Depression and Type 2 Diabetes Mellitus: The Multiethnic Study of Atherosclerosis

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Objective: To assess the cross-sectional association between depression and glucose tolerance status. **Methods:** We conducted a study of 6754 White, Black, Hispanic, and Chinese men and women aged 45 to 84 years in the Multiethnic Study of Atherosclerosis (MESA). Depression was defined as Center for Epidemiologic Studies Depression scale score of ≥16 and/or antidepressant use. Glucose tolerance status was defined as normal, impaired fasting glucose (IFG) or Type 2 diabetes mellitus (untreated and treated). **Results:** In the minimally adjusted model, although depression was not associated with a greater odds of IFG (odds ratio (OR) = 1.01; 95% confidence interval (CI): 0.87–1.18) or untreated diabetes (OR = 1.03; 95% CI: 0.74–1.45), it was associated with a greater odds of treated diabetes (OR = 1.57; 95% CI: 1.27–1.96). This persisted following adjustment for body mass index (OR = 1.52; 95% CI: 1.22–1.90), metabolic (OR = 1.54; 95% CI: 1.23–1.93), and inflammatory (OR=1.53; 95% CI: 1.21–1.92) factors, daily caloric intake and smoking (OR = 1.48; 95% CI: 1.16–1.88), and socioeconomic markers (OR = 1.47; 95% CI: 1.17–1.85). Among individuals with treated diabetes, median depression scores were higher in those with microalbuminuria compared with those without microalbuminuria (median = 7; interquartile range: 3–13 versus median = 6; interquartile range: 2–11; $p = .046$). Depression scores were not associated with homeostatic model assessment of insulin resistance among individuals without diabetes. **Conclusions:** In MESA, depression was significantly associated with treated diabetes. Further studies are needed to determine the temporality of this association. **Key words:** diabetes mellitus, impaired fasting glucose, depression, epidemiology, insulin resistance.

BMI = body mass index; **CES-D** = Center for Epidemiologic Studies Depression (CES-D) scale; **CI** = confidence interval; **CRP** = C-reactive protein; **HOMA-IR** = homeostatic model assessment of insulin resistance; **IFG** = impaired fasting glucose; **IL-6** = interleukin-6; **MESA** = Multiethnic Study of Atherosclerosis; **OR** = odds ratio.

INTRODUCTION

Identification of modifiable risk factors for diabetes is important for its prevention. The prevalence of depression in diabetic individuals is increased compared with in the general population (1,2). Several studies, including one conducted by our group, have found that the presence of depressive symptoms is predictive of incident diabetes (3–7), although at least one study failed to detect a longitudinal association (8). An increased prevalence of depression in patients with diabetes has been documented in several ethnic groups (9–15); however, with the exception of one study that showed a significant association between depression and diabetes only in African-Americans (16), most studies have found rates of depression to be similar among diabetic individuals of different ethnicities (17–19).

Disordered carbohydrate metabolism has also been demonstrated in nondiabetic individuals with depression/mood disorders (20,21). There are several mechanisms through which depression may lead to diabetes, including its effects on health behaviors such as diet, physical activity, and adherence to medications (22–25), its effects on adiposity (26), or its influence on biological factors such as activation of the neuroendocrine response (20,27–29) and/or inflammatory response (30,31). An alternative hypothesis is that a diagnosis of diabetes leads to depression. Depression is more likely to occur in individuals who develop new diabetic complications and who develop complications that impair physical and cognitive functioning (1). A recently published abstract found that depression was associated with diagnosed diabetes but not with unrecognized glucose intolerance (32).

Using data from the Multiethnic Study of Atherosclerosis (MESA), we examined the cross-sectional association between depressive symptoms and diabetes in a large, ethnically diverse group of men and women. We investigated associations of depressive symptoms with various glucose tolerance categories as well as with a measure of insulin resistance in nondiabetic individuals. We also investigated whether these associations varied by race/ethnicity. Although most studies have found that the association between depression and diabetes is similar among different ethnicities, many studies have had smaller sample sizes (17–19). MESA has one of the largest populations, >6000 individuals, in which to examine these and other associations. Because MESA had data on a standardized measure of depressive symptoms and data on health behaviors, socioeconomic status (SES), and metabolic (i.e., adiposity and lipids) and inflammatory variables, we could determine whether this association was independent of risk factors for Type 2 diabetes that are also strongly associated with depression.

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METHODS

Study Population

MESA is a multicenter, longitudinal cohort study of the prevalence and correlates of subclinical cardiovascular disease and the factors that influence the progression of mild subclinical cardiovascular disease to severe subclinical and clinical cardiovascular disease (33). Between July 2000 and August 2002, 6814 men and women who identified themselves as White, Black, Hispanic, or Chinese, 45 to 84 years of age, and free of self-reported clinical cardiovascular disease were recruited from six 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. Details on the sampling frames and the cohort examination procedures have been published (33). Informed consent was obtained from the participants and the study was approved by Institutional Review Boards of each institution.

Assessment of Exposure

Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) Scale, a 20-item questionnaire aimed at measuring depressive symptoms in community populations (34). The 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 scale does not include items for increased appetite or sleep, anhedonia, psychomotor agitation or retardation, guilt, or suicidal thoughts. Cronbach's α for reliability of the instrument has reportedly ranged between 0.84 and 0.93 (35). Participants are 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 ranged from 0 to 60, with higher scores indicating more severe depressive symptoms. For our analyses, depression was defined as a CES-D score of $\geq$16, consistent with mild-to-moderate depression or dysthymia at the population level (36), and/or self-reported use of antidepressant medications (tricyclics, nontricyclics, and monoamine oxidate inhibitors). CES-D was administered in English, Spanish, Cantonese, and Mandarin. The reliability of the CES-D is comparable in European-American, African-American, Mexican-American, and Chinese-American groups (37,38). The CES-D has been used widely in cross-cultural epidemiological studies conducted with the well-validated Spanish and Chinese versions (39,40).

Assessment of Outcome

Participants were asked to fast for 12 hours and 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. Blood specimens were collected 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 (33).

Glucose tolerance status was defined according to the 2003 American Diabetes Association criteria (41). Diabetes was defined as a fasting glucose of $\geq$7.0 mmol/L (126 mg/dl) or use of hypoglycemic medication (oral agents and/or insulin). Impaired fasting glucose (IFG) was defined as a fasting glucose of 5.5 to 6.9 mmol/L (100–125 mg/dl). Diabetes was further subdivided into individuals who were untreated (no pharmacological therapy) and treated (use of oral antidiabetic agents or insulin). Individuals with untreated diabetes who indicated that they were aware of their diagnosis were considered to have self-reported diabetes and had answered yes to the question: "Do you have diabetes?"

Among nondiabetic individuals, insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR = glucose [mmol/L] $\times$ insulin [mIU/L]/22.5) (42). Serum glucose was measured by rate reflectance spectrophotometry using thin film adaptation of the glucose oxidase method (Vitros analyzer, Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY) (Laboratory CV: 1.1%). Insulin was determined by a radioimmunoassay method (Linco Human Insulin Specific RIA Kit, Linco Research, Inc., St. Charles, MO). The lower limit of sensitivity is 2 U/L with a laboratory coefficient of variation of 4.9%.

Covariates

Self-reported information included sex, age, race/ethnicity, years of education, cigarette smoking history, and annual income. Data on prescription and over-the-counter medication use were collected by transcription of medication bottles brought into the clinic. We categorized education as a) less than high school, b) high school, c) some college, technical school, or associates' degree, and d) completed college or greater. Annual income was categorized as $\geq$ or $<$\$30,000. Smoking status was categorized as never, former, or current.

Weight and height were measured using a balance beam scale and a vertical ruler, respectively, with the 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 (kg) divided by height squared (m^2). Waist circumference was measured at the minimum abdominal girth and the hip circumference was measured at the level of the symphysis pubis and maximum protrusion of the buttocks. All anthropometric measures were taken in duplicate and averaged.

Resting blood pressure was measured three times with participants in the seated position with an automated oscillometric sphygmomanometer (Dinamap model Pro 100, Critikon, Tampa, Florida). The average of the last two measurements was used. Hypertension was defined as systolic pressure of $\geq$140 mm Hg, diastolic pressure of $\geq$90 mm Hg, or current use of antihypertensive medication.

Total and high-density lipoprotein (HDL) cholesterol and triglycerides were measured from blood samples obtained after a 12-hour fast. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula (43).

Interleukin (IL)-6 was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay, R&D Systems, Minneapolis, Minnesota) and C-reactive protein (CRP) was measured using the BNII nephelometer (N High Sensitivity CRP, Dade Behring Inc., Deerfield, Illinois). A spot urine sample was collected from each participant, preferable in the early morning at the beginning of the clinic visit. Urine creatinine was measured (Vitros 950IRC, Johnson & Johnson Clinical Diagnostics, Inc., Rochester, New York) and urine albumin was determined (Array 360 CE Protein Analyzer, Beckman Instruments, Inc., Brea, California) (33).

The participant's usual diet and daily caloric intake during the last year 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 individuals (44,45). The MESA dietary assessment was modified to include foods typically eaten by Chinese groups. For our analyses, total daily caloric intake was used as the summary variable.

Analysis

The study design was a cross-sectional study in which the exposure variable was depressive symptoms, assessed via the CES-D and/or antidepressant medication use, and the outcome variables were categories of glucose tolerance status (i.e., normal, impaired fasting glucose, untreated and treated diabetes mellitus) and insulin resistance (i.e., HOMA-IR) among individuals without diabetes. The individuals excluded from the study had missing data on diabetes diagnosis (n = 98) or on depression (n = 36), leaving 6754 study participants.

We first examined differences in glucose tolerance status in persons with (CES-D scale scores of $\geq$16 and/or antidepressant medication use) and without (CES-D scale scores of $<$16) depression. To explore potential mechanisms explaining the relationship between depression and diabetes, a series of multivariable logistic regression models were constructed to calculate the odds ratios of IFG and treated and untreated diabetes in individuals with depression compared with those without depression. In all of these analyses, individuals without depression were the reference group. Glucose tolerance categories were mutually exclusive. For each of the three glucose tolerance categories, individuals with normal glucose tolerance were coded as 0 and individuals with impaired fasting glucose, untreated diabetes, and treated diabetes were coded as 1 for their respective categories. For example, in the analyses in which the odds of untreated diabetes was determined for individ-

uals with depression compared with those without depression, individuals with IFG and treated diabetes were coded as missing.

In the base model, adjustments were made for age, race/ethnicity, sex, and MESA site. We also examined changes in associations after additional adjustment for BMI, metabolic variables (lipids, inflammatory markers), socioeconomic (education, annual household income) and lifestyle variables (smoking, daily caloric intake) that were significantly associated with depression in univariate analyses. In additional models in which CES-D was modeled as a continuous variable, logistic regression analyses were used to calculate the odds of IFG and untreated and treated diabetes for each 1-point increase in CES-D score.

Linear regression models were used to determine the mean difference in CES-D scores among individuals with IFG, untreated diabetes, and treated diabetes compared with individuals with normal glucose tolerance. As in the logistic regression analyses, the base model was adjusted for age, race/ethnicity, sex, and MESA site and multivariable models were adjusted for socioeconomic, metabolic, inflammatory, and lifestyle covariates that were significantly associated with depression in univariate analyses.

In a separate analysis among 5790 individuals without diabetes, the relationship between depressive symptoms and HOMA-IR was determined using linear regression models. Because the distribution of CES-D scores and HOMA-IR were not normally distributed, CES-D scores were divided into quartiles and HOMA-IR was log-transformed for the purpose of analysis. Linear regression models were then used to calculate the mean difference in log HOMA-IR in the second, third, and fourth CES-D quartiles compared with the first.

To examine whether diabetic individuals aware of their disease were more likely to be depressed than those unaware, we compared CES-D scores in untreated diabetic individuals who were and were not aware of their condition. To examine the impact of disease severity, we compared CES-D scores in treated diabetic individuals with different types of treatment (oral agents versus insulin) and in treated diabetic individuals with and without microalbuminuria (defined as a urine albumin/creatinine ratio of $\geq$30 mg/g (46). In these analyses, the median CES-D scores were compared using Wilcoxon rank-sum test.

Finally, we assessed for statistical interactions of depression with age, sex, race/ethnicity, and BMI ($<$25 kg/m^2 versus $\geq$25 kg/m^2) by including appropriate interaction terms in the regression models. Statistical interaction was assessed using likelihood ratio tests to compare nested regression models. Because no interactions were found, results are presented for the whole cohort. Statistical analyses were performed using Stata version 8.2 (College Station, Texas).

RESULTS

Baseline Characteristics

Table 1 summarizes demographic, socioeconomic, lifestyle, and metabolic covariates by depression status. Compared with individuals without depression, those with depression were more likely to be younger, White, female, current cigarette smokers, to have a high school education or less, to have not completed college, to have an annual income $<$\$30,000 per year, and to have a greater daily caloric intake. Chinese-Americans had the lowest prevalence of depression. Depression prevalence also varied by MESA site. Depressed individuals also had greater waist circumference, BMI, triglycerides, IL-6, and CRP than nondepressed individuals. Surprisingly, individuals with depression had lower fasting glucose (after excluding those with diabetes), lower LDL cholesterol, and higher HDL cholesterol than individuals without depression. In univariate analyses, treated diabetes was more prevalent among individuals with depression than among nondepressed individuals. The prevalence of depression in individuals with normal glucose tolerance, IFG, untreated diabetes, and treated diabetes was 18.4%, 16.2%, 15.8%, and 22.8%, respectively.

Multivariable Analyses

Multivariable models were constructed using covariates that were significantly associated with depression in univariate analyses—age, race/ethnicity, MESA site, BMI, metabolic factors (triglycerides, HDL cholesterol, and LDL cholesterol), inflammatory markers (IL-6 and CRP), lifestyle factors (daily caloric intake and smoking status), and markers of SES (education and annual household income). These factors are also known risk factors associated with Type 2 diabetes mellitus.

Analyses Exploring Hypothesis That Depression Leads to Diabetes

In the base model, which was adjusted for age, race/ethnicity, sex, and MESA site, individuals with depression did not have a greater odds of IFG and untreated diabetes compared with individuals without depression (Table 2). However, there was a 57% greater odds of having treated diabetes in depressed individuals compared with nondepressed individuals (Table 2). This association persisted following adjustment for BMI (model 2). Our results were similar when waist circumference was substituted for BMI. To avoid collinearity, only BMI was included in all subsequent multivariable models. Further adjustment for inflammatory covariates (IL-6 and CRP in model 4) did not attenuate the associations. Although the associations were attenuated after the adjustment for metabolic factors (lipids in model 3; OR = 1.47; 95% CI: 1.18–1.84), lifestyle covariates (daily caloric intake and smoking status; OR = 1.48; 95% CI: 1.16–1.88) (Table 2, model 5) and education and annual household income (as markers of SES; OR = 1.47; 95% CI: 1.17–1.85) (Table 2, model 6), they remained statistically significant. In a fully adjusted model that included all covariates (model 2 + log triglycerides, HDL cholesterol, LDL cholesterol, IL-6, CRP, caloric intake, smoking status, education, annual income), the association between depression and treated diabetes was attenuated but remained significant (OR = 1.38; 95% CI: 1.08–1.78).

We found similar associations within each race/ethnic group, although the point estimates in the unadjusted model were not all statistically significant, likely due to the smaller sample sizes. Compared with individuals with normal glucose tolerance, the odds of depression in those with treated diabetes was 1.80 (95% CI: 1.15–2.82), 1.56 (95% CI: 0.71–3.40), 1.36 (95% CI: 0.92–1.97), and 1.68 (95% CI: 1.17–2.41) for White individuals, Chinese-Americans, African-Americans, and Hispanic-Americans, respectively. There were no significant interactions by race/ethnicity, age, sex, or BMI.

Because individuals taking antidepressants may have been using them to treat other conditions, such as diabetic neuropathy, we repeated the analyses defining depression only as CES-D scores of $\geq$16. Although attenuated, the result were very similar for treated diabetes: model 1 (OR = 1.33; 95% CI: 1.08–1.70), model 2 (BMI; OR =

TABLE 1. Baseline Characteristics of 6754 Individuals With and Without Depression in the Multiethnic Study of Atherosclerosis

Covariates	No Depression (CES-D <16), n = 5590	Depression (CES-D ≥16 and/or Antidepressant Medication Use), n = 1224	p*
Age, years	62.4 (10.2)	61.1 (10.4)	.002
Ethnicity (%)			<.001
White	37.8 (n = 2090)	41.8 (n = 511)	
Chinese-American	13.0 (n = 719)	6.7 (n = 82)	
African-American	28.8 (n = 1593)	22.0 (n = 269)	
Hispanic	20.4 (n = 1128)	29.6 (n = 362)	
MESA Site (%)			<.001
Wake Forest University	16.3 (n = 899)	13.6 (n = 166)	
Columbia University	15.2 (n = 843)	20.9 (n = 256)	
Johns Hopkins University	15.7 (n = 872)	14.1 (n = 173)	
University of Minnesota	15.1 (n = 835)	18.8 (n = 230)	
Northwestern University	17.5 (n = 970)	15.6 (n = 191)	
University of California, Los Angeles	20.1 (n = 1111)	17.0 (n = 208)	
Sex (%)			<.001
Male	50.7 (n = 2805)	31.1 (n = 381)	
Female	49.3 (n = 2725)	68.9 (n = 843)	
Cigarette smoking status (%)			.001
Never	51.0 (n = 2810)	48.7 (n = 595)	
Former	36.7 (n = 2025)	35.0 (n = 428)	
Current	12.3 (n = 677)	16.2 (n = 198)	
Education status (%)			<.001
Less than high school	17 (n = 934)	23 (n = 283)	
High school	18 (n = 992)	19 (n = 234)	
Some college, technical school, associates' degree	29 (n = 1588)	28 (n = 341)	
College or greater	36 (n = 2011)	30 (n = 366)	
Annual income <$30,000 (%)	35.3	47.0	<.001
Daily caloric intake (kcal/day)	1649 (812)	1760 (922)	<.001
Glucose tolerance categories (%)			.001
Normal	57.7 (n = 3190)	58.9 (n = 721)	
Impaired fasting glucose	28.5 (n = 1575)	24.8 (n = 304)	
Untreated diabetes	4.4 (n = 246)	3.8 (n = 46)	
Treated diabetes	9.4 (n = 519)	12.5 (n = 153)	
Systolic blood pressure (mm Hg)	127 (21.3)	127 (23.3)	1.0
Diastolic blood pressure (mm Hg)	72.1 (10.2)	71.3 (10.4)	.06
Waist circumference (cm)	97.9 (14.2)	99.2 (15.7)	.004
BMI (kg/m^2)	28.2 (5.4)	29.0 (5.94)	<.001
Fasting glucose (mg/dl)[b]	96.1 (9.7)	95.1 (10.2)	.008
Fasting insulin (mIU/L)[a,b]	5.1 (3.4–7.9)	5.3 (3.4–8.1)	.45
HOMA-IR (mmol/L × mIU/L^2)[a,b]	1.18 (0.77–1.9)	1.21 (0.76–1.93)	.80
Total cholesterol (mg/dl)	194 (35.5)	196 (36.8)	.08
LDL cholesterol (mg/dl)	118 (31.1)	116 (32.7)	.04
HDL cholesterol (mg/dl)	50.5 (14.7)	52.7 (15.0)	.003
Triglycerides (mg/dl)[a]	110 (77–159)	118 (81–169)	.001
IL-6 (pg/ml)	1.53 (1.20)	1.69 (1.31)	<.001
CRP (mg/L)	3.63 (5.67)	4.45 (7.05)	<.001

CES-D = Center for Epidemiologic Studies Depression scale; MESA = multiethnic study of atherosclerosis; BMI = body mass index; HOMA-IR = homeostatic model assessment of insulin resistance; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

* 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 (ANOVA). For the non-normally distributed variables, the p value was generated from the Wilcoxon rank-sum test.

[a] Summary statistic represents median (interquartile range).

[b] Summary estimates exclude individuals with diabetes.

1.32; 95% CI: 1.02–1.69), model 3 (metabolic; OR = 1.35; 95% CI: 1.04–1.74), model 4 (inflammatory; OR = 1.34; 95% CI: 1.04–1.73), model 5 (lifestyle; OR = 1.25; 95% CI: 0.95–1.64), and model 6 (SES; OR=1.26; 95% CI: 0.98–1.63). We also conducted analyses using CES-D score as a continuous variable and found very similar results to the analyses in which CES-D scores were categorized (<16 versus ≥16). For each 1-point increase in CES-D, the odds of treated diabetes were: 1.016 (model 1; p = .004), 1.015 (model 2; p = .015), 1.014 (model 3; p = .018), 1.015 (model 4; p = .014), 1.013 (model 5; p = .04), and 1.012 (model 6; p = .05). IFG and untreated diabetes

TABLE 2. Relative Odds (95% Confidence Interval) of Impaired Fasting Glucose and Diabetes by Depression Status (CES-D Score of ≥16 and/or Antidepressant Medication Use) in 6754 Men and Women*

	Impaired Fasting Glucose, n = 1879	Untreated Diabetes, n = 292	Treated Diabetes, n = 672
Model 1 (base)	1.01 (0.87–1.18)	1.03 (0.74–1.45)	1.57 (1.27–1.96)
Model 2 (BMI)	1.01 (0.86–1.18)	0.98 (0.69–1.39)	1.52 (1.22–1.90)
Model 3 (metabolic)	1.01 (0.86–1.18)	1.05 (0.72–1.45)	1.54 (1.23–1.93)
Model 4 (inflammatory)	1.02 (0.87–1.19)	0.96 (0.67–1.37)	1.53 (1.21–1.92)
Model 5 (lifestyle)	1.00 (0.84–1.78)	1.02 (0.71–1.47)	1.48 (1.16–1.88)
Model 6 (SES)	1.00 (0.85–1.17)	0.92 (0.64–1.32)	1.47 (1.17–1.95)

CES-D = Center for Epidemiologic Studies Depression scale; BMI = body mass index; SES = socioeconomic status; MESA = Multiethnic Study of Atherosclerosis; HDL = high-density lipoprotein; LDL = low-density lipoprotein; IL = interleukin; CRP = C-reactive protein; Model 1 = adjusted for age, sex, race/ethnicity, and MESA site; Model 2 = Model 1 + BMI; Model 3 (metabolic) = Model 2 + log-transformed triglycerides + HDL cholesterol + LDL cholesterol; Model 4 (inflammatory) = Model 2 + IL-6 + CRP; Model 5 (lifestyle) = Model 2 + daily caloric intake + smoking status; Model 6 (SES) = Model 2 + education status + annual household income.

* In all of these analyses, individuals without depression were the reference group.

were not associated with either continuous or categorical CES-D scores.

Table 3 summarizes the results of multivariable linear regression models in which the CES-D score was modeled as a continuous variable. CES-D scores were not significantly different for individuals with IFG (p = .30) and untreated diabetes (p = .61) compared with those with normal glucose tolerance (data not shown). However, compared with individuals with normal glucose tolerance, individuals with treated diabetes had a mean CES-D score that was 0.73 point higher in the base model that was adjusted for age, sex, race/ethnicity, and MESA site (p = .021). This association remained significant after adjustment for BMI (mean CES-D score = 0.79 point higher; p = .01). Further adjustment for metabolic factors (lipids), inflammatory factors (IL-6 and CRP), and markers of SES (income and education) attenuated this association such they were only of borderline significance (p = .05, p = .05, p = .06 respectively). The association was most strongly attenuated after adjustment for lifestyle covariates, including BMI, caloric intake, and smoking, in which individuals with treated diabetes had a mean CES-D score that was only 0.36 point higher than individuals with normal glucose tolerance (p = .30).

TABLE 3. Mean Difference in CES-D Score (95% Confidence Interval) in Individuals With Treated Diabetes, Compared With Individuals With Normal Glucose Tolerance in the Multiethnic Study of Atherosclerosis

	Mean Difference in CES-D Score (95% CI)
Model 1 (base)	0.73 (0.11–1.36)
Model 2 (BMI)	0.79 (0.16–1.42)
Model 3 (metabolic)	0.66 (0.004–1.32)
Model 4 (inflammatory)	0.64 (0.002–1.28)
Model 5 (lifestyle)	0.36 (−0.30–1.03)
Model 6 (SES)	0.60 (−0.03–1.24)

CES-D = Center for Epidemiologic Studies Depression scale; CI = confidence interval; BMI = body mass index; SES = socioeconomic status; MESA = Multiethnic Study of Atherosclerosis; HDL = high-density lipoprotein; LDL = low-density lipoprotein; IL = interleukin; CRP = C-reactive protein; Model 1 = adjusted for age, sex, race/ethnicity, and MESA site; Model 2 = Model 1 + BMI; Model 3 (metabolic) = Model 2 + log-transformed triglycerides + HDL cholesterol + LDL cholesterol; Model 4 (inflammatory) = Model 2 + IL-6 + CRP; Model 5 (lifestyle) = Model 2 + daily caloric intake + smoking status; Model 6 (SES) = Model 2 + education status + annual household income.

In an analysis that excluded individuals with untreated and treated diabetes, we did not find an association between insulin resistance, estimated by HOMA-IR, and CES-D scores in either univariate or multivariable linear regression models (data not shown).

Analyses Exploring the Hypothesis That Diabetes Leads to Depression

We hypothesized that individuals who were aware of their diabetes diagnosis or had more severe diabetes, indicated by the need for insulin or the presence of complications, might be more likely to be depressed. Among the 292 individuals with untreated diabetes, only 50 (17%) were aware of their diagnosis. The median CES-D scores were not different between the 50 individuals who were aware of their diagnosis (median = 6; interquartile range: 3–11) and the 242 individuals who were unaware of their diagnosis (median = 5; interquartile range: 2–10) (p = .28 from Wilcoxon rank-sum test). Among the 653 individuals with treated diabetes, there was no difference in median CES-D scores between individuals treated with insulin (median = 7; interquartile range: 3–13; n = 117) and individuals treated with oral hypoglycemic agents (median = 6; interquartile range: 2–12; n = 536) (p = .11 from Wilcoxon rank-sum test). In contrast, individuals with treated diabetes complicated by microalbuminuria had significantly higher median depression scores (median = 7; interquartile range: 3–13; n = 205) than individuals without microalbuminuria (median = 6; interquartile range: 2–11; n = 467) (p = .046 from Wilcoxon rank-sum test).

DISCUSSION

In the MESA study, depression, defined as a CES-D score of ≥16 and/or antidepressant medication use, was cross-sec-

tionally associated with a greater odds of having treated diabetes but was not associated with IFG or untreated diabetes. The association of depression with treated diabetes, which was similar among all race/ethnicities, was not entirely explained by adiposity, metabolic factors, inflammatory markers, lifestyle factors (i.e., daily caloric intake and smoking status), or markers of SES (i.e., education and income). Among individuals with treated diabetes, the median depression score was higher among those with microalbuminuria, suggesting that depression may be more common among those with more severe diabetes. However, there was no association between depression scores, measured continuously, and HOMA-IR among individuals without diabetes.

Our study has several strengths. First, MESA is a large, ethnically diverse cohort that allowed us to examine race/ethnicity interactions; to our knowledge, MESA is one of the largest studies to examine the association of depression and diabetes by ethnicity. Second, there was standardized ascertainment of glucose tolerance status and diabetes as well as standardized measurements of depression and behavioral and physiological explanatory factors in a rigorously monitored observational study. This allowed us to explore potential explanatory/confounding factors in the association between depression and diabetes. Third, because individuals with prevalent cardiovascular disease were excluded, these results pertain to a relatively healthy, population-based sample.

Several limitations should be kept in mind, however, in interpreting our data. First, this was a cross-sectional study, which does not allow us to determine the temporality of the association between depression and diabetes nor causality; however, the longitudinal structure of MESA will allow for these types of analyses in the future. Second, there are limitations to using the CES-D scale to assess depression. The CES-D scale was not designed to measure clinical depression; it is based on self-report of symptoms and not a psychiatric diagnosis; and it measures depressive symptoms during a short period of time, as opposed to lifetime depression. This scale has been shown, however, to be a valid tool when used in epidemiological studies (47) and is the most commonly used short instrument for assessing mild-to-moderate depression and dysthymia in epidemiological studies conducted in the United States (48). Third, although the mean CES-D score was significantly higher by 0.73 point in individuals with treated diabetes compared with those with normal glucose tolerance, this finding is of uncertain clinical significance. Fourth, including antidepressant use in the definition of depression may have misclassified individuals who were taking antidepressants for other reasons; however, our results were similar when only CES-D scores were used. Also, a recent study indicated the utility in using both markers to define depression as treated individuals may have normal CES-D scores (49). Fifth, the results of our multivariable models may have been influenced by univariate prescreening; however, most of these covariates are established risk factors for diabetes. Finally, our ability to assess the severity of diabetes among individuals with treated diabetes was limited to the assessment of microalbuminuria as MESA did not have data on the presence of retinopathy or glycosylated hemoglobin in the baseline data.

Several studies have shown that depression leads to Type 2 diabetes (3–7) and there are several possible mechanisms that may explain this association. First, depression is associated with neurohormonal changes, including activation of the hypothalamic-pituitary-adrenal axis and sympathoadrenal system and alteration in the hypothalamic-growth hormone axis. This leads to an increase in counterregulatory hormones—cortisol, catecholamines, and growth hormone—which antagonize the hypoglycemic effects of insulin, leading to insulin resistance (50). Second, depression is also associated with alterations in glucose transport (50). Third, depression leads to increased inflammatory activation (30,31,50,51) and chronic cytokinemia can lead to insulin resistance and impaired β cell function—antecedents to the development of Type 2 diabetes (51). Fourth, depression may have a negative impact on behavioral factors such as dietary intake, physical activity, medication adherence, and smoking, which may increase the risk for developing Type 2 diabetes. In our study, depressed individuals had higher caloric intake and were more likely to be smokers. Other studies have found that depressed individuals were less compliant with dietary and weight loss recommendations (52) and were more physically inactive and nonadherent to medications (22–25). Finally, antidepressant medication use is associated with weight gain and obesity (53,54), which could also predispose depressed individuals to the development of Type 2 diabetes.

Our data in MESA suggest that depression may develop in individuals with diagnosed and treated diabetes as we did not see an association of depression with prediabetes (IFG) and we did not see an association between depression and insulin resistance in nondiabetic individuals in the MESA cohort. In accordance with previous studies (55,56), we found that depression was not associated with untreated diabetes. The temporal relationship between depression and diabetes needs to be confirmed through longitudinal follow-up of the MESA cohort.

In addition, individuals with treated diabetes who had evidence of a complication of diabetes, microalbuminuria, had slightly higher depression scores, suggesting that depression may be related to the severity of diabetes. A previous study of individuals with diabetes also found that depression was associated with nephropathy (57). Other diabetic complications associated with depression include macrovascular disease (11,58), retinopathy (15,59), and neuropathy (60,61). Depression is more likely to occur with the development of new diabetic complications and in the setting of multiple diabetic complications, particularly those associated with impaired visual, physical, and cognitive functioning and those associated with the development of sexual dysfunction (1). Although some studies have not found an association between the number of diabetic complications and an increased prevalence of depression (13,62–65), many others have found that individuals with a greater number of complications (11,22,23,66–69)

and comorbid conditions (56) are more likely to be depressed. Depression has also been associated with hyperglycemia in individuals with diabetes (70), suggesting that there may be a physiological association between depression and diabetes as well as a psychological association.

In the MESA cohort, the association between depression and treated diabetes was only partially explained by lifestyle factors (daily caloric intake and smoking status). In our study, individuals with depression were more likely to be current smokers and to have greater daily caloric intake. Diabetic individuals with depression have been shown to have poor adherence to medical and dietary regimens (22–25), a higher attrition rate in a behavioral weight loss intervention program (52), and higher prevalence of smoking (71). This suggests that depression can have a negative impact on health behaviors in individuals who already have diabetes, leading to poor metabolic control and an increased risk of developing complications, or this suggests that poor health behaviors may exacerbate depression. Intervention trials of depression treatment in individuals with diabetes have shown improvement in glycemic control with resolution of depressive symptoms (70,72).

The association between depression and treated diabetes was also attenuated by markers of SES (education and annual income), although the association remained statistically significant. In the MESA cohort, depressed individuals were less likely to have completed college and were more likely to have a high school education or less and to report an annual income of <$30,000. Several studies have shown that lower SES is associated with a greater likelihood of depression among individuals with diabetes (10,13,22,67). A recent study found that depression was more common in diabetic individuals with less than a high school education (18). Carnethon et al. found that depression predicted diabetes only among individuals with less than a high school education (5). It is hypothesized that individuals with lower SES and limited financial resources may be more likely to engage in adverse health behaviors that may worsen metabolic control in diabetes (5).

Despite differences in the prevalence of depression by race/ethnicity, we did not find that the association between depression and treated diabetes varied by the ethnicities included in the MESA study. These results are similar to other studies, which have found that depression among diabetic individuals did not vary by race (17–19), suggesting that all populations with diabetes are at risk for having comorbid depression.

The main implication of our study is that longitudinal analyses are needed to confirm whether diagnosed diabetes leads to incident depression. The structure of subsequent MESA examinations will permit these types of analyses. Our study also suggests that individuals with treated diabetes who have evidence of diabetic complications should be assessed and treated for depression and have interventions directed at behavior modifications and removal of socioeconomic barriers that will prevent worsening of metabolic control and clinical outcomes.

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