Adverse childhood experiences and diurnal cortisol patterns in older people in England

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ABSTRACT

Adverse childhood experiences (ACE) are associated with HPA axis dysregulation at younger ages, but there is scarcity of evidence for this association at older ages. To add to our knowledge of the lifetime impact of ACE on HPA axis function, we examined whether ACE were associated with diurnal cortisol patterns in a national sample of 587 participants (356 women) aged 55–79 years from the English Longitudinal Study of Ageing (ELSA). We conducted descriptive analyses and estimated sex-specific robust regression models of the associations between the 8-item summary ACE score and four measurements of salivary cortisol over a 24-h cycle (upon waking, 30 min later, at 7 pm, and at bedtime) as well as the cortisol awakening response (CAR) and the diurnal cortisol slope. Our models were adjusted for age, then for childhood socioeconomic position and finally for adult socioeconomic position. In men, we found significant differences that were independent of covariates, with more ACE being associated with lower salivary cortisol levels on waking, a greater CAR, and a flatter diurnal cortisol slope. In women, we observed a graded association between ACE and increased 7 pm salivary cortisol levels. Our findings indicate that childhood adversity is related to HPA axis in older people, especially men. The chronological distance (on average >50 years) between ACE and salivary cortisol levels suggests the existence of a lifelong association between childhood adversity and HPA axis and neuroendocrine function. Notwithstanding sex differences, based on our findings we suggest that HPA axis dysregulation could be a pathway that mediates the association between ACE and chronic disease later in life.

1. Introduction

The term adverse childhood experiences (ACE) refers to experiences of abuse, neglect and family disorganisation in childhood. The original ACE study that coined the term focused on abuse, household dysfunction and parental separation (Dietz et al., 1999; Felitti et al., 1998). Since then, health research on ACE has expanded and considered several additional dimensions of childhood adversity including experiences of social and foster care and bullying and victimization (Cronholm et al., 2015; Finkelhor et al., 2013). ACE are a major stressor of lifelong importance that affect the body and mind during critical and sensitive periods of development (Agorastos et al., 2019; Gunnar & Quevedo, 2007; Shonkoff et al., 2012). They are associated with multiple chronic conditions in adulthood (Hughes et al., 2017; Norman et al., 2012; Suglia et al., 2018) and are important to better understand population health. Despite accumulating evidence on the association between ACE and chronic disease at older ages, our understanding of this association remains incomplete. This is because of the lack of evidence on mediating pathways and implicated mechanisms, which would allow the identification of therapeutic targets and the design of more effective population health strategies and policies.

Dysregulation of the HPA axis possibly is a mechanism through which ACE affect health over the life course. HPA axis dysregulation and altered cortisol levels and diurnal patterns are associated with numerous chronic conditions in adulthood (Adam et al., 2017; Chrousos, 2009; O’Connor et al., 2021) But evidence on the association between ACE and cortisol, as a marker of HPA axis functioning, is mixed. Two recent meta-analyses suggest that ACE are associated with blunted cortisol response to social stress (Bunea et al., 2017) and, depending on ACE severity, with either cortisol hypo- and hyper-reactivity (Hosseini–Kamkar et al., 2021). Another meta-analysis reported a great deal of heterogeneity in the studies they identified, with limited support for an overall association between early-life stress and cortisol (Fogelman & Canli, 2018). But most previous studies focused on younger adults and...
used small convenience samples, while evidence on this association from population-based studies of older people is limited.

Against this backdrop, we used data from the English Longitudinal Study of Ageing (ELSA) to explore the association between a summary ACE score and diurnal cortisol patterns in a national sample of older people. We examined four measurements of salivary cortisol over a typical 24-hour cycle as well the cortisol awakening response (CAR) and the diurnal cortisol slope. Because there are marked sex-differences in typical 24-hour cycle as well the cortisol awakening response (CAR) and the diurnal cortisol slope. Because there are marked sex-differences in HPA axis and the stress response (Goel et al., 2014; Liu et al., 2017), our analyses were stratified by sex. Our aim is to add to the evidence on the association between ACE and cortisol in older people and thus scrutinise HPA axis dysregulation as a candidate pathway that might be implicated in the association between ACE and chronic disease at older ages.

2. Materials and methods

2.1. Study population

We used data from the ELSA study (www.elsa-project.ac.uk), a population-based longitudinal study of older people. The ELSA baseline survey (ELSA wave 1) was in 2002–03. It included a face-to-face interview and involved a nationally representative sample of 11,391 individuals (6205 women) aged ≥ 50 years. Follow-up surveys took place at regular intervals, every two years. The first follow-up survey (ELSA wave 2) took place in 2004–05 and included an interview and a health examination that was conducted by a nurse. 7666 ELSA participants took part in the health examination. The salivary cortisol study was a component of the ELSA wave 2 health examination. By design, the cortisol study was restricted to people aged < 80 years. 4732 participants provided saliva samples. So far, salivary cortisol data from 650 of these participants are available. These participants have been selected using non-response and other criteria including continuous presence in the first six waves of the study, participation in the Life History Interview, completion of all components of the study, availability and quality of a DNA sample, and quality of the saliva samples.

The analysis sample consisted of 587 participants (356 women) who had salivary cortisol and self-reported ACE data. The latter were collected during the ELSA Life History survey, which was a one-off survey that took place in 2007 after the second ELSA follow-up survey (ELSA wave 3). The ELSA Life History survey aimed to collect retrospective information about the experiences and life circumstances of the participants before joining ELSA including childhood information.

ELSA has been approved by the London Multi-Centre Research Ethics Committee (MREC/01/2/91) and informed consent has been obtained by the participants.

2.2. Measurement of childhood adversity

We retrospectively measured the following eight binary ACE variables: 1) lived most of childhood in a single natural mother family, 2) lived most of childhood in social care settings (e.g. in children’s home or with foster parents), 3) separation from mother for ≥ 6 months, 4) victim of serious physical assault/attack at age ≤ 16 years, 5) victim of sexual assault at age ≤ 16 years, 6) physically abusive parents, 7) parents with substance abuse or mental health problems, and 8) parents argued or fought very often. All ACE measures refer to adversities experienced at age ≤ 16 years (unless otherwise stated) and cover major domains of psychosocial adversity such as abuse, family disorganization and experiences of social care.

We generated a summary ACE score by adding up all eight ACE items. For the purposes of our analyses, we transformed this score in a categorical variable with the following categories: 0, 1, ≥ 2 ACE. The distribution of the summary ACE score prior to categorising it can be found in the online Appendix (Supplementary Table S1). To avoid the unnecessary exclusion of participants with few missing values in any of the eight ACE variables (the maximum number of missing values was 23 in the physical attack/assault variable), we assumed that participants with missing values in any of the ACE variables had not experienced this ACE and gave them the value of 0. This conservative approach resulted in analyses that were inclusive of more participants and used all ACE information available to us. Due to the small number of cases in some of the ACE variables, we did not use any of the eight ACE variables as individual predictors of cortisol.

2.3. Measurement of salivary cortisol

The ELSA cortisol study included the collection of four saliva samples over a typical weekday. Participants were asked to take the samples on waking (t1), 30 min later (t2), at 7 pm (t3) and bedtime (t4) and record the time they took each sample in labels and the logbook that was provided to them along with colour-coded salivates and tubes. To ascertain that the participants knew how to take and process the saliva samples, a nurse gave them a face-to-face demonstration, answered their questions, and asked them to take a practice saliva sample, which was then discarded and not used in our study. The participants were instructed to take all four samples in the same day, keep them in a provided transparent plastic bag in their fridge and posted them the next day. They were also asked not to eat, drink, or brush their teeth 15 min before taking the samples and take the samples on a weekday and only if necessary on weekend. Participants who had been to the dentist or attended a funeral or wedding were asked to take the saliva samples the next day.

For the needs of our study we used the four observed salivary cortisol measurements (in nmol/L) and two derived variables: i) the cortisol awakening response (in nmol/L), that is the difference between the first and the second measurements (t2-t1) and ii) the diurnal cortisol slope (in nmol/L/h), that is the difference between the first and the fourth measurements divided by the time that has elapsed between the two measurements ((t1-t4)/time elapsed between t1 and t4). Because CAR is sensitive to the time that has elapsed between the first and the second cortisol measurements, we excluded participants who reported taking their second sample later than 45 min after their first sample. A detailed description of all cortisol measures by ACE and sex can be found in Table 1. A description of all cortisol measures by sex only can be found in the online Appendix (Supplementary Table S2).

2.4. Covariates

Our models were adjusted for important confounders such as age and childhood socioeconomic position (number of books in the household at age 10 years and paternal or main carer’s occupational class at age 14 years). Because adult SEP is an important correlate of stress and HPA function (Brisson et al., 2020; Summer & Gallagher, 2017), and can be on the causal pathway, we also adjusted our models for education and tertiles of total net household wealth. A description of covariates by sex can be found in Table 2.

2.5. Statistical analyses

We examined the bivariate associations between the summary ACE score and cortisol and age by sex (Table 1). We estimated linear regression models of the associations between the ACE summary score and all six measures of salivary cortisol (Table 3). To account for the existence of potential outliers and a non-normal (non-linear) distribution of errors and subsequent inefficiency of the ordinary least-squares (OLS) regression, we estimated robust regression models. We used the default option of robust regression in STATA 15.1 (command reg). To ascertain that the use of robust regression did not affect our results, we also present the OLS regression models after the logarithmic transformation of the cortisol measures (see Supplementary Table S3). The results in both analyses follow similar patterns.

In terms of modelling, we first estimated a basic model that was...
In the bivariate analysis, we found significant differences in salivary cortisol measurements associated with ACE in men, but not in women (Table 1). The analysis of the sample characteristics by sex describes a sample that is heterogenous in terms of age and SEP (Table 2). The regression models largely confirm most of the bivariate analysis findings (Table 3). In men, they suggest the existence of significant differences in salivary cortisol levels by ACE, with more ACE being related to lower salivary cortisol levels on waking and a flatter diurnal cortisol slope. Another distinction was made between ACE and increased early evening (7 pm) salivary cortisol levels. We did not find any association of ACE with cortisol diurnal patterns in women except for a graded association between ACE and increased early evening (7 pm) salivary cortisol levels.

### 4. Results

In a national sample of older people, we found that ACE were associated with diurnal cortisol patterns in men. These associations were graded, with more reported ACE having a stronger association with salivary cortisol levels. We did not find any association of ACE with cortisol diurnal patterns in women except for a graded association between ACE and increased early evening (7 pm) salivary cortisol levels.

### 4.1. Previous literature and our findings

There are many studies on childhood adversity and cortisol in adults (Boggero et al., 2017; Bunea et al., 2017; Fogelman & Canli, 2018; Khoury et al., 2019), but few are comparable with ours. Most previous studies focused on younger adults and used convenience samples. A recent meta-analysis examined multiple associations between early-life stress and cortisol and found only few significant ones. They found positive associations between experiences of childhood abuse and cortisol. They also found a negative association between early life stress and baseline cortisol (that is a single measurement in the absence of stressors) in blood, but not in saliva samples (Fogelman & Canli, 2018). Notwithstanding sex and cortisol measurement differences, these findings concur with ours. The same applies to the findings of another meta-analysis (Bunea et al., 2017). They found that childhood adversity is associated with a blunted salivary cortisol response to a social stress test. Although not directly comparable, these findings point to the same direction as our findings, which indicate that ACE are associated with decreased diurnal cortisol levels in men, that is lower cortisol levels on waking and a flatter diurnal cortisol slope.
4.2. Mechanisms and pathways

Our findings add to the limited evidence that stems from non-experimental population-based cohort studies for an association between ACE and altered diurnal salivary cortisol patterns and HPA axis dysregulation in older adults. They suggest the existence of a lifelong association between ACE and the stress response and HPA axis function. The chronological distance between the exposure and the outcome, which on average was > 50 years, is indicative of how disruptive the effect of ACE on the stress system can be and highlights its pathogenic potential over the life course. From an ageing perspective, our findings are consistent with the proposition that HPA axis dysregulation can be a pathway that mediates the association between ACE and chronic disease at older ages. To that end, evidence suggests that a flatter diurnal cortisol slope is associated with mental and physical health conditions and an increased risk of mortality (Adam et al., 2017). The same applies to an increased CAR, which has been associated with poorer psychosocial functioning and depression (Boggero et al., 2017; Chida & Steptoe, 2009), and physical health problems (Eller et al., 2005; Powell & Schlotz, 2012). Further, in terms of biological mechanisms, research has focused on adversity-related stress-induced epigenetic changes. Evidence suggests that early life adversity changes the epigenome and gene expression and has emphasized its epigenetic effect on glucocorticoids signalling and the HPA axis (Anacker et al., 2014; Schar et al., 2022; Tyrka et al., 2016). Meta-analytic evidence also suggests that early life adversity that is related to violence and threat accelerates biological ageing as measured by telomere length and DNA methylation (Collich et al., 2020).

Another finding that needs to be highlighted is the existence of significant sex-differences in the observed associations. Previous research has found significant sex differences in diurnal cortisol and CAR with girls and women usually exhibiting greater diurnal variability and CAR than boys and men, respectively (Hollanders et al., 2017; Kuhlman et al., 2019; Stalder et al., 2016). A review suggests that the HPA axis initiates more rapidly and produces a greater output of stress hormones in women, but also that androgens increase, and oestrogens decrease HPA axis activity in adults (Goel et al., 2014). Within this context, it is difficult to interpret the sex differences we observed in our findings and why childhood adversity affected more the diurnal cortisol patterns in men compared with women. But, given the postmenopausal age of the women in our sample, we can safely conclude that it is not the use of oral contraceptives and menstrual cycle characteristics (Stalder et al., 2016) that can explain the sex differences in our study. We can speculate that if these differences are biological then likely are related to the effect of childhood adversity on the developing brain and the HPA axis during development (Goel et al., 2014). Nevertheless, the observed sex differences may also be related to sex differences in resilience and coping (Hodes & Epperson, 2019; Tamres et al., 2002).

Childhood SEP appears not to explain the association between ACE and salivary cortisol. Notwithstanding the need for dedicated research that focuses on the role of childhood SEP in the examined associations, our findings indicate that the observed associations are not socioecconomic in nature and have a psychosocial core. It should be noted though that we lacked data to examine neglect, which is another important dimension of psychosocial adversity, and clearly one that is closer to socioeconomic disadvantage. The unrelatedness of important adult SEP dimensions of psychosocial adversity, and clearly one that is closer to socioeconomic disadvantage. The unrelatedness of important adult SEP

4.3. Strengths and limitations

Our study is one of the few population-based longitudinal studies on the associations between ACE and the diurnal cortisol patterns in older

| Table 2 Sample characteristics by sex. | Men | Women |
|--------------------------------------|-----|-------|
| Number of participants               | 231 | 356   |
| Age Mean (SD)                        | 66.01 (6.8) | 64.9 (6.5) |
| Father’s or main carer’s occupational class at age 14 years, N (%) | 75 (32.5) | 136 (38.2) |
| Higher (manager, professional, business owner, administrative jobs) | 93 (40.3) | 101 (28.4) |
| Intermediate (trade, sales, and care professions) | 59 (25.5) | 106 (29.8) |
| Lower (plant worker, causal jobs, unemployed) | 4 (1.7) | 13 (3.6) |
| Other | 4 (1.7) | 13 (3.6) |
| Books in the household at age 10 years, N (%) | 35 (15.2) | 74 (20.8) |
| Enough to fill > 2 bookcases (> 100 books) | 73 (31.6) | 119 (33.4) |
| Enough to fill 1 bookshelf (11–26 books) | 59 (25.5) | 79 (22.2) |
| None or very few (0–10 books) | 56 (24.2) | 72 (20.2) |
| Missing | 8 (3.5) | 12 (3.4) |
| Education | 118 (51.1) | 114 (32.0) |
| Higher than secondary (university degree, other higher or A-level) | 74 (32.0) | 141 (39.6) |
| Secondary including other qualifications | 39 (16.9) | 101 (28.4) |
| Total household wealth | 50 (21.7) | 94 (26.4) |
| In the lowest wealth tertile (<$100,000) | 73 (31.6) | 123 (34.6) |
| In the intermediate wealth tertile ($100,000 to $233,600) | 108 (46.7) | 139 (39.0) |
| In the wealthiest tertile ($>233,600) | 66.01 (6.8) | 64.9 (6.5) |
Table 3
The associations between summary ACE score categories and salivary cortisol measurements by sex.

|                | Q1: 1st morning measurement of cortisol (when awake) | Q2: 2nd morning measurement of cortisol (30 min post-awakening) | Q3: 3rd measurement of cortisol (evening – 7 pm) | Q4: 4th measurement of cortisol (before sleeping) | Cortisol Awakening Response (CAR) (Q2-Q1) | Cortisol diurnal slope (Q1-Q4)/ (time elapsed between Q1 and Q4) |
|----------------|-----------------------------------------------------|---------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|--------------------------------------|---------------------------------------------------------------|
| **Model 1**    |                                                    |                                                               |                                                 |                                                 |                                      |                                                               |
| **ACE= 0**     | Reference category                                 | Reference category                                           | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
| Men (n = 227)  | Reference category                                 | Reference category                                           | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
| Women (n = 344)| Reference category                                 | Reference category                                           | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
|                | 0.008                                               | 0.65                                                          | 0.81                                            | 0.74                                            | 0.012                                 | 0.003                                                          | 0.015                                                          | 0.61                                                          |
| **Model 2**    |                                                    |                                                               |                                                 |                                                 |                                      |                                                               |
| **ACE= 0**     | Reference category                                 | Reference category                                           | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
| Women (n = 229)| Reference category                                 | Reference category                                           | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
| Women (n = 346)| Reference category                                 | Reference category                                           | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
|                | 0.018                                               | 0.35                                                          | 0.59                                            | 0.59                                            | 0.020                                 | 0.003                                                          | 0.024                                                          | 0.22                                                          |
| **Model 3**    |                                                    |                                                               |                                                 |                                                 |                                      |                                                               |
| **ACE= 0**     | Reference category                                 | Reference category                                           | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
| Women (n = 225)| Reference category                                 | Reference category                                           | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
| Women (n = 351)| Reference category                                 | Reference category                                           | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
|                | 0.034                                               | 0.29                                                          | 0.43                                            | 0.57                                            | 0.023                                 | 0.003                                                          | 0.031                                                          | 0.21                                                          |
| **Model 1**    |                                                    |                                                               |                                                 |                                                 |                                      |                                                               |
| **ACE= 1**     | Reference category                                 | Reference category                                           | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
| Men (n = 213)  | -2.17 (−5.40 to 1.67)                              | -1.18 (−4.04 to 1.69)                                        | -0.29 (−4.31 to 4.83)                           | -0.26 (−3.94 to 3.42)                           | Reference category                       | Reference category                                           |
| Women (n = 326)| -0.33 (−3.86 to 2.31)                              | 1.69 (−5.73 to 9.11)                                         | 0.44 (−0.88 to 1.75)                            | 0.75                                            | Reference category                       | Reference category                                           |
|                | 0.008                                               | 0.65                                                          | 0.81                                            | 0.74                                            | 0.012                                 | 0.003                                                          | 0.015                                                          | 0.61                                                          |
| **Model 2**    |                                                    |                                                               |                                                 |                                                 |                                      |                                                               |
| **ACE= 1**     | Reference category                                 | Reference category                                           | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
| Women (n = 225)| -1.61 (−4.97 to 1.75)                              | -1.31 (−4.20 to 1.58)                                        | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
| Women (n = 351)| -0.50 (−4.42 to 5.43)                              | 2.38 (−5.24 to 10.00)                                        | 0.45 (−0.88 to 1.79)                            | Reference category                               | Reference category                       | Reference category                                           |
|                | 0.018                                               | 0.35                                                          | 0.59                                            | 0.59                                            | 0.020                                 | 0.003                                                          | 0.024                                                          | 0.22                                                          |
| **Model 3**    |                                                    |                                                               |                                                 |                                                 |                                      |                                                               |
| **ACE= 1**     | Reference category                                 | Reference category                                           | Reference category                               | Reference category                               | Reference category                       | Reference category                                           |
| Women (n = 225)| -1.40 (−4.83 to 2.03)                              | -1.32 (−4.23 to 1.58)                                        | 1.04 (−4.05 to 6.12)                            | -0.02 (−3.77 to 3.74)                           | Reference category                       | Reference category                                           |
| Women (n = 351)| -1.64 (−5.43 to 2.16)                              | 3.16 (−4.60 to 10.92)                                        | 0.10 (−0.77 to 0.97)                            | Reference category                               | Reference category                       | Reference category                                           |
|                | 0.034                                               | 0.29                                                          | 0.43                                            | 0.57                                            | 0.023                                 | 0.003                                                          | 0.031                                                          | 0.21                                                          |
| Model 1 is adjusted for age
Model 2 is adjusted for age and childhood socioeconomic position (paternal/main carer’s occupation at age 14 years and number of books in the household at age 10 years)
Model 3 is adjusted for age, childhood socioeconomic position (paternal/main carer’s occupation at age 14 years and number of books in the household at age 10 years), and adult socioeconomic position (education and total household wealth in 2002-03)
patterns and are a conservative account of them. It should be noted in women.

In men.

Another limitation was our inability to analyse the relationship between specific types of ACE and cortisol owing to the relatively small magnitude of the true associations between ACE and diurnal cortisol levels. Given the associations between HPA axis dysregulation and multiple chronic conditions, we speculate that hormonal and neuroendocrine pathways might be involved in the association between ACE and chronic disease at older ages. More population-based research is needed on the links between ACE and the neuroendocrine and immune systems over the life course and the importance of these associations for chronic disease and mortality. We also observed important sex differences in the examined associations, which are consistent with the literature, but require further investigation.

4.4. Conclusions

Psychosocial adversity experienced in childhood such as abuse and family disorganisation may exert a lifetime influence on the HPA axis function, which can be observed decades later in older people’s salivary cortisol levels. Given the associations between HPA axis dysregulation and multiple chronic conditions, we speculate that hormonal and neuroendocrine pathways might be involved in the association between ACE and chronic disease at older ages. More population-based research is needed on the links between ACE and the neuroendocrine and immune systems over the life course and the importance of these associations for chronic disease and mortality. We also observed important sex differences in the examined associations, which are consistent with the literature, but require further investigation.

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CRediT authorship contribution statement

PD conceived and designed the study, analysed and interpreted the data and drafted the article. AS analysed and interpreted the data and revise the article critically for important intellectual content. Both authors approve of the submitted version of the article.

Data sharing

The ELSA data are available from the UK Data Service: https://beta.ukdataservice.ac.uk/datacatalogue/studies/study?id=5050.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105798.
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