Adverse childhood experiences and premature all-cause mortality

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Abstract  Events causing stress responses during sensitive periods of rapid neurological development in childhood may be early determinants of all-cause premature mortality. Using a British birth cohort study of individuals born in 1958, the relationship between adverse childhood experiences (ACE) and mortality ≤50 year was examined for men (n = 7,816) and women (n = 7,405) separately. ACE were measured using prospectively collected reports from parents and the school: no adversities (70 %); one adversity (22 %), two or more adversities (8 %). A Cox regression model was carried out controlling for early life variables and for characteristics at 23 years. In men the risk of death was 57 % higher among those who had experienced 2+ ACE compared to those with none (HR 1.57, 95 % CI 1.13, 2.18, p = 0.007). In women, a graded relationship was observed between ACE and mortality, the risk increasing as ACE accumulated. Women with one ACE had a 66 % increased risk of death (HR 1.66, 95 % CI 1.19, 2.33, p = 0.003) and those with ≥2 ACE had an 80 % increased risk (HR 1.80, 95 % CI 1.10, 2.95, p = 0.020) versus those with no ACE. Given the small impact of adult life style factors on the association between ACE and premature mortality, biological embedding during sensitive periods in early development is a plausible explanatory mechanism.

Keywords  Premature mortality · Cohort study · Stress responses · Metabolic · Social environment · Health behaviour

Introduction

Early life exposure to adverse childhood experiences (ACE), like trauma, abuse or maltreatment in childhood has been linked to alteration of the brain structure and the neurobiological stress-response systems which have consequences for health and emotional well-being [1]. The hypothesis being tested in this paper is based on an ecobiodevelopmental approach postulating that early adverse events causing toxic stress responses [2], occurring during
sensitive periods of rapid neurological and cognitive development in childhood, may be early determinants of all-cause premature mortality. Three overarching and intertwining pathways across the lifecourse may lead towards premature mortality: (a) a health behaviours pathway, whereby individuals adopt stress-reducing behaviours, (b) a direct physiological pathway, via alterations to neuroendocrine, inflammatory, immune and epigenetic mechanisms, (c) and a socioeconomic/materialist pathway, via toxic environmental exposures—or an intertwining of the three.

The burden of mortality is unequally spread across social groups [3, 4]. Disadvantage in early life has been considered an important determinant of mortality for many years, but the variables used to characterize childhood circumstances were often non-specific and the mechanisms involved remain to be clarified. Galobardes et al. [5] have shown that the mechanisms of sensitive periods and accumulation, as underlined in the life course epidemiology framework [6], are likely to link early life conditions to adult mortality [5, 7]. Premature death, conceptualised as avoidable mortality [8], is characterized both by chronic diseases [9] and by external and often violent causes, including accidents, self-harm or alcohol-related deaths often implicating psychological distress.

Stressful events are likely to be experienced differently depending on an individual’s position on the social gradient. Individuals lower on the social gradient may be more vulnerable to the physiological or behavioural effects of stressful environmental exposures with fewer resources and coping strategies at their disposal compared to individuals with a higher social position [10]. Intra-familial conditions or events occurring from conception into adolescence may program physiological responses during sensitive periods of development, altering an individual’s biology, rendering them poorly adapted to their environment and subsequent exposures later in life [11, 12].

The objective of this study is to examine the relationship between adversity in childhood and adult premature mortality whilst also considering the effects of material disadvantage, health status, health behaviours and education level using a large prospective cohort study.

Methods

Data are from the 1958 National Child Development Study (NCDS) which included all live births during 1 week in 1958 (n = 18,555) in Great Britain. Subsequent data collections (sweeps) were carried out on cohort members aged 7, 11, 16, 23, 33, 42, 46 and 50. At the last sweep, carried out in 2008, 9,790 individuals participated in the self-reported questionnaire and face to face interview, representing 53 % of the original sample. The NCDS has been described in detail elsewhere [13]. Follow-up has been good over time, 84 % participated at the age of 16, with a gradual dwindling in participation throughout adulthood (72 % at age 23, and 65 % at age 42) when participants were most likely to have moved [13]. Refusal rates have been low, with 7 % at age 23 and 13 % at age 42 for example [13].

Adverse childhood experiences (ACE)

In this study we have identified ACE as a set of traumatic and stressful psychosocial conditions that are out of the child’s control, that tend to co-occur [14] and often persist over time [15, 16]. Our definition of ACE is: *intra-familial 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.* The NCDS has an immense wealth of prospectively collected data. ACE have already been extracted from these datasets and used to examine their impact on psychopathology [15, 17]. There are many ways in which the adversity can be conceptualised, including financial difficulties, family dissention, and child physical or sexual abuse. Here, we have attempted to construct a theoretical framework to define ACE prior to extracting any data. Our definition has been influenced by previous epidemiological studies of ACE, notably the San Diego study [18] the Australian study [14], other more general studies related to adversity [19, 20] as well as discussions on ACE by a WHO expert committee [21] in 2009.

Information was extracted on events and conditions that corresponded with the above definition and previous literature from the NCDS datasets. Data were collected in childhood at 7, 11 and 16 years of age from questions posed to the child’s parent or their teacher. Sources of adversity were divided into six categories:

1. Child in care: child has ever been in public/voluntary care services or foster care at age 7, 11 or 16.
2. Physical neglect: child appears undernourished/dirty aged 7 or 11, information collected from the response from child’s teacher to the Bristol Social Adjustment Guide.
3. Household dysfunction, as described by Felitti et al. [16], is a dimension of adversity consisting of four categories each contributing to the score:
   1. Offenders: The child lived in a household where a family member (person living in the same household as the child) was in prison or on probation (age 11 years) or is in contact with probation service at 7 or
11 years; the child has ever been to prison or been on probation at 16 years.
4. Parental separation: The child has been separated from their father or mother due to death, divorce, or separation at 7, 11, or 16 years.
5. Mental illness: Household has contact with mental health services at 7 or 11 years; Family member has mental illness at 7 and 11 or 16 years.
6. Alcohol abuse: Family member has alcohol abuse problem at 7 years.

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 the categories or if they answered ‘no’ to one or more category and the other categories were missing. The main reason for this was to maximise the power of the study by including individuals if they provided any information on adversity variables. Using this construction the variable is a conservative one, whereby the ‘no’ category may consist of some misclassified individuals with adversities. ACE was measured by counting the reports of: child in care, physical neglect, offenders, parental separation, mental illness and alcohol abuse. A three category variable was then constructed (no adversities/one adversity/two or more adversities).

Prior confounders

To examine the relationship between ACE and premature death, prior confounding variables potentially associated with both ACE and mortality were adjusted for in the multivariate models. Among the variables available at baseline, collected from the cohort member’s mothers via a questionnaire at birth, we identified those most likely to be social or biological confounding factors. Household and parental characteristics were included: mother’s age at birth, overcrowding (people-per-room), mother’s partner’s social class (manual/non-manual), and if this was unavailable the mother’s father’s social class was used, mother’s education level (left school before/after minimum leaving age), and maternal smoking during pregnancy (no smoking/sometimes/often/heavy). The respondent’s characteristics and birth variables were also included: sex (male/female), gestational age (calculated as the duration between the first day of the mother’s last menstrual period and childbirth/using the first day of the last menstrual period, and categorized into the following groups: \( \leq 38 \) weeks, \( 39–41 \) weeks, \( >41 \) weeks), parity (mother’s number of previous pregnancies, including miscarriages after 28 weeks), birthweight measured at birth (transformed from pounds and ounces into kilograms), and breastfeeding reported by mother (no/1 month or less/more than 1 month). To control for health problems in childhood, a child pathologies variable was constructed using data collected at 7, 11 and 16 years of age. It took into account both mother’s report and medical examinations including congenital conditions, moderate/severe disabilities, chronic respiratory or circulatory conditions, sensory impairments and special schooling (childhood pathology: yes/no).

Mediators across the lifecourse

In order to determine whether any observed associations between adversity and mortality were due to subsequent adult mediating factors, these were added to the model: respondent’s educational attainment at 23 years (high-school diploma/middle-school diploma/no qualification), respondent’s occupational social class at 23 years (non-manual active/manual active/inactive). The ‘malaise inventory’ was used to identify symptoms of depression at the age of 23. It was based on a set of 24 questions identifying symptoms, if the respondent reported experiencing more than 7 of the symptoms they were considered as having psychological malaise (no malaise/malaise), characterized by symptoms of depression and/or anxiety. The health behaviour variables included were: alcohol consumption at 23 years (normal drinking (women: between 1 and 14 units in the previous week, men: between 1 and 21 units in the previous week)/abstinence (reported not consuming any alcohol in the previous week)/heavy drinking (women: >14 units in the previous week, men: >21 units in the previous week [22]); smoking status at 23 years (never smoked/past smoker/current smoker), and BMI (kg/m\(^2\)) as a continuous variable based on height and weight measurements at 23 years [4]. Adult life-style variables are available at other points along the lifecourse, however in our model, these adult variables at the age of 23 are a proxy for behavioural patterns in early adulthood and controlling for them serves as a first step to understanding possible mechanisms.

All-cause premature mortality

Deaths were ascertained systematically through receipt of death certificates to the Centre for Longitudinal Studies from the National Health Service Central Register. The mortality data currently available to researchers provided information on date-of-death up to December 2008. Since information on death was obtained from the register, even when individuals were lost to follow-up in the cohort, information on their death will have been received. The baseline sample includes participants who were alive from 16 years (1974).
Subsamples, missing data and imputation

For the purposes of these analyses individuals who died during or before information on the exposure of interest was collected, or those with missing data on all ACE (15% of n = 18,555) categories were excluded. When compared to the rest of the sample (n = 15,221) using the variables collected at baseline, individuals in each group did not differ in terms of mother’s education, mother’s partner’s occupation, or breastfeeding. Respondents who were excluded from the analyses (see additional table a) were more likely to be men (53.4% vs 51.4%, p = 0.033), to come from overcrowded households (15.9% vs 14.2%, p = 0.018), more likely to be first born or from single child families (39.6% vs 36.2%, p = 0.003), their mothers were more likely to have been smokers in pregnancy (66.5% vs 65.5%, p = 0.012). Their birthweight was 240 g lighter on average (p < 0.0001), and their gestational age 6.3 days earlier on average (p < 0.0001).

To control for possible bias due to missing data, we imputed data for covariates with missing data using the multiple imputation by chained equations method (using ICE in STATA v11). Twenty imputations were conducted taking the missing at random (MAR) assumption for the covariates: mother’s education, father’s social class, overcrowding, birthweight, gestational age, parity, smoking during pregnancy, mother’s age at birth, breastfeeding, child pathologies, educational attainment at 23, social class at 23, malaise inventory at 23, drinking at age 23 and smoking at age 23. Neither the exposure variable of interest (ACE) nor the outcome were included in the multivariate imputation model. Comparisons were made between complete-case analyses and those run on estimates obtained by imputation. The models yielded the same results until the inclusion of variables at age 23 (model 4). The differences observed in the results for model 4 indicate selection bias in the complete case sample, where individuals who had experienced ACE in childhood were more likely to have missing data at age 23. The multiple imputation model therefore enables adjustment for this bias.

Statistical analyses

Cox regression was used to estimate hazard ratios (HR) for the associations between ACE and mortality controlling for early life potential confounders (socioeconomic, birth and pregnancy characteristics) and adult life potential mediating factors. Participants were censored at the date of death. The proportional hazard assumptions associated with Cox regression were tested separately for each gender on the full model for each imputation and found not to be violated at p = 0.05. All analyses were performed using STATA V11. Four models were run separately by gender, entering the variables in chronological order as they would have occurred over the lifecourse. First the association between early life socioeconomic circumstances and mortality risk was tested. Variables related to perinatal conditions were entered along with childhood pathologies in model 2. In model 3 ACE was added. Finally, model 4 additionally controlled for education, social class, psychological malaise and health behaviours at 23 years.

Results

Given the differences between men and women in premature mortality [8], and the possible sex-specific differences regarding stress [23], the analyses were run separately on 7,816 men and 7,405 women, their overall characteristics are described in Table 1. Among men, 4.1% of the cohort had died between the age of 16 and 50, versus 2.4% for women. In Table 2 the distribution of all cause premature mortality by age group is shown. Over half the observed deaths occurred after the age of 40 for both men and women.

Descriptive and multivariate analyses are shown using the imputed data (Tables 3, 4, 5). In both men and women, a graded increase in the proportion of respondents reporting ACE is observed among the deceased, the gradient being steeper in men (Table 3). Figures 1 and 2 shows the proportion surviving by ACE group, outlining the significant decrease in survival between individuals with no ACE, one ACE or 2 or more ACE (log rank p < 0.0001).

In terms of the early life social environment, father’s social class, overcrowding in the household and parity were all associated with mortality among men, whereas mother’s educational level was related to mortality for women, though not significant at the 5% level. For both men and women the probability of premature death was higher for those who had had childhood pathologies. In men, education level at 23 years (no qualifications), social class at 23 years (being inactive), as well as smoking were related to increased premature mortality. In women, psychological malaise at 23 years was associated with increased premature mortality, and there was a borderline association with women’s education level (no qualifications).

Table 4 shows Cox regression models for men. Early life socioeconomic circumstances were associated with an increased premature mortality risk among men. Those who had lived in an overcrowded household had an increased premature all cause mortality risk of 45% (HR 1.45, 95% CI 1.1–1.9, p = 0.01) versus those from less overcrowded households. When pregnancy, perinatal and childhood variables were added (model 2), this association decreased to a 30% risk, and was no longer statistically significant. Furthermore, men whose mothers had ≥3 children in 1958,
Table 1  Frequencies and percentages for men and women in the National Child Development Study born in 1958

| Variables                                      | Categories                       | Male (7,816) | Female (7,405) |   |
|------------------------------------------------|----------------------------------|--------------|----------------|---|
| Mother’s education level % (n)                 | Left school at 15 or later        | 22.9 (1,788) | 23.9 (1,768)  | 0.165 |
|                                                | Left school before 14             | 72.4 (5,656) | 71.6 (5,301)  |   |
|                                                | Missing                          | 4.8 (372)    | 4.5 (336)     |   |
| Father’s social class at birth % (n)           | Non-manual                       | 25.3 (1,979) | 25.8 (1,907)  | 0.652 |
|                                                | Manual                           | 69.1 (5,403) | 69.1 (5,119)  |   |
|                                                | Missing                          | 5.6 (434)    | 5.1 (379)     |   |
| Overcrowding % (n)                             | <1.5 people per room              | 80.3 (6,275) | 80.0 (5,925)  | 0.314 |
|                                                | ≥1.5 people per room              | 13.0 (1,012) | 13.5 (1,003)  |   |
|                                                | Missing                          | 6.8 (529)    | 6.4 (477)     |   |
| Parity % (n)                                   | Primiparous                      | 34.4 (2,689) | 35.0 (2,594)  | 0.237 |
|                                                | 2 children                       | 30.4 (2,375) | 29.2 (2,162)  |   |
|                                                | 3 or more                        | 31.0 (2,426) | 31.8 (2,353)  |   |
|                                                | Missing                          | 4.2 (326)    | 4.0 (296)     |   |
| Mother smoked during pregnancy % (n)           | No                               | 63.0 (4,926) | 63.1 (4,673)  | 0.422 |
|                                                | Sometimes                        | 5.7 (449)    | 5.3 (391)     |   |
|                                                | Moderately                       | 14.4 (1,125) | 15.1 (1,117)  |   |
|                                                | Heavily                          | 11.6 (903)   | 11.4 (843)    |   |
|                                                | Missing                          | 5.3 (413)    | 5.2 (381)     |   |
| Breastfed % (n)                                | Yes, for more than 1 month       | 39.3 (3,074) | 40.3 (2,986)  | 0.304 |
|                                                | Yes, for up to one month         | 22.5 (1,761) | 23.1 (1,708)  |   |
|                                                | No                               | 29.6 (2,312) | 28.7 (2,122)  |   |
|                                                | Missing                          | 8.6 (669)    | 8.0 (589)     |   |
| Childhood illness % (n)                        | No                               | 58.4 (4,563) | 62.3 (4,613)  | <0.001 |
|                                                | Yes                              | 24.5 (1,911) | 19.7 (1,455)  |   |
|                                                | Missing                          | 17.2 (1,342) | 18.1 (1,337)  |   |
| ACE % (n)                                      | 0                                | 68.5 (5,357) | 71.9 (5,321)  | <0.001 |
|                                                | 1                                | 22.2 (1,735) | 21.1 (1,561)  |   |
|                                                | ≥2                               | 9.3 (724)    | 7.1 (523)     |   |
| Child in care % (n)                            | No                               | 52.6 (4,115) | 54.0 (4,000)  | 0.033 |
|                                                | Yes                              | 4.9 (386)    | 4.3 (317)     |   |
|                                                | Missing                          | 42.4 (3,315) | 41.7 (3,088)  |   |
| Family member on probation or prison % (n)     | No                               | 62.0 (4,849) | 65.1 (4,817)  | <0.001 |
|                                                | Yes                              | 11.9 (930)   | 7.7 (570)     |   |
|                                                | Missing                          | 26.1 (2,037) | 27.3 (2,018)  |   |
| Separation from parent(s) % (n)                | No                               | 59.9 (4,682) | 59.6 (4,411)  | 0.445 |
|                                                | Yes                              | 13.3 (1,041) | 13.8 (1,018)  |   |
|                                                | Missing                          | 26.8 (2,093) | 26.7 (1,976)  |   |
| Family member with mental health Problem % (n) | No                               | 74.8 (5,843) | 75.8 (5,612)  | 0.996 |
|                                                | Yes                              | 5.5 (426)    | 5.5 (409)     |   |
|                                                | Missing                          | 19.8 (1,547) | 18.7 (1,384)  |   |
| Family member has substance abuse Problem % (n)| No                               | 84.0 (6,563) | 85.8 (6,350)  | 0.718 |
|                                                | Yes                              | 0.8 (64)     | 0.9 (66)      |   |
|                                                | Missing                          | 15.2 (1,189) | 13.4 (989)    |   |
| Child appears physically neglected % (n)       | No                               | 82.5 (6,446) | 85.3 (6,318)  | <0.001 |
|                                                | Yes                              | 7.8 (613)    | 5.5 (405)     |   |
|                                                | Missing                          | 9.7 (757)    | 9.2 (682)     |   |
| Education level at 23 % (n)                    | Passed A levels                  | 15.9 (1,243) | 16.8 (1,245)  | <0.001 |
|                                                | Passed O levels                  | 26.8 (2,093) | 33.9 (2,510)  |   |
had a 54% (HR 1.54, 95% CI 1.1–2.1, \( p = 0.01 \)) increased risk of premature mortality versus those whose mother were primiparous. When ACE were added in model 3 the strength of the association between parity and early death decreased slightly (HR 1.40, 95% CI 1.0–2.0, \( p = 0.05 \)). Respondents who had experienced childhood pathologies had a 29% increased risk of premature mortality (HR 1.29, 95% CI 1.0–1.7, \( p = 0.04 \)). Men who had experienced two or more adversities in childhood had a 72% (HR 1.7, 95% CI 1.3–2.4, \( p = 0.001 \)) increased risk of all cause premature mortality versus those who had experienced no adversity in childhood. After controlling for adult mediating factors in model 4, the strength of these associations dropped slightly to a 57% increased risk (HR 1.57, 95% CI 1.1–2.2, \( p = 0.01 \)).

Table 5 shows Cox regression models for women. The results show that early life socioeconomic circumstances were not associated with premature mortality in women. In model 2 the risk of premature mortality was increased if the respondents had experienced childhood pathologies. In model 3 ACE was significantly related to premature mortality in a graded pattern. Women who had experienced one ACE had an increased premature mortality risk of 70% (HR 1.70, 95% CI 1.2–2.4, \( p = 0.002 \)), and those who had accumulated two or more ACE had an increased premature mortality risk of 85% (HR 1.85, 95% CI 1.1–3.0, \( p = 0.013 \)) versus those who had not experienced adversity. In the final model, the strength of these associations dropped slightly to 66% (HR 1.66, 95% CI 1.1–2.3, \( p = 0.003 \)) and 80% (HR 1.80, 95% CI 1.1–3.0, \( p = 0.02 \)) respectively, after controlling for adult mediating factors. Psychological malaise was also associated with a 52% increase in the risk of premature mortality (HR 1.52, 95% CI 1.0–2.3, \( p = 0.057 \)).

**Discussion**

To our knowledge, this study is the first to highlight a relationship between a prospective measure of ACE and...
premature mortality in a longitudinal study. Indeed, a previous study used retrospective measure of childhood adversities collected from adults, therefore susceptible to recall bias [24]. Among women, childhood adversity had a graded relationship with early mortality risk. Women who had experienced one adversity had a 66% increased risk, and those who had experienced two or more adversities had an 80% increased risk of premature death versus women with no childhood adversities. Among men, those who had accumulated two or more adversities in childhood had a 80% increased risk of premature death versus women.

These findings suggest that ACE should be examined as a potentially important initial exposure on a pathway towards adult ill health and early death. The association between ACE and premature mortality observed was only slightly attenuated after adjusting for socioeconomic and behavioural variables. These findings are in line with our hypothesis that exposure to toxic stress [2] in early life may lead to alterations to various biological systems and ultimately to poor health outcomes. It is not possible to pinpoint which biological alterations may have occurred, however, the association between ACE and premature mortality remained after taking mediating factors at the age of 23 into account, including social class, education level, psychological malaise, alcohol and tobacco consumption and BMI. Since childhood socioeconomic conditions are strong determinants of adult social position, this is likely to explain why the addition of adult socioeconomic variables to the model has little impact on the association observed.

As the cohort ages, and their cause-specific mortality becomes driven to a greater extent by chronic diseases, lifestyle factors and behaviours is likely to explain more of observed differences in mortality.

This study has a number of limitations. Attrition is a problem in cohort studies, increasing the potential for selection bias in the remaining sample. In this study up to 30% missing data was present among the adult variables collected at the age of 23. We dealt with this by imputing the missing data in the eligible sample, thereby adjusting the data for selection bias taking the missing at random (MAR) assumption. We consider this assumption to be reasonable because it allows missingness to depend on observed data, such as baseline characteristics and other measures occurring at different time points [25]. 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 [26]. Another limitation in this study relates to the choice of adult mediating variables at 23 years. Adult behavioural variables were collected subsequently at ages 33, 41, and 46. In order to simplify our analytic approach, we chose to use early adult variables as proxy indicators of behaviours typology, and mental health state, bearing in mind that the outcome of interest was mortality before <50 years. At present, cause-specific mortality linked with the cohort is unavailable. There is a risk of misclassification for the ACE variable. Individuals who had ‘no’ adversity for some items, and missing information for the others, were classified as having no adversities overall. Also, parents or teachers may have been reluctant, or ashamed to answer ‘yes’ to some adversities. In both cases this type of misclassification of individuals with ‘no’ adversities renders the variable conservative, meaning that findings showing a significantly increased risk for people identified with adversities are more likely to under-represent any real differences between those who experienced adversities versus those who did not.

The strengths of this study lie in its prospective design, allowing for some understanding of the causal sequencing of events. Furthermore, the ACE measure is a conservative one, meaning that observed relationships are likely to underestimate the true effect of childhood adversity. The use of multiply imputed data adjusts for biases and loss of power due to attrition in the cohort study.

We found differing associations between ACE and mortality for men and women, suggestive of gender-specific differences in possible mechanisms [27]. Our results show that, among men, socioeconomic variables such as overcrowding and parity are associated with the risk of premature death before adding ACE to the model. By adding ACE, any associations attributable to early life socioeconomic factors disappeared, suggesting that ACE may be on the explanatory pathway between early socioeconomic disadvantage and mortality, at least among men. Based on these results, adversity in childhood may explain some associations found elsewhere between childhood material and social disadvantage and early mortality. In a survival analysis of men and women combined, Kuh et al. [28] identified a strong cumulative impact (HR 4.9, 95%
| Variables                               | Categories                      | Male Alive (%) | Died before 50 (%) | p    | Female Alive (%) | Died before 50 (%) | p    |
|-----------------------------------------|---------------------------------|----------------|-------------------|------|------------------|-------------------|------|
| Sex                                     |                                 | 95.9           | 4.1               | <0.0001 | 97.6           | 2.4               |      |
| ACE                                     | 0                               | 96.4           | 3.6               |      | 98.0           | 2.0               |      |
|                                         | 1                               | 95.6           | 4.4               | 0.106 | 96.5           | 3.5               | 0.001 |
|                                         | ≥2                              | 92.5           | 7.5               | <0.0001 | 96.0           | 4.0               |      |
| Mother’s education level                | Left school at 15 or later      | 96.2           | 3.8               |      | 98.2           | 1.8               |      |
|                                         | Left school before 14           | 95.8           | 4.2               | 0.421 | 97.4           | 2.6               | 0.063 |
| Father’s social class at birth          | Non-manual                      | 96.7           | 3.4               |      | 98.0           | 2.0               |      |
|                                         | Manual                          | 95.6           | 4.4               | 0.032 | 97.4           | 2.6               | 0.163 |
| Overcrowding                            | <1.5 people per room            | 96.1           | 3.9               |      | 97.7           | 2.3               |      |
|                                         | ≥1.5 people per room            | 94.2           | 5.8               | 0.004 | 97.1           | 3.0               | 0.251 |
| Parity                                  | Primiparous                     | 96.2           | 3.8               |      | 97.5           | 2.5               |      |
|                                         | 2 children                      | 96.5           | 3.5               | 0.585 | 97.6           | 2.4               | 0.809 |
|                                         | 3 or more                       | 94.9           | 5.1               | 0.031 | 97.6           | 2.4               | 0.772 |
| Mother smoked during pregnancy          | No                              | 96.1           | 3.9               |      | 97.7           | 2.3               |      |
|                                         | Sometimes                       | 94.5           | 5.5               | 0.095 | 97.9           | 2.1               | 0.794 |
|                                         | Moderately                      | 95.9           | 4.1               | 0.744 | 97.2           | 2.8               | 0.325 |
|                                         | Heavily                         | 95.4           | 4.7               | 0.296 | 96.9           | 3.1               | 0.139 |
| Breastfed                               | Yes, for more than 1 month      | 96.3           | 3.7               |      | 97.7           | 2.3               |      |
|                                         | Yes, for up to 1 month          | 95.7           | 4.3               | 0.262 | 97.7           | 2.3               | 0.896 |
|                                         | No                              | 95.5           | 4.5               | 0.133 | 97.3           | 2.7               | 0.344 |
| Childhood illness                       | No                              | 96.3           | 3.7               |      | 97.8           | 2.2               |      |
|                                         | Yes                             | 94.9           | 5.1               | 0.011 | 96.9           | 3.2               | 0.040 |
| Education level at 23                   | Passed A levels                 | 97.2           | 2.8               |      | 98.2           | 1.8               |      |
|                                         | Passed O levels                 | 96.2           | 3.8               | 0.139 | 97.6           | 2.4               | 0.255 |
|                                         | No qualifications               | 95.0           | 5.0               | 0.004 | 97.2           | 2.8               | 0.058 |
| Social class at 23                      | Non-manual active               | 96.8           | 3.2               |      | 97.7           | 2.3               |      |
|                                         | Manual active                   | 95.9           | 4.1               | 0.135 | 96.7           | 3.3               | 0.099 |
|                                         | Inactive                        | 94.4           | 5.6               | 0.002 | 97.7           | 2.3               | 0.993 |
| Smoking status age 23                   | Never smoked                    | 96.3           | 3.7               |      | 97.8           | 2.3               |      |
|                                         | Former smoker                   | 97.2           | 2.9               | 0.175 | 98.2           | 1.8               | 0.345 |
|                                         | Smoker                          | 94.7           | 5.3               | 0.023 | 97.0           | 3.0               | 0.151 |
| Alcohol consumption age 23              | Normal                          | 96.0           | 4.1               |      | 97.6           | 2.4               |      |
|                                         | Abstinence                      | 95.6           | 4.4               | 0.820 | 97.6           | 2.4               | 0.940 |
|                                         | Heavy                           | 95.8           | 4.2               | 0.895 | 97.5           | 2.5               | 0.933 |
### Table 4  Multivariate Cox proportional hazard regression for men [Men n = 7,816 (of whom 323 dead)]

| Variables                        | Categories                      | Male |          |          | Female |          |          |
|----------------------------------|---------------------------------|------|----------|----------|--------|----------|----------|
|                                  |                                 | Alive (%) | Died before 50 (%) | p | Alive (%) | Died before 50 (%) | p |
| Mother’s education level         | Left school at 15 or later      | 0.99 (0.74–1.31) | 0.919 | 0.605 | 0.91 (0.68–1.22) | 0.529 | 0.87 (0.64–1.17) | 0.345 |
|                                  | Left school before 14           | 0.93 (0.70–1.24) | 0.743 | 0.235 | 1.18 (0.88–1.58) | 0.280 | 1.12 (0.83–1.51) | 0.465 |
| Father’s social class at birth   | Non-manual                      | 1.29 (0.96–1.72) | 0.088 | 0.735 | 1.20 (0.89–1.60) | 0.235 | 1.18 (0.88–1.58) | 0.280 |
|                                  | Manual                          | 1.03 (0.76–1.39) | 0.867 | 0.974 | 1.01 (0.74–1.36) | 0.974 | 0.97 (0.71–1.31) | 0.837 |
| Overcrowding                     | <1.5 people per room            | 1.52 (1.10–2.10) | 0.011 | 0.045 | 1.40 (1.01–1.95) | 0.045 | 1.29 (0.92–1.82) | 0.142 |
|                                  | ≥1.5 people per room            | 1.06 (0.76–1.48) | 0.739 | 0.900 | 1.02 (0.73–1.43) | 0.900 | 0.98 (0.69–1.38) | 0.906 |
| Parity                           | Primiparous                     | 1.00 (0.99–1.01) | 0.590 | 0.622 | 1.00 (0.99–1.01) | 0.622 | 1.00 (0.99–1.01) | 0.615 |
|                                 | 2 children                      | 1.29 (0.85–1.96) | 0.238 | 0.317 | 1.24 (0.81–1.89) | 0.317 | 1.20 (0.78–1.83) | 0.400 |
|                                 | 3 or more                       | 0.96 (0.70–1.33) | 0.827 | 0.740 | 0.95 (0.69–1.31) | 0.740 | 0.93 (0.67–1.29) | 0.655 |
| Gestational age (days)           | No                              | 1.06 (0.76–1.48) | 0.739 | 0.900 | 1.02 (0.73–1.43) | 0.900 | 0.98 (0.69–1.38) | 0.906 |
|                                 | Sometimes                       | 1.29 (0.85–1.96) | 0.238 | 0.317 | 1.24 (0.81–1.89) | 0.317 | 1.20 (0.78–1.83) | 0.400 |
|                                 | Moderately                      | 0.96 (0.70–1.33) | 0.827 | 0.740 | 0.95 (0.69–1.31) | 0.740 | 0.93 (0.67–1.29) | 0.655 |
|                                 | Heavily                         | 1.06 (0.76–1.48) | 0.739 | 0.900 | 1.02 (0.73–1.43) | 0.900 | 0.98 (0.69–1.38) | 0.906 |
| Variables                  | Categories                  | Model 1         |          | Model 2         |          | Model 3         |          | Model 4         |          |
|---------------------------|-----------------------------|-----------------|----------|-----------------|----------|-----------------|----------|-----------------|----------|
|                           |                             | HR (95 % CI)    | p        | HR (95 % CI)    | p        | HR (95 % CI)    | p        | HR (95 % CI)    | p        |
| Mother’s age              |                             | 0.97 (0.95–1.0) | 0.036    | 0.98 (0.96–1.01)| 0.074    | 0.98 (0.96–1.01)| 0.182    |                 |          |
| Breastfed                 |                             | 1.12 (0.84–1.50)| 0.429    | 1.12 (0.84–1.5)| 0.436    | 1.10 (0.83–1.47)| 0.500    |                 |          |
|                           | Yes, for more than 1 month  |                 |          |                 |          |                 |          |                 |          |
|                           | Yes, for up to 1 month      |                 |          |                 |          |                 |          |                 |          |
|                           | No                          | 1.13 (0.86–1.49)| 0.392    | 1.12 (0.85–1.48)| 0.423    | 1.11 (0.84–1.46)| 0.479    |                 |          |
| Birthweight (kg)          |                             | 0.82 (0.65–1.04)| 0.108    | 0.84 (0.66–1.07)| 0.162    | 0.85 (0.67–1.09)| 0.204    |                 |          |
| Childhood illness         |                             |                 |          |                 |          |                 |          |                 |          |
|                           | No                          | 1.34 (1.04–1.71)| 0.022    | 1.29 (1.01–1.66)| 0.043    | 1.25 (0.97–1.6)| 0.086    |                 |          |
|                           | Yes                         | 1.13 (0.86–1.47)| 0.385    | 1.06 (0.81–1.39)| 0.688    |                 |          |                 |          |
|                           | ≥2                          | 1.72 (1.25–2.36)| 0.001    |                 |          |                 |          |                 |          |
| ACE                       | 0                           |                 |          |                 |          |                 |          |                 |          |
|                           | 1                           |                 |          |                 |          |                 |          |                 |          |
|                           | ≥2                          |                 |          |                 |          |                 |          |                 |          |
| Education level at 23     | Passed A levels             |                 |          |                 |          |                 |          |                 |          |
|                           | Passed O levels             |                 |          |                 |          |                 |          |                 |          |
|                           | No qualifications           |                 |          |                 |          |                 |          |                 |          |
| Social class at 23        | Non-manual active           |                 |          |                 |          |                 |          |                 |          |
|                           | Manual active               |                 |          |                 |          |                 |          |                 |          |
|                           | Inactive                    |                 |          |                 |          |                 |          |                 |          |
| Malaise inventory age 23  | None identified             |                 |          |                 |          |                 |          |                 |          |
|                           | Malaise                     |                 |          |                 |          |                 |          |                 |          |
| Smoking status age 23     | Never smoked                |                 |          |                 |          |                 |          |                 |          |
|                           | Former smoker               |                 |          |                 |          |                 |          |                 |          |
|                           | Smoker                      |                 |          |                 |          |                 |          |                 |          |
| Alcohol consumption age 23| Normal                      |                 |          |                 |          |                 |          |                 |          |
|                           | Abstinence                  |                 |          |                 |          |                 |          |                 |          |
|                           | Heavy                       |                 |          |                 |          |                 |          |                 |          |
| BMI age 23 (kg/m²)        |                             |                 |          |                 |          |                 |          |                 |          |
| % Imputed data in model   | 8                           | 39              | 39       | 38              |          |                 |          |                 |          |
| Variables                        | Categories                        | Model 1                       | Model 2                       | Model 3                       | Model 4                       |
|---------------------------------|-----------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
|                                 |                                   | HR (95% CI) p                 | HR (95% CI) p                 | HR (95% CI) p                 | HR (95% CI) p                 |
| Mother’s education level        | Left school at 15 or later         | 1.34 (0.89–2.01) 0.157        | 1.30 (0.86–1.96) 0.210        | 1.29 (0.86–1.94) 0.226        | 1.27 (0.83–1.93) 0.273        |
|                                 | Left school before 14             |                               |                               |                               |                               |
| Father’s social class at birth  | Non-manual                        | 1.15 (0.78–1.7) 0.471         | 1.11 (0.75–1.65) 0.603        | 1.07 (0.72–1.59) 0.726        | 1.05 (0.70–1.57) 0.826        |
|                                 | Manual                            |                               |                               |                               |                               |
| Overcrowding                    | <1.5 people per room              | 1.17 (0.78–1.76) 0.445        | 1.14 (0.75–1.74) 0.525        | 1.08 (0.71–1.64) 0.735        | 1.08 (0.71–1.64) 0.725        |
|                                 | ≥1.5 people per room              |                               |                               |                               |                               |
| Parity                          | Primiparous                       |                               |                               |                               |                               |
|                                 | 2 children                        | 1.01 (0.69–1.46) 0.972        | 0.99 (0.68–1.44) 0.946        | 0.96 (0.66–1.4) 0.823         |                               |
|                                 | 3 or more                         | 0.98 (0.63–1.51) 0.922        | 0.89 (0.57–1.38) 0.602        | 0.85 (0.54–1.34) 0.491        |                               |
| Gestational age (days)          | No                                | 1.00 (0.98–1.01) 0.479        | 0.99 (0.98–1.01) 0.456        | 0.99 (0.98–1.01) 0.444        |                               |
|                                 | Sometimes                         | 0.81 (0.39–1.68) 0.576        | 0.76 (0.37–1.58) 0.466        | 0.76 (0.36–1.57) 0.452        |                               |
|                                 | Moderately                        | 1.15 (0.77–1.73) 0.498        | 1.12 (0.75–1.68) 0.576        | 1.11 (0.74–1.67) 0.618        |                               |
|                                 | Heavily                           | 1.31 (0.85–2.02) 0.219        | 1.26 (0.82–1.94) 0.298        | 1.24 (0.80–1.92) 0.329        |                               |
|                                 |                                   |                               |                               |                               |                               |
| Mother’s age                    | No                                | 0.98 (0.95–1.01) 0.244        | 0.99 (0.96–1.02) 0.410        | 0.99 (0.96–1.02) 0.480        |                               |
|                                 | Sometimes                         | 0.91 (0.62–1.35) 0.635        | 0.90 (0.61–1.33) 0.597        | 0.88 (0.60–1.31) 0.535        |                               |
|                                 | Moderately                        | 1.08 (0.76–1.54) 0.655        | 1.05 (0.74–1.49) 0.786        | 1.02 (0.72–1.46) 0.899        |                               |
|                                 | Heavily                           | 0.96 (0.68–1.35) 0.814        | 0.98 (0.7–1.38) 0.908        | 0.99 (0.70–1.40) 0.955        |                               |
|                                 |                                   |                               |                               |                               |                               |
| Breastfed                       | Yes, for more than 1 month        | 1.41 (1.01–1.99) 0.052        | 1.36 (0.96–1.93) 0.082        | 1.35 (0.95–1.92) 0.092        |                               |
|                                 | Yes, for up to 1 month            | 1.70 (1.22–2.37) 0.002        | 1.66 (1.19–2.33) 0.003        |                               |                               |
|                                 | No                                | 1.85 (1.14–3.01) 0.013        | 1.80 (1.10–2.95) 0.020        |                               |                               |
| Childhood illness               | No                                |                               |                               |                               |                               |
|                                 | Yes                               | 1.41 (1.01–1.99) 0.052        | 1.36 (0.96–1.93) 0.082        | 1.35 (0.95–1.92) 0.092        |                               |
|                                 | 0                                 |                               |                               |                               |                               |
|                                 | 1                                 |                               |                               |                               |                               |
|                                 | ≥2                                |                               |                               |                               |                               |
| Education level at 23           | Passed A levels                   |                               |                               |                               |                               |
|                                 | Passed O levels                   |                               |                               |                               |                               |
|                                 | No qualifications                |                               |                               |                               |                               |
|                                 | Non-manual active                 |                               |                               |                               |                               |
|                                 | Manual active                     |                               |                               |                               |                               |
|                                 | Inactive                          |                               |                               |                               |                               |
|                                 |                                   |                               |                               |                               |                               |
| Malaise inventory age 23        | None identified                  |                               |                               |                               |                               |
|                                 | Malaise                           |                               |                               |                               |                               |
| Smoking status age 23           | Never smoked                      |                               |                               |                               |                               |
of manual social class in childhood combined with non-home ownership in adulthood on the risk of death between the ages of 26–54 in the 1946 birth cohort study. This result may also be cohort specific, highlighting differences with the older British birth cohort, who were subject to rationing and different social and health policies. Marked improvements have occurred in premature mortality rates, for both men and women since 1950 [9].

In women, our results showed that psychological malaise remained as a significant predictor of early mortality. This is in line with other studies showing associations between psychiatric symptoms [29] and psychological distress [30] and premature death. Given that the strength of the association between ACE and premature mortality change very little after including psychological malaise, it appears that separate etiological pathways may be operating. It is possible that malaise is associated with mortality via indirect behaviours not taken into account in the models.
such as, non compliance with prescribed treatments, or poorer access/use of health and social services. There may also be direct biological mechanisms such alterations of biological systems implicated in cardiovascular physiology leading to an increased risk of cardiovascular mortality among depressed individuals [31]. The mechanism linking malaise and early death may have a different etiological origin than that identified by ACE. Indeed, ACE may be associated with premature mortality via a socioeconomic/materialist pathway through occupational hazards/poor housing.

A possible interpretation of the results found here is that a mechanism akin to the concept of biological embedding [32] occurs during the sensitive periods of early brain development from the prenatal period into adolescence [33]. Exposure to prolonged activation of physiological stress responses due to events chronically unsupported by positive and secure relationships cause deleterious modifications to biological systems (neuroendocrine, inflammatory, immune) involving epigenetic modifications, that may or may not be reversible. These have a lasting impact on how well individuals adapt to subsequent exposures across their life course, leading them along a trajectory towards increased morbidity and early mortality. Such physiological alterations are also potentially early causal precursors to damaging health behaviours which are adaptive in the short term; tobacco, alcohol and food being pharmacologically stress-reducing, but damaging in the medium and long term.

Though a number of studies have shown a dose–response association between an increasing number of accumulated adversities and a higher risk of morbidity [15, 34, 35], few have studied associations with mortality [16]. In all of these studies, the main methodological flaw is that ACE was self-reported retrospectively by adults who were asked about trauma experienced in childhood. Such questions are vulnerable to recall bias, where adults in poor health are more likely to report adversity during childhood [36].

Conclusion

The findings of this study reinforce the early childhood paradigm in terms of preventive medicine across the life course [37–39]. Our results, based on prospective data, point towards early life stressful events, particularly in a child’s intrafamilial environment, being risk factors for long term health across the life course and premature mortality possibly via the mechanisms of biological embedding with may occur via social, neuro-cognitive, or behavioural pathways.

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Conflict of interest The authors declare having no conflict of interest.

References

1. Anda RF, Felitti VJ, Bremner JD, et al. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci. 2006;256(3):174–86.
2. Shonkoff JP, Garner AS, Siegel BS, et al. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. Pediatrics. 2012;129(1):e224–31. doi:10.1542/peds.2011-2662.
3. Menvielle G, Stirbu I, Roskam AJ, et al. Socioeconomic inequalities in mortality in Europe. Med Sci. 2009;25(2):192–6.
4. Gallo V, Mackenbach JP, Ezzati M, et al. Social inequalities and mortality in Europe—results from a large multi-national cohort. PLoS ONE. 2012;7(7):e39013. doi:10.1371/journal.pone.0039013.
5. Galobardes B, Lynch JW, Davey Smith G. Childhood socioeconomic circumstances and cause-specific mortality in adulthood: systematic review and interpretation. Epidemiol Rev. 2004;26:7–21. doi:10.1093/epirev/mxh008.
6. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31:285–93.
7. Galobardes B, Lynch JW, Smith GD. Is the association between childhood socioeconomic circumstances and cause-specific mortality established? Update of a systematic review. J Epidemiol Community Health. 2008;62(5):387–90. doi:10.1136/jech.2007.065508.
8. Department of Health. Living well for longer: a call to action to reduce avoidable premature mortality. London: Williams Lea; 2013.
9. Wheller L, Baker A, Griffiths C, Rooney C. Tends in avoidable mortality in England and Wales, 1993–2005. Health Stat Q. 2007;34:6–25.
10. Baum A, Garofalo JP, Yali AM. Socioeconomic status and chronic stress: does stress account for SES effects on health? Ann N Y Acad Sci. 1999;896(1):131–44. doi:10.1111/j.1749-6632.1999.tb08111.x.
11. Bailey DBJ, Bruer JT, Symons FJ, Lichtman JW, editors. Critical thinking about critical periods. Baltimore: Paul H. Brookes publishing co.; 2001.
12. Kelly-Irving M, Mabile L, Grosclaude P, Lang T, Delpierre C. The embodiment of adverse childhood experiences and cancer development: potential biological mechanisms and pathways across the life course. Int J Public Health. 2013;58(1):3–11. doi:10.1007/s00127-012-0370-0.
13. Power C, Elliott J. Cohort profile: 1958 British Birth Cohort (National Child Development Study). Int J Epidemiol. 2006;35(1):34–41.
14. Rosenman S, Rodgers B. Childhood adversity in an Australian population. Soc Psychiatry Psychiatr Epidemiol. 2004;39(9):695–702. doi:10.1007/s00127-004-0802-0.
15. Clark C, Caldwell T, Power C, Stansfeld SA. Does the influence of childhood adversity on psychopathology persist across the lifecourse? A 45-year prospective epidemiologic study. Ann Epidemiol. 2010;20(5):385–94. doi:10.1016/j.annepidem.2010.02.008.

16. Felitti VJ, Anda RF, Nordenberg D, et al. 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(4):245–58.

17. Thomas C, Hypponen E, Power C. Obesity and type 2 diabetes risk in midadult life: the role of childhood adversity. Pediatrics. 2008;121(5):E1240–9. doi:10.1542/peds.2007-2403.

18. Dong M, Anda RF, Felitti VJ, et al. The interrelatedness of multiple forms of childhood abuse, neglect, and household dysfunction. Child Abuse Negl. 2004;28(7):771–84. doi:10.1016/j.chiabu.2004.01.008.

19. Surtees PG, Wainwright NWJ. The shackles of misfortune: social adversity assessment and representation in a chronic-disease epidemiological setting. Soc Sci Med. 2007;64(1):95–111. doi:10.1016/j.socscimed.2006.08.013.

20. Benjet C, Borges G, Medina-Mora ME, Zambrano J, Cruz C, Mendez E. Descriptive epidemiology of chronic childhood adversity in Mexican adolescents. J Adolesc Health. 2009;45(5):483–9. doi:10.1016/j.jadohealth.2009.03.002.

21. Anda RF, Butchart A, Felitti VJ, Brown DW. Building a framework for global surveillance of the public health implications of adverse childhood experiences. Am J Prev Med. 2010;39(1):93–8. doi:10.1016/j.amepre.2010.03.015.

22. House of Commons Science and Technology Committee. Alcohol guidelines. London; 2012.

23. Kudielka BM, Buske-Kirschbaum A, Hellhammer DH, Kirschbaum C. HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender. Psychoneuroendocrinology. 2004;29(1):83–98. doi:10.1016/S0306-4530(02)00146-4.

24. Brown DW, Anda RF, Tiemeier H, et al. Adverse childhood experiences and the risk of premature mortality. Am J Prev Med. 2009;37(3):289–96. doi:10.1016/j.amepre.2009.06.021.

25. Little R, Rubin DB. Statistical analysis with missing data. New York: Wiley; 1987.

26. Coley N, Gardette V, Cantet C, Gillette-Guyonnet, S, Nourhashemi F, Vellas B, Andrieu S. How should we deal with missing data in clinical trials involving Alzheimer’s disease patients? Curr Alzheimer Res. 2011;8(4):421–33. doi:10.2174/156720511795745339.

27. Fuller-Thomson E, Filippelli J, Lue-Crisostomo CA. Gender-specific association between childhood adversities and smoking in adulthood: findings from a population-based study. Public Health. 2013;127(5):449–60. doi:10.1016/j.puhe.2013.01.006.

28. Kuh D, Hardy R, Langenberg C, Richards M, Wadsworth M. Mortality in adults aged 26–54 years related to socioeconomic conditions in childhood and adulthood: post was birth cohort study. Br Med J. 2002;325:1076–80.

29. Henderson M, Hotopf M, Shah I, Hayes RD, Kuh D. Psychiatric disorder in early adulthood and risk of premature mortality in the 1946 British birth cohort. BMC Psychi atr. 2011;11:37. doi:10.1186/1471-244X-11-37.

30. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity—a review of potential mechanisms. J Psychosom Res. 2002;53(4):897–902. doi:10.1016/s0227-3999(02)00311-2.

31. Brotman DJ, Golden SH, Wittstein IS. The cardiovascu lar toll of stress. Lancet. 2007;370(9592):1089–100. doi:10.1016/S0140-6736(07)61305-1.

32. Hertzman C. The biological embedding of early experience and its effects on health in adulthood. Ann N Y Acad Sci. 1999;896:85–95.

33. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009;10(6):434–45. doi:10.1038/nrn2639.

34. Danese A, Moffitt TE, Harrington H, et al. Adverse childhood experiences and adult risk factors for age-related disease depression, inflammation, and clustering of metabolic risk markers. Arch Pediatr Adolesc Med. 2009;163(12):1135–43.

35. Dube SR, Felitti VJ, Dong M, Giles WH, Anda RF. The impact of adverse childhood experiences on health problems: evidence from four birth cohorts dating back to 1900. Prev Med. 2003;37(3):268–77.

36. Hardt J, Rutter M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. J Child Psychol Psychiatry. 2004;45(2):260–73.

37. Miller GE, Chen E, Parker JK. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol Bull. 2011;137(6):959–97. doi:10.1037/a0024768.

38. Shonkoff JP, Richter L, van der Gaag J, Bhatta ZA. An integrated scientific framework for child survival and early childhood development. Pediatrics. 2012;129(2):e460–72. doi:10.1542/peds.2011-0366.

39. Taylor SE, Way BM, Seeman TE. Early adversity and adult health outcomes. Dev Psychopathol. 2011;23(3):939–54. doi:10.1017/s0954579411000411.