

The Influence of Educational Attainment on Depression and Risk of Type 2 Diabetes

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Numerous retrospective observational studies have reported higher prevalence of depression among diabetic populations than among controls.^{1,2} In the first prospective analysis, Eaton et al. found approximately 2 times higher risk of type 2 diabetes among those with major depressive disorder (MDD) 13 years previously than among those without depression,³ a finding that has been replicated with remarkable consistency.⁴ It is unclear whether the elevated risk of type 2 diabetes associated with depression is mediated by poor health behaviors (e.g., smoking, physical inactivity), physiological changes, or both. Depression is associated with lower socioeconomic status,⁵ but it is unknown whether indicators such as educational attainment moderate the associated risk of type 2 diabetes. One previous study suggested that the risk of type 2 diabetes among persons with depression was substantially greater among those with less than a high school education than among more-educated groups.⁶

We prospectively examined the relationship between depression and type 2 diabetes, seeking to answer 2 questions: Do established risk factors for diabetes, such as family history, obesity, smoking, alcohol intake, dietary habits, and physical inactivity, explain the association between depression and risk of diabetes? Does educational attainment modify this relationship?

METHODS

The Baltimore Epidemiological Catchment Area (ECA) Study recruited a population-based sample of East Baltimore residents for a study of mental and physical health in 1981; Baltimore was 1 of 5 sites in the National Institute of Mental Health ECA Project. Details on the sampling procedures have been discussed elsewhere.^{7,8} Interviews were completed by 3481 participants 18 years or older in 1981.⁹ The original study sample was 62% female and 63% White, with African Americans making

Objectives. We investigated the association between major depressive disorder and type 2 diabetes, whether that association is explained by health behaviors, and whether it is influenced by educational attainment.

Methods. We used discrete-time Cox proportional hazards models to determine the risk of type 2 diabetes associated with depression in a 23-year population-based cohort study.

Results. Major depressive disorder was associated with higher risk of type 2 diabetes (hazard ratio [HR] = 1.62) after we controlled for age, gender, race, education, smoking status, alcohol use, social network size, and antidepressant use. This association was more pronounced after we controlled for body mass index, family history, and health behaviors (HR = 2.04; 95% confidence interval = 1.09, 3.81). In stratified analyses, the risk associated with major depressive disorder was elevated among those with 12 or fewer years of education compared with those with at least some education beyond high school.

Conclusions. The risk of type 2 diabetes associated with major depressive disorder persists over the life course and is independent of the effects of health behaviors, body mass index, and family history. Education is an important moderator of this association. (*Am J Public Health.* 2008;98:1480–1485. doi:10.2105/AJPH.2007.126441)

up the majority of the remainder (33.9%). Follow-up interviews were conducted in 1982 (n=2768), 1993 to 1996 (n=1920), and 2004 to 2005 (n=1071). In 2004–2005, we interviewed 75% of the surviving cohort from 1993–1996. Analyses of attrition have shown that the participants successfully interviewed in 1993–1996 and 2004–2005 were not significantly different in depression or diabetes status than those lost to follow-up.^{10,11}

Depression Status

We assessed depression with the Diagnostic Interview Schedule (DIS) during all ECA interviews. The DIS is a structured interview administered by laypersons that establishes diagnoses of MDD and depression syndrome and the age of onset and recency of those conditions through diagnostic algorithms.¹² The DIS has been shown to have moderate concordance with clinical examinations such as the Schedules for Clinical Assessment in Neuropsychiatry.¹³

Depression syndrome was determined by a respondent's report of experiencing 3 or more

symptom groups in addition to dysphoric mood or anhedonia (i.e., appetite disturbances, fatigue, sleep disturbances, difficulty in concentration, guilt, motor disturbance, or suicidal ideation or suicide attempt). We determined age of onset of depressive syndrome at each study wave. Because depression is thought to have a prolonged prodromal period before meeting diagnostic criteria,¹⁴ we defined age of onset as the earliest reported age of depressive syndrome onset, regardless of whether or not the participant was determined to have met diagnostic criteria for MDD at that time. We resolved discrepancies in reported age of onset across the waves by using only the earliest age. Only participants who met diagnostic criteria for MDD at some point during the 23-year follow-up were classified as cases of depression.

Diabetes Status

We assessed diabetes status through self-report at each wave. Self-report measures of diabetes have been shown to have good agreement with medical records.¹⁵ Cases of

diabetes present at the 1981 or 1982 interviews were removed from analysis. We identified incident cases of type 2 diabetes in 1993–1996 and 2004–2005 through a stepwise process. All participants were initially asked, “Have you ever had high sugar or diabetes?” Affirmative responses were followed by, “Do you have high sugar or diabetes now?” Only participants who answered that they currently had diabetes were considered incident cases and were then asked, “At what age did the diabetes begin?”

To limit the misclassification of type 1 and type 2 diabetes, only participants who reported an age of onset of diabetes of 30 years or older were included as incident cases. To minimize the effect of recall bias on classification of incident versus prevalent cases of diabetes, we removed from analysis any participant who reported being 30 years or older at disease onset but whose reported age, if accurate, indicated that the diabetes was present before wave 1. We also removed diabetes cases that began within 1 year of depression onset, because of the possibility that the depressive symptoms were attributable to preclinical metabolic disturbances associated with diabetes.

Other Variables

Participants self-reported medication use at all 4 interviews, and interviewers visually inspected medications in the 1993–1996 and 2004–2005 waves. In the 1981 and 1982 interviews, we asked about lifetime use of antidepressant medications individually by name. In the 1993–1996 and 2004–2005 interviews, we asked participants to list all medications they had taken in the past 7 days. We coded medications according to the *Physicians Desk Reference*¹⁶ and by consensus among the investigators. We categorized antidepressant use as a dichotomous variable at each wave.

We identified other variables of interest from the literature of known risk factors for type 2 diabetes and previous studies of the depression–diabetes relationship. Family history of diabetes among first-degree relatives was assessed by self-report at the 1993–1996 and 2004–2005 interviews. Body mass index (BMI; weight in kilograms divided by height in meters squared) was ascertained by

self-reported weight and height in the 1993–1996 interviews and by measured weight and height (without shoes and wearing light clothing) in 2004–2005. Measures of physical activity (number of blocks walked and stairs climbed per day) and frequency of eating balanced meals were ascertained in 1993–1996 and 2004–2005. Alcohol use (number of days when participant drank in the past month) and current smoking status were determined at all 4 waves. Social network characteristics are associated with both depression and diabetes.¹⁷ We included measures of social integration (i.e., network size [all waves] and frequency of contact with friends and relatives [1993–1996 and 2004–2005 only]) and perceived support (1993–1996 and 2004–2005 only),^{18,19} derived from the National Comorbidity Survey.²⁰

Data Setup

We removed prevalent cases of diabetes (identified at either the 1981 or 1982 interviews or by reported age of onset) from analysis. Persons entered the risk set in 1981 and were right censored (i.e., contributed data up to that point) at the year of diabetes onset or year of last interview.

Missing data primarily resulted from 2 sources: attrition and the use of abbreviated questionnaires for shortened forms of the interview (i.e., telephone and proxy interviews). Persons who lived 2 hours or more from the Baltimore metropolitan area were given a shortened (1.5-hour) version of the in-person interview (1993–1996, $n=108$; 2004–2005, $n=93$). For participants who were unable to complete the full interview, we found a proxy to complete a short (approximately 45-minute) interview (1993–1996, $n=97$; 2004–2005, $n=30$).

We imputed missing values for the following (range of percentage missing across all waves): education (0.03%), smoking status (0.03%–0.7%), alcohol intake (3.7%–8.3%), antidepressant use (0.5%–10.0%), blocks walked per day (5.9%–6.0%), stairs climbed per day (3.9%–5.7%), frequency of eating balanced meals (3.4%–4.6%), and family history of diabetes (6.4%–9.3%). Missing values were imputed as the mean (for continuous variables) or mode (for categorical variables), with the

exception of education. For education, we had only 1 missing value, and subsequently, this was imputed as the mean level of education of participants of the same age range (≥ 60 years), gender (female), and race (White) as the observation with the missing value.

Missing data for BMI (12.0%–18.0%) and social network characteristics (1.5%–12.6%) were not imputed because they represented potential mediators of the depression–diabetes relationship and it was unlikely that these variables would be missing at random. Persons missing data for these variables were older and had less education than did the remaining cohort, consistent with proxy interviews as the primary source of missing data. Participants missing BMI data did not differ on MDD or type 2 diabetes from the remaining cohort. Participants missing social network characteristics were more likely to have MDD at wave 3 (but not wave 4) and did not differ in diabetes status at either wave.

Eight cases of depression met criteria for MDD but were missing an age of onset of first episode. Imputation of age of onset for these cases was determined by a decision algorithm: (1) most often reported age of symptom onset prior to meeting diagnostic criteria, if available; (2) youngest reported age of symptom onset prior to meeting diagnostic criteria, if available; or, if no data on symptom onset were available, (3) age at interview when the participant first met diagnostic criteria.

Statistical Analysis

We investigated the predictive association between MDD and incident type 2 diabetes over the study period with semiparametric discrete-time Cox proportional hazards models. The Cox proportional hazards model does not require that the baseline hazard function is specified but does require that the hazard functions are proportional over all survival times. The estimates of the hazard ratio account for the influence of incomplete information from censored observations because they reflect the changing risk set over the study time. They estimate the risk of the outcome associated with a covariate at time $t+\delta$, given that the outcome had not occurred at or prior to time t .²¹

We initially investigated associations between incident type 2 diabetes and potential

modifying variables with bivariate Cox proportional hazards models. We then fit a series of multivariate models evaluating the influence of MDD on incident type 2 diabetes, derived from a base model adjusted for sociodemographic characteristics. MDD, antidepressant use, BMI, smoking status, number of drinks per month, and social network characteristics were modeled as discrete time-varying covariates. Some variables were measured over the entire study period (1981–2005); others were only measured at the 1996–1997 and 2004–2005 interviews. We then evaluated the effect of depression on risk of type 2 diabetes from 1981 to 2005, adjusting only for age, race, gender, education, smoking status, alcohol use, antidepressant use, and social network size. For 1993 to 2005 data, we also adjusted for BMI, family history of diabetes, social support and social contact, dietary habits, and stairs climbed and blocks walked per day. Here we present 2 models, one from 1981 to 2005 and another from 1993 to 2005.

We evaluated competing models by improvement in relative model fit indicated by the likelihood ratio test and by percentage change in the coefficient for MDD attributable to the addition of each individual covariate. To account for the effect of multiple diabetes onsets occurring in the same risk set, we estimated standard errors for the parameter estimates with the Breslow method. For each model, we evaluated the appropriateness of the proportional hazards assumption with graphic displays, testing the effect of interaction terms between covariates and time, and with Schoenfeld residual plots. We used Stata version 9 software (StataCorp LP, College Station, Texas) for all analyses, and all *P* values refer to 2-tailed tests.

RESULTS

Table 1 shows the characteristics of the ECA cohort from 1981 through 2005 and the distribution of sociodemographic characteristics during each wave. We removed 297 prevalent cases of diabetes in 1981 and 1982 from analysis. We removed 4 cases from analysis because the age of diabetes onset was reported as prior to 1980. Overall, we found 169 incident cases of type 2 diabetes among

1803 persons at risk in the cohort that provided age of onset information such that survival models could be developed, representing 36 523 person-years. The average age of depression onset was 30.9 years, and the average age of type 2 diabetes onset was 55.0 years. The average difference between onset of depression and onset of diabetes was 16 years (data not shown).

Persons with incident diabetes tended to be older ($P<.01$), have less education ($P<.05$), and drink less often ($P<.01$) and were less likely to be current smokers ($P<.05$) than were persons who did not develop diabetes between 1981 and 1993. From 1993 to 2005, incident case respondents continued to have less education ($P<.01$) but were also more likely to have a family history of diabetes ($P<.01$) and a higher BMI ($P<.01$) than were persons who never developed diabetes. Depression was positively associated with smoking status and alcohol use, both of which were inversely associated with diabetes risk, likely because of confounding by indication (i.e., persons with diabetes would have been advised by their health care providers to change their lifestyle). Depression was positively associated with antidepressant use ($P<.001$) which was nonsignificantly inversely associated with diabetes risk. The overall incidence of type 2 diabetes in the cohort was 5.1 per 1000 person-years (95% CI=4.4, 5.9), and those with MDD had higher incidence than those without (Table 2).

In initial Cox proportional hazards models of each potential mediator or confounder adjusted for sociodemographic characteristics, significant ($P<.10$) predictors of type 2 diabetes included education, BMI, alcohol use, family history of diabetes, frequency of eating balanced meals, and stairs climbed per day. After additional adjustment for BMI, frequency of social contact with relatives emerged as a predictor of type 2 diabetes (hazard ratio [HR]=0.82; $P<.10$).

Over the entire study period (1981–2005), depression was associated with a higher risk of type 2 diabetes (HR=1.62; Table 3). During 1993 to 2005, depression was associated with a higher risk of type 2 diabetes after additional adjustment for BMI, family history of diabetes, frequency of eating balanced meals, stairs climbed per day, and frequency of contact

with relatives (HR=2.04). The association between MDD and type 2 diabetes increased when sociodemographic characteristics and health behaviors were added to the model, because these variables were differentially associated with exposure and outcome (e.g., women were more likely to have MDD, but being female was associated with a lower risk of type 2 diabetes).

The interaction term between MDD and education was marginally statistically significant after we adjusted for age, gender, race, BMI, and family history of diabetes (HR=0.79; $P<.055$), indicating that depression was associated with a lower risk of type 2 diabetes for each year of education attained. Interaction terms with other sociodemographic characteristics were not significant (data not shown). Among respondents with a high school education or less, the incidence of type 2 diabetes during the 23-year follow-up period was 6.1 per 1000 person-years (95% confidence interval [CI]=4.1, 7.2); the incidence among those with at least some college education was approximately 50% lower at 3.2 per 1000 person-years (95% CI=2.3, 4.4).

In models stratified by highest educational level attained (high school or less vs at least some college), depression was associated with a 73% increase (95% CI=1.04, 2.90) in risk of diabetes among participants with less education after we adjusted for age, race, gender, smoking status, and alcohol use, and the association between depression and diabetes was attenuated among those with more education (HR=1.12; 95% CI=0.46, 2.76). Among respondents with less education, the association between depression and risk of diabetes increased to 2.26 (95% CI=1.11, 4.60) after additional adjustment for BMI and family history. There was no association between depression and risk of diabetes among respondents with more education (HR=0.45; 95% CI=0.11, 1.80).

The joint effects of depression and low educational attainment are illustrated in Figure 1. Compared with participants who never had MDD and had high educational attainment (reference group), those who had ever had MDD and had low educational attainment had 4.10 times (95% CI=1.84, 9.16) greater risk of diabetes, after we adjusted for age, gender, race, smoking status, alcohol use,

TABLE 1—Participant Characteristics by Wave: Baltimore Epidemiological Catchment Area Study, Baltimore, MD, 1981–2005

	Wave 1, 1981 (n = 3481)		Wave 2, 1982 (n = 2768)		Wave 3, 1993–1996 (n = 1920)		Wave 4, 2004–2005 (n = 1071)	
	MDD	No MDD	MDD	No MDD	MDD	No MDD	MDD	No MDD
Total	145	3187	74	2669	112	1660	53	984
Women, no. (%)	108 (74.5)	1947† (61.1)	61 (82.4)	1662† (62.3)	85 (75.9)	1026*** (61.8)	42 (79.3)	607*** (61.7)
Race/ethnicity, no. (%)								
White	92 (63.5)	1985 (62.3)	53 (71.6)	1655 (62.0)	77 (68.8)	1016 (61.2)	38 (71.7)	602 (61.2)
African American	48 (33.1)	1104 (34.6)	19 (25.7)	932 (34.9)	32 (28.6)	587 (35.4)	13 (24.5)	351 (35.7)
Other	5 (3.5)	98 (3.1)	2 (2.7)	82 (3.1)	3 (2.7)	57 (3.4)	2 (3.8)	31 (3.2)
Age, y, mean (SD)	38.5 (14.3)	47.4† (19.8)	39.5 (14.1)	47.77† (19.6)	44.5 (10.2)	53.8† (16.1)	51.2 (6.5)	58.5† (12.3)
Education, y, mean (SD)	11.2 (3.1)	10.4*** (3.2)	10.9 (3.2)	10.6 (10.6)	12.4 (2.6)	11.5*** (3.0)	13.5 (2.6)	12.5*** (2.7)

Note. MDD = major depressive disorder. Because of missing data, n = 3332 at wave 1, n = 2743 at wave 2, n = 1801 at wave 3, and n = 1037 at wave 4. P values are from the χ^2 (categorical variables) or t test (continuous variables) for MDD vs no MDD within each wave. ***P < .01; †P < .001.

TABLE 2—Incidence of Type 2 Diabetes per 1000 Person-Years, by Age Group at Wave 3 and Depression Status: Baltimore Epidemiological Catchment Area Study, Baltimore, MD, 1993–1996

Age, y	Never MDD	Lifetime MDD	Overall
30–39	2.6	2.8	2.7
40–49	4.6	6.6	4.9
50–59	8.6	13.9	9.3
≥ 60	5.3	5.2	5.3
All	4.9	6.5	5.1

Note. MDD = major depressive disorder.

TABLE 3—Association of Depression and Risk of Type 2 Diabetes: Baltimore Epidemiological Catchment Area Study, Baltimore, MD, 1981–2005

Lifetime MDD	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 3, HR (95% CI)	Model 4, HR (95% CI)
1981–2005 ^a	1.44 (0.92, 2.24)	1.48* (0.94, 2.31)	1.56* (1.00, 2.44)	1.62** (1.03, 2.55)
1993–2005 ^b	1.52 (0.82, 2.80)	1.64 (0.99, 3.03)	1.72* (0.93, 3.18)	2.04** (1.09, 3.81)

Note. MDD = major depressive disorder; HR = hazard ratio; CI = confidence interval. Reference category for all models was never diagnosed with MDD.

^aModel 1 adjusted for age, race, gender, education, and body mass index. Model 2 added family history of diabetes to model 1. Model 3 added smoking status, alcohol use, stairs climbed per day, and frequency of eating balanced meals to model 2. Model 4 added frequency of social contact with relatives to model 3.

^bModel 1 adjusted for age, race, gender, and education. Model 2 added smoking status and alcohol use to model 1. Model 3 added social network size to model 2. Model 4 added antidepressant use to model 3.

*P < .10; **P < .05.

BMI, family history of diabetes, and social network characteristics. We observed no difference in risk between the reference group and either participants who had less education

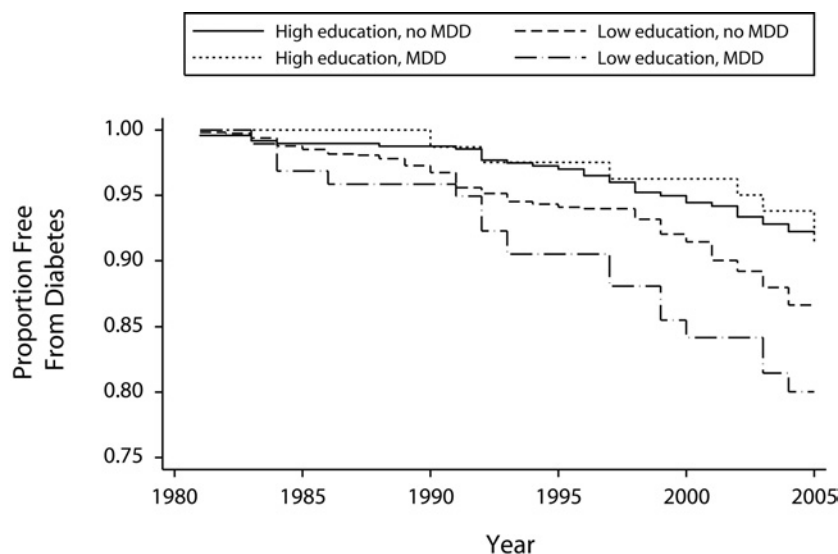
and had never had MDD (HR = 1.44; 95% CI = 0.82, 2.55) or participants who had more education and had ever had MDD (HR = 0.92; 95% CI = 0.27, 3.15).

DISCUSSION

In this population-based 23-year prospective study, depression was associated with increased risk of type 2 diabetes, independent of the effects of age, race, gender, education, BMI, poor health habits (i.e., smoking, alcohol use, sedentary lifestyle [indicated by number of stairs climbed per day], and unbalanced diet), social network characteristics, and family history of diabetes. Compared with clinical psychiatric examinations, the Diagnostic Interview Schedule underreports cases of MDD,¹³ which suggests that the hazard ratios reported here are conservative estimates of the association between depression and diabetes.

Depression was associated with increased risk of type 2 diabetes especially among persons who had completed 12 years or fewer of schooling, a result that is consistent with 1 previous study.⁶ Members of this group are more likely than are more advantaged persons to experience an episode of depression⁵; they may also not have the resources (socially or financially) to cope with a depressive episode when it happens.²² This may lead to an accumulation of poor health outcomes associated with depression among persons with less education or in a lower social class, which is consistent with what is known about the socioeconomic patterns of cardiometabolic disease in the population.²³

It is unclear what mediates the association between depression and type 2 diabetes. Our



Note. Kaplan-Meier plots show incidence of type 2 diabetes by mutually exclusive categorical groups: ever versus never major depressive disorder, and low educational attainment (high school education or less) versus high educational attainment (i.e., at least some college).

FIGURE 1—Joint effects of lifetime major depressive disorder and low educational attainment: Baltimore Epidemiological Catchment Area (ECA) Study, Baltimore, MD, 1981–2005.

results indicate that it is unlikely that the association is attributable to the adoption of poor health behaviors that often co-occur with depression. One proposed mechanism is physiological dysregulation, represented by concepts such as allostasis²⁴ and the metabolic syndrome.²⁵ Depression is associated with dysregulation in multiple physiological systems that are also altered in diabetes, including inflammation,^{26,27} the hypothalamic–pituitary–adrenal axis,²⁸ gonadal hormones,²⁹ and glucose metabolism.³⁰ Future studies should evaluate whether biological markers of physiological dysregulation explain the association between depression and type 2 diabetes.

Although previous studies suggested that antidepressant use may increase the risk of developing diabetes,^{31,32} we did not observe a significant association between antidepressant use and risk of diabetes. Social integration, as indicated by frequency of contact with relatives, was inversely associated with risk of diabetes over the follow-up period, and adjusting for this characteristic strengthened the association between depression and

diabetes, suggesting that social integration may protect individuals with MDD from experiencing subsequent health problems.

Strengths and Limitations

The primary strengths of this study were the population-based sample with 23 years of follow-up, statistical methods that took advantage of the longitudinal nature of the data, and the diagnostic measure of depression. We excluded cases of prevalent diabetes at baseline and all incident cases of diabetes with onset within 1 year of onset of depression, and the average difference between onset of depression and diabetes was 16 years. This indicates that the effect of depression on risk of type 2 diabetes persists over the life course.

A major limitation of our study was the potential for survivor bias caused by attrition in the sample over the 23-year follow-up period. Type 2 diabetes is associated with increased risk of mortality, particularly from cardiovascular disease.³³ However, depression was not associated with attrition in our cohort.¹¹ It is possible that our exclusion of participants

because of missing data on BMI and social network characteristics introduced bias. However, the excluded participants did not differ from the remaining ECA cohort with regard to diabetes status. Thus it is unlikely that these variables materially biased the analytic results, although the findings may not be robustly applicable to older impaired adults. It is possible that the measures of health behaviors were not sensitive enough to accurately capture their associated risk, although the relationships between those behaviors and diabetes were in the expected directions.

Diabetes status may have been misclassified in 2 ways: (1) Although the age of onset in most cases of type 1 diabetes is less than 30 years, and in type 2, 30 years or more, without diagnostic testing we could not definitively determine that all of the cases of diabetes we identified were type 2. (2) Diabetes status was determined by self-report, and because approximately 2.5% of US adults have undiagnosed type 2 diabetes,³⁴ the reliance on self-report data likely resulted in the underdetection of diabetes cases. In post hoc analyses, we compared self-reported diabetes status at wave 4 with diabetes status confirmed by hemoglobin A1c level (diabetes was defined as $\geq 6\%$), which was only measured at wave 4, and found no association between MDD and the proportion of disagreement between self-reported and clinically confirmed diabetes status (data not shown). This suggests that misclassification of diabetes status in this study likely biased the results toward rather than away from the null. Finally, given that follow-up interviews were on average 13 years apart, we may not have accounted for the fluctuation in risk and protective factors. We attempted to address this by using time-varying covariates, but unmeasured variation may have confounded the results.

Conclusions

Depression is a significant risk factor for incident type 2 diabetes, an effect that does not appear to be mediated by poor health behaviors. The association is particularly strong among those with a high school education or less. Future studies should focus on identifying potential mediating pathways of this relationship, such as physiological dysregulation. ■

About the Authors

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Contributors

B. Mezuk was the project coordinator for the Baltimore Epidemiological Catchment Area Study and completed the analyses and led the writing of the article. W.W. Eaton is the principal investigator of the Baltimore Epidemiological Catchment Area Study and supervised all aspects of its implementation. S.H. Golden assisted with the analyses and drafting the article. Y. Ding assisted with the data setup and analyses. All authors helped to originate ideas, interpret findings, and review drafts of the article.

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Human Participant Protection

This study was approved by the Johns Hopkins School of Public Health institutional review board and all participants gave informed consent.

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