



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Hair cortisol as a risk marker for increased depressive symptoms among older adults during the COVID-19 pandemic

J. Feeney^{a,*}, R.A. Kenny^{a,b}

^a The Irish longitudinal Study on Ageing, Department of Medical Gerontology, School of Medicine, Trinity College Dublin, Ireland

^b Mercer's Institute for Successful Ageing, St. James's Hospital, Trinity College Dublin, Ireland

ARTICLE INFO

Keywords:
Cortisol
Stress
Depression
COVID-19

ABSTRACT

Determining pre-existing biological risk markers of incident depression and other mental health sequelae after exposure to a new stressor would help identify vulnerable individuals and mechanistic pathways. This study investigated primarily whether hair cortisol predicted elevated depressive symptoms in middle-aged and older adults during the COVID-19 pandemic, 6 years later. A secondary aim was to deduce whether any association differed by sex.

Methods: We studied 1025 adults aged 50 and older (75% female) as part of The Irish Longitudinal Study on Ageing. Hair cortisol samples were collected at 2014 (Wave 3) and depressive symptoms were assessed using the 8-item Center for Epidemiological Studies Depression Scale in 2014 (Wave 3), 2016 (Wave 4), 2018 (Wave 5) and again in 2020 as part of TILDA's COVID-19 Study. Hierarchical mixed effects logistic regression models were applied to investigate the association between cortisol levels and clinically significant depressive symptoms before and during the COVID-19 pandemic.

Results: In a full covariate adjusted model there was a significant interaction between cortisol and wave on depressive symptoms ($\chi^2 = 8.5$, $p = .03$). Cortisol was positively and significantly associated with elevated depressive symptoms during the COVID-19 Study (OR = 1.3, 95% CI 1.11, 1.56, $p = .003$), and was associated with an increased likelihood of reporting clinically significant depressive symptoms during first year of the COVID-19 pandemic, when compared with before, OR = 1.4, 95% CI 1.05, 1.9, $p = .015$. There was no evidence of effect modification by sex.

Conclusions: Higher hair cortisol, assessed 6 years previously, predicted clinically significant depressive symptoms among middle-aged and older adults during (but not before) the pandemic. Findings suggest a biological phenotype which denotes increased susceptibility to the negative impact of environmental stress on psychological health.

1. Introduction

1.1. HPA axis dysregulation, stress and mental health

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, the body's main stress response system, leads to changes in the output of the glucocorticoid hormone cortisol, and has long been associated with mental health difficulties (Adam et al., 2017; Staufenbiel et al., 2013). Chronic stress causes a prolonged or repeated neuroendocrine stress response, which results in changes in the feedback sensitivity of the HPA axis (De Kloet et al., 1998). Depending on the duration and nature of the

stressor or stressors experienced, combined with the age at exposure, time since stressor onset, and most likely other genetic and environmental factors – this dysregulation may lead to an over-production or an under-production of cortisol (Lupien et al., 2009). A major focus of stress research is on elucidating determinants of susceptibility or resilience to psychosocial adversity in order to try to intervene to prevent or ameliorate poor mental and physical health outcomes. Under a 'vulnerability-stress' model the development of heightened psychological distress and ultimately of depression or a related disorder in response to a new stressor is a function of some predisposition, often biological in nature (Gilbertson et al., 2002; Ingram and Luxton, 2005). Elevated

* Corresponding author.

E-mail address: feeneyjo@tcd.ie (J. Feeney).

¹ The Irish Longitudinal Study on Ageing (TILDA), 152-160 Pearse Street, Trinity Central, Trinity College Dublin, Dublin 2, Ireland.

cortisol levels may represent a marker of biological susceptibility to increased psychological distress and the development of psychopathology in the presence of future life stress (Lupien et al., 2009; Qin et al., 2016). Certain regions of the brain, such as the amygdala, hippocampus and prefrontal cortex, are highly sensitive to cortisol. These particular areas are central to emotion regulation and to control of the HPA axis (Ulrich-Lai and Herman, 2009) and are also implicated in the aetiology of depression and related stress-associated disorders (McEwen et al., 2016). Cortisol hypersecretion is likely shaped by genetics, programming of the HPA axis by early life exposure to stressors, and more recent stress, which all combine to dictate individual stress responsivity and susceptibility to neuropsychiatric disorders. Certain periods in the life-course, namely childhood/adolescence and late adulthood, may coincide with a heightened vulnerability, as a result of the differing trajectories of development and decline of the aforementioned limbic and cortical brain regions which both exert top-down control on the HPA axis and are targets for changes in stress hormone signalling (McEwen et al., 2016).

1.2. Cortisol and risk of depression

There have been a number of studies exploring cortisol secretion and the subsequent development of MDD (Halligan et al., 2007; Kennis et al., 2020; Schuler et al., 2017) which, taken together, have provided modest evidence for an association between the circadian cortisol profile or response to HPA axis challenge and the onset/relapse/recurrence of MDD. The majority have investigated salivary cortisol metrics - which reflect short-term HPA axis activity or specific aspects of HPA axis reactivity only (Stalder et al., 2012), with considerable heterogeneity in the precise metrics. Furthermore, in most, the experience of recent stressful events or chronic stress was not examined as a precipitating factor in the development of depressive symptoms. Analysis of cortisol in hair has been proposed as a better measure of chronic stress than other cortisol metrics as it is not influenced by situational factors in the same way as saliva or blood cortisol (Stalder et al., 2012). Nonetheless, the evidence for an association between hair cortisol and measures of stress has been mixed, with a 2017 meta-analysis finding elevated hair cortisol in groups with objective chronic stress (e.g. caregivers) but no consistent relation with self-reported stress levels or current depressive symptoms (Stalder et al., 2017). A recent study (Shapero et al., 2019), however, found a moderating effect of hair cortisol on the positive association between recent life stress and depression in adolescents, such that this relationship was observed only in those with moderate-to-high cortisol levels. Several studies have also examined cortisol reactivity to stressful life events (Mayer et al., 2018; Petrowski et al., 2020) or laboratory stress tasks (Colich et al., 2015; Morris and Rao, 2014; Morris et al., 2012) and the majority have found, with the exception of Mayer et al., 2018, that higher cortisol reactivity to the stressor predicts future depression, though this may be moderated by depression history (Colich et al., 2015; Morris and Rao, 2014; Morris et al., 2012). The finding of a larger cortisol awakening response in both adults with current MDD and remitted MDD lends further support to the hypothesis that altered HPA axis activity may reflect/confer increased biological vulnerability to depression (Vreeburg et al., 2009). To-date studies have tended to focus on adolescents and young adults, with a paucity of similar investigations in middle-aged and older adults. Changes in HPA axis dynamics with age (Gaffey et al., 2016) and the potential for the onset of late-life depression (Alexopoulos, 2019), as well as the increased likelihood of physical and cognitive comorbidities render this group important to study in this context. Depression is also more prevalent among women than men (Albert, 2015), and one of the proposed mechanisms underlying this disparity is the interaction between sex hormones and stress response systems (Albert and Newhouse, 2019). Yet investigations of sex differences in the association between cortisol and incident depression are also lacking.

1.3. The COVID-19 pandemic as a naturalistic stressor

As the COVID-19 pandemic took hold around the world in early 2020, it very quickly became clear that increased age conferred an increased risk of severe disease and death (Shahid et al., 2020). Consequently, many governments and public health bodies throughout the world recommended that older adults severely restrict their movement (to an even greater degree than other sectors of the population) in order to reduce their risk of contracting COVID-19. In Ireland all adults 70 years and older in were very strongly advised to ‘cocoon’, a form of confinement which meant staying at home with all contact confined to within household only. It is well documented that the experience of quarantine is associated with negative psychological effects (Brooks et al., 2020), and evidence to-date suggests this has also been the case for older adults in Ireland as a result of mitigation policies enacted during the COVID-19 pandemic (Bailey et al., 2021). Furthermore, older adults in Ireland were found to experience higher levels of anxiety about COVID-19 than other age groups (Hyland et al., 2020). Our group has previously reported a sharp increase in the prevalence of clinically significant depressive symptoms among middle aged and older adults during the pandemic compared with the years prior, with adults aged over 70 and those living alone most adversely impacted (Briggs et al., 2021). A negative impact of the pandemic and associated social restrictions on mental health has been reported across many countries (Aknin et al., 2022; Bueno-Notivol et al., 2021), leaving little doubt that it has constituted a naturalistic stressor which has impacted populations worldwide and all sectors within society to varying degrees.

1.4. Aim

We set out to test the hypothesis that higher cortisol levels assessed 6 years prior to the arrival of COVID-19 would be associated with a greater increase in depressive symptoms among middle-aged and older adults during the pandemic. A secondary aim was to examine whether any observed associations differed by sex. Here we hypothesised the relationship between cortisol and depressive symptoms would be stronger for women than men.

2. Methods

2.1. Participants and design

The Irish longitudinal Study on Ageing (TILDA) is an ongoing, nationally representative prospective cohort study of community-dwelling adults aged 50 and older, living in the Republic of Ireland. The study began in 2009 (Wave 1) and participants are followed up on average every 2 years. There are three main modes of data collection: 1) a computer assisted personal interview carried out in the respondent's home; 2) a self-completion questionnaire (SCQ); and 3) a comprehensive health assessment. For full details of the sample design and main study data collection see (Whelan and Savva, 2013) and (Donoghue et al., 2018). The most recent main wave of data collection (Wave 5) was completed in 2018.

The COVID-19 pandemic reached Ireland in March 2020, and subsequently TILDA launched its COVID-19 study in order to assess the impact of the pandemic on the lives of middle-aged and older adults in Ireland. Participants were surveyed by means of SCQ between July and November 2020, with a response rate of 71%. The questionnaire gathered information on a range of topics concerning how the lives of respondents were impacted during the first months of the pandemic, including physical and mental wellbeing (Ward et al., 2021).

2.2. Hair cortisol measurement

Hair cortisol was measured as part of the health assessment at Wave 3 of TILDA (2014–2015). Hair cortisol has advantages over blood or

salivary cortisol in that it is not influenced by circadian or other situational factors, and it reflects circulating cortisol levels over weeks/months rather than days, with high intra-individual stability (Stalder et al., 2012). The sample was cut as close to the scalp as possible and the proximal 3 cm was taken to approximate growth over the previous 3-month period (Wennig, 2000). Steroid hormone analysis was carried out by Dresden LabService GmbH at the Technische Universität Dresden, Germany. Cortisol was measured by high performance liquid chromatography tandem mass spectrometry (LC-MS/MS) as per Gao et al. (2013) and cortisol levels were expressed in pg/mg.

2.3. Depressive symptoms

Depressive symptoms were measured at Wave 3 (2014–2015), Wave 4 (2016), Wave 5 (2018) and during the COVID-19 study (2020). Depressive symptoms were assessed using the 8-item version of the Centre for Epidemiological Studies Depression Scale (CES-D)(Radloff, 1977). The 8-item CES-D has previously been validated against the 20-item scale within the TILDA cohort (Briggs et al., 2014; O’Halloran et al., 2014). A cut-off score of $> = 9$ was taken to indicate clinically significant depressive symptoms (Briggs et al., 2018, 2021).

2.4. Statistical analyses

The distribution of all variables of interest was initially examined via tables, histograms, and Q–Q plots. Cortisol was positively skewed and thus was log transformed prior to analysis. Spearman correlations were calculated to test the bivariate association of hair cortisol and depressive symptoms (continuous) at Waves 3 (2014–2015), 4 (2016), 5 (2018) and during the first year of the COVID-19 pandemic (COVID-19 Study). Analyses of the association between hair cortisol levels (measured in 2014–2015) and clinically significant depressive symptoms at each wave were carried out using mixed-effects (ME) multi-level modelling in Stata 14. Hierarchical ME logit models were fitted, with a nested structure such that depressive symptoms (Level 1) were nested within each individual (individual as a Level 2 random intercept). Each individual in turn, was nested within a household (household as a Level 3 random intercept). Cortisol (log transformed and mean centred), wave and their product (cortisol X wave) were fixed effects of interest. Post-estimation contrasts were specified to compare depressive symptoms and the association of cortisol with depressive symptoms between waves. P-values and confidence intervals for between-wave comparisons were Bonferroni corrected for multiple comparisons. The post-estimation command *lincom* was then used to compute point estimates of the effect of cortisol on clinically significant depressive symptoms at each wave individually. Model covariates (assessed at Wave 3) included demographics (age, sex, marital status) socioeconomic indicators (employment status, highest level of education attained, social class), health behaviours (smoking, physical activity, problem drinking), BMI, chronic conditions, total number of medications, and any antidepressant medication use. Additional information on covariates is provided in the [Supplementary Material](#). In order to fulfil our secondary aim a second ME model was specified, further including the three-way interaction cortisol X wave X sex, to investigate whether the relationship between cortisol and clinically significant depressive symptoms across waves varied by sex.

Several sensitivity analyses were carried out. Firstly, models were run with CES-D score as a continuous variable, to test the robustness of the results. Secondly, the effect of inclusion of covariates measured at Wave 5 (the most recent measurement before the pandemic) rather than at Wave 3 on model estimates was examined. Finally, the models were rerun dichotomising the sample at age 70 years, given the difference in the social restrictions imposed in Ireland upon those aged 70 year and older, and potential implications for increased stress and depression.

Ethical approval was obtained from the Research Ethics Committee at Trinity College Dublin, and all respondents provided written informed

consent prior to participation in the study. All experimental procedures adhered to the Declaration of Helsinki.

2.5. Analytic sample

The sample for analysis comprised 1025 individuals with valid cortisol and questionnaire data at Wave 3, 4, 5 and COVID-19 study. Exclusion criteria and a comparison of the analytic sample with the parent cohort on sociodemographic and health characteristics are provided in the [Supplemental Materials](#) (text and [table S1](#)).

3. Results

3.1. Descriptive statistics and bivariate associations

Sample characteristics are displayed in [Table 1](#). Notably, the number of individuals reporting clinically significant depressive symptoms

Table 1
Descriptive characteristics of the sample (n = 1025).

Variable	Mean (sd)/n (%)
Socio-demographic characteristics	
Age at cortisol measurement	64.0 (7.8)
Age during COVID-19 study	69.7 (7.9)
Sex: Female	775 (75.6)
Education (highest level attained)	
None/Primary	133 (13.0)
Secondary	403 (39.3)
Tertiary/higher	489 (47.7)
Marital status	
Married	751 (73.3)
Never married	92 (9.0)
Separated/divorced	72 (7.0)
Widowed	110 (10.7)
Employment status	
Employed	410 (40.0)
Retired	397 (38.7)
Other	218 (21.3)
Social class (most recent)	
Professional/managerial	406 (39.6)
Non-manual/skilled manual	443 (43.22)
Semi-skilled/unskilled	142 (13.56)
Health behaviours	
Smoking status	
Never	540 (52.7)
Past	400 (39.0)
Current	85 (8.3)
Problem drinking (defined by $> = 2$ on CAGE scale)	126 (12.4)
Physical activity	
Low	366 (35.7)
Moderate	405 (39.5)
High	254 (24.8)
Health conditions and medication use	
BMI	28.3 (5.5)
Chronic/cardiovascular conditions	
0	334 (32.6)
1	351 (34.2)
2	216 (21.1)
3+	124 (12.1)
Antidepressant use	83 (8.1)
Total number of medications	
0	294 (28.7)
1–2	323 (31.5)
3–4	242 (23.6)
5+	166 (16.2)
Cortisol log (pg/mg)	1.8 (1.2)
CESD $> = 9$	
Wave 3	93 (9.1)
Wave 4	83 (8.1)
Wave 5	88 (8.6)
Covid-19 Study	202 (19.7)

Note: BMI= body mass index. CES-D = Center for Epidemiological Studies Depression scale.

increased 2-fold during the COVID-19 study. Spearman rank correlations between cortisol (log transformed) at Wave 3 and CES-D scores at the same wave and each subsequent wave were as follows: Wave 3, $Rho = 0.05, p = .10$; Wave 4, $Rho = 0.03, p = .26$; Wave 5, $Rho = -0.02, p = .51$; COVID-19 Study, $Rho = 0.06, p = .06$.

3.2. Multivariable association between cortisol at Wave 3 and depressive symptoms at Waves 3, 4, 5 and during the COVID-19 Study

Hierarchical ME logistic regression with post-estimation contrasts confirmed a main effect of wave on clinically significant depressive symptoms even after adjustment for covariates ($\chi^2 = 110.7, p < .000$). Comparing the COVID-19 study to Wave 5, the most recent wave of data collection before the pandemic, individuals were much more likely to report clinically significant depressive symptoms during the COVID-19 study, $OR = 4.0, 95\% CI 2.7, 6.1, p < .000$. This result held when the likelihood of clinically significant depressive symptoms during the COVID-19 study was compared to the average probability across the three most recent waves before the pandemic (Waves 3, 4, and 5), $OR = 4.1, 95\% CI 2.9, 5.6, p < .000$. Higher cortisol (Wave 3) was associated with higher likelihood of reporting clinically significant depressive symptoms during the COVID-19 Study, but not at the previous waves. Estimates of the effect of cortisol on the odds of clinically significant depressive symptoms at each wave are given in Table 2. Moreover, the interaction effect of cortisol X wave was also significant ($\chi^2 = 8.5, p = .03$), suggesting that the association between cortisol levels and clinically significant depressive symptoms differed across waves. Having higher cortisol at Wave 3 was associated with an increased likelihood of reporting clinically significant depressive symptoms during the COVID-19 study, when compared with Wave 5 before the pandemic, $OR = 1.4, 95\% CI 1.05, 1.9, p = .015$. When taking the average of the most recent three waves prior to the pandemic as the comparator, this result held, although the Bonferroni corrected p-value was greater than .05 ($OR = 1.2, 95\% CI .99, 1.5, p = .06$). Fig. 1 displays the marginal probability of reporting clinically significant depressive symptoms at each wave, by cortisol at Wave 3.

3.3. Effect modification by sex

A second ME regression model including the higher order three-way interaction between cortisol, wave and sex revealed no significant interaction effect ($\chi^2 = 3.6, p = .31$), suggesting that the relationship of cortisol to depressive symptoms across waves did not differ significantly between men and women.

3.4. Sensitivity analyses

Re- running the models with CES-D score as the dependent variable by way of a sensitivity analysis did not change the results appreciably. Furthermore, using covariates measured at Wave 5 instead of Wave 3 in the models also did not attenuate associations, if anything, they were slightly strengthened. Finally, examining individuals aged 70 and older separately revealed slightly higher odds of clinically significant depressive symptoms and a stronger association of cortisol with increased depressive symptoms in this older group compared with individuals under 70. Full results of sensitivity analyses are reported in the

Table 2
Effect estimates for the association of cortisol with clinically significant depressive symptoms at each wave.

Wave	OR	95% CI	p
Wave 3	1.19	.97, 1.46	.090
Wave 4	1.07	.86, 1.34	.488
Wave 5	.92	.74, 1.16	.488
COVID-19 Study	1.31	1.11, 1.56	.002

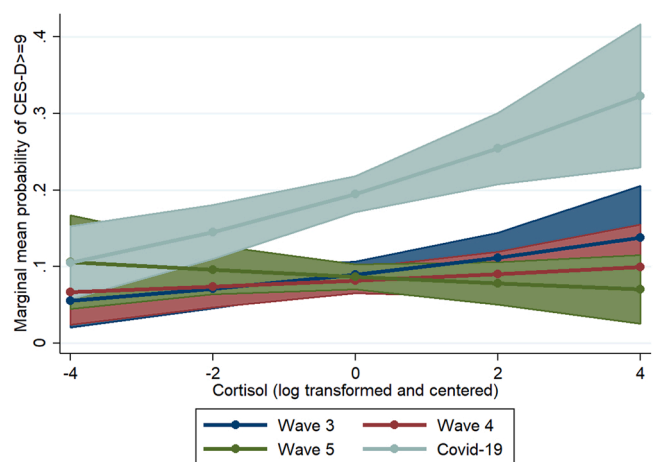


Fig. 1. Marginal estimates for the association between cortisol and clinically significant depressive symptoms (CES-D >=9) before and during the COVID-19 pandemic.

Note: CES-D = Centre for Epidemiological Studies Depression scale. Bands indicate 95% confidence intervals.

Supplementary Materials.

4. Discussion

Many studies have investigated hypercortisolism as a possible mechanism explaining the association between psychological distress and increased risk of poor mental health outcomes; however, comparatively fewer investigations have sought to disentangle whether higher cortisol levels also represent a vulnerability factor for the development of mental health sequelae after stressor exposure. We found that hair cortisol, measured in 2014, was significantly and positively associated with depressive symptoms experienced during the COVID-19 pandemic (2020), but not in the years preceding the pandemic, suggesting that hair cortisol may have utility as a risk marker for future increases in depressive symptoms, though these results require replication. We did not find any evidence of effect modification by sex. To our knowledge this is the first study to examine whether hair cortisol assessed prior to the COVID-19 pandemic predicts increased depressive symptoms during the pandemic independently of any pre-pandemic relationship with depression and the first study to explore the relation among such variables in a population-based sample. These results add to the literature on cortisol levels constituting a biological marker of susceptibility to poor mental health following exposure to a period of heightened stress.

Very few studies have examined hair cortisol as a risk marker for depression, and results have been equivocal (Duncko et al., 2019; Kische et al., 2021). In partial support for an association, Rietschel and colleagues studied the relation between hair cortisol, perceived stress, depressive symptoms and neuroticism in twins and found evidence for a shared heritability between cortisol levels and these psychological constructs (Rietschel et al., 2016). Regarding hair cortisol as a marker of biological susceptibility to depressive symptoms following a specific period of acute stress, Petrowski and colleagues (Petrowski et al., 2020) found that cortisol levels immediately preceding a motor crash were related to subsequent avoidant behaviour but not to depressive symptoms, 3-months later. Notably, to our knowledge, no other studies to-date have investigated hair cortisol as an antecedent to increased depressive symptoms following exposure to a highly stressful event.

Several studies have examined pre-pandemic factors which predict greater psychological distress during the COVID-19 pandemic specifically. These have included sociodemographic factors such as younger age, female gender, low education/income, belong to a minority group, living alone/without a partner, chronic physical health conditions (Aknin et al., 2022; Brooks et al., 2020; Pierce et al., 2020) as well as

prior mental health status such as higher pre-pandemic anxiety or depressive symptoms (Gilbar et al., 2022; Varma et al., 2021). To our knowledge there have been only a small number of studies which have assessed the potential association between cortisol levels and mental health during the COVID-19 pandemic. Rajcani and colleagues assessed hair cortisol levels among nurses immediately prior to and during the first few months of the COVID-19 pandemic in Slovakia and found higher hair cortisol during compared with prior to the pandemic, as well as higher pandemic cortisol levels among nurses working in higher risk environments (Rajcani et al., 2021); however they did not examine whether pre-pandemic cortisol levels independently predicted psychological well-being during the pandemic. Ibar et al. similarly assessed hair cortisol in healthcare workers during the early months of the pandemic and found the higher cortisol was related to increased perceived stress and burnout (Ibar et al., 2021). There have been two studies to-date, to the best of our knowledge, which have investigated the ability of cortisol levels assessed before the pandemic to predict psychological health during the pandemic. Most recently, Marcil et al. studied Canadian healthcare workers, investigating the association of pre- and post-pandemic cortisol levels using retrospective analysis of hair samples, with burnout, depression, anxiety and PTSD assessed 3 months post-pandemic onset. While the authors found that change in cortisol was associated with burnout status, contrary to our findings they didn't observe any relationship between pre-, post-pandemic, or change in cortisol with any of the other psychological indices. However, given that the sample under study was healthcare workers in the first months of the pandemic, findings may not be generalisable to the wider population. Baliyan and colleagues measured diurnal salivary cortisol in 45 young adults at the end of 2019, and assessed perceived stress levels both during this period and again in the early months of the pandemic and found that salivary cortisol predicted increased perceived stress during the pandemic, and this was moderated by resilient coping capacity (Baliyan et al., 2021). Furthermore, they also found an association between pre-pandemic cortisol and depressive symptoms during the pandemic (again moderated by resilient coping). There were some notable differences between the latter study and ours: In Baliyan et al. the pre-pandemic assessment of cortisol was just before the onset of the pandemic (and therefore also much closer in time to the subsequent measure of depression), and measured in saliva; depression was assessed only during the pandemic (though stress was assessed pre- and post); and the sample was a small pool of undergraduate university students. Notwithstanding these differences, their findings are broadly in line with ours and suggest the merit of further research of this nature.

There are multiple stress-sensitive physiological systems which interact with one another in a myriad of ways and as cortisol was the only biomarker investigated in the current study we cannot infer a causal association between higher cortisol levels and increased psychological distress during the pandemic. It is plausible that higher cortisol levels indicate a more general phenotype of stress vulnerability or stress sensitisation which might also be reflected by changes in markers across the autonomic nervous, inflammatory and immune systems. In support of this hypothesis, a recent study in a similar cohort of middle-aged and older adults in the United Kingdom found that higher levels of systemic inflammation, as measured by plasma C-Reactive Protein (CRP), 1–3 years prior to the pandemic predicted increased depressive symptoms during the pandemic (Hamilton et al., 2021). Stress vulnerability and the propensity to develop depression in response to a period of heightened stress may be detectable at a multi-system level. Indeed it would be instructive and interesting to explore the predictive capability of these biological systems together, to more richly characterise the biological 'stress-sensitive' phenotype.

There are some limitations which must be considered when interpreting our findings. Firstly, while the sample was drawn from a population study of middle-aged and older adults, these individuals differed from the overall cohort in several ways (see Table S1 in Supplementary Information). In particular, the lower number of men relative to women

in the sample somewhat tempers confidence with respect the lack of effect modification by sex. Secondly, the data collection period for the COVID-19 Study only covered July to November 2020; therefore we cannot extrapolate to infer depressive symptoms during the latter stages of the pandemic or indeed the initial few weeks of lockdown in Ireland. Finally, we did not have detailed information on mental health of study participants earlier in life and thus could not explore the impact of this on the relationships observed, but as long-term cortisol levels are influenced by prior adverse experiences (Khoury et al., 2019), it is reasonable to speculate that they might explain some of the association of cortisol with the increases in depressive symptoms observed.

Our study also has many strengths including a large, non-clinical sample of middle-aged and older adults and good temporal separation of the measurements of cortisol and psychological distress during the COVID-19 pandemic, thus allowing investigation of cortisol as a risk marker for poor mental health. Most of the previous studies of a similar nature have relied on short-term measurement of salivary cortisol, which is heavily influenced by situational factors and day-to-day fluctuation. We also collected detailed information on a range of potential covariates and controlled for both cross-sectional and longitudinal associations with outcomes.

5. Conclusions

The COVID-19 pandemic and restrictions on social contact represent a unique and unprecedented stressor, and evidence on specific factors influencing the mental health impact of this period is only just beginning to emerge. In a large population-based sample of middle-aged and older adults, we found that higher hair cortisol, assessed 6 years previously, was associated with clinically significant depressive symptoms during (but not before) the COVID-19 pandemic. The findings signify that these individuals may be more biologically susceptible to the negative impact of environmental stressors on psychological health. The current results are also consistent with the life cycle model of stress (Lupien et al., 2018, 2009), and serve as a reminder that late adulthood is a time of relative heightened brain sensitivity to stress, during which the negative impact of a combination of genetics and early-life environmental exposures shaping biological regulation may manifest.

Declaration of interest

Dr Feeney reports no potential conflicts of interest. Prof Kenny reports no potential conflicts of interest.

Acknowledgements

TILDA was supported by the Irish Government, the Atlantic Philanthropies, Irish Life Assurance PLC, and the Health Research Board (HRB) of Ireland.

We are grateful to all TILDA respondents for their participation in the study. Researchers interested in using TILDA data may access the data for free from the following sites:

Irish Social Science Data Archive at University College Dublin, <http://www.ucd.ie/issda/data/tilda/>; and the University of Michigan <http://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/34315>.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.psychneuen.2022.105847](https://doi.org/10.1016/j.psychneuen.2022.105847).

References

- Adam, E.K., Quinn, M.E., Tavernier, R., McQuillan, M.T., Dahlke, K.A., Gilbert, K.E., 2017. Diurnal cortisol slopes and mental and physical health outcomes: a systematic review and meta-analysis. *Psychoneuroendocrinology* 83, 25–41. <https://doi.org/10.1016/j.psychneuen.2017.05.018>.

- Aknin, L.B., De Neve, J.E., Dunn, E.W., Fancourt, D.E., Goldberg, E., Helliwell, J.F., Jones, S.P., Karam, E., Layard, R., Lyubomirsky, S., Rzepa, A., Saxena, S., Thornton, E.M., VanderWeele, T.J., Whillans, A.V., Zaki, J., Karadag, O., Ben Amor, Y., 2022. Mental health during the first year of the COVID-19 pandemic: a review and recommendations for moving forward. *Perspect. Psychol. Sci.*, 17456916211029964 <https://doi.org/10.1177/17456916211029964>.
- Albert, K.M., Newhouse, P.A., 2019. Estrogen, stress, and depression: cognitive and biological interactions. *Annu Rev. Clin. Psychol.* 15, 399–423. <https://doi.org/10.1146/annurev-clinpsy-050718-095557>.
- Albert, P.R., 2015. Why is depression more prevalent in women. *J. Psychiatry Neurosci.* 40 (4), 219–221. <https://doi.org/10.1503/jpn.150205>.
- Alexopoulos, G.S., 2019. Mechanisms and treatment of late-life depression. *Transl. Psychiatry* 9 (1), 188. <https://doi.org/10.1038/s41398-019-0514-6>.
- Bailey, L., Ward, M., DiCosimo, A., Baunta, S., Cunningham, C., Romero-Ortuno, R., Kenny, R.A., Purcell, R., Lannon, R., McCarroll, K., Nee, R., Robinson, D., Lavan, A., Briggs, R., 2021. Physical and mental health of older people while cocooning during the COVID-19 pandemic. *QJM.* <https://doi.org/10.1093/qjmed/hcab015>.
- Baliyan, S., Cimadevilla, J.M., de Vidania, S., Pulpulos, M.M., Sandi, C., Venero, C., 2021. Differential susceptibility to the impact of the COVID-19 pandemic on working memory, empathy, and perceived stress: the role of cortisol and resilience. *Brain Sci.* 11 (3) <https://doi.org/10.3390/brainsci11030348>.
- Briggs, R., Carey, D., O'Halloran, A.M., Kenny, R.A., Kennelly, S.P., 2018. Validation of the 8-item centre for epidemiological studies depression scale in a cohort of community-dwelling older people: data from The Irish Longitudinal Study on Ageing (TILDA). *Eur. Geriatr. Med* 9 (1), 121–126. <https://doi.org/10.1007/s41999-017-0016-0>.
- Briggs, R., McDowell, C.P., De Looze, C., Kenny, R.A., Ward, M., 2021. Depressive symptoms among older adults pre- and post-COVID-19 pandemic. *J. Am. Med. Dir. Assoc.* 22 (11), 2251–2257. <https://doi.org/10.1016/j.jamda.2021.09.003>.
- Brooks, S.K., Webster, R.K., Smith, L.E., Woodland, L., Wessely, S., Greenberg, N., Rubin, G.J., 2020. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet* 395 (10227), 912–920. [https://doi.org/10.1016/S0140-6736\(20\)30460-8](https://doi.org/10.1016/S0140-6736(20)30460-8).
- Bueno-Notivol, J., Gracia-Garcia, P., Olaya, B., Lasheras, I., Lopez-Anton, R., Santabarbara, J., 2021. Prevalence of depression during the COVID-19 outbreak: a meta-analysis of community-based studies. *Int. J. Clin. Health Psychol.* 21 (1), 100196 <https://doi.org/10.1016/j.ijchp.2020.07.007>.
- Colich, N.L., Kircanski, K., Folland-Ross, L.C., Gotlib, I.H., 2015. HPA-axis reactivity interacts with stage of pubertal development to predict the onset of depression. *Psychoneuroendocrinology* 55, 94–101. <https://doi.org/10.1016/j.psyneuen.2015.02.004>.
- De Kloet, E.R., Vreugdenhil, E., Oitzl, M.S., Joels, M., 1998. Brain corticosteroid receptor balance in health and disease. *Endocr. Rev.* 19 (3), 269–301. <https://doi.org/10.1210/edrv.19.3.0331>.
- Donoghue, O.A., McGarrigle, C.A., Foley, M., Fagan, A., Meaney, J., Kenny, R.A., 2018. Cohort profile update: the Irish Longitudinal Study on Ageing (TILDA). *Int. J. Epidemiol.* 47 (5) <https://doi.org/10.1093/ije/dyy163>, 1398–1398.
- Duncko, R., Fischer, S., Hatch, S.L., Frissa, S., Goodwin, L., Papadopoulos, A., Cleare, A. J., Hotopf, M., 2019. Recurrence of depression in relation to history of childhood trauma and hair cortisol concentration in a community-based sample. *Neuropsychobiology* 78 (1), 48–57. <https://doi.org/10.1159/000498920>.
- Gaffey, A.E., Bergeman, C.S., Clark, L.A., Wirth, M.M., 2016. Aging and the HPA axis: stress and resilience in older adults. *Neurosci. Biobehav. Rev.* 68, 928–945. <https://doi.org/10.1016/j.neubiorev.2016.05.036>.
- Gao, W., Stalder, T., Foley, P., Rauh, M., Deng, H., Kirschbaum, C., 2013. Quantitative analysis of steroid hormones in human hair using a column-switching LC-APCI-MS/MS assay. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 928, 1–8. <https://doi.org/10.1016/j.jchromb.2013.03.008>.
- Gilbar, O., Gekopf, M., Berger, R., Greene, T., 2022. Risk factors for depression and anxiety during COVID-19 in Israel: a two-wave study before and during the pandemic. *Stress Health.* <https://doi.org/10.1002/smi.3127>.
- Gilbertson, M.W., Shenton, M.E., Ciszewski, A., Kasai, K., Lasko, N.B., Orr, S.P., Pitman, R.K., 2002. Smaller hippocampal volume predicts pathological vulnerability to psychological trauma. *Nat. Neurosci.* 5 (11), 1242–1247. <https://doi.org/10.1038/nn958>.
- Halligan, S.L., Herbert, J., Goodyer, I., Murray, L., 2007. Disturbances in morning cortisol secretion in association with maternal postnatal depression predict subsequent depressive symptomatology in adolescents. *Biol. Psychiatry* 62 (1), 40–46. <https://doi.org/10.1016/j.biopsych.2006.09.011>.
- Hamilton, O.S., Cadar, D., Steptoe, A., 2021. Systemic inflammation and emotional responses during the COVID-19 pandemic. *Transl. Psychiatry* 11 (1), 626. <https://doi.org/10.1038/s41398-021-01753-5>.
- Hyland, P., Shevlin, M., McBride, O., Murphy, J., Karatzias, T., Bentall, R.P., Martinez, A., Vallieres, F., 2020. Anxiety and depression in the Republic of Ireland during the COVID-19 pandemic. *Acta Psychiatr. Scand.* 142 (3), 249–256. <https://doi.org/10.1111/acps.13219>.
- Ibar, C., Fortuna, F., Gonzalez, D., Jamaro, J., Jacobsen, D., Pugliese, L., Giraudo, L., Ceres, V., Mendoza, C., Repetto, E.M., Reboredo, G., Iglesias, S., Azzara, S., Berg, G., Zopatti, D., Fabre, B., 2021. Evaluation of stress, burnout and hair cortisol levels in health workers at a University Hospital during COVID-19 pandemic. *Psychoneuroendocrinology* 128, 105213. <https://doi.org/10.1016/j.psyneuen.2021.105213>.
- Ingram, R.E., Luxton, D.D., 2005. Vulnerability-stress models. In: Hankin, B.L., Abela, J.R.Z. (Eds.), *Development of psychopathology: A vulnerability-stress perspective*. Sage Publications, Inc, pp. 32–46. <https://doi.org/10.4135/9781452231655.n2>.
- Kennis, M., Gerritsen, L., van Dalen, M., Williams, A., Cuijpers, P., Bockting, C., 2020. Prospective biomarkers of major depressive disorder: a systematic review and meta-analysis. *Mol. Psychiatry* 25 (2), 321–338. <https://doi.org/10.1038/s41380-019-0585-z>.
- Khoury, J.E., Bosquet Enlow, M., Plamondon, A., Lyons-Ruth, K., 2019. The association between adversity and hair cortisol levels in humans: a meta-analysis. *Psychoneuroendocrinology* 103, 104–117. <https://doi.org/10.1016/j.psyneuen.2019.01.009>.
- Kische, H., Ollmann, T.M., Voss, C., Hoyer, J., Ruckert, F., Pieper, L., Kirschbaum, C., Beesdo-Baum, K., 2021. Associations of saliva cortisol and hair cortisol with generalized anxiety, social anxiety, and major depressive disorder: an epidemiological cohort study in adolescents and young adults. *Psychoneuroendocrinology* 126, 105167. <https://doi.org/10.1016/j.psyneuen.2021.105167>.
- Lupien, S.J., Juster, R.P., Raymond, C., Marin, M.F., 2018. The effects of chronic stress on the human brain: from neurotoxicity, to vulnerability, to opportunity. *Front. Neuroendocr.* 49, 91–105. <https://doi.org/10.1016/j.yfrne.2018.02.001>.
- Lupien, S.J., McEwen, B.S., Gunnar, M.R., Heim, C., 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat. Rev. Neurosci.* 10 (6), 434–445. <https://doi.org/10.1038/nrn2639>.
- Mayer, S.E., Lopez-Duran, N.L., Sen, S., Abelson, J.L., 2018. Chronic stress, hair cortisol and depression: a prospective and longitudinal study of medical internship. *Psychoneuroendocrinology* 92, 57–65. <https://doi.org/10.1016/j.psyneuen.2018.03.020>.
- McEwen, B.S., Nasca, C., Gray, J.D., 2016. Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. *Neuropsychopharmacology* 41 (1), 3–23. <https://doi.org/10.1038/npp.2015.171>.
- Morris, M.C., Rao, U., 2014. Cortisol response to psychosocial stress during a depressive episode and remission. *Stress* 17 (1), 51–58. <https://doi.org/10.3109/10253890.2013.857398>.
- Morris, M.C., Rao, U., Garber, J., 2012. Cortisol responses to psychosocial stress predict depression trajectories: social-evaluative threat and prior depressive episodes as moderators. *J. Affect Disord.* 143 (1–3), 223–230. <https://doi.org/10.1016/j.jad.2012.05.059>.
- Petrowski, K., Wichmann, S., Pyrc, J., Steudte-Schmiedgen, S., Kirschbaum, C., 2020. Hair cortisol predicts avoidance behavior and depressiveness after first-time and single-event trauma exposure in motor vehicle crash victims. *Stress* 23 (5), 567–576. <https://doi.org/10.1080/10253890.2020.1714585>.
- Pierce, M., Hope, H., Ford, T., Hatch, S., Hotopf, M., John, A., Kontopantelis, E., Webb, R., Wessely, S., McManus, S., Abel, K.M., 2020. Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population. *Lancet Psychiatry* 7 (10), 883–892. [https://doi.org/10.1016/S2215-0366\(20\)30308-4](https://doi.org/10.1016/S2215-0366(20)30308-4).
- Qin, D.D., Rizak, J., Feng, X.L., Yang, S.C., Lu, L.B., Pan, L., Yin, Y., Hu, X.T., 2016. Prolonged secretion of cortisol as a possible mechanism underlying stress and depressive behaviour. *Sci. Rep.* 6, 30187. <https://doi.org/10.1038/srep30187>.
- Radloff, L.S., 1977. The CES-D scale: a self-report depression scale for research in the general population. *Appl. Psychol. Meas.* 1 (3), 385–397.
- Rajcani, J., Vytvykacova, S., Solarikova, P., Brezina, I., 2021. Stress and hair cortisol concentrations in nurses during the first wave of the COVID-19 pandemic. *Psychoneuroendocrinology* 129, 105245. <https://doi.org/10.1016/j.psyneuen.2021.105245>.
- Rietschel, L., Streit, F., Zhu, G., McAloney, K., Kirschbaum, C., Frank, J., Hansell, N.K., Wright, M.J., McGrath, J.J., Witt, S.H., Rietschel, M., Martin, N.G., 2016. Hair cortisol and its association with psychological risk factors for psychiatric disorders: a pilot study in adolescent twins. *Twin Res. Hum. Genet.* 19 (5), 438–446. <https://doi.org/10.1017/thg.2016.50>.
- Schuler, K.L., Ruggero, C.J., Goldstein, B.L., Perlman, G., Klein, D.N., Kotov, R., 2017. Diurnal cortisol interacts with stressful events to prospectively predict depressive symptoms in adolescent girls. *J. Adolesc. Health* 61 (6), 767–772. <https://doi.org/10.1016/j.jadohealth.2017.06.005>.
- Shahid, Z., Kalayanamitra, R., McClafferty, B., Kepko, D., Ramgobin, D., Patel, R., Aggarwal, C.S., Vunnam, R., Sahu, N., Bhatt, B., Jones, K., Golamari, R., Jain, R., 2020. COVID-19 and older adults: what we know. *J. Am. Geriatr. Soc.* 68 (5), 926–929. <https://doi.org/10.1111/jgs.16472>.
- Shapiro, B.G., Curley, E.E., Black, C.L., Alloy, L.B., 2019. The interactive association of proximal life stress and cumulative HPA axis functioning with depressive symptoms. *Depress Anxiety* 36 (11), 1089–1101. <https://doi.org/10.1002/da.22957>.
- Stalder, T., Steudte, S., Miller, R., Skoluda, N., Dettenborn, L., Kirschbaum, C., 2012. Intraindividual stability of hair cortisol concentrations. *Psychoneuroendocrinology* 37 (5), 602–610. <https://doi.org/10.1016/j.psyneuen.2011.08.007>.
- Stalder, T., Steudte-Schmiedgen, S., Alexander, N., Klucken, T., Vater, A., Wichmann, S., Kirschbaum, C., Miller, R., 2017. Stress-related and basic determinants of hair cortisol in humans: a meta-analysis. *Psychoneuroendocrinology* 77, 261–274. <https://doi.org/10.1016/j.psyneuen.2016.12.017>. Epub 2017 Jan 10. PMID: 28135674.
- Staufenbiel, S.M., Penninx, B.W., Spijker, A.T., Elzinga, B.M., van Rossum, E.F., 2013. Hair cortisol, stress exposure, and mental health in humans: a systematic review. *Psychoneuroendocrinology* 38 (8), 1220–1235. <https://doi.org/10.1016/j.psyneuen.2012.11.015>.
- Ulrich-Lai, Y.M., Herman, J.P., 2009. Neural regulation of endocrine and autonomic stress responses. *Nat. Rev. Neurosci.* 10 (6), 397–409. <https://doi.org/10.1038/nrn2647>.
- Varma, P., Junge, M., Meaklim, H., Jackson, M.L., 2021. Younger people are more vulnerable to stress, anxiety and depression during COVID-19 pandemic: a global

- cross-sectional survey. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 109, 110236. <https://doi.org/10.1016/j.pnpbp.2020.110236>.
- Vreeburg, S.A., Hoogendijk, W.J., van Pelt, J., Derijk, R.H., Verhagen, J.C., van Dyck, R., Smit, J.H., Zitman, F.G., Penninx, B.W., 2009. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch. Gen. Psychiatry* 66 (6), 617–626. <https://doi.org/10.1001/archgenpsychiatry.2009.50>.
- Ward, M., May, P., Normand, C., Kenny, R.A., Nolan, A., 2021. Mortality risk associated with combinations of loneliness and social isolation. Findings from The Irish Longitudinal Study on Ageing (TILDA). *Age Ageing*. <https://doi.org/10.1093/ageing/afab004>.
- Wennig, R., 2000. Potential problems with the interpretation of hair analysis results. *Forensic Sci. Int.* 107 (1–3), 5–12. [https://doi.org/10.1016/s0379-0738\(99\)00146-2](https://doi.org/10.1016/s0379-0738(99)00146-2).
- Whelan, B.J., Savva, G.M., 2013. Design and methodology of the Irish Longitudinal Study on Ageing. *J. Am. Geriatr. Soc.* 61 (Suppl 2), S265–S268. <https://doi.org/10.1111/jgs.12199>.