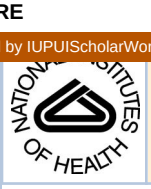

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Depressive Symptom Clusters as Predictors of 6-Year Increases in Insulin Resistance: Data from the Pittsburgh Healthy Heart Project

Tasneem Khambaty, M.S[1], **Jesse C. Stewart, Ph.D**[1], **Matthew F. Muldoon, MD, MPH**[2], and **Thomas W. Kamarck, Ph.D**[3]

[1]Department of Psychology, Indiana University-Purdue University Indianapolis (IUPUI), Indianapolis, IN

[2]Heart & Vascular Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA

[3]Department of Psychology, University of Pittsburgh, Pittsburgh, PA

Abstract

Objective—To examine longitudinal bidirectional associations between two depressive symptom clusters – the cognitive-affective and somatic-vegetative clusters – and insulin resistance, a marker of pre-diabetes.

Methods—Participants were 269 adults aged 50–70 years without diabetes enrolled in the Pittsburgh Healthy Heart Project, a prospective cohort study. At baseline and 6-year visits, participants completed the Beck Depression Inventory-II (BDI-II) and underwent a blood draw to quantify fasting insulin and glucose. We examined baseline BDI-II total, cognitive-affective, and somatic-vegetative scores as predictors of 6-year change in the homeostatic model of assessment (HOMA) score, an estimate of insulin resistance computed from fasting insulin and glucose. We also examined baseline HOMA score as a predictor of 6-year change in BDI-II total and subscale scores.

Results—Regression analyses, adjusted for demographic factors and baseline HOMA score, revealed that the baseline BDI-II somatic-vegetative score ($\beta = .14$, $p = .025$), but not the cognitive-affective ($\beta = .001$, $p = .98$) or total ($\beta = .10$, $p = .11$) scores, predicted 6-year HOMA change. This result persisted in models controlling for anxiety symptoms and hostility. Several factors were examined as candidate mediators; however, only change in body mass index (BMI) was a significant mediator ($p = .042$), accounting for 23% of the observed association. Baseline HOMA score did not predict 6-year change in BDI-II total or subscale scores (all ps >.56).

Conclusions—Among adults aged 50–70 years, the somatic-vegetative symptoms of depression (e.g., fatigue, sleep disturbance, and appetite changes) may worsen insulin resistance and increase diabetes risk, partly, by increasing BMI.

Corresponding Author: Jesse C. Stewart, Ph.D., Department of Psychology, Indiana University-Purdue University Indianapolis, 402 North Blackford Street, LD 100E, Indianapolis, IN 46202. Telephone: (317) 274-6761. Fax: (317) 274-6756. jstew@iupui.edu.

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Keywords

depression; symptom clusters; insulin resistance; homeostatic model of assessment (HOMA); type 2 diabetes; prospective study

Introduction

A growing body of evidence links depression and type 2 diabetes (1–3). Specifically, studies report that depressed adults have a 37–60% increased risk of developing diabetes than nondepressed adults (4, 5), which may partially explain the elevated cardiovascular disease risk in this population (6). In addition, individuals with diabetes exhibit a 15–24% increased risk of developing depression compared to the general population (5, 7). Although not well understood, both behavioral and physiologic mechanisms have been proposed as potential explanations of this bidirectional relationship. For instance, the poor health behaviors (2) and the neuroendocrine (8) and inflammatory (9) activation associated with depression could promote the development of diabetes (10). In the other direction, a sense of threat or loss following a diabetes diagnosis and the high self-management burden of the condition could increase the risk of depression (5).

Recent investigations have also tested whether this association is present in pre-diabetes, as identified by the sentinel risk marker of insulin resistance. Insulin resistance occurs when peripheral insulin receptors exhibit decreased sensitivity to insulin, leading to reduced glucose uptake in fat, muscle, and liver tissue, and consequently, increased glucose levels in the blood stream (11). In a recent meta-analysis of 18 studies, a small but significant association (d = .19) between depressive symptom severity and insulin resistance was found (12). A major limitation, however, was that 17 of 18 studies used a cross-sectional design. The sole prospective study examined one direction of the depression-insulin resistance relationship, finding that depressive symptom severity was associated with the average of the baseline and 3-year homeostatic model of assessment (HOMA) scores but not with 3-year HOMA change (13). Due to the lack of prospective studies, it is not clear whether (a) depressive symptoms contribute to the onset of insulin resistance or (b) insulin resistance promotes the development of depressive symptoms. Determining the directionality of this relationship could have significant implications. If (a) is supported, treating depression in patients at greater diabetes risk might prevent or delay the onset of this metabolic condition, whereas if (b) is supported, elevations in depressive symptoms among patients at greater diabetes risk might be a sign of subclinical disease progression.

In other literatures, researchers have also begun to compare the relative importance of depressive symptom clusters in predicting health outcomes, such as cardiovascular risk (14) and prognosis (15). Depression, a multidimensional construct, consists of affective (e.g., depressed mood), cognitive (e.g., concentration difficulties), behavioral (e.g., psychomotor retardation), and somatic (e.g., fatigue) symptom clusters (16). To our knowledge, no studies have examined whether particular depressive symptom clusters are stronger predictors or consequences of insulin resistance. Pinpointing the key clusters could help to elucidate the mechanisms underlying the depression-insulin resistance relationship (by increasing or

decreasing the plausibility of candidate mediators) and could help to maximize the potential diabetes benefits of depression treatment (by delivering interventions specifically targeting the key clusters).

To fill the aforementioned gaps in the literature, we examined data collected as part of the Pittsburgh Healthy Heart Project (PHHP), a 6-year prospective cohort study of healthy, adults aged 50–70 years (17). Our primary objective was to examine longitudinal bidirectional associations between two depressive symptom clusters – the cognitive-affective and somatic-vegetative clusters – and insulin resistance estimated by the HOMA score (18). We also examined whether any detected associations remained after adjustment for overlapping emotional factors. Because depression, anxiety, and hostility are moderately correlated (19–21) and have each been associated with insulin resistance in isolation (22, 23), it is not known whether the depressive symptoms-insulin resistance association exists independently of other emotional factors (24). Finally, we examined several behavioral (body mass index [BMI], smoking, alcohol intake, physical activity, and sleep duration) and physiologic factors (inflammatory markers) as mediators of any detected associations. These factors have been linked to both depressive symptoms and insulin resistance in past studies and have been hypothesized as candidate mechanisms underlying the depression-insulin resistance relationship (10, 11, 25).

Methods

Participants

Participants enrolled in the parent PHHP study were 464 healthy adults. The PHHP was approved by the University of Pittsburgh Institutional Review Board. Participants provided written informed consent and were paid $700 for attending all study visits. Details regarding participant recruitment and the inclusion/exclusion criteria are reported elsewhere (17, 26). Briefly, individuals were eligible if they were between the ages of 50 and 70 years; reported no history of chronic disease, bipolar disorder, or schizophrenia; and reported no use of medications with lipid-lowering, antihypertensive, or autonomic effects. Exceptions to the chronic disease exclusion criterion were that adults with a diabetes diagnosis who were not taking insulin and adults with mild to moderate rheumatoid arthritis were allowed to enroll in the PHHP.

The 296 adults (64% of those enrolled) who attended the follow-up visits approximately six years after the baseline visits were considered the eligible cohort for the present study. Participants who attended the follow-up visits were older [$t(462) = -2.08$, $p = 0.038$], more educated [$t(461) = -2.63$, $p = 0.009$], more likely to be White [$\chi^2(1, N=463) = 10.18$, $p < .001$], and had lower depressive symptom severity [$t(385) = -1.97$, $p = 0.049$] than those who did not attend these visits; however, group differences were not observed for sex or baseline HOMA scores. From the eligible cohort, we excluded 11 adults who had missing data for the depressive symptoms, glucose, or insulin variables at baseline or the 6-year follow-up. Of the remaining 285 participants, we excluded the four adults enrolled in the PHHP with a diabetes diagnosis but who were not taking insulin at baseline. We then excluded an additional 11 individuals who reported receiving a new diabetes diagnosis or taking a diabetes medication during the follow-up interval, as assessed at the 6-year medical

interview. For the remaining 270 participants, we examined skewness and kurtosis values of our depressive symptom and insulin resistance variables at baseline and follow-up. These values were all within the acceptable ranges (27) with one exception: the kurtosis value for baseline HOMA (15.04) was greater than 10. A single baseline HOMA value was found to be disconnected from the distribution; removing this case resulted in an acceptable kurtosis value (2.55). Consequently, this case was excluded from all analyses, leaving a final sample of 269 participants (see Table 1 for demographic characteristics).

Measures and Procedure

Overview—At baseline (1998–2000), participants attended 11 visits during a 5-month period: a medical screen, seven visits for ambulatory monitoring training and questionnaire assessments, one visit for reactivity testing, and two visits for ultrasound assessments. Approximately six years later (M = 6.3, SD = 0.2), participants attended six follow-up visits, during which they completed a medical update and other assessments similar to those completed at baseline.

Depressive symptoms—At the third baseline visit and third follow-up visit six years later, participants completed the Beck Depression Inventory-II (BDI-II; 18) on a computer. The BDI-II is a widely used self-report measure of depressive symptom severity. The measure consists of 21 items and has demonstrated high internal consistency, test-retest reliability, and construct validity (28, 29). In addition to calculating the baseline and 6-year total scores, we computed BDI-II subscale scores by summing the items loading on the two factors identified by Dozois and colleagues (29). Those researchers performed an exploratory factor analysis using maximum likelihood extraction with oblique rotation on a sample of 1,022 younger adults and identified two moderately correlated factors that accounted for 46% of the variance. The cognitive-affective factor consisted of Items 1 (sadness), 2 (pessimism), 3 (past failure), 5 (guilty feelings), 6 (punishment feelings), 7 (self-dislike), 8 (self-criticalness), 9 (suicidal thoughts), 13 (indecisiveness), and 14 (worthlessness), and the somatic-vegetative factor consisted of Items 4 (loss of pleasure), 10 (crying), 11 (agitation), 12 (loss of interest), 15 (loss of energy), 16 (changes in sleep), 17 (irritability), 18 (changes in appetite), 19 (concentration), 20 (tiredness-fatigue), and 21 (loss of interest in sex) (29). In our sample, the cognitive-affective and somatic-vegetative factors demonstrated adequate internal consistency (Cronbach's α = .66 and .69, respectively). We decided to use the results of Dozois et al. (29) instead of other factor analyses of the BDI-II (28, 30) for the following reasons: (a) their sample (presumably mentally and physically healthy, community-dwelling adults) more closely resembled ours than other samples (e.g., psychiatric or medical patients), (b) their analyses had methodological strengths, including utilizing a larger sample, cross-validating their results, and establishing that their factor structure was similar for men and women, and (c) we have used this approach in past analyses of the PHHP data (26, 31, 32) and want to maintain consistency across reports. We also calculated 6-year change scores by subtracting the baseline total and subscale scores from their corresponding follow-up scores.

Insulin Resistance—At the first baseline visit and the first follow-up visit six years later, participants underwent a blood draw between 8:30 AM and 11:30 AM. They were asked to

fast and to avoid caffeine for 12 hours prior to the start of their baseline visit, which occurred between 8:00 AM and 10:00 AM. If a participant indicated that the fasting instructions were not followed, the blood draw was rescheduled. To assess serum glucose and insulin, blood samples were collected in red-top Vacutainer tubes by standard venous phlebotomy, allowed to clot at room temperature for 40 minutes, and refrigerated for up to three hours until centrifuged at 4°C. Following centrifugation, serum aliquots were frozen at −20°C until assay within 30 days at the University of Pittsburgh Heinz Nutrition Laboratory. Fasting serum glucose was measured by standard colorimetry (33), and fasting serum insulin was measured by radioimmunoassay.

We computed baseline and 6-year HOMA scores from the corresponding insulin and glucose values using this formula: [(fasting insulin (uU/ml) * fasting glucose (mg/dl)/405] (18). Greater HOMA scores denote lower insulin sensitivity or higher insulin resistance (13). Estimates of insulin resistance from HOMA and the gold-standard euglycemic clamp method have found to correlate well with one another (Rs = 0.85–0.88; 34, 35). HOMA is often used as a measure of basal insulin resistance in epidemiologic studies and is appropriate for assessing change in insulin sensitivity over time (36). We calculated 6-year HOMA change scores by subtracting the baseline score from the follow-up score.

Other factors—We included several other factors as covariates in our analyses. These factors were assessed during the baseline visits through questionnaires, a blood draw, and anthropometric measurements. The demographic factors were: age (years), sex (0 = male, 1 = female), race/ethnicity (1 = White, 2 = Black, 3 = Asian, 4 = Hispanic, 5 = Other), and education level (1 = high school or less, 2 = technical school or some college, 3 = Bachelor's degree, 4 = Master's degree or higher). As only six individuals selected the Asian, Hispanic, or Other categories, the race/ethnicity variable was recoded to create a binary variable (0 = White, 1 = non-White).

Other negative emotional factors included were anxiety symptoms and hostility. At the third baseline visit, participants completed the Beck Anxiety Inventory (BAI; 37, 38), an established 21-item measure of anxiety symptom severity. At the fourth baseline visit, participants completed the Cook-Medley Hostility Scale (Ho Scale; 39), a questionnaire that measures several components of hostility, including cynicism, hostile attributions, hostile affect, aggressive responding, and social avoidance. We used the 27-item version of the Ho Scale instead of the 50-item version because this version has been shown to be a stronger predictor of health outcomes (39). Both the BAI and Ho Scales possess good psychometric properties (37, 40–42).

The behavioral candidate mediators were BMI, smoking status (0 = current nonsmoker, 1 = current smoker), daily alcohol intake, physical activity, and self-reported sleep duration. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Daily alcohol intake (g/day) was calculated using the quantity–frequency method (43). Physical activity was computed from participants' responses on the Paffenbarger Physical Activity Questionnaire (44). Specifically, the number of reported blocks walked and stairs climbed per day, and all reported activities (e.g., running, boxing, hiking, swimming etc.) were converted to kilocalories per week and then summed. Self-reported

sleep duration was assessed using Item 4 of the Pittsburgh Sleep Quality Index (45). We log transformed ($X_i + 1$) daily alcohol intake and physical activity variables to normalize the distributions by reducing positive skew.

Lastly, the physiologic candidate mediators were the inflammatory markers, C-reactive protein (CRP) and interleukin-6 (IL-6). To assess inflammatory markers, blood samples were collected in tubes with no additives, were stored at room temperature for 40 minutes, and then were refrigerated until they were centrifuged within three hours of collection to isolate serum. Serum aliquots were frozen at −70 °C until time of assay at the Laboratory for Clinical Biochemistry Research at the University of Vermont. CRP was measured with a BNII nephelometer using a particle-enhanced immunonephelometric assay (Dade Behring, Deerfield, IL), and IL-6 was measured using ultra-sensitive enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN). We excluded individuals with CRP ≥ 10 mg/L ($n = 13$), as levels above this value are likely due to acute infection or trauma and thus not indicative of chronic inflammation (46). We log transformed ($X_i + 1$) baseline CRP and IL-6 variables to normalize the distributions by reducing positive skew.

All behavioral and physiologic candidate mediators, with the exception of sleep duration, were assessed during the 6-year follow-up visits in a manner identical to the baseline visits. We calculated 6-year change in these candidate mediators by subtracting the baseline scores from their corresponding follow-up scores.

Data Analyses

To determine whether (a) baseline depressive symptoms predict 6-year change in HOMA score and (b) baseline HOMA score predicts 6-year change in depressive symptoms, we conducted two sets of linear regression analyses. In the first set, we constructed three models, with BDI-II total score, cognitive-affective score, and somatic-vegetative score as the independent variables in separate models and HOMA change score as the dependent variable. In each model, we also entered age, sex, race/ethnicity, education, and baseline HOMA score (demographics-adjusted models). In the second set, we constructed three additional models, with baseline HOMA score as the independent variable and BDI-II total change score, cognitive affective change score, and somatic-vegetative change score as the dependent variables in separate models. Each of these models also included age, sex, race/ethnicity, education, and the corresponding baseline BDI-II score (demographics-adjusted models).

For any observed relationships, we conducted three sets of additional analyses. First, we examined whether the observed relationship remained after adjustment for anxiety symptoms and hostility by adding BAI and Ho scores one at a time into the demographics-adjusted models. Second, we evaluated the influence of candidate mediators measured at baseline on any observed associations by entering baseline BMI, smoking, alcohol intake, physical activity, sleep duration, CRP, and IL-6 one at a time to the demographics-adjusted models. Third, we evaluated the influence of 6-year change in these candidate mediators. We could not examine change in smoking because only four participants quit smoking during follow-up. The 6-year change variables were entered one at a time to the demographics-adjusted models that also included the baseline candidate mediator variable.

For the last two sets of analyses, we computed Sobel tests (Aroian version) to assess whether these variables statistically mediated any observed relationships (47, 48). For significant mediators, the percent change in the effect size of any observed relationships after adjustment for the mediator was computed as $(B_{adjusted} - B_{unadjusted})/B_{unadjusted} \times 100$, where $B_{adjusted}$ is the unstandardized coefficient for the BDI-II variable from the model with the mediator, and $B_{unadjusted}$ is the same unstandardized coefficient from the model without the mediator. All analyses were performed using SPSS statistical software (version 20).

Results

As shown in Table 1, participants in our sample were older, were predominantly white, and had higher education levels. HOMA, BDI-II total, and somatic-vegetative scores increased significantly from baseline to 6-year follow-up (*p*s < .001), while the cognitive-affective score did not ($p = .069$).

Depressive symptoms as predictors of 6-year change in HOMA score

Results of the demographic-adjusted models revealed that neither the BDI-II total score ($p = .11$) nor the cognitive-affective score ($p = .98$) predicted changes in HOMA over time (Table 2). In contrast, the somatic-vegetative score did predict 6-year increases in the HOMA score ($\beta = .14$, $p = .025$). None of the demographic variables included in this model were associated with HOMA change (all *ps* > .11). Table S1 (Supplemental Digital Content 1) presents the unadjusted correlations between the baseline depressive symptom variables and their change scores and the baseline glucose, insulin, and HOMA scores and their change scores.

The somatic-vegetative score remained predictive of 6-year increases in HOMA when the BAI score (somatic-vegetative score: $\beta = .18$, $p = .009$; BAI total: $\beta = -.10$, $p = .13$) and the Ho score (somatic-vegetative score: $\beta = .14$, $p = .027$; Ho total: $\beta = -.01$, $p = .89$) were added to separate models, although neither anxiety symptoms nor hostility predicted HOMA change. These results indicate that the association between the somatic-vegetative symptoms and HOMA change is independent of comorbid anxiety symptoms and hostility.

Analyses examining the influence of baseline candidate mediators on the observed association revealed that the somatic-vegetative score remained predictive of 6-year increases in HOMA when BMI ($\beta = .16$, $p = .008$), smoking status ($\beta = .14$, $p = .024$), alcohol intake ($\beta = .15$, $p = .018$), and sleep duration ($\beta = .14$, $p = .019$) were entered, and it fell short of significance when physical activity ($\beta = .10$, $p = .11$), CRP ($\beta = .12$, $p = .069$), and IL-6 ($\beta = .12$, $p = .051$) were entered one at a time to the demographic-adjusted models. Sobel tests indicated that none of the baseline candidate mediators statistically mediated the observed relationship (all *ps* > .32).

A similar set of analyses examining the influence of 6-year change in the candidate mediators indicated that that the somatic-vegetative score remained predictive of 6-year increases in HOMA when BMI change ($\beta = .12$, $p = .039$), alcohol intake change ($\beta = .15$, $p = .019$), and CRP change ($\beta = .13$, $p = .044$) were entered, and it fell short of significance when physical activity change ($\beta = .12$, $p = .062$) and IL-6 change ($\beta = .11$, $p = .10$) were

entered one at a time into the demographics-adjusted model that also included the baseline candidate mediator. There was no evidence of statistical mediation by any of these variables (all *p*s for Sobel tests > .19) with the exception of BMI change ($z = 2.03$, $p = .042$). Adjusting for BMI change reduced the magnitude of the association between the somatic-vegetative score and HOMA score by 23%. Because the somatic-vegetative score was positively related to BMI change ($\beta = .14$, $p = .018$) and BMI change was positively related to HOMA change ($\beta = .25$, $p < .001$), these results suggest that increases in BMI partially explain the link between the somatic-vegetative symptoms and increases in HOMA score over time.

HOMA score as predictor of 6-year change in depressive symptoms

Table 3 shows the results of demographic-adjusted models examining HOMA score as a predictor of 6-year change in the depressive symptom variables. These analyses revealed that baseline HOMA score did not predict 6-year change in the BDI-II total score ($p = .70$), the cognitive-affective score ($p = .98$), or the somatic-vegetative score ($p = .56$). None of the demographic variables included in these models was associated with any of the depressive symptom variables (all *ps* > .095).

Discussion

The primary objective of the present study was to examine the longitudinal bidirectional associations between two depressive symptom clusters and insulin resistance. In this sample of healthy adults aged 50–70 years, the somatic-vegetative cluster, but not the cognitive-affective cluster, predicted increases in a well-established estimate of insulin resistance, the HOMA score, over a 6-year period. In the other direction, insulin resistance at baseline did not predict increases in either the cognitive-affective or the somatic-vegetative clusters over the follow-up period. Total depressive symptom severity was unrelated to insulin resistance in either direction. The prospective association between the somatic-vegetative symptoms and 6-year increases in insulin resistance was independent of the overlapping emotional factors of anxiety symptoms and hostility. Several behavioral and physiologic factors were examined as candidate mediators; however, only BMI change was a significant mediator, accounting for almost one quarter of the association of somatic-vegetative symptoms with insulin resistance increases. Taken together, these results suggest that the somatic-vegetative symptoms of depression may worsen insulin resistance and increase diabetes risk, in part, by increasing BMI.

While there exist several cross-sectional studies on the association between depressive symptoms and insulin resistance, only two have examined this relationship longitudinally. In the depressive symptoms-to-insulin resistance direction, Everson-Rose et al. (13) found that elevated depressive symptoms were associated with a higher average HOMA score over a 3-year period, but not with increases in HOMA score over time, as was found in the present study. This inconsistent result may be due to dissimilar sample characteristics; that study used a sample of middle-aged women. In the insulin resistance-to-depressive symptoms direction, Lawlor et al. (49) followed 2,203 middle-aged British men over a 14-year period. Consistent with our results, these researchers found that insulin resistance at baseline did not

predict depressive symptoms 5, 10, or 14 years later. Our results also align with recent meta-analytic findings. Kan et al. (12) reported a small association (d = .19) between depression and insulin resistance, which was attenuated in analyses adjusted for body weight. An important caveat, however, is that this meta-analysis almost exclusively included cross-sectional studies and, therefore, cannot speak to the directionality of this relationship. Our findings add to this literature (a) by suggesting a direction for this relationship (i.e., depressive symptoms to insulin resistance) and (b) by indicating that the somatic-vegetative cluster may be largely responsible for this prospective link.

What factors might explain why the somatic-vegetative cluster of depressive symptoms, but not the cognitive-affective cluster, predicted increases in insulin resistance over time? One possibility is that the somatic-vegetative symptoms – such as fatigue, sleep disturbance, and appetite changes – contribute more to deleterious physical activity and dietary behaviors than do the cognitive-affective symptoms, resulting in a sedentary lifestyle, high caloric intake, and ultimately obesity. A consequence of obesity, particularly central adiposity, is the release of excess cortisol, which increases glucose production and can contribute to insulin resistance (10). Another consequence of obesity is increased release of inflammatory markers, a key component in the pathogenesis of insulin resistance (50), from visceral adipose tissue. Our finding that BMI change was a partial mediator of the association between the somatic-vegetative symptoms and 6-year increases in insulin resistance is consistent with this first possibility. A second possibility involves activation of the innate immune system via pathways other than increased adiposity, such as depression-related hypothalamic-pituitary-adrenal axis dysregulation (51) or autonomic dysfunction (52). Individuals with depressive disorders or elevated symptoms exhibit higher levels of inflammatory markers relative to nondepressed individuals, independent of BMI (25). Moreover, studies have reported that the depression-inflammation association is driven primarily by the somatic symptoms (31, 53). Our finding that inflammatory markers (baseline level or 6-year change) were not mediators conflicts with this second possibility; however, we examined only two markers of systemic inflammation, CRP and IL-6.

A third possibility is that somatic-vegetative cluster predicted increases in insulin resistance because these symptoms are due to a condition other than subsyndromal depression that also promotes insulin resistance, such as insomnia, sleep apnea, or another age-related condition (54, 55). The low depressive symptom scores in our sample increase the likelihood that these symptoms may be signs of another condition, at least in some individuals. It is worth noting, however, that the somatic-vegetative score remained predictive of 6-year increases in HOMA after adjustment for baseline sleep duration and that PHHP participants were generally free of chronic conditions at enrollment. A final possibility is that methodological factors may have contributed to our results. Older adults are more likely to report somatic versus cognitive symptoms of depression, perhaps due to a reporting bias or a difference in the phenomenology of depression in this population (56). In line with these findings, the mean and standard deviation at baseline were greater for the somatic-vegetative subscale (M = 2.83, SD = 2.79) than the cognitive-affective subscale (M = 1.04, SD = 1.65). This increased variability could be partially responsible for the greater predictive utility of the somatic-vegetative subscale.

We did not find a prospective relationship between insulin resistance and change in depressive symptoms over time. One potential explanation for this finding is the "psychological burden hypothesis" (57), which posits that the awareness and burden of being diagnosed with and managing a chronic condition may result in higher levels of depressive symptoms (7). Accordingly, adults who have insulin resistance but who have not yet been diagnosed with diabetes would not experience this burden and, consequently, may not exhibit elevated depressive symptoms. In support of this notion, a recent meta-analysis found that individuals with impaired glucose metabolism and undiagnosed diabetes experienced rates of depression similar to individuals with normal glucose metabolism (7). In contrast, individuals with previously diagnosed type 2 diabetes experienced increased rates of depression compared to individuals with either undiagnosed diabetes or impaired glucose metabolism (7).

In addition to its strengths (e.g., prospective design, validated measures of depressive symptoms and insulin resistance, and bidirectional examination of the key association), limitations of our study should be noted. First, due to an oversight in constructing the computerized version of the BDI-II, the time frame for rating the severity of symptoms was erroneously entered as "during the past week" (the time frame for the original BDI), rather than "the past 2 weeks" (the time frame for the BDI-II). The likely result of this oversight, however, was that the true BDI-II score was underestimated, given that individuals tend to score lower on the original BDI than on the BDI-II (29). The subsequent decrease in the variability of the BDI-II scores may have artificially weakened the relationship between depressive symptoms and 6-year HOMA change. Second, given that our sample was fairly homogeneous, consisting of healthy, predominantly White older adults, our results may not generalize to younger populations, older populations with chronic medical conditions, or other racial groups.

Overall, we found that (a) greater somatic-vegetative symptoms of depression (e.g., fatigue, sleep disturbance, and appetite changes) predict increases in insulin resistance over time and (b) increases in BMI partially mediate this relationship. Our results suggest that adults aged 50–70 years experiencing these symptoms may be at an increased risk of developing insulin resistance and, subsequently, type 2 diabetes. These findings contribute to our yet limited knowledge of the pathways underlying the depression-diabetes relationship and, if replicated in future studies, would support the development and testing of interventions targeting the somatic-vegetative symptoms to prevent insulin resistance and type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acronyms

HOMA	Homeostatic Model of Assessment
BDI-II	Beck Depression Inventory-II
PHHP	Pittsburgh Healthy Heart Project
Ho scale	Cook-Medley Hostility Scale
BAI	Beck Anxiety Inventory
CRP	C-reactive protein
IL-6	interleukin-6
BMI	body mass index

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Table 1

Characteristics of Participants

Variable	Baseline	6-Year Follow-up
Demographic factors		
Age, years	60.7 (4.6)	---
Sex, % female	55.0	---
Race/ethnicity, % non-White	14.1	---
Education level, %		
High school or less	22.3	---
Technical school or some college	25.7	---
Bachelor's degree	25.7	---
Master's degree or higher	26.4	---
Depressive symptom variables		
BDI-II Total	3.8 (3.9)	5.1 (5.1)
Baseline BDI-II Cognitive-Affective Cluster	1.0 (1.6)	1.3 (2.3)
Baseline BDI-II Somatic-Vegetative Cluster	2.8 (2.8)	3.8 (3.4)
Insulin resistance variables		
Glucose, mg/dl	90.3 (8.2)	99.1 (13.8)
Insulin, uU/ml	11.2 (4.3)	13.2 (6.2)
HOMA score	2.5 (1.1)	3.3 (1.9)
Other negative emotional factors		
Beck Anxiety Inventory (possible range: 0–63; *N* = 268)	5.0 (4.7)	---
Cook-Medley Hostility Scale (possible range: 0–27; *N* = 268)	8.0 (4.1)	---
Candidate mediators		
Body mass index, kg/m^2	27.5 (4.6)	27.8 (4.8)
Smoking status, % current smokers	5.6	4.1
Daily alcohol intake, g/day (6-year follow-up: *N* = 265)	6.5 (9.8)	11.9 (16.8)
Physical activity, kilocalories/week (Baseline: *N* = 266; 6-year follow-up: *N* = 259)	6497.6 (15400.7)[a]	6918.9 (9488.0)[b]
Self-reported sleep duration, hours	6.9 (1.1)	---
Serum CRP, mg/L (Baseline: *N* = 247; 6-year follow-up: *N* = 238)	2.1 (1.9)	1.7 (1.8)
Serum IL-6, pg/ml (Baseline: *N* = 260; 6-year follow-up: *N* = 257)	1.9 (1.6)	2.8 (2.5)

Note. *N* = 269, except where otherwise indicated. Continuous data are presented as mean (SD), and categorical data are presented as a percentage. BDI-II = Beck Depression Inventory-II; CRP = C-reactive protein; HOMA = Homeostatic Model of Assessment; IL-6 = interleukin-6.

[a] 219,079 kilocalories/week is an extreme data point (next highest value is 61,339 kilocalories/week). The median value for physical activity was 3088.0 kilocalories/week. Because either inclusion or exclusion of this data point necessitated log transformation to reduce positive skew and led to the same pattern of results, it was included in the baseline physical activity analysis.

[b] 76,921 kilocalories/week is an extreme data point (next highest value is 48,794 kilocalories/week). The median value for physical activity was 3452.8 kilocalories/week. Because either inclusion or exclusion of this data point led to the same pattern of results, it was included in the 6-year change physical activity analysis.

Table 2

Regression Analyses Examining Depressive Symptoms as Predictors of 6-year Change in HOMA Score

	Demographics-adjusted Models[a]					
	B	**SE B**	**β**	**R^2**	**ΔR^2**	**ΔF**
Baseline BDI-II Total	.04	.03	.10	.02	.01	2.56
Baseline BDI-II Cognitive-Affective Score	.001	.06	.001	.01	.00	.00
Baseline BDI-II Somatic-Vegetative Score	.08	.03	.14*	.03	.02	5.07

Note. N = 269. BDI-II = Beck Depression Inventory-II; HOMA = Homeostatic Model of Assessment.

[a] Adjusted for age, sex, race/ethnicity, education, and baseline HOMA score.

* $p < .05$

Table 3

Regression Analyses Examining HOMA Score as a Predictor of 6-year Change in Depressive Symptoms

	Demographics-adjusted Models[a]					
	B	**SE B**	***β***	**R^2**	**ΔR^2**	**ΔF**
BDI-II Total Score Change						
Baseline HOMA Score	.10	.25	.02	.09	.00	.14
BDI-II Cognitive-Affective Score Change						
Baseline HOMA Score	.004	.12	.002	.10	.00	.001
BDI Somatic-Vegetative Score Change						
Baseline HOMA Score	.10	.17	.03	.15	.001	.34

Note. N = 269. BDI-II = Beck Depression Inventory-II; HOMA = Homeostatic Model of Assessment.

[a] Adjusted for age, sex, race/ethnicity, education, and respective baseline BDI-II score

* $p < .05$