Symptoms of Depression as a Risk Factor for Incident Diabetes: Findings from the National Health and Nutrition Examination Epidemiologic Follow-up Study, 1971–1992

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Symptoms of depression may predict incident diabetes independently or through established risk factors for diabetes. US men and women aged 25–74 years who were free of diabetes at baseline (n = 6,190) were followed from 1971 to 1992 (mean, 15.6 years; standard deviation, 6) for incident diabetes. Depressive symptoms were measured by using the General Well-Being Depression subscale and were categorized to compare persons with high (9%), intermediate (32%), and low (59%) numbers of symptoms. The incidence of diabetes was highest among participants reporting high numbers of depressive symptoms (7.3 per 1,000 person-years) and did not differ between persons reporting intermediate and low numbers of symptoms (3.4 and 3.6 per 1,000 person-years, respectively) (p < 0.01 for high vs. low). In the subset of participants with less than a high school education (a marker of low socioeconomic status), the risk of developing diabetes was three times higher (95% confidence interval: 2.0, 4.7) for persons reporting high versus low numbers of depressive symptoms. These results persisted following adjustment for established diabetes risk factors. Depressive symptoms had no impact on diabetes incidence among persons with at least a high school education. Results suggest an independent role for depressive symptoms in the development of diabetes in populations with low educational attainment.

depression; diabetes mellitus; educational status; longitudinal studies; social class
Depressive Symptoms and Incident Diabetes

MATERIALS AND METHODS

Study design and population

Participants from the First National Health and Nutrition Examination Survey (NHANES I) who were followed as part of the National Health and Nutrition Examination Epidemiologic Follow-up Survey (NHEFS) were included in this study. NHANES I, conducted from 1971 to 1975, was a cross-sectional survey of health conditions and health-related behaviors in a probability sample of the noninstitutionalized civilian population of the United States aged 1–74 years. After the baseline examination, participants were contacted and medical and health care records were abstracted in four cycles, 1982–1984, 1986, 1987–1989, and 1990–1992. A detailed description of the study design and sampling methods is available elsewhere (8, 9). The NHEFS traced 93 percent of the original sample of 14,407 adults aged 25–74 years (n = 13,383) through 1992 (10, 11).

This study includes the subset of NHEFS participants who received a more detailed health examination at baseline (n = 6,910). From those participants, we excluded those with prevalent diabetes (based on self-reported physician diagnosis, use of diabetes control medication, urine glucose test, or a diagnosis date prior to the first examination (n = 656)) or those whose race was reported as “other,” because of small numbers (n = 64). This paper includes information on 6,190 participants: 2,858 men and 3,332 women.

Measurements

The General Well-Being survey, administered during NHANES I at mobile examination centers by trained personnel, includes six independent but related components of general psychological well-being (12). This paper focuses on the cheerfulness versus depressed mood subscale, a series of four questions highly correlated to depressive symptomatology. Previous research indicates that the General Well-Being Depression subscale predicts clinically trained personnel, includes six independent but related components of general psychological well-being (12). This paper focuses on the cheerfulness versus depressed mood subscale, a series of four questions highly correlated to depressive symptomatology. Previous research indicates that the General Well-Being Depression subscale predicts clinically trained interviewers’ ratings of depression and is correlated with scores from other instruments designed to assess depression (12).

Participants were asked the following questions: “Have you felt down-hearted or blue?”; “How have you been feeling in general?”; “Have you felt so sad, discouraged, hopeless or had so many problems that you wondered if anything was worthwhile?”; and, “How DEPRESSED or CHEERFUL have you been [in the past month]?” Responses are provided on a Likert scale, with lower values indicating a more depressed mood. In this study, the association between depression and diabetes was examined both continuously (0–25) and in categories. Categories for analysis were based on previous research indicating that scores of 0–12 correspond with high numbers of depressive symptoms (13) and scores of 19–25 indicate few or no depressive symptoms (12). Secondary analyses included the similarly rated anxious versus relaxed subscale (12).

Incident diabetes was defined by the report of this condition on any of the following: death certificates (International Classification of Diseases, Ninth Revision, codes 250.0–250.9), health care facility records (nursing home or hospital), or self-report (11). Biochemical testing to detect diabetes was not available. Previous research in this cohort indicates that at least half of all cases of diabetes were confirmed by two or more sources (14, 15). We could not identify whether incident diabetes was type 1 or type 2, but type 2 diabetes represents over 90 percent of diabetes diagnoses and is much more likely to develop after age 30 years (16). The diagnosis date for diabetes was recorded as the date recorded on death certificates or facility discharge records or at first report by the respondent. In the case of incomplete data, the date was imputed on the basis of the amount of information available (17).

Covariates associated with diabetes and depressive symptoms were ascertained from NHANES I surveys on medical history, health care needs, and cardiovascular conditions as well as from medical examinations that included laboratory determinants and anthropometric measurements (8, 9). Briefly, age at interview, gender, race (Black or White), marital status, and educational attainment were ascertained via self-report. NHANES I interviewers determined whether a participant resided in a low-poverty area by using the US Census (9). On the basis of information collected from health interview surveys, we categorized level of recreational physical activity (low, moderate, or high), cigarette smoking (current, former, or never), and number of drinks of alcohol per day (0, 1–2, or ≥3). At the baseline medical examination, blood pressure was measured while participants were seated. We identified a participant as hypertensive if he or she met one of the following conditions: systolic blood pressure >140 mmHg, diastolic blood pressure of ≥90 mmHg, antihypertensive medication use, or a previous physician diagnosis of hypertension. We calculated baseline body mass index as the ratio of standing height (in meters), squared, to measured weight (in kilograms). Self-reported weight (in pounds; 1 pound = 0.454 kg) was ascertained during follow-up interviews for 5,038 participants; estimated weight change was calculated as the difference between self-reported weight during follow-up and measured weight at baseline (converted from kilograms to pounds).

Statistical methods

We compared the distribution of baseline characteristics by depressive symptom categories and evaluated statistical significance by using t tests for means and χ2 tests for proportions. Poisson regression was used to estimate diabetes incidence rates and corresponding rate ratios by depressive symptoms. Follow-up time was calculated as the difference between the date last seen alive and baseline for persons without diabetes and as the difference between the diabetes diagnosis date and baseline for persons with diabetes. Multivariable Cox proportional hazards regression was used to calculate relative risks and 95 percent confidence intervals of incident diabetes by depressive symptom categories and by a standard deviation increase in continuous depressive symptom scores. We tested and confirmed the

validity of the proportional hazards assumption by using log-negative log survival plots. All covariates were evaluated as potential effect modifiers (heterogeneity) by using first-order interaction terms between each covariate and depressive symptom categories. A significant \((p < 0.05)\) change in the maximum likelihood \(\chi^2\) value following removal of the interaction term from the model indicated statistical interaction. When there was evidence of effect modification, we retained the interaction term in the model.

To investigate the extent to which established risk factors explain the association between depressive symptoms and incident diabetes, we calculated the excess risk attributable to depressive symptoms when groups of covariates were entered into the model. We used the following formula: percentage excess risk = \((RR_1 – RR_2)/(RR_1 – 1)\), where \(RR_1\) is the relative risk of diabetes for persons with high versus low numbers of depressive symptoms in the minimally adjusted model, \(RR_2\) is the relative risk after adjustment for a group of covariates, and \(RR_1 – 1\) is the excess risk of diabetes among persons with high versus low numbers of depressive symptoms (18). The resulting percentage explains how much of the association between depressive symptoms and diabetes can be explained by the covariates; the relative risk following adjustment represents the residual association between depressive symptoms and diabetes.

Older adults, low-income persons, and women of child-bearing age were oversampled in NHANES I. Corresponding sample weights are provided so investigators can make national prevalence estimates. However, the objective of the current study was to examine the association between a specific risk factor, depressive symptoms, and the risk of developing diabetes, not to provide national estimates. Furthermore, there has been controversy surrounding the use of the sampling weights in NHEFS (19). Previous authors reported conducting both weighted and unweighted analyses, but, because the results were generally comparable, authors presented only the unweighted results. Similarly, we report only unweighted results in this paper. All analyses were conducted by using SAS software, version 8.1 (SAS Institute, Inc., Cary, North Carolina). Statistical significance is denoted at \(p < 0.05\).

**RESULTS**

**Baseline characteristics**

At baseline, 3,618 (58.5 percent) participants reported low numbers of depressive symptoms, 2,006 (32.4 percent) reported intermediate numbers of symptoms, and 566 (9.1 percent) reported high numbers of symptoms. There was no age difference across depressive symptom categories, but participants with high or intermediate numbers of symptoms were more likely to be women, to be Black, to be unmarried, to have less than a high school education, and to live in a low-poverty area (table 1). Furthermore, participants with higher numbers of depressive symptoms were less physically active, were less likely to drink alcohol, had a higher baseline body mass index, were more often obese, and were more likely to be current cigarette smokers. We found no differences in systolic or diastolic blood pressure or the prevalence of hypertension by depressive symptoms. On average, participants gained 4.7 pounds during follow-up (standard deviation, 22.6). Weight change was similar between persons with high and low numbers of depressive symptoms, but persons with intermediate numbers of symptoms gained significantly more weight than persons with low numbers of symptoms.

**Incident diabetes**

Over an average of 15.6 years of follow-up (maximum, 21.9; standard deviation, 5.5 years), 15 incident cases of diabetes were identified by death certificate, 362 were self-reported, and 49 were identified by a health care facility stay. In total, 369 participants (6 percent) developed diabetes. The distribution of diabetes incidence by age at follow-up was 4.3 percent, 17.3 percent, 27.4 percent, 27.4 percent, 20.3 percent, and 3.3 percent for participants aged 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years, respectively. The incidence of diabetes was highest among participants reporting high numbers of depressive symptoms (7.3 per 1,000 person-years) and did not differ between persons reporting intermediate and low numbers of symptoms (3.4 and 3.6 per 1,000 person-years, respectively) (figure 1A).
A statistically significant difference was found in the association between depressive symptoms and diabetes for participants with less than a high school education and those with at least a high school education ($\chi^2 2 \text{ df } = 6.25, p = 0.04$). Among persons with less than a high school education, the incidence rate of diabetes was 2.19 times higher (95 percent confidence interval (CI): 1.50, 3.13) for those with high versus low numbers of depressive symptoms (figure 1B). In contrast, the same relation between high numbers of depressive symptoms and diabetes was not significant for persons with intermediate numbers of symptoms (95 percent CI: 1.02, 1.07).

There was some evidence of heterogeneity of effect by gender ($\chi^2 2 \text{ df } = 4.46, p = 0.11$); the association between depressive symptoms and incident diabetes was strongest among women. However, the difference in association was primarily in magnitude and was most likely attributable to the increased prevalence of women with high numbers of depressive symptoms (table 1). Among persons with low levels of education, the effect was identical by gender. Because heterogeneity by gender became less important in the presence of strong effect modification by education, this paper does not present a stratified analysis, but we included an interaction term between gender and depressive symptom categories in all further modeling.

### Multivariate analyses

In the entire cohort, the age-, race-, and gender-adjusted relative risk of developing diabetes was 2.52 (95 percent CI: 1.73, 3.67) for persons with high versus low numbers of depressive symptoms, and it was nonsignificantly elevated for persons with intermediate numbers of symptoms (RR = 1.24, 95 percent CI: 0.91, 1.70 vs. low numbers of symptoms). With adjustment for health behaviors (current vs. never or former smoking, current or former alcohol drinking vs. never drinking, and low vs. moderate or high levels of recreational physical activity) and baseline body mass index, the risk of developing diabetes remained 86 percent higher (95 percent CI: 1.27, 2.71) for persons with high versus low numbers of depressive symptoms. In fully adjusted models, the risk of developing diabetes increased 4 percent per standard deviation (4.5-unit) increase in depressive symptoms (95 percent CI: 1.02, 1.07).

Among persons with low levels of education, those with high depressive symptom scores were three times more likely to develop diabetes than those with low scores (table 2). In this population, the risk increased 8 percent per 4.5-unit increase in depressive symptoms. The relative risk for diabetes attenuated only slightly after further adjustment for behavioral and anthropometric risk factors. A small part (6 percent) of the association between high numbers of depressive symptoms and diabetes was explained by health behaviors (cigarette smoking, alcohol consumption, and physical activity). With the addition of baseline body mass index into the multivari-
Secondary analyses

Symptoms of depression and anxiety are highly correlated ($r = 0.75$, $p < 0.0001$) in this sample, so we conducted additional analyses to evaluate the specific role of depressive symptomatology, independent of anxiety, on diabetes incidence. High numbers of depressive symptoms remained a strong, significant predictor of incident diabetes following adjustment for symptoms of anxiety (RR = 1.77, 95 percent CI: 1.09, 2.87 vs. low numbers of symptoms) and all other covariates in the total population. In the sample of persons with lower levels of education, the risk of developing diabetes remained 2.19 times higher (95 percent CI: 1.31, 3.68) for those with high versus low numbers of depressive symptoms after adjustment for anxiety. The same association was not significant for persons with at least a high school education. Symptoms of anxiety explained an additional 8 percent (excess risk = $(2.30 - 2.19)/(2.30 - 1)$) of the association between depressive symptoms and diabetes risk beyond behavioral and anthropometric risk factors in less-educated persons.

DISCUSSION

In this population-based sample, men and women with less than a high school education who reported the highest numbers of symptoms of depression were at increased risk of developing diabetes. This relation appears to act independently of established risk factors for the development of diabetes and a related psychological construct, anxiety.

Biologic mechanisms that may explain the association between depressive symptoms and diabetes include inflammation, activation of the hypothalamic-pituitary-adrenal axis, or an interaction between genetic predisposition and depression or stress. In cross-sectional studies, inflammatory markers including the cytokines interleukin-$1\beta$, and tumor necrosis factor-$\alpha$ (20) and C-reactive protein (21) were found to be elevated in depressed persons. Two population studies (17, 22) reported that inflammatory markers are associated with the expression of low-grade inflammation that can be detected prior to the development of diabetes (17). Alternatively, inflammation may be associated with oxidative damage and the release of free radicals (23) that damage pancreatic $\beta$ cells (24), thus limiting the release of insulin. The inflammatory process also may inhibit insulin uptake (25), a critical process in glucose regulation. Further research is needed into a possible role for inflammation regarding the relation between depressive symptoms and incident diabetes.

A dysregulation of the hypothalamic-pituitary-adrenal axis in depressed persons may result in elevated cortisol levels (26). Cortisol may antagonize the actions of insulin-mediated glucose disposal or cause preferential deposition of fat in the abdomen (visceral adiposity), which is a risk factor for developing diabetes. It has also been shown that insulin sensitivity, an important mechanism in the development of type 2 diabetes, can be manipulated by treatment for depression. In an experimental study, depressed patients had lower
insulin sensitivity, but, when treated with heterocyclic antidepressants, depressive symptoms improved concurrently with insulin sensitivity, independent of changes in body weight (27).

Depression is highly correlated with physiologic and psychological stress; therefore, it is possible that the reported relation between stress and hyperglycemia may also mediate the relation between depression and diabetes. Stressful situations have been shown to induce hyperglycemia in euglycemic animals (28) and in humans with a genetic predisposition toward developing diabetes (29). After Pima Indians, thought to have a genetic predisposition to developing diabetes, completed a mental arithmetic task, their fasting serum glucose levels were significantly higher and remained higher longer than those in Whites (29). This finding supports the proposal by Wales (30) that stress only precipitates clinical diabetes in persons predisposed to developing diabetes.

Depressed mood is highly correlated with health behaviors associated with the development of diabetes. Previous research indicates that health behaviors such as sedentary lifestyle and poor diet that lead to weight gain are more prevalent among depressed persons (31). Thus, it was unexpected that self-reported weight change over time did not differ between persons with high and low numbers of depressive symptoms in this sample and that only intermediate numbers of symptoms were associated with significantly more weight gain. However, we did confirm that elevated numbers of depressive symptoms were related to a sedentary lifestyle and that baseline body mass index (based on measured weight) was higher and the proportion of obese persons (body mass index of ≥30) at baseline was greater.

Our analysis did not include dietary components, so it is possible that control for lifestyle characteristics was incomplete. Additionally, body weight during follow-up was self-reported, and its accuracy is unknown. Our results may have been biased differentially if the likelihood of accurate self-report was related to depressive symptoms or development of diabetes. Despite these limitations, we estimated that 37 percent of the association between depressive symptoms and diabetes could be explained by health behaviors and baseline body mass index as measured in this sample. The strong residual association between depressive symptoms and diabetes incidence following adjustment for baseline body mass index, which we hypothesize is related to diet (unmeasured in this study) and physical activity (measured), suggests that depressive symptoms play an independent role in the development of diabetes.

We found that the relation between depressive symptoms and diabetes was characterized by strong heterogeneity by educational attainment, a proxy for socioeconomic status. While persons with lower levels of education were more likely to report high numbers of depressive symptoms than were their more highly educated counterparts in this study (13 percent vs. 6 percent) and others (7), the absolute number in each group was still substantial (350 vs. 216). Furthermore, the proportion of persons who developed diabetes, although higher among persons with less education (7.2 percent vs. 5.1 percent) (again, lower socioeconomic status has been reported as a strong risk factor for the development of diabetes (32, 33)), was not subject to sparse numbers in each strata. Thus, statistical power to detect a relation was good in both educational strata. Rather, we think that our findings represent a real (not statistical artifact) difference in the association between depressive symptoms and the risk of diabetes by educational attainment.

Socioeconomic status reflects material and financial resources, social prestige, and knowledge, all of which act independently or in combination to influence health-related behaviors. Persons of lower socioeconomic status may be more likely to consume diets high in fats, carbohydrates, and alcohol; to smoke cigarettes more frequently; and to engage in a sedentary lifestyle, all of which are predisposing factors for developing diabetes. Persons of depressed mood and low socioeconomic status may act synergistically to increase the risk of diabetes.

A second study in the NHEFS cohort that used the Center for Epidemiologic Studies Depression Scale measured in 1982–1984 (second examination) found no effect of depressive symptoms on diabetes incidence (34). The authors did not report investigating the association by education, and participants were followed for a relatively shorter time (average, 4.2 years). Another earlier study (5) tested the temporal relation between major depressive disorder and incident diabetes in a Baltimore, Maryland, population (n = 3,481) by using the National Institute of Mental Health’s Diagnostic Interview Schedule to identify major depressive disorder. In this study, Eaton et al. (5) found a strong twofold increase in the risk of diabetes, but, probably because of the smaller sample size, were unable to confirm the statistical significance of this relation. However, a previous study by Kawakami et al. (35) of 2,764 Japanese men reported findings similar to our own. Men reporting higher numbers of depressive symptoms according to the Zung Self-Rating Depression scale were more likely to develop diabetes.

Our large sample and length of follow-up afforded sufficient power to test our primary and secondary hypotheses. Although we might have observed a stronger association by using a measure of clinical depression, such as that of Eaton et al. (5), depression and diabetes share common symptoms, such as fatigue and weakness (2). The internal consistency of the General Well-Being Depression scale was 0.77 in previously reported studies in this sample (36, 37), and, in a 9-year longitudinal study, the level of negative affect was relatively stable over time (38). Thus, we are confident about the validity, reliability, and robustness of our measure of depressive symptoms and about the related psychological components it may encompass. In addition, our measure of depressive symptoms assessed affect rather than somatic symptoms of depression, so we may have avoided the possibility that persons reporting depressive symptoms were actually experiencing symptoms of diabetes at baseline.

Conclusions from this study must be interpreted in light of some limitations. Incident and prevalent diabetes were based on self-report, medical records, and death certificates. These sources are less rigorous than definitions based on results from oral glucose tolerance testing or fasting serum glucose concentrations. Both misclassification and an underdiag-
nosis of diabetes are possible since a clinical diagnosis is usually made 4–7 years after the beginning of the disease (39); an estimated 2.7 percent of the US population has undiagnosed diabetes (40). Consequently, a diagnosis of diabetes during follow-up may represent a progression from undiagnosed, nonsymptomatic disease at baseline to a clinical diagnosis. In secondary analyses, we excluded 26 persons (7 percent of diabetes diagnoses) who reported a diagnosis of diabetes during the first 10 years of follow-up; our results did not change (data not shown). However, if depressed persons are more likely to have undiagnosed diabetes, then our results may have been confounded. We were also unable to confirm whether diabetes was type 1 or type 2. Because type 2 is more likely to be diagnosed after age 30 years (16), we conducted secondary analyses that excluded 920 participants (19 diabetes events) who were younger than age 30 years at baseline, and our results were similar (data not shown).

The impact of depressive symptoms on diabetes, as reported in this study, suggests that practitioners may have an additional reason to institute targeted screening and treatment programs for depression in low-socioeconomic-status populations. Strategies for diabetes prevention in this population could be more effective if this relation is addressed.

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