Adverse childhood experiences and physiological wear-and-tear in midlife: Findings from the 1958 British birth cohort

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Edited by Bruce S. McEwen, The Rockefeller University, New York, NY, and approved December 30, 2014 (received for review September 8, 2014)

Allostatic load (AL) is a measure of overall physiological wear-and-tear over the life course, which could partially be the consequence of early life exposures. AL could allow a better understanding of the potential biological pathways playing a role in the construction of the social gradient in adult health. To explore the biological embedding hypothesis, we examined whether adverse childhood experiences (ACEs) are associated with elevated AL in midlife. We used imputed data on 3,782 women and 3,753 men of the National Child Development Study in Britain followed up seven times. ACEs were measured using prospective data collected at ages 7, 11, and 16. AL was operationalized using data from the biomedical survey collected at age 44 on 14 parameters representing four biological systems. We examined the role of adult health behaviors, body mass index (BMI), and socioeconomic status as potential mediators using a path analysis. ACEs were associated with higher AL for both men and women after adjustment for early life factors and childhood pathologies. The path analysis showed that the association between ACEs and AL was largely explained by early adult factors at age 23 and 33. For men, the total mediated effect was 59% (for two or more ACEs) via health behaviors, education level, and wealth. For women, the mediated effect represented 76% (for two or more ACEs) via smoking, BMI, education level, and wealth. Our results indicate that early psychosocial stress has an indirect lasting impact on physiological wear-and-tear via health behaviors, BMI, and socioeconomic factors in adulthood.

allostatic load | adverse childhood experiences | biological embedding | health behaviors | cohort study

Health disparities are observed for a wide range of health indicators from risk factors, incidence of chronic diseases, and mortality across the world (1). According to Hertzman, the socioeconomic gradient in health "is capable of replicating itself on new disease processes as they emerge in society" (2). Recently, epidemiological studies have shown that classic determinants are not sufficient for explaining the social gradient in health (3). This may point toward the existence of other mechanisms influencing health, like a potential biological pathway. The notion of allostatic load (AL) may be useful to explore how experiences over the life course may "get under the skin" and become biologically embedded (2, 4, 5).

In the last two decades, epidemiological research has used the concept of AL to explain how chronic stress can lead to physiological dysregulation and disease (6–12). AL is a measure of overall physiological wear-and-tear over the life course, which could be the consequence of early life exposures (13, 14). According to AL theory, cumulative and repeated activation of compensatory physiological mechanism in response to chronic stress can lead to a multisystem predisease state represented by a dysregulation of neuroendocrine, metabolic, inflammatory, or cardiovascular parameters (15, 16). Empirical evidence shows that AL has strong correlations to subclinical conditions, morbidity, and mortality (12, 17), and may be a useful measure of overall health, rather than considering each biomarker separately (6, 18).

Several studies have suggested that exposure to chronic stress during sensitive periods of development may alter the balance and responsiveness of physiological systems and have long-term effects on health (2, 13, 14, 19–21). Early life exposure to adverse childhood experiences (ACEs), like trauma, abuse, or maltreatment has been linked to alterations in brain structure and neurobiological stress–response systems, which have consequences for health and emotional well-being (22, 23). Exposure to ACE could influence health through a broad range of behavioral and socioeconomic mechanisms. For instance, the ACE study explored the relationship between ACE and health behaviors, linking childhood trauma to long-term effects on health via health risk behaviors such as alcohol consumption, smoking, and sexual behaviors, among others. Felitti et al. (24) also suggested that ACE could be a common pathway to social, emotional, and cognitive impairments that may lead to increased risky behaviors. It has been established that the adoption of health behaviors may also be explained by wide and complex psychological processes such as self-regulation, self-efficacy, and self-management mechanisms (25, 26). Furthermore, socioeconomic and material conditions in childhood ap-

Significance

The role of early life experiences on health is of major concern to research. Recent studies have shown that chronic stress may "get under the skin" to alter human developmental processes and impact later health. Our findings suggest that early negative circumstances during childhood, collected prospectively in a British birth cohort, could be associated with physiological wear-and-tear in midlife as measured by allostatic load. This relationship was largely explained by health behaviors, body mass index, and socioeconomic status in adulthood, but not entirely. These results suggest that a biological link between adverse childhood exposures and adult health may be plausible. Our findings contribute to the development of more adapted public health interventions, both at a societal and individual level.

Author contributions: C.B.S., M.K.-I., and C.D. designed research; C.B.S., M.K.-I., R.F., and C.D. performed research; C.B.S., M.K.-I., R.F., M.D., J.T., T.L., and C.D. contributed new reagents/analytic tools; C.B.S., M.K.-I., and R.F. analyzed data; and C.B.S., M.K.-I., and C.D. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1417325112/-/DCSupplemental.

pear to be linked to later brain development and cognition (27). Lately, epidemiological studies have shown that ACEs were associated with mortality and health even after adjusting for socioeconomic and behavioral factors, suggesting that a direct biological effect occurring from early life is plausible (28, 29). It has been suggested that psychosocial factors could protect and buffer early adverse circumstances, such as parental warmth and psychological resources, reducing physiological responses and mitigating disease processes (30, 31). However, only a few studies have analyzed the influence of ACE on health over the life course by examining these different pathways, and fewer have used an AL index.

The main hypothesis tested in this study is that chronic stress resulting from ACE may be biologically embedded (2, 19) and lead to a cumulative multisystem dysregulation via three broad and intertwined pathways across the life course: (*i*) an indirect health behaviors pathway, (*ii*) an indirect socioeconomic/materialist and/or psychosocial pathway, (*iii*) through a direct biological pathway via alterations of physiological stress systems (e.g., hypothalamic-pituitary-adrenal axis) that could influence health in the long term. The aim of this paper is to explore whether ACEs are associated with elevated AL in midlife. We will examine whether cumulative socioeconomic conditions and/or health behaviors mediate such a relationship, and if the relationships still persists after adjusting for these mediating factors.

Materials and Methods

Participants. Data are from the 1958 National Child Development Study (NCDS), which included all births during 1 wk in 1958 (n = 18,558) in Great Britain. Data collection was carried out on cohort members between birth and 50 y. At age 44–45 y, a biomedical survey was conducted including a self-reported questionnaire, physical measurements, blood and saliva samples for a target sample of 12,070 individuals of the original cohort, and data were available for 9,377. The NCDS has been described in detail elsewhere (32).

Ethics and Data. Written informed consent was obtained from parents for childhood measurements and ethical approval for the adult data collection was obtained from the National Research Ethics Advisory Panel. NCDS data are open-access datasets available to nonprofit research organizations. Ethical approval for the age 45 y survey was given by the South East Multicentre Research Ethics Committee.

Measures.

ACEs. ACEs were identified as a set of traumatic and stressful psychosocial conditions that are out of the child's control, that tend to co-occur (33), and that often persist over time (24, 34). ACEs were defined as intrafamilial events or conditions causing chronic stress responses in the child's immediate environment. These include notions of maltreatment and deviation from societal norms, where possible to be distinguished from conditions in the socioeconomic and material environment. Because the NCDS has a large amount of prospective data, we restricted ACE to intrafamilial events or conditions in the child's immediate environment.

Information was extracted via variables collected at ages 7, 11, and 16 from questions asked to the child's parent or their teacher. Sources of adversity were divided into six categories as follows: (*i*) Child in care: child has ever been in public/voluntary care services or foster care at age 7, 11, or 16. (*ii*) Physical neglect: child appears undernourished/dirty at age 7 or 11, information collected from the response from child's teacher to the Bristol Social Adjustment Guide. Household dysfunction, as described by Felitti et al. (24), is a dimension of adversity consisting of four categories each contributing to the score: (*iii*) offenders: the child lived in a household where a family member was in prison or on probation (11 y) or is in contact with probation service at 7 or 11 y; the child has ever been to prison or been on probation at 16 y. (*iv*) Parental separation: the child has been separated from their father or mother due to death, divorce, or separation at 7, 11, or 16 y. (*v*) Mental illness: household has contact with mental health services at 7 or 11 y; family member has mental illness at 7, 11, or 16 y. (*vi*) Alcohol abuse: family member has alcohol abuse problem at 7 y.

Exposure to adversity was identified by a positive response to any of the above categories. Respondents were excluded if they had missing data for all six categories. Respondents were considered as having no adversities if they answered "no" to all of the categories or if they answered "no" to one or more category and the other categories were missing. ACEs were measured by counting the reports of the following: child in care, physical neglect, offenders, parental separation, mental illness, and alcohol abuse. A three-category variable was then constructed (0 adversities, one adversity, two or more adversities).

AL at 44 y. AL is a measure of cumulative physiological wear-and-tear. Among available biomarkers, we selected 14 parameters representing four physiological systems: the neuroendocrine system [salivary cortisol t1 (nanomoles per liter), salivary cortisol t1–t2 (nanomoles per liter)]; the immune and inflammatory system [insulin-like growth factor-1 (IGF1) (nanomoles per liter), C-reactive protein (CRP) (milligrams per liter), fibrinogen (grams per liter), IgE (kilounits per liter)]; the metabolic system [high-density lipoprotein (HDL) (in millimoles per liter), low-density lipoprotein (LDL) (millimoles per liter), triglycerides (millimoles per liter), glycosylated hemoglobin (HbA_{1C}) (millimoles per mole)]; the cardiovascular and respiratory systems: [systolic blood pressure (SBP) (millimeters of mercury), diastolic blood pressure (DBP) (millimeters of mercury), heart rate/pulse pulses per minute), peak expiratory flow (liters per minute)] (detailed information regarding the function and measure of each biomarker is provided in Table S1; descriptive information and high-risk cut points are provided in Table S2). These biomarkers were chosen based on previous measures of AL (11, 12) and according to the evidence of their relationship to stressful conditions over life and later morbidity and mortality (35–38). Each biomarker was then dichotomized into high risk versus low risk according to sex-specific quartiles. The high-risk quartile was the top quartile of all biomarkers, except for those for which a low level confers greater risk for poor health outcomes (HDL, salivary cortisol t1–t2, IGF1, peak expiratory flow). AL score was calculated by summing the 14 dichotomized markers. We excluded from our sample 1,264 individuals (pregnant women and those for whom blood was not obtained). A total of 3,155 individuals had at least one missing data for the 14 biomarkers and, on average, 2.6. We chose to adopt a conservative approach (maximum bias), systematically considering them as not at risk for the missing biomarker.

Early life socioeconomic and biological confounders. We selected variables from a questionnaire completed at birth by the cohort member's mother that were likely to be social or biological confounders based on the literature: household and parental characteristics [mother's education level (left school at 15 y or later/before 14 y), mother's partner's (or father's if unavailable) social class (nonmanual/manual), overcrowded household (people per room >1.5 or ≤1.5)], maternal smoking during pregnancy (no smoking, sometimes, moderately, heavily), mother's body mass index (BMI) (self-reported prepregnancy weight and height measured after the birth): normal/underweight/overweight/obese (18.5–24.9, <18.5, 25–29.9, and ≥30 kg/m^2, respectively). Respondent's characteristics and birth variables were also included: sex, birth weight (categorized in quartiles). We used the perinatal variables as proxies to better capture elements in the early environment potentially related to socioeconomic and psychosocial stressful conditions. These variables (mother's BMI, maternal smoking during pregnancy, mother's age at birth and birth weight) may partly account for the association between ACE and AL acting as confounders. A binary childhood pathologies variable was constructed using data collected at ages 7, 11, and 16 y. It was based both on mother's report and medical examinations including congenital conditions, moderate/severe disabilities, chronic respiratory or circulatory conditions, sensory impairments, and special schooling.

Mediators across the life course. The following adult mediating factors were added to the models: socioeconomic status [respondent's educational attainment at 23 y (A level/O level/no qualification) and respondent's occupational social class at 33 y (nonmanual/manual active)]; socioeconomic status at 33 y was described using a wealth variable constructed based on information about home ownership and the price of the house adjusted for economic inflation of the year of purchase and then divided in quartiles (not owner/Q1—owner lowest price/owner-Q2/owner-Q3/owner-Q4); and marital status at 33 y (couple/single/divorced or widowed); health behaviors at 23 y were considered as a proxy for behavioral patterns in early adulthood (physical activity [physically active/moderately active/inactive], alcohol consumption [moderate (women: between 1 and 14 units in the previous week; men: between 1 and 21 units in the previous week)/abstainers (reported not consuming any alcohol in the previous week)/heavy drinkers (women: >14 units in the previous week; men: >21 units in the previous week)] (39), and smoking status [nonsmoker/former smoker/smoker (<10 cigarettes/smoker; 10–19 cigarettes/smoker; >20 cigarettes)]; BMI [normal/underweight/overweight/obese]); a "malaise inventory" that identifies symptoms of depression and/or anxiety. The individual was considered as having a psychological malaise if

Table 1. Descriptive statistics on the subsample for men and women

Variables	Men, 3,753 (%)	Women, 3,782 (%)
AL		
0	283 (7.54%)	313 (8.28%)
1	589 (15.69%)	670 (17.72%)
2	797 (21.24%)	734 (19.41%)
3	715 (19.05%)	620 (16.39%)
4	554 (14.76%)	538 (14.23%)
5	360 (9.59%)	371 (9.81%)
6	240 (6.40%)	245 (6.48%)
7	135 (3.60%)	140 (3.70%)
8	58 (1.55%)	93 (2.46%)
9	18 (0.48%)	44 (1.16%)
10	4 (0.11%)	7 (0.19%)
11	0 (0.00%)	5 (0.13%)
12	0 (0.00%)	2 (0.05%)
ACEs		
None	2,721 (72.50%)	2,775 (73.37%)
One	786 (20.94%)	764 (20.20%)
Two or more	246 (6.56%)	243 (6.43%)
Mother's education level		
Left school at 15 or later	963 (25.66%)	971 (25.67%)
Left school before 14	2,643 (70.42%)	2,648 (70.02%)
Missing	147 (3.92%)	163 (4.31%)
Father's social class at birth		
Nonmanual	1,063 (28.32%)	1,037 (27.42%)
Manual	2,534 (67.52%)	2,568 (67.90%)
Missing	156 (4.16%)	177 (4.68%)
Overcrowding		
>1.5 people per room	385 (10.26%)	448 (11.85%)
≤1.5 people per room	3,146 (83.83%)	3,103 (82.05%)
Missing	222 (5.92%)	231 (6.11%)
Mother's BMI		
Normal	2,514 (66.99%)	2,472 (65.36%)
Underweight	128 (3.41%)	170 (4.50%)
Overweight	652 (17.37%)	665 (17.58%)
Obese	144 (3.84%)	140 (3.70%)
Missing	315 (8.39%)	335 (8.86%)
Mother smoked during pregnancy		
No	2,448 (65.23%)	2,426 (64.15%)
Sometimes	222 (5.92%)	207 (5.47%)
Moderately	514 (13.70%)	550 (14.54%)
Heavily	405 (10.79%)	413 (10.92%)
Missing	164 (4.37%)	186 (4.92%)
Birth weight		
Q1: low weight	730 (19.45%)	714 (18.88%)
Q2	1,022 (27.23%)	904 (23.90%)
Q3	825 (21.98%)	962 (25.44%)
Q4: high weight	939 (25.02%)	956 (25.28%)
Missing	237 (6.32%)	246 (6.50%)
Childhood pathologies		
No	2,749 (73.25%)	2,883 (76.23%)
Yes	994 (26.49%)	887 (23.45%)
Missing	10 (0.27%)	12 (0.32%)
Smoking status at 23		
Nonsmoker	929 (24.75%)	1,100 (29.09%)
Former smoker	1,045 (27.84%)	939 (24.83%)
Smoker: less than 10 cigarettes	221 (5.89%)	336 (8.88%)
Smoker: 10–19 cigarettes	437 (11.64%)	493 (13.04%)
Smoker: more than 20 cigarettes	576 (15.35%)	467 (12.35%)
Missing	545 (14.52%)	447 (11.82%)
Alcohol consumption at 23		
Moderate	1,553 (41.38%)	1,756 (46.43%)
Abstainers	397 (10.58%)	1,158 (30.62%)
Heavy drinkers	1,256 (33.47%)	420 (11.11%)
Missing	547 (14.58%)	448 (11.85%)
Physical activity at 23		
Physically active	1,389 (37.01%)	797 (21.07%)
Moderately active	587 (15.64%)	474 (12.53%)
Inactive	1,228 (32.72%)	2,064 (54.57%)
Missing	549 (14.63%)	447 (11.82%)
Malaise inventory at 23		
No	3,093 (82.41%)	3,003 (79.40%)
Yes	110 (2.93%)	329 (8.70%)
Missing	550 (14.66%)	450 (11.90%)
Education level at 23		
Passed A levels	788 (21.00%)	762 (20.15%)
Passed O levels	1,239 (33.01%)	1,496 (39.56%)
No qualifications	1,179 (31.42%)	1,075 (28.42%)
Missing	547 (14.58%)	449 (11.87%)
BMI at 23		
Normal	2,522 (67.20%)	2,673 (70.68%)
Underweight	73 (1.95%)	207 (5.47%)
Overweight	502 (13.38%)	334 (8.83%)
Obese	60 (1.60%)	83 (2.20%)
Missing	596 (15.88%)	485 (12.82%)
Social class at 33		
Nonmanual	1,649 (43.94%)	2,249 (59.47%)
Manual	1,464 (39.01%)	950 (25.12%)
Missing	640 (17.05%)	583 (15.42%)
Wealth at 33		
Not owner	732 (19.50%)	777 (20.55%)
Owner: Q1 (low price)	637 (16.97%)	637 (16.84%)
Owner: Q2	610 (16.25%)	663 (17.53%)
Owner: Q3	633 (16.87%)	632 (16.71%)
Owner: Q4	595 (15.85%)	645 (17.05%)
Missing	546 (14.55%)	428 (11.32%)
Marital status at 33		
Couple	2,622 (69.86%)	2,811 (74.33%)
Single	453 (12.07%)	312 (8.25%)
Divorced or widowed	174 (4.64%)	289 (7.64%)
Missing	504 (13.43%)	370 (9.78%)

s/he reported experiencing more than 7 out of 24 symptoms (no malaise/malaise) (40–42).

Data analysis. To control for possible bias due to missing data, we imputed data for covariates with missing data using the multiple imputation program ICE in STATA V11. Twenty imputations were conducted taking the missing-at-random (MAR) assumption. Each covariable with missing values was imputed including all confounders and mediators used in the models as well as variables from other sweeps correlated with the variable to impute (*SI Materials and Methods*), but excluding the exposure variable (ACE) and AL. The sample used for this study is described in Fig. S1.

Descriptive statistics (Table 1) were carried out on nonimputed data. Bivariate (Table S3) and multivariate analyses (Tables 2 and 3) were carried out on the imputed data using linear regression. We performed a multivariate linear analysis that took a life course perspective, whereby variables were added to the model in chronological order. Then, to explore the relationships between ACE and AL, we conducted a path analysis using ACE as the exposure variable (Figs. S2 and S3).

We conducted two different sensitivity analyses (*SI Materials and Methods*). The first one was a series of regression analyses of individual biomarkers for studying the AL score stability by identifying if within our score a parameter was having a stronger effect relatively to the others (Table S4). The second sensitivity analysis was to ensure that our results using a

complete case AL score were not biased by missing values; we thus imputed the missing biomarkers from other measured biomarkers (Table S5).

Recent studies have shown that potential sex/sex differences may exist when analyzing the life course processes of disease development (43–45). When studying the lasting impact of stress-related diseases, the perception, interpretation, and physiological responses to chronic stress could have a differential impact on men and women (for further details, see *SI Materials and Methods*). Therefore, the multivariate linear analysis was run separately by sex. The variables were entered chronologically as they would occur over the life span. First, early life socioeconomic circumstances and perinatal variables were entered. In model 2, we controlled for childhood pathologies and ACE. Model 3 additionally controlled for education, psychological malaise, and health behaviors at 23 y. Finally, model 4 took into account the material and socioeconomic circumstances at 33 y: wealth, social class, and marital status.

Subsequently, we used path modeling to examine all indirect associations between ACE and AL in adulthood. Path analysis allows us to disentangle and describe indirect effect pathways (46) (Figs. S2 and S3). The direct pathway between ACE and AL was calculated using a classic multivariate linear regression after adjustment for confounders and mediation variables. The indirect pathways correspond to the part of the effect observed between ACE and AL score that is explained by the mediating factors. All analyses were performed using STATA V11 taking a statistical significance level of 0.05.

Results

Descriptive statistics of the nonimputed sample are presented in Table 1 for the subsample (n = 3,753 for men; n = 3,782 for women). In *Materials and Methods*, we report the bivariate statistics (Table S3) for both men and women.

The multivariate analyses for men (Table 2) showed that mother's education, parental social class, and childhood pathologies were associated with an increased AL score (model 1). Mother's BMI and smoking heavily during pregnancy were positively associated with AL score. Birth weight was inversely associated to AL: individuals in the highest quartile had a lower AL score compared with those into the lower quartile. With the inclusion of childhood pathologies and ACE (model 2), the socioeconomic variables at birth continued to be predictors of higher AL score, although these relationships were slightly attenuated. Compared with men with no ACE, those classified as having one ACE had an increased AL score (0.18; $P = 0.02$); the increase was greater among men exposed to two or more ACEs (0.46; $P < 0.01$). The effect of ACE on AL score was strongly mediated by health behaviors at 23 y, because the relationship between ACE and AL was no longer significant (model 3). The full model (model 4) shows that the socioeconomic variables at 33 y were important mediators of the relationship between ACE and AL. Parental social class (manual), mother's BMI, birth weight, childhood pathologies, smoking heavily, and being overweight or obese at 23 y were associated with higher AL score even though the strength of these associations dropped slightly. Wealth was significantly related to a lower AL score ($\beta = -0.43$, $P < 0.01$ for the highest quartile) and being single increased AL score by 0.22 ($P = 0.02$). The path analysis, highlighting the direct and indirect effects between ACE and AL, for men showed that the association between ACE and AL was strongly mediated by health behaviors at 23 y and socioeconomic status at 33 y. Among men, 59% (for two or more ACEs) of the total mediated effect was mediated by health behaviors (especially smoking), education level at 23 y and wealth at 33 y.

The multivariate analyses for women are shown in Table 3. Model 1 shows that mother's education, parental social class, and mother's BMI (overweight) were positively and significantly associated with a higher AL score. Birth weight was inversely correlated with AL score. Children of mothers who smoked lightly during pregnancy had a higher AL score. The same patterns were observed for the variables at birth even if the strength of these associations were weakened (model 2). Compared with women with no ACE, those with one ACE had an increased AL score (0.24; $P < 0.01$), as did those with two or more ACEs (0.42; $P < 0.01$). The effect of ACE on AL score was strongly mediated by health behaviors at 23 y, with the association between ACE and AL disappearing (model 3) when these were entered into the model. Being a smoker, overweight, or obese at 23 y and having no qualification were associated with higher AL score. Being a heavy drinker was inversely associated to AL score. In the full model (model 4), early life socioeconomic circumstances remained associated with AL score after controlling for mediators. Being a smoker, overweight, or obese at 23 y and being a home owner at 33 y was significantly and positively associated to AL score at 44 y. Finally the path analysis showed that the link between ACE and AL was strongly mediated by health behaviors and BMI at 23 y as well as socioeconomic characteristics at 33 y. ACE was associated with a higher AL score in midlife mainly via smoking, wealth, BMI, and education level (76% of the mediated effect for two or more ACEs).

Table S4 shows the sensitivity analyses results on individual biomarkers. No significant variances between different AL scores constructed were observed confirming the stability of the 14 AL score. Table S5 reports the results of the second sensitivity analysis comparing the complete case AL score to the imputed AL score showing that missing values did not impact the stability of the AL score. We tested in our model the influence of adding other perinatal variables (mother's age at birth, parity, gestational age, and breastfed), and the results remained unchanged.

Discussion

The main finding of this study was that psychosocial adversity in childhood was related to physiological wear-and-tear at 44 y after taking birth and childhood factors into account, in a large prospective cohort. For men and women, this association was strongly mediated by health behaviors at 23 y (principally smoking) and socioeconomic status (in particular education level at 23 y and wealth at 33 y). For women, BMI at 23 y also explained part of the link between ACE and AL.

Our hypothesis was that early psychosocial adversity can be embedded and impact later health. Our findings add to the literature by testing potential mediating pathways. We have proposed that biological embedding could be the result of three different pathways: two indirect pathways through health behaviors and socioeconomic/or psychosocial factors, and a third direct biological pathway. We use the conceptual framework of AL as a measure of cumulative biological wear-and-tear to examine our hypotheses. These results are suggestive of a link between stressful conditions in early life and health in adulthood largely explained by socioeconomic or behavioral factors but not entirely.

Our results show that, after controlling for confounders and mediators, a sizable part of the initial effect remains unexplained (24–41% in the whole population according to the level of ACE). The lack of statistical significance may be due to a lack of power, because we only have 246 men and 243 women with two or more ACEs. These associations may be explained by measurement error or the omission of confounders, but it may also suggest the existence of a biological path that could have lasting effects over time (47).

Hertzman introduced the term of biological embedding as the processes whereby cumulative disadvantaged could metaphorically "get under the skin" and alter human biological and developmental processes (19). In this context, the study of the relationship between ACE and AL can contribute to a better understanding of early origins of disease and social gradient in health. Recently, Kelly-Irving et al. (28, 29) showed an association between ACE and self-reported cancer as well as mortality, after adjusting for behavioral and socioeconomic factors suggesting

Table 2. Life course multivariate linear regression using data obtained from multiple imputation: men (n = 3,753)

	Model 1		Model 2		Model 3		Model 4	
Variables	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
Mother's education level								
Left school at 15 or later	0		0		0		0	
Left school before 14	0.17 (0.08)	0.03	0.16 (0.08)	0.04	0.07 (0.08)	0.35	0.06 (0.08)	0.44
Father's social class at birth								
Nonmanual	0		0		0		0	
Manual	0.39 (0.08)	<0.01	0.37 (0.08)	<0.01	0.23 (0.08)	<0.01	0.22 (0.08)	<0.01
Overcrowding								
>1.5 people per room	0		0		0		0	
≤1.5 people per room	−0.08 (0.10)	0.46	−0.03 (0.10)	0.79	0.02 (0.10)	0.84	0.04 (0.10)	0.70
Mother's BMI								
Normal	0		0		0		0	
Underweight	0.13 (0.17)	0.46	0.10 (0.17)	0.58	0.19 (0.17)	0.26	0.21 (0.17)	0.22
Overweight	0.29 (0.08)	<0.01	0.29 (0.08)	<0.01	0.23 (0.08)	<0.01	0.22 (0.08)	<0.01
Obese	0.59 (0.16)	<0.01	0.55 (0.16)	<0.01	0.32 (0.16)	0.05	0.30 (0.16)	0.06
Mother smoked during pregnancy								
No	0		0		0		0	
Sometimes	0.29 (0.14)	0.03	0.26 (0.14)	0.05	0.16 (0.13)	0.22	0.16 (0.13)	0.24
Moderately	0.12 (0.09)	0.19	0.11 (0.09)	0.25	0.08 (0.09)	0.39	0.08 (0.09)	0.40
Heavily	0.22 (0.10)	0.03	0.20 (0.10)	0.06	0.09 (0.10)	0.38	0.09 (0.10)	0.39
Birth weight								
Q1: low weight	0		0		0		0	
Q2	−0.27 (0.09)	<0.01	−0.25 (0.09)	<0.01	−0.24 (0.09)	<0.01	−0.22 (0.09)	0.01
Q3	−0.26 (0.09)	<0.01	−0.25 (0.09)	<0.01	−0.26 (0.09)	<0.01	−0.23 (0.09)	0.01
Q4: high weight	−0.31 (0.09)	<0.01	−0.28 (0.09)	<0.01	−0.32 (0.09)	<0.01	−0.30 (0.09)	<0.01
Childhood pathologies								
No			0		0		0	
Yes			0.20 (0.07)	<0.01	0.18 (0.07)	0.01	0.15 (0.07)	0.03
ACEs								
None			0		0		0	
One			0.18 (0.08)	0.02	0.06 (0.08)	0.47	0.05 (0.08)	0.54
Two or more			0.46 (0.13)	<0.01	0.25 (0.13)	0.05	0.19 (0.13)	0.14
Smoking status at 23								
Nonsmoker					0		0	
Former smoker					−0.17 (0.09)	0.05	−0.16 (0.09)	0.06
Smoker: less than 10 cigarettes					−0.06 (0.15)	0.69	−0.07 (0.15)	0.64
Smoker: 10–19 cigarettes					0.42 (0.11)	<0.01	0.40 (0.11)	<0.01
Smoker: more than 20 cigarettes					0.79 (0.10)	<0.01	0.77 (0.10)	<0.01
Alcohol consumption at 23								
Moderate					0		0	
Abstainers					−0.04 (0.11)	0.73	−0.08 (0.11)	0.43
Heavy drinkers					0.06 (0.07)	0.39	0.04 (0.07)	0.54
Physical activity at 23								
Physically active					0		0	
Moderately active					0.09 (0.09)	0.32	0.10 (0.09)	0.28
Inactive					0.16 (0.08)	0.03	0.14 (0.08)	0.08
Malaise inventory at 23								
No					0		0	
Yes					0.06 (0.18)	0.75	0.01 (0.18)	0.95
Education level at 23								
Passed A levels					0		0	
Passed O levels					0.11 (0.09)	0.20	0.09 (0.09)	0.33
No qualifications					0.26 (0.10)	<0.01	0.20 (0.11)	0.07
BMI at 23								
Normal					0		0	
Underweight					−0.15 (0.21)	0.46	−0.24 (0.21)	0.24
Overweight					0.48 (0.09)	<0.01	0.47 (0.09)	<0.01
Obese					1.22 (0.24)	<0.01	1.16 (0.24)	<0.01
Social class at 33								
Nonmanual							0	
Manual							−0.03 (0.08)	0.71

Table 2. Cont.

Variables	Model 1		Model 2		Model 3		Model 4	
	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*
Wealth at 33								
Not owner							0	
Owner: Q1 (Low price)							−0.17 (0.10)	0.10
Owner: Q2							−0.15 (0.11)	0.15
Owner: Q3							−0.39 (0.11)	<0.01
Owner: Q4							−0.43 (0.12)	<0.01
Marital status at 33								
Couple							0	
Single							0.22 (0.10)	0.02
Divorced or widowed							0.15 (0.14)	0.28

a potential direct link. There is growing evidence the early environment could have an adverse effect on mental and physical health and ACE appeared to be associated with increased activation in the nervous, endocrine, and immune systems. To our knowledge, only one study has explored the influence of social adversity over the life span on AL independently of socioeconomic status (48). However, health behaviors were not taken into account in this study, and it remains unclear how to disentangle the potential pathways by which ACE could influence AL. The mechanisms underlying these observations remain unclear (13, 14, 49) and deserve further research.

Our findings showed a link between birth weight and AL. This result is in accordance with Barker's hypothesis, which suggests that exposure to undernutrition in utero was associated with developing coronary heart disease in adulthood (50). Subsequent work based on the developmental origins of adult disease points toward the existence of a sensitive-periods mechanism, and in this case, that low birth weight has a lasting impact on health across the life span (51).

Regarding the mediating role of health behaviors, our findings are consistent with the literature. The common social pattern in health behavior adoption potentially includes a number of processes that have been well described in the literature. The psychological processes highlighted by Bandura (25, 26) suggest that ACEs could be related to health through a number of mechanisms. These may include poor self-regulation, self-efficacy, and self-management mechanisms. Furthermore, it has been suggested that individuals exposed to adversity-induced stress could adopt coping mechanisms by obtaining a pharmacological or psychological benefit from tobacco or alcohol use (22, 24, 52). These results suggest an indirect mechanism of the embodiment of early life experiences via health behaviors and material and/or psychosocial circumstances in adulthood.

The main weakness of this study is related to attrition, missing data, and selection bias. We therefore imputed the missing data in the eligible sample taking the MAR assumption to preserve important aspects of the distribution, variability, and relationships between variables. According to this assumption, missingness depends on observed data, such as baseline characteristics and other measures occurring at different time points (53). However, the assumption of MAR is unverifiable and we cannot rule out that some data are "missing not at random" (MNAR). Multiple imputation models, such as the one used on these data, include large numbers of covariates, helping to render the MAR assumption more plausible and to limit the impact of MNAR missingness (54).

Another limitation is the measurement of AL. Although the concept of AL is consistent with our biological embedding hypothesis, our score remains limited by the pragmatism of variable availability. Our score is strongly focused on the cardiovascular system and we have a lack of "primary" biomarkers (epinephrine and norepinephrine). However, there is currently no consensus regarding the choice of relevant physiological systems, of biomarkers, their interactions (linear relationships), their importance in the chain of physiological stress responses, as well as their measurement, combinations, weighting, and the most suitable statistical analysis (6). Furthermore, as physiological responses to stress may differ according to developmental stage over time, measure of AL may differ in terms of markers and risk thresholds.

It is likely that a number of confounders and mediators have not been taken into account for this analysis. Measurement error is likely in the variable characterizing ACE. Misclassification bias is possible where parents may have responded "no" to any given question due to the sensitive nature of the data. Because of that, the ACE variable we built is also a conservative measure. Our ACE measurement is limited and it remains a proxy for severe circumstances that we hypothesized as being chronically stressful, and it takes into account only the child's condition at age 7, 11, and 16.

Despite these limitations, this study has a number of strengths. It is a longitudinal population-based study collecting data prospectively across the life span. Most studies on childhood adversities use retrospectively collected information, which is highly sensitive and potentially open to a number of different reporting biases. A strength of the childhood adversity measure operationalized here is in its prospective nature, where information collected during childhood about potentially stressful events in the child's life was used to create the variable. Another important strength is in the sample size included in the biomedical survey, and the large number of biomarkers available. Finally, the array and detail of the variables within the cohort allows us to control for a number variables of potential confounding and mediating factors.

Conclusion

These results based on a path analysis show that childhood adversity is associated with physiological wear-and-tear in midlife as measured by AL. This relationship is mediated, but not fully explained, by later life variables. The path analysis suggests that childhood adversities are associated with an increased AL score in midlife for men via health behaviors, education, and wealth, and for women via wealth, education, smoking, and BMI.

This research provides insight into the mechanisms of accumulation of health risk in adults. Groups who experienced adversities may carry the cost across their life expressed by physiological wear-and-tear in adulthood. For instance, men who experienced two or more ACEs are more likely to have a lower education level, to smoke and drink at 23 y, and to be less well-off at 33 y.

Table 3. Life course multivariate linear regression using data obtained from multiple imputation: women (n = 3,782)

	Model 1		Model 2		Model 3		Model 4	
Variables	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
Mother's education level								
Left school at 15 or later	0		0		0		0	
Left school before 14	0.45 (0.08)	<0.01	0.43 (0.08)	<0.01	0.31 (0.09)	<0.01	0.31 (0.09)	<0.01
Father's social class at birth								
Nonmanual	0		0		0		0	
Manual	0.45 (0.08)	<0.01	0.43 (0.08)	<0.01	0.25 (0.08)	<0.01	0.22 (0.08)	<0.01
Overcrowding								
>1.5 people per room	0		0		0		0	
≤1.5 people per room	−0.19 (0.11)	0.10	−0.15 (0.11)	0.17	−0.04 (0.11)	0.68	−0.03 (0.11)	0.76
Mother's BMI								
Normal	0		0		0		0	
Underweight	0.10 (0.17)	0.54	0.07 (0.17)	0.70	0.11 (0.16)	0.49	0.11 (0.16)	0.51
Overweight	0.36 (0.10)	<0.01	0.37 (0.10)	<0.01	0.24 (0.09)	0.01	0.24 (0.09)	0.01
Obese	0.18 (0.18)	0.32	0.16 (0.18)	0.39	−0.19 (0.18)	0.29	−0.21 (0.18)	0.24
Mother smoked during pregnancy								
No	0		0		0		0	
Sometimes	0.41 (0.15)	<0.01	0.36 (0.15)	0.02	0.19 (0.15)	0.21	0.15 (0.15)	0.31
Moderately	0.08 (0.10)	0.44	0.07 (0.10)	0.52	−0.02 (0.10)	0.87	−0.04 (0.10)	0.70
Heavily	0.21 (0.11)	0.07	0.18 (0.11)	0.11	0.01 (0.11)	0.94	0.01 (0.11)	0.96
Birth weight								
Q1: low weight	0		0		0		0	
Q2	−0.17 (0.10)	0.10	−0.17 (0.10)	0.10	−0.12 (0.10)	0.24	−0.12 (0.10)	0.21
Q3	−0.21 (0.10)	0.03	−0.20 (0.10)	0.04	−0.17 (0.10)	0.08	−0.15 (0.10)	0.11
Q4: high weight	−0.36 (0.10)	<0.01	−0.35 (0.10)	<0.01	−0.33 (0.10)	<0.01	−0.33 (0.10)	<0.01
Childhood pathologies								
No			0		0		0	
Yes			0.20 (0.08)	0.02	0.13 (0.08)	0.11	0.12 (0.08)	0.12
ACEs								
None			0		0		0	
One			0.24 (0.09)	<0.01	0.13 (0.08)	0.12	0.10 (0.08)	0.24
Two or more			0.42 (0.14)	<0.01	0.15 (0.14)	0.27	0.10 (0.14)	0.46
Smoking status at 23								
Nonsmoker					0		0	
Former smoker					−0.20 (0.09)	0.03	−0.19 (0.09)	0.04
Smoker: less than 10 cigarettes					−0.06 (0.12)	0.61	−0.10 (0.12)	0.43
Smoker: 10–19 cigarettes					0.41 (0.11)	<0.01	0.35 (0.11)	<0.01
Smoker: more than 20 cigarettes					0.66 (0.11)	<0.01	0.57 (0.11)	<0.01
Alcohol consumption at 23								
Moderate					0		0	
Abstainers					0.02 (0.08)	0.77	−0.02 (0.08)	0.81
Heavy drinkers					−0.36 (0.11)	<0.01	−0.35 (0.11)	<0.01
Physical activity at 23								
Physically active					0		0	
Moderately active					−0.06 (0.11)	0.61	−0.05 (0.11)	0.63
Inactive					0.16 (0.09)	0.06	0.14 (0.09)	0.12
Malaise inventory at 23								
No					0		0	
Yes					0.22 (0.12)	0.06	0.20 (0.12)	0.09
Education level at 23								
Passed A levels					0		0	
Passed O levels					0.08 (0.10)	0.41	0.06 (0.10)	0.51
No qualifications					0.26 (0.11)	0.02	0.17 (0.12)	0.15
BMI at 23								
Normal					0		0	
Underweight					−0.26 (0.14)	0.08	−0.25 (0.14)	0.08
Overweight					0.89 (0.12)	<0.01	0.85 (0.12)	<0.01
Obese					2.01 (0.23)	<0.01	1.88 (0.23)	<0.01
Social class at 33								
Nonmanual							0	
Manual							0.04 (0.09)	0.68

Table 3. Cont.

Variables	Model 1		Model 2		Model 3		Model 4	
	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*
Wealth at 33								
Not owner							0	
Owner: Q1 (low price)							−0.35 (0.11)	<0.01
Owner: Q2							−0.48 (0.11)	<0.01
Owner: Q3							−0.50 (0.12)	<0.01
Owner: Q4							−0.55 (0.12)	<0.01
Marital status at 33								
Couple							0	
Single							0.03 (0.13)	0.81
Divorced or widowed							−0.04 (0.13)	0.74

Women were more likely to have a lower education level, smoke, be overweight, and be less well-off. Nevertheless, this study remains a first approach to understand the potential biological mechanisms that associate ACE with AL. AL represents a useful conceptual tool in measuring the biological effect of biological embedding that can play a role in the production of the social gradient in health.

Childhood is recognized as a window of vulnerability, but also of opportunity. During this period of life, an early form of the socioeconomic gradient in health is set in place. Understanding the origins of health inequalities may lead us to conceptualize better adapted public policy priorities.

ACKNOWLEDGMENTS. We thank the cohort members who are part of the 1958 National Child Development Study. C.B.S. is supported and funded by the University of Costa Rica. The present work is part of the Incorporation Biologique et Inégalités Sociales de Santé project supported by funds from Agence Nationale de la Recherche (ANR-12-DSSA-0004).

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