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Short title: Depressive Symptoms, Hopelessness, and Interleukin-6

Hopelessness the ‘active ingredient’? Associations of Hopelessness and Depressive Symptoms
with Interleukin-6

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Abstract

Objective: Previous research has revealed a relationship of depressive symptoms and hopelessness with cardiovascular diseases (CVDs) which are associated with elevated levels of interleukin-6 (IL-6). The objective of this study was to explore whether depressive symptoms and hopelessness are independent predictors of IL-6 levels. **Method:** Hopelessness, depressive symptoms, and IL-6 were measured in 45 Swedish adults (26 women and 19 men; age range: 31-65 years). Two separated linear regressions were conducted with hopelessness and depressive symptoms serving as individual predictors of IL-6. Another regression analysis examined whether the two predictors predict IL-6 when controlling for each other. The regression coefficients of the models with one predictor and with both predictors were compared. **Results:** As predicted, after adjusting for age, BMI, illness, smoking, and gender, more depressive symptoms and more hopelessness predicted higher IL-6 levels in independent regressions. When controlling for each other, hopelessness, but not depressive symptoms, predicted IL-6 levels. Finally, when controlling for hopelessness, the regression between depressive symptoms and IL-6 level was significantly reduced; however, there was no significant change in the regression between hopelessness and IL-6 level when controlling for depressive symptoms. **Conclusions:** Thus, these results suggest that depressive symptoms and hopelessness are not independent predictors of IL-6 levels. Future research should explore the interplay of hopelessness and depressive symptoms on other risk factors of CVDs.

Index words: cross-sectional study; hopelessness; depressive symptoms; interleukin-6

Introduction

The Global Burden of Disease study launched by the World Health Organization predicts cancer and cardiovascular disorders (CVD) to be one of the leading causes of death worldwide by 2030 [1]. In high-income countries, an estimated 3.17 million people died from CVD in 2001, representing more than 40% of deaths [2]. Presently, psychosocial factors in general, and depressive symptoms in particular, are prospectively associated with incidents of CVD [for a meta-analysis see 3]. As such, the pro-inflammatory cytokine IL-6 is known as the major regulator of acute phase protein synthesis [4] and stimulator of the hypothalamic-pituitary-adrenal (HPA) axis during inflammatory stress [5] and it is also related to a higher risk of CVD [6]. Thus, IL-6 may play a role in the mechanisms linking psychosocial stressors to disease.

Recent literature has emphasized identifying which specific aspects of depression are strong predictors of CVDs, and their corresponding biological risk factors. Hopelessness seems to be characterized as such, a “toxic” symptom of depression. Hopelessness - the negative view of the future - often occurs with severe episodes of depression [7]. Nevertheless, hopelessness is not recognized as a symptom of depression in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [8] and two prominent models explaining the development and maintenance of depression view hopelessness as a risk factor and not as a symptom of depression [9; 10]. Thus, hopelessness may be distinct from depression in its associations with biological risk factors of CVD, a hypothesis supported by multiple studies. For example, in a cross-sectional study [11], hopelessness was a significant predictor of mean and maximum carotid artery intimal-medial thickening (IMT) whereas depressive symptoms marginally predicted IMT. After entering both variables in the same model, hopelessness but not depressive symptoms remained a predictor of IMT. Similarly a 18-year longitudinal study with men without previous

CVD revealed that hopelessness and depressive symptoms predicted myocardial infarction (MI) incidents when not controlling for each other. However, when controlling for each other, depressive symptoms no longer significantly influenced the risk of MI while hopelessness continued to predict MI incidents [12]. Other publications demonstrated that hopelessness predicts hypertension [13] and carotid atherosclerosis [15] even after controlling for depressive symptoms. Given such findings and the significance of IL-6, understanding whether hopelessness and depressive symptoms are independent predictors of IL-6 levels is important to address.

Based on theoretical considerations [9; 10] and empirical findings [e.g., 11-14], it can be predicted that hopelessness and depressive symptoms are independently associated with IL-6 but that the association between depressive symptoms and IL-6 will no longer be significant when controlling for hopelessness; whereas, the association between hopelessness and IL-6 will not be influenced by depressive symptoms.

Method

Participants

Data was collected as part of a broader survey of health that is discussed in detail in prior studies [15]. This study consisted of 45 residents (26 women and 19 men), ranging from age 31 to 65 years (mean age = 48.07 years, $SD = 8.54$), residing in the county of Östergötland in Sweden. The participants reported no chronic conditions that could affect their immune system; however, other health concerns were reported by 19 of the participants, including hypertension, fibromyalgia, musculoskeletal pain, chronic lung disease, psoriasis, allergy, and impaired vision.

Materials

Major Depression Inventory (MDI; 16; 17). The MDI was administered to evaluate symptoms of depression in participants over the past two weeks. The MDI is comprised of ten items that reflect the DSM-IV criteria, with the exception that self-esteem and guilt are measured with two items on the MDI rather than one item on the DSM-IV. Participants utilized a six-point Likert scale to respond to each item, with a range of 0 (at no time) to 5 (all of the time). Item responses were summed to obtain an overall depression score, with a potential range between 0 and 50. The MDI correlates reportedly with the Hamilton Depression Scale [17]. Cronbach's alpha was .0.94.

Hopelessness Scale [18]. Hopelessness was assessed utilizing two items: "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." Responses by participants were recorded on a five-point Likert scale ranging from 0 (absolutely agree) to 4 (absolutely disagree), and the items were reverse-scored and summed to produce a hopelessness score. The correlation between the two items was $r = 0.77$. Prior research has utilized these items to assess hopelessness [e.g., 15].

Demographic Variables. Participants reported demographic information, including age, gender, smoking, BMI ($mean = 25.12$, $SD = 4.27$), and illness. Smoking was coded into one of six groups: never (33.3%, $n = 15$), stopped smoking (31.1%, $n = 14$), sometimes (11.1%, $n = 5$), less than 10 cigarettes per day (13.3%, $n = 6$), 10 to 20 cigarettes per day (11.1%, $n = 5$), or more than 20 cigarettes per day (0%, $n = 0$). Further, Illness was coded as a dichotomous variable and either did (42.2%, $n = 19$) or did not (57.8%, $n = 26$) occur for each participant [cf. 15].

Procedure

Prior to the collection of blood samples and responses on survey items, the procedure and aims of the study were explained to potential participants and they provided written consent, as approved by the university IRB. Participants did not take any medication during or immediately prior to blood collection; further, if participants had some type of illness two weeks prior to the blood sample collection, they were requested to return after recovery. Venous blood samples were drawn between 8:00 and 9:00 in the morning. The blood was centrifuged within one hour and sera were frozen at -70 °C.

Procedure for IL-6

IL-6 [15] was measured in duplicate with a chemiluminescence-based sandwich enzyme immunoassay technique (QuantiGlo Human IL-6 Immunoassay Kit, R&D Systems Europe, Abingdon, UK). The inter- and intra-assay coefficients of variation (CV) for plasma were 9.2% and 2.8%, respectively. The standard curve of IL-6 was linear between 0.15 and 3000 pg/mL and the sensitivity of the assay was 0.15 pg/mL.

Data Analysis

To evaluate the hypotheses, three linear regression models and two paired t-tests were conducted. More specifically, three regression models were calculated with IL-6 levels as the dependent variable: one model with depressive symptoms as the predictor, one model with hopelessness as the predictor, and one model with both depressive symptoms and hopelessness as predictors. All regression models were adjusted for the effects of age, BMI, illness (e.g., hypertension, psoriasis), smoking, and gender. Finally, paired t-tests were conducted to evaluate the regression coefficients from the models with one predictor (depressive symptoms *or* hopelessness) to the model with both predictors (depressive symptoms *and* hopelessness).

The hypotheses would be classified as correct when a) hopelessness and depressive symptoms both significantly predict IL-6 levels when not controlling for each other; b) the regression coefficient of depressive symptoms, but not hopelessness, is significantly reduced in the model with both predictors (hopelessness *and* depressive symptoms) compared to the models with one predictor (hopelessness *or* depressive symptoms).

Results

The relationship between depressive symptoms and hopelessness was positively associated at $r = .34$ ($p < .001$). The regression model with depressive symptoms ($mean = 7.67$, $SD = 8.51$) predicting IL-6 levels ($mean = .12$, $SD = .40$) revealed that greater depression symptomatology was significantly associated with higher IL-6 levels ($p = .027$; Table 1). Similarly, the regression model with hopelessness ($mean = 2.11$, $SD = 2.17$) predicting IL-6 levels revealed that greater hopelessness was significantly associated with higher IL-6 levels ($p = .002$; Table 1). The final regression model included both depressive symptoms and hopelessness as predictors of IL-6 levels, and hopelessness ($p = .022$) remained significantly associated with IL-6; whereas, depressive symptoms was no longer associated with IL-6 levels ($p = .577$; Table 1).

- Insert Table 1 here -

Further, regression coefficients from the models with one predictor (depressive symptoms *or* hopelessness) were compared to the corresponding predictors' regression coefficients in the final model (depressive symptoms *and* hopelessness) using paired t-tests. Results revealed that there was a significant reduction in the regression coefficient of depressive

symptoms ($t(44) = 4.28; p < .001$) but not in the regression coefficient for hopelessness ($t(44) = 1.17; p = .248$).

Discussion

Based on theoretical considerations [9; 10] and empirical findings [11-14], the aim of the study was to test whether depressive symptoms and hopelessness were independent predictors of IL-6 levels. Summarized, the results were consistent with the hypothesis that hopelessness but not depressive symptoms was an independent predictor of IL-6 levels. The relevance of these results is important given that IL-6 has been consistently linked to clinical depression when not controlling for hopelessness [19] and that IL-6 may play a role in linking depressive symptoms to CVD. Thus, if replicated, this finding may explain the bidirectional association between CVDs and depression.

Attempts have been made to reduce IL-6 or CVDs recurrences by reducing depressive symptoms in patients with CVD. However, a recent meta-analysis of studies researching the effects of pharmacotherapeutic interventions to reduce depressive symptoms in patients with CVD did not improve the readmission and the mortality rate although medication decreased depression symptoms [20]. Further, not all pharmaco- and psychotherapeutic interventions effective in treating depressive symptoms impact hopelessness equally well [for a review see 21]. Thus, research combined with the findings of this study might help explaining the results of the meta-analysis. Future studies of therapeutic approaches attempting to reduce CVDs should focus on approaches that demonstrated in other populations to be successful in reducing hopelessness (e.g., Acceptance and Commitment Therapy, Problem-Solving Treatment; 22, 23)

Although theoretical considerations [9; 10] allow for the conclusion that hopelessness is a risk factor of both depressive symptoms and elevated IL-6 levels causing the impression of an

association between depressive symptoms and IL-6, it was not possible to test this hypothesis in this study because depressive symptoms and hopelessness were measured at the same time point. To be able to test the direction of such associations, a study with three equal waves of data collection is needed [24]. This seems especially important because although hopelessness is not a symptom in the DSM-IV-TR [8], some researchers conceptualize hopelessness as a symptom rather than a risk factor of depression [e.g., 25]. Thus, an alternative interpretation of our findings might be that hopelessness is simply the “active factor” that connects depression to IL-6 levels. Further, possible explanations for our findings include but are not limited to (a) hopelessness may mediate the effect of depression on IL-6 levels, (b) a covariate may control for more variability in one predictor than in the other and thereby allow one predictor (e.g., hopelessness) to achieve greater predictive power relative to the other predictor (e.g., depressive symptoms), (c) an omitted covariate (e.g., socio-economic status) is undercontrolled with respect to one predictor (e.g., hopelessness) but not the other (e.g., depressive symptoms), (d) IL-6 causes hopelessness, or (e) a common factor (e.g., disease, obesity) causes both elevated IL-6 and hopelessness levels.

Thus, the findings call not only for replication but also for further explorations of the interplay of hopelessness, depressive symptoms, and other variables on hypertension, atherosclerosis, and heart rate variability as biological risk factors of CVDs. Although previous research has studied the impact of some risk factors of depressive symptoms, such as childhood abuse [26], many other risk factors of depressive symptoms have not been examined. Considering that both above mentioned psychological models of depression [9; 10] propose multiple cognitive risk factors of depression (i.e., dysfunctional attitudes, pessimistic cognitive style), studies including multiple psychosocial factors seem fruitful. Such studies will contribute

to further integration of psychological and biological models into a bio-psycho-social model of heart health.

Beyond the cross-sectional design which precludes drawing of causal conclusions, the use of one format (e.g., self-report questionnaires), compared to a multi-method approach, to measure hopelessness and depressive symptoms is a limitation of the reported study.

Additionally, the 2-item hopelessness scale that was used in this study has not been compared with other hopelessness scales. Nevertheless, it has been well-validated and in previous studies it has predicted various cardiovascular and metabolic outcomes [e.g., 15].

Summarized, the present study supports the hypothesis that hopelessness but not depressive symptoms is an independent predictor of IL-6 levels. Because this study was cross-sectional and many other risk factors of depressive symptoms have not been examined, future research should explore the relationships between risk factors of depression, depressive symptoms, and IL-6 with other biological risk factors of CVDs and CVDs.

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Table 1

Regression models predicting IL-6 from scores on depressive symptoms and hopelessness scales

	Depressive symptoms-IL- 6	Hopelessness- IL-6	Depressive symptoms & Hopelessness-IL-6
	β	β	β
Depressive symptoms	0.34*	---	0.10
Hopelessness	---	0.48**	0.42*
Covariates			
Age	0.54**	0.35*	0.37*
BMI	-0.36*	-0.17	-0.22
Illness	-0.22	-0.17	-0.17
Smoking	-0.04	0.04	0.02
Gender	0.11	-0.10	-0.08
Total R^2	0.37**	0.45**	0.45**

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