# Section II: The Research: Article Summaries and Commentaries

# Hypothesis 1. Depression is a risk factor for the development of type 2 diabetes.

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***Foundation Article***

Eaton WW, Armenian HA, Gallo J, Pratt L, Ford DE: Depression and risk for onset of type II diabetes: a prospective population-based study. *Diabetes Care* 19:1097–1102, 1996

***Summary and Commentary***

Early studies using diagnostic interviews to extract lifetime histories of depression in diabetic subjects indicated that first episodes of major depression typically preceded the diagnosis of type 2 diabetes. A 13-year follow-up of participants in the Epidemiologic Catchment Area (ECA) by Eaton et al. provided some of the first longitudinal evidence that depression might be a risk factor for the development of diabetes. The ECA, a landmark study in psychiatric epidemiology, documented the prevalence of major psychiatric disorders in the United States. Its primary findings were summarized in *Psychiatric Disorders in America* by Robins and Regier.[7]

A structured interview, the Diagnostic Interview Schedule (DIS), was developed for the ECA study. It enabled trained lay interviewers to assess the symptoms that were used to diagnose psychiatric disorders such as major depression according to the American Psychiatric Association's official criteria. The DIS determines whether the subject has ever met the criteria for each disorder and, if so, when the most recent episode occurred. The subjects in the analyses by Eaton et al. were classified according to whether they had ever had a major depressive episode before their ECA interview, regardless of whether they were depressed at the time of the interview.

Utilizing the lifetime diagnosis of depression as a predictor of diabetes made it especially important to take age at enrollment into account. Older subjects had had more time to develop depression, diabetes, or both compared to younger subjects. However, individuals who already had diabetes at enrollment in the ECA were excluded from the analysis. Thus, age at enrollment influenced both inclusion in the sample and the participants' likelihood of ever having been depressed.

Baltimore, Md., was one of several ECA sites; it enrolled 3,481 adult subjects (> 18 years old). Selected items from the National Center for Health Statistics Health Interview Survey (HIS) were used to determine whether each subject had or was being treated for diabetes. Subjects who affirmed any of these items were excluded from the analysis.

The follow-up data were collected from 1993 through 1996. By then, 847 members of the Baltimore cohort had died, according to a National Death Index search. A total of 1,897 (~ 72%) of the 2,652 survivors were interviewed, 1,715 of whom had denied diabetes in 1981. The authors acknowledged that some of these might have had undiagnosed diabetes at the time, but since the study protocol did not include a medical examination, it was impossible to identify undiagnosed cases. The follow-up interview included a more detailed set of questions about diabetes and its treatment than was utilized in 1981. Excluding individuals who experienced only gestational diabetes in the interim, 89 new cases of diabetes were identified among the 1,715 who could

have been at risk in 1981. This represents a cumulative incidence of about 5%. Like the initial assessment, an unknown number of undiagnosed cases might have been missed by the follow-up interview.

Seventy-six of the subjects who had complete diabetes data on the follow-up had met the lifetime major depression in 1981. Six (8%) reported diabetes at follow-up, compared with 80 (5%) of the 1,604 subjects who had never been depressed as of 1981. This represents a relative risk (RR) of 1.6 (95% CI, 0.7–3.5). Thus, the univariate relationship was in the predicted direction, but it was not statistically significant. Major depression was also not a significant predictor of diabetes in a logistic regression model, despite its odds ratio (OR) of 2.2. This model showed age to be a significant risk factor, with ORs of 3.2 and 4.2 for the 45- to 64-year-old and the ≥ 65-year-old groups, respectively, compared to those between 18 and 29 years of age. Body mass index (BMI) was also significant (OR = 1.1), but sex and race were not. Several other forms of depression were explored as potential predictors, as were several anxiety disorders and alcohol dependence, but none was significant.

The report concluded that major depression predicts the development of diabetes. However, the results did not support this conclusion. A significant depression effect might have been found if there had been more new cases of diabetes to model, and consequently greater statistical power to detect an effect, but there were only 86 new cases. The effect was not statistically significant, and therefore the study did not provide compelling evidence that it exists in the population from which the sample was drawn. Nevertheless, the findings were certainly intriguing, and they inspired other investigators to look for evidence that depression is an independent risk factor for diabetes.

Since the publication of this provocative report, several other studies have yielded evidence that depression might increase the risk of developing diabetes. Kawakami et al.[8] conducted an 8-year prospective study of 2,764 male employees of a Japanese company. Subjects were excluded from the analysis if they had diabetes at entry into the study, according to the company's medical records and interviews by research nurses. The Zung Depression Scale was used to measure the severity of depressive symptoms. This is quite different from the approach taken by Eaton et al., in that the Zung is a self-report questionnaire rather than a structured interview, and a high Zung score does not necessarily mean that the subject meets the criteria for major depression. Furthermore, questionnaires such as the Zung assess current symptoms of depression rather than the individual's lifetime history of major depressive disorder.

New cases of diabetes were detected on an annual medical examination that included a fasting glucose test. Over the 8-year follow-up, 43 participants developed type 2 diabetes. Moderate or severe depression (Zung score ≥ 48 was a significant univariate predictor of diabetes (hazard ratio [HR] = 2.3; 95% CI, 1.1–5.1). In contrast, the effect of mild depression was not significant. In a Cox proportional hazards regression analysis, moderate to severe depression remained an independent predictor of time to onset of diabetes (HR = 2.3) after adjusting for age, BMI, smoking, alcohol consumption, physical activity, medical comorbidity, and family history of diabetes. The 17 new cases who were detected in the first 4 years of the follow-up were excluded from a secondary analysis in order to address the possibility that they had had undiagnosed diabetes on the initial assessment. The covariate-adjusted effect of depression (HR = 2.8) was even stronger in this analysis than in the primary model.

Carnethon et al.,[9] in another study, used data from the First National Health and Nutrition Examination Survey (NHANES I) and the National Health and Nutrition Examination Epidemiologic Follow-Up Survey (NHEFS) to determine whether the effect of depression on the onset of type 2 diabetes is mediated by established risk factors for diabetes. Their sample included 2,858 men and 3,332 women. Diabetes was documented by medical records and/or self-report, and current depression was measured by the four-item Depression subscale of the General Well-Being Survey. Over an average of > 15 years of follow-up, 6% of the participants developed type 2 diabetes. The incidence of diabetes was higher among those with high depression scores (7.3/1,000 person-years) than among those with intermediate or low scores (3.4/1,000 person-years and 3.6/1,000 person-years, respectively). The association between depression and diabetes was significant among individuals with less than a high school education, but not among better-educated respondents. The risk of developing diabetes was about three times higher among depressed than nondepressed individuals in the less educated subgroup. In the entire cohort, the covariate-adjusted risk of developing diabetes increased 4% per standard deviation increase in depression. About 31% of the association was explained by differences in BMI and 6% by behaviors including smoking, alcohol use, and physical inactivity.

Arroyo et al.[10] analyzed data from a 4-year follow-up of 72,178 female participants in the Nurses Health Study. They did not have a measure of depression per se, but they did have the five-item Mental Health Index (MHI-5) from the Short-Form 36 quality of life questionnaire. Low scores on the MHI-5 reflect high current levels of depression, anxiety, and/or closely related forms of distress. For the purposes of this study, individuals with an MHI-5 score ≥ 2 were classified as having current depressive symptoms on the initial evaluation. Diabetes was assessed by a detailed biennial questionnaire covering recent symptoms, diagnostic tests, and treatments for diabetes.

During the follow-up period, 973 new cases of type 2 diabetes were reported. Logistic regression was used to adjust for age, smoking, BMI, physical inactivity, alcohol use, menopausal status, parental history of diabetes, and other factors. The RR of developing diabetes for individuals with depressive symptoms in the fully adjusted model was 1.2 (95% CI, 1.0–1.5, $P = 0.05$). The interpretation of this result depends to some extent on whether one views factors such as BMI and physical inactivity as confounders or as mediators of the effect of depression on diabetes. The effect was stronger when adjusting only for age and BMI (RR = 1.4; 95% CI, 1.1–1.7, $P = 0.003$) and stronger still when adjusting only for age (RR = 1.6; 95% CI, 1.3–1.9, $P < 0.0001$).

Finally, Golden et al.[11] used data from 11,615 men and women in the Atherosclerosis Risk in Communities (ARIC) study to analyze the effects of "vital exhaustion" on the development of type 2 diabetes. The symptoms of vital exhaustion overlap with those of depression and include symp-

toms such as fatigue, hopelessness, loss of libido, irritability, crying, and dejection. They were measured by Appel's Vital Exhaustion Scale, and diabetes was documented by medical examinations conducted every 3 years during a 6-year follow-up.

There were 721 new cases of type 2 diabetes, corresponding to an incidence rate of 12.4/1,000 person-years of follow-up. The age-, sex-, and race-adjusted incidence was highest (19.1%) among participants in the highest quartile of vital exhaustion, and it was significantly different from the incidence among those in the lowest quartile ($P < 0.001$). In a Cox proportional hazards regression model adjusting for age, sex, race, education, and ARIC study center, vital exhaustion quartile was an independent predictor of developing type 2 diabetes (HR for the fourth vs. the first quartile = 1.6; 95% CI, 1.3–2.0). In a series of additional models, the effect survived adjustment for metabolic covariates (HR = 1.4, $P = 0.007$), lifestyle covariates (HR = 1.5, $P = 0.0005$), and both sets of covariates (HR = 1.3, $P = 0.04$). The HR exceeded 1.0 but was not significant when adjusted for lifestyle covariates and BMI (HR = 1.3, $P = 0.06$).

In short, these studies provide converging evidence that depression is a risk factor for the development of type 2 diabetes. The instruments used to measure depression differed from one study to the next, and the study by Eaton et al. was the only one to study the effects of major depressive disorder rather than depressive symptoms measured by a self-report questionnaire. The rigor with which diabetes was assessed also differed among the studies. There is still a need for a prospective study in which depression, diabetes, and potential confounders and mediators of the relationship between them are evaluated with comparable rigor in a large cohort. Nevertheless, the existing studies provide reasonably persuasive evidence that depression increases the risk of developing type 2 diabetes and raise the question whether depression treatment might delay or prevent its onset.

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