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Depressive Symptoms are Associated with Allostatic Load among Community-Dwelling Older Adults

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Abstract

The allostatic load model has been used to quantify the physiological costs of the body's response to repeated stressful demands and may provide a useful, integrative perspective on the various correlates of late-life depressive symptoms. We interviewed 125 Rochester, NY adults, ranging in age from 67 to 94 years. We employed an allostatic load score as a measure of multisystem dysfunction in hypothalamic-pituitary-adrenal axis function, immune function, anabolic activity, and cardiovascular activity. Overall, affective, and somatic depressive symptom scores were computed using the 20-item Center for Epidemiologic Studies Depression Scale. Multiple linear regression models were used to estimate associations between allostatic load scores and affective, somatic, and overall depressive symptoms. Among our sample of mean age 76.1 years, the one-week prevalence of clinically significant depressive symptoms was 12.8%. In models adjusting for demographic, socioeconomic, and health-related factors, higher allostatic load scores were associated with elevated scores for overall, affective, and somatic depressive symptoms: beta = 1.21 (95% CI = 0.38, 2.05); beta = 0.14 (95% CI = 0.040, 0.24); beta = 0.60 (95% CI = 0.23, 0.97), respectively. Our results suggest that allostatic load measure is associated with late-life depressive symptoms. This association appears to be of clinical significance, as the magnitude of the effect size was comparable (but opposite in direction) to that of antidepressant use. Future research should examine the inter-relationships of allostatic load, psychological stress, and late-life depressive symptoms.

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Keywords

Allostatic Load; Depression; HPA Axis

1. INTRODUCTION

Depressive symptoms are common among older adults in the U.S., with estimates of the one-week prevalence of clinically significant depressive symptoms ranging from 8% to 16% [1, 2, 3]. As the U.S. population continues to age, the public health burden of late-life depressive symptoms can be expected to increase. The U.S. Census Bureau projects that by the year 2050 adults over the age of 65 will comprise over 20% of the U.S. population as compared to about 13% currently [4, 5]. Thus, the absolute number of older adults affected by depressive symptoms will increase substantially, and understanding the psychosocial and physiological correlates of depressive symptoms among community-dwelling older adults will become increasingly crucial.

The established psychosocial and physiological correlates of late-life depressive symptoms are diverse [6]. Individuals affected by physical conditions spanning multiple systems of the body, such as cardiovascular disease, diabetes, sleep disturbance, cognitive dysfunction (e.g., Parkinson's disease, dementias), and hyperactivity of inflammatory pathways are more likely to experience depressive symptoms [1, 2, 7, 8]. In addition to physical conditions, psychosocial factors linked with late-life depressive symptoms include trait neuroticism, multiple dimensions of poor socioeconomic position, poor social support, stressful life events, and elevated levels of perceived stress [2, 6, 7, 9].

The 'allostatic load model' may provide a useful integrative perspective on these various psychological and physiological correlates of late-life depressive symptoms. Sterling and Eyer developed the concept of 'allostasis' to describe an organism's ability to adjust its physiological functioning in response to the environment [10]. McEwen and Stellar extended this conceptual model to explain how psychosocial phenomena may result in lasting physiological changes in the body [11, 12]. This model has been used to quantify the physiological costs of the body's response to either repeated stressful demands or inadequate responses to these demands [12, 13]. It posits that repeated or inadequate physiological adaption to social and environmental stress over time, as mediated through the dysregulation of glucocorticoids such as cortisol via the hypothalamic-pituitary-adrenal (HPA) axis and catecholamines via the sympathetic nervous system (SNS), can result in dysfunction of the body's cardiovascular, immune, and metabolic systems [13, 14]. Independent of McEwen, Björntorp and Rosmond suggested that how a cluster of metabolic and cardiovascular symptoms might be associated with HPA axis (named Metabolic Syndrome X) and stress [15, 16]. This dysregulation of cortisol and of downstream physiologic systems may promote depressive symptoms [17]. In summary, repeated adaption to stress is thought to result in dysfunction of the HPA axis, and the resulting dysregulation of cortisol and of downstream physiologic systems may be associated with depressive symptoms.

Although this model suggests that the link between allostatic load and depressive symptoms is plausible, and despite the fact that many of the standard physiological components of an allostatic load summary measure have been studied in relation to depressive symptoms [6], only a few analyses have examined the association. Analyses of 972 Taiwanese older adults (mean age 67.7 years at baseline) demonstrated significant associations between elevated allostatic load scores (greater multisystem dysfunction) and greater overall depressive symptoms at baseline and three years later [18, 19]. Another study also provided support for a relationship between allostatic load and depressive symptoms (at baseline and three years

later) among 58 adults of mean age 67.6 years [20]. In a more recent analysis of a large, nationally-representative sample, a physiological dysfunction summary measure, guided by the allostatic load model, was associated with multiple dimensions of depressive symptoms [21].

In this analysis, we examine the association between a measure of allostatic load and overall depressive symptom severity using a sample of community-dwelling older adults. In addition to examining overall (i.e. global) symptoms, we also considered affective and somatic depressive symptoms. These two dimensions were chosen because studies increasingly suggest that physiological factors may be associated with specific dimensions of depressive symptoms [22, 23, 24, 25]. Two such symptom clusters are “affective” (e.g. guilt, dysphoria) and “somatic” (e.g. sleep irregularities, lack of energy, changes in appetite) symptoms. The literature on depressive symptoms rarely delineates the affective and somatic dimensions of depressive symptoms, yet distinguishing these dimensions may be important because they may be associated with unique risk factors and independent neurobiological pathologies in the context of late-life depression [26, 27].

2. MATERIAL AND METHODS

2.1 Study Population

We followed up and collected new data on participants who previously participated in the Mindfulness to Improve Elders’ Immune and Health Status (MIEIHS) study, a randomized controlled trial, completed in 2009, conducted to study Mindfulness Based Stress Reduction and its effects on immune function [28]. Study participants were community-dwelling older adults of at least 65 years of age that were recruited by newspaper advertisements and flyers. Eligibility requirements stipulated that subjects be 65 years of age or older and English speaking. Participants with prescription antidepressant or anxiolytic medication must have had a stable regimen for eight weeks prior to enrollment (except for persons taking sedative-hypnotic sleep medication, low level psychotropic medication for pain management, or beta-blockers for heart conditions). Major, uncorrected sensory impairments or cognitive impairment (defined as a score of 24 or lower on the Mini-Mental State Examination (MMSE)) were considered exclusionary, based on previous recommendations [29]. Exclusions were also made for individuals with major depression with psychotic features, psychosis, lifetime history of schizophrenia, bipolar disorder, organic brain syndrome, mental retardation, or a history of substance abuse within the previous year. Psychiatric-based exclusion criteria were assessed through the Structured Clinical Interview for DSM-IV (SCID) and clinical interview. The MIEIHS study consisted of a baseline assessment with additional assessments at 8 weeks, 11 weeks, and 32 weeks. Various physiological and psychological measures were taken across these four periods.

For this 2010 follow-up study, the 204 subjects that completed all phases of the MIEIHS were re-contacted. The MMSE was re-administered and subjects with a total score of 24 or lower were excluded from follow-up participation. Aside from this, all eligible subjects that completed the MIEIHS study (including both arms of the clinical trial) were offered participation in the follow-up study. Successful telephone contact was made for 165 (81%) subjects and ultimately, interviews were conducted on and full data were available for 125 (61%) subjects. Informed consent was obtained from each participant and the University of Rochester’s Research Subjects Review Board approved the study protocol.

2.2 Biomarker Measurement

Our allostatic load summary measure was constructed using seven component measures, encompassing neuroendocrine function, cytokine status, metabolism, and cardiovascular function. These include diurnal cortisol slope (DCS), interleukin-6 (IL-6), insulin-like

growth factor 1 (IGF-1), waist-to-hip ratio, resting heart rate, systolic blood pressure, and diastolic blood pressure. The DCS, waist-to-hip ratio, resting heart rate, and blood pressure measures were collected during the 2010 follow-up study, while IL-6 and IGF-1 were collected during the original MIEIHS study.

Various measures of HPA axis function status have been proposed, including measures of the cortisol awakening response and the DCS. We selected the DCS because it is thought to reflect chronic stress conditions and has been found to be a particularly sensitive marker of psychiatric disturbances, particularly those involving stress (e.g. post-traumatic stress disorder, depression, generalized anxiety disorder), as well as physical health measures (e.g. obesity, cardiovascular disease) [30]. With the DCS, it is thought that conditions of chronic stress are associated with flatter diurnal pattern, and thus averaged coefficients of smaller magnitude are thought to be indicative of greater stress and poorer HPA axis functionality [30]. We characterized the diurnal cortisol secretion pattern with six salivary cortisol samples obtained over two consecutive days. On each these days, samples were collected: (1) immediately after the subject awakened, (2) 2.5 hours after awakening, and (3) and at bedtime. Subjects were asked to passively drool into labeled, polypropylene tubes at each collection period and document the time of collection. After all six samples were collected, sealed tubes were mailed in padded envelopes to study staff. Upon arrival the sealed tubes were stored in a -80°C freezer. Samples were later thawed and assayed for cortisol using a high sensitivity enzyme-linked immunoassay kit (Salimetrics LLC, PA). The calculation of a DCS involved using linear regression to estimate the best-fitting line through the cortisol values using hours since waking as the predictor. A separate linear regression was performed for each day of sampling. The coefficients or slopes of these two regressions were combined through a weighted average, such that each individual coefficient was inversely weighted by its variance. This weighting was implemented to reduce the influence of laboratory error or subject error in the final estimate. For 21 subjects, one of six saliva samples either contained too little saliva for cortisol quantification or provided invalid results. Adapting a method used in a prior study [31], the missing value was imputed using multiple regression with the following predictors: the two other valid cortisol measures from that day, as well as the subject's sex, age, waking time, and smoking status (current, yes or no).

Blood collection during 8-, 11-, and 34-week assessments in the original MIEIHS study used conventional venipuncture and vacutainer tubes. Blood was centrifuged and serum was stored at -80°C until assayed. Serum levels of IL-6 were assayed with a high sensitivity enzyme-linked immunoassay kit (R&D Systems, Inc., MN). IL-6, a pro-inflammatory cytokine, and IGF-1, a stimulator of systemic cell growth, have both been used in prior studies of allostatic load, and are both considered correlates of immune status [32]. IGF-1 is thought to play a role in resistance to oxidative stress [33], is crucial in the neurogenesis process [34], and has been used previously in studies of allostatic load [35]. Both IL-6 and IGF-1 have demonstrated high normal biological stability over multiple years [36, 37], suggesting that in the absence of incident cardiovascular, cancer, or infectious disease states, their intrapersonal variation in serum levels would be minimal. For both IL-6 and IGF-1, serum levels were averaged across the three assessment periods to reduce the influence of short-term variability in these measurements.

Waist-to-hip ratio, resting pulse, and blood pressure were all collected using standard medical equipment. Subjects were asked to remain seated for pulse and blood pressure measurement. Three resting pulse, systolic, and diastolic measures were collected in succession (two minute intervals between measures) and averaged. A similar approach has been used in the past for combining multiple blood pressure and pulse readings [38].

2.3 Allostatic Load Summary Measure

A composite allostatic load score was assigned to each subject as a count of how many markers an individual exceeded a cutoff, with a maximum score of seven (Table 1). This procedure has been previously used [21]. For all component measures except for IGF-1, higher levels are thought to be indicative of poorer functioning. Accordingly, each subject was assigned one point for each component that exceeded the 75th percentile cutoff for that component. As lower levels of IGF-1 indicate poor immune and metabolic function, subjects were given one point if their IGF-1 levels fell below the 25th percentile. Separate male and female cutoffs were employed for the waist-to-hip ratio component, as sex-specific cutoffs are customary for this metric.

We also created a continuous allostatic load summary measure. We standardized all allostatic load component variables such that observations represented the number of standard deviations above or below the mean (i.e. a z-score transformation). We then summed each of the component z-scores (using z-scores for IGF-1 that had been multiplied by negative one) to create a continuous summary score.

2.4 Depressive Symptoms

Depressive symptoms were assessed during the follow-up study through the Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D scale has been extensively validated in a number of cultural contexts, and is particularly noted for its ability to capture many facets of depression [39]. When evaluated against the DSM-IV (SCID-I) in a group of older adults, the CES-D was found to be a valid screening instrument [40]. The CES-D contains 20 questions relating to average weekly frequency of depressive symptoms. Responses are scored as follows: 0 = “Rarely or none of the time (<1 day),” 1 = “Some or a little of the time (1–2 days),” 2 = “Occasionally or a moderate amount of the time (3–4 days),” and 3 = “Most or all of the time (5–7 days).” For four CES-D items, the scoring pattern is reversed; these questions include: “I felt that I was just as good as other people,” “I felt hopeful about the future,” “I was happy,” and “I enjoyed life.” These 20 response scores are summed resulting in a score that can range from zero to 60.

In order to compute affective and somatic depressive symptom scores, we relied on a recently-completed 28-study meta-analysis of the CES-D factor structure [41]. This analysis revealed a four-factor structure of the CES-D consisting of depressed affect, somatic, positive affect, and interpersonal problem factors. The loadings of the CES-D items on these factors only modestly varied across the reviewed studies. We generated affective and somatic sub-scale scores from items that loaded on these two factors, using the scoring method of the overall CES-D. For instance, affective sub-scale scores were calculated from seven CES-D items: “I felt that I could not shake off the blues even with the help of my family or friends,” “I felt depressed,” “I thought my life had been a failure,” “I felt fearful,” “I felt lonely,” “I had crying spells,” and “I felt sad.” For each of these items, a subject’s answers can be scored as 0 through 3, and a maximum subscale score of 21 can be obtained (7 items $\times$ 3 points). Somatic sub-scale items included: “I was bothered by things that don’t usually bother me,” “I did not feel like eating; my appetite was poor,” “I had trouble keeping my mind on what I was doing,” “I felt everything I did was an effort,” “My sleep was restless,” “I talked less than usual,” and “I could not get going.” This method has been used before to provide sub-scale scores for unique CES-D symptom dimensions [42, 43], and we used it to compute continuous global, affective, and somatic depressive symptom scores.

2.5 Covariates

To avoid overadjustment, only a basic selection of sociodemographic and potentially confounding variables were considered. Confounding variables were selected based on prior

literature showing their associations with cognition or mood as well as physical status [6]. These covariates included: age (years), sex (female or male), educational attainment (years), estimated annual income (<\$ 30,000, \$30,000 – \$79,000, > \$80,000 and, “Don’t Know/Refuse”), average weekly frequency of any type of physical activity (activities/week) calculated from the Community Healthy Activities Model Program for Seniors (CHAMPS) survey [44], and antidepressant medication use in the prior month (yes or no). Data on other types of medication use were not available. Treatment assignment from the original wave of the MIEIHS was not controlled for. This was because all participants received Mindfulness Based Stress Reduction (wait-listed controls were used). Additionally, intervention assignment in the original study was not associated with allostatic load scores ($p = 0.25$) or depressive symptoms during the follow-up study ($p = 0.24$).

2.6 Statistical Analysis

We computed descriptive statistics for allostatic load components and depressive symptom measures, and calculated mean global CES-D scores for covariate values. Spearman rank correlations between all allostatic load components and the overall summary score were calculated. To evaluate the influence of covariates on our findings, our regression analysis consisted of two nested models: (1) an initial model adjusting for age and sex only, and (2) a fully-adjusted model including age, sex, educational attainment, estimated annual income, physical activity, and antidepressant medication use. The full model was of primary interest in this analysis.

Model assumptions were checked for each multiple regression model. For models in which the assumption of normally distributed errors with constant variance was violated, the dependent variable was log transformed to stabilize the variance and produce more normally distributed errors. Variance inflation factors (VIFs) were used as a check for collinearity among variables. Statistical outliers (defined as observations with standardized residuals greater than 3 in absolute value) and influential points (defined as observations with a Cook’s distance larger than 0.50) were identified, and affected models were then run with and without these values. When results differed substantially with the inclusion or exclusion of outliers or influential points the differences are noted, however, when results did not differ the unmodified data are presented.

3. RESULTS

The one-week prevalence of clinically significant depressive symptoms in our final sample was 12.8%, using the standard CES-D 16-point score cutoff [45]. Allostatic load scores ranged from zero to six (out of a potential maximum of seven), with a mean of 1.7 and a median of two. The distributions of global depressive symptoms, affective symptoms, and somatic symptoms were all positively skewed. The basic descriptive statistics of these variables are shown in Table 2. The spearman rank correlations of global depressive symptoms with affective and somatic symptoms were strong (0.84 and 0.90, respectively), while the correlation between somatic and affective symptoms was moderate (0.66).

Table 3 provides details on the demographics of the final study population and the distribution of covariate values in this population. The majority of the sample consisted of Non-Hispanic, White females. Subjects ranged in age from 67 years to 94 years, with a mean age of 76.1 years. All 125 subjects had at least a high school education and 40% had some post-college education. The majority of subjects reported an annual household income between \$30,000 and \$79,000 per year, with 14.4% reporting less than \$30,000. Table 3 also provides mean values of CES-D global, affective, and somatic depressive symptoms across values of covariates that were used in regression modeling. The only covariate statistically

associated with depressive symptoms (of all three varieties) in our study sample was antidepressant use.

Table 4 shows the results of nested linear regression models predicting continuous global depressive symptoms, affective symptoms, and somatic symptoms from each of the seven individual allostatic load components. The cortisol slope measure remained associated with global depressive symptoms and somatic symptoms through the final model: $\beta = 72.05$ (95% CI = 14.71, 129.40) and $\beta = 30.84$ (95% CI = 4.76, 56.91), respectively. These estimates suggest that more positive diurnal cortisol slopes were indicative of more severe depressive symptoms. Although initially resting heart rate was associated with affective depressive symptoms ($\beta = 0.017$ (95% CI = 0.0018, 0.033)), this association was attenuated in the final model ($\beta = 0.014$ (95% CI = -0.0016, 0.03)) and lost significance, perhaps partly due to the loss of degrees of freedom associated with adding covariates. The waist-to-hip ratio measure remained associated with somatic symptoms through the final model: $\beta = 8.39$ (95% CI = 0.97, 15.81). In addition to findings for each of the seven components comprising the allostatic load score, Table 4 also presents the results of nested regression models predicting depressive symptoms from overall allostatic load scores. The allostatic load score remained associated with global depressive symptoms through the final model, with only mild attenuation occurring in model building: $\beta = 1.21$ (95% CI = 0.38, 2.05). This effect estimate can be interpreted as: each biological measure that exceeded the threshold associated with pathology was associated with a 1.21 point increase in the overall CES-D score (a 0.17 SD increase). Figure 1 illustrates the bivariate association between allostatic load scores and global depressive symptoms. When analyzing affective and somatic depressive symptoms, allostatic load remained associated with the outcome in the final models: affective symptoms $\beta = 0.14$ (95% CI = 0.04, 0.24), somatic symptoms $\beta = 0.60$ (95% CI = 0.23, 0.97). When we considered models with continuous allostatic load scores, allostatic load was positively associated with all outcomes in the fully-adjusted models (global symptoms $\beta = 0.43$ (95% CI = 0.06, 0.80); affective symptoms $\beta = 0.06$ (95% CI = 0.02, 0.11); somatic symptoms $\beta = 0.19$ (95% CI = 0.03, 0.36). Scatterplots with loess smoothing suggest linear relationships for allostatic load with global and affective symptoms, yet reveal a potential threshold effect for somatic symptoms (see Appendix Figures 1a–c).

Results presented in Table 4 and in the preceding text were generated from models where outliers and influential points were removed, or where outcome variables were transformed; for transparency, Appendix Table 1 contains results regression results based on unmodified and untransformed data. In all regression models, including models with both the individual allostatic load components and the full summary score, there were both statistical outliers and influential points (ranging from $n=1-3$ for global and somatic depressive symptom scores, see Appendix Table 2). All models predicting global and somatic depressive symptoms had between one and three outliers or influential points per model. Their exclusion, according to the previously mentioned criteria, resulted in considerably different effect estimates. All models predicting affective depressive symptoms had more than ten outliers and model residuals were substantially skewed, and thus affective symptom scores required log-transformation to ensure normality of model residuals. As a result, no outliers were present in the new affective symptom model, but the effect estimates were substantially different due to the log scale of the affective scores. Unfortunately this rendered comparisons of associations across the three outcomes impossible. The association between allostatic load score and global depressive symptoms was attenuated when outliers were removed. The direction of changes in all other regression coefficients varied. Modified regression models (Table 4) were chosen to represent the primary findings of this analysis because the unmodified models violated the assumption of normality of residuals. Even with

transformation of data and exclusion of outliers, the qualitative interpretation of regression results remained the same in both sets of results.

4. DISCUSSION

Late-life depressive symptoms are correlated with a multitude of physiological, psychological, and social factors [2, 6]. These physiological correlates include dysfunction of cardiovascular, metabolic, and immune/inflammatory systems [2, 7], all of which are biological systems involved in the body's response to stress [11]. Psychological and social correlates are oftentimes associated with situations involving psychological stress, including financial difficulties [46], social isolation [6], and experiencing traumatic life events, such as bereavement [47]. The allostatic load model is a conceptual model that may provide a unifying explanation for many of these correlates of late-life depressive symptoms [48]. More specifically, repeated adaptation in the face of social or environmental stress over the lifespan is thought to result in disruption of neuroendocrine systems such as the HPA axis [11, 14]. This disruption is thought to be manifested by poor coordination of cortisol and catecholamines in times of stress and times of rest [14]. Because of the poor coordination of these neuroendocrine mediators, secondary physiological systems involved in the stress response are thought to show evidence of dysregulation [11, 14].

We demonstrated a positive association between our summary measure and all three depressive symptoms outcomes, after adjusting for select covariates. We observed significant associations between allostatic load and both affective and somatic clusters of depressive symptoms. Because associations of allostatic load with both affective and somatic depressive symptoms occurred in the same direction, our results do not lend strong support to the hypothesis that allostatic load might differentially influence these two symptom domains. However, because of the non-prospective nature of the study, we cannot speculate on the causality of this association. There are a myriad of potential mechanisms that could explain our findings. For example, physiological dysfunction and depressive symptoms could independently occur from exposure to stress over time, and thus could be associated despite not being directly causally related.

These results substantiate the conclusions of the few previous reports on this topic. This prior work demonstrated that elevated allostatic load scores predicted increased depressive symptoms at baseline and three years after baseline among older Taiwanese [18, 19] and Québécois populations [20]. A cross-sectional association was also confirmed in a nationally-representative sample of the United States [21]. However, the pattern of component measure associations we observed was inconsistent and partly substantiates and partly fails to support previous findings. For both global and somatic depressive symptoms, averaged diurnal cortisol slope was positively associated with severity of symptoms. This indicated that a flatter diurnal slope (as opposed to a steep, negative slope) were associated with depressive symptoms. The association between dysfunctional cortisol secretion with depressive symptoms is one of the well-supported observations in late-life depression research [6, 49, 50, 51]. Although our results do not indicate differential relationships between an overall allostatic load score, affective symptoms, and somatic symptoms, we did observe a positive association specifically between somatic depressive symptoms and visceral obesity, as measured by the waist-to-hip ratio. One prior study lends support to this association. A cross-sectional analysis of the Nijmegen Biomedical Study reported a positive association between the waist-to-hip ratio and somatic depressive symptoms [52]; this study of a large, community-based sample of adults, age 50 to 70 years ($n = 1,284$), employed the Beck Depression Inventory and derived factors scores for affective and somatic depressive symptoms. It has been suggested that severe somatic depressive symptoms might signal that the physiological alterations of depression have occurred [26].

Supporting this point, somatic depressive symptoms have been shown to predict future cardiovascular events and mortality [26].

It is difficult to directly interpret the clinical significance of the regression effect sizes reported here, but a comparison with an estimated average effect of antidepressant medication provides a reference of clinical significance. A 2006 meta-analysis of 89 pharmacotherapeutic intervention studies for older adults with depressive symptoms calculated an average effect size among studies using self-reported depressive symptom scales [53]. This meta-analysis concluded that, on average, treatment with antidepressants (all types grouped together) reduced depressive symptoms by 0.62 standard deviations on self-reported scales. This average improvement would correspond to an approximately 4 points on overall CES-D scores, given the variability of our CES-D scores ($SD = 7.0$ CES-D points). Given that our allostatic load measure ranged in values from zero to six, based on a slope of 1.21 (Table 4), an individual with dysfunction in six biological systems is predicted to have 7.3 point higher overall CES-D score relative to an individual that did not exceed any of the dysfunction cut-offs, all covariates held constant. It is important to note that only one subject was assigned an allostatic load score of six, and thus this estimate represents the greatest possible effect given the data we observed. Keeping this qualification in mind, this effect is greater in magnitude than the average effect of antidepressant use, and so this association appears to be of potential clinical significance.

Study design was a chief limitation of this analysis. Between the original MIEIHS study and the follow-up RSHMB, multiple waves of data were collected from the initial sample of participants, including data on predictors collected at the same time as the depression symptom assessment. Therefore, this follow-up study combined elements of a cross-sectional and longitudinal design. We cannot make claims as to the directionality of the association we observed because we did not establish a base population without a history of depressive symptoms; that is, we could not establish that allostatic load preceded depressive symptoms. In addition, some components of our exposure variable were not available at baseline. Similarly, we cannot capture the dynamic relationships between HPA axis functionality, allostatic load, and depressive symptoms. This analysis cannot, for instance, capture the dynamic and potentially bi-directional relationship between the pro-inflammatory cytokine IL-6 and depressive symptoms [54, 55]. However, given the scarcity of prior research on this topic, our study should be considered an important initial step.

A second potential concern is the representativeness of our sample. When we compared the demographic statistics of our sample to those reported for Monroe County, NY, based on 2006 census projections, our final sample was disproportionately White Non-Hispanic and was more educated [56]. Thus, it appears that our sample of 125 older adults were more well off than the source population. Higher socioeconomic position is associated with lower depressive symptoms and less reported stress. Thus, our more well off sample could be expected to have a lower prevalence of depression and less stress [57, 58]. This suggests our associations are conservative estimates. The distribution of overall CES-D scores in our final sample was comparable to that in a large representative sample of New Haven, Connecticut elders [59]. In a study that consisted of a multistage probability sample of 2,812 noninstitutionalized older men and women living in New Haven, the mean global CES-D score among 65 to 74 year olds was found to be 8.2 ($SD = 8.2$). Thus, the mean global depressive symptom score in our final sample (7.9) was comparable to that of a large sample.

A third limitation to consider is our use of arbitrary cut-offs in creating an allostatic load score. We employed a summary score method is that frequently used in epidemiology studies of physiological dysfunction [12, 60, 61]. A prior analysis compared the predictive

ability of various allostatic load construction methods within a population-based sample of older adults [62]. The authors concluded that the various constructs produce only modest differences in predicting various outcomes including self-assessed health, mobility scores, and temporal orientation. In addition, we performed a secondary analysis using a continuous allostatic load summary score, which supported the interpretation of our primary analysis. Related to this, we acknowledge that alternative, empirical methods for constructing an allostatic load summary exist (e.g. canonical correlation analysis). However, in this analysis we were interested in the equal contribution of all components. We believe that using methods such as canonical correlation analysis would change the nature of the question in this analysis.

Despite these limitations, there are key strengths worth mentioning. First, as a measure of HPA axis functional status, we generated a two-day averaged diurnal cortisol slope. Averaging multiple days of cortisol slope data, as we did in this analysis, is considered the preferred method of estimating the diurnal pattern [63]. Second, this is the first study we are aware of to combine the slopes of multiple days via a variance-weighted average, which allowed for a more precise estimate than a simple average. A third strength was our use of extensively-validated instruments such as the CHAMPS Physical Activity Questionnaire for Older Adults and the Center for Epidemiologic Studies Depression Scale.

In conclusion, among a sample of community-living older adults, we observed an association between a measure of allostatic load and depressive symptom severity. When the magnitude of this association is compared with the average effect size of antidepressant use in clinical trials, this association appears to be of potential clinical significance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acronyms

HPA	hypothalamic-pituitary-adrenal
SNS	sympathetic nervous system
BMI	body mass index
MIEIHS	Mindfulness to Improve Elders' Immune and Health Status study
MMSE	Mini-Mental State Examination
DCS	diurnal cortisol slope
IL-6	interleukin-6
IGF-1	insulin-like growth factor 1
CES-D	Center for Epidemiologic Studies Depression Scale

CHAMPS Community Healthy Activities Model Program for Seniors survey

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Highlights

- We analyzed associations of allostatic load with late-life depressive symptoms
- Greater allostatic load was associated with more severe depressive symptoms
- We observed associations with overall, affective, and somatic depressive symptoms
- The strength of these associations appear to be of clinical significance
- Future research should explore factors driving these associations

Figure 1. Global depressive symptom boxplots across levels of allostatic load with superimposed locally weighted smoothing line and 95% confidence region

^aAllostatic load score of six excluded from figure because only one observation was available

^bBased on unmodified, untransformed data ($n = 125$)

^cSample size for each allostatic load level: 0: ($N = 24$), 1: ($N = 38$), 2: ($N = 30$), 3: ($N = 19$), 4: ($N = 8$), 5: ($N = 4$)

Table 1

Percentile-based cutoffs used to construct allostatic load composite score in final RSHMB sample (n = 125).

Components of Allostatic Load Score	Percentile-based Algorithm
Average diurnal cortisol slope ¹	> -0.0065 (ug/dL)/hour
IL-6	> 3.00 (pg/mL)
IGF-1	< 81.47 (ng/mL)
Resting Heart Rate	> 70.3 bpm
Waist-to-hip Ratio	> 1.029 (men) > 1.007 (women)
Systolic Blood Pressure	> 136.3 mmHg
Diastolic Blood Pressure	> 79.7 mmHg

Table 2

Descriptive statistics of allostatic load components and depressive symptom measures in final RSHMB sample (n = 125)

	Mean (SD)	Minimum	Median	Maximum
Allostatic load component measures				
Average diurnal cortisol slope (ug/dL)/hour	-0.015 (0.03)	-0.292	-0.011	0.083
IL-6 (pg/mL)	2.5 (1.7)	0.49	1.99	9.77
IGF-1 (ng/mL)	106.3 (32.1)	44.87	105.10	193.67
Resting heart rate (bpm)	66.5 (8.8)	47.33	65.67	96.67
Waist-to-hip ratio	0.96 (0.07)	0.79	0.96	1.10
Systolic blood pressure (mmHg)	128.9 (12.1)	99.0	127.33	166.0
Diastolic blood pressure (mmHg)	74.8 (6.5)	59.33	74.67	91.33
Depressive symptom measures				
Global Symptoms	7.9 (7.0)	0	6	33
Affective Symptoms	2.5 (3.0)	0	2	15
Somatic Symptom	3.8 (3.2)	0	3	15

Table 3

Mean CES-D global, affective, and somatic depressive symptom scores by regression covariate values (p-values in parenthesis) in final sample (n = 125)

Covariate	N (%)	CES-D-G	CES-D-A	CES-D-S
Sex				
Female	83 (66.4%)	8.7	2.7	4.2
Male	42 (33.6%)	6.3	2.1	3.1
		(0.15)	(0.55)	(0.22)
Age (years)				
< 70	12 (9.6%)	6.1	1.3	3.3
70 – 74	46 (36.8%)	8.0	2.7	3.8
75 – 79	32 (25.6%)	8.5	2.9	4.1
80 – 84	24 (19.2%)	8.0	2.6	3.8
85 +	11 (8.8%)	7.4	2.1	4.0
		(0.93)	(0.48)	(0.99)
Education				
High School	19 (15.2%)	10.1	3.0	5.6
2 Year College	12 (9.6%)	6.2	1.8	3.3
Bachelors Degree	44 (35.2%)	7.7	2.6	3.4
Graduate Degree	50 (40%)	7.7	2.5	3.7
		(0.41)	(0.97)	(0.11)
Income				
< \$30000	18 (14.4%)	10.0	3.5	4.3
\$30000 – \$79000	70 (56%)	8.1	2.4	4.1
\$80000+	28 (22.4%)	6.5	2.2	2.9
Don't Know/Refuse	9 (7.2%)	6.6	2.4	3.2
		(0.33)	(0.43)	(0.34)
Exercise Frequency				
< 14 activities/week	27 (21.6%)	7.9	2.9	3.5
14 – 18.25	34 (27.2%)	8.7	2.6	4.4
18.25 – 27	31 (24.8%)	8.6	2.6	4.5
> 27	33 (26.4%)	6.4	2.2	2.9
		(0.60)	(0.69)	(0.26)
Antidepressant Use				
Yes	27 (21.6%)	12.3	4.6	5.7
No	98 (78.4%)	6.7	2.0	3.3
		(0.002)	(0.0006)	(0.007)

Table 4

Regression coefficients of individual models predicting global, affective, and somatic depressive symptoms from continuous allostatic load components, overall allostatic load summary score, and other covariates in final sample (sample size varies).

	Global Depressive Symptoms		Log (Affective Symptom Sub-scale Score)		Somatic Symptom Sub-Scale Factor Score	
	Coefficient (95% CI) ^a	Model N/R ²	Coefficient (95% CI) ^a	Model N/R ²	Coefficient (95% CI) ^a	Model N/R ²
Initial Model^b						
Allostatic Load	1.47 (0.64, 2.30)	124/11.3	0.18 (0.078, 0.28)	125/9.6	0.68 (0.33, 1.04)	123/12.4
Diurnal cortisol slope	72.98 (14.77, 131.20)	122/6.5	4.46 (−0.038, 8.95)	125/3.4	31.72 (5.61, 57.82)	122/6.5
IL-6	−0.12 (−0.78, 0.55)	123/2.0	−0.0053 (−0.088, 0.078)	125/0.4	0.048 (−0.25, 0.35)	123/2.1
IGF-1						
Resting Heart Rate	−0.019 (−0.06, 0.02)	124/3.1	−0.0027 (−0.0072, 0.0017)	125/1.6	−0.0071 (−0.023, 0.009)	123/2.7
Waist-to-hip Ratio	0.11 (−0.02, 0.24)	123/4.1	0.017 (0.00084, 0.033)	125/3.8	0.046 (−0.012, 0.10)	123/4.0
Systolic BP	16.62 (0.29, 31.18)	122/5.1	1.74 (−0.34, 3.82)	125/2.6	9.67 (2.36, 16.97)	123/7.3
Diastolic BP						
	0.030 (−0.065, 0.12)	123/2.2	0.0093 (−0.0023, 0.021)	125/2.4	0.0094 (−0.032, 0.051)	123/2.2
	0.067 (−0.11, 0.25)	123/2.3	0.013 (−0.009, 0.035)	125/1.5	0.012 (−0.069, 0.092)	123/2.1
Final Model^c						
Allostatic Load	1.21 (0.38, 2.05)	124/20.2	0.14 (0.040, 0.24)	125/19.9	0.60 (0.23, 0.97)	123/17.7
Diurnal cortisol slope	72.05 (14.71, 129.40)	122/16.6	4.12 (−0.22, 8.46)	125/17.2	30.84 (4.76, 56.91)	122/14.3
IL-6	−0.10 (−0.76, 0.55)	123/12.3	−0.0043 (−0.084, 0.076)	125/14.7	0.067 (−0.23, 0.36)	123/10.5
IGF-1						
Resting Heart Rate	−0.0077 (−0.044, 0.028)	124/14.6	−0.0013 (−0.0056, 0.0030)	125/15	−0.0036 (−0.019, 0.012)	123/10.5
Waist-to-hip Ratio	0.093 (−0.040, 0.22)	123/13.8	0.014 (−0.0016, 0.030)	125/16.9	0.036 (−0.022, 0.094)	123/11.5
Systolic BP	15.46 (−1.18, 32.10)	122/14.9	1.33 (−0.71, 3.37)	125/15.9	8.39 (0.97, 15.81)	123/14.1
Diastolic BP						
	0.025 (−0.069, 0.12)	123/12.4	0.0088 (−0.0024, 0.020)	125/16.4	0.0059 (−0.036, 0.048)	123/10.4
	0.10 (−0.080, 0.28)	123/13.2	0.016 (−0.0053, 0.038)	125/16.3	0.026 (−0.056, 0.11)	123/10.7

^a Bold coefficients signify two-sided significance at 0.05 level

^b Initial model covariates include: age and sex

^c Final model covariates include: age, sex, educational attainment, estimated annual income, physical activity, and antidepressant medication usage