Depressive Symptoms and Risk of Type 2 Diabetes in Women

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OBJECTIVE — To explore the relationship between depressive symptoms and incidence of type 2 diabetes in women.

RESEARCH DESIGN AND METHODS — We conducted an analysis of 72,178 female nurses aged 45–72 years who did not have diagnosed diabetes and who answered the Medical Outcomes Study 36-Item Short-Form Health Status Survey (SF-36) at baseline in 1992. We calculated relative risks (RR) of type 2 diabetes for women with presence of depressive symptoms (i.e., Five-Item Mental Health Index [MHI-5] score >52).

RESULTS — During 4 years of follow-up (282,317 person-years), 973 incident cases of type 2 diabetes were documented. Age-adjusted RR of developing type 2 diabetes for women with presence of depressive symptoms was 1.55 (95% CI 1.27–1.90). Additional adjustment for BMI resulted in a RR of developing type 2 diabetes of 1.36 (1.11–1.67). The multivariate RR of developing type 2 diabetes was 1.22 (1.00–1.50). After excluding women diagnosed with diabetes between 1992 and 1994, 472 incident cases of type 2 diabetes were documented for the follow-up period from 1994 to 1996 (148,889 person-years). The multivariate RR of developing type 2 diabetes for women with depressive symptoms was 1.29 (0.96–1.72).

CONCLUSIONS — Our data suggest that depressive symptoms are associated with a modest increase in the risk of type 2 diabetes.

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A relationship between depression and risk of diabetes has been hypothesized for some time. Recently, two prospective studies have contributed important new information concerning this association. Eaton et al. (1) and Kawakami et al. (2) both found an approximate twofold increase in the risk of type 2 diabetes for subjects with a history of a major depressive disorder or depressive symptomatology at baseline. Both studies suggest that depression may precede the onset of type 2 diabetes and possibly play an important role in the development of the disease. Studies have suggested that depressive disorders are accompanied by increased sympathoadrenal system activity as measured by norepinephrine, dopamine, and adrenaline in cerebrospinal fluid, plasma, or urine (2–6), which are, in turn, known to be associated with impaired glucose tolerance and increased blood glucose (7). Depressive disorders have also been associated with the dysregulation of the hypothalamic-pituitary-adrenal axis (8), resulting in an increased release of cortisol, decreased glucose uptake, and elevated glucose levels (7). The ability to handle carbohydrate load may be impaired by the increased release of these counterregulatory hormones in depression, which could increase the risk of developing type 2 diabetes. Medical treatment for major depressive disorder or changes in diet and physical activity associated with chronic depression may also contribute to an association between major depressive disorders and the occurrence of type 2 diabetes (1).

In this study, we used a self-reported measure of mental health status to quantify the relationship between depressive symptoms and incidence of type 2 diabetes in women.

RESEARCH DESIGN AND METHODS

— The Nurses' Health Study cohort was established in 1976 when 121,700 female registered nurses aged 30–55 years residing in 11 U.S. states responded to a mailed questionnaire regarding their medical history and health practices. Using both telephone and certified mail since 1990, responses have been received from >90% of the women in the study; details have been published elsewhere (9). For the present analysis, the subjects were 72,178 women from this cohort who in 1992 were free from diagnosed diabetes and who answered the Medical Outcomes Study 36-Item Short-Form Health Status Survey (SF-36).

Assessment of depressive symptoms

In 1992, participants' mental health status was assessed using the five-item Mental Health Index (MHI-5), a subscale of the SF-36. The MHI-5 is used to capture four major dimensions of mental health: anxiety, depression, loss of behavioral/emotional control, and psychological well-being (10,11). Subjects were asked

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Abbreviations: MHI-5, five-item Mental Health Index; SF-36, Medical Outcomes Study 36-Item Short-Form Health Status Survey.

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

how much of the time (all, most, good bit, some, little, or none) during the preceding 4 weeks they felt nervous, felt so down nothing could cheer them up, felt calm and peaceful, felt downhearted and blue, or felt to be a happy person. From the responses to these items, a scale was constructed with scores ranging from 0 to 100 and which can be considered a continuous measure of mental health or a binary indicator of the presence or absence of depressive symptoms. Participants with higher scores enjoy better mental health, while those scoring <52 are likely to satisfy clinical diagnostic criteria for depression and related disorders (12). The MHI-5 was originally constructed by selecting the five items that best predicted the summary score for the 38-item Mental Health Inventory. The sum of the five items, without weights, correlated (r = 0.95) with the 38-item scale (13–17). For the present analysis, the MHI-5 score was considered a dichotomous indicator of the presence (MHI-5 score <52) or absence (MHI-5 score ≥52) of depressive symptoms.

The use of the MHI-5 as a tool for the identification of clinical depression was described by Berwick et al. (13,14) in a receiver operating characteristic analysis with high area under the curve (area = 0.892). The scale has performed well in criterion-based tests of validity, with subjects scoring low more often requiring inpatient and outpatient psychiatric care and exhibiting suicidal ideation (13). The MHI-5 also has high sensitivity and specificity for detecting clinical depression (13). Since the MHI-5 is not a clinical diagnosis tool, it is important to emphasize that participants scoring in the <52 range were classified as exhibiting "depressive symptoms" as opposed to having depression.

Table 1—*Distribution of potential type 2 diabetes risk factors according to presence or absence of depressive symptoms at baseline (1992)

	Depressive symptoms†	
	No	Yes
No. of women	66,385	5,793
Current smokers	13.9	19.0
Past smokers	41.9	43.0
History of hypertension	22.9	28.3
Parental history of diabetes	19.9	21.3
Current postmenopausal hormone use	14.9	13.3
Age (years)	58.8 ± 7.1	57.2 ± 7.2
BMI (kg/m^2)	25.9 ± 4.8	26.3 ± 5.6
Physical activity (total METs/week)	24.4 ± 71.4	21.1 ± 78.9
Polyunsaturated fat (g/day)	10.5 ± 2.8	10.5 ± 2.9
Fiber from cereal (g/day)	5.8 ± 3.3	5.7 ± 3.0
Alcohol (g/day)	5.2 ± 9.5	5.2 ± 10.7

Data are percent or means ± SD. *Percentages and means for variables other than age are standardized according to the age distribution of the overall study group. †If MHI-5 score is <52, participant is said to have "depressive symptoms" (see RESEARCH DESIGN AND METHODS).

Diagnosis of diabetes

A supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy was mailed to women who indicated on any biennial questionnaire that they had been diagnosed as having diabetes. Women reporting a diagnosis of diabetes before 1992 were excluded from these analyses.

A case of diabetes was considered confirmed if at least one of the following was reported on the supplementary questionnaire: *1*) one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger) plus fasting plasma glucose levels of at least 140 mg/dl (7.8 mmol/l) or random plasma glucose levels of at least 200 mg/dl (11.1 mmol/l); *2*) at least two elevated plasma glucose concentrations on different occasions (fasting levels of at least 140 mg/dl [7.8 mmol/l], random plasma glucose levels of at least 200 mg/dl [11.1 mmol/l], and/or concentrations of at least 200 mg/dl after 2 h or more on oral glucose tolerance testing) in the absence of symptoms; or *3*) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent).

Our criteria for diabetes classification are consistent with those proposed by the National Diabetes Data Group (18). The validity of this questionnaire has been verified in a subsample of this study population (19). Among a random sample of 84 women classified by the questionnaire as having type 2 diabetes, 71 gave permission for their medical records to be reviewed, and records were available for 62. An endocrinologist (J.E.M) blinded to the information reported on the supplementary questionnaire reviewed the records according to National Diabetes Data Group criteria (18). The diagnosis of type 2 diabetes was confirmed in 61 (98%) of the 62 women (19).

Statistical analysis

Person-years for each participant were calculated from the date of return of the 1992 questionnaire to the date of confirmed type 2 diabetes, death from any cause, or 1 June 1996, whichever came first. Incidence rates of type 2 diabetes were obtained by dividing the number of cases by person-years in each of the two levels of the MHI-5 score. Relative risks (RRs) were computed as the incidence rate for the presence of depressive symptoms divided by the incidence rate for the absence of depressive symptoms, with adjustment for 5-year age categories. The 1992 MHI-5 score was carried through the analysis for both follow-up periods.

Pooled logistic regression with 2-year intervals (20) was used to adjust simultaneously for potential confounding variables, including age (5-year intervals), smoking status (never, past, or current smoker), BMI (<21, 21–22.9, 23.0–24.9, 25.0–28.9, 29.0–32.0, 32.1–35.0, >35 kg/m^2), quintile of physical activity (<3.5, 3.5–8.9, 9.0–16.7, 16.8–30.8, ≥30.9 MET-h/week), alcohol consumption (0, 1–4, 5–14, ≥15 g per day), menopausal status and postmenopausal hormone use, parental history of diabetes, and history of hypertension. Nutrient intake of magnesium, cereal fiber, glycemic load, and polyunsaturated fat in quintiles were also included in the multivariate models (21).

RESULTS — During the 4 years of follow-up (282,317 person-years), 973 incident cases of type 2 diabetes were confirmed, corresponding to an inci-

Table 2—*RRs (95% CIs) of type 2 diabetes according to presence of depressive symptoms, 1992–1996*

	Depressive symptoms*		
	No	Yes	P
No. of cases	863	110	
Person-years	259,777	22,540	
Age adjusted	1.0	1.55 (1.27–1.90)	<0.0001
Age, BMI adjusted	1.0	1.36 (1.11–1.67)	0.003
Multivariate†	1.0	1.22 (1.00–1.50)	0.05

*See Table 1 for definition of "depressive symptoms." †Model included age (5-year category); time period (two periods), seven categories of BMI (< 21, 21–22.9, 23.0–24.9, 25.0–28.9, 29.0–32.0, 32.1–35.0, >35 kg/m^2), cigarette smoking (never, past, and current smoker), menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, or postmenopausal with current hormone replacement), parental history of diabetes, alcohol consumption (four categories), history of hypertension, and quintile of physical activity (MET score).

dence rate of 345 per 100,000 person-years. Table 1 shows the distribution of selected characteristics according to presence or absence of depressive symptoms, standardized to the age distribution of the study population. Compared with those without depressive symptoms, women with depressive symptoms were more likely to be current smokers or hypertensive. Among the women with depressive symptoms, 19% were current smokers at the start of follow-up compared with 13.9% of women without depressive symptoms. Also, 28.3% of women with depressive symptoms had a history of hypertension, whereas only 22.9% of women without depressive symptoms had this history. Other variables, including BMI, dietary intake of fat, and physical activity score, did not appreciably differ between the two groups.

The age-adjusted RR of type 2 diabetes suggested an increased risk for women with depressive symptoms (Table 2). The RR of type 2 diabetes for women with depressive symptoms compared with women without depressive symptoms was 1.36 (95% CI 1.11–1.67) after additional adjustment for BMI. After adjusting for smoking, alcohol use, parental history of diabetes, level of physical activity, and menopausal status, the RR of type 2 diabetes for women with depressive symptoms compared with women without depressive symptoms was 1.22 (1.00–1.50). Further adjustment for glycemic load, cereal fiber, magnesium, and polyunsaturated fat consumption did not materially alter these results.

Stratified logistic regression models were used to examine the association between depressive symptoms and type 2 diabetes in various cohort subgroups to assess the presence of effect modification (Table 3). Tests for interactions between depressive symptoms and each of the potential effect modifiers were also conducted and are also presented in Table 3. All of the interactions were nonsignificant, and the stratified RRs did not vary appreciably from those of the entire cohort.

An additional analysis excluding cases of type 2 diabetes that occurred during the first 2 years of follow-up (472 cases and 148,889 person-years of follow-up were included in this analysis) was conducted to reduce the potential bias from subclinical disease, i.e., undetected diabetes leading to depressive symptoms, rather than the reverse. The age-adjusted RR of diabetes for women with depressive symptoms compared with those without was 1.59 (95% CI 1.20–2.12) (Table 4). The multivariate RR of diabetes for women with depressive symptoms compared with women without depressive symptoms was 1.29 (0.96–1.72). These findings were comparable to the results for the entire follow-up period.

CONCLUSIONS — In this large prospective cohort study, the presence of depressive symptoms was associated with a modest increase in the risk of type 2 diabetes. Our results agree with previous observations by Eaton et al. (1) and Kawakami et al. (2) that there is a higher risk of type 2 diabetes among individuals who have experienced depressive symptomatology. However, we did not see as strong an association as Eaton et al. (1) or Kawakami et al. (2), but found only a modest, though significant, elevation in the risk of type 2 diabetes for those women who reported depressive symptoms. The difference between the findings of our study and the two previous studies (1,2) may have been due to the definition of depression that was used. Eaton et al. (1), in particular, examined subjects with

Table 3—*Adjusted RRs (95% CIs) according to presence of depressive symptoms in various cohort subgroups

	Multivariate† RR	Interaction‡ *P* value
BMI (kg/m^2)		0.55
<25 (*n*§ = 34,379)	0.87 (0.40–1.89)	
25–29.9 (18,628)	1.43 (0.97–2.11)	
≥30 (14,812)	1.24 (0.96–1.61)	
Smoking		0.82
Yes (10,361)	1.28 (0.77–2.12)	
No (61,817)	1.21 (0.97–1.53)	
Parental history of diabetes		0.47
Yes (14,474)	1.11 (0.79–1.56)	
No (57,687)	1.28 (0.99–1.66)	
Alcohol consumption		0.62
Yes (47,888)	1.24 (0.92–1.67)	
No (24,290)	1.23 (0.92–1.63)	

*Relative risk of developing type 2 diabetes for women with depressive symptoms compared with women without depressive symptoms; †calculated using stratified pooled logistic regression with same covariates as in Table 2; ‡calculated using likelihood ratio test by subtracting −2logL for multivariate model with interaction from −2logL for multivariate model without interaction. Test has a χ^2 distribution with v degrees of freedom, where v = ($df_{\text{model with interaction}}$) − ($df_{\text{model without interaction}}$); §*n* = number of nurses in that category at baseline.

Table 4—*RRs (95% CIs) of type 2 diabetes according to presence of depressive symptoms excluding women with diabetes during the first 2 years of follow-up*

	Depressive symptoms		
	No	Yes	*P*
No. of cases	417	55	
Person-years	136,858	12,031	
Age adjusted	1.0	1.59 (1.20–2.12)	0.001
Age, BMI adjusted	1.0	1.41 (1.06–1.87)	0.02
Multivariate*	1.0	1.29 (0.96–1.72)	0.09

*Adjusted for the same covariates as in Table 2. See footnotes to Table 1 for definition of "depressive symptoms."

a major depressive disorder. In our study, we used a scale that serves as a proxy for depressive symptoms.

The relationship between depressive symptoms and incidence of type 2 diabetes was generally consistent for those at high or low risk for diabetes, and remained significant after adjustment for BMI. Stratified analyses of the relationship revealed that the relationship was consistent even when the cohort was broken down into various subgroups (including smoking status, BMI, alcohol drinking, and parental history of diabetes). Thus, no one subgroup appeared to be driving the association that we found. After adjusting for age, BMI, physical activity, and other factors relevant to the onset of type 2 diabetes, the magnitude of the association decreased, but remained marginally significant.

One of the limitations of the previous studies (1,4) was the inability to address the issue of presence of subclinical diabetes at baseline. In our study, we tried to "adjust" for the problem of undetected diabetes by conducting a secondary analysis excluding women who developed type 2 diabetes during the 2-year follow-up period immediately following the baseline measurement of depressive symptoms. The association found was similar to that in our primary analysis, although with reduced statistical power. It is possible that subclinical diabetes may go undetected for a period longer than the 2 years we allowed in our study. A prospective study of longer duration that can allow a longer period between baseline measurement of depressive symptoms and onset of type 2 diabetes would be desirable.

Eaton et al. (1) suggested that only major depressive disorder was associated with type 2 diabetes. The study contrasted major depressive disorder with milder depression and with other aspects of psychopathology and did not find a relationship with the latter. The present study indicates that there is an association, albeit modest, between depressive symptoms and risk of type 2 diabetes. Eaton's study also explored the relationship between lifetime experiences of depressed or sad moods before baseline and the onset of type 2 diabetes. However, such a long lead time could result in an underestimation of the risk associated with milder depressive symptoms (1). Moreover, even though the study found an association after adjusting for sex, age, race, and obesity, other factors that are relevant to the onset of type 2 diabetes, such as family history of diabetes, physical activity, smoking, and alcohol consumption, were not included as covariates in their analyses.

The study conducted by Kawakami et al. (2) found an elevated risk similar to that found in the study by Eaton et al. (1) and suggested that subjects with milder levels of depressive symptoms had minimal increase in risk. The instrument used to measure depressive symptoms (the Self-Rating Depression Scale) was a self-report with no capacity to capture differences in overreporting or underreporting symptoms, which may lead to misclassification of exposure status. Our measure of "depressive symptomatology" was based on a relatively crude index (the MHI-5 from SF-36), which is not the same as validated screening instrument for clinical depression, nor an interview-derived diagnosis of major depression. This is in contrast to the previous studies, which used validated instruments to measure the presence of depression. Despite this limitation, our findings supported a modest association with diabetes. This suggests that even subclinical symptoms of depression may be associated with increased risk of diabetes. However, this would require further replication using instruments that are specifically designed to measure depressive symptomatology, e.g., the Center for Epidemiological Studies-Depression (CES-D) scale.

Several limitations in the present study also warrant consideration. First, the diagnostic criteria for type 2 diabetes were changed in 1997 (22), such that lower fasting glucose levels (≥126 mg/dl [7.0 mmol/l]) would now be considered diagnostic. We used the criteria proposed by the National Diabetes Data Group (18) because all our cases were diagnosed before 1997. If the new criteria were used, some women in this study classified as being without diabetes would have been reclassified as having diabetes. However, this would not explain our results because inclusion of women with diabetes in the group without diabetes would have attenuated the association and caused bias toward the null. Since the study population was not screened for glucose intolerance, it is possible that subclinical diabetes may have further attenuated the associations observed. Our assessment of depressive symptoms was limited to the MIH-5. We did not collect information sufficient to establish a clinical diagnosis of depression, according to Diagnostic and Statistic Manual criteria. Finally, since our study population was relatively homogeneous, consisting of predominantly white female nurses, our results can be generalized to white women in general. However, there may be limited generalizability to other populations. Future studies that include more ethnically and demographically diverse populations would be desirable.

In conclusion, this large prospective study suggests that the presence of depressive symptoms is associated with a modest elevation of the risk of type 2 diabetes in women. We observed a similar increase in risk after excluding diagnoses of diabetes in the first 2 years of follow-up, although statistical power was reduced. These findings require further corroboration but suggest that depressive symptoms may identify a group at increased risk of subsequent type 2 diabetes and who may benefit from increased screening and/or interventional strategies.

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