sample was predominately composed of White adults with higher levels of income, education, and socioeconomic status than the national average (19,20). Adults of minority ethnic groups and lower socioeconomic status were underrepresented in all waves of the study. The effects of a nonrepresentative sample may reduce the generalizability of our findings, and hence, it is necessary for future studies to use a more diverse ethnic, racial, and social class cohort.

The data collection strategy of this study imposed the additional limitation of not allowing for the collection of biomarker and cognitive data over several time periods, starting from childhood and ending at older age. Without having access to data collected over a longer period of time, we are unable to exhaustively determine the association between ACEs and cardiometabolic dysregulation or ACEs and impaired cognition without excluding confounding factors throughout an individual's life span.

Conclusions

A wide range of studies have established an association between ACEs and chronic disease in adulthood; however, this study is the first to explore how a combination of dysregulated and interconnected biological systems (i.e., cardiovascular and metabolic systems) connects early adverse experiences with the risk of developing chronic cognitive impairments. Using longitudinal data

from a large cohort of adults, our findings showed that cardiometabolic dysregulation weakly mediates the association between ACEs and cognitive status across middle and older age, but not cognitive change. Future research should evaluate how predictive biological mechanisms, together with ACE screening tools, could be used to personalize the approach of ACE management in adults and adolescences. One way to accomplish this is by implementing evidence-based interventions and educating high-risk individuals on life-style changes that improve physiological health, specifically cardiometabolic burden, and in turn the onset of disease.

Source of Funding and Conflicts of Interest: none declared.

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