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The effects of momentary loneliness and COVID-19 stressors on hypothalamic–pituitary adrenal (HPA) axis functioning: A lockdown stage changes the association between loneliness and salivary cortisol

Matthias Haucke^{a,b,*}, Sabrina Golde^b, Silvia Saft^a, Rainer Hellweg^a, Shuyan Liu^{a,*},¹,
Stephan Heinzl^{b,1}

^a Department of Psychiatry and Psychotherapy, Charité – Universitätsmedizin Berlin (Campus Charité Mitte), Berlin, Germany

^b Clinical Psychology and Psychotherapy, Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany

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ABSTRACT

The COVID-19 pandemic can be characterized as a chronic stressor affecting the hypothalamic–pituitary–adrenal (HPA) axis, indexed by glucocorticoids (e.g., cortisol). We investigated whether salivary cortisol level is increased during a lockdown and whether a lockdown condition affects the association between loneliness, specific COVID-19 related stressors and salivary cortisol level. We conducted a smartphone-based ecological momentary assessment (EMA) study with 280 participants in Germany who experienced at least mild loneliness and distress amid COVID-19 from August 2020 to March 2021. We measured their momentary loneliness and COVID-related stressors including worries, information seeking behaviors and feelings of restriction during “no-lockdown” or “lockdown” stages amid COVID-19. Their salivary cortisol was measured 4 times on the last day of a 7-day EMA study. We found a significant increase in salivary cortisol levels during lockdown compared to no-lockdown. Lockdown stage was found to moderate the relationship between momentary loneliness and salivary cortisol level, i.e., loneliness was positively related to cortisol level specifically during lockdown. Mechanisms explaining the effect of forced social isolation on the association between loneliness and salivary cortisol need to be investigated in future studies.

1. Introduction

The coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization in March 2020. Most countries implemented unprecedented lockdown measures to halt the spread of the virus. In addition to the impact of the spreading virus itself, lockdown measures led to an increase in loneliness, anxiety, and distress (Liu et al., 2021a, 2021b; Nelson et al., 2020a). A common biological marker for distress is a product of hypothalamus-pituitary-adrenal (HPA) axis activation, glucocorticoids (i.e., cortisol; McEwen, 2012). Glucocorticoids influence a range of physiological functions, such as metabolism, inflammatory control, cardiovascular activity, reproductive functioning, immune system control and neuronal activity (Charmandari et al., 2005). Therefore, excessive and prolonged

glucocorticoids secretion can have severe impact on physical and mental health (Chrousos, 2009). In this study, we investigated whether a COVID-19 lockdown stage, compared to a no-lockdown stage, is associated with increased salivary cortisol levels. Moreover, we tested whether a lockdown increases the association between loneliness and COVID-19 related stressors and salivary cortisol. On a broader level, comparing COVID-19 lockdown stages allows us to investigate the effect of forced social isolation on HPA axis functioning, indexed by salivary cortisol.

Humans maintain a complex dynamic equilibrium, also called homeostasis, which gets challenged by external or internal stressors (Chrousos and Gold, 1992). Therefore, stress can be defined as a state of non-equilibrium or threatened homeostasis (Chrousos, 2009). To maintain homeostasis, humans react with an interplay between

* Correspondence to: Department of Psychiatry and Psychotherapy, Charité – Universitätsmedizin Berlin (Campus Charité Mitte), Charitéplatz 1, 10117 Berlin, Germany.

E-mail addresses: matthias.haucke@fu-berlin.de, Matthias.haucke@gmx.de (M. Haucke), sabrina.golde@fu-berlin.de (S. Golde), silvia.saft@charite.de (S. Saft), rainer.hellweg@charite.de (R. Hellweg), shuyan.liu@charite.de (S. Liu), stephan.heinzl@fu-berlin.de (S. Heinzl).

¹ Equal contribution.

behavior, mental and physiological responses which can be adaptive, if they are time-limited (e.g., in response to acute threat). Excessive or chronic stressors can lead to excessive/prolonged and therefore inadequate HPA activity, which in turn, leads to a state of cacostasis (i.e., dyshomeostasis) associated with a range of behavioral and somatic disorders (e.g., anxiety, depression, sleep disorders, metabolic disorders, atherosclerotic cardiovascular disease and immune dysfunction; for an overview see Chrousos, 2009).

During the COVID-19 pandemic every social interaction is potentially contagious (Maheshwari and Albert, 2020). To hinder the rapid spreading of the COVID-19 virus, most governments implemented lockdown measures (World Health Organization, 2020). One aim of these measures was to reduce potentially contagious contact to others, which included closing of childcare facilities, schools, offices, businesses, cultural and leisure facilities, restriction on domestic movement, as well as social distancing rules (e.g., restrictions on gatherings). Previous studies indicate that the COVID-19 pandemic and associated lockdown measures led to an increase in loneliness and distress in the general population (Liu et al., 2021a; Nelson et al., 2020b). A study by the OECD (2021) found that the pandemic and lockdown measures increased financial insecurity, fear of infection, unemployment and decreased educational engagement, access to health care services, physical exercise, daily routines, and social connection. Thus, an open empirical question is whether the pandemic and lockdown measures influence HPA axis functioning, indexed by salivary cortisol.

There are mixed findings on the effect of the COVID-19 pandemic and associated lockdowns on HPA axis activity. On the one hand, greater loneliness in young people during the first wave of the COVID-19 pandemic was associated with higher levels of salivary cortisol upon awakening (Jopling et al., 2021). On the other hand, Feneberg et al. (2021) found that there was a general decrease in hair cortisol concentration (HCC) after lockdown measures took place. This mixed finding might result from the usage of HCC as a marker of HPA axis functioning, which is a rather long-term and retrospective biological marker of distress and has a relatively low association with self-reported stress in non-clinical populations (Stalder et al., 2017). There is a lack of studies which include more time sensitive salivary cortisol, and that compare the impact of different lockdown stages on HPA functioning. Moreover, there is a lack of studies that investigate how a lockdown changes the association of loneliness and COVID-19 related stressor with salivary cortisol. The change in association between these stressors and salivary cortisol is a potential reason why a lockdown stage increases HPA axis activity.

Loneliness is a prime candidate, as most lockdown measures aim at reducing social contacts (WHO, 2020). Loneliness can be defined as a subjective state one experiences when there is a discrepancy between the interpersonal relationships one has now and those one wishes to have (Perlman and Peplau, 1984). Loneliness can be further distinguished between more short term and long-term forms, especially chronic loneliness can have severe consequences for the human psyche and body (de Jong Gierveld et al., 2006). In this study we focus on momentary loneliness. Loneliness has been associated with a 26% increase in risk of premature mortality (Cacioppo and Cacioppo, 2018) and a range of mental disorders, such as anxiety disorders (Anderson and Harvey, 1988; Lim et al., 2018), schizizophrenia (Deniro, 1995; Lim et al., 2018) as well as depression (Erzen and Çikrikci, 2018; Nolen-Hoeksema and Ahrens, 2002).

There are two hypotheses that explain the effects of loneliness on mental and physical health (Cacioppo et al., 2015). On the one hand, the social control hypothesis proposes that close friends and family encourage individuals to engage in healthier behaviors, such as exercising, adequate sleep and a better diet (Umberson, 1992). On the other hand, loneliness can have a more direct negative effect on disease risk, due to its effect on the stress-responsive physiological systems. Experimental animal studies have shown that social isolation conditions, compared to control conditions, can lead to higher HPA axis activity in a

range of species (e.g., Bosch et al., 2009; Castro and Matt, 1997; Pournajafi-Nazarloo et al., 2011). However, there is also conflicting evidence from a study that investigated the effect of placing rhesus macaques from a field cage into an individual shelter (Cole et al., 2021). The results indicate not an increase, but a decline of blood plasma cortisol, yet also a decrease of 30–50% of circulating immune cell populations during the social isolation period. Similarly, human studies investigating the impact of loneliness on cortisol level have led to contrary findings, partly because it would be unethical to experimentally manipulate social isolation (Cacioppo et al., 2002). Yet, due to the COVID-19 pandemic, we have the possibility to investigate the effects of forced social isolation on neuroendocrine responses.

In addition to loneliness, we investigate the effects of three COVID-19 related stressors: seeking information about COVID-19, COVID-19 related worries and perceived restriction in one's everyday life. We expect COVID-19 related stressors to increase salivary cortisol, as these factors have been previously associated with self-reported stress during a post-lockdown as well as during a lockdown stage (Gao et al., 2020; Haucke et al., 2022, 2021; Mækela et al., 2020; Stainback et al., 2020).

A central change induced by a lockdown stage is a decrease of control one has over the perceived stressors and loneliness (i.e., high number of COVID-19 cases and deaths, government health measures, including physical distancing). For example, a previous qualitative study found that participants reported frustration about their lack of agency and choice over their social lives during a lockdown stage (McKenna-Plumley et al., 2021). Perceived control or agency has been proposed by a range of theories to have a central role in explaining whether a stressful situation leads to mental health problems (e.g., helplessness (Seligmann, 1975), the cognitive discrepancy theory of loneliness (Perlman and Peplau, 1981), Bandura's theory of self-efficacy (1982)). Bandura (1982) proposes that self-percepts of efficacy, which is perception of how well one can perform actions necessary to deal with a prospective situation, is an important mechanism that explains whether subsequent thought, behavior and physiological stress reactions occur. Thus, we expect that momentary loneliness, COVID-19-related worries, feelings of restriction and information seeking are associated with a higher endocrine stress response during a lockdown, than during a no-lockdown stage (see Fig. 1).

A close correspondence between stressors and physiological state, such as HPA axis activation, is often assumed in previous studies (i.e., response coherence; Mauss et al., 2005). However, there are a range of studies that have not found a link between subjective stress, stressors and endocrine stress responses (for a review see: Mikkelsen et al., 2017). This "lack of psychoendocrine covariance" (Campbell and Ehler, 2012; Schlotz et al., 2008) might result from focusing on between-person effects (i.e., by averaging individual stress ratings across a group of subjects), temporal decoupling (e.g., measuring perceived stress in the evening but measuring salivary cortisol during the day) and reliance on retrospective recall measures, increasing recall bias (Lazarides et al., 2020). Therefore, we used ecological momentary assessment (EMA), allowing real-time, repeated measurement of participants momentary psychological states (Shiffman et al., 2008), which can be temporally closely associated with the salivary cortisol measurements.

In this study, we aimed to investigate whether the COVID-19

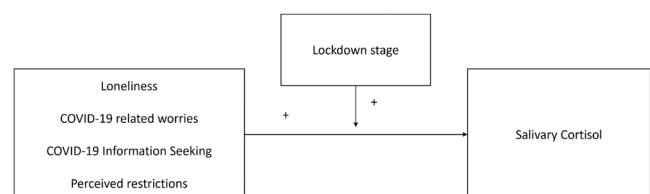


Fig. 1. Lockdown increases the positive association between momentary loneliness, COVID-19 related worries, COVID-19 information seeking as well as perceived restrictions and salivary cortisol.

pandemic and a lockdown stage is associated with HPA axis activation, indexed by salivary cortisol level. We conducted an ecological momentary assessment (EMA) study to investigate momentary loneliness and three stressors (COVID-19 related worries, feeling restricted, COVID-19 information seeking) that are likely associated with an endocrine stress response during a lockdown. We hypothesized that salivary cortisol levels will be higher during a lockdown stage than a no-lockdown stage. Secondly, we hypothesized that momentary loneliness and COVID-19 related stressors are positively associated with salivary cortisol. Finally, we hypothesized that momentary loneliness and COVID-19-related stressors are more positively associated with salivary cortisol during a lockdown, than during a no-lockdown stage.

2. Methods

2.1. Participants, procedure and measurement

A total of 1549 participants were screened for eligibility between August 2020 and March 2021 (45% of the participants fulfilled the inclusion criteria). We recruited via online advertisements on university websites, Twitter, and eBay classifieds. Participants filled in an online screening questionnaire on the Sivo Intelligent Psychological Assessment Platform. After an initial contact via phone and/or email, we sent more study information, an accelerometer, informed consent, and a QR code (to install a smartphone app) by mail. After study completion, participants sent back the study material by mail. 250 participants were eligible, gave informed consent and sent in valid cortisol samples. The exclusion criteria were (1) aged under 18 years, (2) working a night shift, (3) not using an Android Smartphone, (4) not speaking fluent German, (5) and never feeling lonely or (6) distressed according to the COVID-19 Peritraumatic Distress Index (CPDI; cutoff score=28) and a short 8-item UCLA Loneliness Scale (ULS-8; cut-of score = 16, (Hays and DiMatteo, 1987). The CPDI can be used to assess changes in mental health status, cognitive skills, avoidance and compulsive behavior, physical symptoms, and loss of social functioning due to the COVID-19 pandemic and has been validated in Germany (Liu and Heinz, 2020). The recruitment flow is shown in Fig. 2.

The study was conducted during a no-lockdown stage (8 August – 1 November 2020) and a lockdown stage (2 November 2020 – 9 March 2021) in Germany. An overview of the restrictions that were in place, and a power analysis can be found in Supplement A and B. The Ethics Committees of Charité– Universitätsmedizin Berlin (ref: EA2/143/20) and Freie Universität Berlin (ref: 030/2020) approved the study. We did control for sample differences between eligible participants that were excluded and included and found that the two samples did not differ in any characteristic, except distress (see Supplement C). Thus, it might be

possible that the eligible participants who did not participate were too distressed to take part in a relatively time-intensive EMA study.

Our study was conducted within 213 days during the pandemic, starting in a period in which almost all curfew measures from the first wave in March 2021 have been eased “no -lockdown stage”, and a “lockdown stage” in which the severe lockdown measures were in place. Moreover, our study covers a lockdown stage with the highest number of new COVID-19 related deaths during the last 7 days in Germany, as of August 2022 (see Fig. 3).

For the ecological momentary assessment (EMA), the smartphone application “movisensXS” (movisens GmbH, Karlsruhe, Germany) was used, which is compliant with the General Data Protection Regulation (European Union) and Berlin Data Protection Act (Berliner Datenschutzgesetz – BlnDSG). This study was part of a larger study (Haucke et al., 2022), including EMA-assessments for 7 consecutive days. However, we asked participants to take cortisol samples only during the last day of the study, as we assumed more frequent cortisol assessments would have led to drops in compliance rate.

The EMA consisted of 8 randomized prompts between 8 AM and 10 PM (at least 60 min apart). Each question within the EMA started with the sentence “During the last hour.”. This was then followed by “to which extent did you feel lonely” (loneliness), “to which extent did you feel restricted by the pandemic in your everyday life?” (perceived restriction), “to which extent did you worry about how the pandemic affects your personal situation?” (worry), “to which extent did you seek information about the pandemic?” (information-seeking). The items were assessed on a visual analog scale (0–100: 0 =not at all, 100 =most frequent or severe).

2.2. Cortisol assessment

Saliva was collected using cotton rolls (Salivettes, Sarstedt, Nuembrecht, Germany). To increase adherence to the saliva sampling protocol, participants were sent reminders via the movisensXS application one day before the cortisol assessment and during the day of the cortisol sampling. During the last day of the EMA, we asked participants to collect saliva four times a day: 1. Immediately upon awakening, 2. 30 min after awakening, 3. Immediately before lunch 4. Immediately before going to sleep. To collect saliva, participants were instructed to keep the cotton rolls for 2 min in their mouths and move it around to saturate. More, we asked participants to refrain from chewing gum, smoking, eating or drinking 10 min before saliva collection. Participants were instructed to write down the exact times on the cortisol sample and to place them into the fridge. After the study was done, participants sent in their cortisol samples via mail, which were then frozen. Salivary

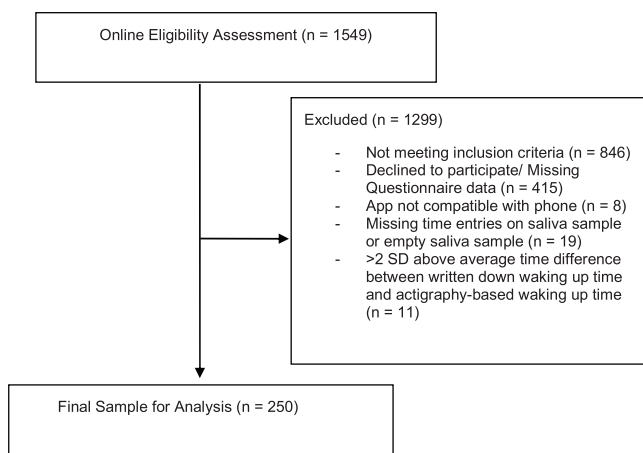


Fig. 2. Recruitment flow.

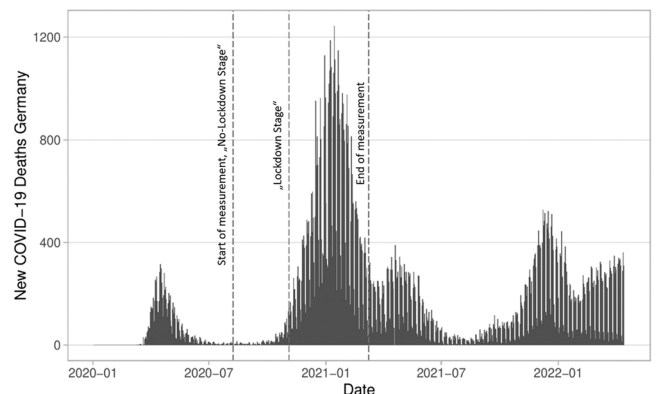


Fig. 3. COVID-19 associated deaths during the last 7 days in Germany, ranging from January 2020 until April 2022. The start and end of our study, as well as the lockdown stages are marked. (ref: WHO COVID-19 dataset. Geneva: World Health Organization (2020). Available online: <https://covid19.who.int/> (assessed: [01.04.2022]).)

cortisol concentrations were analyzed using ELISA (Cortisol ELISA, IBL International, Hamburg, Germany), the manufacturer states that the lower limit of sensitivity is 0.005 µg/dl. The samples were analyzed in the laboratory of Charité – Universitätsmedizin Berlin.

2.3. Data analysis

The statistical analyses were conducted with the R version 4.2.1 (www.r-project.org). The code for the analysis and data can be found online at <https://osf.io/z2tfp/>. In a first step, we conducted two independent-samples t-test to compare the effects of lockdown on cortisol. Specifically, we compared total average cortisol and the area under the curve with respect to ground (AUCG) (Pruessner et al., 2003) during a no-lockdown and lockdown condition.

In a second step, we analyzed the effect of momentary loneliness and COVID-19 related stressor on momentary cortisol levels. We followed the recommendations of several authors (Field et al., 2012; Raudenbush and Bryk, 2002; Twisk, 2006) who recommend to build up multilevel models by starting with a basic model, in which all parameters are fixed, and then add appropriate random coefficients to avoid an overfitted model. We included cortisol as an outcome, and loneliness, COVID-19-related worries, COVID-19 information seeking, well as feelings of restriction caused by the pandemic as continuous predictors. Moreover, we included lockdown stage (no-lockdown, lockdown) as a categorical predictor, with no-lockdown as reference group. We then added an interaction term together with the interaction terms lockdown stage*loneliness, lockdown stage*COVID-19 related worries, lockdown stage*feelings of restriction, lockdown stage*Information Seeking. To counter problems with multicollinearity resulting from the interaction terms, we grand mean centered the continuous predictors (Hamaker and Grasman, 2015). Moreover, we included following covariates that have previously been associated with salivary cortisol (Lazarides et al., 2020): time since awakening (t1-t4), weekend (yes/no), age and gender.

2.4. Data preparation

2.4.1. Salivary cortisol

Self-collection of saliva samples within a domestic setting increases ecological validity; however, does not allow to control for adherence to sampling according to the predetermined sampling schedule (Stalder et al., 2016). To verify compliance with the saliva sampling plan, we calculated the awakening hour via an actigraphy device that the participants were wearing during the night (Van Hees et al., 2015). The actigraphy data was downloaded from the GENEActiv devices via the GENEActiv PC software V3.3. These actigraphy files were then further processed via the R package GGIR V1.2-0 (Migueles et al., 2019). We used the default settings of the GGIR package. 11 samples were outside of 2 standard deviations from the average time difference between the calculated wake-up time and the wake-up time written on the cortisol saliva sample, and thus were excluded from the analyses.

In addition, 19 samples with missing saliva or missing time entries were excluded from the study. The salivary compliance rate was 89%, with 250 participants with usable cortisol samples out of 280. For the comparison of the cortisol response, we aggregated the raw salivary cortisol. The cortisol response was analyzed by computing the area under the curve with respect to ground (AUCG) as described by Pruessner et al. (2003), using the formula:

$$AUCG = (A + B) * t1/2 + (C + B) * t2/2 + (D + C) + t3/2$$

A = measurement point 1, B = measurement point 2, C = measurement point 3, D = measurement point 4, t1 = time difference between A and B, t2 = time difference between B and C, t3 = time difference between C and D.

We log-transformed the cortisol responses, due to their non-normal distribution. Cortisol regularly peaks within 20–30 min after the beginning of stress exposure in laboratory settings (Allen et al., 2014;

Hellhammer and Schubert, 2012), however; everyday life stressors often last longer than laboratory stressors. We followed the approach of Lazarides et al. (2020) and used ratings of loneliness and COVID-19 related stressors within a window of +/- 60 min around cortisol sampling. In case there were more than one response within the defined time window, we took the ratings closest to the cortisol sampling. Because we took EMA responses prior and post cortisol sampling, we investigated the possibility of reverse causation by calculating parameters estimates based on EMA data taken within a time window of 60 min prior to cortisol sampling. The parameter estimates did not change in direction, except for the effect of COVID-19 restrictions on cortisol, thus our main conclusions do not seem to be a result of reverse causation. The analysis results can be found in Supplement D.

3. Results

3.1. Group description

250 participants were included in our study. Sample characteristics between the lockdown (123) and no-lockdown (127) group were statistically compared and are shown in Table 1. Except for higher average loneliness during the lockdown stage, the two groups did not differ in sample characteristics.

3.2. Total lockdown effect on salivary cortisol

Firstly, there was a significant difference in the AUCG for No-lockdown ($M = 139.29$, $SD = 82.39$) and Lockdown ($M = 165.20$, $SD = 113.24$); $t(247) = -2.06$, $p = .04$. Secondly, there was a significant difference in total cortisol for No-lockdown ($M = -2.11$, $SD = 0.51$) and Lockdown ($M = -1.97$, $SD = 0.47$); $t(247) = -2.17$, $p = .031$.

3.3. The effects of momentary loneliness, COVID-related stressors, and lockdown on cortisol

We first tested whether a multilevel approach is needed by comparing a random with a fixed intercept model, with momentary cortisol as the outcome, using the Akaike Information Criterion (AIC; Akaike, 1974), the Bayesian information Criterion (BIC; Schwarz, 1978) and the Log Likelihood Ratio Test (Vuong, 1989). As shown in Table 2, neither the AIC, nor the BIC did not decrease with adding a random intercept, the log likelihood test was non-significant $\chi^2(1) = 1.35$, $p = 0.25$. Therefore, we did not add random effects and continued with a multiple linear regression. In addition, we report the results of a random intercept model and a model with an unstructured covariance matrix in Appendix E, which show that adding random effect does not significantly change the results.

We found that the time since awakening ($b = -0.724$, $t(481) = -16.098$, $p < .001$) did statistically significantly predict cortisol. Log cortisol decreased by 0.724 units for each time point further away from awakening. Moreover, the interaction term loneliness * lockdown ($b = 0.008$, $t(483) = 2.463$, $p = 0.014$) did significantly predict cortisol. As shown in Fig. 4, during lockdown, loneliness was positively associated with log cortisol, whereas during no-lockdown, loneliness was negatively associated with log cortisol. All other variables were non-significant ($p > 0.05$), the exact results are shown in Table 3.

4. Discussion

The coronavirus disease 2019 (COVID-19) and associated lockdown measures are an unprecedented major life event for most people, which can lead to chronic stress and activation of the hypothalamic-pituitary-adrenal (HPA) axis, indexed by cortisol. Chronic and excessive cortisol levels, in turn, can have severe negative impact on physical and mental health (Chrousos, 2009). In this study we investigated whether a lockdown stage is associated with increased salivary

Table 1
Demographics and sample characteristic comparison between lockdown and no-lockdown.

Variable name	Total N = 250 (Mean, SD/Percentage)	No-Lockdown N = 123 (Mean, SD/Percentage)	Lockdown N = 127 (Mean, SD/Percentage)	Statistical test for lockdown group (Welch t-test or chi-square test)
Age	30.94 (11.26)	31.72 (10.9)	30.17 (11.6)	t = - 1.09 (df = 246.65), p = .276
Gender	Female = 172 (69%) Male = 76 (30%) Diverse = 2 (1%)	Female = 79 (64%) Male = 44 (36%) Diverse = 0 (0%)	Female = 93 (73%) Male = 32 (25%) Diverse = 2 (2%)	X-squared = 4.97 (df = 2), p = 0.083
Education (in years)	15.21 (3.79)	14.92 (3.76)	15.5 (3.81)	t = - 1.184 (df = 241.96), p = .238
CPDI	47.4 (14.78)	48.62 (16.45)	46.18 (12.48)	t = 1.293 (df = 228.5), p = .197
Loneliness (UCLA Loneliness Scale)	22.44 (4.01)	21.91 (4.11)	22.98 (3.84)	t = - 2.097 (df = 240.88), p = .038
Family Status*	Single = 108 (44%) In Relationship = 90 (36%) Married = 46 (19%) Other = 4 (1.6%)	Single = 58 (48%) In Relationship = 39 (32%) Married = 22 (18%) Other = 2 (1.7%)	Single = 50 (39%) In Relationship = 51 (40%) Married = 24 (19%) Other = 2 (1.6%)	X-squared = 2.390 (df = 3), p = 0.495
Number of Children*	1.79 (.77)	1.74 (.78)	1.87 (0.76)	t = -.616 (df = 48.217), p = .541
Number of people in household**	2.51 (2.17)	2.48 (1.29)	2.54 (2.75)	t = -.221 (df = 180.97), p = .825
Health status (1 = very bad - 5 = very good)**	3.72 (.87)	3.62 (.93)	3.82 (.81)	t = - 1.820 (df = 236.46), p = .07
Part of COVID-19 risk group	59 (24%)	28 (23%)	31 (24%)	X-squared = .153 (df = 1), p = .696

*2 participants skipped the questionnaire containing this variable
*3 participants skipped the questionnaire containing this variable.

Table 2
Model comparison to test if adding a random intercept increases model fit. The selected model is bold. Based on the AIC, BIC and Log Likelihood Ratio Test χ^2 (1) = 1.35, p = 0.25, we selected the model with a fixed intercept.

Model	AIC	BIC	logLik
Fixed Intercept	1563.165	1571.579	-779.5827
Random Intercept	1563.818	1576.438	-778.9092

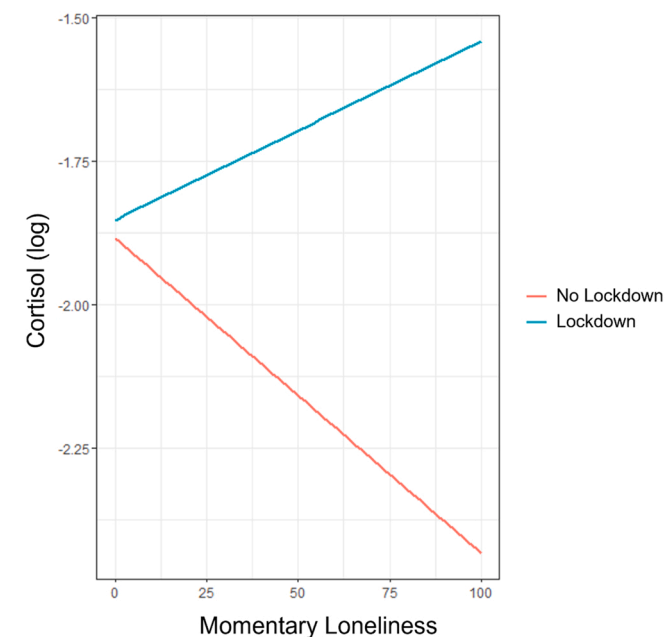


Fig. 4. The effect of loneliness on cortisol. Cortisol is displayed as a function of loneliness during no-lockdown (red) versus lockdown (blue). More loneliness led to higher cortisol during a lockdown and vice versa.

cortisol levels. Moreover, we tested whether a lockdown increased the association between momentary loneliness and COVID-19 related stressors on HPA axis activity. We found higher salivary cortisol levels

Table 3
Multiple regression results with log cortisol as the outcome. $R^2 = 0.4$, Adjusted $R^2 = 0.38$.

Variable	b	SE b	t value	p value
Lockdown stage*	0.109	0.086	1.273	0.2
Loneliness	-0.005	0.002	-1.951	0.052
COVID worries	< -0.001	0.004	-0.044	0.97
COVID restriction	- 0.001	0.004	-0.296	0.77
COVID information seeking	< -0.001	0.003	-0.17	0.87
Loneliness X Lockdown stage	0.008	0.003	2.463	0.014
COVID worries X Lockdown stage	0.001	0.005	0.24	0.81
COVID restriction X Lockdown stage	-0.003	0.005	-0.59	0.56
COVID information seeking X Lockdown stage	0.001	0.004	0.187	0.85
Covariates				
Gender Male**	-0.025	0.093	-0.27	0.79
Gender Diverse**	0.184	0.657	0.281	0.78
Age	-0.008	0.004	-1.884	0.06
Weekend***	0.061	0.093	0.655	0.51
Time since awakening	-0.724	0.045	-16.098	< 0.001

*Baseline: 0 = No-lockdown stage
** Baseline: 0 = Gender Female
*** Baseline: 0 = Weekday.

during a lockdown stage, compared to a no-lockdown stage. We did not find that COVID-19 related stressors (worries, feelings of restriction or information seeking) were associated with salivary cortisol, nor did a lockdown affect their association with cortisol. However, we found that a lockdown stage affects the association between momentary loneliness and salivary cortisol. Specifically, we found that momentary loneliness during a no-lockdown was associated with decreased, whereas momentary loneliness during a lockdown was associated with increased salivary cortisol. Thus, our study indicates that a lockdown is associated with higher salivary cortisol levels, and that a lockdown affects the association between loneliness and cortisol.

Previous studies during pre-COVID-19 times found mixed evidence on the effects of loneliness on cortisol levels (Cacioppo et al., 2002). This “lack of psychoendocrine covariance” (Campbell and Ehlert, 2012; Schlotz et al., 2008) could be caused by a lack of idiographic appraisal of loneliness, temporal coupling and experimental manipulation of loneliness. Notably, there are only few ecological momentary assessment (EMA) studies that investigate the effects of momentary loneliness on

salivary cortisol (Joseph et al., 2021). In this quasi-experimental EMA study, we found that during a lockdown, momentary loneliness is associated with increased salivary cortisol, whereas during a no-lockdown, momentary loneliness is associated with decreased salivary cortisol.

A possible reason for this might be that lockdown measures change the type of experienced loneliness. Weiss (1973) proposed that loneliness has a multidimensional structure with two types of loneliness, emotional and social loneliness. On the one hand, emotional loneliness results from a lack of close and intimate attachment and leads to feelings of anxiety and emptiness. On the other hand, social loneliness results from a lack of network of social relationships, such as a group of friends who share common activities and interests and leads to feelings of aimlessness and boredom. During lockdown, people might experience higher levels of emotional loneliness than during a no-lockdown, as social interactions were limited by public health measures, which also includes close and intimate others (e.g., elderly family members).

A second possibility is that loneliness experienced during a lockdown is uncontrollable. In line with this, a qualitative British study showed that many participants reported a lack of agency and choice over their social lives during the lockdown stage (McKenna-Plumley et al., 2021). According to Perlman and Peplau (1981) an individual's capability to have personal control over his or her relationship influences the experience of loneliness. Moreover, if a stressor exceeds the adaptive resources of an individual, it can be perceived as uncontrollable and can be associated with harmful physical consequences, such as a sustained endocrine stress response (Bornstein and Chrousos, 1999; Habib et al., 2001). For example, experimental studies have found that socio-evaluative threat, which is uncontrollable, rather than controllable, has a stronger impact on subsequent HPA axis activation, indexed by salivary cortisol levels (Dickerson and Kemeny, 2004). Thus, one difference in loneliness experienced during a lockdown stage and a no-lockdown stage, is that lockdown measures make the resulting loneliness more uncontrollable. In addition, this rather uncontrollable loneliness might have a different impact on subsequent stress-related behavioral and cognitive responses. In line with this, loneliness experienced during a lockdown increases subsequent stress-inducing behaviors (i.e., COVID-19 related information seeking) and cognitions (i.e., COVID-19 related worries) more than loneliness during a no-lockdown stage (Haucke et al., 2022).

Finally, these situational factors likely interacted with the personal characteristics (i.e., shyness, social anxiety), according to the interactionist view on loneliness (Weiss, 1982). That is, lockdown measures and forced social isolation confronts people with loneliness, who have not been lonely before. People who have already experienced loneliness might possess better emotional cognitive coping strategies to deal with loneliness. For example, Rice (1999) has shown that people who are single by choice, are more used to solve difficulties and deal with emotional pain on their own. Moreover, people who are single do rely less on social networks and focus on their careers and professions when feeling lonely (Rokach and Brock, 1998), which might be an effective strategy in times of physical distancing. Thus, the effect of momentary loneliness on stress responsive endocrine functioning likely depends on

a combination between the person experiencing it and the situational context of loneliness (e.g., whether loneliness is perceived to be controllable).

To summarize, a lockdown stage might have impacted following factors: 1. the type of interpersonal relationships one is lacking, 2. the person who experiences loneliness, and 3. the perception of loneliness. These factors might influence the association between momentary loneliness and salivary cortisol, indexing HPA activity (Fig. 5).

Our results indicate that there is a near-significant negative association between loneliness and salivary cortisol, specifically during no-lockdown. This is another hint towards the need for a more complex understanding of loneliness and different forms of being alone. For example, solitude refers to the act of being alone voluntarily, and is associated with more pleasant feelings, such as being "free from people's scrutiny and demands" (p. 157; Larson, 1990) and providing time for contemplation, creativity, and personal growth (Andersson, 1998; Larson, 1990). A BBC (Victor et al., 2019) survey with 55,000 respondents, indicates that almost 50% stated that loneliness can be positive as it offers the possibility to grow personally and the enjoyment to be alone. Thus, it might be important to distinguish between different types of being alone and to investigate which underlying mechanisms cause loneliness to become a stress-inducing experience. Whether the trend towards a negative association between momentary loneliness and salivary cortisol is statistically significant needs to be determined in future, well-powered studies.

We did not find that COVID-19 related worries, felt restriction or information seeking led to higher salivary cortisol levels, nor did the lockdown change the impact of these COVID-19 stressors. This is surprising, as these stressors have been found to increase self-reported stress (Haucke et al., 2022). Our study suggest that these stressors are not long-lasting or stress-inducing enough to lead to increased salivary cortisol, beyond the effects of loneliness. Thus, our finding suggests that a lockdown mainly impacts the association between loneliness and salivary cortisol, rather than specific COVID-19 related stressors.

5. Limitations and future studies

As this is a natural study, we cannot rule out the influence of extraneous variables, including seasonal effects on the level of cortisol. COVID-19 cases and associated lockdown measures are highly intertwined with seasonal effects, which is driven by people's behaviors (e.g. meeting people indoors with no or bad ventilation in wintertime) as well as the virus properties (e.g. SARS-CoV-2 survives best in cold, dry conditions, being out of sunlight) (Mallapaty, 2020; Merow and Urban, 2020). Moreover, we have an independent sample of participants in the lockdown and no-lockdown conditions. Although we tested for systematic differences, we cannot fully exclude the possibility that unobserved differences in sample characteristics led to the results. Similarly, we screened for participants who reported at least mild levels of distress as well as loneliness, which were 45% of all screened participants. Therefore, we cannot exclude the possibility that the observed effects are specific to that subpopulation. In addition, we analyzed self-reported mental states within a 60-minute time window prior or

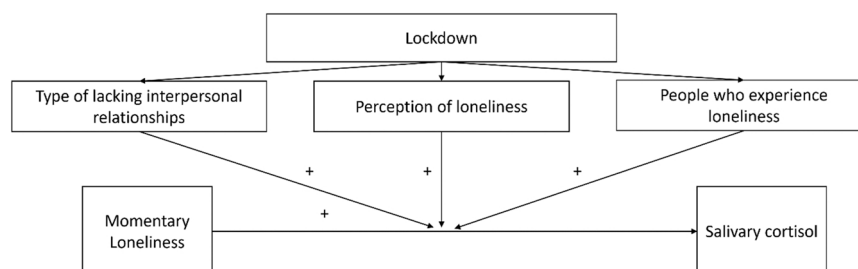


Fig. 5. Three possible factors that explain why a lockdown changes the association between momentary loneliness and salivary cortisol.

past a salivary cortisol sampling, thus we might overlook temporal effects which develop within a different time windows (i.e. in laboratory settings cortisol response typically occur 10–20 min after a stressor (Allen et al., 2014; Hellhammer and Schubert, 2012).

Our study indicates that the effects of loneliness on HPA axis functioning changes across lockdown conditions. One possible reason is a difference in the type of experienced loneliness, which highlights the need for a multidimensional view on loneliness. One possible central aspect that influences whether loneliness increases disease risk, is whether it is perceived as controllable. Future studies should investigate the impact of loneliness on cortisol levels in another context in which loneliness is not experienced by choice, such as elderly people who have lost their social network or the chronically ill.

6. Summary

The COVID-19 pandemic and associated lockdown measures might increase disease risk, by affecting stress-responsive physiological systems. We found higher salivary cortisol levels during a lockdown, than during a no-lockdown. Momentary COVID-19 related worries, information seeking and feeling restricted were not associated with salivary cortisol. However, during a no-lockdown [8th August 2020 – 1st November 2020] momentary loneliness was associated with decreased cortisol, whereas during a lockdown [2nd November 2020 – 11th March 2021] momentary loneliness was associated with increased salivary cortisol. In sum, our study suggests that lockdown can affect the association between loneliness and stress responsive endocrine systems. We proposed possible mechanisms behind this effect, which need to be investigated in future studies.

Declarations of interest

None.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105894.

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