Depressive Symptoms and the Risk of Type 2 Diabetes

The Atherosclerosis Risk in Communities study

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OBJECTIVE — The goal of this study was to determine whether depressive symptoms predict type 2 diabetes.

RESEARCH DESIGN AND METHODS — We analyzed data on depressive symptoms (including recent fatigue, sleep disturbance, feelings of hopelessness, loss of libido, and increased irritability) in a longitudinal, biracial cohort study of 11,615 initially nondiabetic adults aged 48–67 years, who were subsequently followed for 6 years for the development of type 2 diabetes.

RESULTS — At baseline, depressive symptoms were positively associated with BMI, fasting insulin, systolic blood pressure, caloric intake, physical inactivity, and current smoking (all $P <$ 0.05). In prospective analyses, after adjusting for age, race, sex, and education, individuals in the highest quartile of depressive symptoms had a 63% increased risk of developing diabetes compared with those in the lowest quartile (relative hazard [RH] 1.63, 95% CI 1.31–2.02). This relation persisted after adjustment for stress-associated lifestyle factors (smoking, physical activity, caloric intake, and adiposity) (1.28, 1.02–1.60) and metabolic covariates (fasting insulin and glucose, lipids, blood pressure, and adiposity) (1.38, 1.10–1.73).

CONCLUSIONS — In this cohort, depressive symptoms predicted incident type 2 diabetes. This relation is only partially explained by demographic, metabolic, and lifestyle factors. Possible neuroendocrine mediators of the stress-obesity-diabetes relationship require further evaluation in prospective cohort studies that use an established tool to assess depression and incorporate neurohormonal measurements.

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There has been a growing interest in depression as a novel risk factor for the development of type 2 diabetes as several studies have demonstrated that the presence of depressive symptoms is predictive of incident type 2 diabetes (1,2). Possible mechanisms include the influence of depressive symptoms on behaviors, such as physical activity, diet, and adherence to treatment recommendations (3–7), or their influence on the activity of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (8–13). Similar mechanisms have been proposed for parallel observations regarding depressive symptoms as predictors of coronary heart disease (14). Previous epidemiological studies of psychological risk factors as predictors of diabetes, however, have been limited by small sample sizes, limited physiological data, and reliance on self-report of diabetes measures (1,2).

The Atherosclerosis Risk in Communities (ARIC) study is an attractive study in which to evaluate this relationship because data from standardized measurements are available on clinical outcomes, such as type 2 diabetes, and on depressive symptoms (as captured by a Vital Exhaustion Questionnaire) in a large, biracial, community-based cohort of middle-aged adults who were followed over a 6-year period. Therefore, we conducted a prospective analysis of depressive symptoms as predictors of type 2 diabetes in middle-aged adults in ARIC. Because ARIC has data on physiological and behavioral factors, we were also able to explore obesity, lifestyle factors, and markers of the metabolic syndrome as potential explanatory factors and/or confounders of the relationship.

RESEARCH DESIGN AND METHODS

Study population

The ARIC cohort is a sample of 15,972 men and women ages 45–64 years who were recruited from 1987 through 1989 from four U.S. communities. These communities comprise Washington County, Maryland, Forsyth County, North Carolina, the city of Jackson, Mississippi, and several suburbs of Minneapolis, Minnesota. The ARIC study was designed to assess the etiology and natural history of atherosclerosis (15). Participants were evaluated at four visits spaced 3 years apart with the first examination (visit 1) occurring between 1987 and 1989, the second examination (visit 2) occurring between 1990 and 1992, the third examination (visit 3) occurring between 1993 and 1995, and the fourth examination

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; HPA, hypothalamic-pituitary-adrenal.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

(visit 4) occurring between 1996 and 1998.

Exposure

Self-reported depressive symptoms were assessed at visit 2 (1990–1992) using a 21-item questionnaire on Vital Exhaustion developed by Appels et al. (16). The Vital Exhaustion Scale was developed in the Netherlands and has been found to be associated with subsequent myocardial infarction (16). The correlation of vital exhaustion and depression, measured by the Beck Depression Inventory, is 0.62 (17). Vital exhaustion is scored on a scale of 0–42 and is characterized by a state of fatigue, lack of energy, feelings of hopelessness, loss of libido, and increased irritability (see APPENDIX). Loss of self-esteem and feelings of guilt are not measured. Affirmative answers are coded as 2, "don't know" responses are coded as 1, and negative answers are coded as 0 (except for two questions, for which the scoring is reversed) (16). The questions on the vital exhaustion scale were classified a priori, based on an existing framework (18), into three categories: *1*) vegetative depressive symptoms (fatigue, sleep pattern, energy, concentration); *2*) nonvegetative depressive symptoms (crying spells, hopelessness, irritability, enjoyment of sex, suicidality); and *3*) functional depressive symptoms (coping, productivity) (see APPENDIX).

Outcome: type 2 diabetes

Individuals were classified as having diabetes if they met any of the following criteria: fasting serum glucose levels ≥7.0 mmol/l, nonfasting serum glucose ≥11.0 mg/dl, current self-reported use of medications prescribed to treat diabetes (e.g., insulin or sulfonylureas), or a positive response to the question "Has a doctor ever told you that you had diabetes?" Study participants who met any of these criteria at visit 1 or visit 2 were considered to have prevalent diabetes and were excluded from the analysis. Individuals who met any of these criteria at visits 3 and 4 were considered to have incident diabetes.

Covariates

A physical examination was performed on each participant at visit 2 between 1990 and 1992 to ascertain cardiovascular conditions and to measure risk factors (15). For these analyses, visit 2 is considered the "baseline examination." Participants were asked to fast for 12 h and actual fasting times were recorded. Venipuncture was performed in the morning using a 21-gauge butterfly needle with the participant seated. After standardized processing at the clinical site, samples were aliquoted, frozen at −70°C, and shipped on dry ice to the appropriate ARIC central laboratory. Glucose was measured using the hexokinase method, and insulin was measured by radioimmunoassay (125-I Insulin 100 test kit; Cambridge Medical Diagnostics, Billerica, MA). Insulin was only measured at visit 1 (1987–1989). Total cholesterol and triglycerides were measured using enzymatic methods. HDL cholesterol was measured after dextran magnesium precipitation of apolipoprotein B–containing lipoproteins (19).

Anthropometry was performed in the fasting state with the urinary bladder empty. Participants wore lightweight, nonconstricting underwear and scrub suits. Height (without shoes) was measured using a wall-mounted ruler. Weight was measured using a balance scale (Detecto, model #437), which was zeroed daily (19). Waist circumference was measured at the level of the umbilicus. Hip girth was measured at the level of maximal protrusion of the gluteal muscles (19).

Blood pressure was measured in the right arm after the participant had been seated for 5 min, using a random-zero sphygmomanometer and an appropriately sized cuff. Three measurements were taken; the mean of the second and third measurements was used to characterize blood pressure at the visit.

Self-reported cigarette smoking was assessed by a 12-item questionnaire. Responses permitted coding of smoke status as current, ever, and never smokers. Physical activity was assessed by interview using a questionnaire developed by Baecke et al. (20), including 16 items about usual exertion. An index for physical activity in sports was derived at visit 1, ranging from a score of 1 (low) to 5 (high). Dietary energy intake was assessed using an interviewer-administered, modified version of the 61-item food frequency questionnaire developed by Willett et al. (21). At visit 1 (1987–1989), medication usage in the 2 weeks preceding the examination was determined by having participants bring their medications to the field center to be recorded and coded by study personnel certified to perform this function. Educational level was ascertained at visit 1 (1987–1989) by asking, "What is the highest grade or year of school you have ever completed, including trade or vocational school or college?" Education was categorized as ≤high school or >high school.

Statistical analysis

For this study, ARIC participants were excluded from consideration if they had diabetes at either the first or second visit (n = 2,636), if they were missing data regarding diabetes diagnosis at visit 2 (n = 1,209), if they were missing data on any response to the vital exhaustion questionnaire (n = 284), or if they reported race as other than black or white (n = 48). This left a study population of 11,615 individuals without prevalent diabetes for the main analyses.

Depressive symptom scores were divided into quartiles because they were not normally distributed in the study population. Incidence rates of diabetes were calculated for each quartile of depressive symptoms using a person-years approach. Because the primary outcome of incident diabetes was assessed every 3 years, for those participants in whom incident diabetes was diagnosed, person-years were calculated as the sum of the known disease-free period plus one-half of the interval between the last visit date without diabetes and the date of the visit in which the diagnosis was made. For those participants without diabetes, person-years were calculated from baseline to the last visit date. The relative hazards (RH) (and 95% CI) of developing diabetes for categories of depressive symptoms were calculated using Cox proportional hazards regression models (22).

To explore potential mechanisms explaining the relation between depressive symptoms and diabetes, a series of multivariate models were constructed. In the base models assessing the association between depressive symptoms and diabetes, adjustments were made for age, race, ARIC center, sex, and education as a marker of socioeconomic status (≤high school versus >high school). In the model assessing the role of metabolic syndrome factors, adjustments were made for the following as continuous variables measured at visit 2 (except fasting insulin, which was measured only at visit 1): fasting insulin, fasting glucose, HDL cholesterol, log-transformed triglycer-

Table 1—*Demographic, behavioral, and physiological characteristics of 11,615 adults ages 48–67 years without type 2 diabetes by quartile of depressive symptoms*

Covariate	Quartile of depressive symptoms				*P* values for trend*
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
	1.20 (0–3)	5.84 (4–8)	11.5 (9–14)	22.2 (15–42)	
n	2,782	3,468	2,525	2,840	
Age (years)	56.4 ± 5.59	56.7 ± 5.68	56.9 ± 5.71	57.0 ± 5.81	<0.01
African American (%)	15.2	20.1	23.6	27.1	<0.001
Female (%)	39.6	51.3	61.8	70.1	<0.001
High school education or less (%)	41.5	48.5	55.8	65.5	<0.001
Anti-depressant medication use (%)	0.3	0.6	1.5	3.2	<0.001
Physical activity score	2.69 ± 0.83	2.52 ± 0.81	2.42 ± 0.77	2.26 ± 0.73	<0.01
Caloric intake (kcal/day)	1,595 ± 630	1,620 ± 677	1,640 ± 679	1,677 ± 713	<0.01
Current smokers (%)	18.4	19.8	25.3	28.0	<0.001
Fasting insulin (pmol/l)	70.9 ± 52	73.9 ± 57	74.6 ± 53	79.2 ± 62	<0.01
Fasting glucose (mmol/l)	5.63 ± 0.52	5.64 ± 0.51	5.63 ± 0.51	5.63 ± 0.54	0.53
BMI (kg/m^2)	26.8 ± 4.3	27.2 ± 4.8	27.4 ± 5.2	28.2 ± 5.9	<0.01
Waist-to-hip ratio	0.92 ± 0.08	0.92 ± 0.08	0.91 ± 0.08	0.92 ± 0.08	0.30
Triglycerides (mmol/l)	1.42 ± 0.79	1.42 ± 0.90	1.44 ± 0.82	1.49 ± 0.91	<0.01
HDL cholesterol (mmol/l)	1.26 ± 0.41	1.31 ± 0.44	1.34 ± 0.45	1.34 ± 0.44	<0.01
Systolic blood pressure (mmHg)	119 ± 17	120 ± 18	120 ± 19	121 ± 20	<0.01

Data are means (range) and mean ± SD for continuous variables and percentage of individuals with a given characteristic for categorical variables. *For continuous variables, *P* value is from trend test; for categorical variables, *P* value is from χ^2 test.

ides, systolic blood pressure, BMI, and waist-to-hip ratio. In the models assessing the role of lifestyle factors, adjustments were made for physical activity, smoking, and total caloric intake; all of which were measured at visit 2 except physical activity, which was measured only at visit 1. Statistical interactions of depressive symptoms with sex, race, BMI, and prevalent coronary heart disease were assessed. Because there were no statistical interactions of depressive symptoms on the risk of diabetes by these categories, the entire cohort was analyzed as a group.

A subsidiary analysis was performed examining the vital exhaustion depression subscales, in which the total vital exhaustion score was categorized into three depression subscores (vegetative, nonvegetative, and functional symptom scores) to determine the RH of developing diabetes for each subscale. Because the number of items in the three subscales varied, standardizing the RHs to the interquartile range of the scores for each subscale made direct comparisons more comparable. Cronbach's α, a measure of the correlation between a group of variables, was calculated for each subscale (23,24). All statistical analyses were conducted using SAS Version 8.1 (Cary, NC).

RESULTS

Population characteristics

Table 1 summarizes selected baseline clinical and demographic characteristics of the study population at visit 2 (except fasting insulin and physical activity, which were only measured at visit 1) by level of depressive symptoms measured at the same visit. Compared with their counterparts in the lowest quartile of depressive symptoms, those in the highest quartile were more likely to be African American, female, current smoker, user of antidepressant medications, and have a high school education or less (all *P* values <0.0001). They also had higher fasting insulin, BMI, systolic blood pressure, and estimated total caloric intake but lower physical activity scores (all *P* values <0.0001). Surprisingly, they also had higher HDL cholesterol ($P < 0.0001$). There was no difference in waist-to-hip ratio by quartile of depressive symptoms.

Among individuals who did not develop diabetes during follow-up, individuals in the highest quartile of depressive symptoms had a greater change in BMI from visits 2 to 4 than individuals in the lowest quartile of depressive symptoms (1.14 vs. 0.96 kg/m^2; $P = 0.01$ for trend).

Incidence rates of type 2 diabetes

Over 6 years of follow-up, there were 721 cases of incident type 2 diabetes, corresponding to an overall incidence rate of 12.4 per 1,000 person-years (95% CI 11.5 per 1,000 to 13.3 per 1,000 person-years). After adjustment for age, race, and sex, the incidence rate was greatest in the study participants in the highest quartile of depressive symptoms at baseline (19.1 per 1,000 person-years; 95% CI 16.7–21.7 per 1,000 person-years) and was significantly different from those in the lowest depressive symptom quartile (12.0 per 1,000 person-years; 95% CI 9.6–14.5 per 1,000 person-years) at the end of the 6-year follow-up period ($P < 0.001$). The incidence of type 2 diabetes, however, did not increase monotonically across the first, second, and third quartiles (data not shown).

Multivariate analyses of depressive symptoms

In the base model, after adjusting only for age, race, ARIC center, education, and sex, individuals in the highest quartile of depressive symptoms had a 63% increased risk of developing diabetes compared with those in the lowest quartile (RH 1.63, 95% CI 1.31–2.02) (Table 2).

To explore potential physiological

Table 2—*RH of type 2 diabetes over 6 years of follow-up by quartile of depressive symptoms for 11,615 individuals age 48–67 years*

	Quartile of depressive symptoms				*P* value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	for trend
Model 1: adjusted for age, race, ARIC center, education, and sex	1.0	1.22 (0.99–1.51)	1.31 (0.89–1.43)	1.63 (1.31–2.02)‖	<0.0001
Model 2: adjusted for metabolic covariates*	1.0	1.13 (0.9–1.40)	1.06 (0.84–1.35)	1.38 (1.10–1.73)‖	0.0071
Model 3: adjusted for lifestyle covariates†	1.0	1.20 (0.97–1.48)	1.09 (0.86–1.38)	1.51 (1.21–1.89)‖	0.0005
Model 4: adjusted for lifestyle covariates and BMI‡	1.0	1.16 (0.94–1.43)	1.02 (0.81–1.30)	1.28 (1.02–1.60)‖	0.06
Model 5: adjusted for metabolic and lifestyle covariates§	1.0	1.12 (0.90–1.39)	1.03 (0.81–1.31)	1.31 (1.04–1.64)‖	0.04

*Model 2: adjusted for age, race, ARIC center, education, sex, fasting insulin, fasting glucose, log triglycerides, HDL cholesterol, BMI, waist-to-hip ratio, and systolic blood pressure. †Model 3: adjusted for age, race, ARIC center, sex, education, physical activity, total caloric intake, and smoking status. ‡Model 4: adjusted for age, race, ARIC center, sex, education, physical activity, total caloric intake, smoking status, BMI, and waist-to-hip ratio. §Model 5: adjusted for age, race, ARIC center, education, sex, fasting insulin, fasting glucose, log triglycerides, HDL cholesterol, BMI, waist-to-hip ratio, systolic blood pressure, physical activity, total caloric intake, and smoking status. ‖$P < 0.05$.

and behavioral confounders of the relation between depressive symptoms and type 2 diabetes, a series of multivariate Cox proportional hazards models were constructed. After adjustment for covariates related to the metabolic syndrome (fasting insulin, fasting glucose, systolic blood pressure, triglycerides, HDL cholesterol, waist-to-hip ratio, and BMI), individuals in the highest quartile of depressive symptoms still had an increased risk of developing diabetes compared with those in the lowest quartile, although the relationship was attenuated (RH 1.38, 95% CI 1.10–1.73) (Table 2).

In the model that adjusted for behavioral factors (smoking, physical activity, and caloric intake), those in the highest quartile of depressive symptoms had a 51% increased risk of developing diabetes compared with those in the lowest quartile (RH 1.51, 95% CI 1.21–1.89). The association between depressive symptoms and incident diabetes was attenuated but remained significant after an additional adjustment for waist-to-hip ratio and BMI (1.28, 1.02–1.60). In the fully adjusted model, which included sociodemographic, metabolic, and behavioral covariates, individuals in the highest quartile of depressive symptoms had a 31% increased risk of developing diabetes compared with those in the lowest quartile (1.31, 1.01–1.64).

To determine which category of depressive symptoms was most predictive of incident diabetes, vital exhaustion questions were categorized into the three subgroups of depressive symptoms (vegetative, nonvegetative, and functional) (18), and the RH of diabetes was determined. Each estimate was standardized to the interquartile range of the distribution of scores for each subgroup. The vegetative subscale included the "exhaustion" symptoms, and the nonvegetative subscale included the "nonexhaustion" symptoms. The variables in both of these subscales were highly correlated with Cronbach's α of 0.75 for the vegetative subscale and 0.72 for the nonvegetative subscale. Both the vegetative and nonvegetative subscales similarly predicted the development of diabetes over follow-up (Table 3). The functional subscale was also predictive of diabetes; however, because this subscale was only composed of two symptoms, the Cronbach's α was only 0.53, and thus these results should be interpreted with caution.

CONCLUSIONS — We found that individuals in the top quartile of depressive symptoms, as assessed by the vital exhaustion questionnaire, were at slightly increased risk of developing type 2 diabetes. The relationship between depressive symptoms and diabetes was only partially explained by demographic, metabolic, and lifestyle factors in this cohort.

Our study has several strengths. First, ARIC is a large, nonclinical population in which there was standardized ascertainment of incident diabetes for up to 6 years of follow-up. Second, there were standardized measurements of exposures, outcomes, and behavioral and physiological explanatory factors in a rigorously monitored observational study, allowing us to explore potential mechanisms of the association between depressive symptoms and diabetes.

Table 3—*RH of type 2 diabetes over 6 years of follow-up by vital exhaustion depression subscore among 11,615 individuals age 48–67 years*

Vital exhaustion depression subscore category*	Age, race, ARIC center, education, and sex adjusted hazard ratio (95% CI)†	Fully adjusted model (95% CI)‡
Vegetative score	1.22 (1.11–1.36)§	1.10 (0.99–1.23)
Nonvegetative score	1.20 (1.09–1.32)§	1.09 (0.98–1.20)
Functional score	1.23 (1.11–1.36)§	1.11 (1.00–1.23)§

*Vegetative symptoms (fatigue, sleep pattern, energy, concentration); nonvegetative symptoms (crying spells, hopelessness, irritability, enjoyment of sex, suicidality); functional symptoms (coping, productivity). †Risk of incident type 2 diabetes per interquartile range increase in vital exhaustion depression subscore category (each hazard ratio has been standardized to the interquartile range for the distribution of its scores). ‡Adjusted for age, race, ARIC center, education, sex, fasting insulin, fasting glucose, log triglycerides, HDL cholesterol, BMI, waist-to-hip ratio, systolic blood pressure, physical activity, total caloric intake, and smoking status. §$P < 0.05$.

Nonetheless, one main limitation should be kept in mind when interpreting our data. Vital exhaustion is not a commonly used measure of depression and has not been frequently used in the U.S., although it is a standardized assessment tool. There is not a currently used cut point for defining depression based on the vital exhaustion scale, and it has not been compared with the cut points for defining depression by more widely used scales, such as the Beck Depression Inventory or the Center for Epidemiological Studies Depression Scale, which makes it difficult to identify clinically depressed individuals using this scale. The vital exhaustion scale was originally developed by Appels et al. (16) to measure feelings of fatigue, exhaustion, and subclinical depression that precede myocardial infarction. These feelings of loss of vitality, listlessness, tiredness, loss of libido, and increased irritability have been shown to predict myocardial infarction (25). One could argue that "exhaustion symptoms" are physical symptoms associated with other chronic conditions, such as obesity, and may not reflect true depression. There are several indicators, however, that vital exhaustion may be an appropriate surrogate measurement of depressive symptoms. Antidepressant medication use in the ARIC cohort was 3 to 8 times more common in the highest two quartiles of vital exhaustion, although the absolute frequency of antidepressant use was never >4% of the participants in even the highest use category (data not shown). A further suggestion that the vital exhaustion scale is an appropriate measure of clinical depression is the similarity of statements in the vital exhaustion scale with those of standardized clinical depression measurement scales. Of the 21 symptoms on the vital exhaustion scale, 20 symptoms could be related to the subcategories of depressive symptoms (18), and the nonvegetative subscale, which did not include measures of exhaustion, predicted diabetes in a similar manner to the vegetative (or exhaustion) subscale. In addition, if the presence of physiological changes related to the pre-diabetic state caused exhaustion symptoms, one would expect the scale to predict diabetes more strongly at visit 3 than visit 4. We found, however, that vital exhaustion equally predicted diabetes incidence at visits 3 and 4 (data not shown). Finally, the vital exhaustion scale does not have a time frame to determine the duration of symptoms, and data on depressive symptoms were only measured once.

Other studies support the interchangeability of Appels' vital exhaustion scale and more traditional clinical depression scales. In one study of 12,640 Hungarians (17), the correlation between vital exhaustion score and depression scores (assessed by the shortened Beck Depression Inventory) was strong ($r = 0.62$) with both measures sharing a significant common variance (38%). Whereas the cognitive and mood disturbances that characterize depression occurred less frequently in the individuals with vital exhaustion, most of the depressed individuals (77%) also had symptoms of vital exhaustion (17). In a smaller study, men with vital exhaustion reported greater depressive symptoms than their nonexhausted counterparts, although depressed mood was rarely reported (26). There is some evidence, however, that vital exhaustion is associated with similar behavioral and hormonal disturbances, particularly alteration of the HPA axis, as is seen with depression (27).

The temporal relationship of the association between diabetes and depression has not been clearly delineated, as the majority of the studies, summarized in a recent meta-analysis, have been cross-sectional (28). There are only two studies with longitudinal data, both demonstrating a greater than twofold increased risk of developing type 2 diabetes during follow-up in individuals who had moderate to severe depressive symptoms (2) and major depressive disorder (1) at baseline. Although one study adjusted for BMI, physical activity, and family history of diabetes (2) and the other adjusted for socioeconomic status, education, and body weight (1), they were limited by smaller sample sizes (1), suboptimal assessment of diabetes (1), and lack of detailed data on physiological variables (2).

Like a recent study by Carnethon et al. (29), who found a nonlinear relation between depressive symptoms (assessed by the General Well-Being Survey) and the risk of type 2 diabetes among individuals of low socioeconomic status, we similarly found the risk of diabetes to be increased only among those individuals in the highest quartile of depressive symptoms. A potential explanation of our findings is that individuals with vital exhaustion scores in quartile 4 had true clinical depression; however, as noted in the limitations, we cannot confirm this, as there is no clinically established cut point for defining depression according to the vital exhaustion scale.

At least four possible mechanisms might connect depressive symptoms and diabetes risk. First, depressed individuals are less likely to be compliant with dietary and weight loss recommendations (7) and are more likely to be physically inactive and nonadherent with medications (3–6). This can lead to worsening of obesity and insulin resistance, increasing the risk of developing type 2 diabetes. In our population, individuals with greater depressive symptoms were more likely to gain weight over time. The mechanisms (i.e., behavioral versus hormonal) leading to this weight gain warrant further study. They are also more likely to smoke (30) (Table 2), which itself is emerging as a risk factor for type 2 diabetes (31).

Second, obesity and factors such as low socioeconomic status might lead to both depression and diabetes, thus being a confounder in the association. Some studies have found a higher prevalence of depression among individuals with diabetes who are of low socioeconomic status (32,33) and who are obese (34); however, other studies have not found these associations (35). In our population, the relation between depressive symptoms and diabetes persisted after adjustment for education, a marker of socioeconomic status, and measures of adiposity.

Third, some of the medications used to treat depression are associated with weight gain and obesity (36–38), which could predispose depressed individuals to the development of diabetes. In this dataset, there was insufficient information to address this important issue.

Fourth, depression induces neurohormonal changes, specifically activation of the HPA axis and the sympathetic nervous system, resulting in increased levels of the counterregulatory hormones cortisol and catecholamines (9–13). This neuroendocrine profile has been associated with abdominal adiposity (39) and increased triglycerides and insulin (40), which are all established predictors of type 2 diabetes.

The main implication of our study is that depressive symptoms deserve further attention as risk factors for type 2 diabetes. Although the association between

depressive symptoms and type 2 diabetes was modest, these results provide some additional support for the hypothesis that negative affective states, such as depression, can have negative metabolic consequences. Our study serves as a springboard for additional prospective studies using an established assessment tool to demonstrate an association between depression and diabetes with inclusion of neurohormonal measurements. Additional studies should determine whether amelioration of depressive symptoms might facilitate behavioral changes aimed at primary prevention of diabetes and whether HPA axis and sympathetic nervous system activation play an important role in the pathophysiology of weight gain and insulin resistance.

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APPENDIX

Vital Exhaustion Questionnaire

Do you often feel tired? (V)

Do you often have trouble falling asleep? (V)

Do you wake up repeatedly during the night? (V)

Do you feel weak all over?*

Do you have the feeling that you haven't been accomplishing much lately? (F)

Do you have the feeling that you can't cope with everyday problems as well as you used to? (F)

Do you believe that you have come to a "dead end?" (NV)

Do you lately feel more listless than before? (V)

Do you enjoy sex as much as ever? (NV)

Have you experienced a feeling of hopelessness recently? (NV)

Does it take more time to grasp a difficult problem than it did a year ago? (V)

Do little things irritate you more lately than they used to? (NV)

Do you feel you want to give up trying? (NV)

Do you feel fine? (NV)

Do you sometimes feel that your body is like a battery that is losing its power? (V)

Would you want to be dead at times? (NV)

Do you have the feeling these days that you just don't have what it takes any more? (NV)

Do you feel dejected? (NV)

Do you feel like crying sometimes? (NV)

Do you ever wake up with a feeling of exhaustion and fatigue? (V)

Do you have increasing difficulty in concentrating on a single subject for long? (V)

Appendix abbreviations: F, functional depressive symptoms; NV, nonvegetative depressive symptoms; V, vegetative depressive symptoms. *Question does not fit any of the three depressive symptom subscales.

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