HHS Public Access

Author manuscript

Psychoneuroendocrinology. Author manuscript; available in PMC 2016 February 16.

Published in final edited form as:

Psychoneuroendocrinology. 2013 October ; 38(10): 2127–2139. doi:10.1016/j.psyneuen.2013.04.001.

Adult cognitive ability and socioeconomic status as mediators of the effects of childhood disadvantage on salivary cortisol in aging adults

Carol E. Franz[a,*], **Kelly Spoon**[a], **Wesley Thompson**[a], **Richard L. Hauger**[a,b], **Dirk H. Hellhammer**[c], **Kristen C. Jacobson**[d], **Sonia Lupien**[e], **Michael J. Lyons**[f], **Jeanne McCaffery**[g], **Ruth McKenzie**[g], **Sally P. Mendoza**[h], **Matthew S. Panizzon**[a], **Ana Ramundo**[a], **Afrand Shahroudi**[a], and **William S. Kremen**[a,b]

Carol E. Franz: cfranz@ucsd.edu; Kelly Spoon: Kelly@chasecam.com; Wesley Thompson: wes.stat@gmail.com; Richard L. Hauger: rhauger@ucsd.edu; Dirk H. Hellhammer: hellhamm@uni-trier.de; Kristen C. Jacobson: jacobso@bsd.uchicago.edu; Sonia Lupien: sonia.lupien@umontreal.ca; Michael J. Lyons: mlyons@bu.edu; Jeanne McCaffery: Jeanne_mccaffery@brown.edu; Ruth McKenzie: remurray@bu.edu; Sally P. Mendoza: spmendoza101@gmail.com; Matthew S. Panizzon: mspanniz@ucsd.edu; Ana Ramundo: aramundo@ucsd.edu; Afrand Shahroudi: ashahroudi@ucsd.edu; William S. Kremen: wkremen@ucsd.edu

[a]University of California San Diego, Department of Psychiatry, MC0738, La Jolla, CA 92093, USA

[b]Center of Excellence for Stress and Mental Health, VA San Diego Healthcare System, San Diego, CA 92161, USA

[c]Universitat Trier Fachbereich-I, Johanniterufer 15, 54290 Trier, Germany

[d]The University of Chicago, Department of Psychiatry & Behavioral Neuroscience, 5841 S. Maryland Ave., MC 3077, CNPRU, Room L-466D, Chicago, IL 60637, USA

[e]University of Montreal, Mental Health Research Centre Fernand Seguin, Hopital Louis-H Lafontaine, Montreal, Canada

[f]Department of Psychology, Boston University, 64 Cummington Street, Room 147, Boston, MA 02215, USA

[g]Brown University, Psychiatry and Human Behavior, Providence, RI 02912, USA

[h]University of California Davis, California National Primate Research Center, Davis, CA 95616, USA

Summary

[*]Corresponding author at: Department of Psychiatry, University of California San Diego, 9500 Gilman Drive, MC 0738, La Jolla, CA 92093, USA. Tel.: +1 858 822 1793; fax: +1 858 822 5856.

Conflict of interest statement: There are no conflicts of interest for any of the authors.

IRB approval was obtained at all sites, and all participants provided written consent.

Appendix A. Supplementary data: Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/ j.psyneuen.2013.04.001.

Portions of this manuscript were presented at the Gerontological Association of America meetings in New Orleans, Louisiana, November 20—23, 2010.

R is a free statistical package. See: Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., R Development Core Team, 2012. nlme: Linear and Nonlinear Mixed Effects Models., R package version 3, 1-103.

In this longitudinal study we investigate the influence of childhood disadvantage on midlife hypothalamic-pituitary-adrenal (HPA) axis regulation. Two mechanisms by which early life stress may affect later pathophysiology are through its influence on cognitive functioning or later socioeconomic (SES) disadvantage. We predicted that individual differences in young adult cognitive ability and midlife SES would mediate the influence of childhood disadvantage on midlife cortisol. On each of three nonconsecutive days, participants provided five salivary cortisol samples corresponding to their diurnal rhythm (N = 727 men; mean age 55, SD = 2.6). We calculated three measures of cortisol regulation (area-under-the curve cortisol reflecting total daytime cortisol output; cortisol-awakening-response; and wake-to-bed slope), averaging scores for each measure across multiple days. Childhood disadvantage combined four dichotomous indicators used previously by Rutter (1985): father low SES; mother education less than 12th grade; major family disruption/separation before age 18; and large family size (more than 5 siblings). The two mediators were a measure of general cognitive ability assessed at age 20 and highest achieved midlife SES. Men from more disadvantaged childhoods were significantly more likely to have dysregulated cortisol at midlife, with higher daytime cortisol levels decades after their childhood experience. Effects of childhood disadvantage were both direct and indirect. Cognitive ability and adult SES, however, only partially mediated the associations between early life stress and midlife cortisol. Specific indirect effects accounted for 33.8% of the total effect of childhood disadvantage [β = 0.12 (0.05; 0.18)] on total daytime cortisol. Associations remained significant after accounting for ethnicity, smoking status, and self-reported depressive symptoms.

Keywords

Childhood disadvantage; Socioeconomic status; Cortisol; HPA axis; AUC cortisol; Cognitive ability; VETSA; Longitudinal; Midlife; Stress

1. Introduction

A number of studies find that children from disadvantaged backgrounds are more likely to exhibit immediate and long-term dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis—the primary neuroendocrine system initiating the stress response. Forms of childhood disadvantage that disrupt the HPA axis include sociodemographic (parental low SES, maternal low education), environmental (housing, crowding), and psychological risks (family disruptions, seperations from parents, trauma, parental psychiatric illness) (Chen et al., 2010; Decker, 2000; Evans, 2003; Evans and Kim, 2007; Gustafsson et al., 2010a; Hunter et al., 2011; Luecken, 1998; Luecken and Appelhans, 2006; Nicolson, 2004; Pesonen et al., 2010). Furthermore, in response to subsequent stress, children subjected to trauma and other severe early life stress develop anxiety and depression, as well as persistent sensitization of corticotropin releasing factor receptor-mediated HPA responses (Hauger et al., 2006). Researchers find that accumulation of multiple childhood hardships, rather than the impact of individual risks, is particularly pathogenic (Evans, 2004; Rutter and Quinton, 1977; Rutter et al., 1976).

The long-term influence of early life exposure to stress on the HPA axis may have potential implications for healthy aging (Hunter et al., 2011; Seeman et al., 2010; Taylor et al., 2011). The HPA axis has crucial regulatory links with multiple biological systems associated with

allostatic load as well as with sleep, mood, and brain; thus functioning of the HPA axis at midlife may be part of a path ultimately linking childhood disadvantage with later pathophysiology (McEwen and Gia-naros, 2010; Miller et al., 2009). Elevated cortisol in older adults predicts poorer cognitive function as well as higher prevalence of chronic medical illnesses and psychiatric disorders (Franz et al., 2011a; Lupien et al., 2009). Previous research also shows that, in adults, childhood adversity predicts higher levels of stress, lower educational attainment, later marital and occupational difficulties, higher prevalence and incidence of diseases, premature mortality, poorer health habits, poor mental health, and higher use of health care services (Anda et al., 2010; Centers for Disease Control, 2013; Rutter et al., 1976). Given these findings, understanding links between childhood environmental influences and neuroendocrine functioning at midlife has important public health implications.

Two possible mechanisms by which childhood adversity might affect HPA axis functioning in older adults are through its influences on cognitive ability and level of adult socioeconomic success. A sizable literature shows that, within a normal range of experiences, the effects of childhood environment on cognitive development are modest; in childhood environments marked by high levels of disadvantage, however, the effects of environment on cognitive development are substantial (Kremen et al., 2005; Rowe et al., 1999; Rutter, 1985; Turkheimer et al., 2003). A number of paths by which childhood environment potentially influences cognitive ability and subsequent HPA axis functioning have been proposed. It may be that pre- and post- natal experiences in a disadvantaged family environment influence both physical and brain development; the compromised physical and brain development of the child likely affect stress responsivity, cognitive development, and neuroendocrine system functioning. Animal and human studies have shown that early stress and HPA axis dysregulation has deleterious effects on the brain and cognitive functioning (McEwen and Gianaros, 2010, 2011). Children from disadvantaged environments are more likely to develop problematic health behaviors (such as smoking, low exercise or poor diet) that affect HPA axis functioning. Lower cognitive ability is also associated with poorer educational and occupational adult outcomes that are likely to affect the HPA axis through increased stress and health risks (Franz et al., 2010a, 2011a; Hart et al., 2003; Kremen et al., 2007). Low SES adult occupations tend to be more dangerous, physically onerous, and lacking in personal control than higher SES occupations; across the life course, having lower cognitive ability may thus result in more exposure to stressors and less access to resources that enable individuals to cope with stress (Evans and Kim, 2007; Evans et al., 2008). Thus the effects of childhood disadvantage on HPA axis functioning may be indirect, through its influence on cognitive ability and/or through the effects of cognitive ability on adult SES (Bertrand et al., 2004; Hart et al., 2003; Hayward and Gorman, 2004). Alternatively the influence may be direct, and not mediated by accumulated adult disadvantages. Although there are some studies that examine associations between childhood adversity and/or adult SES in relation to adult cortisol regulation, little attention has been paid to the mediating role of cognitive ability. These associations are understudied, primarily because few longitudinal studies have data on indicators of familial disadvantage, early life cognitive ability and later life HPA axis functioning. In two separate longitudinal studies, cognitive ability in early life (childhood/late adolescence) predicted HPA axis

dysregulation in middle age (Franz et al., 2011a; Power et al., 2008); lower cognitive ability was associated with greater dysregulation.

Several studies of adults examined the influence of various indices of adult SES (e.g., education, occupation, income, social status) on HPA axis functioning. Overall there were two consistent patterns of note: (1) education, by itself, was not a strong correlate of cortisol level; and (2) in adult men, but not women, lower SES was associated with indicators of abnormal HPA regulation (e.g. elevated daytime cortisol, flat cortisol slopes). With regard to education, in four of six cross-sectional studies there was no association between participants' education and cortisol levels (Decker, 2000; Dowd and Goldman, 2006; Dowd et al., 2011; Gersten, 2008); findings were mixed in two studies (Brandtstadter et al., 1991; Fiocco et al., 2007). Education per se, however, is a poor indicator of SES or cognitive ability especially in older adults, minorities, or for women.

In contrast to results based on education, in seven out of eight studies adult men with lower adult social class (SES) or lower social power were more likely to have dysregulated cortisol (Cohen et al., 2006a, 2006b; Decker, 2000; Kumari et al., 2010; Rosmond and Bjorntorp, 2000; Steptoe et al., 2003; Wright and Steptoe, 2005). In these studies social class was operationalized using varying combinations of income, occupation, and education. Two longitudinal studies found cumulative longitudinal influences of parental SES and adult SES on adult cortisol from childhood to midlife. Forty-fiveyear-old adults who experienced socioeconomic hardship in both childhood and adulthood had higher cortisol levels than other adults (Li et al., 2007). Similarly, coming from a low SES family background or being consistently low SES at age 16 and in adulthood predicted greater cortisol dysregulation (i.e., a higher cortisol awakening response) at age 43 (Gustafsson et al., 2010b). Neither of these studies accounted for the effects of childhood SES on cognitive ability or the contribution of cognitive ability to adult social class. Lower SES was associated with more problematic health habits such as smoking or poor sleep that have been found to affect cortisol (Cohen et al., 2006a).

In sum, more longitudinal studies are needed to determine the extent to which the effects of a disadvantaged childhood persist into later adulthood; very few studies examine multiple longitudinal influences that might account for the relationship between childhood disadvantage and later life HPA axis regulation. Little is known about whether specific characteristics of the individual, such as cognitive ability and adult socio-economic achievements mediate the long-term effects of a disadvantaged childhood. We reasoned that the effect of experiencing a hardship in childhood on later life cortisol secretion may be indirect—through its influence on early adult cognitive ability and midlife adult SES. Thus, we hypothesized that participants' cognitive ability at age 20 and midlife SES would mediate the association between childhood disadvantage and midlife cortisol.

2. Methods

2.1. Study population

Participants were all part of the Vietnam Era Twin Study of Aging — a longitudinal study of cognitive aging (VETSA 2002—2008) (Kremen et al., 2006). Participants in the VETSA

study were randomly selected from the Vietnam Era Twin Registry sample of over 3322 male—male monozygotic and dizygotic twin pairs who had participated in an earlier study of psychological health (Tsuang et al., 2001). To be eligible for the VETSA, twins had to be between ages 51 and 59 when recruited and both members of a twin pair had to agree to participate. The VETSA cortisol study began two years after the start of VETSA data collection; all 795 remaining VETSA participants were automatically enrolled in the cortisol study. Of these 795 individuals, nine declined participation in the cortisol data collection, saliva samples from four were lost or spilled, five participants were missing more than one assay from a single day, and 35 participants taking corticosteroids were omitted from analyses, leaving a base sample of 742 participants (Franz et al., 2011a, 2010b). An addition 15 participants were excluded from the analyses due to missing data on covariates included in the statistical models. Thus, the final sample for analysis was 727 individuals.

Participants traveled to laboratories either at the University of California, San Diego or to Boston University for a day-long series of assessments. Institutional Review Board approval was obtained at all sites, and all participants provided signed informed consent. The health and demographic status of VETSA cortisol participants was consistent with that of men in the same age group in the United States based on Center for Disease Control statistics (Kremen et al., 2006).

2.2. Salivary cortisol measure

We obtained saliva samples on each of three non-consecutive days: two days in participants' natural environments two to three weeks prior to the day of testing, and on the in-lab day of testing (Franz et al., 2010b). On each day participants provided five passive drool saliva samples: immediately after awakening, 30 min after awakening, 1000 h (or awake plus 4 h), 1500 h (or awake plus 9 h), and bedtime; times were chosen to parallel diurnal cortisol patterns across the day. Participants were contacted in advance about their usual schedules so that reminder watches would be set to their individual daily patterns; participants received reminder calls and reminder watches as well as written instructions. Participants shipped saliva samples overnight to the University of California, Davis to be assayed.

An investigator (SPM) tested all saliva collection materials in advance to ensure that they did not influence cortisol assay results. We conducted salivary cortisol assays according to standardized procedures. Concentrations were estimated in duplicate using commercial radioimmunoassay kits (Siemens Medical Solutions Diagnostics, Los Angeles, CA). Assay procedures were modified to accommodate overall lower levels of cortisol in human saliva relative to plasma by: (1) diluting standards to concentrations ranging from 2.76 to 345 nanomols per liter (nmol/L); (2) increasing sample volume to 200 μL, and (3) extending incubation times to 3 h. The modified assay displayed a linearity of 0.98 and sensitivity (least detectable dose) of 1.3854 nmol/L. Intra- and inter-assay coefficients of variation were 3.962% and 5.662%.

Of the 13,311 possible saliva samples, 149 (1%) were missing due to technical problems. Participants with more than one assay missing from a day were omitted from analyses. If salivary cortisol concentrations at any time point exceeded 50 nmol/L the value was set to missing; in this sample, this value corresponded with cortisol concentrations three standard

deviations above the average awakening mean. We imputed scores for missing values only if the participant had no more than one missing value on a day. Cortisol values were natural log transformed prior to data analysis in order to normalize the distributions. More details about the cortisol protocol are available in previous publications (Franz et al., 2011a, 2010b).

We used cortisol area-under-the-curve (AUC) averaged across the three days as our index of total daytime cortisol secretion; previous analyses showed that AUC cortisol measures are correlated .50-.69 across days [alpha = .79 (Franz et al., 2011a)]. AUC cortisol is based on values from all five time points in a day and accounts for minor differences in the amount of time between cortisol samples by adjusting for the actual times of the samples. AUC cortisol is considered an important summary measure of the magnitude of total cortisol output across a time period, in this case, across the day from wake to bedtime (Pruessner et al., 2003). Higher levels of AUC cortisol indicate higher levels of total daytime cortisol and thus, greater exposure to the effects of cortisol.

In order to compare results with those from other studies we included two other commonly-used measures of cortisol dysregulation: the cortisol-awakening-response (CAR) and the wake-to-bed slope (Fekedulegn et al., 2007; Golden et al., 2011; Hellhammer et al., 2009; Kudielka et al., 2012). Flatter slopes across the day suggest that the individual is lacking the healthy diurnal rhythm (cortisol higher in the morning, low in the evening). CAR reflects the extent to which cortisol rises in the first half hour after awakening. In these data, the cross-day consistency for these measures is much lower than that for AUC cortisol; in each case correlations between the in-lab and at-home days were substantially lower than correlations between the two at-home assessments (approximately r = .14 versus .24 for CAR and r = .21 versus .43 for slope). Because of the low correlations between the in-lab day and the at-home days we averaged the values just for days one and two for these measures.[1] The alphas for the 2 day CAR and wake-to-bed slope (WBslope) measures were .38 and .60 respectively indicating moderate to low levels of cross-day consistency for these measures.

2.3. Childhood disadvantage index

Based on work by Rutter (Rutter and Quinton, 1977; Rutter et al., 1976), Evans and Kim (2007) and Ouellet-Morin et al. (2008), we developed a composite index of childhood disadvantage using interview and questionnaire data about family history from the VETSA participants. A measure of family adversity from the Isle of Wight study summed six dichotomous indicators: (a) overcrowding in the home or large family size, (b) marital discord resulting in separations from one or both parents, (c) father with an unskilled/semiskilled job, (d) maternal psychiatric problems and (e) paternal conviction of criminal behavior; previous research has found that risk is not linear but tends to be low under most “normal” conditions and only associated with poor outcomes at extreme levels (Rutter and

[1] *Note*: In response to a reviewer's comment we analyzed the results for cortisol awakening response (CAR) and wake-to-bed (WBslope) measures of cortisol. Because of the low alphas for these measures when computed across three days and somewhat better alphas for the two-day measures, the results reported in Table 2 reflect two day averages for those cortisol measures. Post hoc, we compared results for a two-day AUC cortisol and a three-day AUC cortisol; results were nearly identical. The only difference in β was that for one value “midlife SES adjusted for Age 20 cognitive ability” the beta was 0.007 (.002; 0.01) rather than 0.006 (0.001; 0.012). In Table 2, we report the three day cortisol as an indicator of average total daytime output.

Quinton, 1977; Rutter et al., 1976). Risk factors were defined dichotomously (0/1; absent/present) based on theoretical and statistical criteria, then summed.

Use of composite indices is common for research questions where researchers want to identify groups with high levels of concomitant risks. When risks are correlated, creating a cumulative risk index reduces the concomitant risks to a single score, which then can be compared with scores from others (Hall, 2006). Examples of such indices include a variety of familial adversity indices based on cutoffs for certain types of familial characteristics (e.g., (Centers for Disease Control, 2013; Evans and Kim, 2007; Franz et al., 1991; Ouellet-Morin et al., 2009; Rutter et al., 1976) and other commonly used measures of allostatic load, Charlson comorbidity index, or metabolic syndrome that involve identification of comorbid risks and relevant cut-offs for extreme values. Using a cumulative risk index based on multiple indicators is valuable for capturing a complex construct such as exposure to familial social and economic risks, particularly when the individual indicators are co-occurring (Evans and Kim, 2007; Rutter et al., 1976). Large-scale research on childhood adversity suggests that because risk factors tend to cluster, using single indicators of risk are problematic because they tend to overestimate the contribution of exposure to a single risk to the outcome, they miss the wider context of the risk factor, and they may underestimate the effects of a meaningful constellation of risk factors on outcomes (Anda et al., 2010; Rutter et al., 1976).

The four indicators of childhood disadvantage from VETSA participants were: (1) low SES father; (2) mother not completing high school (<12 years education); (3) family disruption (separation from either or both parents for most of childhood prior to age 18 due to factors such as parental death, incapacity, separation, or divorce); and (4) family size (Blake, 1989; Rutter et al., 1976). With the exception of paternal criminality and maternal mental disorder which were not available in the VETSA study, these four indicators are comparable to indicators used in the Isle of Wight studies (Rutter and Quinton, 1977; Rutter et al., 1976). Because we only had four of Rutter's six indicators in the VETSA data, we call our measure childhood disadvantage to distinguish it from other adversity indices.

On the day of testing, participants were queried in detail about their parents' primary occupation and formal education level. Paternal SES was calculated based on a standard Hollingshead and Redlich formula that weighted, then combined father's occupation and education; first, the occupation score is weighted ×5 and education is weighted ×3 (Hollingshead and Redlich, 1955). The Hollingshead and Redlich system defines occupational categories ranging from 0 (not working); 1,2,3,4 (menial labor; unskilled labor; semiskilled labor, skilled labor) to 9 (major professional). Levels take into account such characteristics as the training and skills necessary to perform a job, the level of autonomy and responsibility, the size of the business (“mom and pop” business versus international corporations), and managerial responsibilities. These elements are articulated in the scoring system. This way the twin and parental coding is based on comparable coding; for instance a father who was a plumber and a twin who was a plumber would receive the same occupational score. Father SES less than or equal to 32 on the weighted combined scale was considered low SES (reflecting, at maximum, a combination of less than a high school education and semi-skilled manual occupation or lower). Research on large families finds

that large families, especially in the context of other risk factors such as low parental SES is a risk factor for later poor outcomes; large family size had independent effects on educational attainment, even adjusting for other familial factors such as parental SES and education (Blake, 1989; Bradshaw et al., 2006). We defined large family size as families in the top quartile of the full sample; this corresponded with a family size greater than five children. Family size is clearly a contextual variable determined by social and cultural factors as well as fertility in a particular historic period (Blake, 1989; Galobardes et al., 2008). The four dichotomous variables were summed to create the total childhood familial disadvantage score.

2.4. Young adult cognitive ability at age 20

A general cognitive ability test was administered to the participants when they were inducted into the military at, on average, age 20: the Armed Forces Qualification Test (AFQT Form 7A). The AFQT is a 50 min paper-and-pencil test with 100 multiple-choice items. The AFQT correlates highly ($r = 0.84$) with well-established measures of general cognitive ability such as the Wechsler Adult Intelligence Scale WAIS); average AFQT scores in this sample are approximately equivalent to a score of 105 on the WAIS (Lyons et al., 2009; Orme et al., 2001). AFQT scores were acquired from military records.

2.5. Participants' midlife SES

On the day of testing, participants were queried in detail to identify their primary occupation for most of their adulthood to that point in time (midlife) and their highest achieved formal education level. Participants' midlife SES was calculated with the same formula used to compute the fathers' SES (Hollingshead and Redlich, 1955). For the adult analyses, midlife SES was used as a continuous measure.

2.6. Covariates

Ethnicity was coded as white non-Hispanic (85% of sample) versus other. Current smoking was a dichotomous variable; 25% (183/742) of the sample currently smoked. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CESD); Depressive symptoms were re-coded as a dichotomous variable. Having a CESD score greater than or equal to 16(14% of the sample) is considered a clinically meaningful risk for depression (Radloff, 1977). AUC cortisol was not associated with other covariates: cardiovascular problems ($r = .003$, ns), hypertension ($r = .04$, ns), diabetes ($r = .01$, ns), alcohol consumption ($r = -.04$, ns), or age ($r = -.04$, ns), so these covariates were not included in the models.

2.7. Statistical analyses

Linear mixed models were fit using the nlme package in R for each pathway in the multi-step mediation model (see Fig. 1) (Hayes, 2009; Preacher and Hayes, 2008). We estimated and tested the significance of the indirect effects using a non-paramentric bootstrap approach.

Confidence intervals were obtained by performing 1000 bootstrap replicates from the sample of 727 individuals. Bootstrapping samples with replacement twin pairs from the

original sample were constrained to have the same number of monozygotic and dizygotic twins as in the original sample. Resampling with replacement was repeated 1000 times to obtain path estimates for all portions of the full model. The middle 95% of estimates for direct and indirect effects from these samples were used to create 95% confidence intervals (see Table 2). Bootstrapped confidence intervals are often considered to be preferable to traditional Sobel tests because they do not make any assumptions regarding the sampling distribution of the indirect effect (Hayes, 2009; Preacher and Hayes, 2008). Interpretation of bootstrap data is accomplished by examining whether zero is contained within the 95% confidence intervals. Results are significant if zero is not included in the 95% confidence intervals.

This innovative non-parametric bootstrapping procedure was designed to estimate the sampling distribution of the indirect effect when multiple mediators are examined (Hayes, 2009; Preacher and Hayes, 2008). There are multiple benefits to using this approach: multiple mediators can be tested simultaneously, the non-parametric bootstrapping procedure makes no assumptions about the whether the indirect effects are normally distributed, and the number of statistical tests are reduced, thus minimizing the likelihood of Type 1 error. Linear mixed models were used because family-level variance within twin pairs needed to be accounted for. Although the sample is a twin sample, the present analyses were non-twin analyses in which the unit of analysis is the individual rather than the twin pair.

As depicted in Fig. 1, a multistep meditation model was conducted in order to examine the indirect effects of childhood disadvantage through young adult cognitive ability and midlife SES (Preacher and Hayes, 2008). In Fig. 1, the *a* paths reflect the effect of childhood disadvantage (the independent variable) on each mediator (M1; M2). The *b* paths reflect the effect of the mediator on midlife cortisol (the dependent variable) controlling for childhood disadvantage. The path labeled "*e*" reflects the association between age 20 cognitive ability and midlife SES. The specific indirect effects are represented by the product of $a_i \times b_i$. Thus, mediation analyses of specific indirect effects involved simultaneous calculation of the extent to which participants' age 20 cognitive ability (M1) mediated the effect of childhood disadvantage on cortisol (path a_1b_1); the extent to which midlife SES (M2) mediated the childhood disadvantage-cortisol association (a_2b_2); and whether midlife SES mediated the effect of childhood disadvantage on cortisol, even after controlling for age 20 cognitive ability (path a_1eb_2). The c' path reflects the direct effect of childhood disadvantage on midlife cortisol after controlling for the mediators and covariates. Finally, *c* (shown in the bottom portion of Fig. 1) represents the total effect of childhood socioeconomic disadvantage on midlife cortisol.

Ethnicity was included as a covariate in all models. Current smoking and depressive symptoms were only included in analyses involving M2 because they were assessed at midlife. All statistical tests were 2-tailed.

3. Results

3.1. Descriptive statistics

Participants' average age when cortisol samples were collected was 55.9 (SD = 2.6, range 51–60); average education was 13.8 (SD = 2.1) years. Most participants worked full-time (78%) and were married (79%).

Each separate childhood disadvantage indicator was coded as a binary variable (0,1) to indicate low or high risk; the four indicators were then summed to create a childhood disadvantage index. Correlations between the four childhood disadvantage indicators ranged from $r = 0.35$ $p < .0001$ (father SES with mother education); $r = 0.12, 0.13$ between family size and father SES/mother education respectively) to $r = .01$ between family disruption/separation and the other measures; as can be seen in Table 1 these risks have varying influences on each of the later outcomes. Overall, the effect of the composite risk measure is stronger than the effects of the separate measures. High-risk (low SES) fathers had, on average, 9.35 (SD = 2.98) years of education and worked primarily as semiskilled manual laborers (mean occupational status = 3.44; SD = 0.89). Fathers with low-risk SES (scores > 32) on average had completed high school (mean = 12.62 years of education; SD = 3.00) and worked in skilled, semi-professional occupations (mean = 6.43; SD = 1.32). Over half of the men in the VETSA sample came from low SES households (60.5%).

Mothers in the high-risk education group had, on average, 8.26 (SD = 2.18) years of education as compared with 12.59 (SD = 1.36) years of education in the low-risk mothers. Low-education mothers comprised 27.2% of mothers. Large (high-risk) families (>5 children) averaged 7.79 children while low-risk family size averaged 3.73 children. The differences in education, occupation, and family size between high- and low-risk groups were all highly significant ($p < .0001$). Family disruptions occurred in 20.98% of the participants. Childhood disadvantage scores ranged from zero to four (mean 1.24, SD = 1.07): 19.8% of the participants had no risks, 34.1% one risk, 28.8% two risks, 14.9% three risks, and 2.4% had four risks.

As can be seen in Table 1, in the unadjusted correlations, childhood disadvantage was significantly associated with AUC cortisol; that is, at midlife, participants' total daytime cortisol secretion was higher if their childhood environment was more adverse. Associations between childhood disadvantage and cortisol awakening response or wake-to-bed slope were not significant. Men coming from disadvantaged families had significantly lower age 20 AFQTscores, lower midlife SES, and were more likely to still be smoking at midlife. They were also less likely to be non-white ethnicity. AFQT scores at age 20, smoking, and midlife SES were significantly associated with AUC cortisol at midlife, such that men with lower cognitive ability, lower SES and current smoking had higher levels of total daytime cortisol.

3.2. Bootstrapped Multi-Step Mediation Model

Nonparametric bootstrapping procedures for multistep mediation showed that age 20 AFQT scores (M1) and adult SES (M2) significantly mediated the influence of childhood disadvantage on midlife AUC cortisol levels (Table 2). In order to compare results across

measures, measures were standardized before analyses were conducted with the mean = 0 and standard deviation = 1. The direct effect of childhood risks on midlife AUC cortisol adjusting for the influence of the mediators and covariates still remained significant (path c': $\beta = 0.08$, 95% CI: [0.01,0.14]), thus AFQT scores and midlife SES only partially mediated the influence of childhood risks on midlife cortisol. Childhood disadvantage still had a direct influence on total daytime cortisol secretion decades later.

The total effect of childhood risks on midlife AUC cortisol (path c) can be partitioned into direct effects of childhood disadvantage (path c') and total specific indirect effects, the latter referring to the effects of childhood disadvantage that are mediated through both young adult cognitive ability and midlife SES ($a_1b_1 + a_2b_2 + a_1eb_2$). The indirect effect of childhood disadvantage on cortisol secretion through adult SES was still significant even after controlling for the effect of age 20 cognitive ability (path a_1eb_2 $\beta = 0.006$; 95% CI: [0.001, 0.012]). The total specific indirect effects of childhood disadvantage on midlife AUC cortisol were 0.04 whereas the total effect of childhood disadvantage (direct plus indirect) was 0.12; thus, the total specific indirect effects accounted for 33.3% of the total effect of childhood disadvantage on midlife cortisol. This can be interpreted as indicating that, overall, each one standard deviation increase in familial disadvantage (a one unit increase) was associated with 0.12 of a standard deviation or .70 nmol/L increase in total daily output of cortisol at age 55 (Table 2). Most of that effect (two-thirds) was accounted for by the direct effects of childhood adversity. With regard to the indirect effects of childhood disadvantage through age 20 cognitive ability or SES, the increase in AUC cortisol at age 55 was 0.12 and 0.08 nmols/L per standard deviation increase in cognitive ability or SES respectively. Thus men with higher levels of hardship may have been chronically exposed to higher levels of cortisol.

In Fig. 2, standardized individual path estimates and confidence intervals are presented for associations between the independent and mediating variables and AUC cortisol. All of the path estimates are significant (none of the confidence intervals include zero). Because these results are presented in standardized units, they can be interpreted with use of the information on means and standard deviations in Table 1. Here we can see the direct influences between the various childhood disadvantage, the mediators, and total daily cortisol output. Here we see, for instance, that each one standard deviation increase in childhood disadvantage (a one unit increase) predicted the equivalent of a 3.3 unit decrease in IQ points (in terms of WAIS equivalents where one standard deviation equals 15 IQ points). A one standard deviation increase in age 20 cognitive ability represented a 0.583 nmol/L decrease in AUC cortisol; consider here that a score of four on the childhood disadvantage index would predict close to a full standard deviation decrease in age 20 cognitive ability. The effect of lifetime adult SES on AUC cortisol was comparable (path estimate −.10) to that of age 20 AFQT; for SES, a one standard deviation (10.81) difference in SES would be equivalent to the difference between dropping out of high school versus finishing high school or to working a semiskilled job rather than an unskilled job.

As can be seen in Table 2, results for effects of childhood disadvantage on the total indirect effect of childhood disadvantage on midlife WBslope and CAR were significant, but there was no direct effect of childhood disadvantage or total effect of childhood disadvantage on

these cortisol outcomes. For WBslope, the primary indirect effect appears to be through childhood risks' association with cognitive ability at age 20.

3.3. Post hoc analyses at individual time points across the day

These results were stronger for elevated total daytime cortisol rather than other forms of dysregulated cortisol such as the awakening response or a flattened wake to bed slope. We conducted post hoc analyses of extreme groups in the predictor variables to see if this pattern held up across the different predictor measures. Thus, at each of the five diurnal time points, we compared cortisol levels of individuals in the top and bottom quartiles of childhood disadvantage, AFQT age 20, and adult SES; smoking was examined as smokers versus nonsmokers (Fig. 3). Cortisol levels at each time point are the average for the three days. Type III comparisons for the predictor variables were made using mixed models, with family as the random effect and are presented in Table 3. As can be seen in Fig. 3, patterns of cortisol across the day were consistent for the four measures. Differences at individual time points were strongest for adult SES and smoking at awake-plus-30 min, and for AFQT, adult SES, and smoking at bedtime (Table 3). The overall pattern of the results across the day are consistent with the findings for AUC cortisol.

4. Discussion

Few studies have examined intervening measures that may account for the association between childhood socioeconomic disadvantage and HPA functioning in adulthood. In this study we examined two possible ways childhood disadvantage could indirectly affect midlife cortisol secretion: through its influence on the child's later cognitive ability and adulthood socioeconomic achievements. Childhood disadvantage was both directly and indirectly associated with cortisol secretion at age 55, even after adjusting for the effects of adult cognitive ability, adult SES, ethnicity, smoking status, and depressive symptoms. Men who grew up in more disadvantaged childhoods had greater HPA axis dysregulation— in the form of elevated cortisol secretion— at midlife than men coming from less disadvantaged households. However, young adult cognitive ability and midlife SES partially mediated the effects of childhood disadvantage on cortisol.

To our knowledge this is the first multi-step multiple mediation analysis simultaneously examining longitudinal indicators as links between socioeconomic disadvantage in childhood and midlife HPA axis functioning. In two earlier longitudinal studies, lower cognitive ability in childhood or early adulthood was associated with dysregulated cortisol secretion in middle adulthood (Franz et al., 2011a; Power et al., 2008). Both studies provided evidence for long-term influences of cognitive ability on different aspects of cortisol dysregulation as well as evidence that cortisol levels, adjusted for earlier cognitive ability, was associated with current cognitive performance. Other researchers have examined cumulative socioeconomic deprivation (Gustafsson et al., 2011; Li et al., 2007) but have not examined the long term contribution of cognitive ability, which clearly affects socioeconomic status. The present analyses provide evidence that other factors in the life course need to be taken into account when considering the impact of childhood stressful experiences on midlife HPA function.

McEwen (2007) explains links between stress and HPA axis regulation using the concept of allostasis; allostasis refers " to the active process by which the body responds to daily events and maintains homeostasis" (p. 880). Allostatic load occurs when events overload the body due to their frequency or severity, or when there is poor physiological regulation thereby challenging the organism's ability to maintain homeostasis. Both childhood and adulthood socioeconomic disadvantage have been shown to increase allostatic load (Seeman et al., 2010). Allostatic load contributes to changes in multiple physiological systems: cortisol and DHEA secretion, parasympathetic dysregulation, increased inflammation, metabolic dysregulation. Existing pathophysiology, which may also be more likely to exist under conditions of socioeconomic disadvantage, also contributes to the organism's ability to deal with allostatic load. By increasing chronic wear and tear on the body's delicately balanced mutual regulatory systems, allostatic load contributes to the development of central and peripheral pathophysiology which in turn further increases allostatic load. Thus early experiences that challenge the body's ability to maintain homeostasis have the potential to stimulate chains of events that affect physiological functioning decades later.

A number of studies have also shown that allostatic load and/or HPA axis dysregulation are associated with structural changes in the brain, decreased synaptic plasticity, and epigenetic programming of glucocorticoid receptor expression in the brain (Kremen et al., 2010; McEwen and Gianaros, 2010, 2011; McGowan et al., 2009; Miller et al., 2009). Animal research has found associations between stressors and changes in spine density, dendritic length and branching in multiple brain regions connected with HPA axis functioning (e.g., prefrontal cortex, hippocampus, amygdala); yet these alterations appear to be reversible, especially in young adult mammals (Davidson and McEwen, 2012). In this study, it is possible that childhood stress/allostatic load had already affected brain development and HPA axis functioning by age 20.

Cognitive ability and adult SES only partially mediated the childhood influences on adult cortisol. Our analysis indicated that the rest of the association was accounted for by a direct effect of childhood disadvantage on adult cortisol, but it is also possible that additional mechanisms that were not measured might explain some of the effects. Three putative mediators from childhood include childhood adversity/ trauma, maternal warmth/parental responsiveness and birth weight which other researchers have found to contribute directly and indirectly to HPA axis dysregulation (Engert et al., 2010; Heim et al., 2008; Saridjan et al., 2010). However, we did not have detailed information on any of these indicators from childhood in this sample. Some researchers have argued that it may be the quality of the parent—child bond, not the economic stress on the family that is more important in the long run (though economic stress may have adverse influences on the quality of the parent—child bond) but we were unable to examine the quality of childrearing in this sample (Davidson and McEwen, 2012; Levine, 2000).

In addition to the contribution of early life allostatic load to pathophysiology, there are concomitant social and psychological burdens associated with early socioeconomic disadvantage. Adults from disadvantaged family backgrounds are more likely to have experienced greater and more prolonged exposure to circumstances that can have long-term effects on cognition, educational attainment, brain structure, and health (Evans and Kim,

2007; Evans et al., 2008). For instance, children from lower SES backgrounds are more likely to have been exposed to smoking and other environmental toxins than other children, are more likely to experience poor diets, come from larger families, and are more likely to be underweight at birth (Li et al., 2007). As children, adults from large families of origin were less likely to have a place to study or be alone, and had lower than predicted educational attainment (Evans and Kim, 2007). Another possible pathway linking childhood disadvantage with later cortisol secretion and health inequities is that childhood disadvantage contributes to unhealthy habits such as smoking or poor diet (Cohen et al., 2006b). In these analyses, smoking at midlife was associated with childhood disadvantage, lower cognitive ability, and lower adult SES; however childhood disadvantage was still significantly associated with cortisol levels even after controlling for smoking. Thus childhood socioeconomic disadvantage appears to contribute to unhealthy aging through its multifaceted influences on lifelong disadvantage.

4.1. Strengths and limitations

Our study has multiple strengths. It is one of the rare longitudinal studies of adult HPA functioning for which measures of early adult cognitive ability and socioeconomic characteristics of family of origin are available. In addition, having a narrow age range (51—60), and all male participants reduces the confounding effects of age and gender on cortisol and measures of SES. Finally, with cortisol samples collected on three non-consecutive days, at five comparable time points on each day, we have a strong indicator of cortisol secretion at midlife from a large community sample.

There are several limitations to the current research. Our participants were all men, and predominantly white non-Hispanic. Thus, the extent of the generalizability of these results to women, and other ethnicities is unclear. We did not have a measure of earlier life levels of cortisol, but—based on other research on the effects of childhood adversity on the HPA axis—it does seem possible that HPA axis dysregulation may have begun far earlier in life. Thus, early HPA axis dysregulation may have already been influencing brain structures and metabolic processes, influencing young adult cognitive ability and, in turn, affecting midlife SES and cortisol. If that were the case, however, it would not undermine the inferences drawn from our model. We cannot tell when the deleterious impact on HPA axis function began to manifest itself, but our results do suggest that such effects were present after several decades. Another limitation was that we did not have access to information on other childhood risks such as severe trauma (i.e., physical and psychological adversity), birth weight or parental care that are also associated with HPA axis dysregulation and with childhood stress (Heim et al., 2008). A further limitation in this (and other studies) is that three days worth of saliva collection (across two situations—at home and in lab) may not have been adequate to get highly reliable assessments of CAR or slope (Golden et al., 2011; Hellhammer et al., 2009; Kudielka et al., 2012), thus it is unclear if the weaker results for those measures was due to low reliability.

Finally, consistent with other studies, the magnitude of the effects found in this study between our primary predictors and cortisol levels were small, though statistically significant. It is not uncommon to find small effects when studying biomarkers within large

community samples. HPA dysregulation is only a small part of a complex, biological system through which allostatic load has its impact on the body, but multiple small disruptions acting additively or synergistically can lead to clinically significant dysfunction across one's lifetime (McEwen and Gianaros, 2011). Moreover, the fact that associations between childhood disadvantage and levels of cortisol can be detected across four to five decades of the life course in a community sample of men has significant implications for the potential for early life public health interventions to have long term impact on later life pathophysiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Role of the funding source: The project was supported by awards AG018386, AG022381, AG022982 and AG018384 from the National Institute on Aging. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIA/NIH, or the VA. The U.S. Department of Veterans Affairs has provided financial support for the development and maintenance of the Vietnam Era Twin (VET) Registry. Numerous organizations have provided invaluable assistance in the conduct of this study, including: Department of Defense; National Personnel Records Center, National Archives and Records Administration; Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; the Institute for Survey Research, Temple University. Most importantly, the authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families as well as the contributions of many staff members and students. We deeply regret the untimely death of one of our co-investigators—Seymour “Gig” Levine, PhD— which made him unable to see this project come to full fruition. We are grateful for his crucial contributions to this study.

References

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; 39:93–98. [PubMed: 20547282]

Bertrand M, Mullainathan S, Shafir E. A behavioral-economics view of poverty. Am Econ Rev. 2004; 94:419–423.

Blake, J. Family Size and Achievement. University of California Press; Berkeley: 1989.

Bradshaw, J.; FInch, N.; Mayhew, E.; Ritakallio, V.; Skinner, C. Child Poverty in Large Families. JR Foundation; Bristol, UK: 2006.

Brandtstadter J, Baltes-Gotz B, Kirschbaum C, Hellhammer D. Developmental and personality correlates of adrenocortical activity as indexed by salivary cortisol: observations in the age range of 35 to 65 years. J Psychosom Res. 1991; 35:173–185. [PubMed: 2046051]

Centers for Disease Control. Adverse Childhood Experiences Study. 2013. www.cdc.gov/nccdphp/ace

Chen E, Cohen S, Miller GE. How low socioeconomic status affects 2-year hormonal trajectories in children. Psychol Sci. 2010; 21:31–37. [PubMed: 20424019]

Cohen S, Doyle WJ, Baum A. Socioeconomic status is associated with stress hormones. Psychosom Med. 2006a; 68:414–420. [PubMed: 16738073]

Cohen S, Schwartz JE, Epel E, Kirschbaum C, Sidney S, Seeman T. Socioeconomic status, race, and diurnal cortisol decline in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Psychosom Med. 2006b; 68:41–50. [PubMed: 16449410]

Davidson RJ, McEwen BS. Social influences on neuroplasticity: stress and interventions to promote well-being. Nat Neurosci. 2012; 15:689–695. [PubMed: 22534579]

Decker SA. Salivary cortisol and social status among Dominican men. Horm Behav. 2000; 38:29–38. [PubMed: 10924284]

Dowd JB, Goldman N. Do biomarkers of stress mediate the relation between socioeconomic status and health? J Epidemiol Community Health. 2006; 60:633–639. [PubMed: 16790837]

Dowd JB, Ranjit N, Do DP, Young EA, House JS, Kaplan GA. Education and levels of salivary cortisol over the day in US adults. Ann Behav Med. 2011; 41:13–20. [PubMed: 20812036]

Engert V, Buss C, Khalili-Mahani N, Wadiwalla M, Dedovic K, Pruessner JC. Investigating the association between early life parental care and stress responsivity in adulthood. Dev Neuropsychol. 2010; 35:570–581. [PubMed: 20721776]

Evans GW. A multimethodological analysis of cumulative risk and allostatic load among rural children. Dev Psychol. 2003; 39:924–933. [PubMed: 12952404]

Evans GW. The environment of childhood poverty. Am Psychol. 2004; 59:77–92. [PubMed: 14992634]

Evans GW, Kim P. Childhood poverty and health: cumulative risk exposure and stress dysregulation. Psychol Sci. 2007; 18:953–957. [PubMed: 17958708]

Evans GW, Wethington E, Coleman M, Worms M, Frongillo EA. Income health inequalities among older persons: the mediating role of multiple risk exposures. J Aging Health. 2008; 20:107–125. [PubMed: 18089768]

Fekedulegn DB, Andrew ME, Burchfiel CM, Violanti JM, Hartley TA, Charles LE, Miller DB. Area under the curve and other summary indicators of repeated waking cortisol measurements. Psychosom Med. 2007; 69:651–659. [PubMed: 17766693]

Fiocco AJ, Joober R, Lupien SJ. Education modulates cortisol reactivity to the Trier Social Stress Test in middle-aged adults. Psychoneuroendocrinology. 2007; 32:1158–1163. [PubMed: 17920776]

Franz CE, Lyons MJ, O'Brien R, Panizzon MS, Kim K, Bhat R, Grant MD, Toomey R, Eisen S, Xian H, Kremen WS. A 35-year longitudinal assessment of cognition and midlife depression symptoms: the Vietnam Era Twin Study of Aging. Am J Geriatr Psychiatry. 2010a Publish Ahead of Print. 10.1097/JGP.1090b1013e3181ef1079f1091

Franz CE, McClelland DC, Weinberger J. Childhood antecedents of conventional social accomplishment in midlife adults: a 36-year prospective study. J Pers Soc Psychol. 1991; 60:586–595.

Franz CE, O'Brien RC, Hauger RL, Mendoza SP, Panizzon MS, Prom-Wormley E, Eaves LJ, Jacobson K, Lyons MJ, Lupien S, Hellhammer D, Xian H, Kremen WS. Cross-sectional and 35-year longitudinal assessment of salivary cortisol and cognitive functioning: the Vietnam Era Twin Study of Aging. Psychoneuroendocrinology. 2011a; 36:1040–1052. [PubMed: 21295410]

Franz CE, York TP, Eaves LJ, Mendoza SP, Hauger RL, Hellhammer DH, Jacobson KC, Levine S, Lupien SJ, Lyons MJ, Prom-Wormley E, Xian H, Kremen WS. Genetic and environmental influences on cortisol regulation across days and contexts in middle-aged men. Behav Genet. 2010b; 40:467–479. [PubMed: 20238238]

Galobardes B, McCarron P, Jeffreys M, Davey Smith G. Association between number of siblings and cause-specific mortality in the Glasgow alumni cohort study. Eur J Epidemiol. 2008; 23:89–93. [PubMed: 18030589]

Gersten O. Neuroendocrine biomarkers, social relations, and the cumulative costs of stress in Taiwan. Soc Sci Med. 2008; 66:507–519. discussion 520–535. [PubMed: 18022742]

Golden SH, Wand GS, Malhotra S, Kamel I, Horton K. Reliability of hypothalamic-pituitary-adrenal axis assessment methods for use in population-based studies. Eur J Epidemiol. 2011; 26:511–525. [PubMed: 21533585]

Gustafsson PE, Anckarsater H, Lichtenstein P, Nelson N, Gustafsson PA. Does quantity have a quality all its own? Cumulative adversity and up- and down-regulation of circadian salivary cortisol levels in healthy children. Psychoneuroendocrinology. 2010a; 35:1410–1415. [PubMed: 20444551]

Gustafsson PE, Janlert U, Theorell T, Hammarstrom A. Life-course socioeconomic trajectories and diurnal cortisol regulation in adulthood. Psychoneuroendocrinology. 2010b; 35:613–623. [PubMed: 19879057]

Gustafsson PE, Janlert U, Theorell T, Westerlund H, Hammar-strom A. Socioeconomic status over the life course and allostatic load in adulthood: results from the Northern Swedish Cohort. J Epidemiol Community Health. 2011; 65:986–992. [PubMed: 20974835]

Hall SF. A user's guide to selecting a comorbidity index for clinical research. J Clin Epidemiol. 2006; 59:849–855. [PubMed: 16828679]

Hart CL, Taylor MD, Davey Smith G, Whalley LJ, Starr JM, Hole DJ, Wilson V, Deary IJ. Childhood IQ, social class, deprivation, and their relationships with mortality and morbidity risk in later life: prospective observational study linking the Scottish Mental Survey 1932 and the Midspan studies. Psychosom Med. 2003; 65:877–883. [PubMed: 14508035]

Hauger RL, Risbrough V, Brauns O, Dautzenberg FM. Corticotropin releasing factor (CRF) receptor signaling in the central nervous system: new molecular targets. CNS Neurol Disord Drug Targets. 2006; 5:453–479. [PubMed: 16918397]

Hayes AF. Beyond Baron and Kenny: statistical mediation analysis in the New Millennium. Commun Monogr. 2009; 76:4087–4420.

Hayward MD, Gorman BK. The long arm of childhood: the influence of early-life social conditions on men's mortality. Demography. 2004; 41:87–107. [PubMed: 15074126]

Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology. 2008; 33:693–710. [PubMed: 18602762]

Hellhammer DH, Wust S, Kudielka BM. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology. 2009; 34:163–171. [PubMed: 19095358]

Hollingshead AB, Redlich FC. Social mobility and mental illness. Am J Psychiatry. 1955; 112:179–185. [PubMed: 13258872]

Hunter AL, Minnis H, Wilson P. Altered stress responses in children exposed to early adversity: a systematic review of salivary cortisol studies. Stress. 2011; 14:614–626. [PubMed: 21675865]

Kremen WS, Jacobson KC, Xian H, Eisen SA, Waterman B, Toomey R, Neale MC, Tsuang MT, Lyons MJ. Heritability of word recognition in middle-aged men varies as a function of parental education. Behav Genet. 2005; 35:417–433. [PubMed: 15971023]

Kremen WS, Koenen KC, Boake C, Purcell S, Eisen SA, Franz CE, Tsuang MT, Lyons MJ. Pretrauma cognitive ability and risk for posttraumatic stress disorder: a twin study. Arch Gen Psychiatry. 2007; 64:361–368. [PubMed: 17339525]

Kremen WS, O'Brien RC, Panizzon MS, Prom-Wormley E, Eaves LJ, Eisen SA, Eyler LT, Hauger RL, Fennema-Notestine C, Fischl B, Grant MD, Hellhammer DH, Jak AJ, Jacobson KC, Jernigan TL, Lupien SJ, Lyons MJ, Mendoza SP, Neale MC, Seidman LJ, Thermenos HW, Tsuang MT, Dale AM, Franz CE. Salivary cortisol and prefrontal cortical thickness in middle-aged men: a twin study. Neuroimage. 2010; 53:1093–1102. [PubMed: 20156572]

Kremen WS, Thompson-Brenner H, Leung YJ, Grant MD, Franz CE, Eisen SA, Jacobson KC, Boake C, Lyons MJ. Genes, environment, and time: the Vietnam Era Twin Study of Aging (VETSA). Twin Res Human Genet. 2006; 9:1009–1022. [PubMed: 17254445]

Kudielka BM, Gierens A, Hellhammer DH, Wust S, Schlotz W. Salivary cortisol in ambulatory assessment—some dos, some don'ts, and some open questions. Psychosom Med. 2012; 74:418–431. [PubMed: 22582339]

Kumari M, Badrick E, Chandola T, Adler NE, Epel E, Seeman T, Kirschbaum C, Marmot MG. Measures of social position and cortisol secretion in an aging population: findings from the Whitehall II study. Psychosom Med. 2010; 72:27–34. [PubMed: 19995885]

Levine S. Influence of psychological variables on the activity of the hypothalamic-pituitary-adrenal axis. Eur J Pharmacol. 2000; 405:149–160. [PubMed: 11033322]

Li L, Power C, Kelly S, Kirschbaum C, Hertzman C. Lifetime socio-economic position and cortisol patterns in mid-life. Psychoneuroendocrinology. 2007; 32:824–833. [PubMed: 17644268]

Luecken LJ. Childhood attachment and loss experiences affect adult cardiovascular and cortisol function. Psychosom Med. 1998; 60:765–772. [PubMed: 9847038]

Luecken LJ, Appelhans BM. Early parental loss and salivary cortisol in young adulthood: the moderating role of family environment. Dev Psychopathol. 2006; 18:295–308. [PubMed: 16478564]

Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009; 10:434–445. [PubMed: 19401723]

Lyons MJ, York TP, Franz CE, Grant MD, Eaves LJ, Jacobson KC, Schaie KW, Panizzon MS, Boake C, Xian H, Toomey R, Eisen SA, Kremen WS. Genes determine stability and the environment determines change in cognitive ability during 35 years of adulthood. Psychol Sci. 2009; 20:1146–1152. [PubMed: 19686293]

McEwen BS. Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiological Reviews. 2007; 87:873–904. [PubMed: 17615391]

McEwen BS, Gianaros PJ. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. Ann N Y Acad Sci. 2010; 1186:190–222. [PubMed: 20201874]

McEwen BS, Gianaros PJ. Stress- and allostasis-induced brain plasticity. Annu Rev Med. 2011; 62:431–445. [PubMed: 20707675]

McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci. 2009; 12:342–348. [PubMed: 19234457]

Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, Cole S, Kobor MS. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci U S A. 2009; 106:14716–14721. [PubMed: 19617551]

Nicolson NA. Childhood parental loss and cortisol levels in adult men. Psychoneuroendocrinology. 2004; 29:1012–1018. [PubMed: 15219652]

Orme DR, Brehm W, Ree MJ. Armed Forces Qualification Test as a measure of premorbid intelligence. Mil Psychol. 2001; 13:187–197.

Ouellet-Morin I, Boivin M, Dionne G, Lupien SJ, Arseneault L, Barr RG, Perusse D, Tremblay RE. Variations in heritability of cortisol reactivity to stress as a function of early familial adversity among 19-month-old twins. Arch Gen Psychiatry. 2008; 65:211–218. [PubMed: 18250259]

Ouellet-Morin I, Dionne G, Perusse D, Lupien SJ, Arseneault L, Barr RG, Tremblay RE, Boivin M. Daytime cortisol secretion in 6-month-old twins: genetic and environmental contributions as a function of early familial adversity. Biol Psychiatry. 2009; 65:409–416. [PubMed: 19013558]

Pesonen AK, Raikkonen K, Feldt K, Heinonen K, Osmond C, Phillips DI, Barker DJ, Eriksson JG, Kajantie E. Childhood separation experience predicts HPA axis hormonal responses in late adulthood: a natural experiment of World War II. Psychoneuroendocrinology. 2010; 35:758–767. [PubMed: 19963324]

Power C, Li L, Hertzman C. Cognitive development and cortisol patterns in mid-life: findings from a British birth cohort. Psychoneuroendocrinology. 2008; 33:530–539. [PubMed: 18342451]

Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 2008; 40:879–891. [PubMed: 18697684]

Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology. 2003; 28:916–931. [PubMed: 12892658]

Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977; 1:385–401.

Rosmond R, Bjorntorp P. Occupational status, cortisol secretory pattern, and visceral obesity in middle-aged men. Obes Res. 2000; 8:445–450. [PubMed: 11011911]

Rowe DC, Jacobson KC, Van den Oord EJCG. Genetic and environmental influences on vocabulary IQ: parental education level as moderator. Child Dev. 1999; 70:1151–1162. [PubMed: 10546338]

Rutter M. Family and school influences on cognitive development. J Child Psychol Psychiatry. 1985; 26:683–704. [PubMed: 3900115]

Rutter, M.; Quinton, D. Psychiatric disorder: ecological factors and concepts of causation. In: McGurk, H., editor. Ecological Factors in Human Development. North-Holland Publishing; Amsterdam and New York: 1977.

Rutter M, Tizard J, Yule W, Graham P, Whitmore K. Research report: Isle of Wight Studies, 1964–1974. Psychol Med. 1976; 6:313–332. [PubMed: 137412]

Saridjan NS, Huizink AC, Koetsier JA, Jaddoe VW, Mackenbach JP, Hofman A, Kirschbaum C, Verhulst FC, Tiemeier H. Do social disadvantage and early family adversity affect the diurnal

cortisol rhythm in infants? The Generation R Study Horm Behav. 2010; 57:247–254. [PubMed: 20006614]

Seeman T, Epel E, Gruenewald T, Karlamangla A, McEwen BS. Socio-economic differentials in peripheral biology: cumulative allostatic load. Ann N Y Acad Sci. 2010; 1186:223–239. [PubMed: 20201875]

Steptoe A, Kunz-Ebrecht S, Owen N, Feldman PJ, Willemsen G, Kirschbaum C, Marmot M. Socioeconomic status and stress-related biological responses over the working day. Psychosom Med. 2003; 65:461–470. [PubMed: 12764220]

Taylor SE, Karlamangla AS, Friedman EM, Seeman TE. Early environment affects neuroendocrine regulation in adulthood. Soc Cogn Affect Neurosci. 2011; 6:244–251. [PubMed: 20400490]

Tsuang MT, Bar JL, Harley RM, Lyons MJ. The Harvard Twin Study of substance abuse: what we have learned. Harv Rev Psychiatry. 2001; 9:267–279. [PubMed: 11600486]

Turkheimer E, Haley A, Waldron M, D'Onofrio B, Gottesman II. Socieconomic status modifies heritability of IQ in young children. Psychol Sci. 2003; 14:623–628. [PubMed: 14629696]

Wright CE, Steptoe A. Subjective socioeconomic position, gender and cortisol responses to waking in an elderly population. Psychoneuroendocrinology. 2005; 30:582–590. [PubMed: 15808928]

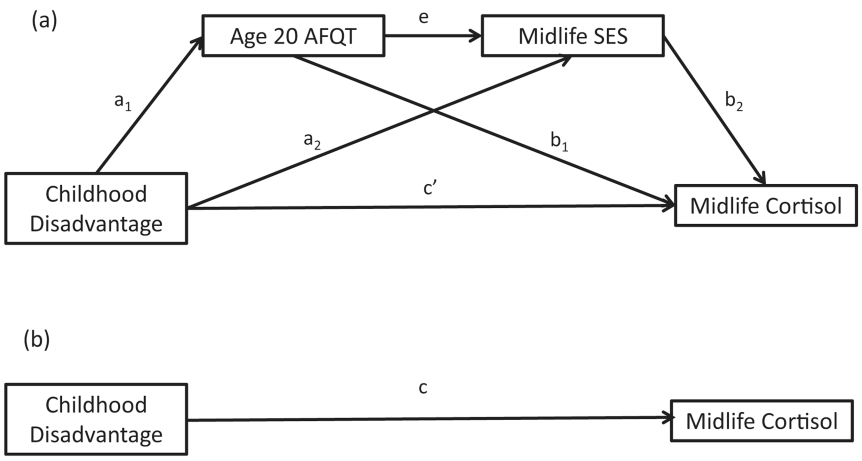

Figure 1.

(a) Schematic of a multi-step multiple mediation model showing direct and specific indirect effects of childhood socioeconomic disadvantage on midlife cortisol. (b) Total effect of childhood disadvantage on midlife cortisol (c). *Notes*: Armed Forces Qualification Test (AFQT); socioeconomic status (SES).

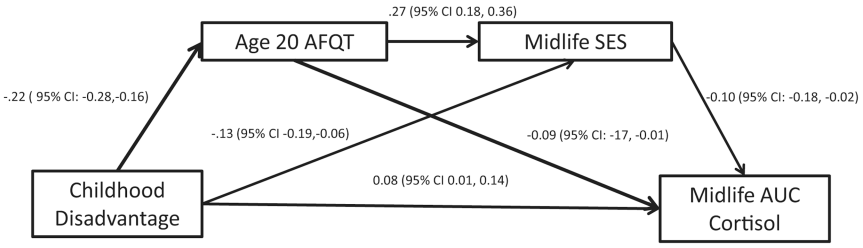

Figure 2.

Multistep Multiple Mediation Model: path estimates of direct and specific indirect effects of childhood socioeconomic disadvantage on midlife AUC cortisol using standardized data. Notes: Armed Forces Qualification Test (AFQT); socioeconomic status (SES); 95% CI: 95% confidence interval.

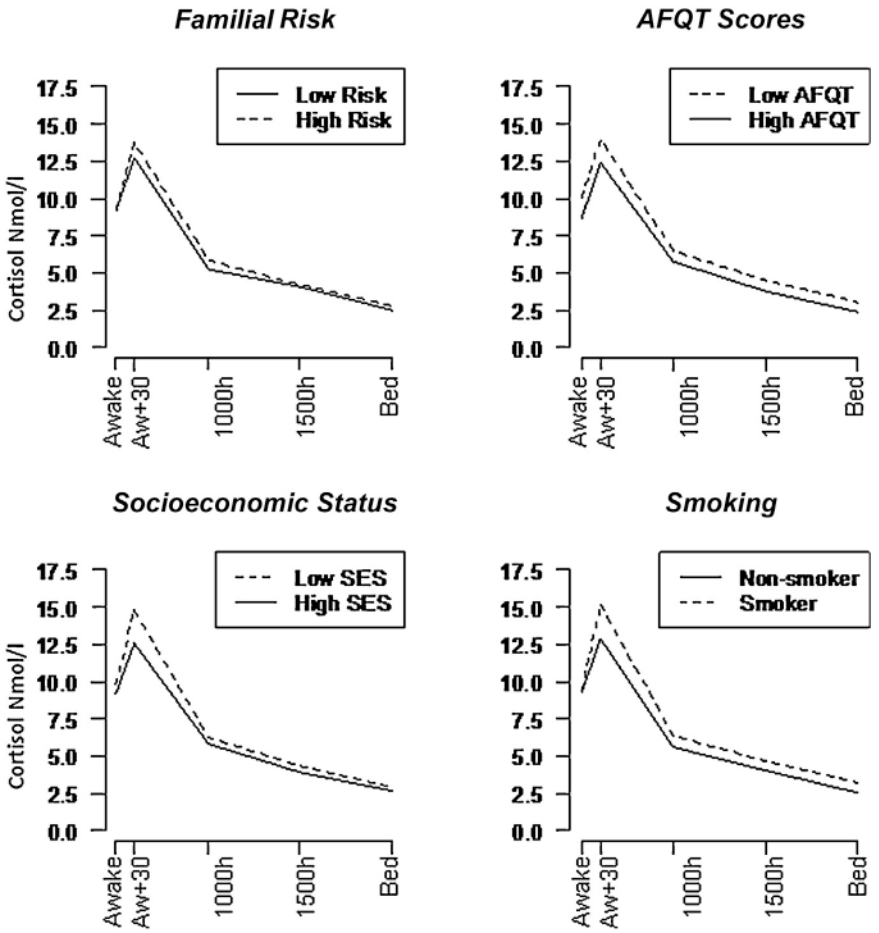

Figure 3.

Comparisons of cortisol levels in independent and mediator variable extreme groups averaged across three days for five time points representing the diurnal pattern.

Table 1

Demographic variables, independent and dependent variables: correlations and descriptive statistics.

	Mean (standard deviation) or %	Childhood disadvantage	AFQT age 20	Midlife SES	AUC cortisol	Cortisol awakening response	Wake-to-Bed Slope	Ethnicity	Currently smokes	CESD
Childhood Disadvantage Index	1.23 (1.07)									
AFQT age 20	0.33 (0.70)	−0.27****								
Midlife SES (participant)	42.2 (10.81)	−0.19 ****	0.34****							
AUC Cortisol age 56	22.99 (5.87)	0.11 **	−0.14***	−0 16 ****						
Cortisol Awakening Response (CAR)	1.21 (0.42)	0.06	−0.12 **	−0 09*	0.42****					
Wake-to-Bed Slope (WBslope)	−.08 (.01)	0.04	−0.12***	−0 12 **	0.32****	−0.20****				
Ethnicity (% non-Hispanic white)	85%	0.23 ****	−0.28****	−0.04	0.02	0.05	0.07			
Currently Smokes	25%	0.10**	−0.17****	−0.21****	0.16****	0.11**	0.14***	0.03		
CESD (score > = 16)	14%	0.07	−0.13 ***	−0 12***	0.06	0.03	0.04	0.09*	0.13***	
Father SES	33.45 (12.17)	−0.49 ***	0.19****	0.26****	−0.08*	−0.04	−0.04	−0.15****	0.06	0.01
Mother Education (Years)	11.45 (2.54)	−0.52****	0.17****	0.12**	−0.06	0.01	−0.07	−0.22	−0.04	0.01
Number of siblings	5.29 (2.42)	0.44****	−0.16****	−0.09*	0.09*	0.07*	0.06	0.22****	0.06	−0.02
Separated from parents	20.98%	0.41****	−0.08*	−0 05*	0.09*	0.05	0.04	0.04	0.08*	0.11**

Notes: N = 727; Armed Forces Qualification Test (AFQT); Socioeconomic status (SES); area under the curve (AUC). Currently smokes cigarettes (0 = no; 1 = yes); Center for Epidemiologic Studies Depression scale (CESD; <16 versus > = 16); Ethnicity (0 = non-Hispanic white; 1 = other); Separated from parents (0 = no; 1 = yes).

* $p < .05$.

** $p < .01$.

*** $p < .001$.

**** $p < .0001$.

Table 2

Specific indirect and direct effects of childhood disadvantage on midlife cortisol levels: all measures standardized.

Mediator	AUC Cortisol β (95% CI lower; 95% CI upper)	Wake to bed slope β (95% CI lower; 95% CI upper)	Cortisol Awakening Response (CAR) β (95% CI lower; 95% CI upper)
Age 20 Cognitive ability (M1: a_1b_1)	**0.02 (0.002; 0.04)**	.02 (0.01; 0.04)	.01 (−0.005; 0.03)
Midlife SES (M2: a b)	**0.013 (0.002; 0.027)**	.007 (−.001; 0.02)	.007 (−.002; 0.02)
Midlife SES adjusted for Age 20 Cognitive Ability (a_1eb_2)	**0.006 (0.001; 0.012)**	.003 (−0.001; 0.008)	.003 (−0.001; 0.009)
Total indirect effect	**0.04 (0.02; 0.06)**	.03 (0.01; 0.05)	.02 (0.002; 0.05)
Direct effect of childhood disadvantage (c′)	**0.08 (0.01; 0.14)**	−.006 (−0.07; 0.05)	.01(−.06; 0.09)
Total effect of childhood disadvantage (c)	**0.12 (0.05; 0.18)**	.02 (−0.04; 0.08)	.04 (−.03; 0.10)

Notes: Confidence intervals based on 1000 bootstrap samples; coefficients are standardized values (x = 0; SD = 1). CI = confidence interval; significant values are **bolded**. M1 = specific indirect effect of childhood risk through age 20 cognitive ability; M2 = specific indirect effect of childhood risk through midlife socioeconomic status (SES).

Table 3

Mixed model Type III t-test comparisons of cortisol levels in high and low risk groups at five different time points.

RISK GROUP	*t*-tests of cortisol levels at different time points				
	Awakening	**Awake plus 30 min**	**1000 h**	**1500 h**	**Bedtime**
High (4,3,) vs low childhood disadvantage (0) (df = 125)	0.023; $p = 0.98$	1.898; $p = 0.06$	0.183; $p = 0.86$	0.162; $p = 0.87$	0.464; $p = .64$
Low vs high AFQT (age 20) (df = 112)	1.171; $p = 0.24$	1.960; $p = 0.06$	1.583; $p = 0.12$	**2.045; $p = .05$**	**3.15; $p = .002$**
Low vs high adult Socioeconomic Status (df 120)	0.789; $p = 0.43$	**2.836; $p = 0.006$**	1.210; $p = .23$	1.821; $p = .07$	**2.78; p = .006**
Smoking vs Not smoking (df = 723)	0.074; $p = 0.94$	**3.526; $p = 0.0005$**	**2.500; $p = 0.02$**	**3.313; $p = .001$**	**4.964; $p < .0001$**

For each predictor, the high risk group is coded as the high score. Cortisol values at each time point are averaged across the three days. *p* values reported are two-tailed. Significant differences are **bolded**.