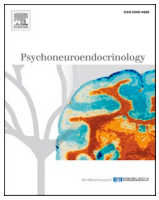
Psychoneuroendocrinology 132 (2021) 105345

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



Short Communication

Impact of loneliness on diurnal cortisol in youth

Ellen Jopling *, Katerina Rnic, Alison Tracy, Joelle LeMoult

University of British Columbia, Canada

ARTICLE INFO

Keywords:
Loneliness
Diurnal cortisol
COVID-19
Adolescence

ABSTRACT

Loneliness is associated with multiple forms of psychopathology in youth. However, we do not yet know how loneliness gets "under the skin" in ways that may impact the long-term health and development of early adolescents. In particular, loneliness may influence youths' patterns of diurnal cortisol, an index of hypothalamic-pituitary-adrenal (HPA) axis functioning and a central predictor of health across the lifespan. The current severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, or COVID-19) pandemic represents a salient period in which to study the consequences of loneliness, as recent work has provided evidence that the physical-distancing measures put in place to contain the virus have resulted in greater loneliness, particularly among youth. Thus, the current study aimed to examine the prospective association between loneliness during the COVID-19 pandemic and diurnal cortisol in early adolescents. We found that greater loneliness was associated with higher levels of cortisol at waking and a blunted cortisol awakening response (CAR). These results held even when controlling for covariates that can influence diurnal trajectories of cortisol. Critically, this pattern of HPA-axis functioning increases risk for adverse mental and physical health outcomes across adolescence and into adulthood. This study is the first to examine the prospective association between loneliness and diurnal cortisol in early adolescence, and the first to identify mechanisms that contribute to biological markers of distress during the COVID-19 pandemic. Findings underscore the importance of developing and distributing strategies to mitigate feelings of loneliness among youth.

1. Introduction

Loneliness has been implicated in multiple forms of psychopathology, and there is reason to believe that loneliness could get "under the skin" in ways that influence youth's long-term health and development (Qualter et al., 2010). One intriguing possibility is that loneliness affects patterns of diurnal cortisol production. Diurnal cortisol, an index of hypothalamic-pituitary-adrenal (HPA) axis functioning, is an important predictor of health among youth (Adam et al., 2017). Moderate responsiveness of the HPA axis, which is considered to be the central stress response system among humans, supports functioning by preparing an individual to respond to both physical and psychological stress (Lucassen et al., 2014). However, cortisol dysregulation in youth, particularly dysregulation of the cortisol awakening response (CAR), is robustly linked to subsequently elevated rates of psychiatric disorders, such as depression, and adverse physical health outcomes, including inflammatory and cardiovascular diseases, obesity, and cancer (e.g., Nederhof et al., 2015; Ruttle et al., 2013).

Although there is limited evidence that loneliness influences trajectories of diurnal cortisol in adults (Adam et al., 2006; Steptoe et al., 2004) researchers have not yet examined prospective associations between loneliness and diurnal cortisol in early adolescence. This is surprising given that there is reason to expect age-related differences in the association between loneliness and diurnal cortisol. In fact, there are age-related differences in patterns of diurnal cortisol production (Van Cauter et al., 1996), and social networks, social support, and interpersonal contact are particularly important during adolescence (Brown and Larson, 2009).

The current severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, or COVID-19) pandemic represents a salient period to study associations between loneliness and wellbeing in youth given the particular relevance of, and substantial individual differences in, loneliness during this time (e.g., Luchetti et al., 2020). Indeed, efforts to contain the COVID-19 virus have necessitated extensive social isolation measures worldwide, and this isolation has been particularly taxing on youth (Young Minds, 2020). Thus, the aim of the current study was two-fold: to examine one way COVID-19 might affect youth's psychoneuroendocrinological health while simultaneously answering a broader

* Correspondence to: Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, British Columbia, Canada V6T 1Z4.
E-mail address: ellen.jopling@psych.ubc.ca (E. Jopling).

https://doi.org/10.1016/j.psyneuen.2021.105345
Received 24 December 2020; Received in revised form 11 June 2021; Accepted 21 June 2021
Available online 29 June 2021

question of critical importance in the field – whether loneliness is prospectively associated with markers of physical health in early adolescence. We examined these questions using a short-term longitudinal design at the height of COVID-19 physical-distancing measures.

2. Materials and methods

In June 2020, three months after a state of emergency was declared and in-person classes were canceled, and when the strictest physical-distancing measures of the first wave of the pandemic were in place, a sample of 52 early adolescent youth (age range 13–14 years; $M = 13.98$) completed the UCLA Loneliness Scale, a well-established measure of loneliness (Russell et al., 1978). Possible scores on the UCLA Loneliness Scale range from 20 to 80, with higher scores indicating greater loneliness. There was excellent reliability for this measure in the present study, Cronbach's $\alpha = 0.97$.

Two weeks later, youth provided eight saliva samples across two days to assess diurnal cortisol using Sarstedt Salivettes. Samples were provided at awakening, 30-minutes post-awakening, mid-afternoon (as close to 15:00 h as possible), and bedtime. Participants were instructed not to eat, drink, or brush their teeth for one hour before providing each sample, and any deviations from these instructions were reported (see online supplement). Saliva samples were stored at −20 °C until analyses were carried out in the endocrinological laboratory at the Technische Universität Dresden (Institute of Biological Psychology). After thawing, Salivettes were centrifuged at 3000 rpm for 5 min; this process resulted in a clear supernatant of low viscosity. Cortisol concentrations were measured using chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany). Following current practices, outliers were winsorized to 2 standard deviations (*SD*s) from the mean to adjust for skew, consistent with past research (Gotlib et al., 2015). The intra- and inter-assay coefficients were both below 9%.

This study was approved by the Behavioural Research Ethics Board at the University of British Columbia. Informed consent was obtained from parents/caregivers, and informed assent was obtained from youth. Anonymized data, study protocols, and both HLM and R code relevant to the present analyses and figures can be accessed by contacting the corresponding author.

3. Results

3.1. Participant characteristics

Participants were a subset of youth enrolled in the *UBC Study on Adolescents*. Demographic characteristics are presented in Table 1. Participants reported a mean level of loneliness of 38.13 when the strictest physical-distancing measures were in place, and there was substantial variability between individuals in levels of loneliness (range 20–77, $SD = 15.63$). The expected pattern of diurnal cortisol was observed: participants' level of cortisol was significantly different than zero at waking, $t(51) = 18.45$, $p < .001$, increased significantly from waking to 30-min post-waking, $t(51) = -3.07$, $p = .003$, and decreased significantly across the remainder of the day, $t(51) = 13.67$, $p < .001$.

Table 1
Participant characteristics.

Variable	All participants	Median split loneliness			
		High loneliness	Low loneliness	Statistic (t or χ^2)	p-value
Age, *M(SD)*	13.98(0.32)	13.95 (0.31)	14.01 (0.32)	0.69	.496
Sex (% Male)	60%	56%	63%	0.26	.609
Gender (% Boys)	60%	56%	63%	0.26	.609
Pubertal Stage, *M(SD)*	3.49(0.91)	3.52 (1.06)	3.46 (0.75)	-0.24	.810
UCLA Loneliness Scale, *M(SD)*	38.13 (15.63)	51.00 (12.62)	26.22 (5.03)	-9.17	**<.001**
Ethnic Identity European-Canadian	62%	56%	67%	0.62	.430

Participants were separated into high and low loneliness samples using a median split of scores on the UCLA Loneliness Scale (≤35, >35).

3.2. Prospective association between loneliness and diurnal cortisol production

Hierarchical linear modeling (HLM) was used to examine the association of loneliness with youths' diurnal cortisol production (Raudenbush and Bryk, 2002). This approach is well-suited to the present analyses as HLM models repeated measurements of cortisol within persons as a function of time and, thus, permits the examination of unevenly spaced measurement occasions. Coefficients, variance components, and standard errors were based on a sample size of 52 at Level 2, which exceeds best-practice recommendations of sample sizes for the stable estimation of variance and covariance components in HLM (Maas and Hox, 2005). Using a multilevel piecewise model, we modeled cortisol levels at waking, the cortisol awakening response (CAR; from awakening to 30-minutes post-awakening), and the daytime cortisol slope (from 30-min post-awakening to bedtime). Models were fit using full information maximum likelihood estimates to calculate deviance and Akaike's Information Criteria ($AIC = 950.96$), and restricted maximum likelihood for estimating model parameters. Robust standard errors were used to reduce bias following recommendations put forth by Raudenbush and Bryk (2002). Further detail regarding the multilevel piecewise model is provided in the online supplement.

Importantly, youth's level of loneliness predicted individual differences in their diurnal cortisol patterns: greater loneliness was associated with higher levels of cortisol at waking, $B = 0.10$, $t(50) = 3.28$, $p = .002$, and with a blunted CAR, $B = -0.003$, $t(50) = -3.07$, $p = .003$ (Fig. 1). A series of variables known to influence trajectories of diurnal cortisol were tested as potential covariates in relation to youths' cortisol production, including age, current use of psychotropic medication, current use of non-psychotropic medication, pubertal stage, sex assigned at birth, minutes between midnight and the first sample, time between loneliness and cortisol assessments, and pre-COVID-19 psychiatric diagnosis (see Online Supplement for additional details). The same pattern of findings emerged when significant covariates were included. Further, findings held even when all possible covariates were included simultaneously in the model ($ps < 0.008$), underscoring the robust association between loneliness and patterns of diurnal cortisol production. To quantify the size of the observed effects, we computed *pseudo-*R^2 values. We found that loneliness explained 31% of the variance in cortisol levels at waking (*pseudo-*$R^2 = .310$) and 8.6% of the explainable variance in the CAR (*pseudo-*$R^2 = .086$).[1]

4. Discussion

This study is the first to examine the prospective association between loneliness and diurnal cortisol patterns in early adolescence. It also documents biological markers of distress during the current pandemic, and in doing so, responds to urgent calls for an examination of mechanisms underlying the biological sequelae of living in the COVID-19 era. As Dantzer et al. (2020) have argued, a psychoneuroendocrinological

[1] We examined whether total cortisol produced acrossthe course of the day, modelled as area under the curve with respect to ground(AUCg) from the second to fourth saliva samples, was associated with lonelinessreporting during the pandemic. A linear regression analysis indicated thatloneliness was not associated with AUCg, $\beta = 0.33$, $t(51) = 0.23$, $p = 0.817$. See the Online Supplement for further detail.

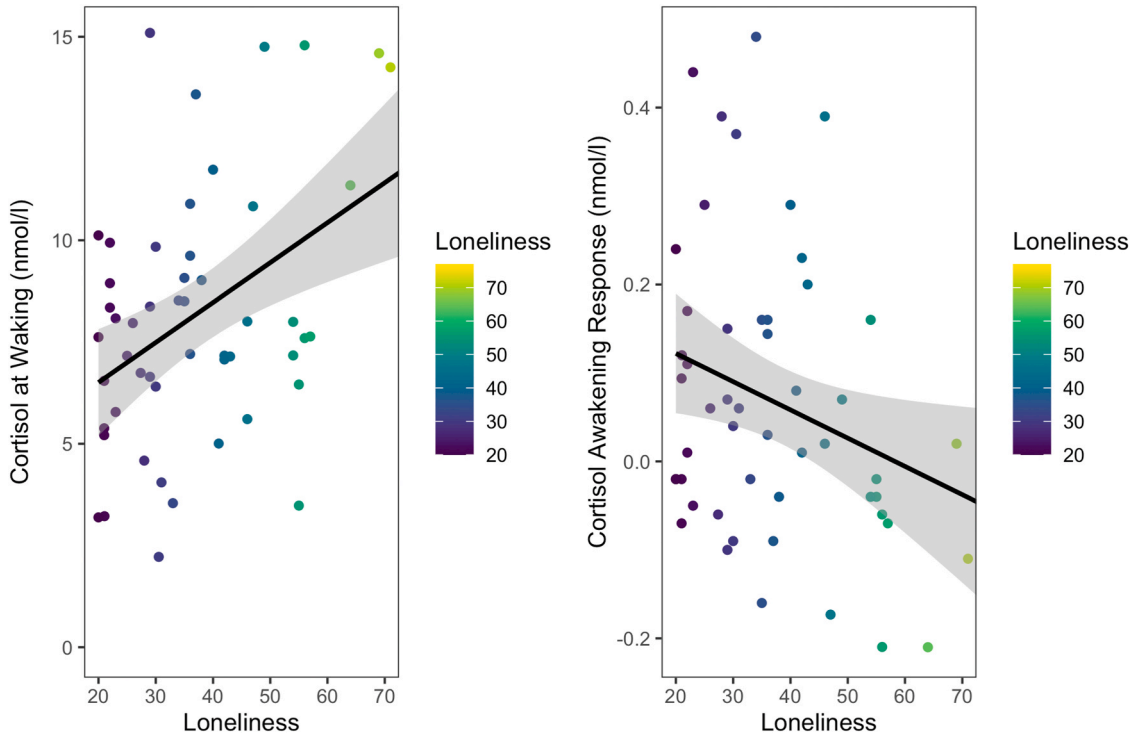


Fig. 1. Associations between loneliness and diurnal cortisol, Loneliness was measured using the UCLA Loneliness Scale, with higher scores (possible range 20–80) indicating greater loneliness.

perspective will allow for a better understanding of the health consequences of the current pandemic. We found that higher levels of loneliness, as reported by youth during the height of the first wave of the COVID-19 lockdown, were associated with a maladaptive diurnal cortisol pattern (Adam et al., 2017). Specifically, we found that greater loneliness was associated with higher levels of cortisol at waking and a blunted CAR. Early adolescence is a developmental period in which aberrant HPA-axis functioning represents an important marker of health. Indeed, a blunted CAR prospectively predicts worsened mental and physical health (e.g., increases in depressive symptoms and body mass index) across the adolescent period (Nederhof et al., 2015; Ruttle et al., 2013) and into adulthood (Chida and Steptoe, 2009).

There is widespread concern regarding the impact of social isolation and loneliness on children and adolescents' wellbeing, and the present findings indicate that there may be an empirical reason for this concern. Prior work has indicated that physical-distancing measures necessitated by the COVID-19 pandemic have resulted in marked loneliness, particularly among youth (e.g., Lee et al., 2020; Young Minds, 2020). Importantly, even outside of the current pandemic, loneliness remains a painful and common experience for adolescents (Laursen and Hartl, 2013). For example, researchers have documented that loneliness increases risk for mental health problems (Qualter et al., 2010; Young Minds, 2020). Extending the existing literature via a psychoneuroendocrinological perspective, the present study documents that loneliness also gets "under the skin" and may therefore have broader consequences for youth's health and development.

Several limitations of this work should be noted. First, although there is evidence that levels of loneliness have increased as a result of the COVID-19 pandemic (Lee et al., 2020; Young Minds, 2020), and then have remained stable during it (e.g., Luchetti et al., 2020), we did not assess levels of loneliness either prior to the pandemic or at later timepoints during the pandemic, and results should be interpreted in light of this fact. Additionally, although two-sample CAR collection protocols are consistent with current expert guidelines for pediatric populations (Stalder et al., 2016), knowledge of factors influencing CAR peak timing in youth continues to develop. Thus, we suggest that future work examining diurnal cortisol in youth should consider using a three- or four-sample CAR protocol. Finally, it is possible that youth experiencing higher levels of loneliness may have been less compliant with the study protocol than youth with lower levels of loneliness, which may have influenced the present results. For instance, it is possible that higher levels of loneliness may have been associated with delayed collections of saliva following waking, which may have resulted in higher levels of cortisol at the first sampling timepoint (i.e., the awakening timepoint) and a blunted CAR. Although we did collect self-reported information regarding compliance (e.g., time at which participants collected each sample, deviations from sampling instructions), and controlled for deviations (see online supplement), replication of the present study using objective assessments of compliance, such as MEMS track cap containers and actigraphy, are needed.

Despite these limitations the current findings provide important evidence that loneliness is associated with a maladaptive pattern of diurnal cortisol production. With this in mind, the development and distribution of strategies designed to attenuate feelings of loneliness among youth is of paramount importance given the prevalence of loneliness in adolescence and its concerning consequences. The urgency of such interventions is underscored by projections that physical-distancing measures will remain crucial through the coming months of the pandemic. Implementation of such strategies has promise to attenuate global increases in psychiatric disorders and physical diseases secondary to the COVID-19 pandemic, and more broadly, to bolster youth's mental and physical health both within and outside of times of crisis.

Acknowledgements

This research was supported by a UBC Four Year Doctoral Fellowship (4YF) Award to EJ, a Vanier Canada Graduate Scholarship 6568 to EJ, a UBC Institute of Mental Health Marshall Postdoctoral Fellowship to KR, a Women's Health Research Institute Fellowship to KR, a UBC 4YF

Award to AT, a Social Sciences and Humanities Research Council (SSHRC) Grant 430-2017-00408 to JL, a Canadian Institutes of Health Research (CIHR) Grant PJT-156053 to JL, a Natural Sciences and Engineering Research Council (NSERC) Grant RGPIN-2018-04837 to JL, and a Michael Smith Foundation for Health Research Scholar Award 17713 to JL.

Conflict of Interest

All authors declare that they have no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105345.

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