

# Increased Mortality Risk in Women With Depression and Diabetes Mellitus

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**Context:** Depression and diabetes mellitus have been associated with an increased risk of all-cause and cardiovascular disease (CVD) mortality. However, data evaluating the joint effects of these 2 conditions on mortality are sparse.

**Objectives:** To evaluate the individual and joint effects of depression and diabetes on all-cause and CVD mortality rate.

**Design:** Prospective cohort study.

**Setting:** The 11 states of the Nurses' Health Study.

**Participants:** A total of 78 282 women who participated in the Nurses' Health Study aged 54 to 79 years at baseline in 2000 were followed up until 2006. Depression was defined as having self-reported diagnosed depression, treatment with antidepressant medications, or a score indicating severe depressive symptoms (ie, a 5-item Mental Health Index score  $\leq 52$ ). Self-reported type 2 diabetes was confirmed using a supplementary questionnaire.

**Main Outcome Measures:** All-cause and CVD-specific mortality rate.

**Results:** During 6 years of follow-up (433 066 person-

years), 4654 deaths were documented, including 979 deaths from CVD. Compared with participants without either condition, the age-adjusted relative risks (RRs) (95% confidence interval) for all-cause mortality were 1.76 (1.64-1.89) for women with depression only, 1.71 (1.54-1.89) for individuals with diabetes only, and 3.11 (2.70-3.58) for women with both conditions. The corresponding age-adjusted RRs of CVD mortality were 1.81 (1.54-2.13), 2.67 (2.20-3.23), and 5.38 (4.19-6.91), respectively. These associations were attenuated after multivariate adjustment for other demographic variables, body mass index, smoking status, alcohol intake, physical activity, and major comorbidities (including hypertension, hypercholesterolemia, heart diseases, stroke, and cancer) but remained significant, with the highest RRs for all-cause and CVD mortality found in those with both conditions (2.07 [1.79-2.40] and 2.72 [2.09-3.54], respectively). Furthermore, the combination of depression with a long duration of diabetes mellitus (ie,  $>10$  years) or insulin therapy was associated with a particularly higher risk of CVD mortality after multivariate adjustment (RRs, 3.22 and 4.90, respectively).

**Conclusions:** Depression and diabetes are associated with a significantly increased risk of all-cause and CVD mortality rate. The coexistence of these conditions identifies women at particularly high risk.

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**D**EPRESSION IS HIGHLY prevalent in the US population, affecting approximately 14.8 million US adults (6.7%) in a given year.<sup>1</sup> Strong evidence from epidemiologic studies suggests that depression is associated with a significantly increased risk of coronary heart disease<sup>2</sup> and all-cause mortality.<sup>3</sup> Diabetes mellitus is also highly prevalent, and more than 23.5 million US adults (10%) have this disorder.<sup>4</sup> It is also well known that diabetes and its related complications are leading causes of mortality globally.<sup>5</sup>

Epidemiologic studies have consistently documented an increased prevalence of depression in patients with diabe-

tes. It is estimated that clinically significant depressive symptoms affect approximately 20% to 25% of individuals with diabetes, nearly twice as many as those without diabetes.<sup>6</sup> The coexistence of diabetes and depression is known to be associated with poor glycemic control,<sup>7</sup> an increased risk of diabetes complications,<sup>8</sup> and poor adherence to diabetes management.<sup>9</sup> A growing body of evidence suggests that the combination of diabetes and depression could substantially increase the risk of mortality.<sup>10-17</sup> However, previous investigations have been limited by small sample size,<sup>10,13,15</sup> short-term follow-up,<sup>14-16</sup> evaluation only in patients with diabetes (with no comparison group of patients without diabetes),<sup>13-15,17</sup> and the use of self-reported, questionnaire-

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derived depressive symptoms as the exposure (with no information regarding depression diagnosis and medication use).<sup>11-13,17</sup> In addition, few studies have been conducted among women, in whom depression is more prevalent than in men.<sup>18</sup> Therefore, using data from the Nurses' Health Study, we aimed to examine the individual and joint effects of depression and type 2 diabetes on all-cause and cardiovascular disease (CVD) mortality rate among middle-aged and elderly women during a 6-year follow-up.

## METHODS

### STUDY POPULATION

The Nurses' Health Study cohort was established in 1976, when 121 700 female registered nurses aged 30 to 55 years residing in 11 states responded to a mailed questionnaire regarding their medical history and health practices. The cohort has been followed up every 2 years with mailed questionnaires that updated exposure information and inquired about newly diagnosed medical illnesses. Details have been published elsewhere.<sup>2,19</sup> Until 2006, the follow-up rate was more than 94%. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard School of Public Health.

We used the 2000 questionnaire cycle as the baseline because self-reported diagnosed depression was addressed in this year (n=94 791). Participants with a history of gestational diabetes (n=339); type 1 diabetes (n=310); secondary diabetes (n=360); no information on depressive symptoms, depression diagnosis, or antidepressant use (n=12 041); unknown diabetes diagnosis date or uncertainty of the diagnosis (n=3361); and missing values for covariates (n=98) at baseline were excluded. Therefore, 78 282 participants (aged 54 to 79 years) were included in this analysis.

### DEPRESSION MEASUREMENT

Self-reported symptoms of depression, use of antidepressant medication, and physician-diagnosed depression were used as measures of depression. Depressive symptoms were assessed in 1992, 1996, and 2000 with the 5-item Mental Health Index (MHI-5) subscale of the 36-Item Short-Form Health Survey designed to capture psychological distress vs well-being.<sup>20-22</sup> The participants were asked how much of the time during the past month (all, most, a good bit, some, little, or none) they felt (1) nervous, (2) so down that nothing could cheer them up, (3) calm and peaceful, (4) down and blue, or (5) happy. The scale was scored from 0 to 100, with lower scores indicating more severe depressive symptoms (SDS). The MHI-5 has been shown to have high sensitivity and specificity for major depression, with an area under the receiver operating characteristic curve of 0.88 to 0.91 for the detection of major depressive disorder.<sup>23</sup> In accordance with a prior study coauthored by 2 of us<sup>19</sup> that used this scale, the MHI-5 score was considered a dichotomous indicator of the presence (MHI-5 score,  $\leq 52$ ) or absence (MHI-5 score,  $>52$ ) of SDS.

Participants were first asked to report regular antidepressant medication use in 1996 and history of physician-diagnosed depression in 2000; hence, 2000 was used as the baseline for this study. The information regarding antidepressant medication and physician-diagnosed depression was updated biennially. Therefore, depression was defined as having diagnosed depression, being treated with antidepressant medications, having SDS, or having any of these conditions.

## ASSESSMENT OF DIABETES

A supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy was mailed to women who indicated on any biennial questionnaire that they had been diagnosed as having diabetes. Several repeated mailings were sent to nonrespondents, and these were followed up by telephone interviews. A case of diabetes was considered confirmed if at least 1 of the following was reported on the supplementary questionnaire according to the National Diabetes Data Group criteria<sup>24</sup>: (1) the presence of 1 or more classic symptoms (excessive thirst, polyuria, weight loss, and/or hunger) plus fasting plasma glucose levels of at least 140 mg/dL or random plasma glucose levels of at least 200 mg/dL (to convert glucose levels to millimoles per liter, multiply by 0.0555); (2) at least 2 elevated plasma glucose concentrations on different occasions (fasting levels of at least 140 mg/dL, random plasma glucose levels of at least 200 mg/dL, and/or concentrations of at least 200 mg/dL after 2 hours or more shown by oral glucose tolerance testing) in the absence of symptoms; or (3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). For cases of type 2 diabetes identified after June 1996, the cut-off point was lowered to 126 mg/dL for fasting plasma glucose concentrations, according to the American Diabetes Association criteria.<sup>25</sup> The self-reported type 2 diabetes diagnosis through supplemental questionnaire confirmation has been demonstrated to be highly accurate in a validation study conducted in a subsample of Nurses' Health Study participants, which consisted of comparisons with medical record review by an endocrinologist (J.E.M.).<sup>26</sup> In addition, another validation study<sup>27</sup> assessing the prevalence of undiagnosed diabetes suggested a low rate of false-negative results.

### DEATH ASCERTAINMENT

The main outcome measures were all-cause and CVD-specific mortality that occurred after the return of the 2000 questionnaire but before June 1, 2006. The ascertainment of death has been documented in previous studies.<sup>2,28</sup> Briefly, deaths were identified by reports from next of kin, postal authorities, or searching the National Death Index, and at least 98% of deaths were identified.<sup>29</sup> We obtained copies of death certificates and medical records and determined causes of death (classified according to the categories of the *International Classification of Diseases, Revision 8 (ICD-8)*). Fatal CVD was confirmed by hospital records or autopsy or if CVD was listed as the cause of death on the death certificate and evidence of previous CVD was available. Probable fatal CVD cases were designated when CVD was the underlying cause on the death certificate but no medical records were available. We also included sudden deaths (5.4% of CVD death). Deaths of all CVD causes included ICD-8 codes 390 through 459 and 795.<sup>28</sup>

### COVARIATES

Demographic, lifestyle behavior, and comorbidity information were collected using the standardized questionnaires mailed to the nurses biennially. Marital status (having a spouse or not), ethnicity (white or other), family history (in the first-degree relatives) of diabetes (yes or no) and cancer (yes or no), and parental history of myocardial infarction (yes or no) were obtained. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared from self-reported weight and height and categorized as less than 23, 23.0 through 24.9, 25.0 through 29.9, 30.0 through 34.9, or 35 or higher. Physical activity level based on the individual's engagement in usual recreational activity was grouped as less than 3,

**Table 1. Baseline Characteristics of 78 282 Women According to Diabetes Mellitus and Depression Status in the Nurses' Health Study in 2000<sup>a</sup>**

Characteristic	Neither Diabetes nor Depression	Depression Only	Diabetes Only	Diabetes and Depression
No. (%)	62 289 (79.6)	11 120 (14.2)	3873 (5.0)	1000 (1.3)
MHI-5 score, mean (SD)	83.1 (10.1)	66.4 (18.7)	82.1 (10.6)	65.0 (18.5)
Age, mean (SD), y	66.1 (7.1)	64.8 (7.2)	67.8 (6.7)	66.7 (7.0)
BMI, mean (SD) <sup>b</sup>	26.2 (5.0)	27.1 (5.6)	30.5 (6.1)	32.2 (7.0)
Physical activity level	18.2 (22.4)	14.3 (19.3)	12.4 (17.6)	9.1 (14.6)
Smoking status				
Never	28 321 (45.5)	4328 (38.9)	1819 (47.0)	349 (34.9)
Past	28 442 (45.7)	5527 (49.7)	1779 (45.9)	557 (55.7)
Current	5526 (8.9)	1265 (11.4)	275 (7.1)	94 (9.4)
Current alcohol consumption				
None (abstainer)	32 774 (52.6)	6493 (58.4)	2906 (75.0)	787 (78.7)
0.1-4.9 g/d	14 822 (23.8)	2421 (21.8)	664 (17.1)	150 (15.0)
≥5.0 g/d	14 693 (23.6)	2206 (19.8)	303 (7.8)	63 (6.3)
Marital status, having spouse	45 943 (73.8)	7650 (68.8)	2651 (68.5)	629 (62.9)
Postmenopausal estrogen hormone use				
Never	15 774 (25.3)	1863 (16.8)	1235 (31.9)	265 (26.5)
Past	16 624 (26.7)	3277 (29.5)	1122 (29.0)	318 (31.8)
Current	26 535 (42.6)	5517 (49.6)	1164 (30.1)	350 (35.0)
Unknown	3356 (5.4)	463 (4.2)	352 (9.1)	67 (6.7)
Current aspirin use	28 058 (45.0)	4759 (42.8)	2084 (53.8)	526 (52.6)
Current multivitamin use	42 055 (67.5)	7685 (69.1)	2456 (63.4)	639 (63.9)
Ethnicity, white	60 809 (97.6)	10 944 (98.4)	3677 (94.9)	974 (97.4)
Family history of diabetes	16 361 (26.3)	2974 (26.7)	1999 (51.6)	542 (54.2)
Parental history of MI	11 403 (18.3)	2205 (19.8)	830 (21.4)	240 (24.0)
Family history of cancer	8417 (13.5)	1444 (13.0)	534 (13.8)	137 (13.7)
Hypertension	28 631 (46.0)	5710 (51.4)	3060 (79.0)	831 (83.1)
Hypercholesterolemia	36 636 (58.8)	7243 (65.1)	2914 (75.2)	820 (82.0)
Heart disease <sup>c</sup>	5945 (9.5)	1547 (13.9)	985 (25.4)	319 (31.9)
Stroke	1191 (1.9)	382 (3.4)	209 (5.4)	70 (7.0)
Cancer	9638 (15.5)	1938 (17.4)	707 (18.3)	207 (20.7)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; MHI, Mental Health Index; MI, myocardial infarction.

<sup>a</sup>Data are expressed as number (percentage) unless otherwise specified. Percentages may not total 100 because of rounding.

<sup>b</sup>Calculated as weight in kilograms divided by height in meters squared.

<sup>c</sup>Including MI, angina, and coronary artery bypass graft.

3.0 through 8.9, 9.0 through 17.9, 18.0 through 26.9, or 27 or more metabolic equivalent hours per week. Smoking was grouped as never, former, or current smoker, and alcohol drinking status was categorized as 0, 0.1 through 4.9, or 5.0 or more g/d of alcohol. Most of the women were postmenopausal or in the perimenopausal period; information regarding estrogen hormone therapy was queried, and participants were categorized as never, former, or current users. Information regarding current aspirin and multivitamin use was also requested and grouped as yes or no. In addition, respondents were asked to report previously diagnosed medical conditions, including hypertension, elevated cholesterol level, heart disease, stroke, and cancer.

## STATISTICAL ANALYSIS

Participants were classified into 4 groups: (1) without diabetes or depression, set as the reference group; (2) with depression but no diabetes; (3) with diabetes but no depression; and (4) with diabetes and depression. Means or proportions of covariates across the 4 groups were computed using the baseline information. For these comparisons, we used Mantel-Haenszel  $\chi^2$  tests for categorical variables and analysis of variance for continuous variables. Person-years for each participant were calculated from the date the 2000 questionnaire was returned to the date of death from any cause; June 1, 2006; or the date of return of their last questionnaire, whichever came first. Time-dependent Cox proportional hazards models were

used to estimate age- and multivariate-adjusted relative risks (RRs) of mortality for each group compared with the reference group. The basic model used the updated depression and diabetes status and included age (continuous), marital status, family history of diabetes and cancer, and parental history of myocardial infarction. The multivariate model included the terms in the basic model and several major lifestyle variables: BMI, physical activity level, smoking and drinking status, use of estrogen hormone therapy, current aspirin use, and current multivitamin use. Major comorbidities (updated status of hypertension, elevated cholesterol level, heart disease, stroke, and cancer) were included in another multivariate model to explore whether the effects of diabetes and depression were independent of these comorbidities, which were more likely to be mediators. All the covariates except family history of diabetes and cancer and parental history of myocardial infarction were updated every 2 years.

A series of stratified analyses were conducted by age, BMI, smoking status, alcohol intake status, physical activity level, postmenopausal estrogen hormone use, and prior hypertension, hypercholesterolemia, heart disease, stroke, and cancer, all using updated information. Several complementary analyses were conducted to assess the robustness of the depression definition. The first analysis used only SDS to define depression and used the information from 1992 to 2006, the second defined depression based on antidepressant medication use and used the information from 1996 to 2006, and the third used

**Table 2. Relative Risks (95% Confidence Intervals) of Death From All Causes and Cardiovascular Disease According to Diabetes Mellitus and Depression Status: the Nurses' Health Study, 2000-2006**

	Neither Diabetes nor Depression	Depression Only	Diabetes Only	Diabetes and Depression
Person-years	333 805	68 799	23 561	6901
All-cause mortality				
No. of deaths (mortality rate) per 1000 person-years	3018 (9.0)	1009 (14.7)	421 (17.9)	206 (29.9)
Age-adjusted model <sup>a</sup>	1 [Reference]	1.76 (1.64-1.89)	1.71 (1.54-1.89)	3.11 (2.70-3.58)
Basic model <sup>b</sup>	1 [Reference]	1.74 (1.62-1.86)	1.70 (1.53-1.89)	3.04 (2.64-3.51)
Multivariate model 1 <sup>c</sup>	1 [Reference]	1.53 (1.42-1.64)	1.52 (1.36-1.69)	2.46 (2.12-2.84)
Multivariate model 2 <sup>d</sup>	1 [Reference]	1.44 (1.34-1.54)	1.35 (1.21-1.51)	2.07 (1.79-2.40)
Cardiovascular disease mortality				
No. of deaths (mortality rate) per 1000 person-years	585 (1.8)	196 (2.9)	129 (5.5)	69 (10.0)
Age-adjusted model <sup>a</sup>	1 [Reference]	1.81 (1.54-2.13)	2.67 (2.20-3.23)	5.38 (4.19-6.91)
Basic model <sup>b</sup>	1 [Reference]	1.78 (1.51-2.09)	2.64 (2.17-3.20)	5.21 (4.05-6.71)
Multivariate model 1 <sup>c</sup>	1 [Reference]	1.56 (1.33-1.84)	2.15 (1.76-2.64)	3.89 (3.00-5.05)
Multivariate model 2 <sup>d</sup>	1 [Reference]	1.37 (1.16-1.62)	1.67 (1.36-2.05)	2.72 (2.09-3.54)

<sup>a</sup>Age as a continuous variable.

<sup>b</sup>Age plus family history of diabetes and cancer, parental history of myocardial infarction, current marital status, and ethnicity (white or other).

<sup>c</sup>Multivariate model 1: basic model plus body mass index (calculated as weight in kilograms divided by height in meters squared) categories (<23, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35; physical activity level (<3, 3-8.9, 9-17.9, 18-26.9, or ≥27 metabolic equivalent hours per week), alcohol consumption (none, 0.1-4.9 g/d, or ≥5.0 g/d), smoking status (never, past, or current), current multivitamin use (yes or no), estrogen hormone use (current, past, or never), and current aspirin use (yes or no).

<sup>d</sup>Multivariate model 1 plus major comorbidities, including hypertension, hypercholesterolemia, heart disease, stroke, and cancer.

only self-reported diagnosed depression from 2000 to 2006. We also conducted subgroup analysis according to duration or treatment of diabetes. The associations of different stages of depression (only SDS, only diagnosed depression, or using antidepressant medication) and the effect of their combination with diabetes on mortality risk were further examined. All reported *P* values were 2-sided, and statistical analyses were performed with SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

## RESULTS

During the 6-year follow-up of these 78 282 middle-aged and elderly women (433 066 person-years), 4654 deaths (6.0%) were documented, with CVD mortality accounting for 979 (21.0%) of all deaths. Generally, participants with diabetes and depression combined had lower MHI-5 scores and physical activity levels, had higher BMIs, and were less likely to have spouses at baseline compared with the other 3 groups (**Table 1**). In addition, they had higher rates of other comorbidities, including histories of hypertension, heart disease, stroke, or cancer at baseline (Table 1). The prevalence of depression in participants with diabetes (20.5%) was higher than that in the individuals without diabetes (15.1%).

### ANALYSES ACCORDING TO UPDATED STATUS OF DIABETES AND DEPRESSION

Compared with the reference group who had neither diabetes nor depression, the age-adjusted RR for all-cause mortality was more than 3-fold higher in those with both conditions (RR, 3.11; 95% confidence interval [CI], 2.70-3.58) (**Table 2**). Multivariate adjustment did not substantially modify the results, with RRs of 1.53 (95% CI, 1.42-1.64) for those with depression only, 1.52 (95% CI, 1.36-1.69) for those with diabetes only, and 2.46 (95%

CI, 2.12-2.84) for those with diabetes and depression. Similar results were found with regard to CVD-specific mortality rate. Compared with the reference group, depression only and diabetes only alone showed a significantly increased risk of CVD mortality, with multivariate-adjusted RRs of 1.56 (95% CI, 1.33-1.84) and 2.15 (95% CI, 1.76-2.64), respectively. The RR for individuals with both conditions was 3.89 (95% CI, 3.00-5.05; *P* for interaction = .49).

All the associations were substantially attenuated after controlling for some major comorbidities (updated status of hypertension, hypercholesterolemia, heart disease, stroke, and cancer) but remained significant. Compared with the reference group who had neither condition, the RRs of total and CVD mortality for individuals with both conditions decreased to 2.07 (95% CI, 1.79-2.40) and 2.72 (2.09-3.54). However, adjustment for major comorbidities might be overadjustment to some extent because depression and diabetes are strong risk factors for those comorbidities, particularly CVD.<sup>30,31</sup>

In subgroup analyses (**Table 3**), the excess risk of CVD mortality associated with diabetes only, depression only, or both conditions was significant in most stratified subgroups. The magnitudes of the RRs varied across different stratifications, whereas the pattern was comparable with the highest RRs found in those with both conditions. The results from the complementary analyses (using different definition of depression and periods) were consistent with the main analysis (**Table 4**).

### EFFECT OF DIABETES DURATION AND TREATMENT AND DEPRESSION ON CVD MORTALITY RATE

As expected, the risk of CVD mortality increased monotonically with increased duration of clinical diabetes. Com-

**Table 3. Multivariate Relative Risks (95% Confidence Intervals) of Cardiovascular Disease Death According to Diabetes and Depression Status: Subgroup Analysis<sup>a</sup>**

	Total No. of Cardiovascular Disease Deaths	Neither Diabetes nor Depression	Depression Only	Diabetes Only	Diabetes and Depression
Age group, y					
<70	179	1.00	1.32 (0.88-1.97)	2.91 (1.86-4.54)	4.39 (2.54-7.57)
≥70	800	1.00	1.38 (1.15-1.66)	1.48 (1.18-1.87)	2.38 (1.75-3.25)
Body mass index					
<25.0	493	1.00	1.37 (1.10-1.71)	1.04 (0.69-1.58)	2.32 (1.42-3.79)
25.0-29.9	267	1.00	1.17 (0.83-1.65)	1.95 (1.38-2.77)	3.13 (1.91-5.11)
≥30.0	219	1.00	1.64 (1.13-2.39)	2.24 (1.58-3.19)	3.44 (2.22-5.33)
Smoking status					
Never	335	1.00	1.16 (0.85-1.57)	1.84 (1.33-2.54)	1.78 (1.03-3.08)
Past	505	1.00	1.46 (1.16-1.82)	1.53 (1.14-2.06)	2.94 (2.08-4.15)
Current	139	1.00	1.46 (0.95-2.23)	1.65 (0.88-3.09)	4.38 (2.19-8.78)
Current drinking status					
No	712	1.00	1.41 (1.16-1.71)	1.72 (1.37-2.16)	2.57 (1.91-3.45)
Yes	267	1.00	1.28 (0.92-1.78)	1.43 (0.85-2.38)	4.03 (2.19-7.43)
Physical activity level					
<9 MET-h/wk	701	1.00	1.39 (1.15-1.69)	1.80 (1.43-2.26)	2.62 (1.94-3.55)
≥9 MET-h/wk	278	1.00	1.40 (1.01-1.94)	1.34 (0.84-2.15)	3.71 (2.12-6.50)
Current estrogen hormone use					
No	837	1.00	1.33 (1.11-1.59)	1.83 (1.48-2.27)	2.90 (2.20-3.84)
Yes	142	1.00	1.34 (0.90-1.99)	1.18 (0.60-2.35)	1.46 (0.61-3.46)
History of hypertension					
No	232	1.00	1.58 (1.13-2.20)	2.23 (1.30-3.80)	3.38 (1.47-7.80)
Yes	747	1.00	1.30 (1.07-1.57)	1.62 (1.30-2.02)	2.64 (2.00-3.50)
History of hypercholesterolemia					
No	252	1.00	1.17 (0.83-1.64)	1.16 (0.69-1.95)	2.97 (1.55-5.68)
Yes	727	1.00	1.43 (1.18-1.73)	1.84 (1.47-2.30)	2.74 (2.05-3.67)
History of heart disease					
No	643	1.00	1.45 (1.17-1.78)	1.58 (1.19-2.10)	2.78 (1.88-4.12)
Yes	336	1.00	1.24 (0.95-1.63)	1.79 (1.33-2.41)	2.72 (1.89-3.93)
History of stroke					
No	838	1.00	1.35 (1.13-1.62)	1.74 (1.40-2.18)	2.97 (2.22-3.97)
Yes	141	1.00	1.44 (0.96-2.17)	1.32 (0.78-2.23)	2.28 (1.18-4.42)
History of cancer					
No	731	1.00	1.24 (1.01-1.50)	1.72 (1.37-2.17)	2.58 (1.87-3.54)
Yes	248	1.00	1.85 (1.35-2.52)	1.55 (1.00-2.39)	3.34 (2.04-5.45)

Abbreviation: MET-h/wk, metabolic equivalent hours per week.

<sup>a</sup>Stratified by baseline information. Adjusted for age (continuous), family history of diabetes and cancer, parental history of myocardial infarction, current marital status, and ethnicity (white or other), body mass index (calculated as weight in kilograms divided by height in meters squared) categories (<23, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35; physical activity level (<3, 3-8.9, 9-17.9, 18-26.9, or ≥27 metabolic equivalent hours per week), alcohol consumption (none, 0.1-4.9 g/d, or ≥5.0 g/d), smoking status (never, past, or current), current multivitamin use (yes or no), estrogen hormone use (current, past, or never), current aspirin use (yes or no), and major comorbidities (including hypertension, hypercholesterolemia, heart disease, stroke, and cancer) but not controlling for itself.

pared with women without diabetes, the multivariate-adjusted RRs of CVD death across categories of diabetes duration (<5, 5-10, and >10 years) were 0.95 (95% CI, 0.66-1.37), 1.75 (95% CI, 1.30-2.37), and 2.40 (95% CI, 1.94-2.97), respectively (data not shown). In the same multivariate model, the RR of CVD mortality for women with depression was 1.54 (95% CI, 1.29-1.83) compared with those without (data not shown). Among each stratum of duration of diabetes, the presence of depression implied a significantly higher risk compared with those without depression (**Figure, A**). The combination of depression and a long duration of diabetes (ie, >10 years) was associated with a RR of 3.22 (95% CI, 2.29-4.52) compared with those with neither diabetes nor depression.

The multivariate RRs of CVD death across categories of diabetes treatment (no treatment, oral diabetes medication use, and insulin therapy) were 1.12 (95% CI, 0.78-

1.52), 1.58 (95% CI, 1.26-1.99), and 3.11 (95% CI, 2.41-4.01), respectively (data not shown). The combination of depression and insulin therapy was associated with an approximate 4.90-fold (95% CI, 3.35-7.15) increased risk of CVD death compared with those with neither diabetes nor depression (**Figure, B**).

#### EFFECT OF DEPRESSION CATEGORIES AND DIABETES ON CVD MORTALITY RATE

The increased risk of CVD mortality was evident in each stage of depression. Compared with participants without depression, the multivariate-adjusted RRs of CVD death in each category of depression (SDS only, diagnosed depression without treatment only, and antidepressant medication use) were 1.73 (95% CI, 1.28-2.33), 1.27 (95% CI, 0.97-1.67), and 1.42 (95% CI, 1.19-

**Table 4. Relative Risks (95% Confidence Intervals) of Cardiovascular Disease Mortality According to Different Definition of Depression and Diabetes Status**

	Neither Diabetes nor Depression	Depression Only	Diabetes Only	Diabetes and Depression
<b>Severe depressive symptoms<sup>a</sup></b>				
Person-years	823 087	53 141	43 166	3838
No. of deaths (mortality rate) per 1000 person-years	1308 (1.6)	127 (2.4)	311 (7.2)	50 (13.0)
Age-adjusted model <sup>b</sup>	1 [Reference]	1.86 (1.55-2.24)	3.43 (3.02-3.88)	6.90 (5.20-9.17)
Multivariate model 1 <sup>c</sup>	1 [Reference]	1.32 (1.10-1.58)	2.62 (2.29-2.99)	4.18 (3.13-5.59)
Multivariate model 2 <sup>d</sup>	1 [Reference]	1.19 (0.99-1.43)	1.94 (1.69-2.22)	2.57 (1.92-3.45)
<b>Antidepressant medication use<sup>e</sup></b>				
Person-years	615 324	60 427	36 790	5923
No. of deaths (mortality rate) per 1000 person-years	1060 (1.7)	169 (2.8)	247 (6.7)	68 (11.5)
Age-adjusted model <sup>b</sup>	1 [Reference]	1.81 (1.53-2.13)	3.14 (2.73-3.61)	6.16 (4.82-7.87)
Multivariate model 1 <sup>c</sup>	1 [Reference]	1.59 (1.35-1.88)	2.56 (2.21-2.97)	4.35 (3.37-5.60)
Multivariate model 2 <sup>d</sup>	1 [Reference]	1.38 (1.17-1.63)	1.96 (1.68-2.27)	2.95 (2.28-3.81)
<b>Self-reported diagnosed depression<sup>f</sup></b>				
Person-years	407 574	47 947	31 486	5078
No. of deaths (mortality rate) per 1000 person-years	837 (2.1)	145 (3.0)	210 (6.7)	51 (10.0)
Age-adjusted model <sup>b</sup>	1 [Reference]	1.67 (1.40-2.00)	2.74 (2.36-3.19)	4.83 (3.64-6.41)
Multivariate model 1 <sup>c</sup>	1 [Reference]	1.50 (1.25-1.79)	2.23 (1.90-2.62)	3.59 (2.68-4.80)
Multivariate model 2 <sup>d</sup>	1 [Reference]	1.30 (1.08-1.55)	1.71 (1.45-2.02)	2.41 (1.80-3.23)

<sup>a</sup>Depression was defined as having severe depressive symptoms (ie, 5-Item Mental Health Index  $\leq 52$ ). The analysis used data from June 1, 1992, through June 1, 2006.

<sup>b</sup>Age as a continuous variable.

<sup>c</sup>Age plus family history of diabetes and cancer, parental history of myocardial infarction, current marital status, ethnicity (white or other), body mass index (calculated as weight in kilograms divided by height in meters squared) categories ( $<23$ , 23.0-24.9, 25.0-29.9, 30.0-34.9, or  $\geq 35$ ), physical activity level ( $<3$ , 3-8.9, 9-17.9, 18-26.9, or  $\geq 27$  metabolic equivalent hours per week), alcohol consumption (none, 0.1-4.9 g/d, or  $\geq 5.0$  g/d), smoking status (never, past, or current), current multivitamin use (yes or no), estrogen hormone use (current, past, or never), and current aspirin use (yes or no).

<sup>d</sup>Multivariate model 1 plus major comorbidities (including hypertension, hypercholesterolemia, heart disease, stroke, and cancer).

<sup>e</sup>Depression was defined as using antidepressant medications. The analysis used data from June 1, 1996, through June 1, 2006.

<sup>f</sup>Depression was defined as having self-reported diagnosed depression. The analysis used data from June 1, 2000, through June 1, 2006.

1.69), respectively (data not shown). Participants with SDS and diabetes combined had the highest RR of 4.54 (95% CI, 2.60-7.92) on death of CVD compared with those who had neither condition (Figure, C).

## DISCUSSION

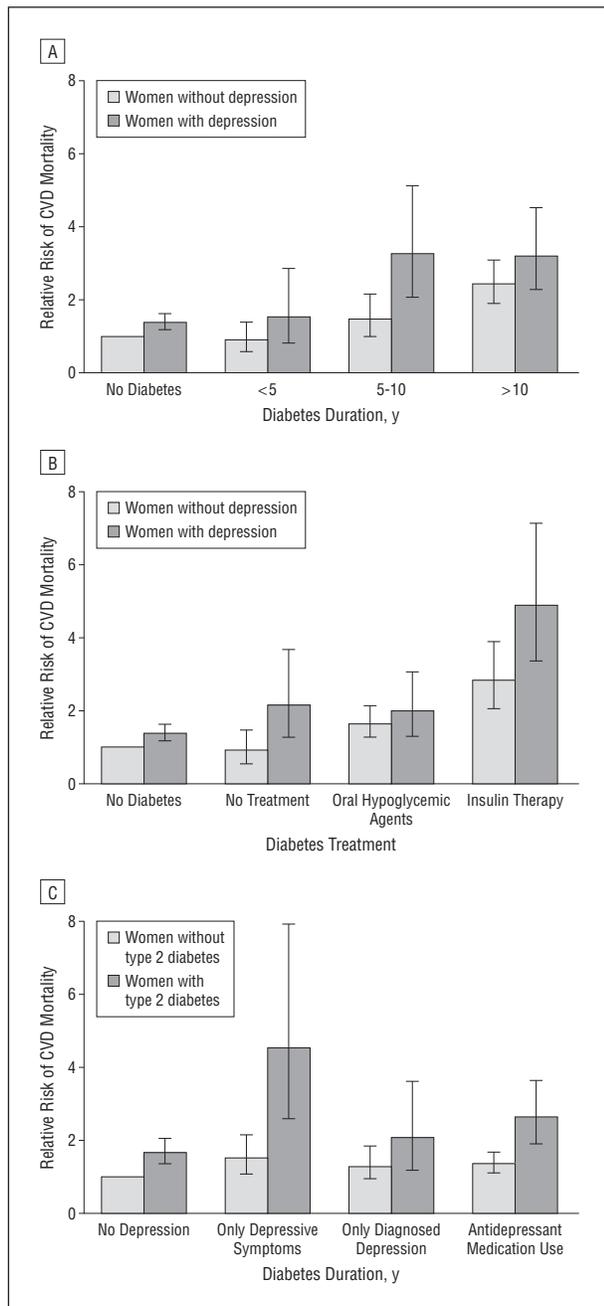
In this large prospective cohort of women, we confirmed that diabetes and depression were significant risk factors for all-cause and CVD mortality, whereas the coexistence of these conditions was associated with a much higher risk. We also observed a strong monotonic relation between diabetes severity (diabetes duration or type of treatment) and CVD mortality rate, with highest risk among women with higher diabetes severity and comorbid depression combined.

Compared with individuals without diabetes, the risk of death in women with diabetes was increased by 35.2% in the current study. This is slightly lower but consistent with several previous publications<sup>32-35</sup> in which a 1.5- to 2-fold increased risk of death was reported. However, it is slightly lower than a previous report coauthored by 3 of us<sup>28</sup> in this cohort in which a 2.5-fold increased risk of all-cause mortality was observed for women with diabetes during 20 years of follow-up (1976-1996). The discrepancy might be because of shorter duration of follow-up, secular trends in treatment for diabetes and cardiovascular disease, and age differences in the present study. We also confirmed that diabetes was a leading cause of CVD mortality with a multivariate adjusted

RR of 1.67. This finding is consistent with most previous publications summarized in 2 meta-analyses.<sup>36,37</sup> In addition, we found that the risk of all-cause and CVD death was approximately 40% higher in women with depression compared with individuals without depression, which is consistent with findings of other investigators<sup>3,38</sup> and a prior publication in the same cohort coauthored by 1 of us,<sup>2</sup> in which a 1.54-fold increased risk of fatal coronary heart disease associated with depression was observed.

We further observed that the coexistence of diabetes and depression was associated with a much higher risk of all-cause mortality (RR, 2.07). Egede and colleagues<sup>11</sup> also found similar results, with a 2.5-fold increased mortality risk for the combination of diabetes and depression compared with those without either condition. Black et al<sup>10</sup> observed a much higher risk of the diabetes-depression combination with an RR of 4.94, which might occur because of using a reference group with neither diabetes nor depressive symptoms (Center for Epidemiologic Study of Depression score of 0 instead of the commonly used cutoff point of 16<sup>39</sup>). It could also occur because of differences in the study populations. The study by Black et al comprised Mexican Americans 65 years or older, whereas our study included primarily white women.

In our multivariate-adjusted model, we also found that the diabetes-and-depression combination was associated with a 2.7-fold increased risk of CVD mortality compared with those who had neither condition. This risk was much higher than that owing to diabetes (RR, 1.67) or depres-



**Figure 3.** Multivariate relative risks and 95% confidence intervals (error bars) of cardiovascular disease (CVD) mortality. A, Relative risk of CVD mortality according to diabetes duration stratified by depression. B, Relative risk of CVD mortality according to diabetes treatment stratified by depression. C, Relative risk of CVD mortality according to depression categories stratified by diabetes. Relative risks were adjusted for age (continuous), family history of diabetes and cancer, parental history of myocardial infarction, current marital status, ethnicity (white or other), body mass index (calculated as weight in kilograms divided by height in meters squared) categories (<23, 23.0-24.9, 25.0-29.9, 30.0-34.9, or  $\geq 35$ ; physical activity level (<3, 3-8.9, 9-17.9, 18-26.9, or  $\geq 27$  metabolic equivalent hours per week), alcohol consumption (none, 0.1-4.9 g/d, or  $\geq 5.0$  g/d), smoking status (never, past, or current), current multivitamin use (yes or no), current estrogen hormone use (never, past, or current), current aspirin use (yes or no), and major comorbidities, including hypertension, hypercholesterolemia, heart disease, stroke, and cancer.

sion (RR, 1.37) only. Egede et al<sup>11</sup> observed similar risks of coronary heart disease mortality among participants with both conditions (RR, 2.43) and those with diabetes only

(RR, 2.26). However, they used a Center for Epidemiologic Study of Depression score of 16 to categorize depression status, which might represent less severe depressive symptoms than clinical diagnosis. In our study, the formal interaction test was not statistically significant, suggesting that the joint effects of diabetes and depression on CVD mortality rate are likely to be additive. Nevertheless, the RR (2.72) was still moderately higher than the additive risk ( $1.67 \times 1.37 = 2.29$ ). Depression affects approximately 20% to 25% of the diabetic population<sup>6</sup>; therefore, considering the size of the potential populations affected, the excess risk of all-cause and CVD death associated with depression among individuals with type 2 diabetes deserves additional attention.

The underlying mechanisms of the increased mortality risk associated with depression in patients with diabetes remain to be elucidated. Numerous studies have found that depression and diabetes are highly correlated<sup>40</sup> and the association is bidirectional.<sup>41</sup> It is generally suggested that depression is associated with poor glycemic control,<sup>7</sup> an increased risk of diabetes complications,<sup>8</sup> poor adherence to diabetes management by patients,<sup>9</sup> and isolation from the social network.<sup>42</sup> Diabetes and depression are linked to unhealthy behaviors (such as tobacco use, poor diet quality, sedentary lifestyle, and inadequate exercise),<sup>43,44</sup> and these behaviors are particularly prevalent in individuals with both conditions. With regard to CVD death, depression could trigger episodes of transient ischemia,<sup>45</sup> increase hypothalamic-pituitary-adrenal axis activity and sympathetic nervous system tone, decrease heart rate variability and the cardiac fibrillation threshold, and alter thrombogenesis.<sup>46,47</sup> Alterations in platelet serotonin receptors and increased catecholamine and serotonin levels associated with depression may also promote platelet clumping and subsequent thrombosis.<sup>48</sup>

Ours is one of few cohort studies that investigated the joint effect of diabetes and depression on all-cause and CVD-specific mortality rate among women. The large sample size and long duration of follow-up provide the opportunity to examine the association of diabetes and depression by themselves and in combination with risk of mortality. The follow-up rate of this well-established cohort was high (>94.0%), and more than 98.0% of the deaths were ascertained. Thus, our study results are unlikely to be biased by losses to follow-up. In addition, we have collected detailed information on disease assessments (diabetes, depression, and related comorbidities) and other risk factors, such as smoking, BMI, and physical activity through repeated assessments.

Several limitations of the study should be considered. The study sample was a homogeneous population, all the participants were registered nurses, and more than 97.6% of participants were white. They had greater concern about their health and better understanding of health-related issues, which enhanced the reliability of our questionnaire assessment; however, the results might not be generalizable to other populations. Recruitment bias and survival bias of the cohort might also restrict the generalizability. In addition, the information regarding diagnosed diabetes and depression was based on self-report, and the exact diagnosis date of depression was not avail-

able. This may lead to some misclassification of the exposure variables. However, previous studies coauthored by 2 of us<sup>26,27</sup> have found self-reporting of diabetes to be highly reliable, although undiagnosed diabetes was possible in this cohort. On the other hand, the physician recognition rate of major depression is not generally considered to be high compared with the Structured Clinical Interview for *DSM-IV*,<sup>49</sup> and the prevalence of untreated mental disorders is relatively high in the United States.<sup>50</sup> Therefore, history of depression is likely to be underreported, which might have led to an overestimation of the risk in the depression-free population. Furthermore, we did not have information regarding medication adherence, glycemic control, diabetes complications, and disability levels, restricting our ability to explore the underlying mechanisms.

The comorbidity of depression and diabetes is associated with a substantial increase in the risk of mortality, particularly death from CVD. Considering the size of the population that could be affected by these 2 prevalent disorders, further consideration is required to design strategies aimed to provide adequate psychological management and support among those with longstanding chronic conditions, such as diabetes.

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