



Increases in stress hormone levels in a UK population during the COVID-19 pandemic: A prospective cohort study

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ABSTRACT

Background: Research suggests that psychological factors may influence vulnerability to SARS-CoV-2 infection, although the mechanisms are unclear.

Purpose: We examined whether the hypothalamic-pituitary-adrenal axis may be a possible mechanism, by measuring the relationship between indices of psychological distress and cortisone in hair (hairE) in a UK cohort during the COVID-19 pandemic.

Methods: Participants (N = 827) provided two 3 cm hair samples over a 6-month period between April-September 2020. Samples reflected hairE in the 3 months prior to the collection date.

Results: HairE in the first samples (T1: commenced April 2020) did not differ significantly from pre-pandemic population norms. However, hairE in the second samples (T2: commenced July 2020) were significantly higher than T1 and pre-pandemic population norms, with a 23% increase between T1 and T2. Linear regressions, controlling for age and gender, demonstrated that at both timepoints, hairE levels were greatest in people with a history of mental health difficulties. In addition, stress reported at T1 predicted greater hairE at T2 and a greater change in hairE between T1 and T2.

Conclusions: These findings demonstrate that during the COVID-19 pandemic hairE was substantially elevated across a large community cohort, with greatest levels in those with a history of mental health difficulties and greatest changes in those reporting greatest levels of stress early in the pandemic. Further research is required with verified SARS-CoV-2 outcomes to determine whether the HPA axis is among the mechanisms by which a history of mental health difficulties and stress influence SARS-CoV-2 outcomes.

1. Introduction

The COVID-19 (Coronavirus, 2019) pandemic caused by the SARS-CoV-2 virus has resulted in unprecedented disruption to societies, health services, and economies. Increases in mental health difficulties (e.g., anxiety and depression) and risk factors associated with poorer mental health (e.g., loneliness) are now well-documented consequences of the pandemic (Jia et al., 2020; Kwong et al., 2020; Luchetti et al., 2020; Torales et al., 2020). In view of the established associations between adverse emotional experiences and physical health (Vedhara

et al., 1999; Vedhara et al., 2010; Pantell et al., 2013), these findings raise important questions about the role of mental health, and related psychological constructs, as possible risk factors for SARS-CoV-2 infection and, critically, the mechanisms underlying any such effects. We provide evidence here regarding the potential role of the hypothalamic-pituitary-adrenal (HPA) axis.

The empirical basis for this hypothesis comes principally from viral challenge studies. These studies typically involve quarantining healthy volunteers for several days during which they are exposed to one or more respiratory viruses and followed up for evidence of infection and/

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or the presence of symptomatic illness. One of the first, and perhaps most well-known studies showed a dose response relationship between a composite measure of psychological stress (stressful life events, negative affect, and perceived stress) and the likelihood of viral infection and the severity of subsequent illness (Cohen et al., 1991). These results not only showed that increased levels of stress predicted an increased risk of developing a respiratory illness; but also that these effects occurred across a range of different viruses (rhinovirus type 2, 9, 14, respiratory syncytial virus and coronavirus type 229E). Since this ground-breaking work, several related studies have shown that psychological factors influence susceptibility to viral infections (Cohen et al., 1997; Cohen et al., 1998; Cohen, 1999; Cohen et al., 2003; Cohen et al., 2004; Cohen, 2005; Cohen et al., 2015). Evidence is emerging that these same pathways may be relevant in the context of SARS-CoV-2. For example, research from the UK biobank compared the risk of COVID-19 outcomes in participants diagnosed with a psychiatric disorder pre-pandemic, with those who had not (Yang et al., 2020). They observed that participants with a history of psychiatric disorder were at greater risk of COVID-19 infection, hospitalisation, and mortality. Further support comes from a recent systematic review of COVID-19-related mortality risk in people with severe mental illness (De Hert et al., 2021). Results from 13 studies suggested an association between severe mental illness and COVID-19 mortality (De Hert et al., 2021). Although the underlying mechanisms for the increased risk of disease for those with psychiatric disorders are unclear, these studies point to a potential common pathway involving compromised immunity (Yang et al., 2020; De Hert et al., 2021).

One possibility for a common pathway that links psychological health to infection susceptibility may be the HPA axis and, specifically the hormone cortisol. Observational and experimental evidence has shown that psychological distress can dysregulate the HPA axis (Søndergaard and Theorell, 2003; Hsiao et al., 2011) and this in turn, through the immunomodulatory properties of cortisol, can compromise immune function (Ibar et al., 2021; O'Connor et al., 2021). The secretion of cortisol can suppress the activity of the natural killer (NK) cells and the transcription of proinflammatory cytokines via direct interactions with glucocorticoid receptors, which are present on many immune cells (Theoharides and Conti, 2020; Peters et al., 2021). Cohen and colleagues (2012) hypothesized that chronic increases in cortisol can lead to decreased sensitivity of immune cells to glucocorticoid hormones. This, in turn, can interfere with the production of proinflammatory cytokines in response to viral infections and promote an exaggerated response to infection (Cohen et al., 2012) as observed in some patients who become critically ill following COVID-19 infection (Peters et al., 2021). Evidence of an association between cortisol and SARS-CoV-2 outcomes is also emerging. For example, Tan et al. (2020) measured serum cortisol in 535 patients admitted to hospital during the first wave of COVID-19 infections in the UK. They reported that the risk of mortality increased significantly by 42% per doubling of cortisol concentrations, after adjusting for age, other comorbidities, and laboratory tests (Tan et al., 2020). These findings resonate with those of the RECOVERY trial (Horby et al., 2021) and a recent meta-analysis (Sterne et al., 2020) which demonstrated lower mortality in COVID-19 patients receiving synthetic corticosteroid treatments such as dexamethasone. These synthetic versions of cortisol alter the body's own production of the hormone and, could, therefore, interfere with its capacity to dysregulate the immune system including its response to COVID-19 infection. Recent observational studies have also reported a relationship between cortisol and mental health during the COVID-19 pandemic. For example, Rajcani et al. (2021) and Marcil et al. (2021) reported that cortisol measured in hair during the COVID-19 pandemic increased by 22–27% among healthcare workers (Rajcani et al., 2021; Marcil et al., 2022). Ibar et al. (2021) found that health workers with burnout also had significantly higher hair cortisol levels during the pandemic.

Taken together, the evidence suggests that the increased risk of SARS-CoV-2 infection and poorer disease outcomes observed in people

with a history of psychiatric illness, may be mediated by the HPA axis and an increase in the production of cortisol. To examine this further, we measured concentrations of cortisone (a metabolite of cortisol) in hair (hairE), in a general population sample of adults in the United Kingdom (UK), during the COVID-19 pandemic. Our aims were to: (i) report on whether and how levels of hairE changed in a UK cohort over a 6 month period early in the UK's experience of the pandemic; (ii) compare these levels with existing pre-pandemic population data; and (iii) examine whether hairE levels differed significantly between people with or without a history of mental health difficulties as well as assess the relationship between hairE and levels of stress, anxiety and depression reported during the pandemic.

2. Methods

2.1. Patient and public involvement (PPI)

We convened a virtual PPI group to support this research, the aims of which were to advise on the development of the survey, the participant information sheet, and methods for optimising recruitment and retention. Individuals participated via Microsoft Teams in one-to-one or group-based discussions at the design phase of the research. These discussions informed the length and structure of the survey, language in the information sheet, and strategies for recruiting via media and social media. For example, the PPI group suggested using social media campaigns with daily interactive posts during the recruitment period. They also supported the idea of snowball recruitment. Snowball recruitment is a common sampling method in research where the researcher expands their pool of potential participants by encourages initial participants to reach out to their contacts to inform them about the research, and potentially participate (Marcus et al., 2017). The PPI group also advised on the frequency of providing feedback to participants and reporting study findings through the study website and between each wave of data collection.

2.2. Ethics, recruitment and eligibility

Ethical approval was granted from the University of Nottingham Faculty of Medicine & Health Sciences Research Ethics Committee (FMHS 506–2003) and recruitment commenced on 3 April 2020. Participants were recruited in the community via a social and mainstream media campaign involving, but not limited to, Facebook and Twitter. Dedicated social media accounts were created and engaging, interactive posts were posted daily through these accounts to encourage participation. We also sought to encourage the participation of healthcare workers and achieved this by seeking additional approvals through the Health Research Authority (HRA, approval number 20/HRA/1858). This enabled us to approach National Health Service (NHS) organisations and request that they advertise the research through their routine communications to staff (e.g., newsletters, emails). Recruitment continued until 30 April 2020.

All media and promotion directed potential participants to the study website through which they accessed the participant information sheet, consent form, online surveys, and instructions on how to take hair samples. Participants were informed through follow-up email communications that they would be entered into a prize draw of a £ 200 Amazon voucher at the end of the study if they completed all study surveys and provided two hair samples. Once recruited we used snowball recruitment (Marcus et al., 2017) to encourage rapid growth in the size of the cohort. This involved: (1) an email to existing participants to thank them for taking part and encouraging them to reach out to another 10 people they know (e.g., other members of the family or friends) to consider taking part. This email was sent to the first $n = 335$ participants one week after launching the study, and then new participants at the end of every week. (2) a similar thank you email to all participants alongside an encouragement to reach out to a further two people to consider

taking part 10 days, three days, one day before closure of recruitment (i.e., 30th April 2020).

Eligibility criteria specified that participants should be: aged 18 and over; able to give informed consent; able to read English; residing in the UK at the time of completing the survey; and able to provide a sample of hair at least 1 cm long. The latter was collected to permit measurement of the hairE.

2.3. Procedures

Data were collected at three timepoints during 2020. Fig. 1 provides an overview of data collection in relation to the timeline of the pandemic in the UK. We report here data from Timepoint 1 (T1: commenced April 2020) and Timepoint 2 (T2: commenced July 2020) during which online surveys were completed and hair samples collected for the measurement of hairE. Online surveys were implemented through JISC Online Survey (<https://www.onlinesurveys.ac.uk/>). These collected demographic information (e.g., age, gender) and self-report measures of anxiety (7-item Generalized Anxiety Disorder Scale, GAD-7, T1 $\alpha = 0.92$, T2 $\alpha = 0.91$), depression (Patient Health Questionnaire, PHQ-9, T1 $\alpha = 0.88$, T2 $\alpha = 0.87$) and stress (4-item Perceived Stress Scale, T1 $\alpha = 0.76$, T2 $\alpha = 0.75$) (Cohen, 1988; Spitzer et al., 2006; Kroenke et al., 2010). Previous diagnosis of mental health disorders was measured by a single item 'do you have a history of anxiety, depression or any other mental health issue for which you have received treatment in the past' (yes/no/prefer not to say).

Collection of hair samples for the measurement of hairE followed standard methods (Staufenbiel et al., 2015). In brief, participants were provided with a step-by-step guide on the study website. This included text and video guidance on how to cut a hair sample of no less than 1 cm and approximate width of a pencil (3 mm) from the vertex posterior of the head. After taking the sample, participants were instructed to wrap the sample in kitchen foil and clearly label it with their study identifier, denote the root end (i.e., the end closest to the scalp) of the sample, and date the sample was taken. These instructions were repeated at T2 and participants were asked to return their samples using a freepost address. As the majority of participants who returned hair samples provided samples of 3 cm or longer (T1: $n = 849$, 95%; T2: $n = 857$, 96%) we analysed the first 3 cm of each sample to indicate hairE in the preceding

3 months (Staufenbiel et al., 2015) i.e., the T1 sample captured hairE in the 3 months prior to sample collection at T1, and the T2 sample captured hairE in the 3 months prior to sample collection at T2.

2.4. HairE measurement

Hair samples were prepared for the cortisone assay following standard methods described by Gao et al. (2013). Specifically, a minimum of 7.5 mg of hair was obtained from each hair sample ≥ 3 cm. Hair samples shorter than 3 cm were not assayed. The hair washing and cortisone extraction procedures were based on the protocol previously described in Stalder et al. (2012). In brief, hair strands were washed by shaking them in 2.5 mL isopropanol for 3 min at room temperature and then dried under a fume hood for at least 12 h. 7.5 mg of whole non-pulverised hair was then carefully weighed out and transferred into a 2 mL tube (Eppendorf, Hamburg, Germany). 50 μ L internal standard and 1.8 mL methanol were added and the hair was incubated for 18 h at room temperature for cortisone extraction. Samples were spun in a centrifuge at 10,000 rpm for 2 min and the clear supernatant was transferred into a new 2 mL tube. The alcohol was evaporated at 65 °C under a constant stream of nitrogen for approximately 20 min until the samples were completely dried. The dry residue was resuspended using 250 μ L distilled water, 200 μ L of which was used for liquid chromatography tandem mass spectrometry (LC-MC) analysis. More details of the protocol are provided by Gao et al. (2013).

2.5. Sample size

The cohort was recruited to track the psychological and physical effects of the COVID-19 pandemic on the UK population. As such, we did not place an upper limit on participant numbers to enable us to obtain as precise estimates of population values and associations as possible, and to permit subgroup analysis where applicable. Nonetheless, power calculations indicate that to detect a small effect size change ($d_z = 0.2$) on cortisone levels from T1 to T2 in a two-tailed t-test with 90% power and alpha set at 0.05, a minimum of 265 participants would be needed to provide hair samples at both timepoints.

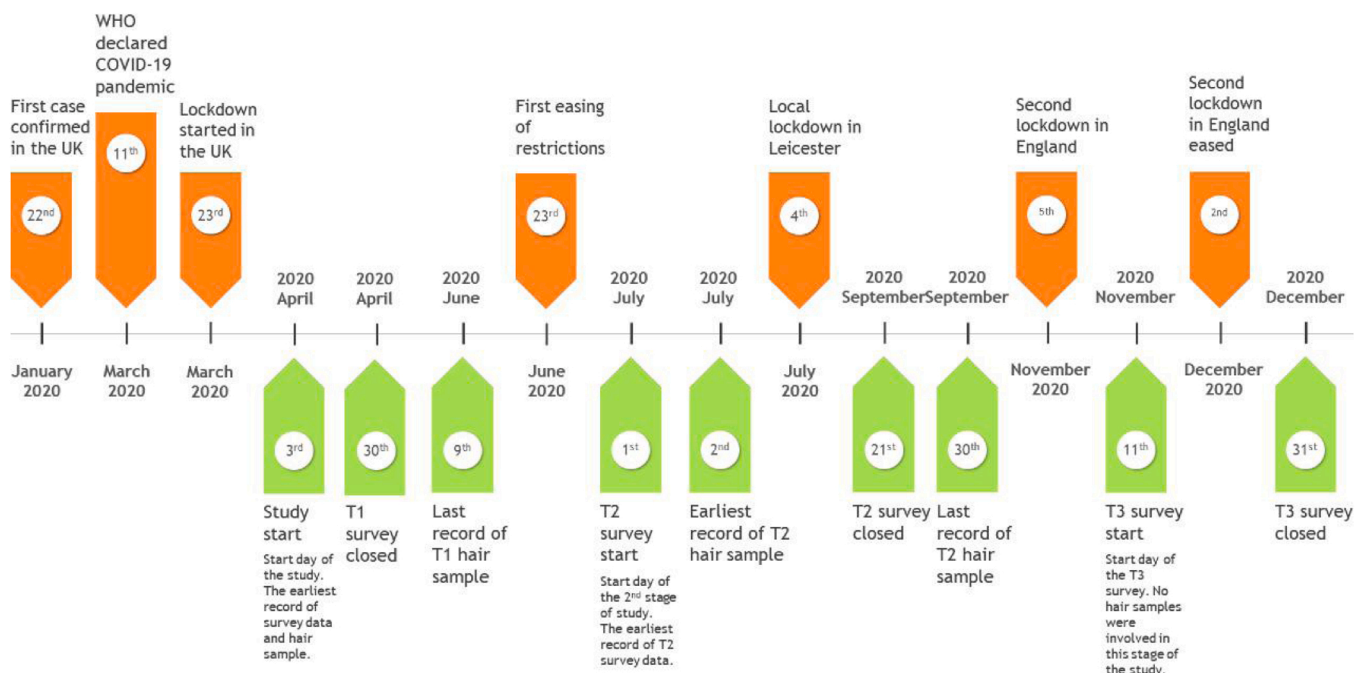


Fig. 1. Trajectory of the COVID-19 pandemic in the UK and relationship with assessments in the current study.

2.6. Statistical analysis

Summary statistics were used to describe characteristics of participants, hairE levels, and levels of stress, anxiety and depression at T1 and T2. Comparisons between hairE at T1 and T2 were conducted using a paired-samples t-test with log-transformed hairE values. Comparisons between mean hairE values at T1 and T2 with pre-pandemic population mean data were also conducted. These latter means were derived from a cohort of 10,814 individuals with a mean age of 47 years (SD 24.21) and 65% of whom were female (manuscript in preparation). As the raw data from this cohort were not available, independent t-tests were conducted. While t-tests are robust to deviations from normality when sample sizes are large, results of these specific analyses should be interpreted with caution (Lumley et al., 2002).

Four hairE outcomes were considered in the analyses: hairE values at T1, hairE values at T2, mean of T1 and T2 hairE values, and change in hairE from T1 to T2. Multivariable linear regressions were used to examine the associations between the hairE outcomes and history of mental health difficulties as well as stress, anxiety and depression reported at T1. Histograms showed that the distributions of the absolute hairE values at T1 and T2, and mean hairE across T1 and T2 were not normally distributed. Thus, log-transformed scores for these three outcomes were used in all multivariable linear regressions. For the history of mental health difficulties, relationships with all four hairE outcomes were considered. Analyses with stress, anxiety, and depression took into account temporal differences between when the measures of mood were captured and the periods covered by the hair samples (i.e., T1 hair samples captured hairE in the 3 months prior to the T1 mood measures and T2 hair samples captured hairE in the 3 months prior to the T2 mood measures). Thus, analyses examining the relationship between stress, anxiety and depression reported during the pandemic and hairE involved stress, anxiety and depression at T1 predicting (i) hairE at T2 and (ii) change in hairE between T1 and T2 only. For all analyses, anxiety and depression were determined by dichotomising scores on the GAD-7 and PHQ-9 (Spitzer et al., 2006; Kroenke et al., 2010) according to established cut-offs for high intensity psychological support in the National Health Service (National Collaborating Centre for Mental Health, 2019). Age and gender were controlled for in all regression analyses.

2.7. Additional analysis

Although we instructed participants to take the first hair sample in April and the second hair sample in July, some of the samples were dated later than suggested. Further, the time intervals between each sample from participants varied. To account for the influence of these time variations on our findings, we calculated an additional variable to represent these temporal factors. For T1 and T2 the first and last dates of sample collection covered a period of 97 and 91 days respectively. Accordingly, at both timepoints, an individual who provided a sample on the first day was allocated a score of 0; while samples collected on the last day were allocated a score of 97 for T1 and 91 for T2. The time interval between the two hair samples was then calculated as the number of calendar days between the two samples (median=92, range: 48–166). This was then included as a covariate in all regression models as an additional analysis to examine the influence of the differing time intervals between samples.

All analyses were performed using STATA (version 16) and GraphPad Prism (version 9.1.2).

Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Cohort characteristics

Hair samples at both time points were received from 980 (32%)

participants of our original cohort who completed the T1 survey ($N = 3097$). Of these, $n = 89$ (9%) were excluded for a variety of reasons including the samples being labelled with an incorrect study ID, the hair sample being insufficient/missing, or the root end of the sample being unclear (see Supplementary Appendix Fig. 1). The remaining 891 (91% of $n = 980$) pairs of samples were assayed. Of these, 64 participants (7% of $n = 895$) were excluded due to their samples being less than 3 cm in length ($n = 56$); participants collecting their T2 hair sample before the date requested ($n = 4$); participants providing both hair samples within 5 calendar days ($n = 2$); and hairE being undetectable in the samples ($n = 2$). Thus, the final cohort included in all analyses were 827 participants (84% of $n = 980$) who provided two hair samples. $N = 788$ participants (95% of $n = 827$) provided responses to the question regarding previous mental health difficulties. Thus, analyses pertaining to the relationship between hairE and previous mental health difficulties were restricted to this subsample.

Comparisons between participants who provided two hair samples ($n = 827$) and those who did not ($n = 2268$) indicated that older participants ($t = -11.43$, $p < .001$, Cohen's $d = -0.46$), female participants ($X^2 = 91.96$, $p < .001$), White British participants ($X^2 = 16.21$, $p < .001$), and those with lower baseline depression ($t = 8.93$, $p < .001$, Cohen's $d = 0.36$), anxiety ($t = 7.02$, $p < .001$, Cohen's $d = 0.29$), and stress ($t = 7.03$, $p < .001$, Cohen's $d = 0.29$) were more likely to return two hair samples (see Table 1).

3.2. HairE during the COVID-19 pandemic and comparisons with pre-pandemic data

Medians (IQRs) of cortisol values in the study participants at T1 and T2 and for pre-pandemic population data are presented in Table 2 and Fig. 2. A Paired-sample t-test showed that hairE levels (log-transformed values) were significantly higher over the 3-month period captured at T2 than the 3 month period captured at T1 ($t = -8.42$, $p < .001$, Cohen's $d = -0.51$), with mean values 23% higher at T2. Independent t-tests were used to compare the mean values of hairE in our cohort at T1 and T2 with pre-pandemic population data. Results showed no significant differences in mean hairE values at T1 compared with pre-pandemic data ($t = 1.64$, $p = .10$, Cohen's $d = 0.06$). However, mean hairE levels at T2 were significantly higher than pre-pandemic data ($t = 5.44$, $p < .001$, Cohen's $d = 0.19$).

3.3. Relationship between hairE and history of mental health difficulties

Multivariable linear regressions (Table 3) examined the relationship between hairE outcomes and having a history of mental health difficulties, after controlling for age and gender. For hairE at T1, being female ($p < .001$) was significantly associated with lower hairE values, and having a history of mental health difficulties ($p < .001$) was significantly associated with higher hairE values. Similar associations were evident for hairE at T2 (female: $p = .002$; history of mental health difficulties: $p = .045$). With regard to mean hairE values across T1 and T2, the results showed that having a history of mental health difficulties ($p < .001$) was associated with significantly elevated average levels of hairE of T1 and T2 combined. It was, however, unrelated to the changes in hairE between T1 and T2 ($p = .19$). Greater change in hairE between T1 and T2 was, however, associated with being female ($p = .019$) and older ($p = .041$). Our additional analysis of the influence of differing time intervals between samples showed that after adding the number of days between the two hair samples as a covariate, these results were largely unaffected (see Appendix Table 1).

3.4. Relationship between hairE and depression, anxiety and stress reported during the pandemic

Multivariable linear regressions examined prospective associations between stress, anxiety and depression reported at T1 and (i) hairE at T2

Table 1
Characteristics of participants who provided two hair samples and those who did not.

| | Participants who provided two samples | Participants who provided < 2 samples |
|--|---------------------------------------|---------------------------------------|
| N | n (%) 827 (27%) | n (%) 2268 (73%) |
| Gender* | | |
| Male | 77 (9%) | 399 (18%) |
| Female | 749 (91%) | 1866 (82%) |
| Prefer not to say | 0 | 3 (0.1%) |
| Age (mean, SD)* | 49.61 (15.32) | 42.78 (14.46) |
| Age groups (years) | | |
| 18–24 | 60 (7%) | 302 (13%) |
| 25–34 | 102 (12%) | 525 (19%) |
| 35–44 | 138 (17%) | 499 (22%) |
| 45–54 | 168 (20%) | 522 (23%) |
| 55–64 | 213 (26%) | 357 (16%) |
| 65–74 | 119 (14%) | 138 (6%) |
| ≥ 75 | 26 (3%) | 23 (1%) |
| Ethnicity* | | |
| White British | 776 (94%) | 2017 (89%) |
| Black, Asian, and Minority Ethnic | 50 (6%) | 246 (11%) |
| Prefer not to say | 0 | 5 (0.2%) |
| Education | | |
| No qualifications | 9 (1%) | 24 (1%) |
| GCSE/CSE/O-levels or equivalent | 49 (6%) | 203 (9%) |
| Post-16 vocational course | 30 (4%) | 71 (3%) |
| A-levels or equivalent | 83 (10%) | 318 (14%) |
| Undergraduate degree | 377 (46%) | 929 (41%) |
| Postgraduate degree | 276 (33%) | 699 (31%) |
| Prefer not to say | 2 (0.2%) | 24 (1%) |
| Previous diagnosis of mental health disorders | | |
| Yes | 297 (36%) | 222 (10%) |
| No | 491 (59%) | 359 (16%) |
| Indices of psychological well-being | | |
| T1 Depression (median, IQR)* | 5 (2–8) | 7 (3–12) |
| T1 Depression cases (mean ≥10) ^a | 170 (20.6%) | 806 (36%) |
| T1 Depression non-cases (mean <10) ^a | 656 (79.4%) | 1462 (64%) |
| T1 Anxiety (median, IQR)* | 4 (1–8) | 6 (2–11) |
| T1 Anxiety cases (mean ≥8) ^a | 208 (25%) | 844 (37%) |
| T1 Anxiety non-cases (mean <8) ^a | 618 (75%) | 1424 (62.8%) |
| T1 Stress (mean, SD)* | 5.79 (3.12) | 6.72 (3.30) |

*significant differences between participants who provided at least two hair samples and who did not.

^a A 'case' is defined as the PHQ-9 score greater or equal to 10 for depression, or the GAD-7 score greater or equal to 8 for anxiety, at which level someone would qualify for high intensity psychological support in the English National Health Service.

Table 2
HairE at T1 and T2 compared with pre-pandemic norms.

| | Pre-pandemic population data for hairE (N = 10,814) | T1 hairE (N = 827) Sample 1 | T2 hairE (N = 827) Sample 2 |
|--------------|---|-----------------------------|-----------------------------|
| Median (IQR) | 8.55 (5.23–14.18) | 8.20 (5.52–12.22) | 9.68 (6.18–15.44) |

and (ii) change in hairE between T1 and T2. These analyses (see Table 4) revealed that, after controlling for age and gender, meeting the criteria for high intensity support for anxiety and depression at T1 was not associated with hairE values at T2 or the change in hairE between T1 and T2 (see models 1–4 in Table 4). However, stress at T1 was significantly associated with hairE at T2 (model 5, $p = .017$) as well as the

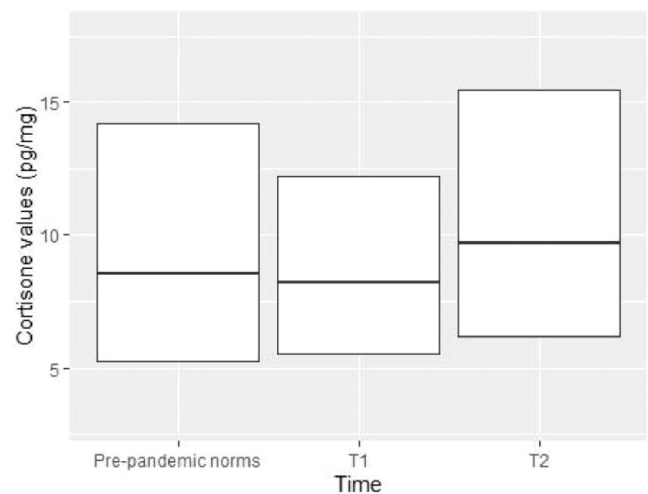


Fig. 2. Mean values of hairE at T1 and T2 and pre-pandemic population data. The boxes represent 25% quartiles to 75% quartiles. The solid lines inside the box represent medians.

change in hairE between T1 and T2 (model 6, $p = .032$). The additional analysis of the influence of differing time intervals between samples showed that, after adding the number of days between the two hair samples as a covariate, these results were largely unaffected (see Appendix, Table 2).

4. Discussion

The present study examined whether the HPA axis, as measured by hairE, was altered in a convenience sample of UK citizens during the COVID-19 pandemic and the extent to which hairE was related to an individual's previous experience of mental health difficulties, as well as their experiences of stress, anxiety and depression during the pandemic. The findings indicate that in the 3-month period immediately before the UK's first national lockdown (captured by hairE at T1), hairE levels in our cohort were not significantly different to pre-pandemic population levels. However, hairE at T2, which captured a 3-month period of both local and national restrictions in the UK, was significantly greater than hairE at T1 and also pre-pandemic population levels. Indeed, the mean hairE at T2 was 23% greater than mean levels observed at T1. Furthermore, we observed that individuals with a history of mental health difficulties had the greatest hairE (for three out of four hairE outcomes) and that higher stress scores at the start of the pandemic also predicted higher levels of hairE by T2 and a greater increase in hairE between T1 and T2.

Several issues are worthy of further discussion. First, the present work replicates and extends early findings on the experiences of health care workers during the pandemic which has shown an increase in cortisol levels when compared with pre-pandemic levels and positive associations between stress and cortisol in these populations (Ibar et al., 2021; Rajcani et al., 2021; Marcil et al., 2022). Here we show evidence that these psychobiological perturbations were also evident amongst a general population sample. Furthermore, our study, and that by Racjani et al. (2021) and Marcil et al. (2022), report comparable changes in cortisol/cortisone during the pandemic: with Rajcani et al., reporting an increase of 22% on pre-pandemic levels in health care professionals, Marcil et al. reporting an increase of 27%, while our data show a 23% increase in hair cortisone.

Second, the positive associations between hairE outcomes and having a history of mental health difficulties in this study, may provide a plausible mechanism for the observation (Yang et al., 2020; De Hert et al., 2021) that people with a history of psychiatric disorders appear to be at greater risk of COVID-19 infection, hospitalisation, and/or

Table 3

Multivariable regression models showing the associations between previous diagnosis of mental health disorders and hairEs controlling for age and gender.

| | HairE ^a T1 β, B (95% CI), p | HairE ^a T2 β, B (95% CI), p | HairE ^a Average of T1 and T2 values β, B (95% CI), p | HairE ^a Changes from T1 to T2 β, B (95% CI), p |
|--|---|---|--|--|
| Age (per 10 years increase) | 0.004, 0.002 (−0.03, 0.04), .91 | 0.05, 0.02 (−0.01, 0.06), .19 | 0.03, 0.01 (−0.02, 0.04), .37 | 0.08, 0.50 (0.08, 0.91), .019 * |
| Female (Y/N) | −0.14, − 0.38 (−0.56, −0.19), < .001 *** | −0.11, − 0.29 (−0.47, −0.10), .002 ** | −0.14, − 0.32 (−0.48, −0.15), < .001 *** | 0.07, 2.30 (0.10, 4.50), .041 * |
| Previous diagnosis of mental health disorder (Y/N) | 0.11, 0.18 (0.07, 0.28), .001 ** | 0.07, 0.11 (0.003, 0.22), .045 * | 0.10, 0.14 (0.04, 0.23), .005 ** | −0.05, − 0.88 (−2.20, 0.44), .19 |
| Intercept | 2.35 (2.10, 2.60), < .001 ** Adjusted R ² = 0.03, n = 788 | 2.38 (2.13, 2.64), < .001 ** Adjusted R ² = 0.01, n = 788 | 2.40 (2.18–2.60), < .001 ** Adjusted R ² = 0.02, n = 788 | 1.66 (−4.71, 1.39), .29 Adjusted R ² = 0.01, n = 788 |

*** p < .001, ** p < .01, * p < .05

^a A log transformation was applied to the dependent variable.

Table 4

Multivariable regression models showing demographic and psychological predictors of hairE outcomes.

| | T2 hairE β, B (95% CI), p | hairE change from T1 to T2 β, B (95% CI), p |
|---|---|---|
| | Model 1 | Model 2 |
| Age (per 10 years increase) | 0.06, 0.03 (−0.002, 0.07), .007 | 0.10, 0.60 (0.16, 1.03), .007 ** |
| Female (Y/N) | −0.11, − 0.29 (−0.47, −0.12), .001 ** | 0.05, 1.76 (−0.45, 3.97), .12 |
| Depression cases ^a at T1 (Y/N) | 0.07, 0.13 (−0.01, 0.26), .06 | 0.01, 0.27 (−1.37, 1.92), .75 |
| Intercept | 2.37 (2.12, 2.62), < .001 ** Adjusted R ² = 0.02, n = 826 | −2.15 (−5.26, 0.96), .18 Adjusted R ² = 0.01, n = 826 |
| | Model 3 | Model 4 |
| Age (per 10 years increase) | 0.05, 0.03 (−0.01, 0.06), .14 | 0.10, 0.60 (0.15, 1.02), .009 ** |
| Female (Y/N) | −0.11, 0.29 (−0.46, −0.11), .002 ** | 0.05, 1.78 (−0.43, 3.98), .12 |
| Anxiety cases at T1 ^a (Y/N) | 0.02, 0.04 (−0.09, 0.16), .55 | 0.005, 0.11 (−1.44, 1.65), .89 |
| Intercept | 2.40 (2.15, 2.66), < .001 ** Adjusted R ² = 0.02, n = 826 | −2.09 (−5.24, 1.07), .19 Adjusted R ² = 0.01, n = 826 |
| | Model 5 | Model 6 |
| Age (per 10 years increase) | 0.07, 0.03 (−0.001, 0.07), .054 | 0.11, 0.69 (0.26, 1.13), .002 ** |
| Female (Y/N) | −0.11, − 0.29 (−0.47, −0.12), .001 ** | 0.05, 1.66 (−0.55, 3.86), .14 |
| T1 stress (per unit) | 0.09, 0.02 (0.00, 0.04), .017 * | 0.08, 0.23 (0.02, 0.44), .032 * |
| Intercept | 2.26 (1.98, 2.54), < .001 ** Adjusted R ² = 0.02, n = 826 | −3.84 (−7.27, −0.40), .03 * Adjusted R ² = 0.01, n = 826 |

*** p < .001, ** p < .01, * p < .05

^a A 'case' is defined as the PHQ-9 depression score greater or equal to 10, or the GAD-7 anxiety score greater or equal to 8, at which level someone would qualify for high intensity psychological support in the National Health Service.

mortality. Cortisol is one of the primary products of the HPA axis and alterations in this hormone are a well-established consequence of psychological distress (Ibar et al., 2021; O'Connor et al., 2021). Furthermore, cortisol has immunomodulatory properties which enable distress-induced changes in cortisol to influence a range of health outcomes (Adam et al., 2017). Although we measured cortisone, rather than cortisol, the two hormones are structurally very similar, are highly correlated, and both can be measured in hair (Stalder et al., 2013; Staufenbiel et al., 2015). Cortisone is considered an acceptable surrogate for the measurement of free cortisol (i.e., the unbound biological active levels of the hormone) (Raul et al., 2004; Staufenbiel et al., 2015) and less prone to external contamination from cortisol-containing products

(Raul et al., 2004; Wang et al., 2019; Feeney et al., 2020). Thus, it is plausible that the elevations in hairE observed in this cohort, offer insight into the mechanisms underlying the increased risk of COVID-19 infection and poorer outcomes in people with a history of psychiatric illness. (Yang et al., 2020).

A third, and related observation concerns the fact that the associations between hairE and psychological well-being were not restricted to those with a history of mental health difficulties. We observed that stress experienced early in the pandemic at T1 was also related to later increases in hairE. This may suggest that, as found with previous viral challenge studies, people experiencing greater psychological stress may be at greater risk from SARS-CoV-2 infection as well symptomatic illness, as a result of increases in cortisol and the consequent dysregulation of the immune system. However, the present study did not specifically examine relationships with SARS-CoV-2 infections. Future studies of serologically verified infections would further shed light on these relationships. The absence of comparable relationships with anxiety and depression at T1 and subsequent hairE may simply reflect the smaller effect sizes associated with psychopathology and hairE (Staufenbiel et al., 2013). It should be acknowledged, however, that the proportion of variance in hairE accounted for by both stress and history of mental health difficulties was small to modest. This is consistent with that reported in previous work. For example, Rajcani et al. (2021) reported small effect of stress (effect size <0.001) on nurses during COVID-19. (Rajcani et al., 2021), and Ibar et al. (2021) reported small association between stress and hair cortisol in health workers (r = 0.14) (Ibar et al., 2021). This indicates that the HPA axis is likely to be just one of the pathways by which stress and mental health alter the risk of SARS-CoV-2 infection. Other pathways such as through neurotransmitters (e.g., adrenaline and noradrenaline), other hormones involved in the HPA axis (e.g., corticotrophin-releasing hormone), and lifestyle factors (e.g., sleep, diet, physical activity) may also be involved in this relationship (DuPre et al., 2021; Peters et al., 2021). Future work may, therefore, want to consider a broader range of mechanisms through which stress and mental health influence the risks of SARS-CoV-2 infection.

Some limitations of this work should also be acknowledged. These include that our assessment of previous mental health difficulties was based on self-report and not verified through clinical records. The current findings are derived from an opportunistic self-selected cohort. Individuals who provided us with two hair samples suitable for analysis were more likely to be female, older but also less stressed, anxious and depressed than the remainder of participants in the original cohort. Although this has implications for the generalisability of our findings to the original cohort, it does also suggest that the magnitude of the change in hairE during the COVID-19 pandemic is likely to be an underestimate as the most distressed individuals did not participate in this aspect of the research. There are likely several reasons for the predominance of female participants in our study. Firstly, one of the eligibility

criteria was that participants had to be able to provide a sample of hair at least 1 cm long. This might have prevented men with no or shorter hair from participating. Secondly, a substantial portion of our recruitment came through promoting this study in NHS settings, with 39% of our cohort identified as healthcare workers. According to NHS figures, 76.7% of the 1.3 million members of NHS staff are women (NHS, 2021), therefore it is likely that a higher proportion of women were made aware of our study and ultimately chose to participate. Thirdly, typical of previous online research studies concerning mental health, women were overrepresented in our sample (Crisp and Griffiths, 2014). Although we controlled for age and gender in the analyses, other potential confounders of hairE such as BMI, smoking status, hair washing frequency, and use of hair products were not accounted for in this study (Stalder et al., 2013; Staufenbiel et al., 2015). Furthermore, the effect sizes of the associations between having a history of mental health difficulties, stress and increases in hairE were small. This suggests that there may be other factors contributing to elevated hairE levels which we did not measure in the present study e.g., socioeconomic status, lifestyle behaviours such as physical activity and sleep. Such parameters have been shown to be related to both cortisol (Cohen et al., 2006; Jia et al., 2022) and COVID-19 outcomes (Caroppo et al., 2021; DuPre et al., 2021).

5. Conclusion

This prospective cohort study has shown a 23% increase in hairE in a large general population sample, during a 3-month period early in the course of the COVID-19 pandemic, with the greatest levels seen in people with a history of mental health difficulties as well as those reporting elevated stress early in the pandemic. In view of the role of cortisol in regulating the immune system, this evidence of chronic increases in hairE may explain some of the increased risk of SARS CoV-2 infection and poorer clinical outcomes observed in people with a history of mental health difficulties.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval was granted from the University of Nottingham Faculty of Medicine & Health Sciences Research Ethics Committee (FMHS 506–2003) and the Health Research Authority (HRA, approval number 20/HRA/1858).

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Role of sponsor

The study sponsor did not play a role in the study design, collection; analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Statement for disclosure of sample, conditions, measures, and exclusions

We have reported all measures, conditions, data exclusions, and determination of sample size for the study described in this manuscript. We confirm that this statement is accurate.

CRediT authorship contribution statement

Jia – conceptualization; data curation; formal analysis; investigation; methodology; writing original draft; writing review and editing. Ayling – conceptualization; data curation; formal analysis; investigation; methodology; writing original draft; writing review and editing. Coupland – conceptualization; data curation; formal analysis; investigation; methodology; writing review and editing. Chalder – conceptualization; data curation; formal analysis; investigation; methodology; writing review and editing. Massey – conceptualization; writing review and editing. Natar – conceptualization; methodology; writing review and editing. Broadbent – conceptualization; writing review and editing. Gasteiger – conceptualization; writing review and editing. Gao – data curation; methodology; writing review and editing. Kirschbaum – methodology; supervision; writing review and editing. Vedhara – conceptualization; data curation; formal analysis; investigation; methodology; writing original draft; writing review and editing.

Conflict of interest

AM is the director of Cortigenix (www.cortigenix.com). Cortigenix provided guidance on remote self-collection of hair samples by participants.

Analytic code availability

There is not analytic code associated with this study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.psyneuen.2022.105992](https://doi.org/10.1016/j.psyneuen.2022.105992).

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