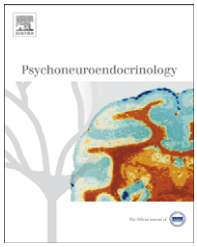
Psychoneuroendocrinology (2007) 32, 824–833

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen



Life-time socio-economic position and cortisol patterns in mid-life

Leah Li[a,*], Chris Power[a], Shona Kelly[b], Clemens Kirschbaum[c], Clyde Hertzman[d]

[a]*Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH, UK*
[b]*Division of Epidemiology and Public Health, Queen's Medical Centre, University of Nottingham, Nottingham NG7 2RD, UK*
[c]*Department of Psychology, TU Dresden, D-01062 Dresden, Germany*
[d]*University of British Columbia, Vancouver, BC, Canada V6T 1Z3*

Received 19 January 2007; received in revised form 16 May 2007; accepted 18 May 2007

KEYWORDS
Hypothalamic–pituitary–adrenal (HPA) axis;
Cortisol;
Birth cohort;
Life-time socio-economic position;
Chronic adversity

Summary
The influence of adversity over long periods of the life-span on adult cortisol metabolism is not established. We assess whether morning cortisol levels are associated with socio-economic position (SEP) from birth to mid-adulthood, and if so, whether the association is due primarily to SEP in childhood, adulthood or both. Data are from 6335 participants in the 1958 British birth cohort, with salivary cortisol samples collected at 45 yr. Two saliva samples were obtained on the same day: 45 min post-waking (t1) and 3 h later (t2). Median t1 and t2 cortisol values were 18.80 and 7.10 nmol/l for men; 19.60 and 6.60 nmol/l for women. Three outcomes were constructed: (1) extreme t1 cortisol (top and bottom 5%), (2) area-under-curve (AUC), and (3) abnormal t1–t2 pattern. All three outcomes were associated with lifetime SEP but the relative contribution of childhood and adulthood SEP varied by outcome measure. Our results suggest that the impact of less advantaged SEP over a lifetime would lead to an approximate doubling of the proportion of extreme post-waking cortisol levels for both sexes; an 8% and 10% increase, respectively for females and males in AUC, and an increased risk of having an abnormal cortisol pattern of 60% and 91%. SEP differences were independent of time of waking and sample collection, and in most instances, remained after adjustment for smoking and body mas index (BMI). Thus, our study provides evidence for effects of chronic adversity on cortisol in mid-adult life.

1. Introduction

It is now clear that socio-economic position in early life influences health status several decades later and that, for

*Corresponding author. Tel.: +44 207 813 8393; fax: +44 020 7905 2381.
E-mail address: l.li@ich.ucl.ac.uk (L. Li).

0306-4530/$ - see front matter
doi:10.1016/j.psyneuen.2007.05.014

some outcomes, early life factors operate over and above any effect they have on adult position (Kuh et al., 2004). What is not well-established is how the socio-economic environment "gets under the skin" and translates into biological risk. Among the possible contributors is the hypothalamic–pituitary–adrenal (HPA) axis and its role in the regulation of secretion of cortisol. Cortisol secretion patterns vary among individuals and certain of these patterns are thought to represent dysregulation of the HPA axis. Effects of dysregulation have been investigated in humans in relation to several health outcomes, including blood pressure (Phillips et al., 1998, 2000), glucose tolerance (Phillips et al., 1998), type 2 diabetes (Rosmond and Bjorntorp, 2000), stroke and cardiovascular disease risk (Rosmond and Bjorntorp, 2000; Reynolds et al., 2001), memory loss (Seeman et al., 1997) and breast cancer survival (Sephton et al., 2000).

Studies of several animal species suggest that cortisol levels are influenced by early nurturant experience (Suomi, 1997; Meaney, 2001). In children, differences in cortisol levels have been reported by socio-economic status (Lupien et al., 2000, 2005), mother's depressive symptoms (Lupien et al., 2001; Essex et al., 2002), childhood adversity (Carlson and Earls, 1997; Gunnar et al., 2001) and stressful environments (Flinn and England, 1997; Gunnar and Vazquez, 2001). Elsewhere, it is reported that cortisol levels are associated with adult socio-economic status (Brandstadter, 1991; Steptoe et al., 2003; Kristenson et al., 2004; Kunz-Ebrecht et al., 2004; Cohen et al., 2006a, 2006b) and chronic stress due to unemployment (Ockenfels et al., 1995). With few exceptions (Decker, 2000), studies of adult populations have lacked information on environment in early life. Hence, we do not know whether early socio-economic environment permanently alters cortisol metabolism, with effects of adversity persisting beyond childhood. More generally, we have a poor understanding of how a complex adaptive system, such as that regulating cortisol metabolism, might operate over the life course.

It has long been known that health and cognition risks are attendant on the pathophysiological states of both hyper-cortisolism (Cushing's disease) and hypo-cortisolism (Addison's disease). In sub-clinical settings, variations in cortisol secretion may be normative and adaptive in the short term, exposure to extremes of circulating cortisol over a prolonged period of the life-course may be detrimental to health. In experimental studies in animals, chronically elevated cortisol levels endanger memory and learning cells in the hippocampus and accelerate the ageing of a wide range of organ systems (Sapolsky, 2000). In humans higher cortisol levels are associated with greater cognitive decline in the elderly (Karlamangla et al., 2005). Chronic, repeated adversity may change the regulation of the HPA axis, (McEwen, 1998, 2000) and may lead to either hyper or hypo secretory states, either of which may have adverse consequences, with the mid-range having the most favourable outcomes (Belanoff et al., 2001; Davis et al., 2002; Haley et al., 2006; Herbert et al., 2006). Some evidence exists suggesting that hypo-secretion is associated with health outcomes such as breast cancer survival (Sephton et al., 2000), and physiological risk factors for cardiovascular disease, diabetes and stroke (Rosmond and Bjorntorp, 2000).

In order to examine the role of chronic adversity on cortisol levels, we need to take account of cortisol secretion patterns. Largely on the basis of small study samples with multiple cortisol measures over the day(s), it has been established that cortisol typically follows a diurnal rhythm, with a peak soon after waking in the morning and a gradual decline throughout the day (Stone et al., 2001). However, in studies examining effects of environmental stimuli, other patterns have been observed, including an absence of the early morning peak or alternatively, prolongation of the high awakening level or rises later in the day (Gunnar and Vazquez, 2001). In sum, the literature suggests that an early morning peak followed by decline is a normative pattern but that alternate diurnal cortisol patterns are seen (Stone et al., 2001). These may include an absence of the morning peak in cortisol and its associated decline (Gunnar and Vazquez, 2001; Rohleder et al., 2004; Buchanan et al., 2004).

Our overall objective is to test whether chronic adversity contributes to cortisol levels, using lifetime socio-economic position (SEP) to indicate chronic adversity. For those with least advantaged SEP there is greater exposure to poor housing, poorer cognitive development, increased family disruption in childhood and, in adulthood, greater job insecurity, early parenthood and financial problems (Power and Matthews, 1997). We use data from a population followed at regular intervals from birth, the 1958 British birth cohort, with salivary cortisol samples at age 44–45 (Power and Elliott, 2006). These data provide a unique opportunity to understand the relationships between life-course SEP and cortisol in mid-life. This paper specifically addresses whether adult cortisol levels are associated with socio-economic position from birth to mid-adult life, and if so, whether the association is due primarily to SEP in childhood or in adulthood or both. We also examine the possible contribution of smoking and adult body mass index (BMI) to the associations between SEP and adult cortisol levels.

2. Methods

2.1. Study population

The 1958 birth cohort includes all children born in England, Scotland and Wales, in one week in March, 1958. A population of about 17,000 live births were followed-up at ages 7, 11, 16, 23, 33, 42 yr (Power and Elliott, 2006). More recently, at 44–45 yr, a target sample of 11,971 participants identified as still in contact with the study, and at age 42 had not required a proxy interview (due to learning disability) were invited to a clinical examination undertaken in their home by a trained nurse; 9377 (78%) participants were seen September 2002–March 2004. Ethical approval for the 45 yr biomedical survey was given by the South East Multi-Centre Research Ethics Committee.

2.2. Measures

2.2.1. Socio-economic measures

Social class in childhood was based on father's occupation at birth, and ages 7, 11 and 16 yr, and categorised 1–4 as

classes I & II (professional/managerial), IIINM (skilled non-manual), IIIM (skilled manual), and IV & V (semi-unskilled manual). Social class in adulthood was based on the cohort member's current or most recent occupation at ages 23, 33, and 42 yr, and categorised as above. A life-time SEP score was derived by summing across social class at all seven ages, from birth to age 42 yr and then dividing by the number of ages for which social class was recorded. The lifetime SEP score was derived for cohort members who had at least one social class measure in childhood and adulthood. Separate SEP scores were derived similarly for childhood and adulthood using social class at (1) the four childhood ages (at birth, ages 7, 11, or 16 yr), (2) the three adult ages (ages 23, 33, or 42 yr). All SEP scores ranged between 1 and 4 (corresponding to the highest and lowest SEP, respectively, i.e. social class I & II and IV & V).

2.2.2. Salivary cortisol

Although absolute levels of cortisol in saliva are significantly lower than in blood, they are strongly correlated with serum cortisol (between $r = 0.71$ and 0.96) and are more closely correlated with the "free" cortisol fraction (Kirschbaum and Hellhammer, 1994). Thus, not only are salivary measures relatively easy and inexpensive to collect, and therefore well-suited for population studies, they are also a good measure of the metabolically active ("free") fraction of cortisol. Collecting saliva from a large number of individuals resident throughout Britain poses feasibility issues not encountered in smaller studies. Among the latter, Kirschbaum, Cohen and Smyth collected as many as 49 saliva samples on a given day, or collected samples on 24 separate days (Stone et al., 2001). Whereas, in the 1958 population-based cohort, it was feasible and affordable to collect only two samples per participant on one day. The two samples were timed to capture the main features of the diurnal rhythm of cortisol secretion, namely the post-waking peak and subsequent rapid decline. Accordingly, at 45 yr, participants were requested to collect two saliva samples on the next convenient day, the first to be collected 45 min after awakening (time 1) and the second, 3 h later on the same day (time 2). A reminder letter was sent to 53% of those consenting to return a saliva sample, if they had not done so within 2 weeks of the nurse visit to their home. Saliva samples were received from 6568 participants: of these 6527 yielded usable information on cortisol levels, and 6452 (69% of those who had a nurse visit) yielded information at both time 1 and time 2.

Participants were instructed to avoid brushing or flossing their teeth, or eating or drinking for at least 15 min before taking each sample. They were asked to chew on the salivette until it was soaked, record the time of collection, and store the sample at room temperature until mailed to the laboratory. Salivary cortisol is stable at room temperature for up to 30 days but the samples were frozen after reaching the laboratory to reduce microbial growth.

Cortisol levels were measured at the University of Dresden with a commercial immunoassay kit with chemiluminescence detection (CLIA, IBL-Hamburg, Hamburg, Germany). The lower sensitivity of this assay is 0.44 nmol/l, with intraassay and interassay precision of $<10\%$ for a wide range of cortisol concentrations. High cortisol levels (>50 nmol/l) were rerun in at least two, in most cases three to four assays for confirmation. Information was also collected on whether the participant regularly worked at night (shift worker), were awake during the previous night (24:00—06:00h), had dental work within the last 3 days or had cuts or other damage inside mouth that may bleed, and the day of the week. Any medication(s) currently taken by the participant was also recorded.

Based on theoretical models and empirical observations of atypical cortisol secretion, we constructed three outcome measures using the two cortisol samples. First, based on observations showing the mid-range to have most favourable outcomes, the t1 cortisol level was used to indicate a hyper, hypo or normal cortisol post-waking response. Second, the relationship between t1 and t2 cortisol was used to indicate whether the individual had a "normal" decline over the morning. Finally, the area-under-the-curve (AUC) from t1 to t2, was used as an estimate of total 3 h exposure to "free" cortisol. Since cortisol tends to be lower after the initial 3–4 h post-waking, the AUC of morning samples is likely to capture most of the between-subject variation in "free" cortisol.

2.3. Data analysis

Analyses are based on 6335 (3125 male and 3210 female) participants with information on social class on at least one age in childhood (birth, 7, 11, 16 yr) and adulthood (23, 33, or 42 yr) and cortisol level at age 44–45. This analysis sample ($n = 6335$) is similar to the original birth study with respect to social class of origin and in adulthood: 21% of our sample with cortisol was from classes IV and V at birth, compared to 23.8% in the 45-yr biomedical sample and 24.3% of the original birth sample. For adult class at 42 yr, 10.9% of men and 19.6% of women in the cortisol study sample were from classes IV and V compared to 10.8% and 19.9%, respectively, in the 45-yr biomedical sample and 11.4% and 20.6% in the original sample.

Extreme outliers for time 1 and time 2 were truncated: at 2 nmol/l for <2 nmol/l ($n = 24$ at t1; $n = 123$ at t2) and also at 100 nmol/l for >100 nmol/l ($n = 22$ at t1; $n = 20$ at t2) in order that potentially implausible values did not exert a strong influence on the analyses. Not all samples were collected at the specified times, leading to variation in times around the target for t1 (mean (s.d.) of 49(15) min after awakening) and t2 (mean (s.d.) of 3 h 5 min (23 min)). Cortisol values were skewed and therefore transformed using Log 10. Cortisol level was influenced by both time of awaking and time since awaking, the transformed cortisol values were therefore centred at 08:08 h (45 min after mean waking time) and t2 values at 11:08 h (3 h 45 min after mean awakening time of 07:23 h), using predictions from linear regression models, then back transformed to the original scale (nmol/l). Thus, t1 and t2 cortisol values used in all analyses, are adjusted for both time of awaking and time since awaking.

We examined associations for potential confounding factors in relation to t1 and t2 cortisol. Regular shift working, recent dental treatment, cuts inside mouth, current medication, and sleep disturbance were not associated with t1 cortisol level. However, shift working

was weakly associated with a reduced t2 cortisol, while cuts and sleep disturbance during the previous night, i.e. awake between 12pm and 6am, was weakly associated with an increased t2 cortisol level, but only in women. Smoking was strongly associated with increased t1 and t2 cortisol levels, while adult BMI was associated with reduced cortisol levels. We therefore adjusted for smoking and BMI. All analyses were conducted for men and women separately.

As expected, the most common pattern was of relatively high post-waking cortisol with a steep decline to pre-lunch, but other patterns were also observed in approximately one of every 6 subjects. For example, for some individuals there was little difference between the two measures. In order to characterise and differentiate cortisol patterns, namely, extremes (hyper and hypo-secretion) of the distribution, ''normal'' diurnal decline, and total exposure to ''free'' cortisol, we constructed three outcomes from the two cortisol samples. First, we derived a categorical measure based on t1 cortisol level, by classifying extreme (top and bottom 5%) or intermediate values (middle 90%). Cut-offs were 40.7 and 7.24 nmol/l for men; 41.7 and 7.94 nmol/l for women. Second, to differentiate ''normal'' diurnal decline from atypical cortisol patterns, we used arbitrary cut-offs, in the absence of a validated definition, with ''normal'' having a t1 cortisol value >7.5 nmol/l and a t2 value that is 20% lower than the t1 value; t1 and t2 values not fulfilling these criteria were defined as 'abnormal'. Third, to capture the total 3hr exposure to cortisol we used a continuous outcome measure, AUC, calculated using predicted t1 and t2 cortisol values at targeted measurement time. AUC was Log 10 transformed to reduce skewness of the distribution.

The association of SEP with AUC was examined using linear regression models. Because AUC was log 10 transformed, percentage change of AUC was calculated from the regression coefficient (β) as $100^*(10^{\beta}-1)$%. For example, t1 cortisol changes from value X1 to 10^{β} X1 for a unit increase in lifetime SEP. Thus, the increase will differ at different AUC values. Associations of SEP with extreme cortisol t1 values and with 'abnormal' t1–t2 change were assessed using logistic regression.

We first examined the unadjusted association of lifetime, childhood, or adult SEP with each of the three cortisol measures in univariate models, and then, examined separate contributions of childhood and adult SEP using models including both simultaneously. Using a quadratic term, we tested whether associations between cortisol measures and SEP were non-linear. Models that simultaneously adjusted for child and adult SEP were further adjusted for smoking (at age 42) and BMI (at age 45). In addition, we plotted the distribution of extreme t1 cortisol by lifetime SEP, for men and women separately, but here we used quintiles (rather than the four categories described above) to obtain similar numbers of participants per group. Similarly, the geometric mean of AUC and proportion of individuals with an abnormal t1–t2 cortisol pattern are plotted against the lifetime SEP.

Finally, we addressed the question of whether or not the pattern of change from high to low SEP is associated with cortisol patterns. Accordingly, the four social class groups in childhood and adulthood were collapsed into 'manual' and 'non-manual' and were then cross-classified to indicate social stability or mobility from childhood to adulthood. Cortisol values for the four resulting groups were compared.

3. Results

Men had a lower time 1 cortisol level (median 18.8 nmol/l), but a higher time 2 level (median 7.1 nmol/l), compared to women (19.6 and 6.6 nmol/l, respectively). Some participants had a higher t2 measure than t1, but on average, cortisol levels declined, with women having a greater decline than men. Total 3 h 'free' cortisol (AUC) was similar for men and women; for both the range of AUC values is wide, indicating large differences. The majority showed a 'normal' decline (82.4% for men, 86.6% for women), namely a t1 level >7.5 nmol/l and a decline of >20% to t2 (Table 1).

3.1. Time 1 cortisol and socioeconomic position

Fig. 1 shows the percentage of extreme t1 cortisol values according to quintiles of lifetime SEP. The percentage of extreme values increased from the most to the least favourable socio-economic position: from 8.0% to 13.0% for men and 8.4% to 13.8% for women. The ORs in Table 2 of 1.30 for men and 1.28 for women indicate that the odds of having an extreme value increased by 30 and 28% respectively per unit decrease in lifetime SEP (equivalent, for example to an average life-time change between classes IIIm to IV & V). Both childhood and adulthood SEP were associated with having an extreme cortisol value, but after simultaneous adjustment, only adulthood SEP had an independent effect. With further adjustment for smoking and BMI the effects of SEP attenuated (Table 2), in particular due to adjustments for smoking. Thus, the primary contribution to extreme t1 cortisol values at age 44–45 appears to be in relation to adult SEP, with childhood SEP operating through its contribution to adult position.

3.2. AUC and socioeconomic position

For both men and women, AUC increased as life-time SEP decreased (Fig. 2). The estimates in Table 2 indicate that for men and women there is respectively a 3.28% and 2.57% increase in AUC per unit decrease in life-time SEP (for example, from I & II to III nm): equivalent to a 10% and 8% increase from life-time class I & II to IV & V. For men, childhood SEP was associated with AUC before adjustment for adult SEP and the effect was little altered with adjustment for adult SEP (Table 2). No independent effect of adult SEP was evident after allowance for childhood SEP. Thus for men, SEP in childhood appears to be the predominant influence on AUC, whereas for women, neither child nor adult SEP predominated. Opposing effects on the SEP/AUC association were found, with a weakening of the association after adjustment for smoking, but strengthening associations with adjustment for BMI (data not presented). The combined effect of adjustment (smoking and BMI) was to attenuate SEP associations in males, whereas the association with lifetime SEP in women was unaffected by adjustment (Table 2).

3.3. Abnormal (time 1–time 2) cortisol pattern and socioeconomic position

Fig. 3 illustrates the trend by lifetime SEP in the percentage of participants whose t1–t2 cortisol levels did not show a

Table 1 Summary of cortisol values and time of measurement at the 45-year follow-up of the 1958 British birth cohort.

Times of measures (h:min) mean (s.d.)	Men	*n*	Women	*n*	*p*-Value[a]
Waking up time	7:23 (1:22)	3015	7:24 (1:12)	3200	
Time 1	8:12 (1:22)	3173	8:13 (1:12)	3298	
Time since waking	0:49 (0:15)	3014	0:49 (0:15)	3197	
Time 2	11:17 (1:26)	3061	11:17 (1:13)	3170	
Interval (time 2-time 1)	3:06 (0:26)	3059	3:04 (0:18)	3166	
Time 1 cortisol (nmol/l)[b] mean (s.d)	21.01 (11.94)	3187	21.88 (12.15)	3283	0.001
Median	18.80		19.60		
Time 2 cortisol (nmol/l)[b] mean (s.d)	9.20 (9.02)	3200	8.24 (7.63)	3309	<0.001
Median	7.10		6.60		
AUC (nmol/l) mean (s.d.)	44.82 (24.82)	3176	44.75 (22.58)	3276	0.28
Median	40.11		40.68		
Range	(6, 300)		(6, 300)		
Typology for the t1–t2 change[c] (%)					<0.001
Normal decline	82.4	2617	86.6	2836	
Abnormal	17.6	559	13.4	440	

[a]Gender difference.
[b]Truncated at 2 and 100 nmol/l.
[c]"Normal" diurnal decline i.e. having a t1 cortisol value $>$ 7.5 nmol/l and a t2 value that is 20% lower than the t1 value; t1 and t2 values not fulfilling these criteria were defined as 'abnormal'.

'normal' decline. For both men and women there is a modest increase in risk of an 'abnormal' pattern across the quintiles of lifetime SEP. The models in Table 2 predict a 24% increase in abnormal t1–t2 cortisol for men and 17% increase for women per unit decrease in lifetime social class that, across four social class 'units', is equivalent to 91 and 60% increases, respectively. Table 2 shows that for women the principal contribution to the lifetime SEP effect is from adulthood SEP, whereas for men effects of childhood SEP operated through their contribution to adult position. There was attenuation of SEP associations after adjustment for smoking and BMI, particularly in women for whom the association with lifetime SEP was largely accounted for by these factors. Nonetheless in men associations remained after adjusting for smoking and BMI (Table 2).

The four social class groups in childhood and adulthood were collapsed into 'manual' and 'non-manual' and were then cross-classified to indicate social stability or mobility from childhood to adulthood. Upwardly mobile men from manual to non-manual class were less likely to have an extreme t1 cortisol measure than those remaining in the manual class (8.8% vs. 12.6%). Downwardly mobile men (non-manual to manual) had a lower AUC than those always in the manual class (mean log 10 AUC was 1.56 vs. 1.62) and also, had a lower AUC than the upwardly mobile (1.56 vs. 1.60). There was a lower prevalence of abnormal t1 to t2 pattern in upwardly mobile men versus those remaining in the manual class (14.7% vs. 21.1%).

4. Discussion

In this large population-based study, in mid adult life, the majority (82.4% of men and 86.6% of women) showed a post-waking level of more than 7.5 nmol/l, and a decline of more than 20% from time 1 to time 2. The remaining 17.6% of men and 13.4% of women had abnormal patterns. Although there have been many previous studies on short-term influences on cortisol, there are far fewer studies, like ours, that examine long-term relationships. Our focus is on chronicity of adversity over decades, and is not limited to acute events. The main finding of this study is that cortisol levels are associated with lifetime SEP; with a greater risk of extreme post-waking values, abnormal t1 to t2 pattern, and higher AUCs as lifetime SEP becomes less favourable. SEP differences were independent of time of waking and sample collection, and in most instances, remained after adjustment for smoking and BMI. There are four ways in which a long-term association between SEP and cortisol in mid-life could emerge. There could be an independent contribution of childhood SEP with no contribution from adulthood; an independent adulthood contribution with no childhood contribution; a contribution from both adulthood and childhood; and an indirect childhood contribution, through its influence on adult SEP. All four of these patterns occurred in this study. Since cortisol patterns were measured for the first time on the 1958 cohort in mid-life, we are unable to determine whether SEP preceded or followed the establishment of cortisol patterns.

4.1. Methodological considerations

Ideally, an individual's daily rhythm of cortisol is obtained from multiple collections of saliva throughout a day, repeated over several days in order to obtain a cortisol pattern with high reliability. In the case of measures around the time of waking, the level of variability is high and may require up to 6 days of sampling to characterize an individual's mean waking response (Hellhammer et al.,

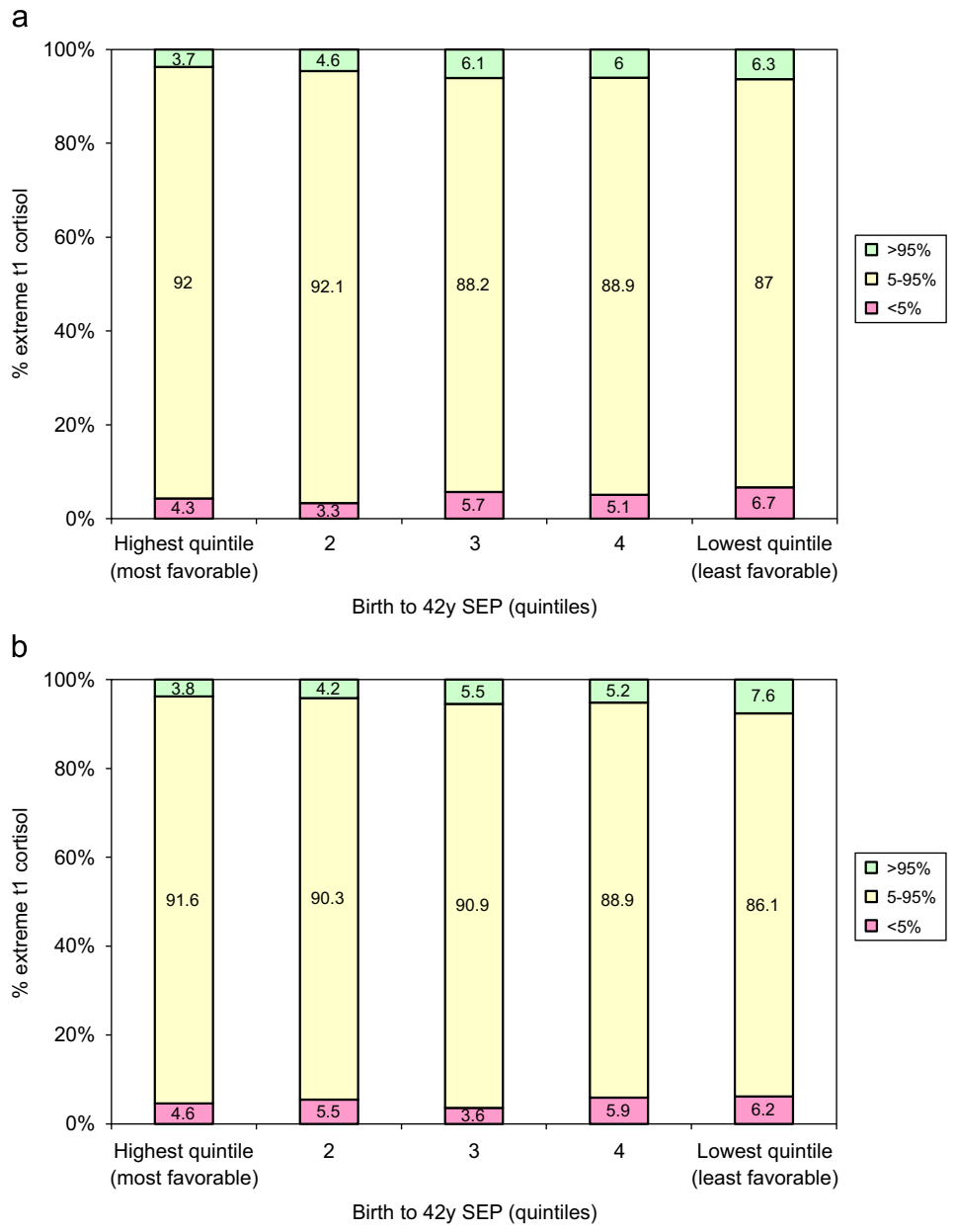


Figure 1 Lifetime (birth to 42 yr) socio-economic position (quintiles)* and % extreme time 1 cortisol values[#]. [#]Cut-offs for extreme t1 values were 40.7 and 7.24 nmol/l for men; 41.7 and 7.94 nmol/l for women. *In order to equalise the number of study participants in each group lifetime SEP scores were categorised into quintiles, with the highest quintile representing the most favourable SEP.

2007), which may affect the reliability of the outcome measures for each individual, i.e. AUC and patterns of decline from t1 to t2 (based on slope) (Kraemer et al., 2006). We acknowledge that this consideration applies to our t1 measure that was taken 45 min post-waking. Furthermore, we lack information on cortisol level on wakening, which may be needed to adequately characterize the post-waking peak. However, limitations regarding reliability of individual cortisol measures are likely to be offset by the large sample size in our study.

The literature on diurnal rhythm has established that decline in cortisol from the post-waking level occurs mainly within the first few hours of the day and this represents the normative pattern (Stone et al., 2001). In our large population study a maximum of two saliva measures on one day was feasible and affordable. Moreover, in the absence of unambiguous guidance from the literature on optimal timing for two samples, based on the evidence and expert opinion available at the start of fieldwork, we selected a post-waking measure followed by a pre-lunch measure three hours later and thus, our measure of AUC captures partial rather than ''total exposure''. However, our two samples were collected when cortisol levels are highest and changes in daytime cortisol appear to be greatest, and we would therefore expect that our AUC measure would capture most of the variability.

Analytic strategies have been described for cortisol sampling with several measures throughout the day (Hruschka et al., 2005; Ranjit et al., 2005). Our analytic strategy for two measures was directed towards extreme cortisol values,

Table 2 Associations[a] between socio-economic position (SEP) and cortisol measures at age 45 yr, for lifetime SEP and separately for child and adult SEP.

	T1 cortisol (<5th or >95th percentile) OR (95% CI)	AUC % Change (95% CI)	Abnormal[b] pattern OR (95% CI)
Males ($n = 3125$)			
Lifetime (birth–42 yr) SEP	1.30 (1.12, 1.52)	3.28 (0.97, 5.63)	1.24 (1.10, 1.40)
Adjusted for confounders[d]	1.24 (1.06, 1.46)	2.33 (0.05, 4.66)	1.18 (1.04, 1.34)
Childhood SEP (birth–16 yr)			
Unadjusted	1.15 (1.01, 1.31)	2.80 (0.96, 4.67)	1.10 (1.00, 1.23)
Adjusted for adult SEP	1.06 (0.92, 1.22)	2.57 (0.73, 4.43)	1.04 (0.93, 1.16)
Adjusted for confounders[e]	1.04 (0.90, 1.21)	2.33(0.50, 4.19)	1.02 (0.91, 1.14)
Adult SEP (23–42 yr)			
Unadjusted	1.25 (1.11, 1.41)	1.62 (−0.19, 3.48)	1.21 (1.10, 1.33)
Adjusted for child SEP	1.22 (1.07, 1.39)	0.69 (−1.11, 2.53)	1.19 (1.07, 1.32)
Adjusted for confounders[e]	1.19 (1.03, 1.36)	0.06 (−1.73, 1.88)	1.16 (1.04, 1.29)
Females ($n = 3210$)			
Lifetime (birth–42 yr) SEP	1.28 (1.10, 1.49)	2.57 (0.73, 4.43)	1.17 (1.02, 1.34)
Adjusted for confounders[d]	1.22 (1.04, 1.44)	2.57 (0.28, 4.91)	1.04 (0.90, 1.21)
Childhood SEP (birth–16 yr)			
Unadjusted	1.16 (1.02, 1.32)	1.62 (−0.19, 3.48)	1.04 (0.93, 1.16)
Adjusted for adult SEP	1.11 (0.97, 1.27)	1.16 (−0.65, 3.00)	0.99 (0.88, 1.11)
Adjusted for confounders[e]	1.10 (0.96, 1.26)	1.62 (−0.19, 3.48)	0.94 (0.83, 1.05)
Adult SEP (23–42 yr)			
Unadjusted	1.19 (1.05, 1.34)	1.62 (−0.19, 3.48)	1.17 (1.05, 1.30)[c]
Adjusted for child SEP	1.15 (1.01, 1.31)	1.16 (−0.65, 3.00)	1.18 (1.05, 1.32)[c]
Adjusted for confounders[e]	1.11 (0.97, 1.27)	0.93 (−0.88, 2.76)	1.12 (0.99, 1.26)

[a]All associations are for a unit decrease in SEP.
[b]All groups except 'normal' decline in Table 1.
[c]Significant quadratic relationship.
[d]Adult smoking (at age 42) and BMI (at age 45).
[e]The model includes childhood and adult SEP, adult smoking (at age 42) and BMI (at age 45).

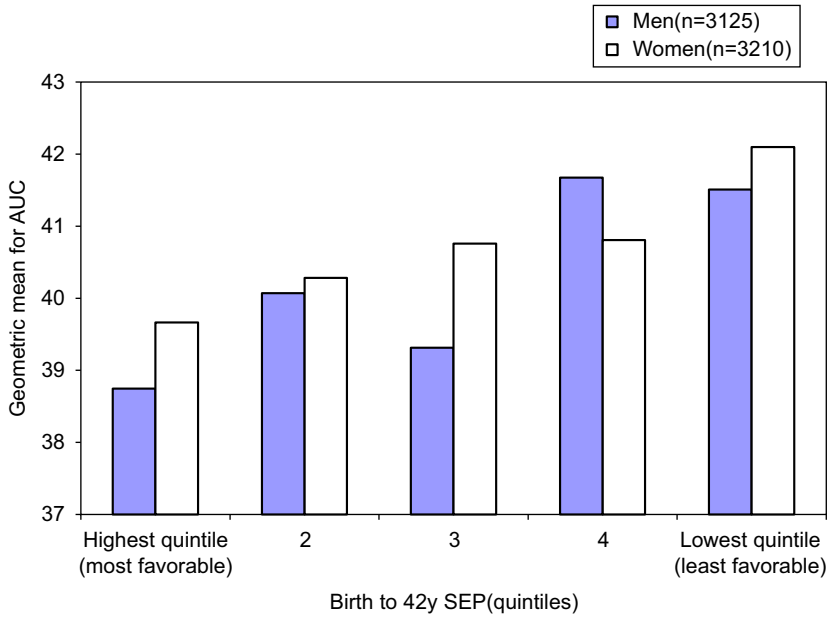


Figure 2 Lifetime (birth to 42 yr) socio-economic position (quintiles)* and geometric mean for AUC.

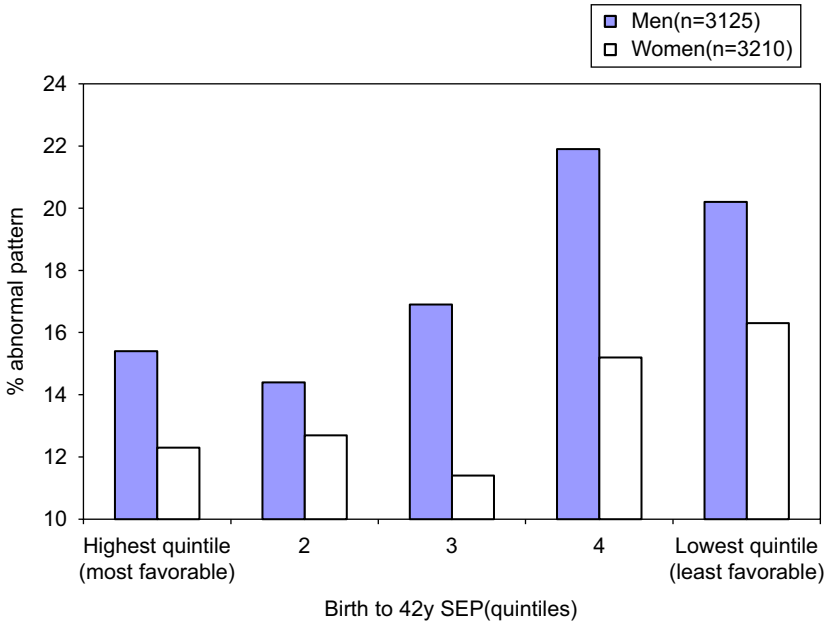


Figure 3 Lifetime (birth to 42 yr) socio-economic position (quintiles)* and abnormal# cortisol pattern (%). #"normal" diurnal decline i.e. having a t1 cortisol value >7.5 nmol/l and a t2 value that is 20% lower than the t1 value; t1 and t2 values not fulfilling these criteria were defined as 'abnormal'. *In order to equalise the number of study participants in each group lifetime SEP scores were categorised into quintiles, with the highest quintile representing the most favourable SEP.

total exposure and abnormal diurnal patterns. The three separate outcome measures were shown to be associated with different patterns of childhood and adulthood SEP; an important result of an exploratory study that would potentially have been obscured by other analytic strategies. Since our samples were collected starting in 2002, conflicting evidence has emerged on the relationship between SEP and diurnal cortisol patterns. One study shows higher evening cortisol levels for lower SES, defined according to income and educational level, (Cohen et al., 2006b) whereas, another study found no social differences in evening cortisol, but differences during the working day (Steptoe et al., 2003). Our study also suggests that SEP differences can be detected during the working day, but we are unable to assess differences in the evening.

Due to attrition, the sample with complete cortisol and SEP data was less than half of the original birth cohort, leading to an under-representation of cohort members from classes IV & V at birth. The distribution of SEP did not differ, however, between the study sample and the 45-year biomedical sample. We have no reason to suspect that the SEP/cortisol association seen for those included in our study differs systematically from those excluded. Further, we cannot discount the possibility of differential adherence to the saliva collection protocol, according to SEP, and this could be a particular problem for t1 cortisol (Hellhammer et al.; 2007). Nonetheless, mean values, 45 min post waking, in our study of 45 year-old men and women (21.01 and 21.88 nmol/l, respectively) are comparable to other studies: for example, 509 healthy adults aged 18–71 yr (22.3 nmol/l for men and women combined) (Wust et al., 2000). We were also able to consider an extensive range of potential confounding factors, such as shift work and medications.

4.2. Interpretation of findings

Our objective was to establish whether socio-economic adversity becomes biologically embedded via HPA axis regulation. Our results suggest that the impact of less advantaged SEP over a lifetime would lead to an approximate doubling of the proportion of extreme post-waking cortisol levels, 8–10% increase in AUC, and an increased risk of having an abnormal cortisol pattern of 60–91%. Although it is difficult to make judgements about effect sizes, these results, especially the latter one, would seem to be important. Associations for abnormal cortisol pattern were most affected by allowance for smoking and BMI, which is consistent with our finding of adult rather than childhood SEP associations. In addition, our findings for upwardly mobile men show that they have a more favourable profile for t1 cortisol and abnormal pattern than men who remain in the manual social classes, while downwardly mobile men retain a relatively low AUC similar to their childhood counterparts from the non-manual classes. This latter finding is consistent with a childhood influence on AUC.

It is difficult to compare our results with other studies of socio-economic position, foremost because few, if any, studies have examined SEP over a long period of the life span. Nonetheless, our study agrees with other studies that have shown gradients in cortisol levels, by income, education and occupation in adult life (Kunz-Ebrecht et al., 2004; Cohen et al., 2006b) and also the previous reports of gender difference (Steptoe et al., 2003). However, there is inconsistency in the previous literature regarding the association between cortisol and SEP, which may reflect differences in the frequency, timing and method (serum, saliva, urine) of cortisol measurement and whether the focus is on diurnal patterns or response to a challenge

protocol (Brandtstadter et al., 1991; Decker, 2000; Steptoe et al., 2003; Kunz-Ebrecht et al., 2004; Ranjit et al., 2005; Cohen et al., 2006b). In particular, the literature shows disagreement about the time of day when SEP differences can be detected, with studies suggesting that differences occur in the morning (Brandtstadter et al., 1991), the working day (Steptoe et al., 2003) or the evening (Cohen et al., 2006b). Our finding of SEP differences in the morning peak was detected with a t1 cortisol measure indicating either hyper and hypo-secretion, whereas previous researchers have not always looked for evidence of hypo-secretion. Others have demonstrated, using multiple cortisol samples over three days, that men and women with lower SEP in adulthood have a greater AUC than higher SEP groups, with an effect size similar to our study (Cohen et al., 2006a). Our findings suggest that, at least in men, this association can largely be attributed to childhood rather adult SEP. As we have shown, previous research also suggests that the association between adult SEP and cortisol is mediated by smoking (Steptoe et al., 2003; Cohen et al., 2006b). Other factors not examined here, such as depression, social relationships, job demands and unemployment, have also been suggested as contributing to the SEP/ cortisol relationship (Ockenfels et al., 1995; Kunz-Ebrecht et al., 2004; Cohen et al., 2006b).

By using socio-economic position as a general indicator we cannot discount the possibility that specific life circumstances, such as extreme deprivation or neglect, would produce different relationships. In this context, although in a very different population setting (Caribbean children in a rural village), associations with child cortisol levels were weak for SEP but stronger for family conflict (Flinn and England, 1997). We argue, however, that it is important to establish cortisol patterns across the full SEP spectrum, as we do in our study population, as a first step to understanding the relationship of social circumstances to the HPA axis over the life-course. Future studies will be needed to examine the factors underlying the associations with SEP shown here, including for example, the role of pre- and postnatal growth (Power et al., 2006) and more specific measures of adversity and neglect during childhood; as well as factors in adult life. Building this understanding of the pathways from early circumstances to adult cortisol patterns will then inform studies seeking to establish the role of cortisol on health outcomes in adult life.

Role of the funding source

Data collection at age 45 years was funded by the Medical Research Council (MRC), Grant G0000934.

Analysis was funded by the MRC and the Human Early Learning Partnership (HELP), Vancouver, Canada.

Research at the Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust benefits from R&D funding received from the NHS Executive.

Conflict of interest

We confirm that there is no conflict of interest associated with any contribution to this paper.

Acknowledgements

Data collection at age 45 years was funded by the Medical Research Council, Grant G0000934. Analysis was funded by the MRC and the Human Early Learning Partnership (HELP), Vancouver, Canada. Research at the Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust benefits from R & D funding received from the NHS Executive. *Data providers*: Centre for Longitudinal Studies, Institute of Education and National Birthday Trust Fund, National Children's Bureau, City University Social Statistics Research Unit.

References

Belanoff, J.K., Gross, K., Yager, A., Schatzberg, A.F., 2001. Corticosteroids and cognition. J. Psychiatr. Res. 35, 127–145.

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

Buchanan, T.W., Kern, S., Allen, J.S., Tranel, D., Kirschbaum, C., 2004. Circadian regulation of cortisol after hippocampal damage in humans. Biol. Psych. 56, 651–656.

Carlson, M., Earls, F., 1997. Psychological and neuroendocrinological sequelae of early social deprivation in institutionalized children in Romania. Ann. N. Y. Acad. Sci. 807, 419–428.

Cohen, S., Doyle, W.J., Baum, A., 2006a. Socioeconomic status is associated with stress hormones. Psychosom. Med. 68, 414–420.

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

Davis, E.P., Bruce, J., Gunnar, M.R., 2002. The anterior attention network: Associations with temperament and neuroendocrine activity in 6-year-old children. Dev. Psychobiol. 40, 43–56.

Decker, S.A., 2000. Salivary cortisol and social status among Dominican men. Horm. Behav. 38, 29–38.

Essex, M.J., Klein, M.H., Cho, E., Kalin, N.H., 2002. Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. Biol. Psych. 52 (8), 776–784.

Flinn, M.V., England, B.G., 1997. Social economics of childhood glucocorticoid stress response and health. Am. J. Phys. Anthropol. 102, 33–53.

Gunnar, M.R., Vazquez, D.M., 2001. Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. Dev. Psychopathol. 13, 515–538.

Gunnar, M.R., Morison, S.J., Chisholm, K., Schuder, M., 2001. Salivary cortisol levels in children adopted from romanian orphanages. Dev. Psychopathol. 13, 611–628.

Haley, D.W., Weinberg, J., Grunau, R.E., 2006. Cortisol, contingency learning, and memory in preterm and full-term infants. Psychoneuroendocrinology 31, 108–117.

Hellhammer, J., Fries, E., Schweisthal, O.W., Schlotz, W., Stone, A.A., Hagemann, D., 2007. Several daily measurements are necessary to reliably assess the cortisol rise after awakening: state- and trait components. Psychoneuroendocrinology 32, 80–86.

Herbert, J., Goodyer, I.M., Grossman, A.B., Hastings, M.H., de Kloet, E.R., Lightman, S.L., Lupien, S.J., Roozendaal, B., Seckl, J.R., 2006. Do corticosteroids damage the brain? J. Neuroendocrinol. 18, 393–411.

Hruschka, D.J., Kohrt, B.A., Worthman, C.M., 2005. Estimating between- and within-individual variation in cortisol levels using multilevel models. Psychoneuroendocrinology 30, 698–714.

Karlamangla, A.S., Singer, B.H., Chodosh, J., McEwen, B.S., Seeman, T.E., 2005. Urinary cortisol excretion as a predictor of incident cognitive impairment. Neurobiol. Aging 26 (Suppl 1), 80–84.

Kirschbaum, C., Hellhammer, D.H., 1994. Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology 19, 313–333.

Kraemer, H.C., Giese-Davis, J., Yutsis, M., O'Hara, R., Neri, E., Gallagher-Thompson, D., Taylor, C.B., Spiegel, D., 2006. Design decisions to optimize reliability of daytime cortisol slopes in an older population. Am. J. Geriatr. Psych. 14, 325–333.

Kristenson, M., Eriksen, H.R., Sluiter, J.K., Starke, D., Ursin, H., 2004. Psychobiological mechanisms of socioeconomic differences in health. Soc. Sci. Med. 58, 1511–1522.

Kuh, D., Power, C., Blane, D., Bartley, M., 2004. Socio-economic pathways between childhood and adult health. In: Kuh, D., Ben-Shlomo, Y. (Eds.), A life Course Approach to Chronic Disease Epidemiology. Oxford University Press, Oxford, pp. 371–395.

Kunz-Ebrecht, S.R., Kirschbaum, C., Steptoe, A., 2004. Work stress, socioeconomic status and neuroendocrine activation over the working day. Soc. Sci. Med. 58, 1523–1530.

Lupien, S.J., King, S., Meaney, M.J., McEwen, B.S., 2000. Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. Biol. Psych. 48, 976–980.

Lupien, S.J., King, S., Meaney, M.J., McEwen, B.S., 2001. Can poverty get under your skin? Basal cortisol levels and cognitive function in children from low and high socioeconomic status. Dev. Psychopathol. 13, 653–676.

Lupien, S.J., Fiocco, A., Wan, N., Maheu, F., Lord, C., Schramek, T., Tu, M.T., 2005. Stress hormones and human memory function across the lifespan. Psychoneuroendocrinology 30, 225–242.

McEwen, B.S., 1998. Protective and damaging effects of stress mediators. N. Engl. J. Med. 338, 171–179.

McEwen, B.S., 2000. Effects of adverse experiences for brain structure and function. Biol. Psych. 48, 721–731.

Meaney, M.J., 2001. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annu. Rev. Neurosci. 24, 1161–1192.

Ockenfels, M.C., Porter, L., Smyth, J., Kirschbaum, C., Hellhammer, D.H., Stone, A.A., 1995. Effect of chronic stress associated with unemployment on salivary cortisol: overall cortisol levels, diurnal rhythm, and acute stress reactivity. Psychosom. Med. 57, 460–467.

Phillips, D.I., Barker, D.J., Fall, C.H., Seckl, J.R., Whorwood, C.B., Wood, P.J., Walker, B.R., 1998. Elevated plasma cortisol concentrations: a link between low birth weight and the insulin resistance syndrome? J. Clin. Endocrinol. Metab 83, 757–760.

Phillips, D.I., Walker, B.R., Reynolds, R.M., Flanagan, D.E., Wood, P.J., Osmond, C., Barker, D.J., Whorwood, C.B., 2000. Low birth weight predicts elevated plasma cortisol concentrations in adults from 3 populations. Hypertension 35, 1301–1306.

Power, C., Elliott, J., 2006. Cohort profile: 1958 British birth cohort (National Child Development Study). Int. J. Epidemiol. 35, 34–41.

Power, C., Matthews, S., 1997. Origins of health inequalities in a national population sample. Lancet 350, 1584–1589.

Power, C., Li, L., Hertzman, C., 2006. Associations of early growth and adult adiposity with patterns of salivary cortisol in adulthood. J. Clin. Endocrinol. Metab. 91, 4264–4270.

Ranjit, N., Young, E.A., Raghunathan, T.E., Kaplan, G.A., 2005. Modeling cortisol rhythms in a population-based study. Psychoneuroendocrinology 30, 615–624.

Reynolds, R.M., Walker, B.R., Syddall, H.E., Andrew, R., Wood, P.J., Whorwood, C.B., Phillips, D.I., 2001. Altered control of cortisol secretion in adult men with low birth weight and cardiovascular risk factors. J. Clin. Endocrinol. Metab 86, 245–250.

Rohleder, N., Joksimovic, L., Wolf, J.M., Kirschbaum, C., 2004. Hypocortisolism and increased glucocorticoid sensitivity of pro-Inflammatory cytokine production in Bosnian war refugees with posttraumatic stress disorder. Biol. Psych. 55, 745–751.

Rosmond, R., Bjorntorp, P., 2000. The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. J. Intern. Med. 247, 188–197.

Sapolsky, R.M., 2000. Stress hormones: good and bad. Neurobiol. Dis. 7, 540–542.

Seeman, T.E., McEwen, B.S., Singer, B.H., Albert, M.S., Rowe, J.W., 1997. Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. J. Clin. Endocrinol. Metab 82, 2458–2465.

Sephton, S.E., Sapolsky, R.M., Kraemer, H.C., Spiegel, D., 2000. Diurnal cortisol rhythm as a predictor of breast cancer survival. J. Natl. Cancer Inst. 92, 994–1000.

Steptoe, A., Kunz-Ebrecht, S., Owen. N, Feldman.P.J., Willemsen, G., Kirschbaum, C., Marmot, M., 2003. Socioeconomic status and stress-related biological responses over the working day. Psychosom. Med. 65, 461–470.

Stone, A.A., Schwartz, J.E., Smyth, J., Kirschbaum, C., Cohen, S., Hellhammer, D., Grossman, S., 2001. Individual differences in the diurnal cycle of salivary free cortisol: a replication of flattened cycles for some individuals. Psychoneuroendocrinology 26, 295–306.

Suomi, S.J., 1997. Early determinants of behaviour: evidence from primate studies. Br. Med. Bull. 53, 170–184.

Wust, S., Wolf, J., Hellhammer, D.H., Federenko, I., Schommer, N., Kirschbaum, C., 2000. The cortisol awakening response-normal values and confounds. Noise Health 2, 79–88.