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Multisystem Physiological Dysfunction Is Associated with Depressive Symptoms in a Population-Based Sample of Older Adults

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Abstract

Objective—To evaluate the association between multi-system physiological dysfunction and depressive symptom severity in United States older adults.

Methods—We examined 2,405 adults of age 60 years and older using data from the 2005–2008 National Health and Nutrition Examination Survey. We constructed a summary score of "physiological dysfunction", encompassing cardiovascular function, glucose regulation, liver function, and renal function. Overall depressive symptoms were obtained from the 9-item Patient Health Questionnaire (PHQ-9) depression scale and factor analysis was used to derive affective and somatic symptom scores. We employed multiple linear regression models to estimate associations between physiological dysfunction scores and affective, somatic, and overall depressive symptoms, while adjusting for demographic, socioeconomic factors, and other potentially confounding factors.

Results—Greater multisystem physiological dysfunction scores were associated with an increased severity of overall, affective, and somatic depressive symptoms. These associations persisted after adjusting for all covariates: beta = 0.23 (95% CI = 0.13, 0.32); beta = 0.08 (95% CI = 0.04, 0.11); beta = 0.12 (95% CI = 0.06, 0.18), respectively.

Conclusions—Our results suggest that the multisystem physiological dysfunction is associated with late-life depressive symptoms. Additional longitudinal studies of links between allostatic load, psychosocial stress events throughout the life course, and late-life depressive symptoms may shed further light on this association.

Keywords

Allostatic Load; Cross-Sectional Studies; Depression; National Health and Nutrition Survey Examination

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COMPETING INTEREST STATEMENT
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INTRODUCTION

Both major depression and clinically-significant depressive symptoms are common among older adults in the United States. In the US, the 12-month prevalence of major depression is estimated to be 2.9%, while the prevalence of clinically-significant depressive symptoms ranges from 8% to 16%(Fiske et al., 2009, Kessler et al., 2007). The presence of these symptoms can greatly reduce one's quality of life, as they may be both emotionally and physically disabling(Alexopoulos, 2005).

Despite its great public health significance, the etiology of late-life depressive symptoms is less understood than that among middle aged and young adults (Blazer and Hybels, 2005, Alexopoulos, 2005, Fiske et al., 2009). Nevertheless, a range of clinical conditions and psychosocial characteristics have been proposed as putative risk factors for late-life depressive symptoms. Clinical conditions span multiple systems of the body, such as cardiovascular disease, diabetes, sleep disturbance, physical disability, cognitive dysfunction (e.g., Parkinson's disease, dementias), and hyperactivity of inflammatory pathways(Fiske et al., 2009, Cole and Dendukuri, 2003). Psychosocial factors linked with late-life depressive symptoms include trait neuroticism, multiple dimensions of poor socioeconomic position, poor social support, stressful life events, and high levels of perceived stress(Blazer and Hybels, 2005, Cole and Dendukuri, 2003, Alexopoulos, 2005, Fiske et al., 2009).

The "allostatic load" model has been used to link psychosocial phenomena to changes in the adaptive capacity of the body, and thus may provide a useful integrative perspective on the etiology of late-life depression (Dowd et al., 2009). Allostatic load is a developing epidemiologic concept that has been utilized to quantify the physiological costs of the body's response to either repeated stressful demands or inadequate responses to these demands(McEwen, 1998b). This framework 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 multisystem physiological dysfunction (McEwen, 1998a). Chronic hyper- or hyposecretion of glucocorticoids is thought to be reflected by dysfunction of the body's cardiovascular, endocrine, immune, renal, and metabolic systems(McEwen, 1998a, McEwen, 1998b).

Although several studies have investigated HPA axis dysfunction among depressed older adults(Ferrari et al., 2001), only three prior analyses have explored the association between multisystem physiological dysfunction and late-life depressive symptoms. A cross-sectional study of 972 Taiwanese older adults (mean age 67.7 years) noted significant associations between greater physiological dysfunction and increasingly severe global depressive symptoms, across multiple summary scores of physiological dysfunction (Seplaki et al., 2006). A re-analysis of this same study examined noted that greater physiological dysfunction was associated with increasingly severe global depressive symptoms three years later (Goldman et al., 2006). A more recent study also provided support for a relationship between physiological dysfunction and depressive symptoms among 58 adults of mean age 67.6 years (Juster et al., 2011).

Furthermore, studies examining depressive symptom etiology increasingly suggest that physiologic factors may be associated with clusters of depressive symptoms (Bosch et al., 2009, de Jonge et al., 2007, Krause et al., 2010, Wijeratne et al., 2006); two such symptom clusters described in the literature are "affective" (e.g. guilt, dysphoria) and "somatic" (e.g. sleep irregularities, lack of energy, changes in appetite) symptoms. Although the literature on depressive symptom etiology rarely delineates the affective and somatic dimensions of depressive symptoms, 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(Linke et al., 2009, Capuron and Miller, 2004).

We examined the association between multi-system physiological dysfunction with overall (i.e., global) depressive symptom severity, as well as separately for affective, and somatic symptoms, among a nationally representative sample of United States older adults. To our knowledge, this is the first analysis to examine how physiological dysfunction (as guided by the allostatic load model) relates to multi-dimensional late-life depressive symptoms in a large, population-based sample.

METHOD

Study Population

The NHANES is a national survey of the non-institutionalized, civilian United States population that utilizes a complex, multistage, probability-sampling design, oversampling certain groups such as ethnic minorities and the elderly(Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS), 2009). Participants completed an initial household interview and were invited to complete a standardized medical examination in the Mobile Examination Center (MEC). Further information on sampling and interview procedures are available elsewhere(Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS), 2009). All survey protocols were approved by the National Center for Health Statistics Ethics Review Board and informed consent was acquired from all study participants.

We pooled the datasets of two distinct NHANES cycles: the 2005–2006 and 2007–2008 cycles. The analysis focused on NHANES participants who were age 60 years and older. Of the 51,610 US residents that were sampled in both NHANES cycles and sent an initial invitation letter, 5,437 residents (10.5%) of age 60 years and older were sampled. Of these 5,437 sampled subjects, 3,724 (68.5%) consented to be interviewed at their home with 3,150 (57.9%) subsequently undergoing depressive symptom screening at a MEC. Subjects underwent both depressive symptoms screening and physiological assessment at the MEC visit. Of these 3,150 subjects that were given a depressive symptom screening at a MEC, 450 subjects were missing physiological data either because of NHANES subsampling design of the laboratory components (for some laboratory-based measures, only a random subsample of the overall MEC-screen sample was tested) or because of ineligibility for the blood draw (Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS)). As a result, complete depression-screening data and complete measures of all physiological dysfunction components were available for 2,700 participants, 49.7% of those sampled age 60 years and older. We ultimately analyzed 2,405 (44.2% of initial sample) subjects after excluding those with incomplete data on additional covariates. Subjects who were excluded from our analysis because of missing physiological dysfunction or covariate data had significantly higher scores for global depressive symptoms, relative to our final sample ($p = 0.04$). In terms of other covariate characteristics, excluded subjects were more likely to be women (0.005), older ($p < 0.0001$), of non-white ethnicity ($p = 0.0005$), lower education ($p = 0.03$), and be taking antidepressant medication ($p = 0.02$).

Measurement of Physiological Dysfunction

The inclusion of measures of neuroendocrine hormones and sympathetic nervous system function such as cortisol and epinephrine is typically considered the gold standard in capturing the physiologic dysfunction underlying allostatic load (Dowd et al., 2009). Yet, multiple studies, including those based on NHANES, have employed summary scores of allostatic load that do not include neuroendocrine or sympathetic nervous system component

measures (Allsworth et al., 2005, Geronimus et al., 2006, Sabbah et al., 2008, Merkin et al., 2009, Kaestner et al., 2009). We created a score for physiological dysfunction from 10 biological and physical measures including: a ratio of urinary albumin to urinary creatinine, body mass index, white blood cell count, serum total bilirubin, systolic blood pressure, diastolic blood pressure, serum glycosylated hemoglobin, total cholesterol, resting heart rate, and triglyceride levels. These measures encompass cardiovascular function, glucose regulation, liver function, and renal function, similar to measures utilized in other studies employing a physiological dysfunction score (Allsworth et al., 2005, Geronimus et al., 2006, Merkin et al., 2009, Bird et al., 2009, Borrell et al., 2010).

Two versions of an overall scoring procedure were utilized, following both recent (Merkin et al., 2009) and original work (Seeman et al., 1997) on the allostatic load model. The first algorithm utilized clinically-relevant cutoffs for each biomarker and physical measure (Table 1) (Merkin et al., 2009). A physiological dysfunction score was assigned to each subject as a count of the number of markers on which a participant exceeded the clinically significant level, yielding a maximum score of 10. Clearly established clinical cutoffs could not be identified for white blood cell count and serum bilirubin measures; accordingly, the 75th percentile value for MEC sample subjects was used for these two components. This scoring method assumes that each component equally contributes to one's physiological dysfunction score and does not explicitly consider endocrine hormones such as cortisol, which were not available in NHANES.

To verify the robustness of potential associations, a second construction of physiological dysfunction was created based on percentiles(Seeman et al., 1997). We calculated quartiles from the survey- weighted distribution of each biomarker derived from the 2407 subjects with complete data. Similar to the first construction, a composite physiological dysfunction score was assigned to study subjects based on whether individuals exceeded the 75th percentile of each marker (Table 1).

Measurement of Depressive Symptoms

The depression screening portion of NHANES utilized questions from the nine-item Patient Health Questionnaire (PHQ-9)(Kroenke et al., 2001). The PHQ-9 is a self-reported depression assessment based on symptoms described in the DSM-IV. The depression assessment process consists of totaling the frequency responses of the nine questions such that 0 = "Not at all," 1 = "Several days," 2 = "More than half the days," and 3 = "Nearly everyday." It is estimated that the sensitivity and specificity of the PHQ in the identification of major depressive disorder are both 88% (relative to the gold standard, clinician-based diagnosis with the DSM-IV)(Kroenke et al., 2001), and this depressive symptoms inventory has been extensively validated(Kroenke et al., 2001, Martin et al., 2006).

We conducted a confirmatory factor analysis of individual items of the PHQ-9 to operationalize the (1) affective and (2) somatic dimensions of depression symptoms(Krause et al., 2010, de Jonge et al., 2007). We identified two factors using an oblique "Promax" rotation, which allows the two factors to freely correlate with each other and yields a simple structure that is easily interpretable(Kim and Mueller, 1978). Factor scores for affective and somatic dimensions were calculated using the unit-weighted scheme discussed by Grice(Thomson, 1939, Grice, 2001). This method entailed identifying survey items that load strongly on chosen factors (using a commonly accepted factor loading cutoff of 0.4)(Ford et al., 1986, Grice, 2001). The raw survey scores for these items (0–3 for each PHQ-9 item) were then summed for each respective factor.

In summary, our primary outcomes comprise the following continuous scores: global depressive symptoms (a standard PHQ-9 score), affective symptom factor scores, and

somatic symptom factor scores. In secondary analyses, we created a polytomous measure of global depressive symptoms and estimated a multinomial logistic regression model. This polytomous measure consisted of three categories of depression that have been previously proposed as a way of interpreting the clinical significance of symptoms (Kroenke et al., 2001): no depression to mild depression (score: 0–4), moderate to moderately severe depression (score: 5–14), and severe depression (score: 15+).

Covariates

Covariates comprised basic sociodemographic factors, potential confounding factors, and important predictors of depressive symptoms (based on prior literature and bivariate associations with depressive symptom severity). Basic sociodemographic factors included: age (continuous), sex, ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican American, other), educational attainment (college education or beyond, some college, high school or GED, and less than high school), and household income/poverty ratio (continuous). Plausible confounding variables and important predictors of depressive symptoms included: the presence of social/emotional support during difficult times (Yes or No), consuming at least 12 alcoholic beverages in any one year (Yes or No), performing leisure time physical activity (Yes or No), and antidepressant medication use within the prior month (Yes or No).

Statistical Analysis

We conducted probability-weighted, descriptive analyses of the distribution of covariate values across the three severity levels of global depressive symptoms. We used chi-squared tests to test for bivariate associations between covariates and depressive symptom severity.

The regression models focus on four primary outcomes variables: continuous global depressive symptoms, ordinal global depressive symptom severity (no-to-mild symptoms, moderate symptoms, and moderately severe to severe symptoms), continuous affective factor scores, and continuous somatic factor scores. Multinomial logistic regression of categorized global depressive symptoms was conducted because the results of this method would be more robust against nonlinearity than standard linear regression (Agresti, 2010). Affective factor and somatic factor scores were not transformed into ordinal variables and instead analyzed through linear regression because no clear, clinically-significant cutoffs were available.

We estimated a series of two nested linear regression models to examine the link between physiological dysfunction scores and depression symptom severity, while observing the effect of confounding on the association of interest. The two nested models comprise: (1) an initial model only with physiological dysfunction, sex, and age as predictors, (2) and a final model additionally adjusting for demographic and socioeconomic variables (ethnicity, educational attainment, and family income/poverty ratio), the presence of social support, alcohol consumption, self-reported physical activity level, and antidepressant use. The final analytic sample of 2,405 subjects was used in both the initial and final model to compare the impact of covariates on findings between different models. We also estimated associations between the individual, continuous components of the physiological dysfunction score with the global depressive symptoms score and the two depressive symptom factor scores, to examine which components might be the primary contributors to an association between the overall physiological dysfunction score and depressive symptoms. Multiple linear regression assumptions were graphically verified (Berry, 1993).

We also performed an imputation analysis to examine whether the excluded NHANES subjects that completed a MEC examination, yet did not have the complete laboratory data

required for our analysis (n = 450), would have substantially altered our effect estimates had they been included. We conducted multiple imputation using the EM-algorithm (Dempster et al., 1977) to generate 2,000 datasets of the 2,405 subjects from the final sample with an additional 450 subjects with imputed physiological dysfunction scores. Physiological dysfunction scores (clinical cut-off version only) were imputed from the global depressive symptom variable and all covariates used in modeling. We estimated the association between physiological dysfunction and overall depressive symptoms in fully adjusted models for each of these 2,000 datasets of 2,855 subjects (2,405 + 450), resulting in a distribution of 2,000 regression coefficients. From this distribution, an overall mean coefficient for the association of interest was calculated along with bootstrap 95% confidence intervals (using the 2.5 and 97.5 percentiles of the 2,000 imputed coefficients). We then compared this mean, imputed coefficient with the coefficient from our non-imputed sample of 2,405 subjects. This procedure was repeated for affective and somatic depressive symptoms as well.

Factor analysis of PHQ-9 items, descriptive statistics, and all multiple linear regression analyses were conducted with the "*survey*" package of R 2.12.0 (R Foundation for Statistical Computing, Vienna, Austria). The R factor analysis function utilizes a weighted maximum likelihood algorithm, accounting for complex survey design. Multinomial logistic regression was conducted with Stata10.0 (StataCorp, College Station, TX, USA) The complex survey design and probability weighting of NHANES was accounted for in all analyses.

RESULTS

Among all individuals in our final analysis sample of 2,405, 1,952 (81.2%) were classified as having no to mild depressive symptoms, 411 (17.1%) were classified as having moderate to moderately severe depressive symptoms, and 42 (1.7%) presented severe depressive symptoms (Table 2). The mean age was 69.9 years and comprised roughly equal proportions of men and women. The majority of subjects in the final sample classified themselves as White Non-Hispanic and, with the exception of age and ethnicity, all other covariates were associated with global symptom severity. Subjects with a greater severity of depressive symptoms tended to come from the adverse categories of each covariate (i.e., less educated, greater poverty, not receiving emotional support, history of alcohol consumption, did not pursue leisure time physical activities, and more likely to report taking antidepressants) (Table 2).

Factor loadings for each PHQ-9 item are presented in Table 3. Factor analysis model fit was verified and acceptable: RMSEA = 0.087. Four items contributed towards affective symptom factor scores, three items contributed towards somatic symptom factor scores and two PHQ-9 items did not contribute towards either factor score. Thus, the possible factor scores for each subject ranged from 0 – 12 and 0 – 9 for affective and somatic factors, respectively.

Physiological dysfunction scores based on clinical cutoffs ranged from 0 to 7, with a median score of 2 (i.e., having two biological or physical measures that exceeded a clinical-relevant value); the percentile-based physiological dysfunction score ranged from 0 to 9, also with a median of 2. These two constructions of physiological dysfunction were highly correlated (Spearman's $\rho = 0.78$, $p < 0.0001$).

Table 4 shows the results of nested linear regression models using physiological dysfunction scores (based on clinical cutoffs) to predict continuous global depressive symptoms, affective symptom factor scores, and somatic symptom factor scores, sequentially controlling for an additional set of covariates. In the model controlling only for age and sex,

greater physiological dysfunction was associated with increasingly severe global depressive symptoms: beta = 0.26 (95% CI = 0.16, 0.37), corresponding to a 0.26-point increase in the overall depressive symptom score for each unit increase in the physiological dysfunction score. Similarly, both affective and somatic depressive symptoms were positively associated with physiological dysfunction: beta = 0.098 (95% CI = 0.06, 0.13); beta = 0.13 (95% CI = 0.06, 0.19), respectively. The component measures driving these three associations were highly similar: body mass index, white blood cell count, glycosylated hemoglobin, resting heart rate, and triglyceride levels. In the fully adjusted models, physiological dysfunction remained positively and significantly associated with global, affective, and somatic depressive symptoms: beta = 0.23 (95% CI = 0.13, 0.32); beta = 0.076 (95% CI = 0.043, 0.11); beta = 0.12 (95% CI = 0.06, 0.18), respectively. Component measure associations from the initial model remained significant in the final models.

Multinomial logistic regression verified the positive association between physiological dysfunction (clinical cutoffs version) and global depressive symptoms. In a fully adjusted model, an increase in the physiological dysfunction score was associated with increased odds of having “moderate to moderately severe depression” (OR = 1.08, 95% CI = 1.001, 1.16) as well as “severe depression” (OR = 1.61, 95% CI = 1.36, 1.91), relative to the “no depression to mild depression” classification.

Linear regression coefficients were smaller in magnitude, yet interpretations were essentially unchanged in all cases when percentile-based physiological dysfunction scores were employed (results not shown); in fully-adjusted models, the associations with global, affective, and somatic depressive symptoms were: beta = 0.17 (95% CI = 0.07, 0.27); beta = 0.05 (95% CI = 0.02, 0.09); beta = 0.10 (95% CI = 0.04, 0.15), respectively.

Multiple imputation analysis produced a fully-adjusted mean coefficient of 0.21 (95% CI = 0.18 – 0.25) for the association between physiological dysfunction (clinical cutoffs version) and global depressive symptoms. This method provided estimates of 0.07 (95% CI = 0.06 – 0.09) and 0.11 (95% CI = 0.09 – 0.13) for affective and somatic symptoms, respectively.

DISCUSSION

Despite the high prevalence of clinically significant depressive symptoms among older adults, the etiology of these symptoms is less understood than the symptoms of middle-aged and young adults. However, it is well known that the etiology highly multifactorial, and psychological, social, and biological factors are all thought to play a role(Alexopoulos, 2005, Fiske et al., 2009). Allostatic load is one such model that has been previously suggested as a useful framework in which to study depression(McEwen, 2003, McEwen and Stellar, 1993, McEwen and Seeman, 1999, Seeman et al., 2009). Adaptation in the face of social or environmental demands over the lifespan, or allostasis, is thought to affect multiple organ systems, influencing the endocrine system, levels of immune system effectors, cardiovascular function, and metabolism(McEwen and Seeman, 1999, McEwen and Stellar, 1993, McEwen, 1998b, Seeman et al., 2010). As suggested by the allostatic load model, the dysfunction of these multiple biological systems may be associated with depressive symptoms(McEwen, 1998a, McEwen, 1998b).

We found a small but robust association between multisystem physiological dysfunction and global depressive symptoms. Although this is the first empirical study to examine the association between overall physiological dysfunction and different facets of depressive symptoms, results of prior studies examining individual components of our physiological dysfunction measure are consistent with our findings. For example, elevated levels of acute phase proteins, cytokines, and other markers of systemic inflammation have been

consistently linked with depressive symptoms in a dose-related fashion(Tiemeier, 2003, Howren et al., 2009, Kobrosly and van Wijngaarden, 2009). Cardiovascular disorders, specifically cerebrovascular pathologies such as stroke, as well as blood pressure dysregulation have also been linked with late-life depressive symptoms(Tiemeier, 2003, Burvill et al., 1995, Paterniti et al., 2000). A large, prospective study demonstrated that dysregulation of cholesterol and blood glucose was associated with depressive symptomatology in older adults(Mast et al., 2008). The allostatic load model describes how both hyperactivity and hypoactivity of the HPA axis could result in physiological dysfunction, and indeed both conditions have been associated with late-life depressive symptoms(Penninx et al., 2007).

We also noted associations between physiological dysfunction and specific dimensions of depressive symptoms: affective and somatic-clustered symptoms. However, our results do not lend support to the hypothesis that multisystem dysfunction might differentially influence these two symptom domains; both domains were both positively associated with our measure of physiological dysfunction and the component measures driving these associations appeared similar. Consistent with the literature (Tiemeier, 2003, Howren et al., 2009), markers of cardiovascular, metabolic, and immune function were associated with depressive symptoms. These conditions are often characterized by increased levels of inflammation; however, the pathophysiologic mechanisms underlying these associations remain uncertain. We found no relationship of depressive symptoms with markers of hepatic or renal function.

Several limitations of our analysis merit close attention. First, the present study employed a cross-sectional design. Therefore, although we originally hypothesized that neuroendocrine disruption and their clinical sequelae predispose individuals to depressive symptoms, we in fact cannot make claims as to the direction of the association between multisystem physiological dysfunction and depressive symptoms. For example, it has been suggested that neuroendocrine changes occurring as a result of depressive symptomatology may give rise to greater central adiposity, hypertension, and greater levels of blood sugar(Brown et al., 2004). Additionally, it has been shown that adults with depressive symptoms are vulnerable to declines in health-related behavior(Jones et al., 2009), which in turn may promote physiologic dysfunction. Our large, population-based cross-sectional study should be considered an important first step in a line of research elucidating these complex temporal relationships.

In addition, no biological measures of HPA axis functional status were available, the inclusion of which would have provided a more solid foundation for supporting the allostatic load model of depressive symptoms. However, because our analysis considers multiple systems, it may better encompass the allostatic load model of depressive symptoms as opposed to other studies that examine HPA axis function only.

Third, our measure of physiological dysfunction was built upon somewhat arbitrary cutoffs. We attempted to address this concern through the use a clinical and percentile-based of physiological dysfunction scores, both of which produced similar results. Although scores were constructed from such cutpoints, this had little impact on the ranking of physiological dysfunction scores among subjects.

Fourth, although we noted no differential association between physiological dysfunction and global, affective, and somatic depressive symptoms, we were unable to examine associations with any several depressive subtypes. Physiological dysfunction could be uniquely associated with atypical or melancholic depressive symptoms, as differences in HPA axis function have been noted between these depressive subtypes (Stewart et al., 2005). Future

research aimed at examining multisystem dysfunction among depressive subtypes may be useful.

Finally, concerns of missing data bias were raised, as we were unable to examine a sizable proportion of subjects due to missing physiological measure data. Multiple imputation analysis suggested that the exclusion of these subjects did not result in a meaningful bias as the imputed and observed point estimates were similar.

In conclusion, in this analysis we demonstrated an association between physiological dysfunction and depressive symptom severity. Additional longitudinal studies employing measures of HPA axis and autonomic nervous system function are warranted to confirm and expand upon these findings. Future research should also attempt to parse the intricate connections between personality traits, interpersonal relations, socioeconomic factors, and physiological dysfunction in relation to late-life depressive symptoms.

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Key points

1. We analyzed associations of multisystem physiologic dysfunction with multiple dimensions of depressive symptoms in a population-based sample of older adults
2. Greater physiological dysfunction scores were associated with depressive symptoms
3. Future longitudinal research should explore factors driving these associations

Table 1

Clinically-relevant and percentile-based cutoffs used to construct total physiological dysfunction composite score

Components of Physiological Dysfunction Score	Clinically-relevant Algorithm(Merkin et al., 2009)	Percentile-based Algorithm[b]
Ratio of Urinary Albumin/Creatinine(Levey et al., 2005)	> 30 mg/g	> 2.3 mg/g
Body Mass Index(National Heart Lung and Blood Institute, 1998)	> 25 kg/m^2	> 31.6 kg/m^2
White Blood Cell Count[a]	> 8.1×10^9 cells/L	> 8.1×10^9 cells/L
Serum Bilirubin[a]	> 0.9 mg/dL	> 0.9 mg/dL
Systolic Blood Pressure(2001)	> 140 mmHg	> 148 mmHg
Diastolic Blood Pressure(2001)	> 90 mmHg	> 78 mmHg
Serum Glycosylated Hemoglobin(Golden et al., 2003)	> 6.4%	> 6 %
Total Cholesterol(2001)	> 240 mg/dL	> 227 mg/dL
Resting Heart Rate(Seccareccia et al., 2001)	> 90 bpm	> 78 bpm
Triglyceride Count(2001)	> 200 mg/dL	> 200 mg/dL

[a] Established clinically-relevant cutoff could not be identified

[b] Accounting for complex survey design

Table 2

Frequencies of covariate values across categories of global depressive symptom severity in final sample (N = 2,405)

	No/Mild Depressive Symptoms (n = 1952)	Moderate/Moderately Severe Depressive Symptoms (n = 411)	Severe Depressive Symptoms (n = 42)	p-value[a]
Sex				
Female	882 (45.2%)	250 (60.8%)	26 (61.9%)	<0.0001
Male	1070 (54.8%)	161 (39.2%)	16 (38.1%)	
Age				
60–64	541 (27.7%)	123 (29.9%)	21 (50.0%)	0.30
65–69	418 (21.4%)	73 (17.8%)	7 (16.7%)	
70–74	381 (19.5%)	91 (22.1%)	8 (19.0%)	
75–79	279 (14.3%)	62 (15.1%)	3 (7.1%)	
80–84	278 (14.2%)	55 (13.4%)	2 (4.8%)	
85 +	55 (2.8%)	7 (1.7%)	1 (2.4%)	
Ethnicity				
NH White	1189 (60.9%)	251 (61.1%)	18 (42.9%)	0.60
NH Black	366 (18.8%)	66 (16.0%)	8 (19.0%)	
Mexican Am	249 (12.8%)	53 (12.9%)	10 (23.8%)	
Other	148 (7.6%)	41 (10.0%)	6 (14.3%)	
Education				
College +	392 (20.1%)	57 (13.9%)	5 (11.9%)	0.001
Some college	430 (22.0%)	75 (18.2%)	9 (21.4%)	
HS/GED	519 (26.6%)	103 (25.1%)	8 (19.0%)	
< HS	611 (31.3%)	176 (42.8%)	20 (47.6%)	
Income/Poverty Ratio				
5+ (less poverty)	355 (18.2%)	41 (10.0%)	3 (7.1%)	0.0001
4 – 5	146 (7.5%)	21 (5.1%)	0 (0%)	
3 – 4	239 (12.2%)	38 (9.2%)	1 (2.4%)	
2 – 3	389 (19.9%)	70 (17.0%)	6 (14.3%)	
1 – 2	567 (29.1%)	159 (38.7%)	15 (35.7%)	
< 1 (more poverty)	256 (13.1%)	82 (20.0%)	17 (40.5%)	
Emotional Support				
Yes	1809 (92.7%)	363 (88.3%)	33 (78.6%)	0.0005
No	143 (7.3%)	48 (11.7%)	9 (21.4%)	
Alcohol Consumption				
No	650 (33.3%)	169 (41.1%)	17 (40.5%)	0.02
Yes	1302 (66.7%)	242 (58.9%)	25 (59.5%)	

	No/Mild Depressive Symptoms (n = 1952)	Moderate/Moderately Severe Depressive Symptoms (n = 411)	Severe Depressive Symptoms (n = 42)	p-value[a]
Leisure Time Physical Activity				
Yes	411 (21.1%)	73 (17.8%)	7 (16.7%)	0.015
No	1541 (78.9%)	338 (82.2%)	35 (83.3%)	
Antidepressant Use				
No	1802 (92.3%)	310 (75.4%)	27 (64.3%)	<0.0001
Yes	150 (7.7%)	101 (24.6%)	15 (35.7%)	

[a]Accounting for complex survey design

Table 3

Factor loadings of individual PHQ-9 items in final sample (N = 2,405)

PHQ-9 Item	Factor Loadings[a]	
	Affective	Somatic
1) Little interest or pleasure in doing things[b]	0.41	0.25
2) Feeling down, depressed, or hopeless[b]	0.60	0.10
3) Trouble falling or staying asleep, or sleeping too much[c]	−0.05	0.55
4) Feeling tired or having little energy[c]	−0.10	0.81
5) Poor appetite or overeating[c]	0.04	0.45
6) Feeling bad about yourself—or that you are a failure or have let yourself or your family down[b]	0.81	−0.12
7) Trouble concentrating on things, such as reading the newspaper or watching television	0.39	0.18
8) Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0.38	0.14
9) Thoughts that you would be better off dead, or of hurting yourself in some way[b]	0.57	−0.15

[a] Accounting for complex survey design

[b] Survey items contributing towards affective symptom factor scores (bold font)

[c] Survey items contributing towards somatic symptom factor scores (italicized font)

Table 4

Results of multiple regression models predicting global, affective, and somatic depressive symptoms from physiological dysfunction (based on clinical cutoffs), and other covariates (N= 2,405)

		Global Depressive Symptoms	Affective Symptom Factor Score	Somatic Symptom Factor Score
		Coefficient (95% CI)[a,b]	**Coefficient (95% CI)[a,b]**	**Coefficient (95% CI)[a,b]**
Initial Model[c]	Physiological Dysfunction	**0.26 (0.2, 0.4)**	**0.098 (0.06, 0.1)**	**0.13 (0.06, 0.2)**
	Ratio of Urinary Albumin/Creatinine	0.29 (−0.2, 0.7)	0.10 (−0.1, 0.3)	0.18 (−0.1, 0.5)
	Body Mass Index	**0.045 (0.02, 0.07)**	**0.016 (0.006, 0.03)**	**0.022 (0.008, 0.04)**
	White Blood Cell Count	**0.076 (0.02, 0.1)**	0.020 (−0.0006, 0.04)	**0.045 (0.01, 0.08)**
	Serum Bilirubin	−0.24 (−0.7, 0.3)	−0.051 (−0.2, 0.1)	−0.19 (−0.5, 0.1)
	Systolic Blood Pressure	−0.0036 (−0.01, 0.004)	−0.00029 (−0.003, 0.002)	−0.0022 (−0.006, 0.002)
	Diastolic Blood Pressure	−0.0033 (−0.009, 0.003)	0.00016 (−0.004, 0.004)	**−0.0047 (−0.008, −0.001)**
	Serum Glycosylated Hemoglobin	**0.28 (0.10, 0.5)**	**0.11 (0.03, 0.2)**	**0.13 (0.04, 0.2)**
	Total Cholesterol	−0.0011 (−0.006, 0.004)	−0.000031 (−0.002, 0.002)	−0.0011 (−0.003, 0.001)
	Resting Heart Rate	**0.027 (0.007, 0.05)**	**0.011 (0.003, 0.02)**	**0.013 (0.0003, 0.03)**
	Triglyceride Count	**0.0021 (0.001, 0.003)**	**0.00068 (0.0002, 0.001)**	**0.0013 (0.0008, 0.002)**
Final Model[d]	Physiological Dysfunction	**0.23 (0.1, 0.3)**	**0.076 (0.04, 0.1)**	**0.12 (0.06, 0.2)**
	Ratio of Urinary Albumin/Creatinine	0.24 (−0.1, 0.6)	0.074 (−0.09, 0.2)	0.17 (−0.09, 0.4)
	Body Mass Index	**0.034 (0.011, 0.06)**	**0.012 (0.002, 0.02)**	**0.018 (0.003, 0.03)**
	White Blood Cell Count	**0.057 (0.006, 0.1)**	**0.012 (−0.005, 0.03)**	**0.038 (0.009, 0.07)**
	Serum Bilirubin	0.16 (−0.3, 0.6)	0.13 (−0.04, 0.3)	−0.044 (−0.4, 0.3)
	Systolic Blood Pressure	−0.0049 (−0.01, 0.002)	−0.0012 (−0.004, 0.001)	−0.0023 (−0.006, 0.002)
	Diastolic Blood Pressure	−0.0033 (−0.009, 0.003)	0.00017 (−0.004, 0.004)	**−0.0047 (−0.008, −0.0009)**
	Serum Glycosylated Hemoglobin	**0.21 (0.03, 0.4)**	0.065 (−0.003, 0.1)	**0.12 (0.02, 0.2)**
	Total Cholesterol	−0.00088 (−0.005, 0.003)	−0.000058 (−0.002, 0.001)	−0.000089 (−0.003, 0.001)
	Resting Heart Rate	**0.020 (0.002, 0.04)**	**0.0073 (0.00002, 0.01)**	0.011 (−0.001, 0.02)
	Triglyceride Count	**0.0018 (0.0009, 0.002)**	**0.00050 (0.00008, 0.0009)**	**0.0013 (0.0008, 0.002)**

[a] Accounting for complex survey design

[b] Bold coefficients signify two-sided significance at 0.05 level

[c] Initial model covariates include: age and sex

[d] Final model covariates include: age, sex, ethnicity, educational attainment, family income/poverty ratio, social support, alcohol consumption, physical activity level, and antidepressant use