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Do depressive symptoms mediate the relationship between hopelessness and diurnal cortisol rhythm?

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Running head: Depressive Symptoms, Hopelessness, and Cortisol

Do Depressive Symptoms Mediate the Relationship Between Hopelessness and Diurnal Cortisol Rhythm?

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Abstract

Purpose: Research has revealed a well-established relationship of depressive symptoms and hopelessness with a variety of physical illnesses that are associated with a dysfunction of the hypothalamic-pituitary-adrenal-axis. The purpose of this study was to test if depressive symptoms mediate the relationship between hopelessness and cortisol, a measure of the hypothalamic-pituitary-adrenal-axis. **Methods:** Hopelessness, depressive symptoms, and diurnal cortisol rhythm were measured in 257 adults (128 women and 129 men; age range: 20-74 years) in this cross-sectional study. To test the hypothesis, two linear regression analyses and asymmetrical confidence intervals around the regression weights were conducted. A second set of analyses was calculated to be able to exclude the possibility of hopelessness as a mediator between depressive symptoms and cortisol. **Results:** As predicted, after adjusting for age, gender, awakening time, medication use, more hopelessness predicted more depressive symptoms and more depressive symptoms predicted a flatter diurnal cortisol rhythm. The 95% confidence intervals revealed that the indirect relationship between hopelessness and diurnal cortisol rhythm was significant. The analyses with hopelessness as a potential mediator revealed that hopelessness does not mediate the association between depressive symptoms and cortisol. **Conclusions:** While the relationship between hopelessness and cortisol was mediated by depressive symptoms in this cross-sectional study, many other risk factors of depression have not been examined. Thus, future longitudinal studies should examine the relationships between those risk factors of depression and the hypothalamic-pituitary-adrenal-axis.

Keywords: population-based; cross-sectional study; mediation model; hopelessness; depressive symptoms; diurnal cortisol rhythm

Presently, psychosocial factors in general, and depressive symptoms in particular, are prospectively associated with incidents of both cancer and cardiovascular disease (CVD) [for meta-analyses see 1 and 2; 3; 4, respectively]. In the field of clinical psychology, two prominent models explaining the development of depressive symptoms based on cognitive risk factors have been well-supported by decades of research: Beck's cognitive theory [5] and the hopelessness model [6]. One crucial risk factor for the development and maintenance of depressive symptoms in both models is hopelessness. Hopelessness is a negative view of the future, or in other words, hopeless persons make long-range projections, anticipating that current difficulties or suffering will continue indefinitely [5, 6]. Hopelessness is important for the purpose of this study, as empirical studies have also found it to be associated with cancer and CVD incidents. For example, a 6-year longitudinal study with middle aged men without a history of CVD or other serious illness at baseline revealed that hopelessness is associated with incidence rates of myocardial infarction (MI) and cancer, even after controlling for age and depressive symptoms [7]. This raises the question of whether hopelessness predicts depessive symptoms which is associated with physical illness. In other words, it is possible that depressive symptoms mediate the association between hopelessness and physical illness.

While we are not aware of any study testing if depressive symptoms mediate the associations between hopelessness and physical illness, one cross-sectional study [8] with healthy women found that hopelessness significantly predicts mean and maximum carotid artery intima-media thickening (IMT) while depressive symptoms predicted IMT only marginally, both while controlling for age, race/ethnicity (European-American & African-American), income, BMI, SBP, and smoking. After entering hopelessness and depressive symptoms in the same model and continuing to control for all other variables, hopelessness but not depressive

symptoms remained a predictor of IMT. In addition, another study tested whether hopelessness and depressive symptoms were independently associated with instances of myocardial infarctions [9]. This 18-year longitudinal study with men without previous MI revealed that hopelessness and depressive symptoms predicted MI incidents when not controlling for each other. However, when controlling for hopelessness, depressive symptoms no longer significantly influenced the men's risk of an MI. Further, hopelessness continued to predict MI incidents even after controlling for depressive symptoms. Thus, while this particular study did not identify whether depressive symptoms mediated the association between hopelessness and MI, results suggested that hopelessness and depressive symptoms are not independently associated with this particular health condition.

A possible pathway for the associations between depressive symptoms and hopelessness with cancer and CVD is the psychobiological response to stress. The term stress is ambiguous and is often used to describe a variety of constructs. However, in this instance, stress is understood as one or more events that are seen by the individual which experiences the event(s) as threatening and therefore trigger(s) a psychobiological response. A central component of this stress response is the (hypothalamic-pituitary-adrenal-axis) HPA-axis involving the release of the corticosteroid cortisol [10]. The release of cortisol is an adaptive and necessary response for survival, mobilizing resources to meet new demands [11]; however, if not in balance, the stress response may lead to an increased risk of disease through the metabolic effects of sustained high cortisol levels, the immunosuppressive effects of cortisol, or effects resulting from the inability to respond to new demands (or a combination of these effects). Thus, both the capacity to respond to a stressful event and subsequently relax after the event is important [12]. To assess this capacity, methods have been developed to test stress response. One measure of stress

response is the decline of cortisol from morning to evening (i.e., diurnal cortisol rhythm). Similar to chronic stress [e.g., 13; 14] and other psychosocial variables such as bereavement [15] and loneliness [16], both depressive symptoms and hopelessness have been related to smaller differences between morning and evening values [i.e., flatter rhythm; e.g., 17; 18]. However, as far as we know, no study has tested whether hopelessness is a risk factor of both depressive symptoms and flatter cortisol rhythm and if depressive symptoms mediate the association between hopelessness and diurnal cortisol rhythm.

Based on the above presented theoretical considerations and previously published data finding significant and marginally significant associations of depressive symptoms and hopelessness with flatter diurnal cortisol rhythms, respectively [17; 18], it will be expected that depressive symptoms mediate the association between hopelessness and diurnal cortisol rhythm. However, it can not be excluded that hopelessness mediates the association between depressive symptoms and cortisol rhythm. Thus, an alternative model reflecting that depressive symptoms mediate the association between hopelessness and diurnal cortisol rhythm will be tested as well.

Method

Participants

This study utilized data obtained from a public health survey that was administered in two phases. In the first phase of data collection, participants consisted of a random sample of 10,000 residents of the county of Östergötland in Sweden, with a response rate of 61%. The second phase of data collection invited a random sample of 400 participants (200 women and 200 men) from the first phase of data collection to participate in a study examining the current constructs of interest. The response rate was 64.5% and included 257 participants from the greater population. Relevant demographic information was collected from participants,

including age (mean = 48.12, SD = 9.64), gender (128 women and 129 men), awakening time (mean = 6:08 a.m., SD = 1.05 hours), medication (153 do not take medication regularly and 95 take medication regularly), education (128 basic school and two years of upper secondary and 119 three years of upper secondary and/or university studies), type of labor (66 blue-collar and 132 white-collar), and skill level of employment (37 unskilled, 29 partly skilled, 35 skilled manual, 66 skilled non-manual, 31 managerial). The sample and methodology are also discussed in a previous article [19].

Materials and Methods

Major Depression Inventory [MDI; 20; 21]. The MDI is comprised of 10 items, which assess emotional and somatic symptoms of depression present in individuals during the past two weeks. These items reflect the DSM-IV major depression criteria. Participants responded to each item utilizing a six-point Likert scale, ranging from 0 (at no time) to 5 (all of the time). Depression scores were calculated by summing the (mean = 7.76, SD = 7.82) participants' responses on each item, with a potential range of 0 to 50. A MDI score of 26 is considered to be the accepted clinical cut-off [22], and 11 participants in this study reported MDI scores above such value. Cronbach's alpha for the scores of the items on the MDI with this particular population was 0.92.

Hopelessness Scale [7]. To assess hopelessness, two items were included in the survey: "I feel that it is impossible to reach the goals I would like to strive for" and "The future seems to me to be hopeless, and I can't believe that things are changing for the better." Participants responded to both items on a five-point Likert scale (0 = absolutely agree to 4 = absolutely disagree). The two items were reverse scored and summed, so higher scores reflected greater

levels of hopelessness (mean = 2.00, SD = 2.07). The correlation between the two items was 0.82. These items have been utilized to assess hopelessness in previous research [7, 23; 24].

Cortisol [cf. 19]. The samples were mailed to the laboratory, centrifuged, transferred to 1.5 ml Eppendorf tubes, and frozen at -20 ºC. A time-resolved fluorescence detection method was used to determine cortisol [cf. 25]. Intra-assay coefficients were less than 10%.

Procedure

Before information and materials regarding saliva collection were mailed home to the participants, the procedures and aims of the study were explained to potential participants and all provided written consent. The instructions requested that participants collect saliva on three consecutive working days that did not include Fridays, Mondays, or holidays (i.e., Tuesdays, Wednesdays, and Thursdays) 30 minutes after awakening (prior to breakfast) and in the evening (prior to sleeping). These time points were selected because diurnal cortisol deviation from morning to evening is widely used [26], and a recent review found the most consistent associations between depressive symptoms and saliva cortisol when diurnal cortisol deviation was measured compared to other methods to measure saliva cortisol [e.g., single time point measures; 27]. Thus, participants were instructed to collect saliva samples 30 minutes after awakening (prior to breakfast) and in the evening (prior to sleeping). Participants were provided Salivette collection devices to collect the saliva samples and instructed to freeze them immediately after collection.

The time in which saliva samples are obtained can affect the evaluation of the cortisol response [cf. 28; 29]. Thus, participants were instructed to complete a form detailing their awakening and sampling time. The forms were all completed. Samples that were to be obtained 30 minutes after awakening were excluded if they were collected outside of a 10 minute grace

period (i.e., 20 minutes or less, 40 minutes or more). Moreover, samples were excluded if the participants did not adhere to the fasting instructions, cortisol responses were not able to be determined due to insufficient amount of saliva or technical error, or the cortisol value was an outlier (i.e., ±2 *SD*s from mean). Overall, 9, 11, and 16 samples were excluded from the first, second, and third day, respectively.

Data Analysis

Mean values for both sampling times were calculated across the three consecutive days. After the exclusion criteria were applied and mean values calculated, eight missing values were reported for the 30 minutes after awakening sample and two missing values were reported for the evening sample. Because the cortisol data were skewed, logarithmic transformation was used. To calculate diurnal cortisol rhythm, the arithmetic difference between the logarithmic transformed morning value (i.e., 30 minutes after awakening samples; mean = 1.49, SD = 0.18) and the logarithmic evening value (mean = 0.63, SD = 0.22) was obtained.

Based on Preacher and Hayes' [30] widely used approach to test for mediation, mediation is characterized by an indirect relationship between a predictor variable and dependent variable through a mediator. Thus, to test the hypothesis that depressive symptoms mediate the association between hopelessness and diurnal cortisol rhythm, two linear regression analyses and asymmetrical confidence intervals around the regressions weights were calculated using SPSS 21. One linear regression was conducted to examine whether hopelessness predicts depressive symptoms while controlling for the effects of age, gender, awakening time, and medication use on this association. A second linear regression analysis was conducted to examine whether depressive symptoms predict diurnal cortisol rhythm, while controlling for the above mentioned variables and for the effect of hopelessness. Finally, 95% confidence intervals for the regression

weights were calculated using PRODCLIN [31]. The upper and lower confidence limits have different critical values because PRODCLIN uses the product method, which follows an asymmetrical distribution [31]. A statistically significant mediation effect exists when the confidence limits do not contain zero. To evaluate an alternative model in which hopelessness mediates the association between depressive symptoms and diurnal cortisol rhythm, a second set of analyses was conducted. This set of analyses included (a) a linear regression analysis with depressive symptoms predicting hopelessness while controlling for the effects of age, gender, awakening time, and medication use on this association; (b) a linear regression analysis with hopelessness predicting diurnal cortisol rhythm while controlling for the above mentioned variables and depressive symptoms; (c) calculations of the confidence intervals around the regression weights of the association of hopelessness with depressive symptoms and of hopelessness with diurnal cortisol rhythm.

Results

Means and standard deviations for the variables and correlations between the variables utilized in the study are reported in Table 1.

Depressive Symptoms as Mediator. As expected, after adjusting for age, gender, awakening time, and medication use, more hopelessness predicted more depressive symptoms ($p < .001$; Table 2). Moreover, there was a negative association between depressive symptoms and diurnal cortisol rhythm ($p < .01$), after controlling for age, gender, awakening time, and medication use. This association remained significant after including hopelessness as a control variable as well ($p < .05$; Table 2). In other words, replicating previous findings, more depressive symptoms predicted a flatter diurnal cortisol rhythm. An examination of the 95% confidence intervals revealed that the indirect relationship between hopelenessness and diurnal

cortisol rhythm did not include zero and was therefore significant (-.015, -.003). Thus, the hypothesis that depressive symptoms mediate the assocation between hopelessness and diurnal cortisol rhythm was supported.

Hopelessness as Mediator. As expected, after adjusting for age, gender, awakening time, and medication use, more depressive symptoms predicted more hopelessness ($p < .001$; Table 3). However, there was only a non-significant direct association between hopelessness and diurnal cortisol rhythm (p = n.s.), after controlling for age, gender, awakening time, and medication use. As to be expected, this association remained non-significant when controlling for depressive symptoms as well (p = n.s.; Table 3). In addition, an examination of the 95% confidence intervals revealed that the indirect relationship between depressive symptoms and diurnal cortisol rhythm did include zero and was therefore not significant (-.003, .000). Thus, hopelessness does not mediate the assocation between depressive symptoms and diurnal cortisol rhythm.

Discussion

Based on theoretical considerations [6; 5] and empirical findings [e.g., 17; 18] the aim of the study was to test the hypothesis that depressive symptoms mediate the association between hopelessness and diurnal cortisol rhythm. Consistent with the prediction, hopelessness predicted more depressive symptoms and more depressive symptoms predicted a flatter diurnal cortisol rhythm. Further, depressive symptoms mediated the relationship between hopelenessness and diurnal cortisol rhythm. Although contrary to previous literature, an alternative model examining whether hopelessness mediated the association between depressive symptoms and diurnal cortisol rhythm was also explored. Results revealed that depressive symptoms predicted hopelessness while hopelessness was not directly associated with a flattened diurnal cortisol

rhythm. Thus, hopelessness did not mediate the assocation between depressive symptoms and diurnal cortisol rhythm. Summarized, the hypothesis that depressive symptoms mediate the assocation between hopelessness and diurnal cortisol rhythm was supported. Additionally, there was no support for the model of hopelessness mediating the association between depressive symptoms and diurnal cortisol rhythm. This pattern of results even allows to conclude that hopelessness is not directly but only through depressive symptoms associated with diurnal cortisol rhythm.

A flattened diurnal cortisol rhythms has been proposed to be associated with a decreased responsiveness of the immune system to cortisol mediated signaling. In other words, cortisol is less able to suppress inflammatory control pathways which results in increased concentrations of inflammatory biomarkers, such as IL-6 and CRP [32]. This hypothesis is supported by findings of a recent meta-analysis [33]. In parallel, depressive symptoms and hopelessness have been shown to be predictors of mean and maximum carotid artery IMT [8]. Because chronically elevated inflammatory biomarkers and IMT are associated with increased risk for cancer and CVD [34], future research should replicate the findings of this study and examine the relationship between hopelessness, depressive symptoms, inflammatory biomarkers, and IMT, cancer, and CVD.

Previous research has explored the effects of some factors associated with depression on physical health outcomes, including childhood abuse [35], a negative attribution style [36], and low self-esteem [37]; however, additional factors associated with depression still remain unexplored. Considering that both Beck's cognitive theory [5] and the hopelessness model [6] propose multiple cognitive vulnerability factors associated with depression (i.e., dysfunctional attitudes, cognitive errors, cognitive triad, negative automatic thoughts, pessimistic cognitive

style), studies including multiple psychosocial factors seem fruitful, especially given the interplay that exists between these factors [e.g., 38]. Further, Beck's cognitive theory proposes that hopelessness is only one part of the cognitive triad. The cognitive triad is a set of negative cognitions focusing on the future (hopelessness), the self, and the world. As such, not only long-range projections, anticipating that current difficulties or suffering will continue indefinitely (negative view of the future) but also attributions of negative events to personal psychological, moral, or physical defect (negative view of the self) and the view that the world makes exorbitant demands and/or presents insuperable obstacles to reach life goals (negative view of the world) increase the risk to develop depressive symptoms [5]. Thus, it would be especially interesting to study the associations between all three parts of the cognitive triad, depressive symptoms, and physical health. Such studies will contribute to a further integration of psychological and biological models into a bio-psycho-social model of heart health.

Limitations of this study should be considered while interpreting the findings. Self-report measures were utilized to assess hopelessness and depressive symptoms, rather than structured interviews. Additionally, the hopelessness scale lacks convergent and divergent validity; however, it has produced valid scores and predicted cardiovascular and metabolic outcomes in prior research [19, 39]. Further and probably most important is the cross-sectional design of the study. This precludes drawing of causal conclusions. In addition, while hopelessness is not a symptom in the DSM-5 [40], some researchers conceptualize hopelessness not as risk factor of depression but as a symptom of depression [e.g., 41]. Thus, an alternative interpretation of our findings is that hopelessness is simply the "active symptom" that impacts other depressive symptoms which are associated with diurnal cortisol rhythm. To overcome the limitations of a

cross-sectional study, a three wave longitudinal study with equal time lags between the waves is needed [42].

Summarized, the present study supports the hypothesis that the relationship between hopelessness and diurnal cortisol rhythm is mediated by depressive symptoms. However, based on the present findings, asking for hopelessness does not substitute for screening of major depressive disorder when investigating the impact of depression on diurnal cortisol rhythm. As this study was cross-sectional and many other factors associated with depression have not been examined, future research should explore the relationships between such factors, depressive symptoms, and biological risk factors of cancer and CVD.

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Table 1

Means and Standard Deviations for and Correlations between Hopelessness, Depressive Symptoms, Cortisol Rhythm, and Control Variables

Variable	1	2	3	4	5	6	7
1 Hopelessness	--						
2 Depressive symptoms	.41***	--					
3 Cortisol rhythm	-.15*	-.19**	--				
4 Age	.11	-.06	-.10	--			
5 Gender	.13*	.29***	-.01	-.01	--		
6 Awakening time	-.09	.13*	.06	-.10	.23***	--	
7 Medication use	.18**	.22***	-.10	.37***	.23***	.07	--

*$p < .05$; **$p < .01$; ***$p < .001$

Table 2

Regression results with Hopelessness as Predictor of Depressive Symptoms (upper part) and Depressive Symptoms and Hopelessness as Predictors of Diurnal Cortisol Rhythm (lower part) to test the Model of Depressive Symptoms as Mediator between Hopelessness and Cortisol

Dependent Variable	Depressive Symptoms			
	Step 1		Step 2	
Predictors	R^2	β	R^2	β
Age		-.13*		-.15*
Gender		.24***		.20***
Awakening time		.04		.08
Medication use		.20**		.15*
Hopelessness				.38***
R^2 change	.13***		.14***	
Total R^2	.13		.27	

Dependent Variable	Cortisol Rhythm					
	Step 1		Step 2		Step 3	
Predictors	R^2	β	R^2	β	R^2	β
Age		-.07		-.10		-.09
Gender		-.01		.04		.04
Awakening time		.06		.06		.06
Medication use		-.08		-.04		-.04
Depressive Symptoms				-.21**		-.19*
Hopelessness						.05
R^2 change	.02		.04**		.00	
Total R^2	.02		.06		.06	

Note. + $p < .10$; *$p < .05$; **$p < .01$; ***$p < .001$

Table 3

Regression results with Depressive Symptoms as Predictor of Hopelessness (upper part) and Depressive Symptoms and Hopelessness as Predictors of Diurnal Cortisol Rhythm (lower part) to test the Model of Hopelessness as Mediator between Depressive Symptoms and Cortisol

Dependent Variable	Hopelessness					
	Step 1		Step 2		Step 3	
Predictors	R^2	β	R^2	β	R^2	β
Age		.04		.09		
Gender		.13+		.03		
Awakening time		-.13+		-.14*		
Medication use		.15*		.06		
Depressive Symptoms				.42***		
R^2 change	.06**		.15***			
Total R^2	.06		.21			
Dependent Variable	Cortisol Rhythm					
	Step 1		Step 2		Step 3	
Predictors	R^2	β	R^2	β	R^2	β
Age		-.07		-.06		-.09
Gender		-.01		.01		.04
Awakening time		.06		.04		.06
Medication use		.08		-.06		-.04
Hopelessness				-.13+		-.05
Depressive Symptoms						-.19*
R^2 change	.02		.02+		.03*	
Total R^2	.02		.03		.06	

Note. + $p < .10$; *$p < .05$; **$p < .01$; ***$p < .001$