Early Life Adversity and Adult Biological Risk Profiles

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ABSTRACT

Objectives: To determine whether there is a relationship between early life adversity (ELA) and biological parameters known to predict health risks and to examine the extent to which circumstances in midlife mediate this relationship.

Methods: We analyzed data on 1180 respondents from the biomarker subsample of the second wave of the National Survey of Midlife Development in the United States. ELA assessments were based on childhood socioeconomic disadvantage (i.e., on welfare, perceived low income, and less educated parents) and other stressors (e.g., parental death, parental divorce, and parental physical abuse). The outcome variable was cumulative allostatic load (AL), a marker of biological risk. We also incorporate information on adult circumstances, including than following: education, social relationships, and health behaviors.

Results: Childhood socioeconomic adversity and physical abuse were associated with increased AL ($B = 0.094$, standard error = 0.041, and $B = 0.263$, standard error = 0.091 respectively), with nonsignificant associations for parental divorce and death with AL. Adult education mediated the relationship between socioeconomic ELA and cumulative AL to the point of nonsignificance, with this factor alone explaining nearly 40% of the relationship. The association between childhood physical abuse and AL remained even after adjusting for adult educational attainments, social relationships, and health behaviors. These associations were most pronounced for secondary stress systems, including inflammation, cardiovascular function, and lipid metabolism.

Conclusions: The physiological consequences of early life socioeconomic adversity are attenuated by achieving high levels of schooling later on. The adverse consequences of childhood physical abuse, on the other hand, persist in multivariable-adjusted analysis.

Key words: early life adversity, biological risk factor, allostatic load, life course.

INTRODUCTION

Early life adversity (ELA) has been linked to many facets of adult health, including increased risk of cardiovascular diseases, diabetes, cancer, inflammation, incidence of chronic disease, and overall mortality (1–16). Where people have looked at actual biology, work tends to focus on one or another parameter, but not cumulative biological risk profiles (14,17,18). One exception is recent work examining histories of socioeconomic status (SES) from childhood and beyond and its relationship to allostatic load (AL) in midlife (7). However, this work focuses exclusively on socioeconomic ELA, and less is known about links to other aspects of ELA.

The current analyses take as their primary focus the question of whether socioeconomic and other aspects of ELA are related to adult biological health risk profiles. Our outcome uses information on a wide array of biomarkers and biological systems and examines multisystem physiological indices of biological dysregulation, often referred to as measures of AL (19). The concept of AL is a useful perspective for understanding the processes that link early life and adult health outcomes. AL is based on the notion of allostasis—that regulatory systems are constantly adjusting to the demands of everyday life. Systems that face frequent insults and more frequent adjustments may eventually lose their abilities to function effectively. AL refers to the cumulative load on the body of these constant

AL = allostatic load, **ELA** = early life adversity, **HPA** = hypothalamic-pituitary-adrenal axis, **ICAM-1** = intercellular adhesion molecule 1, **ICC** = intraclass correlation coefficient, **MIDUS** = Midlife in the US Survey, **SES** = socioeconomic status

SDC Supplemental Content

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efforts to adapt. For instance, frequent or persistent stress in early life may influence the physiological stress response and cause changes in physiology that lead to poorer health. We also consider different types of ELA and their relationship to cumulative biological risk. Distinguishing among different types of ELA allows us to better understand their respective relationships with later life outcomes and can provide potentially important information to support targeting of interventions in children (to minimize such exposures) and to identify "at risk" adults who have had such childhood exposures for subsequent efforts to mitigate the later adult health risks. Much of the research to date examining multiple types of ELA treats childhood adversity in terms of cumulative indices, which may include socioeconomic factors, family relationships, or some combination (2,7,11,14,20). This approach captures cumulative exposure to childhood stress, which has been suggested as a potential mechanism through which childhood circumstances alter physiology (4,15). Cumulative indices are often preferred as they take account of the fact that adversities frequently co-occur (2). Although less common, other work distinguishes among several different types of ELA (8,21,22), allowing for more in-depth comparison of the relative effects of different types of childhood events and their consequences for adulthood health. This line of research allows for uncovering the differential effects of several different types of adversities and consequently provides opportunities for comparing across types of ELA to determine where effects are greatest.

The effects of ELA for health may be transmitted through a variety of social, environmental, or biological pathways into adulthood (23). However, there has been little attention in the literature to whether different types of ELA respond differently to different mediators. The two most commonly explored mediators are adult SES and health behaviors. Both these factors have been linked to early life socioeconomic adversity and adult health. For instance, it is well known that individuals who grow up with socioeconomically disadvantaged parents are more likely to be socioeconomicly disadvantaged themselves (24), and adult SES is also related to health (25). In addition, individuals of low SES tend to have worse health behaviors (26,27).

Another factor that may link ELA and adult health but is not often examined is adult social relationships. The quality of adult social relationships may be a mechanism through which childhood circumstances influence adult health. Children who grow up with abusive or neglectful parents have less stable, supportive, and satisfying social relationships later in life (28–31). Growing up with divorced parents also has long-run implications for marriage outcomes and social networks (32,33). Substantial research also suggests that both positive and negative social relationships are critical for adult health (34–36). Inadequate social support networks, then, may be one factor linking early life hardship to adverse later life health. Moreover, although adult educational attainments may be expected to mediate many types of ELA, adult social relationships may be particularly salient for explaining the association between early social instability and health.

To date, formal evaluation of mediators of ELA remains sparse, and an examination of the extent to which different mechanisms mediate different types of childhood adversities is even less well studied. Work that captures different aspects of early life already shows that the extent to which adult factors mediate early life circumstances varies by the type of early life condition (8,21,22). One study, for instance, found that the link between early life socioeconomic conditions and mortality can be fully explained by adjusting for adult socioeconomic circumstances, but associations persist for family structure, even after controlling for adult socioeconomic circumstances, marital status, and health behaviors (8). Other work shows that childhood abuse has lasting effects on health even after controlling for adult education. Early financial strain and family structure, on the other hand, show fewer associations with health in similarly adjusted models (22). Although relatively sparse, available evidence suggests that the health consequences of childhood family circumstances and abuse seem to have more persistent independent effects than those of early life socioeconomic circumstances after controlling for other aspects of early and later life (21).

Current Study

We use data on a variety of measures of early life circumstances from the National Survey of Midlife Development in the United States (MIDUS) along with information on adult education, social relationships, and health behaviors and biophysical information. Analyses encompass several novel components including our use of an outcome reflecting cumulative adult biological risk profiles (rather than focusing on specific biological or disease outcomes) as well as our attention to ELAs that include both socioeconomic as well as other aspects of family adversity.

We build on prior work by explicitly addressing three central questions: a) is ELA related to adult biological risk profiles? b) how are different aspects of such ELA related to adult biological profiles? and c) If such relationships are seen, to what extent do major adult socioeconomic, social relationship, and health behaviors mediate those relationships?

DATA AND METHODS

The MIDUS study was initiated in 1995 to determine how social, psychological, and behavioral factors interrelate to influence mental and physical health. The first wave collected sociodemographic and psychosocial data on 7108 Americans aged 25 to 74 years, from a representative sample of English-speaking, noninstitutionalized adults residing in the contiguous 48 states, with oversampling of five metropolitan areas, twin pairs, and siblings. Of the original 7108 MIDUS participants, 4963 were successfully

recontacted 9 to 10 years later and completed the MIDUS II 30-minute phone interview and two self-assessment questionnaires using the original MIDUS protocols. The second wave of data also included an additional supplemental sample of 592 African Americans from Milwaukee to enhance the racial diversity of the sample.

The current study focuses on a subset of individuals from the main sample and Milwaukee supplement who participated in the biomarker substudy at the second wave. Participants were recruited for this subsample if they responded to the primary interview and lived in the Continental United States. Participation in the MIDUS II biomarker project required a 2-day commitment and included travel to one of the three clinical research centers: University of California at Los Angeles, Georgetown University, and University of Wisconsin. Individuals who participated in this subsample were remarkably similar to the full MIDUS sample in terms of their health, age, sex, race, income, and marital status. The main difference was in educational attainment, with the participants in the biomarker subsample more likely to have a college degree and less likely to have completed only high school or some college (37). Of the 1255 individuals who participated in the biomarker study, 12 individuals were excluded from this analysis because of missing information on AL, 1 was missing information on childhood adversity, 40 were missing information on demographic characteristics (mainly race), 8 had incomplete information on social relationships, and 14 had incomplete reports on health behaviors, for a total of 1180 individuals in the analytic sample. Mean AL scores were nearly identical for individuals excluded from this analysis due to missing data on childhood conditions and demographics as compared with those for individuals included in the final analytic sample.

Measures

Cumulative Biological Risk Profiles

The key outcome variable in these analyses is AL, a marker of cumulative biological risk that has been hypothesized to capture the biological pathways through which stressful experiences lead to chronic disease. This measure was constructed as a composite index combining information from a variety of biomarkers available for this subsample of MIDUS respondents. Biomarker measures reflect the functioning of seven physiological systems. C*ardiovascular functioning* included resting systolic and diastolic blood pressure and resting pulse. Measures of the *sympathetic nervous system* included overnight urinary measures of epinephrine and norepinephrine. The *parasympathetic nervous system* was indexed through several parameters of heart rate variability: low- and high-frequency spectral power, the standard deviation of R-R (heartbeat to heartbeat) intervals, and the root mean square of successive differences. Indicators of *hypothalamic-pituitary-adrenal axis* (HPA) activity included a measure of overnight urinary cortisol and a serum measure of the hormone dehydroepiandrosterone sulfate. Measures of *inflammation* included plasma C-reactive protein, fibrinogen, and serum measures of interleukin-6 and the soluble adhesion molecule-1. *Lipid metabolism* included high-density lipoproteins cholesterol, triglycerides, body mass index, and waist-hip ratio. *Glucose metabolism* was captured by levels of glycosylated hemoglobin, fasting glucose, and the homeostasis model of insulin resistance.

A multisystem AL score was calculated as the sum of the seven physiological risk systems described above (i.e., sympathetic nervous system, parasympathetic nervous system, HPA, cardiovascular, glucose metabolism, lipid, and inflammation). This measure has been validated and used in other articles using the MIDUS data (7). To capture physiological dysregulation across multiple systems, system risk indices were calculated as the proportion of individual biomarker indices within each system (ranging from 2 to 6) for which respondents fell into high-risk quartiles. The risk categories were calculated for the main sample and were applied to the data for the main sample and Milwaukee (see Ref. (7) for details regarding the construction of AL).

System risk scores range from 0 to 1, with 1 indicating that all biomarkers in a particular system are high risk. Averaging within systems allows us to create a summary index with equal weighting for the seven systems, avoiding "overweighting" systems where, for methodological reasons alone, more system parameters could be measured. Scores were only calculated if individuals had data for at least half of the biomarkers within a system. Most individuals had enough information for a score, with only 1% of respondents treated as missing. AL was calculated as the sum across these seven systems and thus ranges from 0 to 7, with higher scores indicating higher physiological dysregulation. Figure 1 shows the distribution of AL for the analytic sample. In addition, sensitivity analyses were performed using two alternate constructions of these measures. The first used

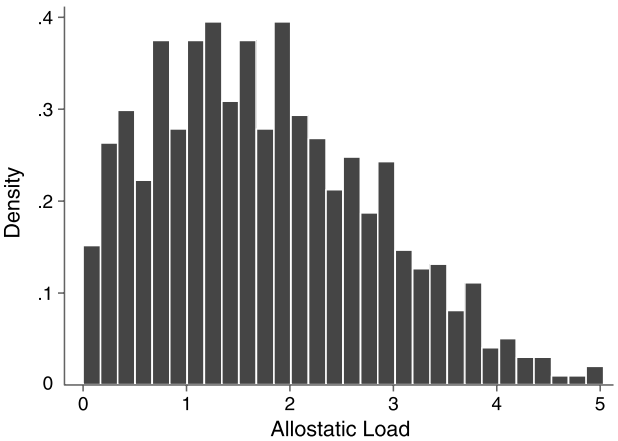

FIGURE 1. Histogram of allostatic load.

extensive medication information to reclassify individuals as at risk even if their outcomes are controlled through drugs (e.g., someone on blood pressure medications would now be classified as "high risk"). Another version included additional information on cortisol response to stress tests in a laboratory setting in the marker of HPA activity. Results were consistent with those reported here.

Early Life Adversity

Socioeconomic adversity

Early life socioeconomic adversity was measured as the sum of three variables reported by respondents in the first wave of MIDUS data (Milwaukee respondents were asked this information at enrollment at Wave 2). All items are retrospective self-reports. The first two measures capture the financial situation in childhood. The first question asks respondents: "During your childhood and adolescence (up to age 18), was there ever a period of six months or more when your family was on welfare or ADC?" A response of yes was coded 1; no was coded 0. The next measure asked respondents to rate their relative financial situation on a 4-point scale. They were asked, "When you were growing up (up to age 18), was your family better off or worse off financially than the average family was at that time?" Responses ranged from 1 (a lot better off) to 7 (a lot worse off). Responses of "somewhat worse off" and "a lot worse off" were coded 1 and 0 otherwise. The final measure captured parental education and was coded 1 if neither parent had a high school degree and 0 if at least one parent graduated from high school. In sensitivity analyses, we also consider a version of this index without relative poverty, to account for the fact that measures of absolute and relative SES have different relationships with health (38); however, results were consistent, so we present the full index here.

Other Adversities

Retrospective self-reports of three aspects of other family hardships in childhood are investigated. All items are self-reports of adverse social events that occurred before the age of 18 years, as reported in the first wave of the MIDUS study (Wave 2 for Milwaukee). Two aspects of early childhood adversity include whether a parent died before the participant reached the age of 18 and whether parents divorced before the participant reached the age of 18. In addition, items in the Conflict Tactics Inventory (39) were used to capture potential physical abuse by mothers, fathers, and other family members. Respondents were asked to rate whether this occurred on a 4-point scale ranging from "never" to "often." Consistent with other work using thresholds to delineate abuse (40), we coded individuals as 1 (indicating that they had experienced physical abuse) if they reported having *sometimes* or *often* experienced physical abuse by their mother or father. If they report never or rarely being physically abused by a parent, they are coded 0.

Total Adversity

All adversity scores were added together to capture total ELA. The possible range was from 0 to 6 adverse early life events.

Demographic Covariates

Analyses also control for race, age, and sex. Both race and sex were coded as dichotomous indicator variables, with the first indicating whether a respondent was white or nonwhite (using information from both waves of data) and the latter, whether male or female. Age in years at Wave 2 was included in these models. Nonlinearity in the age effect was tested as well, but the association between age and AL was determined to be linear.

Educational Attainment

Educational attainment was captured through three categories indicating whether the respondent completed a) high school or less schooling, b) some college, or c) a college degree or more (16+ years of education).

Social Strain and Support

We include measures of both negative and positive aspects of social relationships—strain and support. Perceived social strain and support were assessed from items in the self-administered mail questionnaires at Wave 2 asking about participants' perceptions of the frequency of various types of social relationships with spouse/partner (six items), friends (four items), and other family members (four items). Scores for social support were calculated by taking the mean of four ratings (1 [not at all] to 4 [a lot]) across items capturing support (e.g., "how much can you rely on family (or friends) for help with a serious problem?") and four ratings to assess reported levels of conflict/demands (e.g., "how often do family members (or friends) make too many demands on you?"). This measure may be interpreted as an average across domains and across family members.

Health Behaviors

Three measures of health behaviors were included in the full models as potential mediating factors, as prior work suggests that the association between ELA may partially operate through the influence of health behaviors (2,4,14). Smoking status was coded as nonsmoker, ex-smoker, or current smoker. Alcohol consumption was grouped into three categories: heavy, moderate, and light, based on NIAAA guidelines.[1] Physical activity was a weighted average of

[1]"Helping Patients Who Drink Too Much: A Clinician's Guide," National Institute on Alcohol Abuse and Alcoholism. From: http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm. Downloaded 3/01/10.

the number of hours of exercise per week weighted by the reported vigorousness of activity. That is, (1 × hours of light exercise) + (2 × hours of moderate exercise) + (3 × hours of vigorous exercise)/3.

Analyses

Linear regression models, accounting for clustering by family membership (the sample included some twin and sibling pairs), were used to assess the relationship between ELA and total AL. Models were run separately for total ELA, and then separately for the index of early life socioeconomic adversities, for parental death, parental divorce, and abuse from a parent. The baseline models control for age, race, sex, site of data collection (e.g., whether data were collected and processed in Georgetown, Madison, or Los Angeles), and for whether respondents were part of the Milwaukee subsample. Extended analyses incorporate information on adult circumstances including educational attainment, relationship quality (i.e., support/strain), and health behaviors as potential mediators. We test for mediation of the relationship between childhood adversity and adult biological risk using the KHB method developed by Karlson, Holm, and Breen (41,42). The KHB method decomposes the total effect of a variable into direct and indirect effects and is specifically used to overcome problems with mediation in analyses with binary or categorical variables. Some measures of nonlinear decomposition are problematic because the coefficients estimated in different models are not comparable with each other. The KHB method rescales the models to make them comparable. Because several of our mediators are categorical (e.g., educational attainment and smoking), we use this method to compute the indirect effects. This analysis was performed using the KHB module in Stata 12. In addition, we use bootstrapping methods to calculate 95% confidence intervals around this estimate. Bootstrapped confidence intervals around the indirect effects are the recommended method for assessing significance of the indirect effects as they are not generally normally distributed (43,44).

RESULTS

Table 1 shows the descriptive characteristics of the sample overall. The average age was 54.5 years. The sample was largely white and relatively well educated, with more than 40% having a college degree. There was substantial variance in reported adversity, although the average was about one adverse event for the full sample (of a possible six).

A quarter of the sample grew up in families where neither parent had a college degree. Nine percent of the sample was on welfare at some point in childhood, and 11% of the sample rated their families as being relatively less well off than that of their peers. Approximately 19% of respondents were sometimes or often physically abused by a parent. This is comparable to rates found in the National Child Abuse and Neglect Data System, which reports that 17.8% of children were physically abused between 2005 and 2006 (45). Fourteen percent of the overall sample experienced parental divorce, and 8% of respondents lost a parent before they reach adulthood.

TABLE 1. Descriptive Characteristics of the Sample (n = 1180)

Characteristics	Overall
Age, y	54.52 (11.65)
Race	
White	0.78
Nonwhite	0.22
Education	
HS degree or less	0.28
Some college	0.29
College degree or more	0.43
Sex	
Male	0.44
Female	0.57
Site of data collection	
West Coast	0.34
Midwest	0.44
East Coast	0.22
Smoking	
Past smoker	0.33
Currently smokes	0.15
Never smoked	0.52
Physical activity	
Weighted hours of exercise/wk	3.53 (6.01)
Drinking	
Light drinker	0.35
Moderate drinker	0.52
Heavy drinker	0.14
Adult social support (possible range, 1–4)	3.44 (0.49)
Adult social strain (possible range, 1–4)	2.02 (0.48)
Total ELA (possible range, 0–6)	1.02 (1.05)
Socioeconomic ELA (possible range, 0–3)	0.45 (0.70)
On welfare in childhood	0.09
Parents low education	0.25
Perceived low SES in childhood	0.11
Parental death before age 18	0.08
Parental divorce before age 18	0.14
Physical abuse by parents	0.19
Allostatic load, sum of dysregulation	1.77 (1.05)

HS = high school; ELA = early life adversity; SES = socioeconomic status.
Values are presented as mean (standard deviation) or proportion.

TABLE 2. Coefficients and Standard Errors of Regression Models Predicting the Association Between Total Early Life Adversity and Overall Biological Risk Score (n = 1180)

Characteristics	M1 Adversity Only	M2 + Educational Attainment	M3 + Social Relationships	M4 + Health Behaviors	M5 Full Model
Total Early Life Adversity (possible range, 0–6)	0.093** (0.027)	0.070* (0.027)	0.080** (0.028)	0.082** (0.027)	0.052† (0.027)
Education (reference: college or higher)					
HS or less		0.335** (0.073)			0.331** (0.074)
Some college		0.244** (0.070)			0.227** (0.070)
Social relationships					
Adult social support			−0.073 (0.061)		−0.033 (0.062)
Adult social strain			0.113† (0.068)		0.117† (0.067)
Health behaviors					
Smoking (reference: nonsmoker)					
Current				0.320** (0.095)	0.232* (0.097)
Past				0.063 (0.065)	0.037 (0.065)
Drinking (reference: heavy drinker)					
Light				0.283** (0.094)	0.286** (0.095)
Moderate				0.053 (0.085)	0.077 (0.086)
Hours of exercise per week				−0.019** (0.004)	−0.021** (0.004)

M1 = Model 1; M2 = Model 2; M3 =Model 3; M4 = Model 4; M5 = Model 5; HS = high school.

Results of regression models. Standard errors in parentheses. Standard errors adjusted for families with multiple respondents. All models control for age, sex, race, Milwaukee, and site of data collection.

* $p < .05$, ** $p < .01$, † $p < .10$.

Tables 2 and 3 examine the relationship between ELA and AL, first with only basic controls, then with models adjusting for adult circumstances including adult education, social relationships, and health behaviors. The key difference between the two tables is that Table 2 examines overall ELA as an index, and in Table 3, we distinguish among different types of ELA.

In Table 2, we explore the association between AL and total ELA—that is, the total combined score of the six possible adverse childhood events. Table 2 depicts five models. The first controls for only age, sex, race, whether Milwaukee sample, and site of data collection. Models 2 to 4 incorporate additional information on several of the hypothesized pathways through which ELA may be linked to AL, including adult education, social relationships, and health behaviors, respectively. The final model includes all controls.

Results of Model 1 show that total ELA is significantly and positively associated with biological risk score. Indeed, for each additional adverse childhood experience, AL increases by 0.093. Adjusting for educational attainments results in a decrease in the magnitude of the effect—to 0.070—yet the association remains statistically significant. Controls for social relationships and health behaviors also reduce the magnitude of the effect, though to a lesser extent. It is only once all three pathways are included in the model that the association between ELA and AL is reduced to marginal statistical significance.

We also ran additional models predicting dysfunction in each of the seven subscales that make up the measure of AL. These results are displayed in Table S1 (Supplemental Digital Content, http://links.lww.com/PSYMED/A185). The strongest associations were for the secondary stress systems, including inflammation, cardiovascular function, and lipid metabolism, although the other systems also show trends in the expected direction, with more adversity in childhood predicting more physiological dysregulation in each of these domains. These findings are consistent with that of other work (7,46).

Table 3 shows the results of analyses examining whether different types of ELA have different associations with biological risk in adulthood. We examine the three measures of socioeconomic adversity that comprise our index as well as

TABLE 3. Coefficients and Standard Errors of Regression Models Predicting the Association Between Socioeconomic and Sociorelational Early Life Adversity and Overall Biological Risk Score (n = 1180)

Characteristics	M1 Adversity Only	M2 + Educational Attainment	M3 + Social Relationships	M4 + Health Behaviors	M5 Full Model
Early life socioeconomic adversity (all)	0.094* (0.041)	0.058 (0.041)	0.076† (0.041)	0.082* (0.041)	0.037 (0.041)
On welfare in childhood	0.125 (0.101)	0.065 (0.101)	0.085 (0.101)	0.131 (0.102)	0.047 (0.101)
Parents low education	0.150* (0.073)	0.088 (0.072)	0.137† (0.073)	0.115 (0.071)	0.051 (0.071)
Perceived low SES in childhood	0.098 (0.089)	0.064 (0.090)	0.070 (0.089)	0.095 (0.090)	0.043 (0.091)
Parental death before age 18 y	−0.067 (0.107)	−0.087 (0.108)	−0.057 (0.108)	−0.080 (0.105)	−0.087 (0.106)
Parental divorce before age 18 y	0.084 (0.085)	0.054 (0.083)	0.069 (0.084)	0.049 (0.084)	0.019 (0.081)
Physical abuse by parents	0.263** (0.091)	0.242** (0.089)	0.227* (0.094)	0.235** (0.089)	0.198* (0.090)

M1 = Model 1; M2 = Model 2; M3 =Model 3; M4 = Model 4; M5 = Model 5; SES = socioeconomic status.

Results of seven separate regression models. Standard errors in parentheses. Standard errors adjusted for families with multiple respondents. All models control for age, sex, race, Milwaukee, and site of data collection. In addition, M2 controls for educational categories; M3 controls for adult social support and adult social strain, M4 controls for smoking, drinking, and physical activity; and M5 is the full model with all controls, including educational attainments, social relationships, and health behaviors.

* $p < .05$, ** $p < .01$, † $p < .10$.

other measures of ELA, including parental divorce, parental death, and parental physical abuse. The first model depicted in Table 3 shows the relationships between these measures of ELA and AL for a model that controls only for demographic and survey factors. These results show that for the socioeconomic components, all items—on welfare, perceived, low income, and parental low SES—have fairly large coefficients, although only parental low education is statistically significantly related to overall biological risk score. For the nonsocioeconomic measures of ELA, only physical abuse by parents is statistically significant. Because only socioeconomic ELA and physical abuse are statistically significantly related to AL, these are the focus of the remaining analyses.

We next examined the question of whether adult circumstances such as education, social relationships, and health behaviors mediate the relationship between ELA and biological risk, and whether the strength of mediation differs for different types of adversity. In Table 3, Models 2-4 control for the adult mechanisms discussed above. Model 2 shows that adult education alone completely mediates the relationship between overall socioeconomic adversity and AL to the point of nonsignificance. Model 3 indicates that adult social relationships also reduce the magnitude of the effect, although to a lesser extent than educational attainment. Model 4 includes health behaviors, which do little to explain the relationship between socioeconomic adversity and AL. The association between childhood physical abuse and AL, on the other hand, is not explained by the mechanisms examined here. In and of themselves, each pathway does little to mediate this association. Even in the fully adjusted model, the relationship between childhood physical abuse and AL remains statistically significant.

Table 4 shows the results of a formal mediation analysis using the KHB method with bootstrapped confidence intervals for the indirect effect, for early life socioeconomic adversity, and for childhood physical abuse; the two factors significantly related to AL in Table 3. Table 4 shows that educational attainment alone explains 38% of the relationship between early life socioeconomic adversity and AL. This is a statistically significant indirect effect. Social relationships explain 19% of this relationship (not statistically significant), health behaviors explain 12% (not statistically significant), and the full model of all adult mechanisms explains 61% of the relationship between socioeconomic ELA and AL (statistically significant indirect effect).

For childhood physical abuse, adult educational attainment explains much less—only 8% of this relationship—and is not a statistically significant mediator (95% confidence interval includes 0). Social relationships explain 14% of this relationship, and health behaviors explain 11% of this relationship, but the indirect effects of both of these factors are also not statistically significant. Even with all adult factors included in one model, only 25% of the relationships

TABLE 4. Test of Mediation Including Percent Variance Explained by Mediating Factors, Bootstrapped Point Estimate for Indirect Effects, and 95% Confidence Intervals for Indirect Effects (n = 1180)

Characteristics	M1 Baseline + Educational Attainment	M2 Baseline + Social Relationships	M3 Baseline + Health Behaviors	M4 Full Model
Early life socioeconomic adversity (all)				
Percent explained	38.40	18.67	12.08	60.73
Estimate of indirect effect	0.0360	0.0175	0.0113	0.0569
Bootstrapped 95% confidence intervals for indirect effect	0.0138 to 0.0582	−0.0001 to 0.0351	−0.0078 to 0.0305	0.0254 to 0.0885
Early life physical abuse				
Percent explained	8.22	13.87	10.78	24.65
Estimate of indirect effect	0.0216	0.0365	0.0284	0.0649
Bootstrapped 95% confidence intervals for indirect effect	−0.0079 to 0.0512	−0.0092 to 0.0822	−0.0111 to 0.0678	0.0097 to 0.1200

M1 = Model 1; M2 = Model 2; M3 =Model 3; M4 = Model 4.

Results of regression models. Percent explained and indirect effects of adversity on allostatic load were calculated using the -khb- module in Stata12, developed by Karlson, Holm and Breen, with bootstrapped confidence interval. Standard errors in parentheses. Standard errors adjusted for families with multiple respondents. All models control for age, sex, race, Milwaukee, and site of data collection. In addition, M1 controls for educational categories; M2 for adult social support and adult social strain, M3 for smoking, drinking, and physical activity; and M4 is the full model with all controls, including educational attainments, social relationships, and health behaviors.

between early life physical abuse and AL are explained (indirect effects are statistically significant).

DISCUSSION

Consistent with the life course theory of chronic disease (47) and other work examining ELA and biomarkers of health (7,18,48,49), our results show that early life circumstances have a lasting imprint on physiological regulation in midlife. More specifically, in our simplest model, for each adverse experience in childhood, AL in middle life increased by 0.093. To put this in perspective, someone with three adverse experiences in childhood has the biological risk profile equivalent to an individual 9 years his senior. Total ELA remains marginally related to biological risk score in midlife, even after adjusting for adult educational attainment, adult social support and strain, and health behaviors. In supplemental analyses (see Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A185), we also find stronger signals for secondary stress systems than primary ones, likely because secondary systems reflect long-term influences of exposures and primary (hormonal) ones reflect both long- and short-term influences. Thus, the childhood signal in the latter may be hidden in the "noise" from current (adult) stressors. As noted, analyses of individual subscales suggested more modest (and frequently nonsignificant) associations, whereas examination of an index reflecting the cumulative biological toll of ELA across multiple systems revealed significantly stronger effects. This highlights the potential importance of examining such multisystems indices when investigating health effects of psychosocial factors that likely affect multiple rather than individual regulatory systems.

Unlike many studies that consider the accumulation of different adversities (2,7,11,14,20), our study examined differences in the associations of *different types* of ELA with AL and found that parental education and physical abuse by parents were statistically significant. We also found evidence of variation in terms of the extent to which different adult factors explain away the relationship between ELA and adult biological risk score. For instance, we find that childhood socioeconomic adversity is completely mediated by adult education. The detrimental effect of physical abuse in early life, on the other hand, is more persistent even after controlling for multiple adult circumstances. This is consistent with a long line of work showing the inexorable consequences of abuse across multiple biological domains even after controlling for adult circumstances (4,6,22). In the mediation analyses, we further show that adult education explains nearly 40% of the association between early life socioeconomic adversity and AL, but only 8% of the association between childhood physical abuse and AL. This suggests that a primary way of overcoming childhood socioeconomic adversity may be by achieving higher levels of education in adulthood. In contrast, educational attainment does not seem to ameliorate the consequences of childhood abuse to the same extent. In addition, although no mediator investigated here explains a large portion of the association between physical abuse and AL, adult

social relationships explain more of this relationship than does educational attainments (14% as compared with 8%, respectively).

Although we find that educational attainment can compensate for early life socioeconomic adversity, it must be noted that it is not so easy for everyone to obtain these higher levels of schooling. Individuals who experience ELA may not be as well positioned to obtain higher levels of schooling as those who do not experience ELA. In this sample, for instance, 54% of individuals without ELA complete college as compared with only 23% of those with three or more adverse experiences. Having supportive social relationships and engaging in a healthy lifestyle are also more common among individuals who do not experience hardship in early life.

The key limitation of this work is its reliance on retrospective reports of early life and self-reports, which may be subject to recall bias. However, a review paper examining the validity of retrospective recall of abuse, neglect, and family discord suggests that retrospective reports should lead to downwardly biased estimates, making it harder to achieve significant results (50). In addition, in results not shown here, we find high concordance in reports of early life characteristics among twin and sibling pairs in this data set, which provides further confirmation that reports for most of these measures are probably accurate or at the very least perceived similarly by multiple family members.

In sum, we expand upon previous work by examining the impact of ELA on cumulative adult biological risk profiles—a known predictor of increased risks for major adult health outcomes such as cognitive and physical impairment, CVD, and mortality (51). We also parse out specific aspects of ELA (e.g., parental abuse, parental death, parental divorce, and socioeconomic factors) to see how these compare in their associations with health and to uncover how adult circumstances mediate these different aspects of childhood adversity. Our work suggests that it is important to distinguish among different types of ELA so as to understand how different early experiences alter trajectories of health, and to determine how to best ameliorate the effects of early life inequality. More work is needed to examine adverse events over the entire life course, and particularly at key developmental life stages, to assess more fully how hardships in early life relate to health over the long run. Better understanding of these risk processes is essential to any effective efforts to reduce or prevent the negative adult health consequences of ELA.

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REFERENCES

1. Danesh J. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998;279:1477–82.
2. Dong M, Anda RF, Felitti VJ, Dube SR, Williamson DF, Thompson TJ, Loo CM, Giles WH. The interrelatedness of multiple forms of childhood abuse, neglect, and household dysfunction. Child Abuse Negl 2004;28:771–84.
3. Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, Chapman DP, Anda RF. Coronary heart disease—insights into causal pathways for ischemic heart disease: Adverse Childhood Experiences study. Circulation 2004;1101761:245–66.
4. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences (ACE) study. Am J Prev Med 1998;14:245–58.
5. Fuller-Thomson E, Brennenstuhl S. Making a link between childhood physical abuse and cancer. Cancer 2009;115: 3341–50.
6. Fuller-Thomson E, Brennenstuhl S, Frank J. The association between childhood physical abuse and heart disease in adulthood: findings from a representative community sample. Child Abuse Negl 2010;34:689–98.
7. Gruenewald TL, Karlamangla AS, Hu P, Stein-Merkin S, Crandall C, Koretz B, Seeman TE. History of socioeconomic disadvantage and allostatic load in later life. Soc Sci Med 2012;74:75–83.
8. Hayward M, Gorman B. The long arm of childhood: the influence of early-life social conditions on men's mortality. Demography 2004;41:87–107.
9. Montez JK, Hayward MD. Early life conditions and later life mortality. In: Rogers RG, Crimmins EM, editors. International Handbook of Adult Mortality. the Netherlands: Springer; 2011:187–206.
10. O'Rand AM, Hamil-Luker J. Processes of cumulative adversity: childhood disadvantage and increased risk of heart attack across the life course. J Gerontol B Psychol Sci Soc Sci 2005; 60B:117–24.
11. Schafer MH, Ferraro KF. Childhood misfortune as a threat to successful aging: avoiding disease. Gerontologist 2012;52: 111–20.
12. Shonkoff JP, Boyce WT, McEwen BC. Neuroscience, molecular biology, and the childhood roots of health disparities: Building a new framework for health promotion and disease prevention. JAMA 2009;301:2252–9.
13. Slopen N, Kubzansky LD, McLaughlin KA, Koenen KC. Childhood adversity and inflammatory processes in youth: a prospective study. Psychoneuroendocrinology 2013;38: 188–200

14. Slopen N, Lewis TT, Gruenewald TL, Mujahid MS, Ryff CD, Albert MA, Williams DR. Early life adversity and inflammation in African Americans and whites in the Midlife in the United States Survey. Psychosom Med 2010;72:694–701.
15. Taylor SE, Way BM, Seeman TE. Early adversity and adult health outcomes. Dev Psychopathol 2011;23:939–54.
16. White HR, Widom CS. Does childhood victimization increase the risk of early death? A 25-year prospective study. Child Abuse Negl 2003;27:841–53.
17. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol Behav 2012;106:29–39.
18. Taylor SE, Karlamangla AS, Friedman EM, Seeman TE. Early environment affects neuroendocrine regulation in adulthood. Soc Cogn Affect Neurosci 2011;6:244–51.
19. McEwen BS, Stellar E. Stress and the individual: mechanisms leading to disease. Arch Intern Med 1993;153:2093–101.
20. Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, Chapman DP, Anda RF. Insights into causal pathways for ischemic heart disease adverse childhood experiences study. Circulation 2004;110:1761–6.
21. Lundberg O. The impact of childhood living conditions on illness and mortality in adulthood. Soc Sci Med 1993;36: 1047–52.
22. Schafer MH, Ferraro KF. Childhood misfortune and adult health enduring and cascadic effects on somatic and psychological symptoms? J Aging Health 2013;25:3–28.
23. Cohen S, Janicki-Deverts D, Chen E, Matthews KA. Childhood socioeconomic status and adult health. Ann N Y Acad Sci 2010;1186:37–55.
24. Blanden J, Haveman R, Smeeding T, Wilson K. Intergenerational mobility in the United States and Great Britain: a comparative study of parent-child pathways. Rev Income Wealth 2014;60:425–49.
25. Braveman P, Egerter S, Williams DR. The social determinants of health: coming of age. Ann Rev Public Health 2011;32: 381–98.
26. Hiscock R, Bauld L, Amos A, Fidler JA, Munafo M. Socioeconomic status and smoking: a review. Ann N Y Acad Sci 2012;1248:107–23.
27. Shankar A, McMunn A, Steptoe A. Health-related behaviors in older adults: relationships with socioeconomic status. Am J Prev Med 2010;38:39–46.
28. Friesen MD, Woodward LJ, Horwood LJ, Fergusson DM. Childhood exposure to sexual abuse and partnership outcomes at age 30. Psychol Med 2010;40:679–88.
29. Hornor G. Child sexual abuse: consequences and implications. J Pediatr Health Care 2010;24:358–64.
30. Repetti RL, Taylor SE, Seeman TE. Risky families: family social environments and the mental and physical health of offspring. Psychol Bull 2002;128:330–66.
31. Savla JT, Roberto KA, Jaramillo-Sierra AL, Gambrel LE, Karimi H, Butner LM. Childhood abuse affects emotional closeness with family in mid- and later life. Child Abuse Negl 2013;37:288–99.
32. Amato PR, Booth A. Consequences of parental divorce and marital unhappiness for adult well-being. Soc Forces 1991; 69:895–914.
33. White HR, Widom CS. Intimate partner violence among abused and neglected children in young adulthood: the mediating effects of early aggression, antisocial personality, hostility and alcohol problems. Aggressive Behav 2003;29: 332–45.
34. Berkman LF, Glass T, Brissette I, Seeman TE. From social integration to health: Durkheim in the new millennium. Soc Sci Med 2000;51:843–57.
35. Berkman LF, Syme SL. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda county residents. Am J Epidemiol 1979;109:186–204.
36. House JS, Umberson D, Landis KR. Structures and processes of social support. Annu Rev Sociol 1988;14:293–318.
37. Dienberg Love G, Seeman TE, Weinstein M, Ryff CD. Bioindicators in the MIDUS National Study: protocol, measures, sample, and comparative context. J Aging Health 2010; 22:1059–80.
38. McLaughlin KA, Costello EJ, Leblanc W, Sampson NA, Kessler RC. Socioeconomic status and adolescent mental disorders. Am J Public Health 2012;102:1742–50.
39. Straus MA. Measuring intrafamily conflict and violence: the Conflict Tactics (CT) scales. J Marriage Fam 1979;41:75–88.
40. Dube S, Anda RF, Felitti VJ, Chapman DP, Williamson DF, Giles WH. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences study. JAMA 2001;286:3089–96.
41. Karlson KB, Holm A. Decomposing primary and secondary effects: a new decomposition method. Res Soc Strat Mobil 2011;29:221–37.
42. Kohler U, Karlson KB, Holm A. Comparing coefficients of nested nonlinear probability models. Stata J 2006;11:420–38.
43. MacKinnon DP, Fritz MS, Williams J, Lockwood CM. Distribution of the product confidence limits for the indirect effect: program PRODCLIN. Behav Res Methods 2007;39:384–9.
44. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 2008;40:879–91.
45. US Department of Health and Human Services AfCaF, Administration on Children, Youth and Families, Children's Bureau Child Maltreatment 2010. Available at: http://archive.acf.hhs.gov/programs/cb/pubs/cm10/cm10.pdf.
46. Crandall CJ, Merkin SS, Seeman TE, Greendale GA, Binkley N, Karlamangla AS. Socioeconomic status over the lifecourse and adult bone mineral density: the Midlife in the U.S. Study. Bone 2012;51:107–13.
47. Lynch J, Smith GD. A life course approach to chronic disease epidemiology. Annu Rev Public Health 2005;26:35.
48. Blair C, Raver CC, Granger D, Mills-Koonce R, Hibel L. Allostasis and allostatic load in the context of poverty in early childhood. Dev Psychopathol 2011;23:845–57.
49. Slopen N, Koenen KC, Kubzansky LD. Childhood adversity and immune and inflammatory biomarkers associated with cardiovascular risk in youth: a systematic review. Brain Behav Immun 2012;26:239–50.
50. Hardt J, Rutter M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. J Child Psychol Psychiatry 2004;45:260–73.
51. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci 2001;98: 4770–5.