

# Depressive Symptoms and Occurrence of Type 2 Diabetes Among Japanese Men

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**OBJECTIVE**— To examine the relationship between depressive symptoms and the incidence of type 2 diabetes.

**RESEARCH DESIGN AND METHODS**— In 1984, 2,764 male employees of an electrical company in Japan completed a self-administered questionnaire including the Zung Self-Rating Depression Scale (SDS). They were followed for the next 8 years, and 2,380 (86%) responded to the follow-up survey in 1992. During the follow-up survey, occurrence of type 2 diabetes was diagnosed according to World Health Organization criteria.

**RESULTS**— A total of 41 cases of type 2 diabetes were identified during the 8-year follow-up survey. After controlling for other known risk factors for type 2 diabetes, a proportional hazard analysis indicated that subjects who had moderate or severe levels of depressive symptoms ( $\geq 48$  on the SDS) at baseline had a 2.3 times higher risk of having type 2 diabetes at the follow-up survey than those who were not depressed ( $\leq 39$  on the SDS) ( $P < 0.05$ ).

**CONCLUSIONS**— Depressive symptoms may be associated with the onset of type 2 diabetes.

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It has been long recognized that patients with type 2 diabetes have a higher prevalence of major depressive disorder and depressive symptoms than the general population (1–4). Several hypotheses have been raised to explain this association that mainly focus on the effects of severity, complications, and poor glycemic control resulting from type 2 diabetes on the development of depression (2). Recently, Eaton et al. (5) reported that subjects who had ever experienced a major depressive disorder before the baseline had a 2.2 times higher risk of developing type 2 diabetes during the next 13 years. Depression may precede the onset of type 2 diabetes and may play an important role in the development of type 2 diabetes. Studies have suggested that depressive disorders (6–9) are accompanied by increased sympathoadrenal system activity as measured by nora-

drenaline, dopamine, and adrenaline in cerebrospinal fluid, plasma, or urine, which are known to be associated with increased blood glucose and impaired glucose tolerance (10). Depressive disorders have also been associated with the dysregulation of the hypothalamopituitary adrenal axis (11), which results in an increased release of glucocorticoids, decreased glucose uptake, and elevated glucose levels (10). Depression may impair the ability to handle a carbohydrate load and then increase the risk of developing type 2 diabetes through a greater release of these counterregulatory hormones. The association between major depressive disorder and occurrence of type 2 diabetes may also be explained by medical treatment for the disorder or changes in diet and physical activity associated with chronic depression (5).

The findings by Eaton et al. (5) have not been replicated. Eaton et al. (5) sug-

gested that only major depressive disorder is associated with type 2 diabetes because a depressed or sad mood that did not fulfill the diagnostic criteria for major depressive disorder was not associated with an increased risk of type 2 diabetes in their study. However, their study linked lifetime experiences of depressed or sad moods before the baseline with the succeeding onset of type 2 diabetes. Such long lead time may result in an underestimation of the risk associated with milder depressive symptoms. Furthermore, the study had several methodological limitations. The study relied on self-reported data of diabetes at baseline and during the follow-up survey. Although the study found the association after adjustment for sex, age, race, and obesity, other factors relevant to the onset of type 2 diabetes (e.g., physical exercise, smoking, alcohol drinking, other chronic diseases, and family history of diabetes) were not considered.

We analyzed data from an 8-year prospective cohort of Japanese male employees (12) to study the relationship between self-reported depressive symptoms and the incidence of type 2 diabetes. Our data were based on a systematic screening of the onset of diabetes during the follow-up, and the diagnosis was made according to the standard World Health Organization (WHO) criteria (13). We also controlled for relevant variables for type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Subjects

In 1984, at baseline, all employees ( $n = 3,863$ ) were surveyed by using a mailed questionnaire concerning depression and other covariates. A total of 3,551 (92%) employees returned the questionnaires. Because of the small number of female respondents ( $n = 485$ ), we limited the analysis to the 3,066 male respondents. The subjects were also interviewed at baseline by nurses to learn their history of medical treatment for diabetes. Of male respondents, 46 (1.5%) were excluded from the analyses because they were iden-

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**Abbreviations:** SDS, Self-Rating Depression Scale; WHO, World Health Organization.

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

tified as having a medical history of diabetes according to the interview by nurses or the company medical record. Of the respondents, 256 were excluded because they had a missing response on variables relevant to this study in the questionnaire. A total of 2,764 male respondents were followed for the next 8 years and were surveyed in 1992 by using a mailed questionnaire to assess a family history of diabetes. Data from 2,380 (86%) male respondents who were completely followed at the 1992 survey were analyzed.

### Incidence of diabetes

Incidence of type 2 diabetes was assessed each year based on an annual screening program for diabetes. During the follow-up period, all the subjects received a medical checkup once a year that included a semi-quantitative test for glucose in a urine sample. Fasting plasma glucose was measured in subjects who had glycosuria, and a 75-g oral glucose tolerance test was conducted for subjects who had a fasting plasma glucose level  $\geq 110$  mg/dl to determine the diagnosis of type 2 diabetes according to the WHO criteria (13).

### Assessment of depressive symptoms

Depressive symptoms were assessed by means of the Zung Self-Rating Depression Scale (SDS) at baseline (14,15). The SDS consists of 10 negatively worded items and 10 positively worded items on symptoms of depression. The original English scale was translated into Japanese, and the Japanese version has been well validated (16). The sensitivity was 80–90%, and the specificity was 90–95% for clinical or *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., rev.) diagnosis of major depression when the SDS score of 48 was used as a cutoff. The level of depression was classified on the basis of the SDS scores: “normal” (20–39), “mild” (40–47), and “moderate or severe” ( $\geq 48$ ) (15,17).

### Other covariates

Other covariates included age, education, occupation, work shift, obesity, leisure-time physical activity, smoking, alcohol consumption, chronic medical conditions, and family history of diabetes. All variables except family history were assessed at the baseline survey. Age at baseline was classified into 18–34, 35–44, and 45–53 years of age (37.8, 39.3, and 22.9%, respectively). Years of education were categorized into three groups: 5–9, 10–12, and 13+ years

(38.7, 46.8, and 14.5%, respectively). Occupation was categorized into three groups: white-collar workers (managers, technicians, and clerical workers), mechanics/repair workers, and machine operators/transportation workers (30.1, 12.4, and 57.5%, respectively). The respondents were classified into daytime and rotating shift workers on the basis of the type of work shift (54.5 and 45.5%, respectively). Frequency of physical activity in leisure time was assessed by using a single question and was categorized as physically active (sometimes or often) or inactive (hardly none) (62.8 and 37.2%, respectively). Number of cigarettes smoked per day was assessed at baseline. Alcohol consumption was assessed by inquiring about whether subjects drank any alcoholic beverages. Alcohol drinkers were asked to recall the mean amount of alcoholic beverages per week that they typically drank during the past year. Amount of pure ethanol consumed in milligrams per week was estimated by multiplying the concentration of ethanol and amount of each beverage and then adding them together. Obesity was measured by BMI ( $\text{kg}/\text{m}^2$ ) from physical examination data at baseline. The subjects were interviewed by nurses to learn their history of medical treatment for any of the following chronic medical conditions according to the *International Classification of Disease* 9th revision: hypertension, coronary heart diseases, cerebrovascular diseases, or metabolic diseases, other than diabetes (any of these 4.5%, none of these 95.5%). Family history of diabetes in first-degree relatives was assessed by using the questionnaire at the 1992 survey (any 13.1, none 86.9%). Average values  $\pm$  SD of BMI, number of cigarettes smoked per day, and alcohol consumption per week for the 2,380 respondents were  $22.1 \pm 2.5$   $\text{kg}/\text{m}^2$ ,  $12.9 \pm 12.2$  cigarettes/day, and  $291 \pm 194.1$  mg/week, respectively.

### Statistical analysis

Age-adjusted incidence rates of type 2 diabetes were compared among the groups classified by level of depressive symptoms at baseline. The age-adjusted incidence rates were calculated with the direct method by using the total male subjects ( $n = 2,380$ ) as a standard population. Cox's proportional hazards regression analysis for discrete time (18) was conducted to ascertain age-adjusted risks of type 2 diabetes among the levels of depression and to assess the unique effect (i.e., multivariate

risk) of the levels of depression on the incidence of type 2 diabetes when controlling for the nine covariates (age, education, occupation, work shift, obesity, leisure-time physical activity, smoking, alcohol consumption, chronic medical conditions, and family history). For three continuous variables (BMI, number of cigarettes smoked per day, and alcohol consumption), hazard ratios for changes of 1  $\text{kg}/\text{m}^2$ , 10 cigarettes, and 100 mg/week, respectively, were estimated. The analyses were carried out on a personal computer by using the PHREG computer program of the SAS Version 6.11 (19).

**RESULTS** — During the observation of 18,912 patient-years, 43 subjects develop type 2 diabetes. None of the respondents developed insulin-dependent diabetes during the period. The crude incidence rate was 2.3 per 1,000 patient-years.

The age-adjusted incidence rates of type 2 diabetes were higher in those who had moderate to severe levels of depressive symptoms at baseline than those who had normal levels of depression (Table 1). Age-adjusted hazard ratios were significantly higher for those who had moderate or severe levels of depressive symptoms. In the proportional hazard model when controlling for all covariates, subjects who had moderate or severe levels of depressive symptoms had a significantly higher hazard ratio of type 2 diabetes than subjects who had normal levels of depressive symptoms (Table 2). When we excluded 17 cases with type 2 diabetes that were found within the first half of the follow-up period (1985–1988) from the analyses, a proportional hazard analysis of the remaining 26 cases indicated that the age-adjusted hazard ratios were 0.79 (95% CI 0.30–2.08) for mild depressive symptoms and 2.85 (95% CI 1.13–7.19) for moderate or severe depressive symptoms; the hazard ratios after controlling all covariates were 0.82 (95% CI 0.31–2.18) for mild depressive symptoms and 2.77 (95% CI 1.06–7.26) for moderate or severe depressive symptoms. Examination of company medical records at the end of the follow-up identified 35 study subjects who received medical treatment for psychiatric disorders during follow-up. Excluding these known subjects who had psychiatric treatment from the analysis did not change the results.

A comparison of subjects who were lost to the follow-up survey ( $n = 348$ ) with

**Table 1—Age-adjusted incidence rates and hazard ratios of type 2 diabetes during the 8-year follow-up period (1984–1992)**

Level of depression (SDS score)	Subjects followed (n)	Cases (observed patient-years [n])	Age-adjusted incidence/1,000 patient-years	Age-adjusted hazard ratios (95% CI)
Normal (20–39)	1,316	21 (10,469)	1.96	1.00
Mild (40–47)	786	13 (6,241)	2.10	1.07 (0.53–2.13)
Moderate or severe (48–80)	278	9 (2,202)	4.37	2.32 (1.06–5.08)*
P for trend				0.081

A total of 2,380 male Japanese employees classified by levels of depression at baseline according to the Zung SDS were studied. Age-adjusted hazard ratios were estimated by a discrete failure time analysis, and the *P* value for this trend was 0.081. \**P* < 0.05.

those who were completely followed indicated that older age, lower levels of depressive symptoms at baseline, and chronic conditions were significantly associated with dropping out of the follow-up survey (Table 3). After controlling for age with the Mantel extension  $\chi^2$  test or two-way analysis of variance, only chronic medical conditions were significantly associated with being lost to the follow-up survey (*P* < 0.05).

**CONCLUSIONS** — Our study indicates that moderate or severe levels of depressive symptoms were associated with later occurrence of type 2 diabetes in Japanese male employees. Our finding agrees with a previous observation by Eaton et al. (5) that a higher risk of type 2 diabetes exists among those who experienced major depressive disorder, and our study further suggests that those who have depressive symptoms (a less severe form of depression) also have a higher risk of developing type 2 diabetes.

The incidence rate during follow-up is slightly lower than that in a male community population in Japan (3–7/1,000 person-years) (20). This may be attributable to a younger age range in our study sample. The incidence is even similar with rates reported in the U.S. (2–6/1,000 person-years for subjects aged  $\geq 40$  years) (21). Comparisons of several indicators (i.e., mean height, weight, and BMI) with a Japanese national sample suggest that our sample does not greatly differ from the Japanese male population (12). Our 8-year follow-up rate was relatively high. Depressive symptoms or the covariates other than chronic medical conditions were not statistically significant between subjects who were completely followed and subjects who dropped out after controlling for age. Thus the results are unlikely to be biased by losses to follow-up. Depressed subjects may be more likely to visit a physician to seek treatment, which may result in a greater likelihood of their diabetes being

detected. In this study, all cases of diabetes were found by a periodic screening in our study, and we used a systematic screening for the onset of diabetes, and the diagnosis was made based on objective examination according to the WHO criteria. Possible bias in case finding is unlikely. However, depressive symptoms may interact with other covariates to influence the onset of type 2 diabetes. In such cases, statistical control for many covariates may result in over- or underestimation of the association and may not be sufficiently useful to rule out a possible confounding bias due to these variables (22). The observed risk of type 2 diabetes (hazard ratio 2.3) associated

with moderate or severe depressive symptoms were statistically significant but relatively small, which can probably be explained by undetected bias. These limitations should be considered in the interpretation of the finding.

We found that subjects with an SDS score  $\geq 48$  had a higher risk of type 2 diabetes than subjects with an SDS score  $\leq 39$ . The degree of risk is very similar to that reported by Eaton et al. (5) for major depressive disorder. On the other hand, the subjects with an SDS score of 40–47 showed little increase in risk of type 2 diabetes. Although our study suggests a higher risk of type 2 diabetes among subjects with

**Table 2—Effects of age, depressive symptoms assessed by the Zung SDS, and other covariates on the 8-year incidence of type 2 diabetes for 2,380 male Japanese employees\***

Variable	Hazard ratio (95% CI)
Age (years)	
18–34	1.00
35–44	2.35 (0.98–5.61)
$\geq 45$	3.17 (1.27–7.89)†
Depressive symptoms (SDS score)	
Normal (20–39)	1.00
Mild (40–47)	1.13 (0.56–2.28)
Moderate or severe ( $\geq 48$ )	2.31 (1.03–5.20)†
BMI (kg/m <sup>2</sup> )‡	1.25 (1.13–1.38)§
Smoking (10 cigarettes smoked per day)‡	1.38 (1.09–1.74)§
Alcohol consumption (100 mg pure ethanol per week)‡	0.98 (0.75–1.27)
Leisure-time physical activity	
Inactive	1.00
Active	0.70 (0.38–1.28)
Chronic medical conditions¶	
None	1.00
Any	1.90 (0.72–5.03)
Family history of diabetes	
None	1.00
Any	2.25 (1.12–4.51)†

\*Hazard ratios were estimated using the Cox's proportional hazard model; age, depression level, education, shift work, occupation, BMI, smoking, leisure-time physical activity, alcohol consumption, chronic medical conditions, and family history of diabetes were simultaneously entered in the model; coefficients were not shown for education, shift work, and occupation; †*P* < 0.05; ‡hazard ratios for changes of 1 BMI (kg/m<sup>2</sup>), 10 cigarettes smoked per day, or 100 mg pure ethanol intake per week (mg/week) were shown; §*P* < 0.01; ¶history of medical treatment for any circulatory disease (e.g., hypertension, heart diseases, cerebrovascular diseases) or metabolic disease other than diabetes.

Table 3—Comparison of age, depressive symptoms, and other covariates between subjects who were completely followed and those who dropped out in an 8-year cohort of male Japanese employees

Variable	Followed up (n = 2,380)		Dropped out (n = 384)	
	%	Mean ± SD	%	Mean ± SD
Age (years)*				
18–34	37.8		24.0	
35–44	39.3		34.9	
45–60	22.9		41.1	
Depressive symptoms†				
None	55.3		63.0	
Mild	33.0		28.9	
Moderate or severe	11.7		8.1	
Leisure-time physical activity				
Inactive	37.2		37.2	
Active	62.8		62.8	
Chronic medical conditions*				
None	95.5		90.9	
Any	4.5		9.1	
BMI (kg/m <sup>2</sup> )		22.1 ± 2.5		22.3 ± 2.5
Number of cigarettes smoked per day		12.9 ± 12.1		13.8 ± 12.7
Alcohol consumption (mg/week of pure ethanol)		128 ± 184		136 ± 152

\*P < 0.01, difference between subjects who were completely followed and those who dropped out by using  $\chi^2$  test or *t* test; †P < 0.05.

depressive symptoms, this pattern may be observed only for depressive symptoms greater than a certain level. Because we assessed depressive symptoms only once at baseline, we do not know whether depressive symptoms changed during the follow-up. However, our previous study (23) indicated that half of those subjects who had an SDS score  $\geq 48$  at baseline reported the same level of depressive symptoms 1 year later, and 20% did so even 5 years later. Thus our finding can be interpreted as evidence for the effects of long-term depressive symptoms on onset of type 2 diabetes. It was reported that those who had moderate or severe levels of depressive symptoms (SDS score  $\geq 48$ ) were more likely to maintain the same levels of depressive symptoms than those who had mild levels (SDS score of 40–47) (17). This may partially explain a greater risk of developing type 2 diabetes among subjects who had moderate or severe levels of depressive symptoms than for those who had mild levels.

However, the instrument that we used to measure depressive symptoms (the SDS) was a self-report with no capacity to capture differences in overreporting or underreporting symptoms. The possibility exists that subjects' response tendencies regarding higher depression scores may affect the findings. Furthermore, it has been reported that Japanese people have a tendency to suppress their expression of positive feelings (e.g., being happy) on a self-reported

depression scale, which results in a greater depression score in Japan than that in the U.S., although no such response bias was observed for negatively worded items (e.g., depressed) between the two countries (24). Because the subjects were all Japanese in our study and shared this tendency, suppressing positive feelings may not necessarily be a confounding bias for the finding, but it may inflate the baseline scores of depressive symptoms. The relationship between levels of depressive symptoms and the risk of type 2 diabetes should be examined in other countries.

Because we excluded cases with known diabetes at baseline from the analysis, the observed relationship between depressive symptoms and type 2 diabetes is not likely a result of impairment in daily life or threat to life due to diabetes. We observed a significantly higher risk of type 2 diabetes among subjects who had depressive symptoms at baseline when we excluded cases found in the first half of the follow-up period who may have had undetected type 2 diabetes at baseline. This finding supports the hypothesis that antecedent depressive symptoms increase the risk of future onset of type 2 diabetes. However, we did not conduct 75-g oral glucose tolerance tests for all cases at baseline. Some of the subjects may have had undetected diabetes at baseline and been later found to be incident cases. Diabetic disturbances in glucose metabolism may start 5–10 years

before the diagnosis of type 2 diabetes. Depressive symptoms may worsen glycemic control exclusively among those who already had diabetic metabolic disturbance, thus leading them to an overt diagnosis (25). The possibility that increased depressive symptoms at baseline and an increased risk of type 2 diabetes may stem from a common subclinical metabolic disturbance could not be ruled out by our study (2).

The risk of type 2 diabetes was still higher among subjects who had depressive symptoms at baseline after excluding known cases who received treatment for psychiatric disorders. The use of psychiatric services is still not popular in Japan possibly because of unawareness of mental health problems or the stigma associated with mental illness. A community-based survey reported that 23% of community residents who suffered from ICD-10 mood and anxiety disorders sought medical treatment; only 4% of them visited a psychiatrist (26). These tendencies are comparable with subjects in the U.S. (27). Most subjects who had depressive symptoms at baseline were to receive no treatment for their symptoms. Thus it seems unlikely that the finding was due to psychiatric treatment for those who were depressed.

We found that the association between depressive symptoms and the occurrence of type 2 diabetes was independent of obesity, smoking, drinking, leisure-time phys-

ical activity, chronic medical conditions at baseline, and family history of diabetes. The effect of depressive symptoms on the occurrence of type 2 diabetes is not likely due to changes in these health habits or physical conditions. It has been reported that anger and hostility (28) or psychologically stressful conditions (29) positively correlated with greater levels of blood glucose or glycosylated hemoglobin in nondiabetic men. Depressive symptoms may not simply be a less severe form of depressive disorders; there may be a discontinuity in the etiology and consequences between these two categories of depression. However, studies have suggested that psychological distress (10), as well as depressive disorders (6–9), are accompanied by increased activities of the sympathoadrenal system activity and hypothalamopituitary-adrenal axis followed by greater release of counterregulatory hormones and cortisol, respectively, which are known to be associated with increased blood glucose and glucose intolerance (10). Chronic depressive symptoms may impair the ability to handle a carbohydrate load because of a greater release of counterregulatory hormones or cortisol into blood, activated sympathetic nervous system functioning, or other endocrine disturbances. Another possible explanation for the higher risk of type 2 diabetes among those who had depressive symptoms at baseline is changes in diet associated with depressive symptoms, which could not be examined in our study.

The observed higher risk of type 2 diabetes among subjects who had moderate or severe levels of depressive symptoms at baseline in our study may suggest that physicians need to pay more attention to diabetic metabolic changes among depressed patients for prevention and earlier detection of type 2 diabetes. When considering that depressive symptoms are relatively prevalent in a general population (e.g., 12% in our study sample), an increased risk of type 2 diabetes among those who have depressive symptoms may be important in prevention of type 2 diabetes. A future study is needed to establish a causal relationship between depressive symptoms and occurrence of type 2 diabetes. In such studies, all subjects should have a 75-g oral glucose tolerance test to determine their subclinical metabolic disturbances at baseline and during follow-up; the duration and severity of depressive disorders or depressive symptoms should be consid-

ered. Depression is manifested in various ways, including vegetative, cognitive, or emotional symptoms, and some specific symptoms, such as sleep disturbances, are often clearer indicators of depressive symptoms. It would be useful to address the association of these specific symptoms of depression with the risk of type 2 diabetes. Once established, this association may add a new dimension of primary prevention of type 2 diabetes to the treatment of traditional risk factors such as obesity, diet, and physical inactivity.

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