Depression and Risk for Onset of Type II Diabetes

A prospective population-based study

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OBJECTIVE — To determine whether depression is associated with an increased risk for onset of diabetes.

RESEARCH DESIGN AND METHODS — In 1981, a total of 3,481 household-residing adults participated in the Epidemiologic Catchment Area (ECA) Program survey at the East Baltimore site. A follow-up of that cohort after 13 years completed 1,897 interviews, amounting to >72% of survivors. In 1981, depression was assessed with the National Insitutes of Mental Health (NIMH) Diagnostic Interview Schedule and diabetes, by self-report. This prospective analysis focused on subjects at risk for onset of diabetes by removing from the analysis individuals with diabetes in 1981.

RESULTS — There were 89 new cases of diabetes among 1,715 individuals at risk, yielding a 13-year cumulative incidence of diabetes of 5.2%. In logistic models, major depressive disorder, but not milder forms of depression or other forms of psychiatric disorder, predicted the onset of diabetes (estimated relative risk, 2.23; 95% CI 0.90–5.55). Controlling for age, race, sex, socioeconomic status, education, use of health services, other psychiatric disorders, and body weight did not weaken the relationship.

CONCLUSIONS — Major depressive disorder signals increased risk for onset of type II diabetes. Limitations of the findings arise from the difficulty in determining temporal order with two chronic conditions, even when the temporal order of measurement is clear. In addition, even though control variables were introduced for the use of health services, it is possible that the treatment for depression led to an earlier diagnosis of diabetes in this sample.

There has been speculation for a long time that psychopathology and specifically depression are related to the onset and course of diabetes (1–5). Most studies of diabetes and depression have focused on adults, and results would be expected to be dominated by type II diabetes, since it is more prevalent among adults. Seven out of eight controlled studies reviewed by Gavard et al. (4) that were limited to type II diabetic subjects showed a positive relationship between diabetes and depression, as did two later studies of type II diabetic subjects (6,7). In studies of samples containing both type I and type II diabetic subjects, the association with depression did not differ by type of diabetes (8,9). Wing et al. (10) reported that depressive symptomatology was more common among type II diabetic subjects than control subjects. A study of adults with type I diabetes who were awaiting pancreas transplant also found a higher than expected rate of depression in the diabetic subjects than in the control subjects (11). In summary, the research literature has not focused on the subtypes of diabetes, but the evidence presented does not suggest strong differences between subtypes in the cross-sectional relationship of diabetes to depression.

The relationship of age to diabetes and depression is important since the age of onset is related to the subtype of diabetes. Depression has its peak period of onset in the early adult years (12). A review of 17 studies of children and adolescents with type I diabetes concluded that the findings concerning the association of psychiatric disorders to diabetes were equivocal (13). However, one study found a higher rate of "introversive" disorders (i.e., anxiety and depression) among insulin-dependent diabetic subjects (14). Most studies adjusted for age but none reported whether there was a statistical interaction between age, diabetes subtype, and the association between diabetes and depression. Thus, there is nothing in the literature to suggest differences between age groups in the relationship of diabetes to depression.

The cross-sectional relationship of depression to diabetes could arise in several ways. There may be a common neuroendocrine basis that underlies or precedes both disorders (14,15). It may be that this common basis is stimulated by an episode of depression or the onset of diabetes so that the direction of causation could be either from diabetes to depression, from depression to diabetes, or both. It could be that a depressive episode produces a bodily change, such as in the immune system (16), that raises the risk for diabetes. The cross-sectional relationship could arise because diabetes, similar to other severe medical conditions (17,18), causes a psychological reaction to the stress of illness or to the threat of loss of life or function as a consequence of diabetes or its complications (5,6,19). Finally, depression may be related to a variety of confounding factors, such as obesity, exercise, and use of medications, that could increase the risk for diabetes and lead to poor control after the onset of diabetes (8,20–22). Our research examines, for the first time, the relationship of clinical depression to diabetes in a prospective fashion.

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DIS, Diagnostic Interview Schedule; ECA, Epidemiologic Catchment Area; NIMH, National Insitutes of Mental Health; OR, odds ratio.

RESEARCH DESIGN AND METHODS

— The Epidemiologic Catchment Area (ECA) Program was a national effort to assess the prevalence and incidence of specific psychopathological disorders by interviewing >20,000 persons in five cities who were over 18 years of age (23,24). The target population for the Baltimore site of the ECA in 1981 was household residents of East Baltimore, an area of 175,000 adult inhabitants. In 1981, 3,481 individuals were selected based on probability sampling methods and interviewed in their households, with a completion rate of 82%. Details of the ECA method are available elsewhere (25).

The instrument used in the ECA program was the NIMH Diagnostic Interview Schedule (DIS) (26). The DIS is a highly structured survey interview that is designed to produce diagnoses of specific mental disorders according to criteria established by the American Psychiatric Association (27). In the DIS, close-ended (mostly yes or no) questions are asked by interviewers who have had ~1 week of training but no clinical experience. To be rated as a "plausible psychiatric symptom" that contributes to diagnosis, the report of the symptom must meet criteria of impairment (i.e., seeking help from a professional, taking medication more than once, or having one's life or activities disrupted "a lot"). The respondents must state that the symptom was not always caused by drugs, alcohol, medical illness, or injury. A computer algorithm combines the responses into diagnostic categories. The symptoms and diagnoses have a temporal dimension, including the report that a symptom or diagnosis has ever occurred over the lifetime of the respondent. This "lifetime prevalence" report of the diagnosis of a major depressive disorder is the subject of analysis here. Studies of the reliability and validity of the DIS show that it has good reliability and acceptable validity (26). The DIS has been used in some diabetes research (8), including an analysis of diabetes in another ECA site in Los Angeles (28).

Depression denotes sad mood (dysphoria); it also denotes a psychiatric syndrome or disorder involving sad mood and the accompanying somatic symptoms that surpass a threshold of clinical importance. The operational criteria for the psychiatric disorder, major depressive disorder, are laid out in the *Diagnostic and Statistical Manual of Mental Disorders* (27) and are assessed via the DIS. But the literature on diabetes and depression does not indicate whether the precise criteria for establishing the presence or absence of a psychiatric disorder yields the strongest relationship to risk for diabetes onset; thus, a depression syndrome below the threshold of diagnosis—or simply dysphoria itself—could possibly be related to onset of diabetes under any of the possible theoretical models discussed above. Therefore, indicators of depressive syndrome and dysphoria as used in prior ECA research studies (29) are entertained as predictors of diabetes onset. The DIS includes anxiety and other disorders that have been the subject of prior research on diabetes. The wide range of psychopathologies assessed in 1981 by the DIS allows the examination of many other possible predictors in an exploratory mode of analysis.

Table 1—*Comparison of 1981 cohort with 1993–1994 sample*

	1981 cohort	1981 survivors	1993–1994 interviewed
Men			
Sample size	1,322	951	700
18–29 years	27.2	36.1	35.0
30–44 years	23.4	30.6	29.0
45–64 years	22.9	21.9	24.0
65+ years	26.6	11.5	12.1
	100.1	100.1	100.0
Women			
Sample size	2,159	1,683	1,197
18–29 years	26.2	33.2	29.5
30–44 years	22.3	27.6	28.3
45–64 years	25.0	24.8	26.7
65+ years	26.5	14.5	15.5
	100.0	100.1	100.0
Total sample	3,481	2,634	1,897

Data are *n* or %.

The 1981 ECA surveys in Baltimore included questions on diabetes that were drawn from the Health Interview Survey that was conducted by the National Center for Health Statistics. The questions were: *1*) Have you ever had high sugar or diabetes? *2*) Do you have diabetes now? and *3*) Are you being treated by a health professional for diabetes? Positive answers to one or more of these questions were used to define a subset of individuals who already had diabetes and, therefore, were not at risk for onset of diabetes. Subjects not at risk were excluded from the analyses.

In 1993 and 1994, the Baltimore cohort of 3,481 was the target for tracing and interviewing. These individuals included males and females and a range of ages >18 (Table 1). Credible information on death (in most cases, a positive match from the National Death Index) was available on 847 respondents who died during the follow-up period. The address of 437 individuals of the 3,481 could not be established, and 300 refused to participate. Mortality was a significant factor in the 13-year follow-up, as shown in Table 1. The bulk of tracing and interviewing was completed in 1993 and 1994, with a handful of respondents being located and interviewed in 1995 and 1996. By the end of field work in 1996, over 72% of the 2,652 survivors had been located and interviewed. Respondents with completed interviews did not differ appreciably in terms of age and sex with those survivors who were not interviewed. In another analysis (30), it was shown that certain aspects of psychopathology, such as substance abuse and antisocial behavior, are related to attrition among survivors, but that depression is not related to attrition. For 1993–1996, 1,897 respondents completed interviews.

The follow-up survey contained more detailed questions on diabetes, since it was anticipated that there would be ~100 persons who had become diabetic during the follow-up period. The pertinent section of the questionnaire included the same questions as asked in 1981 and 1982, with additional questions on the age of onset, gestational diabetes, treatment, complica-

Table 2—*Cumulative incidence of diabetes between 1981 and 1993–1994 by age and sex, Baltimore ECA follow-up*

	Men	Women	Total
Age in 1981 (years)			
18–29	2.1 (5/239)	3.7 (12/327)	3.0 (566)
30–44	4.2 (8/189)	3.8 (11/304)	4.0 (503)
45–64	6.0 (9/149)	9.4 (26/276)	8.2 (425)
65+	6.9 (5/72)	8.1 (12/149	7.7 (221)
Total	4.2 (27/649)	5.8 (62/1,066)	5.2 (89/1,715)

Data are % (frequency). Individuals not at risk, 103; missing, 79; total, 1,897.

tions, and the use of health care services. New cases of diabetes were identified by positive answers to the questions on diabetes, combined with a negative answer to the question on gestational diabetes. Eight individuals reported an age of onset younger than their age in 1981; they were eliminated from the group of new cases in order to make the definition of incident cases as conservative as possible. Of the 1,897 interviews, 98 were conducted with informants, and there were 6 incident cases of diabetes reported by these informants that were included in the analysis. In this sample, which had a minimum age of 18 in 1981, there were two respondents who reported ages of onset below the age of 30 (22 and 28 years, respectively).

A series of multiple logistic regressions was estimated to assess the effects of depression on diabetes while controlling for factors that might confound the relationship. First, a best fitting model for sociodemographic variables related to diabetes or to depression was estimated, testing variables one by one and then exhausting all combinations of variables (i.e., not using opportunistic selection procedures). The variables examined (age, sex, race, and socioeconomic status) were those related to diabetes or depression in either our data or prior research. Then, an initial depression model focused on major depressive disorder; additional models, estimated separately, used a variety of measures of depression to assess whether the degree of depression affected the relationship. Consistent with interpretations of some earlier work in other samples (29), the findings were strongest for major depressive disorder; the models for that variable are presented below.

RESULTS — Before considering the prospective results the cross-sectional associations were examined. The prevalence of DIS–*Diagnostic and Statistical Manual* (DSM-III) major depressive disorder in the 148 diabetic respondents interviewed during the 1993–1996 period was 6.1%, compared with 5.3% in the 1,600 nondiabetic respondents. This cross-sectional association was not as strong as it has been found to be in some prior studies, reviewed above, wherein the prevalence of depression was ≥50% higher in diabetic subjects than in nondiabetic subjects. However, age adjustment is required to compare rates because depression is more common in young adults and diabetes, in older adults. When the age range is restricted to those >54 years, the results appeared similar to previous studies. For example, among the 92 individuals with diabetes who were >54 years of age in 1993–1996, the prevalence of major depressive disorder was 3.3%, compared with 2.2% in the 598 nondiabetic respondents.

There were 89 new cases of diabetes among 1,715 individuals at risk. The cumulative incidence, or proportion of the at-risk group having a first onset (31), was 5.2% (Table 2). This ECA incidence compares roughly with a 16-year cumulative incidence of 7.9% in the NHANES I follow-up study (32). Incidence was slightly higher in women than in men, and was substantially higher in middle-aged and elderly persons than in young adults (Table 2).

Estimation of annual incidence rates allows further comparison with other similar surveys. In Table 3, the annual incidence is estimated approximately by adjusting the age categories and dividing age- and sex-specific estimates by 13, allowing a rough comparison with rates presented in work of the National Diabetes Data Group (33). The annual age-specific incidence rates per 1,000 individuals in the population are quite close in the two studies, but the ECA data (weakly) suggest an increased rate for females, a trend not seen in the national data.

There were 76 Baltimore ECA follow-up respondents who, in 1981, met the criteria for the diagnosis of major depressive disorder and had complete data on diabetes in the follow-up. Among these there were 6 new cases of diabetes (7.9%), compared with 80 new cases of diabetes (5.0%) among the 1,604 respondents who did not meet criteria for major depressive disorder in 1981. The relative risk for this two-by-two cross-classification is 1.58, with 95% confidence interval of 0.71–3.51.

Major depressive disorder has a moderate-sized relationship to the risk of becoming diabetic (Table 4). The table includes three hierarchical models that show the independent effects of major potential confounding and mediating variables. In Table 4, odds ratios (ORs) with values close to 1.0 show no or weak association; ORs >1.0 show a direct relationship; ORs <1.0 reveal a protective relationship. Reference categories for sex, age, and race are shown with ORs of 1.0; the reference category for depressive disorder consists of those in the sample who do not meet the criteria for diagnosis. The left-most model in Table 4 shows the relationship of age, sex, and race to the onset

Table 3—*Annual incidence of diabetes per 1,000**

	Baltimore 1981 and 1993–1994			U.S. 1979–1981†		
Age (years)‡	Men	Women	Total	Men	Women	Total
18–24	—	—	—	0.3	0.5	0.4
25–44	2.4	2.5	2.4	1.6	2.4	2.0
45–54	3.8	6.9	5.8	6.2	2.7	4.4
55–64	3.9	7.3	6.0	6.2	5.6	5.9
65–74	6.1	6.8	6.5	4.1	5.0	4.6
75+	2.7	5.6	5.0	4.2	6.0	5.4

*Annual incidence obtained by dividing cumulative incidence from 1981 through 1993/1994 by 13. †Adapted from Table 2 in Everhart et al. (33). ‡Age at midpoint of follow-up.

Table 4—*Predictors of diabetes onset, Baltimore ECA follow-up, logistic regression model adjusted odds ratios*

Predictors	Model 1	Model 2	Model 3
Male (reference)	1.00	1.00	1.00
Female	1.29	1.20	1.08
White (reference)	1.00	1.00	1.00
Black	1.49*	1.50‡	1.27
18–29 years (reference)	1.00	1.00	1.00
30–44 years	1.34	1.33	1.23
45–64 years	3.05‡	3.09‡	3.15‡
≥65 years	2.98‡	3.00‡	4.24‡
Major depressive disorder (1981)	—	2.05	2.23*
BMI			1.09‡

*$P < 0.1$; ‡$P < 0.01$.

of diabetes, with a significantly higher OR for older age-groups, as suggested in Tables 2 and 3. This basic sociodemographic model was also estimated with measures of socioeconomic status, including the Nam-Powers index (34), and grade of schooling achieved forced into the model, both together and singly. These variables of socioeconomic status never had anything larger than a trivial effect and were not included in further analyses. Sex was retained throughout the analyses, even though its effect was not significant, because of its known relationship to depression. Race was retained because of its relationship to treatment for diabetes (35).

The second model, in the middle column of Table 4, shows that major depressive disorder was associated with an increased risk of becoming diabetic by a factor of about two (OR = 2.05). This moderately strong OR is different from the reference value of 1.0 at a marginal level of significance ($P = 0.113$).

Even though the design is prospective, many confounding variables may explain the relationship between depression and the onset of diabetes. The most important possibility is the body weight. Being overweight is associated with onset of diabetes (33), and depressed individuals sometimes suffer from problems with appetite and weight (both too much appetite and weight gain and too little appetite and weight loss). Therefore, BMI was estimated from height and weight as reported by the respondent in the follow-up. The BMI ranged from 15.2 to 85.8 kg/m^2, with a mean of 27.3 kg/m^2. (A single individual who reported weighing 514 lb generated the high end of the range.) In a logistic model by itself, BMI was associated with an 8% increase in the risk for onset of diabetes (OR = 1.08, 95% CI 1.06–1.12). The effect of BMI is not changed greatly by entry into the model with depression; as shown in the right-most column of Table 4, each unit of BMI raised the odds of becoming diabetic by 9% over the follow-up. However, the estimated odds of becoming diabetic associated with major depressive disorder grew slightly stronger when BMI was included in the model (Table 3; OR = 2.23, 95% CI 0.90–5.55). The level of significance with a conservative two-tailed approach is $P = 0.084$, indicating that the strength of relationship would occur less than 9 times out of 100 purely by chance.

Another possible explanation for the relationship between depression and the onset of diabetes is ascertainment bias. For example, it may be that depressive individuals are more likely to obtain health care, either in order to receive treatment for depression or because they are more likely to seek treatment in general for ordinary or trivial somatic symptoms. Diabetic individuals may be more likely to be noticed by a physician and to be reported by the respondent in the follow-up interview. To attempt to adjust for this possibility, the third model was estimated with measures of the use of health services in 1981, such as whether the respondent reported having a usual source of health care and the number of medical visits made in the 6 months prior to the 1981 interview. Subjects with depression were more likely to have seen a medical care provider in the 6 months prior to the interview in 1981 (data not shown), but neither of these variables had significant parameters in the model, and none of the adjustments had any appreciable effect on the parameter for depression.

Other types of psychopathology were investigated in the same manner as depression. These included depression defined at different levels of severity. Relative risk, estimated via the OR, for the various measures of depression from mildest to most severe included: dysphoria (defined as feeling sad or depressed nearly all the time for 2 weeks or more; OR = 1.02, 95% CI 0.61–1.68); depression syndrome (defined as dysphoria clustered with symptoms in at least three symptom groups in criterion B of the DSM-III definition; OR = 1.02, 95% CI 0.50–2.07); major depressive disorder without exclusions (defined as dysphoria clustered with symptoms in at least four of the criterion B symptom groups and not disallowed either for reason of recent grief or organic mental disorder; OR = 1.83, 95% CI 0.74–4.53); and major depressive disorder (defined as major depressive disorder not attributable to grief or other psychopathology and that led to seeking treatment or the disruption of normal life or activities; OR = 2.23 [as in Table 4], 95% CI 0.90–5.55). ORs for other types of psychopathology, estimated in logistic models analogous to model 3 with adjustments for age, sex, race, and BMI, were: DIS/DSM-III panic disorder, 1.07 (95% CI 0.14–8.33); DIS/DSM-III phobia, 0.84 (95% CI 0.48–1.48); DIS/DSM-III alcohol abuse or dependence, 0.66 (95% CI 0.28–1.57); and DIS/DSM-III obsessive-compulsive disorder, 1.23 (95% CI 0.37–4.18). Models were also estimated that included major depressive disorder and many other types of psychopathology simultaneously and a variable indicating the number of different psychiatric disorders for which the respondent met diagnostic criteria. These other models are not shown because the parameters were trivial in size, were not statistically significant, and did not affect the estimates for major depressive disorder. Thus, no other area of psychopathology had findings as strong as for major depressive disorder.

CONCLUSION — In 1684, Thomas Willis wrote about diabetes: "Sadness, or long sorrow . . . and other depressions and disorders of the animal spirits, are

used to generate or foment this morbid disposition" (cited in ref. 15). The data presented above address, for the first time, Willis' idea with the same precision of temporal orientation as his conception. This prospective study lends support to the hypothesis that antecedent depression raises risk for future onset of diabetes. This study contrasted major depressive disorder with milder depression and with other aspects of psychopathology for which no such prospective relationship was shown. The data suggest that reactive depression is unlikely as a total explanation for the cross-sectional association of diabetes and depression.

An important limitation of this work is the problem of undetected diabetes. A recent estimate is that as many as 50% of diabetic subjects who would be diagnosed by hemoglobin assay or glucose challenge do not report having the illness (35). The implications for this prospective design are that some of those designated "at risk" for diabetes onset may have already had onset. Factors that predict whether an individual has undiagnosed diabetes (i.e., age, race, and sex, as in ref. 36) were adjusted for in this analysis or had no effect on the depression or diabetes OR. But it is possible that undetected onset could have elevated the prevalence of depression before the baseline interview in 1981, thus contributing to the apparent incidence of diabetes among depressive subjects versus nondepressive subjects. This possibility suggests that certain symptoms shared by diabetic subjects and depressive subjects, such as fatigue, should be more common among new cases of diabetes, even before the apparent onset of diabetes in 1981. The data, however, do not show this pattern. For example, among 86 new cases of diabetes with data on self-reported fatigue (i.e., DIS question 79), 14.0% reported fatigue; among the 1,595 at-risk subjects who did not become diabetic and had good data on fatigue, 13.6% reported fatigue. Unrecognized diabetes could not reasonably affect depression through a reaction to the diabetes, which suggests that, if undiagnosed diabetes explains the longitudinal association between diabetes and depression, the effect is mediated by factors that are not psychological.

The literature on diabetes and depression reveals cross-sectional associations across the span of ages from adolescence through adult life and including both subtypes of diabetes. The prospective findings reported here pertain to type II diabetes. These results suggest the direction of influence from depression to diabetes, but they should not be extrapolated to type I diabetes. The research literature is now reaching the stage in which distinctions between types of diabetes and age ranges of samples are increasingly important in furthering understanding of the direction of causality and possible causal mechanisms in the association of diabetes and depression. For example, the cross-sectional relationship of depression to diabetes in adolescence, if it exists (13,14), could possibly occur because the onset of diabetes in childhood or adolescence contributes to the risk for onset of mild reactive depression, as distinct from the relationship demonstrated in this analysis where severe forms of depression were associated with an elevated risk for the onset of diabetes later in life. These possibilities can be explored in future longitudinal research.

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