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Early-life stress and recurrent psychological distress over the lifecourse predict divergent cortisol reactivity patterns in adulthood

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Summary Early-life stress (ELS) is associated with substantially increased lifetime risk for recurrent psychological problems, with evidence indicating that dysregulation of the physiological stress reactivity system may be partly responsible. However, some ELS-exposed people remain psychologically resilient. Although two distinct patterns of hypothalamic—pituitary—adrenal axis (HPA) stress reactivity have been observed in ELS-exposed samples (hyper- and hypo-reactive), the hypothesis that these patterns may be associated with long-term history of psychological problems has not been explored. We used healthy Whitehall II study subjects ($n = 543$) who participated in the 2008 Heart Scan Study (HSS) to assess salivary cortisol responses to a cognitive stressor, ELS exposure, and other psychosocial factors. Mean age of the sample at the HSS was 63 years. HSS data were linked to nearly 20 years of participants' Whitehall data, including repeated measures of psychological distress (GHQ-28). Piecewise growth curve analyses revealed that ELS-exposed persons with a history of recurrent psychological distress in adulthood had significantly blunted cortisol reactivity compared to non-ELS-exposed participants, while ELS-exposed persons with little or no history of distress had significantly elevated baseline cortisol, prolonged responses, and greater total cortisol production. Our findings indicate that for ELS-exposed individuals, different trajectories in psychological health over their adult lifetimes predict different cortisol reactivity patterns. These findings have important implications for our understanding of ELS-related mental health risk and treatment of these disorders.

1. Introduction

Exposure to inadequate caregiving or other early-life stress (ELS) is one of the strongest predictors of recurrent psychological problems in later life, particularly mood and anxiety disorders (Kessler and Magee, 1993; Felitti et al., 1998;

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Widom et al., 2007; Scott et al., 2010). Worldwide, psychological disorders and ELS experiences are both highly prevalent (Menard et al., 2004; Cohen et al., 2006; Kessler et al., 2007; Danese et al., 2009), and some estimates suggest that more than 50% of depression and nearly 60% of suicide attempts may be attributable to ELS, particularly among women (Felitti and Anda, 2009). ELS-associated psychological disorders are also more likely to be early-onset, comparatively severe, and highly recurrent (Kessler and Magee, 1993; Gilman et al., 2003; Heim et al., 2004; Widom et al., 2007). However, many ELS-exposed people remain psychologically resilient throughout their lives, never experiencing the disorders otherwise common in this group (Silk et al., 2007). We need to identify mechanisms through which such divergent outcomes emerge.

Theoretical and empirical research based on the developmental programming paradigm indicates that suboptimal early-life environments can encode vulnerability to later-life psychological impairment through permanent alterations of organ systems and functioning (Hales and Barker, 2001; Raikkonen and Pesonen, 2009). Alterations in the physiological systems that regulate individuals' reactivity to stress — particularly the hypothalamic–pituitary–adrenal (HPA) axis and its end-product, glucocorticoids — appear to play an especially important role (Lupien et al., 2000; McEwen, 2000; van Harmelen et al., 2010), although many biological processes are implicated (Kiecolt-Glaser et al., 2011; Gunnar and Quevedo, 2007; Eisenberg et al., 2010; Jackowski et al., 2011; Pechtel and Pizzagalli, 2011). Atypical glucocorticoid stress responses have been extensively documented in persons with mood and anxiety disorders (e.g., Burke et al., 2005a,b; Yehuda, 2009; de Rooij et al., 2010). A range of studies examining ELS-exposed individuals have also consistently reported significant alterations in cortisol reactivity when compared to non-ELS-exposed controls (Heim et al., 2000, 2002, 2008; Girdler et al., 2003; Taylor et al., 2004; Carpenter et al., 2007, 2009; Elzinga et al., 2008; Gordis et al., 2008; Rao et al., 2008; MacMillan et al., 2009; Engert et al., 2010).

Theoretical research indicates that two (or more) different patterns of atypical HPA axis reactivity — in particular, blunted or heightened responses — may be encoded in the aftermath of ELS (McEwen and Seeman, 1999; Boyce and Ellis, 2005). These different stress-response patterns may, in turn, promote differential susceptibility to lifetime psychological disorder (Carpenter et al., 2007; Miller et al., 2007; Gunnar et al., 2009). Therefore, distinct cortisol reactivity patterns may be one of the mechanisms underlying the divergent long-term mental health outcomes observed in ELS-exposed populations.

Research in this field has mostly been characterized by small cross-sectional samples, with participants' long-term histories of psychological problems generally left unexamined. These samples are usually restricted such that participants are either currently psychologically healthy or have a current mood disorder; in both situations, depression symptoms are treated as a statistical confounder. In this literature, blunted cortisol reactivity has been reported in ELS-exposed but currently psychologically healthy adults and adolescents (Girdler et al., 2003; Taylor et al., 2004; Carpenter et al., 2007, 2009; Elzinga et al., 2008; Gordis et al., 2008; MacMillan et al., 2009; Engert et al., 2010), while those with a history of ELS and current major depression have exhibited exaggerated cortisol responses to stress (Heim et al., 2008; Rao et al., 2008).

Two cross-sectional studies have examined cortisol reactivity among ELS-exposed persons with different levels of current psychological disorder (Heim et al., 2000; Harkness et al., 2011). In the first study, adult women with a history of childhood abuse and current major depression exhibited significantly higher cortisol responses compared to abused women without current depression, as well as compared to non-abused women with current depression and non-abused, non-depressed control women (Heim et al., 2000). In the second study, the opposite effect was found: adolescents with a history of childhood maltreatment and current moderate-to-severe depression exhibited blunted cortisol stress responses, while those with a history of maltreatment but only minimal (or no) current depression symptoms exhibited higher and more prolonged cortisol responses (Harkness et al., 2011).

The explanation for these conflicting results is not clear. However, the design of previous studies may have resulted in the misclassification of study participants with respect to their long-term vulnerability to psychological disorder. High levels of depression symptoms among ELS-exposed participants are often reported even in studies where they are required to be free of psychiatric disorder. Additionally, age of onset for mood disorders is typically between 20 and 30 years in ELS-exposed persons (Kessler et al., 1997; Widom et al., 2007), but many of these studies used adolescent (<18 years) (Gordis et al., 2008; Rao et al., 2008; MacMillan et al., 2009; Harkness et al., 2011) or young adult (<30 years) (Elzinga et al., 2008; Engert et al., 2010) samples, leaving their participants' future lifetime psychological vulnerability unclear. Although examining the relationship between early-life stress and cortisol reactivity in young populations has many advantages, including the ability to assess cortisol functioning in those with early-onset psychological disorder at a crucial period of development, investigations in older populations that can incorporate measures of their *long-term*, recurrent psychological disorder are also needed.

Functioning of the HPA axis is known to change over the lifecourse, although evidence regarding the impact of age on cortisol reactivity is conflicting. In a review, Kudielka et al. (2009) reported no significant differences between younger and older adults' cortisol responses to psychosocial stress challenges, but other studies have reported comparatively heightened cortisol responses among older adults (e.g., Almela et al., 2011; Carpenter et al., 2009; Otte et al., 2005). No studies have examined the impact of early-life stress and recurrent psychological distress on cortisol reactivity among older adults.

We used data collected as part of an ancillary study to the ongoing Whitehall II cohort to examine the joint relationships of ELS exposure, psychological history, and cortisol reactivity among a group of older adults for whom long-term recurrence of psychological distress symptoms could be established. We hypothesized that cortisol reactivity patterns observed in the ELS-exposed adults would differ from those observed in non-ELS-exposed adults, but that the patterns would be differential according to psychological history: namely, that the non-ELS-exposed participants would exhibit a median response, while ELS-exposed adults *without* a history of

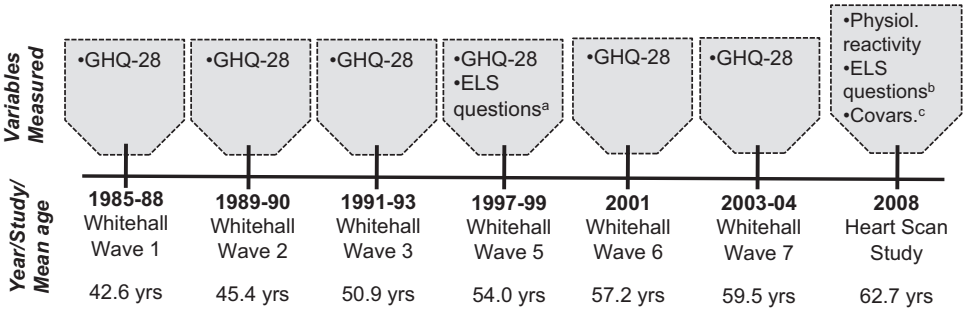

Figure 1 Overall design of the current study. Data collected during Whitehall II waves 1—3 and 5—7 were available for all Heart Scan Study (HSS) participants. Timeline shows year(s) of each data collection and mean age of HSS participants at each collection. Gray boxes list key variables collected during each study wave that were used in the present analysis: [a]physical abuse, parental divorce, parental conflict, parenting style, separation from mother/time spent in orphanage; [b]age at death of parents, family mental illness/ substance abuse; [c]covariates: BMI, smoking status, last Whitehall employment grade, CESD score, age, gender, time of laboratory visit. GHQ-28, General Health Questionnaire-28 item version.

psychological symptoms in adulthood would exhibit comparatively heightened cortisol responses to stress, while ELS-exposed adults *with* a history of recurrent psychological symptoms would exhibit comparatively blunted cortisol responses.

2. Methods

2.1. Participants

Data are from the Heart Scan Study (HSS), which comprises a sample of healthy older adults (n = 543) drawn from the Whitehall II cohort in 2008 to investigate the association between physiological reactivity to an experimental stressor and sub-clinical coronary artery calcification. The physiological reactivity parameters included cortisol and cardiovascular and inflammatory protein markers. HSS data were subsequently linked to six waves (1985—1988, 1989—1990, 1991—1993, 1997—1999, 2001, 2003—2004) of participants' Whitehall II study data using their Whitehall identification numbers. Fig. 1 depicts the overall design of the study, including the year(s), study wave, and mean participant age when each key variable was collected. Details on the Whitehall II and Heart Scan Studies have been published elsewhere (Marmot et al., 1991; Hamer et al., 2010; Steptoe et al., 2010). Questions on a range of early-life experiences, included in either the HSS protocol or in a previous Whitehall wave, were used for the current analysis.

As the HSS was designed to examine whether psychobiological stress responses predict coronary atherosclerosis, it was necessary to avoid enrolling individuals with any disease state that might affect both their physiological stress reactivity and atherosclerosis risk, thus leading to a spurious association between stress reactivity and atherosclerosis. Therefore, potential participants were excluded if they were currently taking anti-inflammatory medications or reported a serious illness within the past five years (n = 228). As major depression has been associated with altered stress responses (Burke et al., 2005a) and cardiovascular disease (Pan et al., 2011; Saleptsis et al., 2011; Low et al., 2010), we also opted to exclude individuals who had been diagnosed with major depression within the previous five years, or were *currently* taking anti-depressants or anti-psychotics (n = 18). This information was collected from Whitehall II study members during screening phone calls for participation in the HSS (i.e., in 2008), and was verified from data collected in previous phases of the Whitehall II study. We note that psychiatric diagnoses prior to 2003 and/or usage of psychotropic medication prior to 2008 were allowed, as were psychological problems that remained undiagnosed.

The youngest woman in the HSS was aged 55 years, and all women reported postmenopausal status. Female HSS participants were not excluded if they were taking hormone replacement therapy. Approximately half of the female participants (51.8%; n = 58) reported taking hormone replacement therapy in Whitehall wave 7 (2003—2004), but we did not collect additional information on HRT in 2008.

The final analytic sample for the current investigation included all HSS participants who responded to questions regarding their ELS exposure (n = 467). Mean age of the final HSS sample, in 2008, was 62.7 years (range: 54—76); 54.7% were male. The original study was approved by the Research Ethics Committee for University College London/UCL Hospitals. The current report was a secondary analysis of de-identified data and did not require further Institutional Review Board approval.

2.2. Measures

We used questionnaire-based measures of ELS exposure taken either from the HSS or Whitehall wave 5 (1997—1999). Possible reported ELS categories (all occurring before age 16) included physical abuse, separation from mother or time spent in an orphanage for 1+ years, parental death, serious familial mental illness or substance abuse, parental divorce, frequent parental conflict, and harsh parenting style (see Table 1, and below). As such, ELS as defined in this study includes categories of general adversity (Taylor et al., 2004; Rao et al., 2008), and is not limited to childhood maltreatment.

Death of a parent was assessed in the HSS questionnaire using the following text: "Up until the age of 15, did anyone in your household die, and if so, who?" Written responses were visually inspected and participants were coded as

Table 1 Early life stress (ELS) questions.

Up until the age of 15, did any of the following things happen:
1. Did someone in your household die (if so, who)?
2. Did someone in your household become seriously depressed, attempt suicide, or have a serious problem with alcohol or drugs?
3. Your parents were divorced.
4. Your parents very often argued or fought.
5. You were ever separated from your mother or in an orphanage for a year or more.
6. You were physically abused by someone close to you.

Please show how you remember your mother/father during the years you were growing up.
1. How much did she/he understand your problems and worries?
2. How much could you confide in her/him about things that were bothering you?
3. How much love and affection did she/he give you?
4. How much time and attention did she/he give you when you needed it?
5. How strict was she/he with her/his rules for you?
6. How harsh was she/he when she/he punished you?
7. How much did she/he expect you to do your best in everything you did?

having experienced the death of a parent if they had written in "mother" or "father" or both.

Other ELS questions, except those on parenting style, used binary yes/no responses. Responses to parenting style questions (drawn from the MIDUS study; Brim et al., 1996; Shaw et al., 2004) were based on a 4-point Likert scale, with higher scores corresponding to higher parental harshness and strictness, and lower affection, understanding, confiding, attention, and expectations. Following the example of Stansfeld et al. (2008), participants whose parenting style scores were in the top tertile (score $\geq$14; range: 0–21) for either their mother or father were classified as having a "harsh parent." For example, a participant could be classified as having a "harsh parent" because they reported having a parent whom they could not confide in and who had very low expectations of them.

The final ELS exposure variable was summed across ELS categories and then dichotomized into any ELS (ELS+) vs. none (ELS−). This categorization method was chosen on the basis of evidence that even exposure to only one type of early-life adversity can substantially increase risk for psychological problems (Felitti et al., 1998; Edwards et al., 2003), and because we did not have measures of certain categories of ELS exposure (e.g., sexual abuse and severe neglect) that frequently co-occur with other categories (Kessler et al., 1997; Breslau et al., 1998; Edwards et al., 2003; Dong et al., 2004). In particular, people exposed to sexual abuse have been shown to experience, on average, four other types of adversity (Kessler et al., 1997). Similarly, in the Adverse Childhood Experiences Study, among those exposed to at least one adversity the probability of exposure to another adversity was as much as 87% (Felitti and Anda, 2009).

Participants' psychological distress symptoms were measured at each Whitehall wave using the General Health Questionnaire-28 (GHQ-28), when participants' mean ages were 42.6, 45.4, 50.9, 54.0, 57.2, and 59.5 years, respectively. Mean duration of time between the baseline and final GHQ-28 assessments was 17 years (range: 15–19 years). The GHQ-28 is a widely used and validated Likert-scale instrument that identifies individuals with an increased likelihood of current psychiatric disorder, particularly depression and anxiety (Cleary et al., 1982; Koeter, 1992). Sensitivity and specificity of the GHQ-28 in the Whitehall II sample are approximately 73% and 78% (Stansfeld and Marmot, 1992) compared to the Clinical Interview Survey, which uses "case criteria" to determine probable psychiatric cases vs. non-cases (Cooper and Schwarz, 1982). A cutoff score of $\geq$5 indicates presence of significant psychological distress. Participants who never scored $\geq$5 at any of the 6 Whitehall waves were classified as having no history of psychological distress in adulthood ("no distress"); those with a $\geq$5 score at 1 or 2 waves were classified as having a minimal history of adulthood psychological distress ("minimal distress"); those with a $\geq$5 score at 3 or more waves were classified as having a history of recurrent psychological distress in adulthood ("recurrent distress"). Finally, participants were classified into one of six combined ELS/distress indicator groups: non-ELS/non-distress, non-ELS/minimal-distress, non-ELS/recurrent-distress; ELS/non-distress, ELS/minimal-distress, and ELS/recurrent-distress.

2.3. Laboratory session protocol

Laboratory visits for the HSS took place in the morning (9:15 am) or afternoon (1:00 pm). Participants were instructed to refrain from vigorous exercise and alcohol the evening prior to the laboratory visit, and from smoking or drinking caffeine for 2 h prior. Upon arrival, participants provided written informed consent and were allowed to rest for 30 min, after which they underwent the stress reactivity tasks.

The stress task protocol consisted of two 5-min cognitive-behavioral challenges designed to elicit mental stress. Order of the challenges was randomized. The first challenge was the Stroop test, a computerized color-word interference task where a color word (e.g., yellow) is presented on the screen in an incongruent color. Participants are instructed to choose a word matching the printed font color. The program indicates whether the selection was correct, and continues to a new set of words. Presentation speed was programmed to vary in response to performance accuracy to maintain pressure. The second challenge was mirror tracing, involving the tracing of a star with a metal stylus using only a mirror image. Errors are registered with a loud beep emitted by the apparatus (Lafayette Instruments Corp., Lafayette, IN, USA). A laboratory assistant timed each task and recorded the number of errors to augment the psychological pressure. Both tasks have been used in similar studies examining the physiological effects of acute stress, and reliably elicit HPA axis reactivity (e.g., Hamer and Steptoe, 2007; O'Donnell et al., 2008). Immediately after each task, participants rated its perceived stressfulness using Likert scales; scores were averaged to create an overall task-stressfulness rating.

Salivary cortisol, measured five times over the 85-min period, was used to assess HPA responses (Kirschbaum and

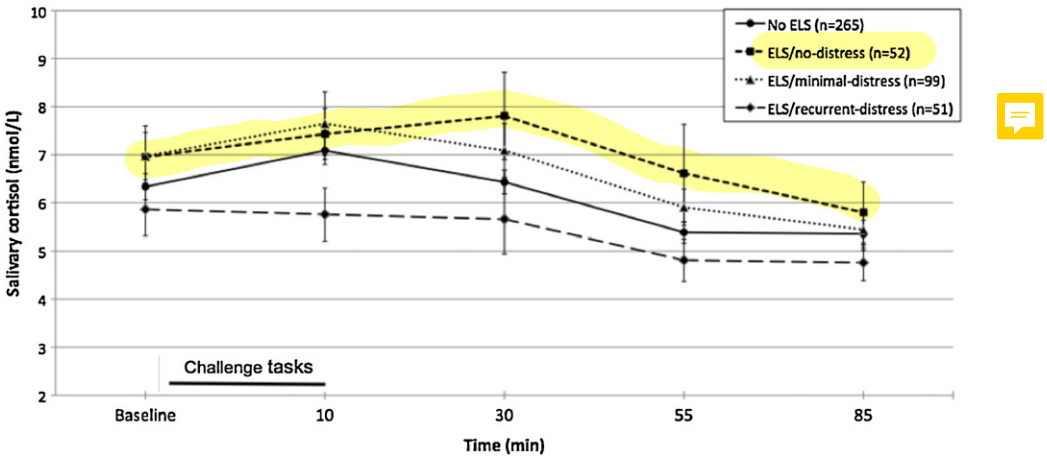

Figure 2 Salivary cortisol responses to the cognitive-behavioral challenge tasks in the Heart Scan Study sample, grouped by ELS/distress category. Values are mean raw cortisol levels.

Hellhammer, 1994). After the resting period, a baseline saliva sample was taken. Samples were then taken immediately after the stress tasks (~10 min after the baseline sample) and at 30, 55, and 85 min post-baseline. Samples were obtained using Salivette cotton roll collection devices (Sarstedt, Rommelsdorf, Germany). Samples were stored immediately at −30 °C until assaying. Cortisol levels were assessed at the University of Dresden using a time-resolved immunoassay with fluorescence detection. Intra- and inter-assay coefficients of variation were less than 8%. All statistical analyses used the natural logarithm of cortisol values to correct for skewness; for ease of interpretation, raw data are displayed in figures.

2.4. Statistical methods

Group differences in sociodemographic characteristics were examined using analysis of variance (ANOVAs) for continuous variables and chi-square analyses for categorical variables. The data had a hierarchical structure, with cortisol measurements over time (level 1) nested within individuals (level 2). We used piecewise multilevel growth-curve modeling to describe participants' cortisol response trajectories, and to assess whether combined ELS/distress history explained any of the variance in these trajectories after controlling for covariates. Growth-curve modeling, like other methods used to analyze repeated-measures data, can handle multiple independent predictors and data that violate assumptions of independence. It also offers certain additional unique advantages: it allows for incomplete participant data and occasions of measurement that are unequally spaced in time (Willett et al., 1998). Although its use in modeling repeated-measures biomarker data is still relatively novel, it has been used in similar previous studies (Adam and Gunnar, 2001; MacMillan et al., 2009; Taylor et al., 2011). All analyses were conducted in Stata 11 (StataCorp, College Station, TX); coding for the growth-curve modeling was derived from Rabe-Hesketh and Skrondal (2008) and Llabre et al. (2001).

We plotted the mean observed cortisol values for each ELS/distress group as a function of the five sample times (see Fig. 2). Visual examination of the plotted data suggested a linear function for the reactivity period (baseline to immediately post-task) and a combined linear and quadratic function for the recovery period (immediately post-task to 85 min post-task).

Model 1 examined baseline cortisol levels and growth trajectories over the reactivity and recovery periods separately, controlling for time of laboratory visit. Model 2 added fixed effects for each of the ELS/distress groups and their interactions with the time vectors (reactivity and recovery), which allowed us to test for group differences in both baseline levels and slopes during the two time periods. Model 3 added individual-level covariates (see paragraph below). Random effects were specified for the overall intercept and for slope coefficients corresponding to each ELS/distress group × time-vector interaction.

Age, gender and time of laboratory visit were considered potential confounders, while last Whitehall employment grade (as a measure of social class), body mass index (BMI) and smoking status (current smoker yes/no) were possible mediating variables (Hamer et al., 2010; Kidd et al., 2011). We did not include current depression symptoms (as measured by the CESD scale during the HSS) as a covariate in our models, since past history of psychological symptoms was a significant predictor of CESD score (OR = 5.8, $p < .0001$), and including CESD score would have been overcontrolling for this important aspect of our analysis.

To increase the robustness of our inference, we performed a nonparametric clustered bootstrap analysis with replacement, where participants were the clustering variable ($n = 50$ repetitions). All reported SEs are from the bootstrap analysis. Lastly, (unlogged) cortisol area-under-the-curve analysis (AUC_{ground}) (Pruessner et al., 2003) was used to examine total output of cortisol over the laboratory session.

3. Results

3.1. Participant characteristics

Sociodemographic characteristics of the participants are presented in Table 2, separated by ELS/distress status. Upon analysis, cortisol trajectories for the three non-ELS groups were determined to be nearly identical, with all $ps > .46$ for mean differences in log (and raw) cortisol at each sample

Table 2 Sociodemographic characteristics of study participants by ELS/distress group.

Characteristic	Non-ELS (N = 265)	ELS/no-distress (N = 52)	ELS/minimal-distress (N = 99)	ELS/recurrent-distress (N = 51)
Age in years (mean (SD))	62.1 (5.58)	64.6 (5.71)	63.2 (5.36)	61.7 (5.05)
Female, *N* (%)	111 (41.9%)	29 (55.8%)	42 (42.1%)	32 (62.8%)
Last employment grade, N (%)				
High	122 (46.0%)	14 (26.9%)	33 (33.3%)	21 (41.18%)
Intermediate	104 (39.3%)	22 (42.3%)	45 (45.5%)	19 (37.25%)
Low	39 (14.7%)	16 (30.8%)	21 (21.2%)	11 (21.6%)
Body mass index (mean (SD))	25.8 (4.11)	25.0 (3.60)	25.8 (3.43)	26.45 (4.41)
Current smoker, *N* (%)	12 (4.53%)	0 (.0%)	9 (9.09%)	4 (7.84%)
Reported HRT in 2003, *N* (%)	21 (7.9%)	3 (5.8%)	15 (15.2%)	7 (13.7%)

HRT, Hormone replacement therapy usage.

time (F-test (1, 418)) between these three groups. Accordingly, we grouped these participants into one (''non-ELS'') category for the piecewise growth curve modeling. Likewise, log (and raw) cortisol trajectories for the ELS/no-distress and ELS/minimal-distress groups were statistically identical, with all $ps > .58$ for mean differences between these groups at each sample time (F-test (1, 419)). We therefore combined these two groups into a single (''ELS/low-distress'') category for growth curve modeling, although their descriptive statistics and graphed cortisol trajectories are presented separately. Grouping the participants in this way did not affect inference from our results.

A substantial proportion of the analytic sample had a history of psychological distress episodes during adulthood. Overall, 19.6% (n = 83) participants experienced three or more episodes of GHQ scores $\geq$5, 20.1% (n = 85) experienced two such episodes, and 26.2% (n = 111) participants experienced one such episode. More than one-third of the participants (34.2%, n = 145) experienced no episodes of GHQ scores $\geq$5 over the six Whitehall waves. ELS-exposed participants were significantly more likely than non-ELS-exposed participants to have experienced any psychological distress episodes (OR = 1.81, p = .004) and somewhat more likely to have experienced three or more episodes (OR = 1.45, p = .098). Mean GHQ scores for each ELS/distress group at each wave are shown in Fig. 3. Across the six waves, the combined non-ELS group had an average GHQ score of 2.55, ELS/no-distress participants had an average score of .47, ELS/minimal-distress participants had an average score of 2.55, and ELS/recurrent-distress participants had an average score of 8.74.

Participants in the ELS/recurrent-distress category were more likely to be female compared to participants in the non-ELS (p = .054) and ELS/minimal-distress ($p < .01$) groups. There were no differences in proportion female between the other groups. The ELS/minimal-distress group was more likely than the non-ELS group to have a lower average employment grade (p = .001). The ELS/no-distress and ELS/minimal-distress groups tended to be older on average than the non-ELS group ($ps < .10$), but no other groups differed by age. Task stressfulness ratings indicated that the majority of participants in all groups found the tasks to be at least somewhat stressful, with no statistically

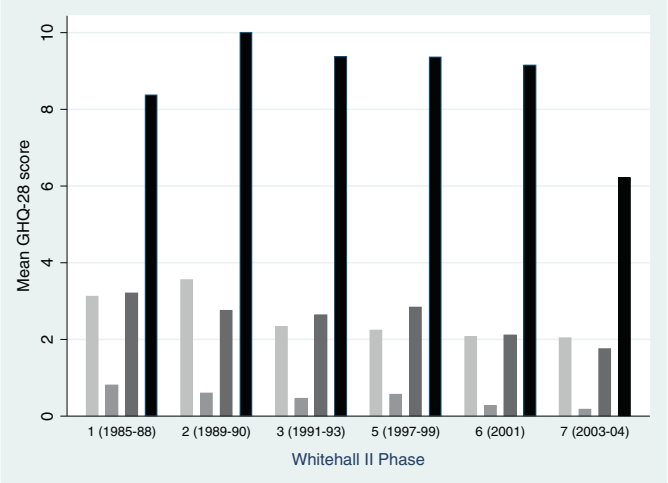

Figure 3 Mean GHQ-28 scores in the Heart Scan Study sample across each Whitehall II study wave, grouped according to participants' exposure to early-life stress and 20-year history of psychological distress. From left to right, in each Whitehall wave: lightest gray bars, non-ELS group; light gray bars, ELS/no-distress group; darker gray bars, ELS/minimal-distress group; black bars, ELS/recurrent-distress group.

Table 3 Frequencies of self-reported early-life stress (ELS) categories, by ELS/distress group.

ELS type	Non-ELS (N = 265)	ELS/no-distress (N = 52)	ELS/minimal-distress (N = 99)	ELS/recurrent-distress (N = 51)
Physical abuse	0	2 (3.85%)	9 (9.09%)	3 (5.88%)
1+ years of maternal separation/orphanage	0	12 (23.0%)	16 (16.16%)	11 (2156%)
Parental death	0	10 (19.23%)	28 (28.28%)	22 (43.13%)
Family substance abuse/ mental illness	0	8 (15.38%)	12 (12.12%)	9 (17.65%)
Parental divorce	0	3 (5.77%)	4 (4.04%)	2 (3.92%)
Parental conflict	0	26 (50.0%)	55 (55.55%)	24 (47.05%)
Harsh parenting	0	18 (34.62%)	44 (44.44%)	26 (50.98%)

significant group differences (Pearson's χ^2 p = .93). Table 3 presents the various ELS categories (parental death, physical abuse, etc.) and their respective frequencies in each ELS/distress group. There were no significant differences in the proportion of each ELS/distress group exposed to the individual ELS categories except that the ELS/recurrent-distress group was more likely to have experienced a parent's death (Pearson's χ^2 p = .027; all other ps $>$ .24).

Table 4 Fixed effects and random parameter estimates for piecewise growth curve models of reactivity and recovery levels of log cortisol.

	Model 1 Est (SE)	Model 2 Est (SE)	Model 3 Est (SE)
Fixed effects, β (SE)			
Intercept	2.029 (.029)	2.001 (.025)	1.808 (.151)
Time of visit	−.204 (.034)[a]	−.209 (.026)[a]	−.227 (.026)[a]
Reactivity (linear)	.007 (.001)[a]	.010 (.002)[a]	.010 (.002)[a]
Recovery (linear)	−.005 (.0006)[a]	−.007 (.0006)[a]	−.007 (.0006)[a]
Recovery^2 (quadratic)	.00003 (.000007)[a]	.00004 (.000007)[a]	.00004 (.00001)[a]
ELS/low-distress		.083 (.035)[c]	.054 (.033)
ELS/recurrent-distress		−.070 (.044)	−.064 (.056)
ELS/low-distress by reactivity		−.002 (.002)	−.001 (.002)
ELS/low-distress by recovery		.003 (.001)[c]	.003 (.001)[c]
ELS/low-distress by recovery^2		−.00004 (.00001)[b]	−.00004 (.00001)[b]
ELS/recurrent-distress by reactivity		−.011 (.003)[b]	−.011 (.003)[a]
ELS/recurrent-distress by recovery		.002 (.001)	.002 (.002)
ELS/recurrent-distress by recovery^2		.000004 (.00003)	.000005 (.00003)
Age			.007 (.003)[c]
Gender			−.002 (.032)
Civil service grade			.038 (.009)[a]
BMI			−.012 (.004)[a]
Current smoker			−.180 (.051)[a]
Random-effects parameters			
Standard deviations			
Intercept	.429	.413	.403
Reactivity	.023	.023	.023
Recovery	.011	.011	.011
Recovery^2	.0001	.0001	.0001
Correlations			
Intercept/recovery	−.14	−.45	−.47
Reactivity/recovery	.50	.50	.50
Reactivity/recovery^2	−.61	−.59	−.59
Recovery/recovery^2	−.87	−.88	−.88
−2 × log likelihood	1101.11	894.96	863.50

[a] $p < .001$.
[b] $p < .01$.
[c] $p < .05$.

3.2. Cortisol response to the stress tasks

Average raw cortisol values for the four groups are shown in Fig. 2. Plots for the non-ELS, ELS/no-distress and ELS/minimal-distress groups show a moderate increase in cortisol from baseline to immediately post-task (or 30 min post-baseline). This was followed by a gradual decline during the recovery period, with average final cortisol levels lower than those at baseline. Compared to the non-ELS group, the ELS/no- and minimal-distress groups' cortisol responses appear higher and more prolonged. In contrast, the ELS/recurrent-distress group did not show an increase in cortisol during the reactivity period, instead remaining flat or declining over both reactivity and recovery periods.

Results from multivariate piecewise growth curve models are shown in Table 4. The model 1 intercept indicates that the mean baseline value for log-cortisol, adjusted for time of visit, was 2.03 nmol/L. Baseline cortisol levels were significantly lower in the afternoon visits compared to the morning visits, but time of visit did not affect cortisol responses to stress. The mean baseline value for the morning sessions, in raw cortisol nmol/L, was 7.86 nmol/L (SD: 5.25); mean baseline value for the afternoon sessions was 5.85 nmol/L (SD: 4.14). Log-cortisol levels increased significantly during the reactivity period, by an average of .007 nmol/L per minute from baseline (model 1, reactivity). After the tasks ended, log-cortisol declined from its peak by an average of .005 nmol/L per minute (model 1, recovery), but this decline decreased in magnitude by an average of .00003 nmol/L per minute over the recovery period (model 1, recovery^2). Standard deviations for each random parameter in the model are shown under "Random-effects parameters" in Table 4. The intercept, reactivity, recovery, and recovery^2 random parameters indicate the amount of between-individual variability in cortisol baseline value or slopes during the two time periods.

Models 2 and 3 explored group differences in mean log-cortisol for baseline values and growth trajectories during the reactivity and recovery periods. The ELS/low-distress group had significantly higher baseline log-cortisol levels (mean = 1.95 nmol/L; $p = .052$) compared to the non-ELS group (mean = 1.88 nmol/L), although this difference was diminished after adjustment for covariates. Examination of the group $\times$ reactivity interaction vectors indicated that the ELS/recurrent-distress group differed significantly from the non-ELS group for cortisol slope during the reactivity period. As hypothesized, ELS/recurrent-distress participants had a blunted log-cortisol response to the stressor tasks, differing from the non-ELS group's response by an average of $-.001$ ($.010-.011$) nmol/L per minute. The ELS/low-distress and non-ELS groups' reactivity slopes were parallel, but the ELS/low-distress group's recovery slope remained elevated and did not decline as quickly as the non-ELS group's (model 3, ELS/low-distress by recovery and ELS/low-distress by recovery^2). Post hoc analyses also showed that the ELS/recurrent-distress and ELS/low-distress groups' reactivity slopes significantly differed from each other.

Gender was not a significant confounder. Older and higher-pay grade participants had significantly higher baseline cortisol values, while smokers and those with higher BMI had lower baseline cortisol. Likelihood ratio tests indicated that model 3 was a significantly better fit than models 1 and 2 (χ^2 $p < .00001$). Results from the nonparametric clustered bootstrap analysis gave inference that was identical, in comparison to non-bootstrap-based SEs, for all models.

Cortisol AUC_G analyses (available upon request) indicated that the ELS/low-distress group had significantly higher average cortisol output over the laboratory session compared to the ELS/recurrent-distress group ($p < .05$), controlling for the same covariates. Predicted group total cortisol outputs were 496.02 nmol/L (non-ELS), 545.23 nmol/L (ELS/low-distress), and 430.65 nmol/L (ELS/recurrent-distress). The AUC_G statistics comparing the ELS/recurrent-distress and ELS/low-distress groups to the non-ELS group did not reach significance ($p < .20$).

3.3. Sensitivity analyses

3.3.1. Hormone replacement therapy

Although we did not collect information on hormone replacement therapy (HRT) usage in the HSS, approximately half of the women (51.8%) had reported taking HRT in Whitehall wave 7 (2003–2004). To assess the sensitivity of our results to this factor, we added HRT usage in 2003–2004 (yes or no) as a further control variable to the final model. Hormone therapy usage significantly predicted lower cortisol levels ($\beta = -.18$, $p < .001$), but as other studies have found, our results were otherwise unaffected (Otte et al., 2005).

3.3.2. Current depression symptoms

Depression symptomatology at the HSS data collection differed significantly by ELS/distress group (mean CESD score [SD]: no-ELS group, 5.81 [5.81]; ELS/low-distress group, 5.33 [4.98]; ELS/recurrent-distress group, 11.73 [8.42]). To ensure that our results were not driven by these differences, we ran another model that included CESD score as a covariate. Our results remained robust; model coefficients did not change appreciably and CESD score was not a significant predictor of cortisol levels ($p > .30$).

3.3.3. Effect of continuously measured ELS

Although the complexity of the data analysis necessitated substantial data reduction for both ELS and longitudinal GHQ measures, we also explored the effect of ELS as a continuous variable. Increasing ELS scores significantly predicted more episodes of psychological distress ($p < .05$). There was no significant continuous association between higher summed ELS score and log cortisol reactivity slope, recovery slope, or baseline values (all $p > .14$).

3.3.4. Moderation by gender

As a final sensitivity analysis, we examined whether the observed effects were modified by gender (Otte et al., 2005). Because testing an overall three-way ELS $\times$ distress $\times$ gender term was not possible due to the analytic complexity of the model, we instead stratified the models by gender (results available upon request; see Fig. 4). Visually, these results showed evidence of effect modification. In both men and women, the ELS/recurrent-distress groups exhibited very blunted cortisol responses, remaining essentially flat or declining across the laboratory session, although baseline values were higher among men. Among women, as in the combined sample, the ELS/low-distress group exhibited high, prolonged cortisol levels across both response and recovery

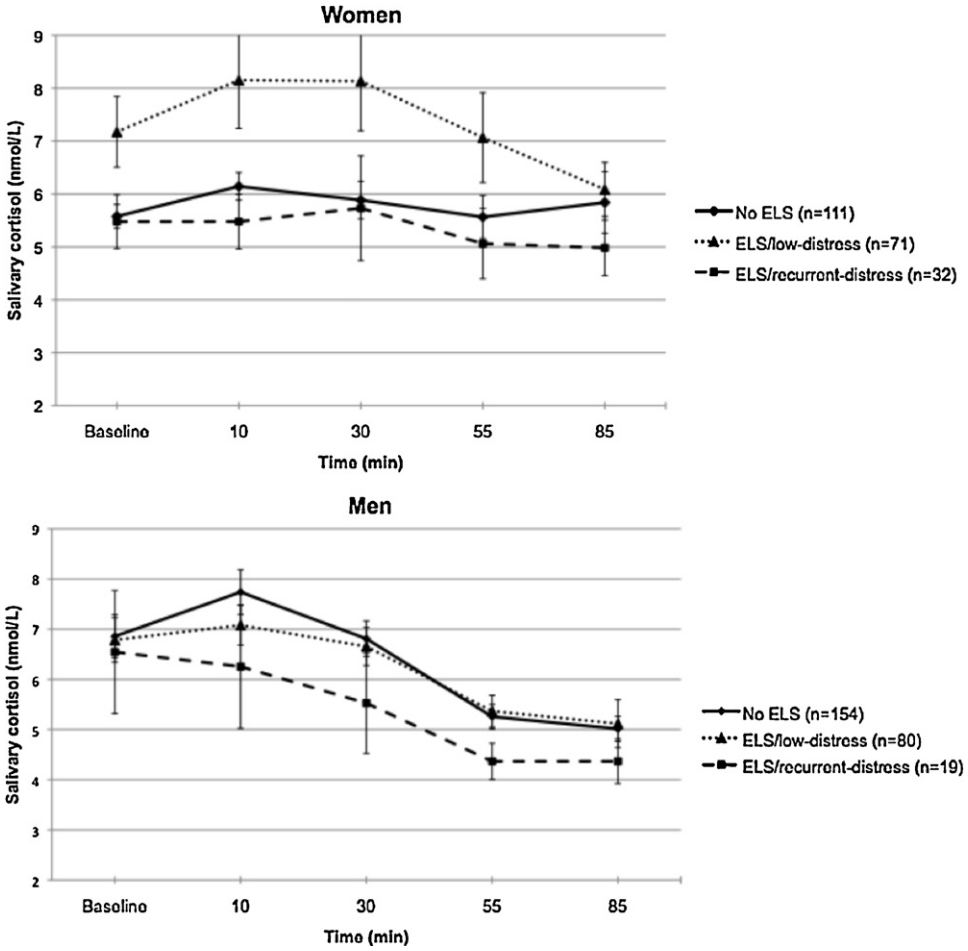

Figure 4 Salivary cortisol responses to the cognitive-behavioral challenge tasks in the Heart Scan Study sample, stratified by gender and grouped by ELS/distress category. Values are mean raw cortisol levels.

periods in comparison to the other two groups. Among men, the ELS/low-distress group exhibited a mean cortisol response curve that was higher than the ELS/recurrent-distress group's, but very similar to the non-ELS group's.

Statistically, the gender-stratified models also differed. Among men, of the model terms for log-cortisol baseline and response periods, only the term for a blunted reactivity slope ($p < .001$) in the ELS/recurrent-distress group was significant. Among women, model terms for heightened baseline cortisol in the ELS/low-distress group ($p < .05$), and heightened reactivity ($p < .05$) and flatter recovery ($p < .05$) slopes for the ELS/low-distress group, were significant. There was a trend indicating that the female ELS/recurrent-distress group's cortisol slopes were blunted compared to the no-ELS group's, but it did not reach significance ($p = .12$).

4. Discussion

To our knowledge, this is the first study to explicitly examine the role of recurrent, long-term psychological symptoms in the relationship between ELS and cortisol reactivity. Our findings suggest, consistent with our hypotheses, that adults exposed to early-life adversity have dysregulated cortisol reactivity trajectories, but that the pattern of those trajectories differs based on their history of psychological distress during adulthood. ELS-exposed older adults with recurrent psychological distress had blunted cortisol responses compared to non-ELS-exposed adults, as well as decreased overall cortisol output compared to ELS-exposed adults with a history of no or minimal psychological distress. In contrast, these ELS-exposed adults with minimal psychological distress had elevated levels of cortisol at baseline and prolonged responses to stress. Our results could not be explained by differences in participants' socioeconomic status, age, BMI, smoking status, or current depression symptoms. There was also some evidence that this association was modified by gender, with the effect in the ELS/low-distress group more pronounced among women, and the effect in the ELS/recurrent-distress group more pronounced among men. Effect modification by gender in the association between early-life factors and HPA axis stress reactivity has been observed in previous studies, and further research on this topic is clearly warranted (Kajantie and Raikkonen, 2010).

The divergent cortisol response patterns we observed are similar to those reported in one previous study that analyzed current psychological symptoms as a moderator of the ELS—HPA axis reactivity relationship (Harkness et al., 2011). These patterns are different from those found in some other

previous studies (Heim et al., 2000, 2002, 2008; Carpenter et al., 2007, 2009; Rao et al., 2008; MacMillan et al., 2009). However, mixed or non-significant results have also been reported (Heim et al., 2000, 2001, 2008). Other differences may also shed light on the inconsistencies. Most of these previous studies did not stratify their ELS-exposed participants by psychological status. Although many studies restricted their samples to only include ELS-exposed individuals who were psychologically healthy (or, alternatively, had current clinical depression), those "healthy" ELS-exposed groups very often had significantly higher levels of depression symptomatology when compared to the control groups. These psychologically "healthy" ELS-exposed samples could therefore have included people who, while not meeting clinical criteria depression, may still have had subclinical disorder. By not stratifying further on depression symptoms *among* the ELS-exposed groups, previous analyses may have missed additional heterogeneity that existed within these groups.

Furthermore, most prior studies used adolescent or young-adult samples, compared to our sample of older adults, which may partly explain the inconsistent results: a meta-analysis found that as sample age increased, depressed individuals showed increasingly blunted cortisol stress responses (Burke et al., 2005a). Lastly, many studies used the dexamethasone suppression test (DST) rather than psychological challenge tests, leaving the comparability of their results uncertain (Rao et al., 2008). Our findings are consistent with literature showing that depression and anxiety symptoms are associated with blunted cortisol reactivity (Burke et al., 2005a,b; Brooks and Robles, 2009; Ahrens et al., 2008; de Rooij et al., 2010). In our study, participants (particularly men) with a history of ELS and recurrent severe psychological distress — which may have qualified at one or more times as clinically significant — demonstrated this same cortisol response blunting. Dysregulation of the HPA axis in depression is believed to result, in part, from reduced feedback inhibition by endogenous glucocorticoids (Raison and Miller, 2003). However, data on HPA axis functioning in depression are generally complex and often difficult to interpret, and observed effects can depend on numerous factors (Stetler and Miller, 2011).

The processes underlying the connections between early-life adversity, HPA axis functioning, and psychological disorder are the subject of intense research. Several genetic polymorphisms (particularly the serotonin transporter gene promoter, 5-HTTLPR; Polanczyk et al., 2009; Uher et al., 2011) appear to moderate vulnerability to major depression following adverse early experiences. Animal models (Szyf et al., 2005; Stevens et al., 2009) and some human data (McGowan et al., 2009; Polanczyk et al., 2009) suggest that such gene—environment interactions may operate through the developmental programming of gene expression and epigenetic modifications in both brain and peripheral tissues (Seckl and Holmes, 2007). The physiological processes regulated by these genetic loci are often closely intertwined with HPA axis functioning (Gotlib et al., 2008; Alexander et al., 2009; Way and Taylor, 2010), and the effects of one or more such polymorphisms may help explain our findings.

Our study has certain limitations. Temporality of the relationship between cortisol reactivity pattern and history of psychological symptoms cannot be established using this dataset. As with all studies in this field, multiple lifelong prospective assessments of cortisol reactivity and psychological symptoms among ELS-exposed subjects would be necessary to demonstrate a causal relationship. However, our analysis provides a unique contribution through its use of a large study population and a longitudinal, prospective measure of psychological distress symptoms, measured over nearly 20 years. Prospective ascertainment of psychological symptoms is substantially more reliable than retrospective recalls (Wells and Horwood, 2004). Likewise, we (as other studies in this field) conceptualized our later-life measure of cortisol reactivity as a proxy for that in earlier in life, based on several methodological studies that have provided support for the supposition that cortisol reactivity is a stable trait (Kirschbaum et al., 1995; van Eck et al., 1996; Cohen et al., 2000). Needless to say, further investigation of this assumption is warranted. It is also possible that another, unknown factor is responsible for both psychological vulnerability and cortisol reactivity pattern. For example, there is some evidence that chronic exposure to stressful events is associated with reduced physiological reactivity to new stressors over time (Musante et al., 2000; Fries et al., 2005; Murali and Chen, 2005), a hypothesis that we were unable to examine.

All self-reported measures of ELS are subject to some bias, and the measures used in this study are relatively crude. However, there is evidence that the magnitude of such bias is often modest, that ELS is more likely to be underreported than overreported, and that basic questions pertaining to serious, readily operationalized experiences (such as those used in the Whitehall and HSS protocols) are more reliable than detailed queries (Dellafemina et al., 1990; Hardt and Rutter, 2004; Anda et al., 2006; Brown et al., 2007). We also were not able to use information on clinical psychiatric diagnoses or treatments in our measure of psychological history, as that information was not collected in the Whitehall II study. However, the GHQ-28 is a valid measure of severe psychological distress, and can function as a proxy for likely clinical disorder (Cleary et al., 1982; Koeter, 1992; Stansfeld and Marmot, 1992). Psychological distress is also a legitimate concern in its own right, both as an important source of population morbidity (Dohrenwend et al., 1980; Broadhead et al., 1990) and as a risk factor for coronary heart disease (Stansfeld et al., 2002) and other outcomes. Similar analyses in studies that have used validated measures of ELS and long-term psychiatric disorder would be valuable.

Lastly, selection criteria for HSS participants limits the study's generalizability in terms of the original Whitehall II cohort and its British source population. Individuals exposed to ELS who had severe mental and physical disorders in 2008 would have been excluded from the HSS sample, resulting in an atypically resilient study population. However, the HSS sample was similar to the overall baseline WH sample on many characteristics (Marmot et al., 1991), and their healthiness means that our findings cannot be attributed to underlying disease. Furthermore, their Whitehall GHQ scores indicate that a substantial proportion of them had significant prior psychological problems, despite the exclusion criteria. As with any study, replication will be necessary; until then our findings should be interpreted with caution.

Despite these limitations, the present study's results are strengthened by its large sample size, prospectively collected longitudinal psychological measures, and our use of

relatively novel and rigorous statistical methods. Our findings have important potential implications. Childhood adversity has been repeatedly shown to dramatically increase risk for multiple psychological disorders, often in an early-onset, severe, and highly recurrent form (Heim et al., 2004; Anda et al., 2006; Widom et al., 2007). Our investigation suggests that recurrent psychological vulnerability and comparative resiliency in the aftermath of ELS are linked to distinct cortisol reactivity patterns. If these associations between different patterns of HPA reactivity and long-term psychological vulnerability are causal in nature, employing treatment or prevention strategies that recognize the neurochemical changes underlying the psychological and physical sequelae of adversity may help to reduce the mental health impact of early-life stress (Heim et al., 2004; Danese et al., 2009).

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Conflict of interest

None declared.

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