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Authors

Davis, Mary C
Lemery-Chalfant, Kathryn
Yeung, Ellen WanHeung
et al.

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REGULAR ARTICLE

Interleukin-6 and Depressive Mood Symptoms: Mediators of the Association Between Childhood Abuse and Cognitive Performance in Middle-Aged Adults

Mary C. Davis, PhD[1] • Kathryn Lemery-Chalfant, PhD[1] • Ellen WanHeung Yeung, PhD[2] • Linda J. Luecken, PhD[1] • Alex J. Zautra, PhD[1] • Michael R. Irwin, MD[3,4]

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Abstract

Background Childhood abuse is a risk factor for the development of cognitive deficits in adulthood, a relation that is likely mediated by stress-sensitive psychological and physiological indicators.

Purpose To evaluate whether the link between exposure to childhood abuse and cognitive function in middle adulthood is mediated by interleukin-6 (IL-6), metabolic risk, and depressive mood symptoms.

Methods Participants were 770 adults aged 40–65 recruited from the community, who completed the following: (i) a questionnaire assessing exposure to abuse prior to age 18, (ii) a phone interview assessing current depressive mood symptoms, and (iii) a home visit that included blood sampling for evaluation of IL-6 and assessment of metabolic risk indices. A follow-up telephone assessment evaluating cognitive function was completed by 555 of the participants. Structural equation modeling was used to test study hypotheses.

Results Childhood abuse predicted higher levels of IL-6, depressive mood symptoms, and metabolic risk scores ($p < .05$). The relation between childhood abuse and poorer cognitive performance was mediated by IL-6 ($p = .046$) and depressive mood symptoms ($p = .023$), but not metabolic risk. IL-6 and depressive mood symptoms significantly mediated the relation between childhood abuse and adult cognitive function.

Conclusions Exposure to early abuse conveys enduring physiological and psychological effects, which may contribute to cognitive deficits that are evident by middle adulthood. Increased vulnerability for cognitive decline among adults with a history of early trauma and the mediating roles of IL-6 and depressive mood symptoms point to the potential value of interventions that address inflammation or depression, singly or together, to prevent cognitive decline in this at-risk population.

Keywords Childhood abuse • Depression • Metabolic risk • Inflammation • Interleukin-6 • Cognitive function

Mary C. Davis
mary.davis@asu.edu

[1] Department of Psychology, Arizona State University, Box 871104, Tempe, AZ 85287-1104, USA

[2] Department of Psychological Sciences, University of Missouri, Columbia, MO, USA

[3] Cousins Center for Psychoneuroimmunology, University of California, Los Angeles, CA, USA

[4] Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA

Introduction

Exposure to abuse during childhood is highly prevalent; between 30% and 50% of adults indicate that they have experienced abuse, neglect, or both when they were children [1]. Early abuse has been linked with a range of health outcomes that persist well into adulthood, including cognitive dysfunction [2]. Over the past two decades, the bulk of the evidence regarding the relation of early abuse to subsequent cognitive performance suggests

detrimental effects of early abuse. Perhaps the strongest evidence to date is provided by a large prospective cohort study of individuals recruited for participation in childhood and assessed for cognitive function at age 41 [3]. Of the 792 individuals who underwent cognitive assessment, 450 had court-substantiated exposure to childhood physical abuse, sexual abuse, and/or neglect prior to age 12, and 342 were controls who did not experience early maltreatment. Individuals who had been exposed to childhood abuse showed deficits in executive function and nonverbal reasoning relative to controls, relations that were not accounted for by current depressive symptoms or excessive alcohol consumption. A similar pattern of findings linking childhood abuse via retrospective self-report of adults with adult cognitive function is evident in the majority of studies [4, 5], with some indication that effects may depend on timing of the abuse [6].

Assessment of important biomarkers of physiological systems, particularly those that are likely to be primary mediators, is a key means to gain insight into the mechanisms linking childhood abuse with later cognitive dysfunction [7, 8]. Among the most compelling hypotheses regarding physiological mechanisms is that the early abuse becomes "biologically embedded" in immune cells, changing them in a manner that promotes excessive, enduring inflammation [2]. The inflammation, in turn, is thought to play a role in pathophysiological processes that fuel cognitive decline [9]. Existing cross-sectional and prospective evidence, in fact, suggests that exposure to early abuse leads to inflammation in adulthood, reflected in elevated interleukin-6 (IL-6) and/or C-reactive protein (CRP [10, 11]).

Inflammation, in turn, has been linked with cognitive decline. In prospective cohort studies, higher levels of IL-6 and/or CRP predicted increased risk of cognitive decline over follow-up periods ranging from 3 to 25 years [9, 12, 13], associations also observed in cross-sectional studies [14–16]. A recent prospective investigation evaluated whether IL-6 and CRP levels were related to a similar extent with cognitive decline over a 10 year period and found that elevations in IL-6 but not CRP were associated with cognitive decline [13]. IL-6 may be a more appropriate marker than CRP for evaluating the association between peripheral inflammation and cognition, possibly because IL-6 drives the production of downstream markers, including CRP. Despite evidence that early abuse predicts elevated inflammation and that inflammation leads to cognitive decline, no study to our knowledge has tested whether inflammation mediates the abuse–cognitive function relation.

Chronic inflammation is not the only plausible mechanism linking childhood abuse with cognitive functioning in middle age. Indeed, a 20-year prospective study of children reported that childhood maltreatment predicted elevations in not only inflammation, but also multiple metabolic risk factors (e.g., overweight, high blood pressure) and depression 32 years later [17], findings consistent with those of other investigations [18]. Like inflammation, metabolic disturbance and depression, in turn, have been related to poor cognitive function [19, 20]. Thus, a body of evidence points to the possibility that inflammation, metabolic disturbance, and depression are correlated risk factors [21, 22] that mediate the relation between childhood maltreatment and adult cognitive function.

The current study addresses an important gap in the literature by evaluating whether fundamental physiological and psychological mechanisms explain the association between childhood abuse and cognitive function among middle-aged adults. We aimed to test whether the relation between exposure to childhood abuse and cognitive function in adulthood is mediated by inflammation, metabolic disturbance, and/or depressive mood symptoms.

Methods

Participants

The 770 participants for the current study were recruited between 2007 and 2012 to participate in a study of healthy aging via mailings and informational flyers. Individuals were eligible if they met the following criteria: (i) aged 40–65 years, (ii) fluent in English and/or Spanish, and (iii) resided within 1 of 20 Census tracts in the Phoenix, Arizona metropolitan area that were selected to capture communities that reflected the racial and economic diversity of the region.

Eight hundred and nine individuals were enrolled in the parent study, 770 of whom completed the initial questionnaire, phone assessment, and the home visit (described later). Of the 770 individuals who were enrolled in the parent study, we were able to re-contact and enroll 555 individuals for cognitive assessment. Individuals from the parent study who were (n = 555) or were not enrolled (n = 215) for cognitive assessments were compared on 11 demographic, psychological, and biological measures, applying a Bonferroni-corrected p-value of .005. Groups were similar in (i) demographic characteristics (i.e., sex, income, race, age) and (ii) variables that are the focus of the current report (i.e., childhood abuse, IL-6, metabolic risk, and depressive mood symptoms). However, individuals who did versus did not undergo the cognitive assessment were significantly more educated (e.g., 23.8% vs. 12.4% with less than a high school degree, respectively; $\chi^2_{(5,\, N = 770)} = 23.57$, $p < .001$).

Procedure

Study procedures were approved by the Institutional Review Board at Arizona State University, and participants provided written informed consent to initiate

enrollment. Participants first completed self-report questionnaires that included questions regarding demographic characteristics and exposure to childhood abuse. They then completed a phone interview to assess mental health and physical health history, which included questions regarding depressive mood symptoms, smoker status, and alcohol and medication use. Subsequently, participants received a home visit by study personnel, which included collection of blood samples and blood pressure and anthropometric measures to determine metabolic risk indicators and IL-6 levels.

Childhood abuse and depressive symptoms scores were available for all 770 participants. Metabolic risk scores were available for 698 individuals, and IL-6 data were available for 610 individuals, with loss of data primarily due to (i) insufficient blood volume to complete all assays, (ii) unsuccessful venipuncture, and (iii) loss of sample integrity during shipment.

During the home visit, waist circumference (WC) in centimeter was assessed with a Gulick tape measure placed directly on the skin surface at the narrowest point between the iliac crest and lowest rib. Systolic and diastolic blood pressure (SBP and DBP, respectively) were calculated by averaging three blood pressure readings (in mm/Hg) taken at 2-min intervals via an Industrial and Biomedical Corporation automated blood pressure monitor (Model SD-700A; Waltham, MA) while participants were seated and at rest. Blood samples were collected into Vacutainer tubes (Becton–Dickinson, Franklin Lakes, NJ). Samples from red/black serum separator tubes (SST) were used to quantify levels of fasting glucose, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels, and from lavender top tubes (with the anticoagulant EDTA as an additive) to quantify IL-6 levels. Samples were held on ice and processed and frozen within 2 hr of collection. Samples for metabolic indicators and IL-6 were centrifuged at 4°C for 15 min at 1500 rpm. Serum or plasma was then aspirated, aliquoted, and frozen at −80°C until assayed. SST serum samples were shipped frozen to and assayed by the UCLA Clinical Laboratory to determine the levels of glucose (mg/dL), HDL-C (mg/DL), and triglyceride (mg/dL). EDTA plasma samples were shipped frozen to the UCLA Cousins Center for Psychoneuroimmunology Inflammatory Biology Laboratory, and tested in duplicate. Plasma levels of IL-6 were quantified using Quantikine High Sensitivity human IL-6 ELISA (R&D Systems, Inc., Minneapolis, MN; lower limit of detection 0.2 pg/mL), according to the manufacturer's protocol; intra-assay and inter-assay coefficients of variation were <10%.

After their completion of the questionnaire, interview, and home visit components of the parent study, participants were re-contacted and invited to enroll for an additional evaluation that included a phone interview assessment of cognitive performance, which occurred between 6 and 53 months (M = 20.21, SD = 11.27) following the home visit of the parent study.

Measures

Predictor

Childhood sexual, physical, and emotional abuse prior to age 18 was assessed via use of three abbreviated subscales of the Childhood Trauma Questionnaire–Short Form (CTQ [23]), a widely used, validated self-report retrospective measure. The current study included 10 items that tapped the scales assessing items from the abuse but not the neglect subscales for two reasons: (i) to minimize participant burden and (ii) because reliabilities tend to be higher for abuse relative to neglect subscales [23]. Items assessed emotional abuse (three items; e.g., "People in my family called me things like 'stupid,' 'lazy,' or 'ugly'"), physical abuse (three items; e.g., "People in my family hit me so hard that it left me with bruises or marks"), and sexual abuse (four items; e.g., "Someone threatened to hurt me or tell lies about me unless I did something sexual with them"). Each item was rated on a 5-point scale from 1 (*never true*) to 5 (*very often true*). A total abuse score was computed by generating a mean across all items, yielding a range of possible scores between 1 and 5. The CTQ demonstrated excellent internal consistency in the current sample (α = .91).

Outcome

Cognitive functioning was assessed via The Telephone Interview for Cognitive Status (TICS), a brief 11-item (total of 41 subitems) test of cognitive impairment [24]. Items include questions and tasks related to orientation (e.g., "What is the date?"), concentration (i.e., counting backwards), word reasoning (e.g., "What do people usually use to cut paper?"), verbal knowledge (e.g., "What is the opposite of generous?"), calculation (i.e., serial subtraction), immediate verbal memory (i.e., word list learning), and language processing (i.e., finger taps). Correct responses are summed to yield a total score that can range from 0 to 41, with higher scores reflecting better cognitive functioning. The TICS is a reliable and valid assessment of cognitive impairment, showing good sensitivity (69%–87%) and specificity (69%–90%) for distinguishing healthy controls from individuals with mild cognitive impairment and dementia in multiethnic samples [24–26].

Mediators

Depressive mood symptom frequency was assessed via the four items that comprise the depression subscale of the Mental Health Inventory (MHI), a widely used

self-administered measure of mental health and well-being in community samples [27]. Participants rated the extent to which they experienced each item during the past 4 weeks on a scale ranging from 1 (*none of the time*) to 6 (*all the time*). Items assessed how much of the time individuals had experienced mood symptoms, including being (i) in low or very low spirits, (ii) depressed, (iii) moody and brooding about things, and (iv) downhearted and blue. A total score was computed by summing all four items, yielding a range of possible scores between 4 and 24, with higher scores reflecting more frequent experience of depressive mood symptoms. Of note, there is no overlap between the items from the MHI Depression Scale and cognitive symptoms of depression. This approach minimizes "criterion-contamination" by avoiding items reflecting cognitive dysfunction—concentration or decision-making problems. The original psychometric work conducted in a large sample of community-dwelling individuals across six geographic regions of the USA established that the scale is highly internally consistent (α = .86) and stable across 1 year (r = .56 [27]). The internal consistency of this scale in the current sample was excellent (α = .89).

Metabolic risk indicators included WC, SBP and DBP, and glucose, HDL-C, and triglycerides assessed following an 8-hr fast [28]. A metabolic risk score was calculated consistent with the indices and cutoff scores recommended by the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [28]. For each participant, a count was computed of each biomarker that was either above a clinically relevant cut point for elevated risk for metabolic syndrome or being treated pharmacologically. Five biomarkers were included in the count: (i) WC (≥88 cm for women and 102 cm for men), (ii) blood pressure (SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHG or use of antihypertensive medication), (iii) fasting glucose (≥100 mg/dL or use of glucose-lowering medication), (iv) HDL-C (<40 mg/dL for women and <50 mg/dL for men), and (v) triglycerides (≥150 mg/dL or use of lipid-lowering medication).

Inflammation was indexed by IL-6, one of the most frequently examined, sensitive, and appropriate serologic markers of systemic inflammation and one that has been used in prior research to predict cognitive decline [13, 29]. Values of IL-6 greater than 10 pg/mL (n = 12) were excluded from analyses because they suggest presence of an acute illness, and the current hypotheses were focused on the mediating effects of chronic rather than acute inflammation. To address its non-normal distribution, the IL-6 variable was transformed using a natural log function prior to analysis; however, raw values for means and standard deviations are reported in text for ease of interpretation and comparison with other studies that included IL-6.

Control variables

Control variables included the time interval between assessment of mediators and cognitive performance (in months), and demographic and behavioral factors that prior studies have indicated are related to cognitive performance [30–32]. Demographic factors included age, sex, education level (less than high school degree, high school degree, some college, college degree, post-graduate degree, doctoral degree), and ethnicity (coded 0 = *White*, 1 = *other*). Health behaviors included tobacco use (0 = *no*, 1 = *yes*); problematic alcohol use, assessed via the Alcohol Use Disorders Identification Test (AUDIT [33]); physical activity level, expressed as metabolic expenditure per minute of a task × the number of minutes engaged in the task (MET-minutes) and assessed via the International Physical Activity Questionnaire–Short Version (IPAQ [34]); and sleep disturbance, assessed via the Insomnia Severity Index [35]. IPAQ scores were not normally distributed and therefore were transformed using a natural log function prior to analysis; however, raw values for medians and standard deviations are reported in text for ease of interpretation and comparison with other studies that included the IPAQ.

Data Analytic Approach

The hypothesized mediation model included three parallel mediated paths: (i) the path from childhood abuse to IL-6 (a_1 path), and IL-6 to cognitive function (b_1 path); (ii) the path from childhood abuse to metabolic risk (a_2 path), and metabolic risk to cognitive function (b_2 path); and (iii) the path from childhood abuse to depressive mood symptoms (a_3 path), and depressive mood symptoms to cognitive function (b_3 path). A direct path from childhood abuse to cognitive function (c' path) was also modeled. The model solution also was adjusted by modeling the covariation among the covariates (i.e., age, ethnicity, sex, education, smoker status, tobacco and problematic alcohol use, sleep disturbance, and physical activity levels), as well as the covariation between the covariates and childhood abuse and cognitive performance. The models for the current study were conducted through use of M*plus* version 7 [36]. A significant indirect effect was captured by "zero" residing outside the bootstrapped asymmetric confidence intervals [37, 38]. M*plus* version 7 employs full information maximum likelihood (FIML) estimation [36]. FIML estimates parameters and standard errors using all the available data. By including the partially complete cases, FIML produces parameter estimates and standard errors robust to data assumed to be missing at random [39]. Standardized solutions and standard errors are presented in the results. Because missing data for cognitive performance may not be missing at random, we ran the model twice, first including all

770 participants and then including only those 555 participants for whom a measure of cognitive performance was available to determine whether the mediated effects observed in the larger sample were still apparent.

Results

Sample Characteristics

In the current sample of 770 participants, 55% were female, with a mean age of 53.50 years (*SD* = 7.24; range = 40–65). The racial/ethnic composition of the sample was as follows: 80.4% White, 3.2% African American, 1.8% Asian, 1.3% Native American, and 13.3% multiracial, with 13.7% endorsing Hispanic ethnicity. Thus, the racial/ethnic distribution of the current sample of middle-aged adults was roughly comparable with that of all residents of Maricopa County with one exception: a higher proportion of county residents endorsed being of Hispanic ethnicity (24.9% [40]). In general, the participants were well educated; a minority of participants had obtained less than a high school degree (6.7%) or a high school degree (9.0%), whereas most participants had attended college (27.9%) or graduated with a bachelor's degree (24.4%; range: ≤high school degree to doctoral degree).

With regard to health behaviors, participants were primarily nonsmokers (80.6%). On average, their self-reported alcohol consumption was consistent with low levels of drinking (*M* = 2.77, *SD* = 3.16); however, 8.8% scored in a range consistent with problem drinking (i.e., score > 7 on the AUDIT [31]). Participants indicated that they engaged in a median level of weekly physical activity of 2,536 MET-minutes per week (*SD* = 6178), comparable with the median level of 2,514 MET-minutes per week reported in an international sample of 1974 aged 18–65 years [34]. This level of activity corresponds to a median level of 300 min of moderate to vigorous activity per week (*SD* = 864), which meets the level of physical activity recommended for adults to obtain extensive health benefits [41]. As a whole, the sample reported low levels of sleep disturbance (*M* = 5.49, *SD* = 4.89; observed range = 0–22), with only 5% reporting a level of insomnia that is considered to be clinically significant (i.e., score >14 [35]).

Descriptives

Table 1 depicts the means, standard deviations, and intercorrelations of independent, mediator, and dependent variables. On average, the sample reported a mean level of childhood abuse comparable with that of the large community sample used to validate the CTQ [42]. Cognitive function scores ranged from 23 to 40, with 5.1% of the sample with scores suggestive of at least mild cognitive impairment (i.e., TICS score ≤28 [26]).

With regard to purported mediators, the median value and interquartile range (IQR) of IL-6 in the current sample (*Mdn* = 1.49 pg/mL; IQR = 1.01–2.45) were comparable with those of a large community based sample of middle-aged adults (*Mdn* = 1.43 pg/mL; IQR = 1.07–1.99) [13]. With regard to metabolic risk scores, the mean value was approximately 2 risk indicators (range = 0–5). The MHI average depressive mood symptom score suggested that the sample as a whole reported experiencing infrequent depressive mood symptoms during the prior month (*M* = 7.15, *SD* = 3.50; possible range = 1–24). The mean MHI score of the current sample is comparable with that of a sample of 5,089 community-dwelling individuals (*M* = 8.05, *SD* = 2.97 [27]). The pattern of intercorrelations indicates that childhood abuse exposure, cognitive function, and mediating variables were all significantly related in the expected directions (see Table 1).

Mediated Relation of Childhood Abuse With Cognitive Performance

Figure 1 depicts the model in which IL-6, metabolic risk, and depressive mood symptoms are simultaneously

Table 1 Means, standard deviations, and intercorrelations of key study measures

Variable	*n*	*M*	*SD*	2	3	4	5
1. TICS (0–41)	555	34.33	3.01	–.184***	–.174***	–.165***	–.233***
2. CTQ abuse mean item score (1–5)	770	1.74	0.87		.140**	.115*	.360***
3. IL-6 (pg/ml)	613	2.37	3.88			.366***	.105*
4. Metabolic risk score (0–5)	703	2.01	1.55				.146***
5. MHI depressive mood symptom mean item score (1–6)	770	1.78	0.88				–

IL-6 *M* and *SD* values are presented as raw scores; intercorrelations are based on natural log-transformed scores. Metabolic risk score comprised of waist circumference, blood pressure, high-density lipoprotein cholesterol, triglycerides, and glucose.

TICS Telephone Interview for Cognitive Status; *CTQ* Child Trauma Questionnaire; *IL-6* interleuckin-6; *MHI* Mental Health Inventory.

*$p < .01$; **$p < .001$; ***$p < .0001$.

tested as mediators of the relation between early abuse and cognitive performance. The findings showed that higher levels of abuse were associated with higher levels of IL-6 (a_1, p = .001), which, in turn, predicted poorer cognitive performance (b_1, p = .012). Similarly, higher levels of abuse were associated with higher levels of depressive mood symptoms (a_3, p < .0001), which, in turn, predicted poorer cognitive performance (b_3, p = .002). With regard to metabolic risk, higher levels of abuse predicted greater metabolic risk (a_2, p = .003), but metabolic risk was unrelated to cognitive function (b_2, *ns*). The indirect effect from abuse to IL-6 to cognitive performance was significant, with zero residing outside the bootstrap asymmetric CIs (95% CIs: –0.035 to –0.004). Likewise, the indirect effect from abuse to depressive mood symptoms to cognitive performance was significant, with zero residing outside the bootstrap asymmetric CIs (95% CIs: –0.104 to –0.022). In contrast, metabolic risk did not mediate the abuse–cognitive performance relation (95% CIs: –0.014 to 0.009). Of note, the direct relation between abuse and cognitive performance was nonsignificant (c' = –0.051, SE = 0.051, *ns*), suggesting that the abuse–cognitive performance relation was significantly mediated by IL-6 and depressive mood symptoms. The proportions of variance explained by the model were 29.8% for cognitive performance, 2% for IL-6, 13.4% for depressive symptoms, and 1.3% for metabolic risk scores.

Findings for the model that included only the 555 participants who completed the cognitive assessment showed that higher levels of abuse were associated with higher levels of IL-6 (a_1, p = .004), which, in turn, predicted poorer cognitive performance (b_1, p = 0.013). Similarly, higher levels of abuse were associated with higher levels of depressive mood symptoms (a_3, p < .0001), which, in turn, predicted poorer cognitive performance (b_3, p = .002). With regard to metabolic risk, higher levels of abuse predicted greater metabolic risk (a_2, p = .004), but metabolic risk was unrelated to cognitive function (b_2, *ns*). The indirect effect from abuse to IL-6 to cognitive performance was statistically significant, with zero residing outside the bootstrap asymmetric CIs (95% CIs:–0.040 to –0.004). The indirect effect from abuse to depressive mood symptoms to cognitive performance was also significant, with zero residing outside the bootstrap asymmetric CIs (95% CIs: –0.117 to –0.026). In contrast, metabolic risk did not mediate the abuse–cognitive performance relation (95% CIs: –0.017 to 0.009). The proportions of variance explained by the model were 27.7% for cognitive performance, 2.1% for IL-6, 15.7% for depressive symptoms, and 1.6% for metabolic risk scores.

Discussion

The current findings add to the substantial body of evidence suggesting that the influence of childhood trauma on health endures well into adulthood. Among community-dwelling middle-aged adults, childhood abuse predicted increased IL-6, metabolic risk, and depressive mood symptoms, in line with prior results based on longitudinal data in adults [17]. Moreover, IL-6 and depressive mood symptoms together significantly and independently mediated the relation between exposure to childhood abuse and poorer cognitive performance. To our knowledge, this study is the first to demonstrate that inflammation and depressive mood symptoms may serve as fundamental mechanisms linking abuse experienced early in life with cognitive health in adulthood. The findings are also consistent with recent theories that emphasize the role of heightened chronic inflammation as a key physiological process that accounts for the host of chronic health problems in adults that are associated with childhood abuse [2]. Of note, these relations were

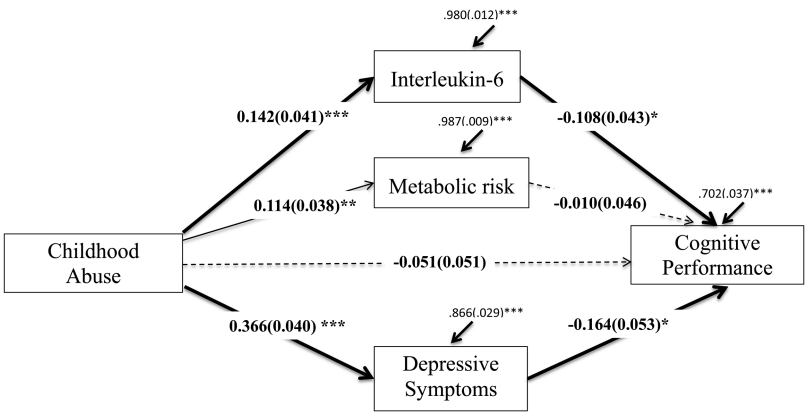

Fig. 1. Results of the structural equation model depicting the relations among childhood abuse, interleukin-6, metabolic risk, depressive mood symptoms, and cognitive performance for total sample (N = 770). Associations are presented as standardized path coefficients (SE). *p < .05; **p < .01; ***p < .001. 95% bootstrap confidence intervals for the indirect effects are: CIs = –0.035 to –0.004 for IL-6; CIs = –0.104 to –0.022 for depressive symptoms; CIs = –0.014 to 0.009 for metabolic risk. Significant mediated paths are in bold.

evident in a sample of individuals with low rates of clinically meaningful cognitive dysfunction and low levels of childhood abuse akin to those in other large, diverse community samples of middle-aged adults that have also used the CTQ [23, 42].

Beyond its effects on the inflammatory system, early abuse may impart a lasting signature on other physiological systems that may plausibly contribute to poorer cognitive function. In the current study, we observed a relation between early abuse and metabolic risk, replicating earlier reports [17]. However, contrary to expectation, metabolic risk did not predict cognitive performance [20]. One possible explanation for the discrepant findings is that metabolic risk among individuals in the current sample relative to those included in other investigations was not elevated enough and/or sustained over a sufficient period of time to influence cognitive function. In fact, approximately 36.5% of the current sample met criteria for metabolic syndrome, defined as elevations on at least three of the five metabolic risk measures [28]. This rate is comparable with the U.S. prevalence rate of approximately 33% for adults aged 50–59 [43]. It is also in line with the 39% prevalence rate of metabolic syndrome reported in a large study of elderly individuals, which observed an association between metabolic syndrome and poorer cognitive performance [20]. Thus, the rate of metabolic syndrome in the current sample of middle-aged adults was roughly comparable with those observed in the older samples in which the metabolic risk–cognitive function relation was evident. Together, these findings suggest that the impact of metabolic disturbance on cognitive function may only become apparent among the elderly, possibly because they have experienced a longer period of exposure to metabolic disturbance [44].

What can account for the links between early abuse, levels of IL-6 and depressive mood symptoms, and cognitive performance? Some compelling evidence regarding the nature of these associations is provided by research employing a rodent model of early trauma (neonatal maternal deprivation stress: MS). Relative to nonstressed control animals, MS in rodent pups results in neurophysiological alterations that promote enhanced expression of pro-inflammatory molecules in the prefrontal cortex [45], increases in proinflammatory cytokines in peripheral circulation [46], "depression-like" sickness behaviors [47], and memory deficits [45, 48]. Of particular relevance to the current study, the memory deficits associated with MS are prevented when animals receive pharmacological treatment during their adolescence that inhibits expression of these proinflammatory molecules [45, 48]. Specifically, MS animals randomly assigned to receive a cyclooxygenase-2 inhibitor, an anti-inflammatory medication, exhibited memory performance that was significantly better than MS animals randomized to receive placebo, and equivalent to that of nonstressed control animals. These findings suggest that exposure to early trauma promotes changes in the central nervous system that facilitate enduring pro-inflammatory processes, which then drive changes in cognitive function.

Behavioral mechanisms may also play a role in the link between early abuse and adult cognitive performance. Among the possibilities is that early abuse contributes to the development of poor health habits that can fuel increased inflammation and depressive mood symptoms, which can have long-term implications for cognitive function. In fact, individuals with greater exposure to childhood adversity do evince poorer health behaviors, including less physical activity, more alcohol and tobacco use, and greater sleep disturbance [49], all of which have been associated with increased IL-6 levels and depression [50–52]. Because we assessed contemporaneous but not early health behaviors, we elected to model health behaviors as control variables and found that they did not diminish the mediating effects of IL-6 and depression in the abuse–cognitive performance relation. However, elaboration of the timing and impact of behavioral factors on affective and physiological mechanisms driving the abuse–inflammation–cognition relation will require prospective research that extends over critical developmental periods, including adolescence.

We focused on inflammation, metabolic risk, and depressive mood symptoms as indicators of disturbance in stress-sensitive systems [17], but there are clearly other alternatives that are worthy of consideration. Among the most plausible candidates is the hypothalamic-pituitary-adrenal axis (HPA), a neuroendocrine system that is responsive to stress. Stressful stimuli activate the HPA axis, culminating in the production by the adrenal cortex of glucocorticoids, which have receptors expressed throughout the brain. Chronic or repeated exposure to early abuse may result in enduring HPA axis dysregulation [18], which has the potential not only to promote a more proinflammatory state [53], but also to increase risk for depression [54] and to negatively affect brain structures central to cognitive function, including the hippocampus, amygdala, and prefrontal cortex [55]. The extent to which HPA axis dysregulation exerts direct effects on cognitive function beyond its documented impact on inflammation and depression, however, has not yet been investigated to our knowledge.

Strengths and Limitations

Although the current findings are intriguing, they should be interpreted within the context of the methodological limitations of the study. First, the study included a limited assessment of cognitive functioning, leaving unanswered the question regarding whether the paths from early abuse to inflammation and depression are relevant for specific deficits in cognitive performance. Existing prospective data gleaned from adults point to

the possibility that abuse-related deficits are most consistently evident for processing speed [12, 16] and aspects of memory [16, 29]. Additional research that includes a comprehensive cognitive battery would build on the existing literature and current findings. Second, childhood abuse was assessed via retrospective self-report, a limitation that the current study shares with much of the literature in this area. Nevertheless, prospective research has noted the association between objectively documented childhood abuse and cognitive function among adults [3], lending some confidence to the validity of the current findings. Moreover, measurement error in retrospective reports of childhood maltreatment does not appear to significantly influence estimates of the associations between exposure to childhood maltreatment and adult outcomes and thus is unlikely to pose a significant threat to study validity [56]. Third, the current focus on childhood abuse prior to age 18 leaves open the question of whether timing of abuse and/or exposure to alternative forms of early adversity (e.g., neglect, poverty, early parental loss) produce similar effects. With regard to the timing of exposure to abuse, the available data are surprisingly scarce. The experience of sexual abuse in adolescence versus early childhood has been associated with poorer performance on memory tasks in young adults [6], suggesting that developmental stage at which abuse occurs may be of central importance [55]. More evidence is available linking early hardships with pro-inflammatory tendencies [2] and cognitive dysfunction [8] in adulthood. Although it is plausible that the mediating roles of inflammation and depressive mood symptoms in the childhood abuse–cognition relation observed here are relevant for other forms of childhood adversity, the generalizability of the findings in that regard remains to be evaluated. Indeed, there has been a call for future work to examine specificity in the associations between different types of adversity and the emotional, cognitive, and neurobiological pathways that predict health outcomes [57]. A fourth limitation is that we tested IL-6 as the only index of inflammation, which, as suggested in a recent work, is a prospective predictor of cognitive decline in middle age whereas CRP is not [13]. Nevertheless, our approach leaves open the possibility that other serotologic markers of inflammation may also predict cognitive function. Finally, the timeframe during which we assessed mediators and outcomes was very constrained. The issue of establishing temporal precedence for processes that occur over decades is a thorny one in human research, and one that can only be addressed definitively by longitudinal studies that assess individuals in childhood on all relevant variables and continued to assess them over the ensuing decades. Human data of this kind are not available to address the questions addressed in the current study, to our knowledge. In fact, Brunson and colleagues [58] have stated that "models for delayed consequences of early-life stress on cognitive function, with onset during adulthood, are uncommon" (p. 9328), a limitation in the field that remains to be rectified.

The study also has a number of noteworthy strengths. First, the purposive sampling strategy employed to recruit middle-aged participants from diverse communities in the Phoenix metropolitan region yielded a large sample that was diverse in terms of ethnicity and income. Second, assessments included widely used, validated self-report, physiological, and objective measures to quantify key variables, linking the current work with the extant literature. Of note, the base rate of early abuse was comparable with that reported in other community-based samples [42]. Third, we tested hypotheses that were theory based and founded on a body of earlier work documenting associations between early abuse, psychological and biological indicators of health, and cognitive function [13]. We also controlled for the covariation among mediators to establish that they served as distinct pathways between childhood trauma and cognitive performance, employed a multilevel analytic approach that allowed for use of all available data, and controlled for potential confounders in the mediation models. When the analysis was repeated, including only 555 participants who completed the follow-up cognitive assessment, the mediation findings held. Importantly, the standardized path estimates and standard errors were comparable across models that included the entire sample and the subsample. Finally, the assessment of IL-6, depressive mood symptoms, and metabolic risk preceded the cognitive assessment by an average of 20 months, capturing at least to some extent the temporal relation between the hypothesized mediators and the outcome.

Conclusion

Consistent with prior evidence and theoretical models detailing the lasting impact of early abuse on health, childhood abuse is associated with poorer cognitive functioning in middle age through elevations in IL-6 and depressive mood symptoms. It is noteworthy that these relations are evident even in healthy middle-aged individuals, a population where these associations are likely to be small in magnitude. Future research conducted with less healthy, more impaired populations may yield even more robust associations than those we observed here. If the relations between early abuse, inflammation, depressive mood symptoms, and cognitive dysfunction prove to be causal, prevention efforts can be targeted to defer the onset of cognitive impairment as people age. Such efforts could include not only pharmacologic agents but also behavioral treatments that target health behaviors with the potential to decrease inflammation and preserve cognitive function among individuals with a history of childhood abuse.

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Compliance with Ethical Standards

Conflict of Interest: No author on this paper has any conflicts of interest with regard to this manuscript.

Authors' Contribution: All authors made significant contributions to the development of this manuscript, which is not under consideration for publication in any other journal.

Ethical Approval: The data upon which this manuscript is based were acquired in accordance with the Code of Ethics of the World Medical Association, and the project approved and overseen by the human subjects institutional review board at our institution.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

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