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The relationship of childhood adversity with diurnal cortisol patterns and C-reactive protein at 60-64 years of age in the 1946 National Survey of Health and Development

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Abstract

Background

Early life adversity is increasingly prevalent and associated with greater morbidity and mortality. It is hypothesised that the link between psychosocial early life adversity and poor health in adulthood is due to abnormal hypothalamic-pituitary-adrenal (HPA) axis functioning (often measured as cortisol patterning) and inflammation (often measured via c-reactive protein (CRP)). This study aimed to investigate the relationship between early life psychosocial adversity and cortisol patterning and CRP at 60-64 years of age.

Methods

The MRC National Survey of Health and Development (NSHD) was used. The analytic "cortisol sample" included 843 individuals and the "CRP sample" included 1,150 individuals. Data on adversity experienced between ages 0-15 years were utilised to compose a cumulative childhood psychosocial early life adversity (ELA) score (0, 1, 2, 3+). CRP and salivary cortisol (waking, 30 min after waking, and evening) were collected at 60-64 years. Associations between the psychosocial ELA score and cortisol outcomes (cortisol awakening response (CAR), diurnal slope (DS), and evening and morning cortisol) were assessed using general linear regression. Tobit regression was used to assess the association between psychosocial ELA score and CRP. Adjustments were made for age at follow-up, sex, childhood maternal education, childhood paternal social class, childhood housing tenure, and birth weight. After testing for sex by ELA score interactions, analyses were repeated stratified by sex for the CRP sample.

Results

In fully adjusted models, individuals who experienced the highest level of childhood psychosocial adversity (3+) had a 24.63 (-41.49, -7.76) % lower waking cortisol and a 7.30 (1.49, 13.12) % lower decline in cortisol across the day compared to those with a psychosocial ELA score of zero. In females, the highest level of childhood psychosocial adversity, compared to the lowest, was associated with 32.61 (2.98, 62.25) % higher CRP at 60-64 years, which attenuated to 20.38 % (-9.38, 50.14) upon adjustment for measures of early life socioeconomic position. Conversely, the association between childhood psychosocial adversity and CRP in males was null.

Conclusions

Our results suggest that high-levels of psychosocial adversity in childhood might result in a lower morning cortisol and flatter DS in mid-to-late-adulthood. The finding that adversity was related to higher CRP in females but not males requires replication and further investigation.

Adverse childhood experiences (ACEs)

Psychosocial stress

Early life adversity (ELA)

Cortisol

Inflammation

Longitudinal

Introduction

Psychosocial early life adversity (ELA) represents negative childhood life events that can lead to intense stress. Psychosocial ELAs constitute a major public health issue, due to their high and increasing prevalence and association with negative lifelong health outcomes (Annual Report of the Director of Public Health, 2018; Stoltenborgh et al., 2015). It has, for example, been shown that

adverse childhood experiences (ACEs) (a subset of ten psychosocial ELA's, identified by the seminal CDC- Kaiser study i.e., Abuse: physical, emotional, sexual; Neglect: physical or emotional; Household dysfunction: mental illness, incarcerated relative, mother treated violently, substance abuse, and divorce) are linked to increased risk for obesity and related non-communicable diseases (i.e., ischemic heart disease and type 2 diabetes mellitus (T2DM) (Hughes et al., 2017) and increased risk of mortality (Rod et al., 2020). A recent paper from our group demonstrated that the relationship between psychosocial ELA and increased cardiometabolic disease risk existed even in the absence of adulthood obesity (Robson et al., 2020). This suggests that early life adversity may be related to poor cardiometabolic health independently of the intervening lifestyle behaviours that are typically involved in the development of obesity (e.g., poor diet and a sedentary lifestyle).

Allostatic load is a key theory postulated to underpin the relationship between ELAs and poor long-term health outcomes (Danese and McEwen, 2012). The normal physiological reaction to acute stress includes hypothalamic-pituitary-adrenal (HPA) axis activation, causing an acute increase in glucocorticoid levels and anti-inflammatory effects, which help fight or flee the stressor, hence reflecting that of an adaptive process. Once the stressor has passed, homeostasis is regained and levels of physiological mediators return to normal, a concept described as allostasis. However, during chronic stress (exposure to repeated or severe psychosocial stress), the HPA axis may become dysregulated resulting in prolonged release of glucocorticoids and inflammatory markers, a concept described as increased allostatic load, and its more severe form as allostatic overload. It is at this point which the physiological mediators switch from being adaptive to damaging, causing physiological "wear and tear" on the body. Exposure to this type of stress and subsequent corticosteroids and inflammation may be particularly harmful during childhood, during which time physiological systems

are undergoing maturational changes (Andersen and Teicher, 2008; Bunea et al., 2017; Lupien et al., 2009), so increased allostatic load or allostatic overload may potentially lead to long-lasting effects on the body's nervous, endocrine, and immune systems (Danese and McEwen, 2012).

Studies often investigate long term impacts of early life adversity using cortisol response as a proxy for HPA axis functioning. Findings summarising the relationship between early life adversity and later life cortisol have been equivocal (Bunea et al., 2017; Fogelman and Canli, 2018; Hunter et al., 2011; Karlamangla et al., 2018; Power et al., 2012). Recent findings from longitudinal studies in the United Kingdom (UK) have not found early life adversity to be related to altered cortisol later in life. For example, Lob et al. (2020) using the English Longitudinal Study of Ageing (ELSA) found no strong evidence that cumulative retrospectively reported ACEs were related to hair cortisol in a sample of older adults (N= 2,600, aged 49-69 years). Tang et al (2020) also found no evidence that ACEs were associated with plasma cortisol in childhood (15.5 years). The reason for the null findings of these studies may be due to limitations in methods, as both of these studies investigated cortisol at one time point, which gives no indication of cortisol patterns across the day. Hair cortisol is also more indicative of chronic cortisol output over 2-3 months rather than acute diurnal cortisol patterns (Stalder and Kirschbaum, 2012). In addition, mixed findings in the literature may be due to a lack of longitudinal analyses using prospectively measured early life adversity.

Some studies have also investigated the long-term impacts of early life adversity on the immune system, using CRP as a biomarker of inflammation. Reviews summarising the evidence have found that adversity is associated with increased CRP (Baumeister et al., 2016; Coelho et al., 2014). Recent longitudinal studies in the UK have supported these findings. Lob et al. (2020) and Lob and

Steptoe (2019) investigated retrospectively reported early life adversity and CRP in the ELSA and found an ACE score of three or more (compared to zero) to be associated with higher CRP levels in adults aged over 50 years. Further, a series of papers using the 1958 National Child Development Study (NCDS) have also found that childhood adversity is related to increased inflammation at 44 years of age (Chen and Lacey, 2018; Lacey et al., 2020; Pinto Pereira et al., 2019).

The majority of studies investigating the relationship between childhood adversity and later life health outcomes use retrospectively measured psychosocial childhood adversity data. The Medical Research Council (MRC) National Survey for Health and Development (NSHD) is a birth cohort study of individuals born in 1946, inclusive of serial heterogenous measures of early life adversity, with the majority of data prospectively measured. To date, the Medical Research Council (MRC) National Survey for Health and Development (NSHD) has not been used to examine the relationship between childhood adversity and later life inflammation and cortisol response. Using a study with a high proportion of prospective data may help overcome the gap in the literature that currently exists, as to how early life adversity really 'gets under the skin' (Karlamangla et al., 2018).

The aim of our study was to investigate the relationship between cumulative early-life psychosocial adversity and diurnal cortisol patterns and CRP levels at age 60-64 years, using data from the MRC NSHD.

2.0 Methods

2.1 Cohort

The MRC NSHD is based on a socially stratified sample of 5,362 births out of all the single births to married mothers that occurred in one week in 1946 in England, Scotland, and Wales (Wadsworth et al., 2006). Participating individuals have been followed-up regularly since birth. Between 2006-2011, eligible participants (those known to be alive and living with an address in England, Scotland, or Wales) were invited to an assessment at one of six clinical research facilities or to be visited by a research nurse at home (n= 2,856). Invitations were not sent to those who had died (n= 778), were living abroad (n= 570), had previously withdrawn from the study (n= 594) or had been lost to follow up (n= 564). A total 2,229 participants out of the 2,856 invited (78%) underwent assessment: 1,690 attended a clinical research facility and the remaining 539 were seen in their homes. The study obtained ethical approval from Greater Manchester Local Research Ethics Committee and the Scotland Research Ethics committee (Kuh et al., 2011).

2.2 Samples

Figure 1 presents a flow diagram describing the selection of the analytic samples, however they are described in brief below.

2.2.1 CRP analytic sample

Of the eligible 2,229 participants who underwent clinical assessment at ages 60-64 years, the sample with valid CRP measures comprised 1,150 individuals.

2.2.2 Cortisol analytic sample

Of the eligible 2,229 participants who underwent clinical assessment at ages 60-64 years, the sample with valid complete cortisol measures comprised 843 individuals. Multiple steps were carried out as part of data cleaning; further information can be found in Figure 1.

2.3 Psychosocial early life adversity (ELA) score

Data on eight psychosocial adversities between birth and 15 years of age were used. Low parental concern for child's education, parental psychiatric history, parental divorce, maternal separation, and parental death were assessed by maternal or guardian report, augmented by health visitor and teacher reports and collected prospectively. Maltreatment, maternal affectionless control and paternal affectionless control were retrospectively assessed at age 43 years (see Supplementary Table 1 for a full breakdown of adversities). Each individual psychosocial adversity was coded as zero (no adversity) or one (presence of adversity). A psychosocial ELA score was created by summing these values. Due to low sample sizes in the higher groups, we categorised psychosocial ELA score as zero, one, two, and three or more adversities. This score has been used previously in this cohort (Caleyachetty et al., 2018; Robson et al., 2020).

2.4 Cortisol measures

Survey members were trained on the protocol for saliva collection at the clinic or home visit by the research nurse and requested to provide three saliva samples in salivettes; upon waking (waking), 30 minutes post waking (waking + 30), and one in the evening between 9.00 and 9.30pm (evening). Members were asked not to eat, drink, brush their teeth, or smoke a cigarette 30 minutes before each sample was taken. Salivettes and accompanying reports (e.g., times of samples) were returned via post. The samples were assayed by radioimmunoassay in a laboratory (Dresden) that specialised in high through-put cortisol analysis (Kirschbaum and Hellhammer, 1989). Intra- and inter-assay coefficients of variation were <10%.

Cortisol is secreted throughout the day, with high levels upon waking in the morning, and then decreases to a nadir at midnight, representing a pulsatile ultradian pattern superimposed upon a circadian rhythm (Hunter et al., 2011). Commonly studied markers of this rhythm include cortisol awakening response (CAR) (the change in cortisol concentration within the first hour of waking), diurnal slope (DS) (changes in cortisol concentration from morning to evening), and evening cortisol (Adam and Kumari, 2009). To adjust for cortisol at waking + 30 minutes for variation in time since waking, we regressed this variable on time since waking and saved the individual level predictions (i.e., mean fitted value plus individual residual). Cortisol awakening response (CAR) was then calculated by subtracting cortisol at waking from this new variable. This is an approach used in the literature to correct for differences in the lapsed time between the first and second samples (Mai Stafford et al., 2013). Diurnal slope was calculated by subtracting waking cortisol from evening cortisol and is expressed as change per hour.

2.5 CRP measures

CRP was measured in blood samples taken after an overnight fast by a trained research nurse during the clinic or home visit. Blood samples were initially processed at clinical research facility laboratories and stored at -80 °C before being couriered monthly on dry ice to the MRC Human Nutrition Research laboratory in Cambridge, where c-reactive protein was analysed according to standard protocols. Inter-assay coefficients of variation were 4.3% at 3.4 mg/L and 1.8% at 11.9 mg/L. Values lower than the detection limit of 1.1mg/L were assigned a notional value of -28. 84614 which was equal to the detection limit divided by the square root of two (Hornung and Reed, 1990).

2.6 Covariates

Age in months at the 60-64 years of age assessment was recorded, as was sex at birth. Birth weight to the nearest quarter of a pound was obtained via hospital records within a few weeks of birth and converted into kilograms (kg). Childhood socioeconomic variables included maternal education and paternal occupational social class, collected via maternal report, and housing tenure, collected via maternal and health visitor reports (See supplementary table 1 for more details).

2.7 Statistical analysis

We compared the characteristics of those included in the analytic sample with those who were excluded, using chi-square tests for categorical variables and t-tests for continuous variables.

In the sample included in analyses, descriptive statistics for each variable were produced. Average values of the outcome stratified by psychosocial ELA score were also produced.

Associations between the adversity score and the cortisol outcomes were estimated using general linear regression. Evening cortisol and CRP were skewed, so the transformation 100*log(y) was used for these outcomes. To ensure all outcomes are on the same scale, all other outcomes were too transformed using 100*log(y). As DS and CAR included negative values, a constant was added to all values before they were log transformed, a constant of five was added for DS and 35 for CAR. Resulting coefficients can be interpreted as symmetrical percentage differences (Cole, 2000). Tobit regression was used for CRP because the distribution was left censored (at the lowest detectable limit). Two sets of models were fitted for each outcome. Model one was was minimally adjusted for age at outcome assessment and sex, and model two was fully adjusted for age at outcome assessment, sex, birth weight, housing tenure, maternal education, and paternal social class. Tests for linear trend across all categories were carried out by entering the adversity score exposure into the models as a continuous variable. We also ran additional sensitivity analysis by re-fitting all the models considering each adversity (0=no adversity, 1= adversity) separately. To investigate whether estimates between ELA score and outcomes were different for each sex, we fitted models with sex by adversity score interaction terms. No evidence of effect modification was found for cortisol, so we present sex-combined estimates. Tentative evidence of effect modification was found for CRP so we present sex stratified estimates in addition to sex combined estimates.

Salivary cortisol can be influenced by sources of situational and inter-individual fluctuations (Stalder and Kirschbaum, 2012). To account for this, a sensitivity analysis was conducted excluding those who reported that they smoked, drank, ate, or were stressed shortly before cortisol measurements (n=216).

To understand the potential impact of missing data, we re-ran the main cortisol analyses using full information maximum likelihood (FIML) estimation. This increased the sample size from 843 to 1,462 (i.e., 1475 – 13 who were taking steroid medication). We did not re-run the CRP analyses using FIML because 1) there was less missing data for this outcome and 2) FIML cannot be used with tobit models.

All analyses were carried out using Stata MP version 14 (StataCorp LP, College Station, TX, USA).

3. Results

Those excluded from both cortisol and CRP analyses had less well-educated mothers, lower paternal social class, and were more likely to live in accommodation rented from private landlords. Those excluded also had a higher prevalence of maltreatment, low parental concern for child's education, parental divorce, parental death and parental separation. In the cortisol sample evening cortisol was higher in those excluded (supplementary table 2 & 3).

Table 1 shows the descriptive statistics for each sample. The mean age of the cortisol sample at follow-up was 63.6 years and females made up 52.9 % of this sample. The mean age of the CRP sample was 63.3 years and females made up 50.6% of this sample.

3.1 Cortisol

Average values for each of the cortisol measures according to their psychosocial ELA scores are shown in Table 2. As the number of adversities experienced increases, morning cortisol decreases, and the DS becomes less negative. CAR shows an increase and evening cortisol does not show any real pattern of change.

Table 3 shows the associations between the psychosocial ELA score and cortisol outcomes. In the fully - adjusted models, increasing adversity score was associated with lower morning cortisol and a higher DS (i.e. less negative DS), but not to evening cortisol or CAR. P-values for trend provided evidence that higher ELA score was related to lower morning cortisol and a higher DS (i.e., a less negative DS). When psychosocial ELA score was entered as a categorical variable, individuals with an ELA score of three or more had a 24.63 (-41.49, -7.76) % lower morning cortisol compared to individuals with a score of zero. Consequently, an adversity score of three or more was also related to a less negative DS. For example, a score of three or more was associated with an increase in DS of 7.3 (1.49, 13.12) % compared with a score of 0 adversities.

3.1.1 Cortisol sample sensitivity analyses

Sensitivity analysis with each ELA considered separately (supplementary table 4 & 5), found all adversities to be in the same direction for morning cortisol, and all except parental divorce to be in the same direction for DS. Although generally confidence intervals were wide due to small numbers experiencing each adversity (supplementary table 5)

Sensitivity analyses, where individuals who had eaten, drank, or were stressed shortly before cortisol measurements were excluded from analyses, demonstrated no change in results compared to the main analysis for morning cortisol and evening cortisol (supplementary table 6). However, there was an attenuation in the strength of the evidence for the linear trend for DS. An association between higher ELA score and higher CAR (p-value for trend=0.025) was also observed, although when entered categorically the confidence intervals for the three-or-more group was considerably widened.

3.2 CRP

Average values for CRP measures in the whole sample and stratified by gender according to their adversity scores are shown in table 2. In both females and males combined, and in females separately CRP shows an overall increase as the number of childhood psychosocial adversities increase, and in males CRP shows an overall decline.

Results of multiple general linear regression in both sexes combined revealed no associations between psychosocial ELA score and later CRP (supplementary table 7). However, sex differences were observed in the association between the highest psychosocial ELA score ($\geq$ 3) group and CRP, such that in the minimally - adjusted model, the differences in CRP between 0 and 3+ adversity groups was 36.69% greater in females compared to men (Table 4, % Difference Beta Coefficient: 36.69, 95% CI: -5.08, 78.45). In fully adjusted models, the effect size was attenuated but remained large, such that CRP was 29.3% stronger in females compared to males (Beta coefficient: 29.3, 95% CI: -12.22, 70.82). The likelihood ratio test comparing the adjusted models with and without the sex interaction terms revealed no difference between the models (chi square, p= 0.12).

3.2.1 CRP sample sensitivity analyses

Sensitivity analysis with each ELA fitted separately (supplementary table 8), found estimates were not in a consistent direction for both sexes combined. When stratified by sex, estimates were generally positive for females, but inconsistent for males. Sex-by-ELA interaction terms supported evidence for sex differences.

3.3 FIML analysis

Results for the cortisol outcomes did not differ compared to our main analyses when FIML estimation was used to handle missing data (Supplementary Table 9).

4.0 Discussion

This study has two key findings. Firstly, individuals who experienced the highest level of childhood psychosocial adversity had lower waking cortisol at 60-64 years and had a lower decline in cortisol across the day (i.e., a less negative DS). Secondly there was suggestive evidence that the highest level of childhood psychosocial adversity was associated with greater CRP at 60-64 years in females. There was no evidence that early life adversity was related to adulthood CRP in males.

4.1 Cortisol

Our findings that childhood adversity is related to lower morning cortisol and flattened diurnal slope are in line with other findings in the literature. Gerritsen et al. (2010) found an association between exposure to more than one early life event (< 18 years) (war experiences, death of a parent, divorce of a parents, sexual abuse, severe problems at home, poverty/un-employment, physical illness) and lower levels of morning cortisol and flattened diurnal variability of cortisol (mean age: 74.8 years) using a sample from the Longitudinal Aging Study Amsterdam (LASA).

Another study, although not investigating cumulative psychosocial adversity, investigated exposure to childhood abuse using the Netherlands Study of Depression in Older Persons (NESDO), and found it to be associated with lower basal cortisol levels at awakening (mean age 70.8 years) (Wielaard et al., 2018). In addition, a meta-analysis (not inclusive of the above studies) assessed the association between maltreatment and indicators of diurnal rhythm: waking cortisol levels, the cortisol awakening response

(CAR) and the diurnal slope (DS). They found a small, but significant association between maltreatment and blunted morning wakening cortisol levels (Bernard et al., 2017).

Our results are in agreement with the evidence that already exists which links adversity and a decreased morning cortisol level and flatter DS later in life. A flatter DS as has been associated with poorer health outcomes, for example worse inflammation and immune system outcomes (Adam et al., 2017), impaired fasting glucose and T2DM (Hackett et al., 2016), and cardiovascular disease mortality (Kumari et al., 2011). Hence, it is of public health benefit to investigate what is associated with a flatter DS. We found evidence for a linear trend between early life psychosocial adversity score and decreasing morning cortisol and a less negative DS. We also found when the score was investigated as a categorical variable, that a score of three or more had the biggest estimate for an association between reduced morning cortisol and increased DS.

Similarly to our own study, Power et al. (2012) investigated cumulative childhood adversity scores, including investigation of maltreatment and household dysfunction scores and two morning cortisol samples in mid-adulthood. They found a dose-response relationship in females between a maltreatment score of 0-7 and a lower morning cortisol, and an effect in both sexes of a score of $\geq$ 5 and lower morning cortisol. However, scores such as ours and Power et al. (2012) assume equal weighting of adversity scores, whereas this is not necessarily the case, as some adversities that make up the scores may be more severe stressors, and thus elicit a stronger stress response. However, when those with high numbers of ELAs are grouped together due to small numbers of people with higher numbers of ELAs, detail is lost above the cut-point. We grouped those with 3 or more ELAs due to small numbers of

people experiencing high numbers of ELAs and it is, therefore, difficult to ascertain from our results whether relationships exhibit dose response relationships or threshold effects. A threshold effect might be expected, as it is hypothesised that it is chronic stress (repetitive stress exposure or extreme stressful exposures), that contributes to dysregulation of the stress response. We found our sensitivity analyses of individual adversities were consistent with our main findings, as estimates were in support of an accumulation of ELAs and a decreased morning cortisol and increased DS.

In our main analyses no relationship was found between childhood psychosocial adversity and CAR at 60-64 years. However, sensitivity analyses excluding those who smoked, drank, ate, or were stressed shortly before cortisol measurements revealed an increase in CAR as levels of adversity score increased. However, the estimate for the ELA of three or more had a wide confidence interval due to the decrease in sample size in that group. Similar to our primary analysis, a systematic review by Bernard et al. (2017) did not find any association between childhood maltreatment and CAR. However, the studies included in this review did not investigate cumulative levels of psychosocial adversity, therefore they could not discriminate between levels of adversity. Our inconsistent results coupled with the lack of research that discriminates between levels of childhood psychosocial adversity warrant further investigation of inter-mediatory levels of adversity in addition to extreme adversity.

4.2 CRP

We found evidence of a relationship between the highest level of childhood psychosocial adversity with a 20% increase in CRP at 60-64 years in females but no effect in males. However, sample sizes in the highest psychosocial adversity group were lower when stratified by sex, so this finding needs replicating with a bigger sample size.

To our knowledge there are no studies that present evidence of a sex by ELA interaction on later life inflammation. A systematic review by Baumeister et al. (2016) on trauma and inflammatory markers did not find any moderating effects of sex. Chen and Lacey (2018) hypothesised that the more ACEs a child has experienced, the higher the level of inflammation in mid-life, and that the strength of the association would differ by sex, with a stronger association likely for females. Their hypothesis of sex differences was based on findings from previous work that has found increased risk for of heart disease and cardiovascular disease for females who experienced ACEs (Friedman et al., 2015; Garad et al., 2017). However, Chen and Lacey (2018) failed to find any sex differences in their findings of graded associations between ACE's and CRP and fibrinogen in mid-life (44-45yrs). Lob et al. (2020) also found no evidence for effect modification by sex in relation to ACE scores and CRP at 70 years. Our results provide novel tentative evidence which supports the hypothesis of Chen and Lacey (2018). Reasons for our findings are unknown, however there are some possible explanations. It may be that females have a higher stress sensitivity, as studies have demonstrated stress to have more deleterious consequences for females (Iso et al., 2002; McKee et al., 2003). Not every psychosocial stressor holds the same weight of severity, and it may be that females have experienced more severe stressors. such as sexual abuse, as previous findings demonstrate a higher prevalence of childhood sexual abuse in females compared to males (Finkelhor et al., 1990; MacMillan, 1997).

In our study, sexual abuse comes under the umbrella variable ‘maltreatment’, so we were unable to specifically investigate sexual abuse. However, we did investigate the percentage exposed to maltreatment in males versus females and found a higher percentage of females to experience maltreatment versus males in both our samples. Finally, it could be due to adiposity, as on average females have higher adiposity which is a key production site for inflammatory cytokines (Russo et al., 2018).

4.3 Potential mechanisms

Many mediating factors may explain the associations between early life adversity and later altered HPA axis functioning and inflammation. For example socio-economic factors and health behaviours have been found to partly explain the association between childhood abuse and inflammation (Chen and Lacey, 2018; Danese et al., 2007). Behavioural lifestyle factors mediating these relationships are likely because early life adversity is associated with changes in the brain that alter reward/pleasure systems (Herzog and Schmahl, 2018), hence increasing the likelihood of participation in unhealthy lifestyle behaviours.

There may be some biological programming occurring in childhood to cause abnormal HPA axis functioning and increased inflammation later in life, irrespective of the uptake of these unhealthy lifestyle behaviours. Danese et al. (2009) found evidence to support this hypothesis, observing an association between ACEs and poor cardiometabolic health independent of lifestyle behaviours. Our study did not include investigation of mediating factors, so this would be an interesting area of potential investigation in the future.

4.4 Strengths and limitations

A key strength of our study is the use of a prospective study spanning 64 years, with the majority of our childhood psychosocial measurements being prospective, which limits recall bias. Our adversity measurements were also collected using multiple informants (i.e. parents and guardian reports augmented by health visitor and teacher reports), which may overcome issues of socially desirable responding and concealment if informants were solely parents or guardians. We ran sensitivity analyses excluding participants if they reported having eaten, drank, or been exposed to stress shortly before measurement, to account for salivary cortisol being subject to situational and inter-individual fluctuations. In addition, we created a cumulative adversity variable, which has enabled us to unpick the gradient of association between early life adversity and later inflammation and cortisol. This is in contrast to many previous analyses, in which a dichotomous adversity variable was created, representing adversity versus no adversity.

It is important to note that three variables that make up the adversity scores were retrospectively reported (maltreatment and parental bonding), and retrospective measures (i.e. maltreatment) may be subject to low agreement with prospective measures (Baldwin et al., 2019). A measure such as maltreatment may also be subject to underreporting due to its sensitive nature, which may have caused measurement error of the adversity score and contributed to regression dilution bias (Hutcheon et al., 2010). As with any observational study, residual confounding is a possibility. Other limitations of our study include no ethnic diversity in the NSHD cohort, therefore limiting generalisability, no psychometric evaluation (i.e., validity and reliability) of adversity scores and cumulative risk scores assume equal weighting of adversities, which may not be the case. Further, generalisability of the results to the

population of Great Britain is limited, as only 41.7% of the initial NSHD cohort participated in the sweep at 60 - 64 years. Those who have been exposed to adversity were more likely to be excluded from our analyses as they had higher prevalence of many of the ELAs than those included. We also observed that those excluded were from more disadvantaged socioeconomic background which is consistent with previous findings that lower educational attainment, and manual social class, along with socially distributed health-related characteristics of lifelong smoking and obesity, predicted overall response and lower clinical research facility cooperation in the 60-64 sweep of this NSHD cohort (Stafford et al., 2013). Therefore, differential selection into our sample may have biased results (Munafò et al., 2018). Further, cohort context must be considered, as ELAs are likely to be different today compared to what they used to be, thus again limiting the generalisability.

5. Conclusions

Our results suggest that high-levels of psychosocial adversity in childhood might result in a lower morning cortisol and flatter DS in mid-to-late-adulthood. The finding that adversity was related to higher CRP in females but not males requires replication and further investigation.

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All authors declare no conflicts of interest.

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Table 1. Description of study samples

		Cortisol sample	CRP sample		
			All	Female	Male
		N=843	N=1150	N=582	N=568
Age	Mean (SD)	63.6 (0.76)	63.3 (1.2)	63.3 (1.1)	63.2 (1.2)
Sex					
Female	N (%)	446 (52.9)	582 (50.6)	-	-
Male	N (%)	397 (47.1)	568 (49.4)	-	-
Birth weight (kg)	Mean (SD)	3.4 (0.5)	3.4 (0.5)	3.3 (0.5)	3.5 (0.5)
ELA score					
0	N (%)	399 (47.3)	532 (46.3)	256 (44)	276 (48.6)
1	N (%)	223 (26.5)	316 (27.5)	175 (30.1)	141 (24.8)
2	N (%)	164 (19.5)	225 (19.6)	112 (19.2)	113 (19.9)
≥ 3	N (%)	57 (6.8)	77 (6.7)	39 (6.7)	38 (6.7)
Maternal education					
Primary	N (%)	480 (56.9)	653 (56.8)	349 (60)	304 (53.5)
Other	N (%)	363 (43.1)	497 (43.2)	233 (40)	264 (46.5)
Paternal social class					
Professional & intermediate	N (%)	259 (30.7)	346 (30.1)	173 (29.7)	173 (30.5)
Skilled nonmanual	N (%)	156 (18.5)	206 (17.9)	98 (16.8)	108 (19.0)
Skilled manual	N (%)	253 (30)	352 (30.6)	177 (30.4)	175 (30.8)
Partly skilled & unskilled	N (%)	175 (20.8)	246 (21.4)	134 (23)	112 (19.7)
Housing tenure					
Private landlord	N (%)	430 (51)	565 (49.1)	287 (49.3)	278 (48.9)
Other	N (%)	413 (49)	585 (50.9)	295 (50.7)	290 (51.1)
Waking cortisol (nmol/L)	Mean (SD)	20.11 (9.6)	-	-	-
Evening cortisol (nmol/L)	Median (IQR)	2.36 (1.87)	-	-	-
DS (nmol/L/h)	Mean (SD)	-1.2 (0.69)	-	-	-
CAR (nmol/L/h)	Mean (SD)	6.25 (11.97)	-	-	-
CRP (mg/L)	Median (IQR)	-	2.0 (2.3)	2.15 (2.46)	1.9 (2.22)

Abbreviations: ELA: early life adversity, SD: standard deviation, DS: diurnal slope, CAR: cortisol awakening response, CRP: c-reactive protein

Table 2. Cortisol and CRP outcomes at 60-64 years by psychosocial ELA score

ELA score	Morning cortisol (nmol/L)	Evening cortisol (nmol/L)	DS (nmol/L/h)	CAR (nmol/L)	CRP (mg/L) All	CRP (mg/L) Female	CRP (mg/L) Male
	Mean (SD)	Median (SD)	Mean (SD)	Mean (SD)	Median (IQR)	Median (IQR)	Median (IQR)
0	20.89 (9.4)	2.35 (1.87)	-1.26 (0.66)	5.42 (11.13)	1.95 (2.15)	1.94 (2.12)	1.96 (2.38)
1	19.64 (9.88)	2.4 (1.85)	-1.16 (0.7)	7.1 (12.69)	2.26 (2.46)	2.47 (2.69)	1.86 (2.16)
2	19.91 (9.82)	2.38 (1.79)	-1.18 (0.73)	6.93 (13.06)	1.94 (2.2)	1.99 (2.35)	1.91 (2.1)
≥3	17.11 (8.67)	2.33 (2.0)	-1.00 (0.62)	6.79 (11.36)	2.26 (2.84)	3.19 (4.72)	1.72 (2.88)

Abbreviations: ELA: early life adversity, SD: standard deviation, DS: diurnal slope, CAR: cortisol awakening response, CRP: c-reactive protein

Table 3. Associations between the psychosocial ELA score and cortisol outcomes at 60-64 years, estimated using general linear regression models

	CAR (nmol/L)		DS (nmol/L)		Evening cortisol (nmol/L)		Morning cortisol (nmol/L)	
	s% (95% CI)	p-value for trend	s% (95% CI)	p-value for trend	s% (95% CI)	p-value for trend	s% (95% CI)	p-value for trend
Model 2								
ELA Score (Reference group= 0)								
1	3.30 (-2.45, 9.05)		2.08 (-1.34, 5.49)		1.67 (-8.95, 12.30)		-8.35 (-18.27, 1.57)	
2	3.06 (-3.31, 9.44)		1.35 (-2.44, 5.14)		1.76 (-10.03, 13.54)		-4.56 (-15.56, 6.44)	
≥ 3	4.82 (-4.91, 14.55)	0.193	7.31 (1.53, 13.09)	0.036	-3.56 (-21.54, 14.43)	0.977	-25.92 (-42.70, -9.13)	0.011
Model 3								
ELA Score (Reference group = 0)								
1	3.06 (-2.70, 8.82)		2.08 (-1.35, 5.51)		2.13 (-8.54, 12.80)		-7.97 (-17.93, 1.99)	
2	2.76 (-3.62, 9.14)		1.36 (-2.44, 5.16)		1.87 (-9.94, 13.69)		- 4.13 (-15.16, 6.90)	
≥ 3	4.27 (-5.48, 14.03)	0.245	7.30 (1.49, 13.12)	0.038	-3.41 (-21.48, 14.66)	0.999	-24.63 (-41.49, -7.76)	0.017

Footnote:
Model 1. Adjusted for age and sex
Model 2: Adjusted for age, sex, birth weight, paternal social class, maternal education, and housing tenure
s% estimates are symmetrical percentage differences
Abbreviations: ELA: early life adversity, CI: confidence interval, DS: diurnal slope, CAR: cortisol awakening response

Table 4. Associations between the ELA score and CRP at 60-64 years, estimated using sex stratified tobit models

	CRP (mg/L)				
	Females		Males		Males - females
	s% (95% CI)	p-value for trend	s% (95% CI)	p-value for trend	s% (95% CI)
Model 2					
ELA Score (Reference group=0)					
1	10.89 (-6.02, 27.80)		-7.42 (-25.08, 10.25)		18.57 (-5.84, 42.98)
2	0.51 (-19.00, 20.02)		6.73 (-12.31, 25.78)		-6.18 (-33.41, 21.06)
≥ 3	32.61 (2.98, 62.25)	0.138	-4.31 (-33.80, 25.19)	0.855	36.69 (-5.08, 78.45)
Model 3					
ELA Score (Reference group=0)					
1	9.40 (-7.23, 26.02)		-6.79 (-24.42,10.85)		16.00 (-8.20, 40.21)
2	-3.01 (-22.19, 16.17)		5.34 (-13.67, 24.34)		-6.40 (-33.37, 20.56)
≥ 3	20.38 (-9.38, 50.14)	0.473	-5.30 (-34.71, 24.11)	0.955	29.30 (-12.22, 70.82)

Footnote:
Model 1. Adjusted for age
Model 2: Adjusted for age, birth weight, paternal social class, maternal education, and housing tenure
s% estimates are symmetrical percentage differences
Abbreviations: ELA: early life adversity, CI: confidence interval, CRP: c-reactive protein
* males - females: difference in effect sizes between males and females from a model with sex-by-adversity interaction terms

Figure 1. Sample flow of cortisol and CRP samples

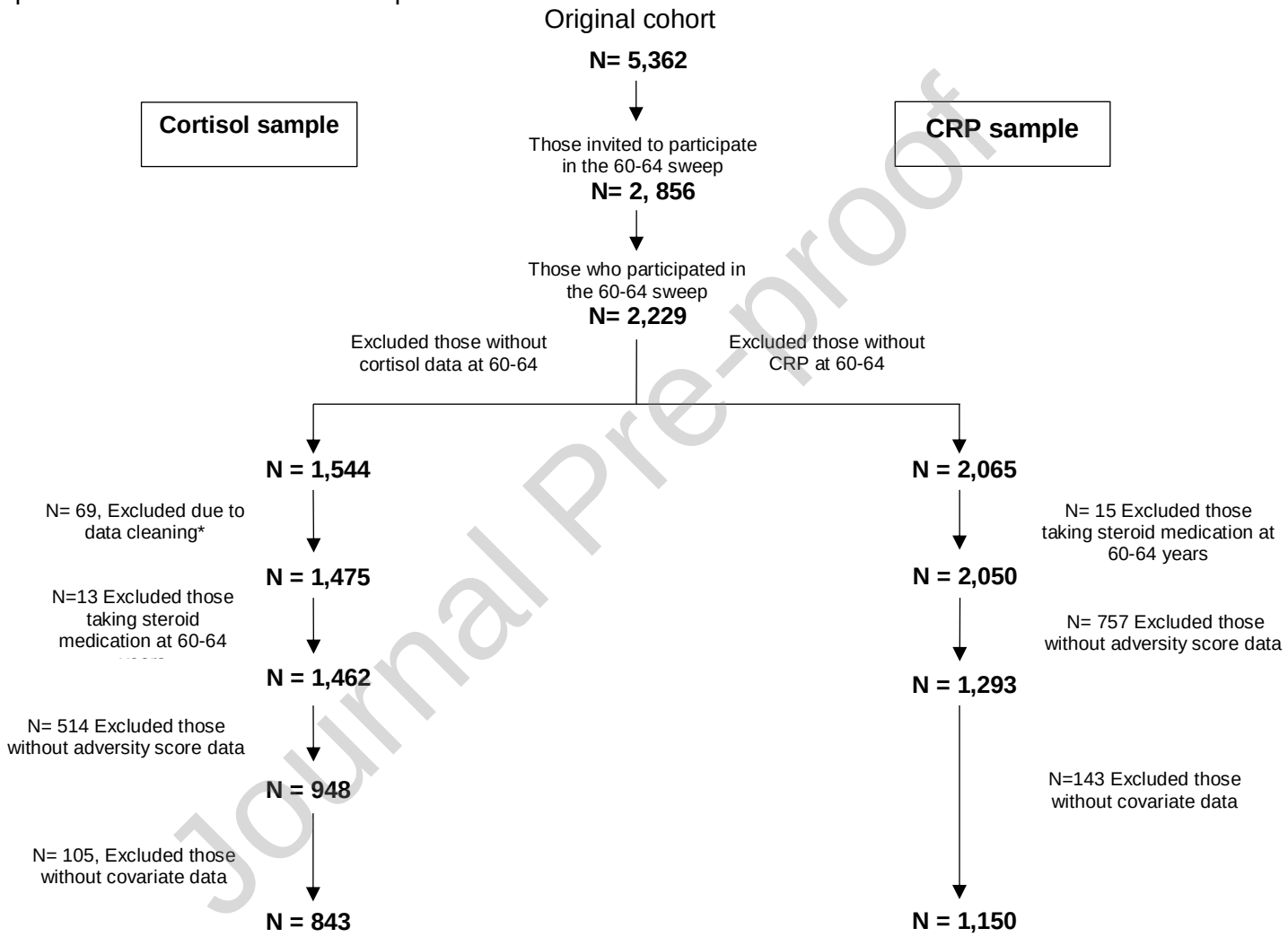

Figure 1 – footnote: *Data cleaning, data excluded if: cortisol values > 99.5th centile at each sampling time due to there being a number of abnormally high values, cortisol values with a cortisol sample time > 99.5th centile or < 0.5th centile as a very early or late sample time is indicative of shift working, cortisol values where waking +30 was taken before waking cortisol due to this representing impossible time
Abbreviations: CRP: c-reactive protein

Highlights

- This study used data from a large birth cohort study of individuals born in 1946 in the United Kingdom.
- Early-life adversity data was assessed using a high proportion of heterogenous, prospective measures collected between 0-15 years.
- Diurnal cortisol patterns were assessed at 60-64 years via multiple saliva samples and C-reactive protein was assayed using fasting blood samples.
- A high level of early-life adversity was associated with lower waking cortisol at 60-64 years and a less steep decline in cortisol across the day, indicative of a blunted cortisol response.
- A high level of early-life adversity was also related to higher C-reactive protein at 60-64 years, but this association was only present in females not males.

Conflict of interest

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