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Association of Depression With Increased Risk of Dementia in Patients With Type 2 Diabetes

The Diabetes and Aging Study

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Context: Although depression is a risk factor for dementia in the general population, its association with dementia among patients with diabetes mellitus has not been well studied.

Objective: To determine whether comorbid depression in patients with type 2 diabetes increases the risk of development of dementia.

Design: The Diabetes and Aging Study was a cohort investigation that surveyed a racially/ethnically stratified random sample of patients with type 2 diabetes.

Setting: A large, integrated, nonprofit managed care setting in Northern California.

Participants: A sample of 19 239 diabetes registry members 30 to 75 years of age.

Main Outcome Measures: The Patient Health Questionnaire 8, *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnoses of depression, and/or antidepressant prescriptions in the 12 months prior to baseline were used to identify prevalent cases of depression. Clinically recognized dementia was identified among subjects with no prior *ICD-9 Clinical Modification* (*ICD-9-CM*) diagnoses of dementia. To exclude the possibility that depression was a prodrome of dementia, dementia diagnoses were only based on *ICD-9-CM* diagnoses identified in years 3 to 5 postbaseline. The risk of dementia for patients with depression and diabetes relative to patients with diabetes alone was estimated using Cox proportional hazard regression models that adjusted for sociodemographic, clinical, and health risk factors and health use.

Results: During the 3- to 5-year period, 80 of 3766 patients (2.1%) with comorbid depression and diabetes (incidence rate of 5.5 per 1000 person-years) vs 158 of 15 473 patients (1.0%) with diabetes alone (incidence rate of 2.6 per 1000 person-years) had 1 or more *ICD-9-CM* diagnoses of dementia. Patients with comorbid depression had a 100% increased risk of dementia during the 3 to 5 years postbaseline (adjusted hazard ratio, 2.02; 95% confidence interval, 1.73-2.35).

Conclusion: Depression in patients with diabetes was associated with a substantively increased risk for development of dementia compared with those with diabetes alone.

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DEPRESSION AND DIABETES mellitus are 2 of the most common illnesses in older primary care populations. The link between these 2 disorders appears to be bidirectional, with depressive episodes developing earlier in life leading to an increased risk of diabetes[1,2] and adult-onset diabetes increasing the subsequent risk of depression.[2]

Recent systematic reviews have found that both depression and diabetes independently increase the risk of dementia. Lu and colleagues[3] found 16 studies examining the association of diabetes with dementia. Persons with diabetes compared with those without had a 47% increased risk of all-cause dementia, a 39% increased risk of Alzheimer disease (AD), and more than a 2-fold increased risk of vascular dementia.[3] Two recent systematic reviews found that depression doubled the risk of subsequent AD and all-cause dementia.[4,5]

Up to 20% of adult patients with type 2 diabetes meet criteria for comorbid major depression.[6] Comorbid depression in patients with diabetes is associated with poor self-care (nonadherence to diet, exercise, smoking, and taking prescribed medication),[7] poor glycemic control,[8] and

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an increased risk of microvascular and macrovascular complications.[9,10] Poor glycemic control,[8] vascular risk factors, and vascular changes[10] associated with depression in patients with diabetes may increase the risk of dementia. In addition, both depression and type 2 diabetes are associated with biologic changes such as increased proinflammatory factors,[11,12] decreased insulin sensitivity,[12,13] and abnormalities in autonomic nervous system homeostasis,[14,15] which may also increase the risk of dementia.

We are aware of only 1 study examining whether patients with comorbid depression and diabetes compared with those with diabetes alone are at increased risk of all-cause dementia.[16] Since depression affects up to 20% of diabetic patients, it is critical to estimate if it is a risk factor for dementia since it is potentially modifiable. The previous study of approximately 4000 patients with type 2 diabetes found a 2-fold increased risk of dementia (3-5 years postbaseline) among patients with comorbid depression and type 2 diabetes compared with those with diabetes alone.[16] Limitations of this prior study include that it was completed in a single large health care system serving 1 geographical region and included a population with limited racial/ethnic diversity. The current study replicates these results in a much larger and more diverse population of approximately 20 000 patients enrolled in a managed care setting.

METHODS

The Diabetes Study of Northern California (DISTANCE) is a cohort investigation to address significant gaps in existing knowledge regarding the natural history, service use, and self-care of adults living with diabetes.[17] Subjects come from a well-characterized, multiethnic cohort of insured patients with diabetes, the Kaiser Permanente Northern California (KPNC) Diabetes Registry.[18] The registry has been maintained since 1993; is updated annually by adding all patients identified as having diabetes using standardized criteria from automated health records including pharmacy, laboratory, hospitalization records, and outpatient diagnoses; and has an estimated sensitivity of 99% based on medical record review validation.[18] In addition to the extensive electronic records, DISTANCE collected patient-reported information through a survey of a race-stratified random sample of members of the registry.[17] The DISTANCE survey assessed a range of social, behavioral, clinical, and health care–related factors that might influence diabetes outcomes. Surveys were offered in 5 languages and could be completed by mail or telephone or on the Web. The Diabetes and Aging Study is an ancillary study of DISTANCE that focuses on medical issues particularly relevant to older patients with diabetes (eg, dementia).[19] This research has been approved by the review boards of the Kaiser Foundation Research Institute and the University of California, San Francisco, School of Medicine and the University of Chicago.

STUDY SETTING AND PARTICIPANTS

Kaiser Permanente Northern California is a nonprofit, prepaid, integrated health care delivery system serving approximately 3.2 million members in Northern California. The KPNC enrollment is demographically similar to that of the area population, except in the extremes of the income distribution. From May 2005 to December 2006, researchers conducted the baseline DISTANCE survey among a racially/ethnically stratified, random sample of diabetes registry members aged 30 to 75 years, targeting 6871 African American, 4333 white, and 7018 Latino individuals and 11 417 members of unknown race/ethnicity and achieving a 62% overall response rate (N = 20 188).[17] Participation was somewhat lower in racial/ethnic minority groups compared with white individuals and those with a high school or less education compared with those with 1 or more years of college.[17] Further details about the study methods[17] and diabetes registry[18] have been previously published.

PREDICTORS OF INTEREST

The main predictor of interest was having clinically significant depression symptoms[20] as determined by a score of 10 or more on the Patient Health Questionnaire 8 (PHQ-8)[21] and either a physician diagnosis of depression in the 12 months prior to baseline survey, which was based on *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes 296.2, 296.3, 298.0, 300.4, 309.0, 309.28, or 311, or a prescription of 1 or more of the following medications: citalopram hydrobromide, fluoxetine, fluvoxamine, paroxetine hydrochloride, sertraline hydrochloride, escitalopram oxalate, bupropion hydrochloride, isocarboxazid, maprotiline, mirtazapine, nefazodone hydrochloride, phenelzine sulfate, tranylcypromine sulfate, trazodone hydrochloride, venlafaxine hydrochloride, and duloxetine hydrochloride. The PHQ-8 is a self-report measure based on the *DSM-IV* criteria[22] for major depression. A PHQ-8 score of 10 or more has been found to have 88% sensitivity and 88% specificity for diagnosis of major depression based on clinical interview.[21] To meet *DSM-IV* criteria for major depression, patients were required to have at least 5 symptoms endorsed for more than half the time, including at least 1 of the cardinal symptoms: depressed mood or anhedonia.

A positive response to a patient self-report question that asked "Has a clinician ever diagnosed you as having depression?" was also used as evidence of depression in a sensitivity analysis. This depression diagnosis allowed estimation of lifetime history of depression rather than current depression diagnosis with risk of dementia.

POTENTIAL CONFOUNDERS

Potential confounders obtained from the DISTANCE survey included sociodemographic characteristics (age, sex, education, and race/ethnicity), diabetes duration, height, weight, and standardized questions on health risk behaviors, including smoking[23] and physical activity.[24] Individual diabetes complications (nephropathy, neuropathy, myocardial infarction, retinopathy, stroke, peripheral vascular disease, and cerebrovascular disease), clinical control (hypertension and glycated hemoglobin [HbA_{1c}] level), and a validated comorbidity index (DxCG) to summarize illness burden[25] were based on the prior 12 months of KPNC automated *ICD-9* diagnostic data and laboratory data (based on the test result closest to the baseline survey). Type 1 diabetes was identified by self-report or age at onset less than 30 years and treatment with insulin alone at baseline. Because depression has been shown to increase health care use in patients with diabetes[26] and potentially provide more opportunity for the physician to diagnose dementia, we used KPNC automated data to ascertain number of primary care visits per year over the 5-year period.

OUTCOME OF INTEREST: DEMENTIA

Incident cases of clinically recognized dementia were identified from both outpatient and inpatient databases based on the

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presence of 1 or more *ICD-9 Clinical Modification* (*ICD-9-CM*) diagnostic codes of uncomplicated senile dementia (290.0), AD (331.01), vascular dementia (290.4), or dementia not otherwise specified (290.1) over the 5-year period after baseline. We excluded patients with evidence of 1 or more dementia diagnoses prior to baseline.

These *ICD-9-CM* codes have been used successfully in recent studies to identify patients with dementia among those with diabetes.[27,28] In a recent study in another large health care setting, having 1 of these *ICD-9-CM* diagnoses for dementia was found to have a sensitivity of 77% and a specificity of 95% compared with a consensus diagnosis of dementia based on a neuropsychiatric battery, physical examination, structured interview with informants, and review of medical records (P. Crane, MD, MPH, written communication, 2009). A similar battery of *ICD-9-CM* codes from 5 years of Medicare claims data had sensitivity of 87% for identifying cognitive impairment compared with a neuropsychiatric battery among patients in an AD registry, and patients with more severe cognitive impairment were more likely to be identified.[29]

STATISTICAL ANALYSES

We described baseline demographic and clinical characteristics and health risk variables of the depressed and nondepressed groups. We estimated the association between depression and incident dementia diagnosis in years 3 through 5 of follow-up using the proportional hazards model. The primary outcome ignored the first 2 years of dementia diagnoses to minimize the possibility that depression may occur as a prodrome of dementia or secondary to dementia.[30]

We censored individuals at the time for development of dementia, disenrollment, death from any cause, or the end of the follow-up period, whichever came first. We fit 4 proportional hazards models to the dementia outcome: the first model included only baseline depression (depression vs no depression); the second model added demographic characteristics (age, sex, education, and race); the third model added demographic characteristics and clinical characteristics (duration of diabetes and evidence in prior year of stroke, myocardial infarction, hypertension, neuropathy, nephropathy, retinopathy, cerebrovascular disease, and peripheral vascular disease as well as HbA_{1c} level and a claims-based comorbidity score (DxCG)[25]; and the fourth model added demographic and clinical characteristics and health risk behaviors (body mass index [BMI] [calculated as weight in kilograms divided by height in meters squared] and smoking) and number of health care visits during the 5-year follow-up.

Effect modification of depression on risk of dementia was also evaluated by specifying interactions (with depression) for 5 variable categories: age (<65 vs ≥65 years), race/ethnicity (white, African American, Latino, East Asian, Filipino, mixed race, and other/unknown), number of diabetes complications (<3 vs ≥3), intensity of diabetes treatment (insulin vs diet and/or oral hypoglycemic drugs), and health risk behaviors including BMI (<30 vs ≥30), current smoker vs past or nonsmoker, and HbA_{1c} level (<8.0% vs ≥8.0% [to convert to proportion of total hemoglobin, multiply by 0.01]).

The DISTANCE used a stratified random sampling design that oversampled minority patients to provide adequate power for ethnic contrasts. To account for this design effect, we weighted analyses using expansion weights (reciprocal of the nonproportional sampling fractions for each ethnic group) in all multivariable models. While the amount of missing data for the survey-derived covariates was small (<3%), a complete case analysis would include only 11 310 of the available 19 239 observations, resulting in a loss of approximately 41% of the data. To eliminate bias due to missing data, we created a multiple imputed data set (20 iterations) using the multivariate normal model and Markov chain Monte Carlo approach and used this in our analyses.[31,32]

We conducted a series of sensitivity analyses. The first included all incident dementia diagnosis in the 5-year postbaseline period to examine differences from our primary analyses that excluded dementia diagnosis in years 1 and 2. A second sensitivity analysis estimated the association between depression and incident dementia diagnosis during follow-up in years 4 and 5 only. A third sensitivity analysis specified a proportional hazard model of incident dementia (in years 3-5), using patient self-report of receiving a prior diagnosis of depression before baseline survey as the independent predictor. A fourth and final sensitivity analysis estimated the association of depression defined by a PHQ-8 score of 10 or more alone and incident dementia (in years 3-5).

RESULTS

Of the 20 188 consenting patients in DISTANCE, 161 were excluded based on 1 or more *ICD-9-CM* dementia diagnoses prior to baseline, 163 were excluded based on a dementia *ICD-9-CM* diagnosis within the first 2 years after baseline, 477 were excluded because of meeting criteria for type 1 diabetes, and 148 were excluded because of lack of any follow-up, leaving a study cohort of 19 239.

A total of 3766 (19.6%) of the 19 239 patients with diabetes met criteria for clinically significant depression. Compared with those without depression, patients with depression were younger; more likely to be female; had a shorter duration of diabetes; had less education; were more likely to be white and less likely to be Asian or Filipino; had higher BMI; were more likely to smoke; had higher rates of nephropathy, neuropathy, myocardial infarction, retinopathy, peripheral vascular disease, and cerebrovascular disease, poorer glycemic control (HbA_{1c} level >9%), and a greater burden of comorbidities; and had a higher number of primary care visits per year (**Table 1**).

During the follow-up period, a total of 238 participants (1.2%), representing 76 002 person-years of follow-up, met our definition of dementia based on 1 or more *ICD-9-CM* dementia diagnoses in years 3 through 5 for an incidence rate of 3.1 cases per 1000 patient-years. When examining this by depression status, a total of 80 of 3766 patients (2.1%) with comorbid depression and diabetes, representing 14 528 person-years of follow-up, met our definition of dementia in years 3 to 5 for an incidence rate of 5.5 per 1000 person-years. In contrast, a total of 158 of 15 473 participants (1.0%) without depression, representing 61 474 person-years of follow-up, met our definition of included dementia diagnosis in years 3 through 5 for an incidence rate of 2.6 cases per 1000 patient-years.

Our primary analysis included proportional hazard models of dementia occurring in years 3 through 5 as the primary outcome using a fully imputed data set to account for missing covariate information (**Table 2**). Depression at baseline based on a PHQ-8 score of 10 or more and/or evidence of diagnosis or treatment of depression in the year prior to baseline (mean [SD] PHQ-8 score of this group was 9.5 [5.8]) was associated with a 2.02 (95% CI, 1.73-2.35) greater risk of dementia compared with those with diabetes alone after adjustment for age, sex,

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Table 1. Baseline Characteristics of the DISTANCE Sample Without Cognitive Impairment by Depression Status

	No. (%)		
	Total Sample (n = 19 239)	No Depression (n = 15 473)	Depression (n = 3766)[a]
Age, mean (SD), y	58.8 (10.0)	59.1 (10.0)	57.7 (9.8)
Sex			
M	9867 (51)	8497 (55)	1370 (36)
F	9372 (49)	6976 (45)	2396 (64)
Duration, y			
0-9	10 992 (57)	8978 (58)	2014 (53)
10-19	5118 (27)	4007 (26)	1111 (30)
≥20	2029 (11)	1557 (10)	472 (13)
Missing	1110 (6)	931 (6)	169 (4)
Education			
High school or less	8598 (45)	6802 (44)	1796 (48)
Some college	4713 (25)	3664 (24)	1049 (28)
College graduate	3774 (20)	3218 (21)	556 (15)
Professional degree	1755 (9)	1453 (9)	302 (8)
Missing	399 (2)	336 (2)	60 (2)
Race/ethnicity			
Black	3237 (17)	2582 (17)	655 (17)
Latino	3579 (19)	2780 (19)	799 (21)
White	4264 (22)	3187 (21)	1077 (29)
Asian	2246 (12)	1998 (13)	248 (7)
Filipino	2351 (12)	2076 (13)	275 (7)
Mixed race	2112 (11)	1623 (11)	489 (13)
Other/unknown	1450 (8)	1227 (8)	223 (6)
Exercise			
Insufficient	5647 (29)	4192 (27)	1455 (39)
Sufficient	2890 (15)	2322 (15)	568 (15)
Highly active	5725 (30)	4605 (30)	1120 (30)
Missing	4977 (26)	4354 (28)	623 (17)
BMI			
<25	3285 (17)	2822 (18)	463 (12)
25-<30	6256 (33)	5248 (34)	1008 (27)
30-<35	4513 (23)	3582 (23)	931 (24)
≥35	4483 (23)	3201 (21)	1282 (34)
Missing	702 (4)	620 (4)	82 (2)
Ever smoked			
Current	1570 (8)	1121 (7)	449 (12)
Former	6264 (33)	4915 (32)	1349 (36)
Nonsmoker	11 081 (58)	9136 (59)	1945 (52)
Missing	324 (2)	301 (2)	23 (1)

(continued)

Table 1. Baseline Characteristics of the DISTANCE Sample Without Cognitive Impairment by Depression Status (continued)

	No. (%)		
	Total Sample (n = 19 239)	No Depression (n = 15 473)	Depression (n = 3766)[a]
Nephropathy			
No	14 576 (76)	11 857 (77)	2719 (72)
Yes	4663 (24)	3616 (23)	1047 (28)
Neuropathy			
No	4002 (21)	2822 (18)	1180 (31)
Yes	15 237 (79)	12 651 (82)	2586 (69)
MI			
No	18 346 (95)	14 816 (96)	3530 (94)
Yes	893 (5)	657 (4)	236 (6)
Retinopathy			
No	16 063 (83)	12 961 (84)	3102 (82)
Yes	3176 (17)	2512 (16)	664 (18)
Stroke			
No	19 017 (99)	15 317 (99)	3700 (98)
Yes	222 (1)	156 (1)	66 (2)
PVD			
No	17 968 (94)	14 564 (94)	3404 (90)
Yes	1271 (7)	909 (6)	362 (10)
CVD			
No	16 202 (84)	13 231 (86)	2971 (79)
Yes	3037 (16)	2242 (14)	795 (21)
Hypertension			
No	1283 (7)	1022 (7)	261 (7)
Yes	16 372 (85)	13 043 (84)	3329 (88)
Missing	1584 (8)	1408 (9)	176 (5)
HbA_{1c} level, %			
<7	8024 (42)	6458 (42)	1556 (42)
7-9	6903 (36)	5598 (36)	1305 (35)
>9	2454 (13)	1895 (12)	559 (15)
Missing	1858 (10)	1522 (10)	336 (9)
DxCG score			
<3	10 370 (54)	8955 (58)	1415 (38)
≥3	8810 (46)	6472 (42)	2338 (62)
Missing	59 (0.3)	46 (0.3)	13 (0.4)
No. of primary care visits			
<4	9584 (50)	8208 (53)	1376 (37)
≥4	9655 (50)	7265 (47)	2390 (63)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVD, cerebrovascular disease; DISTANCE, Diabetes Study of Northern California; DxCG, a validated comorbidity index; HbA_{1c}, glycated hemoglobin; MI, myocardial infarction; PVD, peripheral vascular disease.

SI conversion factor: To convert to proportion of total hemoglobin, multiply by 0.01.

[a] Patient Health Questionnaire 8 score of 10 or more or diagnosis of depression or antidepressant treatment during prior year.

education, race/ethnicity, duration of retinopathy, cerebrovascular disease, peripheral vascular disease, HbA_{1c} level, comorbidity score (DxCG), BMI, smoking, and number of primary care visits per year.

No evidence of effect modification of depression with number of diabetes complications, BMI, current smoking, or HbA_{1c} levels was found. There was a significant depression × age interaction (χ^2_1=26.8; P<.001); in stratified models, those younger than 65 years had a substantially higher risk of dementia associated with depression (hazard ratio [HR] =4.42; 95% CI, 3.11-6.29) compared with those 65 years and older (HR=2.01; 95% CI, 1.65-2.45). There was a significant depression × treatment intensity interaction (χ^2_1=7.9; P=.005); in stratified models, those taking insulin (with or without oral hypoglycemic treatment) had a substantially lower risk of dementia associated with depression (HR=1.59; 95% CI, 1.17-2.18) compared with those not treated with insulin (HR=2.82; 95% CI, 2.33-3.42). There was also a significant depression × racial/ethnic group interaction (χ^2_6=33.2; P<.001); in stratified models, the risk of dementia associated with depression with each racial/ethnic group was white: HR=2.01; 95% CI, 1.62-2.49; African American: HR=1.86; 95% CI, 1.03-3.39; Latino: HR=3.28; 95% CI, 1.92-5.63; mixed race: HR=4.43; 95% CI, 2.59-7.59; other/unknown category: HR=4.25; 95% CI, 1.15-15.68; East Asian: HR=0.82; 95% CI, 0.20-3.43; and Filipino: HR=0.59; 95% CI, 0.05-6.90.

The first sensitivity analysis included the incident cases of dementia in all 5 years of follow-up, including those

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Table 2. HRs With 95% CIs in Patients With Depression Compared With Controls Without Depression With 2-Year Time Lag for Dementia Diagnosis

	HR (95% CI)	*P* Value
Unadjusted	1.85 (1.61-2.14)	<.001
Model 1[a]	2.36 (2.04-2.73)	<.001
Model 2[b]	2.00 (1.72-2.32)	<.001
Model 3[c]	2.02 (1.73-2.35)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Adjusted for age, sex, education, and race.
[b] Also adjusted for duration of diabetes mellitus, stroke, myocardial infarction, hypertension, neuropathy, nephropathy, retinopathy, cerebrovascular disease, peripheral vascular disease, glycated hemoglobin level, and comorbidity score.
[c] Also adjusted for body mass index, smoking, and number of visits.

Table 3. HRs With 95% CIs in Patients With Depression Compared With Controls Without Depression Without 2-Year Time Lag for Dementia Diagnosis

	HR (95% CI)	*P* Value
Unadjusted	2.14 (1.92-2.38)	<.001
Model 1[a]	2.77 (2.48-3.09)	<.001
Model 2[b]	2.34 (2.09-2.61)	<.001
Model 3[c]	2.35 (2.10-2.63)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Adjusted for age, sex, education, and race.
[b] Also adjusted for duration of diabetes mellitus, stroke, myocardial infarction, hypertension, neuropathy, nephropathy, retinopathy, cerebrovascular disease, peripheral vascular disease, glycated hemoglobin level, and comorbidity score.
[c] Also adjusted for body mass index, smoking, and number of visits.

from years 1 and 2, which were ignored in the primary analysis. In this analysis, the increased risk of dementia associated with depression was slightly higher (HR=2.35; 95% CI, 2.10-2.63), as seen in **Table 3**. The second sensitivity analysis only included dementia diagnoses farther from baseline (ie, in years 4 and 5) and also found a slightly higher HR (HR=2.30; 95% CI, 1.93-2.74). The third sensitivity analysis that examined patient self-report about having a prior diagnosis of depression from a clinician (mean [SD] PHQ-8 score, 7.4 [5.7]) in relation to dementia diagnoses in years 3 to 5 found an HR associated with depression of 2.60 (95% CI, 2.14-3.15). The fourth sensitivity analysis that used a baseline PHQ-8 score of 10 or more alone to define depression (mean [SD] PHQ-8 score, 13.9 [3.6]) and examined dementia diagnoses in years 3 to 5 found an HR associated with this depression definition of 3.29 (95% CI, 2.67-4.04).

We also compared these results with complete case analysis among the 11 310 respondents who had full covariate information. While the imputed results showed a 2-fold increased risk for developing dementia in years 3 to 5 among those with depression, the complete case results showed a slightly higher risk (HR=2.37; 95% CI, 1.97-2.85).

COMMENT

In this prospective study in patients with type 2 diabetes, comorbid depression was associated with an approximately 2-fold increased risk of dementia compared with patients with diabetes alone. Prior meta-analyses have found that both depression and diabetes are risk factors for dementia,[3-5] and our study suggests that having both of these illnesses occurring together is associated with even greater risk. Our findings with a diverse sample of approximately 20 000 patients with type 2 diabetes are consistent with the only prior smaller study, which found an approximately 2-fold increase in risk of dementia over 5 years in patients with depression and diabetes.[16] Effect sizes were quite robust across the primary and sensitivity analyses. The sensitivity analyses that only included dementia diagnoses in years 4 and 5 or that used 1 question about having had a previous diagnosis of depression or that only used the PHQ-8 score of 10 or more each showed an even higher risk of dementia associated with depression, suggesting that these results are not due to depression being a prodromal phase of dementia or the depression definition.

Depression in patients with diabetes compared with those with diabetes alone is associated with poorer adherence to diet and exercise regimens, increased rates of smoking, and higher HbA_{1c} levels,[7,8] which could worsen the course of diabetes[33,34] and increase the risk of dementia associated with depression. However, controlling for these behaviors and intermediate risk factors had a negligible effect on risk of dementia. These data suggest that biologic factors associated with depression may be important risk factors for dementia in patients with type 2 diabetes.

There are several biologic mechanisms that could link depression and dementia. The fact that the PHQ-8 score of 10 or more was associated with a higher risk of development of depression compared with those with a patient report of having a prior depressive episode or those identified by either a PHQ-8 score of 10 or more and/or a physician diagnosis of depression or treatment with an antidepressant in the prior 12 months suggests that severity of depression may be an important factor. Depression severity has been associated with a higher risk of biologic abnormalities such as hypothalamic-pituitary axis dysfunction.[35,36] Dysregulation of the hypothalamic-pituitary axis associated with depression has been linked to higher glucocorticoid production and impaired negative feedback.[30] Dysregulation of cortisol may damage brain areas involved in cognition such as the hypothalamus[37,38] as well as decrease neurogenesis in key brain areas.[39] Several studies have reported that chronic or recurrent depression is associated with hippocampal atrophy.[40,41] Elevated cortisol levels also independently predict several components of the metabolic syndrome such as abdominal obesity, hypertriglyceridemia, and decreased high-density lipoproteins, all of which are thought to be risk factors for vascular dementia and AD.[30,42,43] Depression has also been linked to increased proinflammatory factors, such as increased cytokine levels including interleukin 6 and tumor necrosis factor α,[44] as well as increased platelet aggregation.[45] Dysregulation of the hypothalamic-pituitary axis and increased proinflammatory factors both are associated with increased insulin re-

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sistance, which has been identified as a risk factor for vascular dementia and AD.[46]

Patients with depression and diabetes compared with those with diabetes alone have been found to be twice as likely to have 3 or more cardiovascular risk factors.[47] Higher numbers of cardiovascular risk factors have been linked to a higher risk of AD and vascular dementia.[48,49] Both depression and diabetes are also associated with a higher risk of cardiovascular and cerebrovascular events, which may increase the risk of dementia in an additive fashion.[9,10,50-52]

The finding that depression is associated with a greater risk of dementia in patients with diabetes younger than 65 years compared with those 65 years and older is worrisome from a public health and cost perspective. Depressive episodes often begin early in life and depression increases the risk for development of type 2 diabetes.[1,2] Prior research reported a 5 to 6 years' earlier onset of diabetes among patients with comorbid depression and diabetes than among those without a history of depression.[53] The temporal patterning (earlier onset of diabetes with depression and greater risk of dementia in younger compared with older patients with comorbid depression and diabetes) underscores the importance of developing early interventions to potentially reduce the incidence of dementia.

The finding that depression is associated with a higher risk of dementia in diabetic individuals who are not being treated with insulin is interesting given that both depression and diabetes have been found to be associated with decreased insulin sensitivity.[12,13] There is increasing evidence that insulin dysregulation contributes to the pathophysiology of AD.[54] Insulin modulates levels of β-amyloid in the brain and protects synapses against the negative effects of β-amyloid.[55,56] Moreover, intranasal insulin may preserve memory and general cognitive abilities in patients with mild cognitive impairment or mild to moderate AD.[54]

Although we detected differences in risk of dementia in patients with depression among the 7 racial/ethnic groups, there was a strong and consistent risk of dementia associated with depression in 5 of the 7 groups (white, African American, Latino, mixed race, and other/unknown) but no significant association in 2 groups (East Asian and Filipino). Racial/ethnic differences in risk of dementia among depressed, diabetic patients needs replication, with further exploration for putative mechanisms that may explain why an effect is observed in some, but not other, ethnic groups.

Recent data based on prospective follow-up of a cohort of 1433 persons in the general population older than 65 years found that effectively treating depression and diabetes as well as increasing fruit and vegetable consumption could potentially lead to a 20.7% reduction in incidence of dementia.[57] Eliminating depression from this elderly population made the greatest potential contribution with an estimated 10% reduction in the number of dementia cases over 7 years.[57] Primary care–based health services models have been developed that have been shown to reduce the burden of depression in elderly populations with chronic medical illnesses such as diabetes.[58,59] Depression interventions in chronic-condition populations should be tested for their potential to decrease incidence rates of dementia.

A limitation of this study is that the population was derived from 1 large health care system in 1 geographic region, potentially limiting generalizability. While rates of depression and dementia may differ in the uninsured, observed associations between depression and dementia are likely not substantively different across populations. Depression ascertainment was based on either the PHQ-8 score or physician diagnosis and treatment of depression, not clinical interviews. However, the relatively high specificity of the PHQ-8 score compared with the diagnosis of depression by clinical interview suggests few false positives.[21] We lacked a control population of patients without diabetes and thus were unable to estimate the strength of the depression-dementia association in nondiabetic patients. Using clinically recognized dementia rather than cognitive testing is also a limitation. However, a prior study in a similar health care organization has shown that *ICD-9-CM* codes of dementia have high specificity (ie, 95%) but only about 77% sensitivity compared with prospective comprehensive case ascertainment (P. Crane, MD, MPH, written communication, 2009). This suggests low rates of false positives based on physician diagnoses. The majority of our dementia diagnoses came from a primary care setting since we were interested in the first indication of dementia; thus, we were unable to accurately evaluate the role of depression on risk of dementia subtypes. An aim of our future work is to understand the role of depression on the risk of vascular dementia and AD in patients evaluated in one of Kaiser Permanente's memory clinics. The 5-year follow-up period is also a relatively short time to determine risk of dementia. A final limitation is that, although our model adjusted for a range of socioeconomic, clinical, and health risk behavior factors, residual confounding may still be a factor.

Depression was associated with significantly increased risk of dementia among patients with type 2 diabetes. Given that depression is potentially modifiable, future studies are needed to further evaluate whether effective depression interventions reduce the risk of dementia and identify the mechanisms that may explain our observation.

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