Examining a Bidirectional Association Between Depressive Symptoms and Diabetes

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THE PREVALENCE OF CLINICAL depression and presence of elevated depressive symptoms are higher among persons with diabetes compared with the general population.[1,2] These associations may be related to increased risk of depressive symptoms in individuals with diabetes, increased risk of type 2 diabetes in individuals with depressive symptoms, or both. Several but not all[3] longitudinal studies have reported that elevated depressive symptoms are associated with incident type 2 diabetes.[4-12] Several factors associated with depressive symptoms, including obesity-promoting health behaviors (eg, physical inactivity, hypercaloric diets)[6-10,12] and activation of the neuroendocrine[13-17] and inflammatory responses[18,19] (resulting in increased cortisol, catecholamines, and cytokines), can induce insulin resistance and the development of type 2 diabetes.

A diagnosis of diabetes or the burden of dealing with its complications might might also lead to symptoms of depression.[1] We previously showed an association between prevalent depressive symptoms and treated type 2 diabetes; however, because our analysis was cross-sectional, we could not determine the temporality of this asso-

See also Patient Page.

Context Depressive symptoms are associated with development of type 2 diabetes, but it is unclear whether type 2 diabetes is a risk factor for elevated depressive symptoms.

Objective To examine the bidirectional association between depressive symptoms and type 2 diabetes.

Design, Setting, and Participants Multi-Ethnic Study of Atherosclerosis, a longitudinal, ethnically diverse cohort study of US men and women aged 45 to 84 years enrolled in 2000-2002 and followed up until 2004-2005.

Main Outcome Measures Elevated depressive symptoms defined by Center for Epidemiologic Studies Depression Scale (CES-D) score of 16 or higher, use of antidepressant medications, or both. The CES-D score was also modeled continuously. Participants were categorized as normal fasting glucose (<100 mg/dL), impaired fasting glucose (100-125 mg/dL), or type 2 diabetes (≥126 mg/dL or receiving treatment). Analysis 1 included 5201 participants without type 2 diabetes at baseline and estimated the relative hazard of incident type 2 diabetes over 3.2 years for those with and without depressive symptoms. Analysis 2 included 4847 participants without depressive symptoms at baseline and calculated the relative odds of developing depressive symptoms over 3.1 years for those with and without type 2 diabetes.

Results In analysis 1, the incidence rate of type 2 diabetes was 22.0 and 16.6 per 1000 person-years for those with and without elevated depressive symptoms, respectively. The risk of incident type 2 diabetes was 1.10 times higher for each 5-unit increment in CES-D score (95% confidence interval [CI], 1.02-1.19) after adjustment for demographic factors and body mass index. This association persisted following adjustment for metabolic, inflammatory, socioeconomic, or lifestyle factors, although it was no longer statistically significant following adjustment for the latter (relative hazard, 1.08; 95% CI, 0.99-1.19). In analysis 2, the incidence rates of elevated depressive symptoms per 1000-person years were 36.8 for participants with normal fasting glucose; 27.9 for impaired fasting glucose; 31.2 for untreated type 2 diabetes, and 61.9 for treated type 2 diabetes. Compared with normal fasting glucose, the demographic–adjusted odds ratios of developing elevated depressive symptoms were 0.79 (95% CI, 0.63-0.99) for impaired fasting glucose, 0.75 (95% CI, 0.44-1.27) for untreated type 2 diabetes, and 1.54 (95% CI, 1.13-2.09) for treated type 2 diabetes. None of these associations with incident depressive symptoms were materially altered with adjustment for body mass index, socioeconomic and lifestyle factors, and comorbidities. Findings in both analyses were comparable across ethnic groups.

Conclusions A modest association of baseline depressive symptoms with incident type 2 diabetes existed that was partially explained by lifestyle factors. Impaired fasting glucose and untreated type 2 diabetes were inversely associated with incident depressive symptoms, whereas treated type 2 diabetes showed a positive association with depressive symptoms. These associations were not substantively affected by adjustment for potential confounding or mediating factors.

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ciation.[20] Two prospective studies of adults have shown that type 2 diabetes is associated with an increased risk of depressive symptoms[21,22]; however, several other studies have shown no association.[11,12,23-25] Other research suggested that obesity and insulin resistance, precursors to type 2 diabetes, are associated with a lower risk of developing depression.[26-28]

Prior studies examining diabetes as a predictor of elevated depressive symptoms have been limited by being conducted only in elderly individuals[21,22,25] or using only self-reported diabetes.[21,23,25] Because of contradictory findings thus far, additional population-based studies that include measurements of diabetes treatment and the presence of comorbidities are needed to investigate whether type 2 diabetes is associated with the development of elevated depressive symptoms. In this article, we used repeated measures of fasting blood glucose and depressive symptoms collected over time to test whether depressive symptoms predicted incident type 2 diabetes and whether participants with type 2 diabetes at baseline were more likely to develop elevated depressive symptoms over follow-up than participants without it.

METHODS
Study Population
The Multi-Ethnic Study of Atherosclerosis is a multicenter, longitudinal cohort study of the occurrence and correlates of subclinical cardiovascular disease and its progression.[29] Because an additional objective of the study was to assess ethnic differences in subclinical disease prevalence, risk of progression, and rates of clinical cardiovascular disease, participants were recruited from 4 prespecified racial/ethnic groups.[29] Between July 2000 and August 2002, 6814 men and women aged 45 through 84 years who identified themselves as white, black, Hispanic, or Chinese and who were free of self-reported clinical cardiovascular disease were recruited from 6 US communities: Baltimore City and Baltimore County, Maryland; Chicago, Illinois;

Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St Paul, Minnesota. Additional details about the design and objectives of the study have been previously published.[29] The first examination took place between 2000 and 2002. The second examination occurred between 2002 and 2004, and the third examination occurred between 2004 and 2005. Written informed consent was obtained from participants and the study was approved by institutional review boards of each institution. Participants were notified by letter of all laboratory results, including glucose values, with a copy to their physician if they requested it. Because the Center for Epidemiologic Studies Depression Scale (CES-D) is not designed to ascertain clinical depression, participants were not notified about elevated symptoms.

Assessment of Depressive Symptoms
Depressive symptoms were assessed at visits 1 and 3 using the CES-D, a 20-item questionnaire developed to assess depressive symptoms in community populations.[30] The CES-D items represent the major components of depression and include depressed mood, feelings of worthlessness, feelings of hopelessness, loss of appetite, poor concentration, and sleep disturbance. The Cronbach α for its reliability ranges between 0.84 and 0.93.[31] Participants were asked to rate each item on a scale from 0 to 3 based on "how often you have felt this way during the past week." Scores range from 0 to 60, with higher scores indicating more severe depressive symptoms. We recognize that the CES-D assesses self-reported depressive symptoms and not clinical depression. For the purpose of our analyses, elevated depressive symptoms were defined by a CES-D score of 16 or higher, consistent with mild to moderate depression or dysthymia,[32] self-reported use of antidepressant medications (tricyclics, nontricyclics, and monoamine oxidate inhibitors), or both. Par-

ticipants with a CES-D score of 16 or higher or who were taking antidepressant medications at visit 3 who did not meet these criteria at visit 1 were considered to have incident elevated depressive symptoms, as previously defined by our group.[20]

The CES-D was administered in English, Spanish, Cantonese, and Mandarin. The reliability of the CES-D is comparable with European American, African American, Mexican American, and Chinese American groups.[33,34]

Assessment of Diabetes Status
Impaired fasting glucose and type 2 diabetes status were determined at each visit. Participants were asked to fast for 12 hours and to avoid smoking and heavy physical activity for 2 hours before each examination. Fasting blood samples were drawn by venipuncture from an antecubital vein into vacuum tubes between 7:30 AM and 10:30 AM. Serum samples were frozen and stored at −70°C. Details of serum sampling and processing have been described previously.[29]

Impaired fasting glucose (100 to 125 mg/dL) and type 2 diabetes (fasting glucose, ≥126 mg/dL; or use of oral hypoglycemic medication, insulin, or both) were defined according to the 2003 American Diabetes Association criteria.[35] Those with diabetes were further subdivided into participants who were untreated or treated. Incident diabetes was defined among participants who did not have diabetes at baseline but developed diabetes at subsequent visits. The date of incident diabetes was estimated at one-half the interval between the last known date without diabetes and the examination at which it was diagnosed.

Covariates
Covariates were assessed at baseline examination using standard protocols as previously described.[20,29] Sex, age, race/ethnicity, years of education, cigarette smoking history, and annual income were self-reported. Prescription and over-the-counter medications were determined by transcription of medications brought into clinic. Weight and height

were measured using a balance beam scale and a stadiometer, respectively, with participants wearing light clothing and no shoes. Height was recorded to the nearest 0.5 cm and weight to the nearest 0.5 lb. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. All anthropometric measures were taken in duplicate and averaged. Blood pressure and lipid levels were measured and categorized using standard procedures and current recommendations.[20,36-38]

Interleukin 6 (IL-6) and C-reactive protein (CRP) were measured using standard techniques previously described.[20] A spot urine sample was collected from each participant, preferably in the early morning at the beginning of the clinic visit. Urinary creatinine and albumin were measured using previously described techniques.[20]

Participants' usual diet was characterized using a 120-item food frequency questionnaire, modified from the validated Insulin Resistance Atherosclerosis Study in which comparable validity was observed for non-Hispanic white, African American, and Hispanic participants.[39,40] The dietary assessment was modified to include foods typically eaten by Chinese groups. We used total daily caloric intake as a summary variable of diet. Physical activity was assessed using the 28-item Typical Week Physical Activity Survey.[29,41] We summarized physical activity as the metabolic equivalent task of minutes per week spent in moderate to vigorous household, outdoor, sporting, conditioning, and volunteer activities.

Analysis

Because the 2 objectives of our study required different population samples, we describe the analysis samples and procedures separately below. However, for both sets of analyses, we began by comparing the distribution of baseline characteristics by depressive symptom status (analysis 1) or type 2 diabetes status (analysis 2) using *t* tests for continuous variables and χ^2 tests for categorical variables. For the nonnormally distributed continuous variables, comparisons were

made using the Wilcoxon rank sum test for the 2-group comparison (analysis 1) or the Kruskal-Wallis test for the 4-group comparison (analysis 2). Prior to modeling, we tested for effect modification by creating interaction terms between categorically elevated depressive symptoms and covariates of interest (ie, age, sex, race/ethnicity, BMI) or between type 2 diabetes status and covariates of interest. Although there was a suggestion that the association of depressive symptoms with incident type 2 diabetes was stronger for whites and Chinese Americans, the direction of association was similar for all ethnicities. Because no interactions were found for either analysis, pooled analyses are presented. Incidence rates for type 2 diabetes were calculated using a Poisson regression person-years approach (analysis 1). The cumulative incidence of elevated depressive symptoms is presented for analysis 2. A 2-sided *P* value <.05 was used to determine statistical significance. Statistical analyses were performed using Stata version 8.2 (Stata Corp, College Station, Texas).

Depressive Symptoms and Incident Diabetes (Analysis 1)

Participants were excluded if they had prevalent untreated or treated type 2 diabetes at the first visit (n=1209); were missing data on type 2 diabetes status at any of the 3 visits, or on the CES-D score at baseline (n=201), or on covariates of interest (n=203), leaving 5201 participants for analysis. Incidence rates of type 2 diabetes were calculated for participants with elevated depressive symptoms or who were taking antidepressant medication and compared with incidence rates among those without elevated depressive symptoms. The relative hazard (RH) of developing type 2 diabetes in participants with elevated depressive symptoms compared with those without was calculated using Cox proportional hazards regression models. Additionally, we modeled CES-D as a continuous variable and reported the RH per 5-point increase in CES-D score.

To explore mechanisms explaining the relation between elevated depressive

symptoms and type 2 diabetes, we used the following strategies: model 1 included terms for age, race/ethnicity, sex, and examination site. Model 2 included the terms in model 1 plus baseline BMI. Models 3 through 6 included the terms in model 2 plus the following terms: model 3, metabolic variables (lipid levels, blood pressure, fasting insulin concentration); model 4, inflammatory markers (IL-6 and CRP levels); model 5, socioeconomic variables (educational achievement, annual household income); and model 6, lifestyle variables (smoking history, daily caloric intake, alcohol use, physical activity level).

Diabetes and Incident Depressive Symptoms (Analysis 2)

Participants were excluded if they had prevalent depressive symptoms (CES-D≥16, antidepressant medication use, or both) at baseline (n=1022), if they were missing data on CES-D score at baseline and visit 3 or on type 2 diabetes status at baseline (n=908), or on covariates of interest (n=37), leaving 4847 who were included in this analysis. The cumulative incidence of elevated depressive symptoms was calculated for participants by baseline fasting glucose status. Because incident depressive symptoms were only assessed at 1 follow-up visit, we used logistic regression to calculate the odds ratio (OR) of developing elevated depressive symptoms in participants with impaired fasting glucose and untreated and treated type 2 diabetes compared with participants who had normal fasting glucose at baseline. We again used a series of multivariate models to investigate mechanisms explaining the relation between type 2 diabetes status and elevated depressive symptoms. The base model was the same as that described above. Subsequent models included terms for BMI, socioeconomic status, lifestyle variables, and markers of diabetes severity (dyslipidemia [triglycerides ≥200 mg/dL, high-density lipoprotein<40 mg/dL, or both], presence of hypertension [blood pressure ≥140/90 mm Hg or antihypertensive medication use], and microalbumin-

uria [urinary albumin:creatinine ratio ≥30 mg/g]).[42] We selected these factors a priori because of their previously reported association with the development of depression in individuals with preexisting type 2 diabetes.

To convert triglycerides to millimoles per liter, multiply by 0.0113; high-density lipoprotein to millimoles per liter, multiply by 0.0259; and glucose to millimoles per liter, multiply by 0.0555.

Table 1. Characteristics of 5201 Men and Women Without Prevalent Diabetes by Depressive Symptom Status in the Multiethnic Study of Atherosclerosis, 2000-2002

	CES-D<16 (n = 4290)	CES-D≥16 or Use of Antidepressant Medications (n = 911)	P Value[a]
Age, mean (SD), y	61.5 (10.1)	59.8 (10.2)	<.001
Sex, No. (%)			
Men	2146 (50.0)	272 (29.9)	<.001
Women	2144 (50.0)	639 (70.1)	
Ethnicity, No. (%)			
White	1813 (42.3)	427 (46.9)	
Chinese American	549 (12.8)	64 (7.0)	<.001
African American	1115 (25.9)	177 (19.4)	
Hispanic	813 (18.9)	243 (26.7)	
Educational status, No. (%)			
<High school	759 (17.7)	163 (17.9)	
High school	601 (14)	188 (20.6)	<.001
≥College	2930 (68.3)	560 (61.5)	
Annual income, No. (%), $			
<15 000	729 (16.9)	219 (24)	
≥15 000 and <24 000	478 (11.1)	127 (13.9)	
≥24 000 and <34 000	525 (12.2)	116 (12.7)	<.001
≥34 000 and <49 000	681 (15.9)	146 (16)	
≥49 000 and <74 000	754 (17.6)	149 (16.4)	
≥74 000	1123 (26.2)	154 (16.9)	
Cigarette smoking status, No. (%)			
Never	2198 (51.3)	444 (48.9)	
Former	1570 (36.7)	319 (35.1)	.004
Current	513 (11.9)	146 (16.1)	
Current alcohol drinking, No (%)	2551 (73.1)	508 (68.2)	.007
Daily caloric intake, median (IQR), calories/d	1483 (1102-2014)	1571 (1159-2175)	<.001
Intentional exercise, median (IQR), MET-min/wk[b]	945 (210-2130)	630 (0-1837.5)	<.001
Systolic blood pressure, mean (SD), mm Hg	125.2 (20.8)	122.9 (21)	.004
BMI, mean (SD)	27.8 (5.2)	28.4 (5.6)	.004
Fasting insulin, median (IQR), mIU/L	5.1 (3.4-7.8)	5.2 (3.4-8.1)	.55
Cholesterol, mean (SD), mg/dL			
LDL	118.6 (30.7)	116.8 (31.9)	.11
HDL	51.4 (14.8)	53.6 (14.8)	<.001
Triglycerides, median (IQR), mg/dL	108 (76-155)	114 (80-160)	.13
IL-6, median (IQR), pg/mL	1.1 (0.7-1.8)	1.3 (0.8-1.9)	<.001
C-reactive protein, median (IQR), mg/L[b]	1.7 (0.8-3.9)	2.2 (0.9-4.7)	<.001
Incident cases of diabetes, No.	215	60	
Person-year	12 968	2729	

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CES-D, Center for Epidemiologic Studies Depression Scale; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MET, metabolic equivalent task.
SI conversion factors: To convert C-reactive protein to nmol/L, multiply by 9.524; HDL and LDL cholesterol to mmol/L, multiply by 0.0259; insulin to pmol/L, multiply by 6.945; triglycerides to mmol/L, multiply by 0.0113.
[a] For categorical covariates, the P value was generated from the χ^2 test. For continuous covariates, the P value was generated from the analysis of variance. For the nonnormally distributed variables, the P value was generated from the Wilcoxon rank sum test.

RESULTS
Depressive Symptoms and Incident Diabetes

Baseline Characteristics. TABLE 1 summarizes the characteristics of the participants who did not have prevalent type 2 diabetes by baseline depressive symptom status. Compared with participants without elevated depressive symptoms, those with depressive symptoms were more likely to be younger, female, less educated, have a lower annual income, smoke cigarettes, and have higher caloric intake and were less likely to consume alcohol. Elevated depressive symptoms were more common among Hispanic and less common among Chinese American and African American participants and varied by site. Participants with elevated depressive symptoms had lower systolic blood pressure and higher BMI, high-density lipoprotein cholesterol, IL-6, and CRP than those without depressive symptoms.

Univariate and Multivariate Analyses. There were 215 incident cases of type 2 diabetes among individuals without elevated depressive symptoms and 60 incident cases among those with elevated depressive symptoms (Table 1). The crude incidence of type 2 diabetes over 3.2 years was 22.0 per 1000-person years for those with elevated depresive symptoms and 16.6 per 1000 person-years for those without elevated depressive symptoms (RH, 1.37; 95% confidence interval [CI], 1.02-1.90). There was a significant graded association between CES-D per 5-unit higher score and incident diabtes in models adjusted for demographic characteristics and BMI (RH, 1.12; 95% CI, 1.03-1.21 for model 1; RH, 1.10; 95% CI, 1.02-1.19 for model 2; TABLE 2). The association persisted following adjustment for metabolic, inflammatory, and socioeconomic factors; however, the association was no longer statistically significant following adjustment for lifestyle factors, even though the point estimates were not substantially changed (RH, 1.08; 95% CI, 0.99-1.19). We observed similar results when we categorized participants by depressive symptom status (RH range, 1.42-1.21 with increasing statistical adjust-

ment; Table 2). Associations in the fully adjusted models were similar to those in the lifestyle-adjusted model.

Diabetes Status and Incident Depressive Symptoms

Baseline Characteristics. **TABLE 3** summarizes the characteristics of participants by type 2 diabetes status who did not have prevalent elevated depressive symptoms at baseline. Compared with normal participants, those with impaired fasting glucose and type 2 diabetes were more likely to be older, male, and nonwhite, and less physically active and to have higher BMI. Participants with untreated and treated type 2 diabetes had lower educational attainment and annual income, were more likely to have microalbuminuria and hypertension, and had lower high-density lipoprotein cholesterol and higher triglycerides. Participants with treated type 2 diabetes were least likely to consume alcohol and had the lowest daily caloric intake.

Univariate and Multivariate Analyses. There were 336 incident cases of elevated depressive symptoms among individuals with normal fasting glucose, 112 with impaired fasting glucose, 15 with untreated type 2 diabetes, and 60 with treated type 2 diabetes (Table 3). The incidence rates of elevated depressive symptoms over 3.1 years were 36.8 for participants with normal fasting glucose, 27.9 for those with impaired fasting glucose, 31.2 for those with untreated type 2 diabetes , and 61.9 for those with treated type 2 diabetes per 1000 person-years. Compared with participants with normal fasting glucose, the odds of developing depressive symptoms were 20% lower in participants with impaired fasting glucose and the point estimates changed little following multivariate adjustment (OR range, 0.78-0.80 with increasing statistical adjustment; **TABLE 4**).

Although individuals with untreated type 2 diabetes were not at increased risk of developing elevated depressive symptoms, those with treated type 2 diabetes were at increased risk of developing elevated depressive symptoms, which per-

Table 2. Relative Hazards of Type 2 Diabetes for Each 5-Point Increase in CES-D Score by Baseline Depressive Symptoms Status in 5201 Men and Women

Model	Relative Hazard (95% Confidence Interval)	
	Per 5-Unit Increase in Continuous Depressive Symptoms (CES-D) Score	Elevated Depressive Symptoms Compared With Normal or Low Depressive Symptoms[a]
1, Base[b]	1.12 (1.03-1.21)	1.42 (1.02-1.95)
2, BMI[c]	1.10 (1.02-1.19)	1.39 (1.02-1.93)
3, Metabolic[d]	1.11 (1.03-1.19)	1.39 (1.01-1.91)
4, Inflammatory[e]	1.10 (1.02-1.19)	1.35 (0.98-1.86)
5, SES[f]	1.11 (1.02-1.20)	1.39 (1.01-1.92)
6, Lifestyle[g]	1.08 (0.99-1.19)	1.34 (0.94-1.88)
7, Fully-adjusted[h]	1.10 (1.02-1.20)	1.21 (0.87-1.67)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CES-D, Center for Epidemiologic Studies Depression Scale; SES, socioeconomic status.
[a] Elevated depressive symptoms were attributed to those whose CES-D score was 16 or higher, were taking antidepressant medication, or both.
[b] Adjusted for age, sex, race/ethnicity, and examination site.
[c] Adjusted using model 1 criteria and BMI.
[d] Adjusted using model 2 criteria and log-transformed triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, systolic blood pressure, and log-transformed fasting insulin.
[e] Adjusted using model 2 criteria and for inflammatory markers IL-6 and C-reactive protein.
[f] Adjusted using model 2 criteria and SES factors: educational status (categorized as <high school, high school, and ≥high school), annual household income (categorized as <$15 000, ≥$15 000-<$24 000, ≥$24 000-<$34 000, ≥$34 000-<$49 000, ≥$49 000-<$74 000, and ≥$74 000).
[g] Adjusted using model 2 criteria and daily caloric intake, smoking status, alcohol use, and physical activity.
[h] Fully adjusted using criteria from all models.

sisted following multivariate adjustment (Table 4). In the fully adjusted model, treated type 2 diabetes was associated with a 52% higher odds of developing elevated depressive symptoms (OR, 1.52; 95% CI, 1.09-2.12).

Because antidepressants can be used to treat other conditions, such as diabetic neuropathy, we repeated the analyses defining incident depressive symptoms only as CES-D scores of 16 or higher (n=130) and found similar results. Compared with participants with normal glucose tolerance, those with treated type 2 diabetes had a 64% higher odds (95% CI, 1.18-2.28) of depressive symptoms following adjustment for age, sex, race/ethnicity, and examination site. The magnitude of association increased to 86% (95% CI, 1.10-3.10) following additional adjustment for BMI, socioeconomic status, lifestyle variables, and markers of diabetes severity.

COMMENT

These findings suggest that individuals with elevated depressive symptoms have a modest increased risk of developing type 2 diabetes during follow-up, independent of sociodemographic, economic, and metabolic factors. Although this association was no longer

statistically significant after adjustment for lifestyle factors, point estimates were largely unchanged by adjustment, suggesting that the association between depressive symptoms and incident type 2 diabetes is not fully explained by lifestyle risk factors. We also found that among individuals without elevated depressive symptoms at baseline, treated type 2 diabetes was associated with a significantly higher odds of developing depressive symptoms during follow-up, independent of BMI, socioeconomic status, and comorbidities.

In contrast with the findings for treated type 2 diabetes, individuals with impaired fasting glucose and those with untreated type 2 diabetes had reduced risk of incident depressive symptoms, although the association with untreated type 2 diabetes was imprecisely estimated and did not reach our prespecified level of statistical significance due to small numbers. In both analyses, findings were comparable across race/ethnicity. To our knowledge, this is the first population-based study to show a bidirectional longitudinal association between type 2 diabetes and elevated depressive symptoms within the same cohort.

Depressive Symptoms and Incident Type 2 Diabetes

Several other population-based studies report an association between depressive symptoms and incident type 2 diabetes.[4-12] Depressive symptoms are associated with several metabolic and behavioral risk factors for type 2 diabetes. First, depressed individuals are less likely to comply with dietary and weight loss recommendations[43] and more likely to be physically inactive,[6-10,12] contributing to obesity, a strong risk factor. Participants in our study with more depressive symptoms had poor health behaviors associated with diabetes risk. This corroborates findings from prior studies showing that depressed individuals have higher caloric intake,[8,20] are less physically active,[6-10,12] and are more likely to be smokers.[6-9,12] However, adjustment for these characteristics in our analyses resulted in minimal attenuation of the association of depressive symptoms with incident type 2 diabetes, suggesting that this does not fully explain the association. Additionally, depressive symptoms are associated with activation of the hypothalamic-pituitary-adrenal and sympathoadrenal systems[44] and increased inflammation.[18,19,44,45] Inflammatory markers are known risk factors for type 2 diabetes,[46] and we observed higher IL-6 and CRP levels in depressed persons compared with those without elevated depressive symptoms. However, in our study, adjustment for markers of in-

Table 3. Characteristics of 4847 Men and Women Without Prevalent Depressive Symptoms by Impaired Fasting Glucose and Type 2 Diabetes Status, 2000-2002

	Fasting Glucose		Type 2 Diabetes		
	Normal (n=2868) (59.2%)	Impaired (n=1357) (28.0%)	Untreated (n=203) (4.2%)	Treated (n=417) (8.6%)	P Value[a]
Age, mean (SD), y	60.7 (10.1)	63.4 (9.8)	63.7 (9.5)	64.9 (9.4)	<.001
Sex, No. (%)					
Men	1298 (45.3)	803 (59.3)	125 (61.6)	226 (54.5)	<.001
Women	1565 (54.7)	552 (40.7)	78 (38.4)	189 (45.5)	
Ethnicity, No. (%)					
White	1322 (46.2)	468 (34.5)	53 (26.1)	69 (16.6)	<.001
Chinese American	331 (11.6)	204 (15.1)	30 (14.8)	59 (14.2)	
African American	722 (25.2)	388 (28.6)	71 (34.9)	173 (41.7)	
Hispanic	488 (17.1)	295 (21.8)	49 (24.1)	114 (27.5)	
Education status, No. (%)					
<High school	339 (11.8)	225 (16.6)	53 (26.1)	110 (26.5)	<.001
High school	461 (16.1)	280 (20.7)	40 (19.7)	79 (19.0)	
≥College	2063 (72.1)	850 (62.7)	110 (54.2)	226 (54.5)	
Annual income, No. (%), $					
<15 000	427 (14.9)	267 (19.7)	56 (27.6)	116 (27.9)	<.001
≥15 000-<24 000	275 (9.6)	180 (13.3)	26 (12.8)	68 (16.4)	
≥24 000-<34 000	334 (11.7)	185 (13.7)	22 (10.8)	70 (16.9)	
≥34 000-<49 000	466 (16.3)	209 (15.4)	31 (15.3)	55 (13.3)	
≥49 000-<74 000	532 (18.6)	211 (15.6)	31 (15.3)	54 (13.0)	
≥74 000	829 (28.9)	303 (22.4)	37 (18.2)	52 (12.5)	
Cigarette smoking status, No. (%)					
Never	1495 (52.3)	660 (48.8)	99 (49.0)	212 (51.5)	.02
Former	1008 (35.3)	541 (40.0)	88 (43.6)	150 (36.4)	
Current	354 (12.4)	151 (11.2)	15 (7.4)	50 (12.4)	
Daily caloric intake, median (IQR), calories/d	1469 (1094-1980)	1530 (1140-2108)	1548 (1050-2100)	1342 (972-1866)	<.001
Intentional exercise, median (IQR), MET-min/wk	990 (300-2220)	840 (52-1935)	735 (0-1890)	698 (0-1680)	<.001
Current alcohol drinking, No. (%)	1743 (74.5)	776 (69.9)	104 (63.8)	164 (50.8)	<.001
Microalbuminuria, No. (%)	129 (4.5)	125 (9.3)	39 (19.2)	100 (24.2)	<.001
Hypertension, No. (%)	1007 (35)	667 (49.2)	113 (55.7)	279 (67.2)	<.001
BMI, mean (SD)	27.2 (4.9)	29.3 (5.3)	30.1 (5.2)	30.1 (5.7)	<.001
HDL cholesterol, mean (SD), mg/dL	53.1 (15.4)	48.1 (13.3)	45.4 (11.8)	46.2 (12.5)	<.001
Triglycerides, mean (SD), mg/dL	104 (72-147)	113 (83-167)	129 (89-203)	126.5 (85-188)	<.001
Incident cases of elevated depressive symptoms, No.	336	112	15	60	
Person-years	9139	4013	481	969	

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CES-D, Center for Epidemiologic Studies Depression Scale; HDL, high-density lipoprotein; IQR, interquartile range; MET, metabolic equivalent task.
SI conversion factors: To convert HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.
[a]For categorical covariates, the P value was generated from the χ^2 test. For continuous covariates, the P value was generated from the analysis of variance. For the nonnormally distributed variables, the P value was generated from the Kruskal-Wallis Test.

flammation did not substantially alter or explain our observed association. Finally, antidepressant medication use can cause weight gain and obesity,[47,48] risk factors for type 2 diabetes. We did not have enough participants (n=374) using antidepressants to examine the association between antidepressant medication use and incident type 2 diabetes.

Type 2 Diabetes and Incident Depressive Symptoms

In our previous cross-sectional study, treated type 2 diabetes, but not impaired fasting glucose or untreated type 2 diabetes, was associated with depressive symptoms.[20] The finding in our present analysis that treated type 2 diabetes is associated with incident depressive symptoms confirms our earlier cross-sectional observation and those of 2 prior studies.[21,22] However, although our prior analysis showed no cross-sectional association between impaired fasting glucose and untreated type 2 diabetes and depressive symptoms,[20] the present analysis suggests a lower risk of depressive symptoms in these individuals. Our findings of an association in participants with treated but not untreated type 2 diabetes suggests that the psychological stress associated with diabetes management may lead to elevated depressive symptoms. In addition, adults with treated type 2 diabetes may have a greater number of diabetic complications and comorbidities than those who are untreated and these complications and comorbidities may lead to elevated depressive symptoms. Prior studies have shown that depressive symptoms were associated with nephropathy,[49] retinopathy,[50,51] neuropathy,[52,53] and macrovascular disease.[54,55] Some,[54,56-61] but not all,[62-66] studies report a positive association between the presence and number of diabetes complications and depressive symptoms. Miraldi et al[22] found that the association between type 2 diabetes and incident depressive symptoms was attenuated following adjustment for comorbidities. In our study, however, adjustment for comor-

bidities, including dyslipidemia, hypertension, and microalbuminuria, did not explain the association, although we lacked more specific data on potentially disabling diabetes complications, such as retinopathy and neuropathy.

We were surprised to find that impaired fasting glucose was associated with a lower risk of elevated depressive symptoms. This might be due to the complex relationship between obesity and depressive symptoms, with cross-sectional studies showing either an inverse, positive, or lack of association between the 2.[26] In a large middle-aged European cohort, Lawlor et al[26] showed that obese individuals had a lower risk of depression over 29 years. Insulin resistance has also been associated with a lower risk of incident depression,[27,28] although not in all studies.[67] Although this might have explained our finding of impaired fasting glucose, a prediabetic condition, being associated with lower risk of depressive symptoms, the BMI was similar in those with impaired fasting glucose and treated type 2 diabetes, and point estimates were not changed following adjustment for BMI. Finally, untreated type 2 diabetes was not associated with incidence of elevated depressive symptoms, which may be related to less severe disease or fewer comorbidities. Participants with un-

treated type 2 diabetes had a slightly lower prevalence of microalbuminuria and hypertension than those with treated type 2 diabetes. However, adjustment for these factors did not substantially affect the associations of untreated and treated type 2 diabetes with incident depressive symptoms. Further studies are needed to confirm that impaired fasting glucose and untreated type 2 diabetes are inversely associated while treated type 2 diabetes is positively associated with depressive symptoms and to fully ascertain the mechanisms underlying these associations.

Strengths

This study was well suited to investigate the complex association between depressive symptoms and type 2 diabetes because it included repeated measures of both over time along with characterization of many diabetes complications. Consequently, we could examine the 2 temporal hypotheses in the same cohort while simultaneously investigating mechanisms that might explain these associations. Furthermore, participants were selected based on the absence of coronary heart disease at baseline, a chronic disease also known to be associated with development of depressive symptoms, which could confound any associations we might have observed.

Table 4. Relative Odds of Elevated Depressive Symptoms in 4847 Men and Women by Glucose Tolerance Category

Model	Normal Fasting Glucose	Relative Odds (95% Confidence Interval)		
		Impaired Fasting Glucose	Untreated Diabetes	Treated Diabetes
1, Base[a]	1 [Reference]	0.79 (0.63-0.99)	0.75 (0.44-1.27)	1.54 (1.13-2.09)
2, BMI[b]	1 [Reference]	0.80 (0.63-1.01)	0.77 (0.45-1.31)	1.59 (1.17-2.18)
3, SES[c]	1 [Reference]	0.78 (0.62-0.99)	0.71 (0.41-1.21)	1.47 (1.07-2.01)
4, Lifestyle[d]	1 [Reference]	0.81 (0.63-1.03)	0.77 (0.44-1.37)	1.61 (1.16-2.24)
5, Diabetes severity[e]	1 [Reference]	0.79 (0.62-0.99)	0.76 (0.45-1.30)	1.56 (1.13-2.15)
6, Fully adjusted[f]	1 [Reference]	0.80 (0.63-1.02)	0.73 (0.41-1.30)	1.52 (1.09-2.12)

[a] Adjusted for age, sex, race/ethnicity, examination site.
[b] Adjusted for model 1 criteria and Body Mass Index (BMI).
[c] Adjusted for model 2 criteria and socioeconomic status (SES). For definition of variables, see footnote "f" in Table 2.
[d] Adjusted for model 2 criteria and lifestyle factors (see footnote "g" in Table 2 for a definition).
[e] Adjusted for Model 2 criteria and markers of diabetes severity (dyslipidemia [triglycerides ≥200 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, or both; for conversion factors to SI units see Table 1 footnotes], presence of hypertension [blood pressure ≥140/90 mm Hg, antihypertensive medication use, or both], and microalbuminuria [urinary albumin:creatinine ratio ≥30mg/g]).
[f] Fully adjusted using criteria from all models.

Limitations

The CES-D was not designed to measure clinical depression; rather, it is a self-report of symptoms over the past week and should not be used to make a psychiatric diagnosis of depression. However, CES-D is an efficient and valid tool for epidemiological studies[68] and is commonly used to assess mild to moderate depression and dysthymia in epidemiological studies conducted in the United States.[69] Furthermore, depressive symptoms were only assessed at 1 follow-up time point over a relatively short duration. Although including antidepressant use in the definition of elevated depressive symptoms may have misclassified participants who were taking antidepressants for other reasons, results were similar when CES-D scores alone were used to define elevated depressive symptoms. Additionally, a recent study illustrates the utility of using both markers to define depression because treated participants may have normal CES-D scores.[70] Although we did not find significant interactions by race/ethnicity or sex, the study may have lacked power to fully examine these interactions. However, the direction of the associations was similar among all ethnicities for both analyses. For the analysis of depressive symptoms and incident type 2 diabetes, we had limited data on inflammatory markers and no data on neuroendocrine markers, limiting our ability to explore these biological hypotheses in our analyses. Finally, for the analysis of treated type 2 diabetes and incident depressive symptoms, we had limited data on additional diabetes-specific comorbidities and their severity, which impaired our ability to determine whether this explained the observed association.

CONCLUSION

The biological mechanisms by which depression and type 2 diabetes are associated remain unclear. However, the present study contributes to a growing body of literature indicating a bidirectional association between these 2 serious long-term diseases. Future studies should determine whether interventions aimed at modifying behavioral factors associated with depression will complement current type 2 diabetes prevention strategies. Finally, these findings suggest that clinicians should be aware of increased risk of elevated depressive symptoms in individuals with treated type 2 diabetes and consider routine screening for depressive symptoms among these patients.

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