Depression as a Risk Factor for Diabetes: A Meta-Analysis of Longitudinal Studies

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ABSTRACT

Objective: The present meta-analysis aimed to assess the risk of incident diabetes associated with clinical depression, depressive symptoms, or both in nondiabetic subjects.

Data Sources: We performed a MEDLINE search for studies published in the English language using the search string *diabetes* AND (*depression* OR *antidepressant*). The search included studies from any date to December 30, 2011.

Study Selection: 1,898 studies were independently assessed for eligibility, and longitudinal studies that assessed the risk of incident diabetes in subjects with or without clinical depression were selected.

Data Extraction: Study design and characteristics were verified for each study. A meta-analysis was performed for unadjusted and adjusted risk ratios of incident diabetes in subjects with depression by using a random-effects model. Additional analyses were performed to assess heterogeneity, publication bias, and specific hazard ratios for diabetes associated with antidepressant drug use.

Results: The 23 studies included in the meta-analysis enrolled 424,557 subjects, with a mean follow-up of 8.3 years and 19,977 cases of incident diabetes. A higher incidence of diabetes was found in depressed versus nondepressed subjects (0.72% vs 0.47% yearly), with unadjusted and adjusted risk (95% CI) of 1.56 (1.37–1.77) and 1.38 (1.23–1.55), respectively (both P values < .001). The use of antidepressant drugs and untreated depression were associated with an adjusted risk of diabetes of 1.68 (1.17–2.40) (P = .005) and 1.56 (0.92–2.65) (P = .09).

Conclusions: Depressive symptoms are associated with a significantly increased risk for incident diabetes. This association cannot be entirely explained by the use of antidepressant drugs or being overweight. Pathogenetic mechanisms connecting depression with diabetes deserve further exploration. Depression should be included among risk factors that indicate intensified screening for diabetes.

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The prevalence of clinical depression and depressive symptoms in persons with diabetes is higher than in nondiabetic individuals.[1–5] The comorbidity of diabetes and depression poses relevant clinical issues, as depressive symptoms are associated with impaired glucose control,[6–8] whereas the burden of a chronic somatic condition such as diabetes can represent an obstacle to depression management.[9,10]

A number of putative pathogenetic mechanisms could facilitate the onset of diabetes in subjects with depression. Those include eating disturbances, sedentary lifestyle, or both induced by depressed mood, weight gain related to antidepressant drugs, activation of stress-related hormonal pathways (eg, hypothalamic-pituitary-adrenal axis), and proinflammatory cytokines, which interfere with glucose metabolism.[6,7,11,12] Conversely, it is also possible that diabetes induces mood depression due to the burden of the disease and its complications, diabetes-related symptoms (eg, fatigue induced by hyperglycemia), and limitations on diet and physical and social activities imposed by the needs for disease management.[4] The 2 mechanisms (ie, diabetes leading to depression and depression leading to diabetes) are not mutually exclusive and they could coexist, even in the same subject.

Cross-sectional studies that demonstrate the association between depression and diabetes do not allow one to discriminate which of the 2 conditions comes first. In order to verify whether depression is a risk factor for diabetes, we need to refer to the results of longitudinal studies. Results of available surveys on this topic, which are widely heterogeneous for sample selection and assessment methods, are not univocal.[13–16]

It should also be recognized that epidemiologic studies do not allow one to draw conclusions on causal relationships. In particular, depression is often not a chronic condition. It can spontaneously remit, be successfully treated, and be present among different individuals for different periods of time, at different frequencies, at varying severities, and at different levels of treatment; this range of possibilities makes observational data only partially reliable. Furthermore, both depression and diabetes are continuous conditions with artificially dichotomized diagnostic standards; this means that a depressive state could have been preceded by a mild elevation of blood glucose that did not reach the diagnostic threshold for diabetes or a case of diabetes could follow an undiagnosed or subthreshold depressive syndrome. These considerations suggest caution in the interpretation of observational data.

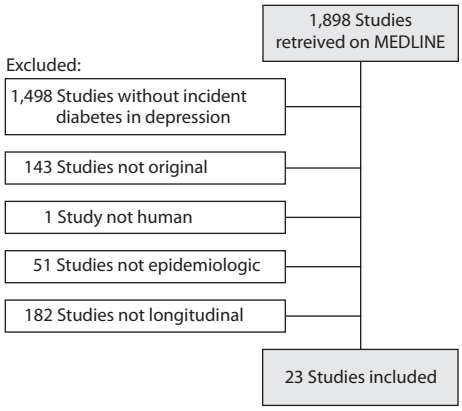
Two previous meta-analyses have reported an increased risk of incident diabetes in depressed subjects[6,7]; however, in the most recent years, some large-scale studies were published, which could not be included in those meta-analyses and which provided discordant results.[15–26]

The aim of the present meta-analysis is the assessment of the risk of incident diabetes associated with clinical depression, depressive symptoms, or both in nondiabetic subjects, as reported in longitudinal observational (cohort or case-control) studies.

DATA SOURCES

We performed a MEDLINE search for human studies published in the English language from any date to December 30, 2011, using the search string *diabetes* AND (*depression* OR *antidepressant*). References of retrieved

Figure 1. Study Flow Summary



papers were manually searched for the identification of further studies.

STUDY SELECTION

We retrieved 1,898 studies, which were independently assessed for eligibility on the basis of the following criteria: the observational studies that (1) were longitudinal (with either cohort or case-control design), (2) assessed incident diabetes, and (3) compared diabetes risk in subjects with or without clinical depression/depressive symptoms.

Studies were included regardless of the method used for the assessment of depression (eg, self-reported questionnaires, clinical interviews, or use of drugs) and of the definition of the threshold for depression. Therefore, "depression" does not correspond to any specific diagnostic category, but it rather indicates the occurrence of depressive symptoms.

Study selection was independently performed by both authors; conflicts were resolved through discussion between the investigators.

DATA EXTRACTION

Data extraction from publication was independently performed by both authors; conflicts were resolved through discussion between the investigators. Study design and characteristics were verified for each study together with the incidence of diabetes in subjects with and without depression and the risk of diabetes associated with depression using unadjusted and adjusted models; confounders used in multivariate analyses were also listed. The methods used for diagnosis of depression and diabetes together with some other descriptive characteristics affecting the quality of study (ie, representativeness of sampling and appropriateness of description of lost at follow-up) were also retrieved.

A random-effects model was used for the main outcomes, which were the unadjusted and adjusted risk ratios of incident diabetes in subjects with depression versus nondepressed individuals. For studies investigating depressive symptoms with questionnaires, cut-point definitions of depression were used with the thresholds reported in the original studies. The I^2 statistic was applied for the assessment of heterogeneity.

Clinical Points

- Depressed mood is associated with increased risk of incident diabetes in nondiabetic subjects.
- The association between depression and diabetes is not entirely mediated by weight gain or the effects of antidepressant drugs.
- Depression deserves to be included among the risk factors that should drive diabetes screening.

Subgroup analyses of hazard ratios (HRs) from multivariate models were performed for studies by using different confounders (body mass index, medical comorbidity, general psychopathology, concurrent treatments, alcohol, physical activity). Furthermore, separate additional analyses were performed for those studies that reported specific HRs for antidepressant drugs or for untreated depression.

A meta-analysis was performed for unadjusted odds ratios (ORs) and adjusted HRs by using a random-effects model. Publication bias was assessed for unadjusted and adjusted risk by using Funnel plot analysis and Kendall τ. Duvall and Tweedie's trim-and-fill method[27] was used for the estimation of risk after correction for publication bias.

No review protocol for this analysis had been previously published. All analyses were performed using Comprehensive Meta-Analysis 2.2.064 (Biostat, Englewood, New Jersey).

RESULTS

The study flow summary is reported in Figure 1. Of the 23 studies included in the analysis, only 1[28] reported separately on the incidence of type 1 diabetes, whereas all the others considered only incident type 2 diabetes or did not specify the type of diabetes. The characteristics of the studies included in the meta-analysis[13–26,28–36] are summarized in Table 1. Most of the studies had a cohort design, although some were performed as case-control studies nested within a cohort. Overall, the total sample consisted of 424,557 subjects, with a mean follow-up for incident diabetes of 8.3 years. In most instances, depression was assessed by using standardized self-reported questionnaires only (usually the Center for Epidemiologic Studies Depression Scale [CES-D])[37] for depressive symptoms; only a few surveys performed interviews for clinical diagnosis of depression,[13,19,30] whereas others collected only data on use of antidepressant drugs.[15,17,25]

A total of 19,977 cases of diabetes was detected during follow-up, with a yearly incidence rate of 0.57%. The observed incidence of diabetes was 0.72% and 0.47% in patients with and without depression, respectively. Estimated risk of incident diabetes associated with depression in each study is reported in Table 2. A heterogeneity was detected ($I^2 = 86.5$, $P < .001$), which lends support for the use of random-effects models. Kendall τ was −0.01 ($P = .95$), a finding that suggests no publication bias. When the results of available studies were combined, depression was associated with a significantly

Table 1. Characteristics of the Studies

Study	Design	Area	Depression Diagnosis	Diabetes Diagnosis	Diabetes Type	Patients, N	Follow-Up, y
Andersohn et al[17]	Case-control	United Kingdom	Drugs	Clinical	2	Not reported	2.8
Atlantis et al[18]	Cohort	Australia	Questionnaire (PAS > 5)	Self-report	Not specified	1,000	4.2
Campayo et al[19]	Cohort	Spain	Interview	Interview	Not specified	3,521	3.5
Carnethon et al[28]	Cohort	United States	Questionnaire (CES-D ≥ 8)	Drugs + fasting plasma glucose	Not specified	4,681	7.3
Demakakos et al[20]	Cohort	United Kingdom	Questionnaire (CES-D ≥ 4)	Self-report + drugs	2	6,111	3.8
Eaton et al[29]	Cohort	United States	Interview	Self-report	2	1,680	13
Engum[27]	Cohort	Norway	Questionnaire (HADS-D ≥ 8)	Laboratory + self-report	1	37,291	10
Engum[27]	Cohort	Norway	Questionnaire (HADS-D ≥ 8)	Laboratory + self-report	2	37,291	10
Eriksson et al[21]	Cohort	Sweden	Questionnaire (not specified)	OGTT	2	5,227	9
Everson-Rose et al[30]	Cohort	United States	Questionnaire (CES-D ≥ 16)	Self-report + fasting plasma glucose	Not specified	2,662	3
Golden et al[31]	Cohort	United States	Questionnaire (VES ≥ 15)	Not specified	2	11,615	6
Golden et al[22]	Cohort	United States	Questionnaire (CES-D ≥ 16)	Fasting plasma glucose + self-report	2	5,201	3
Karakus and Patton[23]	Cohort	United States	Questionnaire (CES-D8 ≥ 3)	Self-report	Not specified	3,645	12
Kawakami et al[32]	Cohort	Japan	Questionnaire (Zung SDS > 48)	Self-report	2	2,380	8
Kivimäki et al[24]	Case-control	Finland	Drugs/hospitalization	Drugs	2	5,085	4
Kivimäki et al[25]	Case-control	Finland	Drugs	Drugs	2	54,855	4.3
Knol et al[15]	Cohort	Netherlands	Drugs	Drugs	Not specified	42,426	2.3
Kumari et al[33]	Cohort	United Kingdom	Questionnaire (GHQ ≥ 4)	Self-report + OGTT	2	Not reported	10.5
Maty et al[14]	Cohort	United States	Questionnaire (HPL 18 DI ≥ 5)	Self-report	Not specified	6,147	34
Nichols and Moler[26]	Cohort	United States	Not specified	Fasting plasma glucose, drugs, *ICD-9-CM*	Not specified	58,056	5
Palinkas et al[34]	Cohort	United States	Questionnaire (BDI ≥ 11)	Fasting plasma glucose + OGTT	2	855	8
Pan et al[16]	Cohort	United States	Questionnaire (MHI-5 < 52)	Questionnaire	2	57,880	9.2
Saydah et al[35]	Cohort	United States	Questionnaire (CES-D ≥ 16)	Self-report	2	8,944	9
Van den Akker et al[13]	Cohort	Netherlands	Interview	Not specified	Not specified	68,004	14.8

Abbreviations: BDI = Beck Depression Inventory, CES-D = Center for Epidemiologic Studies Depression Scale, CES-D8 = 8-item CES-D, GHQ = General Health Questionnaire, HADS-D = Hospital Anxiety and Depression Scale-Depression, HPL 18 DI = Human Population Laboratory 18-Item Depression Index, *ICD-9-CM* = *International Classification of Diseases-9-Clinical Modification*, MHI-5 = Mental Health Index-5, OGTT = Oral Glucose Tolerance Test, PAS = Psychogeriatric Assessment Scale, SDS = Self-Rating Depression Scale, VES = Vital Exhaustion Scale.

increased risk of incident diabetes (Figure 2). Similar results were obtained when separately analyzing studies in which diagnosis of incident diabetes was self-reported or assessed with other and more objective methods (OR [95% CI]: 1.54 [1.30–1.83] and 1.48 [1.27–1.72], both P values < .001). No significant difference in estimated ORs for diabetes associated with depression was observed when comparing studies in which depression was assessed through questionnaires only or interviews (OR [95% CI]: 1.62 [1.37–1.91], P < .001 and 1.44 [1.16–1.79], P = .001, respectively).

The majority of studies reported multivariate analyses adjusted for multiple confounders, although parameters included in multivariate models varied across studies (Table 2). All studies with multivariate analyses were adjusted for age, and all except 1[16] were adjusted for sex, if applicable. Overall, in adjusted analyses, depression was still associated with incident diabetes. When applied to HR estimates, Kendall τ was 0.34 (P = .05), suggesting the possibility of a publication bias in favor of positive results. When Duvall and Tweedie's trim-and-fill method was used, the estimated number of unpublished studies was 7, with an HR (95% CI) corrected for publication bias of 1.19 (1.04–1.35) (P < .05). The choice of confounders to be imputed in multivariate models did not appear to affect in a relevant manner the estimates of HR (Table 3). Furthermore, for studies that reported this analysis, the use of an antidepressant drug was associated with a significantly higher risk of diabetes (HR [95% CI]: 1.68 [1.17–2.40], P = .005; 5 studies); conversely, only a nonsignificant trend was observed for the association of depressive symptoms without use of antidepressant drugs with incident diabetes (HR [95% CI]: 1.56 [0.92–2.65], P = .09) in the only 3 studies that reported this information.

DISCUSSION

The present meta-analysis demonstrates that depressed mood is associated with increased incident diabetes. This

Table 2. Estimated Risk of Incident Diabetes Associated With Depression in Each Study, With and Without Adjustments

Study	With Depression, n	Without Depression, n	Incident Diabetes With Depression, n	Incident Diabetes Without Depression, n	Odds Ratio (95% CI)	Adjusted Variables						Hazard Ratio (95% CI)
						BMI	Medical Comorbidity	General Psychopathology	Other Drugs	Alcohol	Physical Activity	
Andersohn et al[17]	…	…	851	1,392	…	Yes	Yes	No	Yes	No	No	1.84 (1.35–2.52)
Atlantis et al[18]	110	890	20	135	2.23 (1.4–3.58)	Yes	Yes	No	No	Yes	Yes	2.13 (1.32–3.44)
Campayo et al[19]	379	3,142	25	138	1.59 (0.99–2.37)	Yes	Yes	Yes	Yes	Yes	Yes	1.65 (1.02–2.66)
Carnethon et al[28]	936	3,745	39	108	1.59 (1.1–2.3)	Yes	No	No	No	Yes	Yes	1.29 (1.07–1.57)
Demakakos et al[20]	823	5,288	51	158	2.14 (1.53–2.82)	Yes	Yes	No	Yes	Yes	Yes	1.62 (1.15–2.29)
Eaton et al[29]	76	1,604	6	80	1.58 (0.71–3.51)	Yes	No	No	No	No	No	2.23 (0.9–5.55)
Engum[27]	8,311	28,980	33	116	1.17 (0.7–1.95)	Yes	Yes	No	No	No	Yes	…
Engum[27]	8,311	28,980	249	580	1.51 (1.27–1.81)	Yes	Yes	No	No	No	Yes	1.4 (1.16–1.69)
Eriksson et al[21]	1,162	4,065	42	118	1.24 (0.88–1.8)	Yes	No	No	No	No	Yes	…
Everson-Rose et al[30]	606	2,056	35	62	1.66 (1.05–2.6)	Yes	No	No	Yes	No	Yes	1.46 (0.9–2.36)
Golden et al[31]	2,840	8,775	325	396	2.56 (2.35–3.19)	Yes	Yes	No	No	No	Yes	1.31 (1.04–1.64)
Golden et al[22]	911	4,290	60	215	1.34 (0.99–1.8)	Yes	No	No	No	Yes	Yes	1.21 (0.87–1.67)
Karakus and Patton[23]	190	3,455	…	…	…	Yes	No	No	No	No	Yes	1.5 (1.01–2.24)
Kawakami et al[32]	278	2,102	9	34	2.03 (0.96–4.29)	Yes	Yes	No	No	Yes	Yes	2.31 (1.03–5.2)
Kivimäki et al[24]	555	4,530	155	696	2.13 (1.74–2.61)	No	Yes	No	No	No	No	…
Kivimäki et al[25]	9,197	45,658	712	2,160	1.69 (1.55–1.84)	No	Yes	No	No	No	No	…
Knol et al[15]	18,507	23,919	247	252	1.03 (0.86–1.22)	No	Yes	No	No	No	No	1.06 (0.89–1.26)
Kumari et al[33]	…	…	…	…	…	Yes	Yes	Yes	Yes	No	Yes	1.12 (0.54–1.7)
Maty et al[14]	889	5,258	49	269	1.08 (0.79–1.48)	Yes	Yes	No	Yes	Yes	Yes	…
Nichols and Moler[26]	11,970	46,086	846	2,681	1.23 (1.14–1.33)	Yes	Yes	No	Yes	No	No	1.1 (1–1.2)
Palinkas et al[34]	70	785	10	69	2.5 (1.29–4.87)	Yes	No	No	No	No	Yes	…
Pan et al[16]	7,051	50,829	524	2,320	1.68 (1.52–1.85)	Yes	No	No	No	Yes	Yes	1.17 (1.05–1.3)
Saydah et al[35]	1,444	7,500	86	379	1.39 (1.03–1.89)	Yes	No	No	No	No	Yes	1.11 (0.79–1.56)
Van den Akker et al[13]	1,334	66,670	89	3,156	1.44 (1.16–1.79)	Yes	No	No	No	No	No	0.98 (0.79–1.21)

Abbreviation: BMI = body mass index.

result confirms those of previous meta-analyses performed on smaller data sets.[6,7]

The main strength of current evidence is represented by the remarkable overall size of the sample, with many studies enrolling an elevated number of patients. The length of follow-up is adequate in most instances, with an average of more than 8 years. On the other hand, the majority of investigations included in the analysis suffer from relevant methodological limitations. First, only 3 studies[13,19,30] used interviews for the diagnosis of clinical depression; some others assessed the use of antidepressant drugs as a proxy for depressive syndromes.[15,17,24,25] The majority of studies measured depressive symptoms with self-reported questionnaires. Although the instruments used were usually validated, these assessments of depressive symptomatology cannot be considered equivalent to a clinical diagnosis. Furthermore, a variety of questionnaires was used across studies, with different sensitivity and reliability for the assessment of depressive symptoms. For the most widely used questionnaire, the CES-D,[37] different thresholds were chosen by different investigators. As a consequence, the definition of "depressed" subjects varies across studies, probably contributing to the observed heterogeneity.

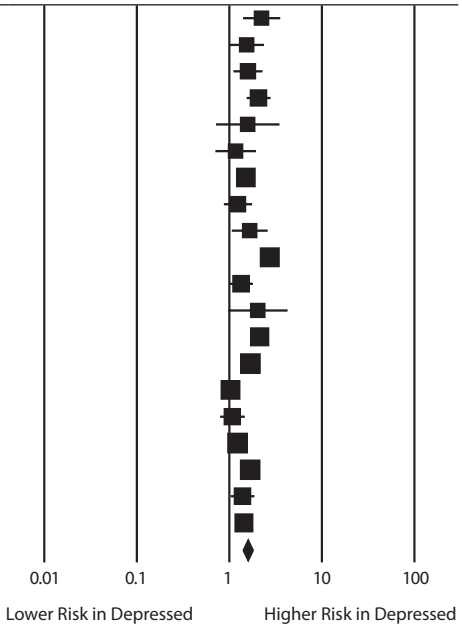
Another relevant problem is represented by the methods used for screening and diagnosis of incident diabetes. In most studies, the diagnosis of diabetes was assessed only through self-report[14,16,18,19,23,30,33,36] and/or use of glucose-lowering drugs.[15,20,24,25] Considering that type 2 diabetes is often asymptomatic or oligosymptomatic, subjects with depressed mood, with a reduced motivation for health care, could remain undiagnosed for longer periods of time, thus producing an underestimation of the actual impact of depression on the risk of diabetes. Furthermore, systematic screening for diabetes was usually performed through fasting plasma glucose only,[22,26,28,29,31] whereas only 2 studies[14,21] measured blood glucose after an oral glucose load.

There are many possible confounders that could interfere with the association of depression with incident diabetes. For example, medical comorbidities potentially affecting mood (ie, hepatic, renal, or cardiac disease) could increase the risk of diabetes. Substance or alcohol abuse could also be risk factors for both depression and diabetes. Overweight and obesity, which are typical risk factors for diabetes, may also reduce quality of life and therefore facilitate the onset of depressive symptoms. Almost all the available studies considered some confounders and provided adjusted analyses that confirmed the association of depressive symptoms with incident

Figure 2. Odds Ratios and Hazard Ratios With 95% CIs for Incident Diabetes in Subjects With and Without Depression

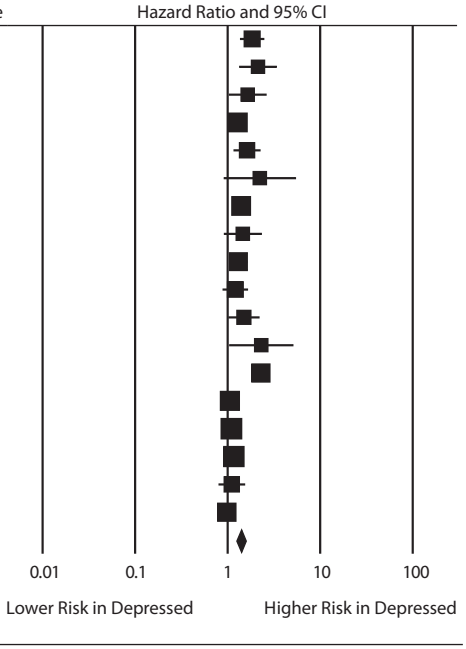
A. Unadjusted Risk

Study	Odds Ratio	95% CI Lower Limit	95% CI Upper Limit	*Z* Value	*P* Value
Andersohn et al[17]	2.230	1.395	3.566	3.348	.001
Campayo et al[19]	1.540	0.995	2.383	1.939	.053
Carnethon et al[28]	1.590	1.100	2.299	2.464	.014
Demakakos et al[20]	2.070	1.525	2.810	4.664	.000
Eaton et al[29]	1.580	0.711	3.513	1.122	.262
Engum[27]	1.170	0.701	1.953	0.601	.548
Engum[27]	1.510	1.265	1.803	4.559	.000
Eriksson et al[21]	1.240	0.867	1.773	1.178	.239
Everson-Rose et al[30]	1.660	1.055	2.612	2.191	.028
Golden et al[31]	2.740	2.352	3.192	12.929	.000
Golden et al[22]	1.340	0.994	1.807	1.919	.055
Kawakami et al[32]	2.030	0.960	4.291	1.854	.064
Kivimäki et al[24]	2.130	1.739	2.609	7.310	.000
Kivimäki et al[25]	1.690	1.551	1.841	11.993	.000
Knol et al[15]	1.030	0.865	1.227	0.331	.740
Maty et al[14]	1.080	0.789	1.478	0.481	.631
Nichols and Moler[26]	1.230	1.139	1.329	5.264	.000
Pan et al[16]	1.680	1.523	1.853	10.351	.000
Saydah et al[35]	1.390	1.026	1.883	2.127	.033
Van den Akker et al[13]	1.440	1.159	1.789	3.295	.001
Overall	1.560	1.374	1.772	6.859	.000



B. Adjusted Risk

Study	Hazard Ratio	95% CI Lower Limit	95% CI Upper Limit	*Z* Value	*P* Value
Andersohn et al[17]	1.840	1.347	2.514	3.830	.000
Atlantis et al[18]	2.130	1.319	3.439	3.094	.002
Campayo et al[19]	1.650	1.022	2.665	2.048	.041
Carnethon et al[28]	1.290	1.065	1.563	2.603	.009
Demakakos et al[20]	1.620	1.148	2.286	2.746	.006
Eaton et al[29]	2.230	0.898	5.538	1.728	.084
Engum[27]	1.400	1.160	1.690	3.505	.000
Everson-Rose et al[30]	1.460	0.902	2.364	1.539	.124
Golden et al[31]	1.310	1.043	1.645	2.324	.020
Golden et al[22]	1.210	0.873	1.676	1.146	.252
Karakus and Patton[23]	1.500	1.007	2.234	1.995	.046
Kawakami et al[32]	2.310	1.028	5.190	2.027	.043
Kivimäki et al[24]	2.290	1.852	2.832	7.640	.000
Knol et al[15]	1.060	0.891	1.261	0.657	.511
Nichols and Moler[26]	1.100	1.004	1.205	2.049	.040
Pan et al[16]	1.170	1.051	1.302	2.882	.004
Saydah et al[35]	1.110	0.790	1.560	0.601	.548
Van den Akker et al[13]	0.980	0.792	1.213	–0.186	.853
Overall	1.379	1.227	1.550	5.392	.000



diabetes. The meta-analysis of adjusted risks should be considered with caution because the different pattern of confounders assessed across studies added to the heterogeneity of results; despite the use of (more conservative) random-effects models, the possibility of casual results cannot be entirely excluded.

Despite all the limitations reported above, the association of depressive symptoms with incident diabetes is clear. The underlying mechanisms are difficult to determine on the basis of epidemiologic data. One possible explanation is represented by antidepressant drugs, which induce carbohydrate craving and weight gain, thus interfering with the regulation of glucose metabolism.[38] In fact, in 1 study,[16] patients on antidepressant drugs showed an increased incidence of diabetes, which was not observed in those with depressed mood who received no treatment; however, in another investigation[18] a similar risk of diabetes was reported in depressed patients with or without drug treatment. Many studies,[17,20,24,25] but

Table 3. Hazard Ratios With 95% CIs for Incident Diabetes in Subjects With Depression

Adjustment	No. of Studies	Hazard Ratio (95% CI)	*P*
Body Mass Index			
No	2	1.55 (0.73–3.31)	.25
Yes	16	1.32 (1.20–1.45)	< .01
Comorbidity			
No	8	1.19 (1.08–1.30)	< .001
Yes	10	1.53 (1.26–1.86)	< .001
General psychopathology			
No	17	1.37 (1.22–1.54)	< .001
Yes	1	1.65 (1.02–2.66)	.04
Other drugs			
No	13	1.36 (1.18–1.57)	< .001
Yes	5	1.47 (1.12–1.93)	< .01
Alcohol			
No	11	1.36 (1.15–1.61)	< .001
Yes	7	1.39 (1.19–1.63)	< .001
Physical activity			
No	6	1.40 (1.06–1.85)	.02
Yes	12	1.33 (1.22–1.46)	< .001
Diagnosis of diabetes with fasting and/or postload glucose			
No	11	1.29 (1.13–1.47)	< .001
Yes	7	1.32 (1.13–1.53)	< .001

not all,[15,29] specifically investigating patients on drug treatment found an increased risk of diabetes in this population. On the other hand, 2 studies[18,19] described an increased incidence of diabetes in patients with depressed mood who did not receive any antidepressant medication, whereas another 1[16] did not find such association. When combining the 3 studies reporting on depressed patients with no drug treatment,[16,18,19] only a nonsignificant trend was observed, although the estimated HR was similar to that obtained in the whole sample. Overall, available data suggest that depressed mood could be a risk factor for diabetes independent of antidepressant drugs; conversely, an effect of those medications on diabetes risk cannot be excluded.

Another possible mediator of the interaction of depression with diabetes is represented by weight gain, which is a possible consequence of eating disturbances and sedentary behaviors associated with depressed mood.[5,6] In 3 studies,[13,31,36] a significant risk of diabetes in depressed subjects was no longer observed when adjusting for body mass index (BMI). However, in a larger number of investigations, the association of depressive symptoms with diabetes risk was confirmed after adjustment was made for BMI.[16–20,23,26,28,29,32,33] The meta-analysis of results adjusted for BMI confirms the association. This finding suggests that, although overweight could play a role, the association of depression with diabetes is at least partly due to other mechanisms.

Mood depression is characterized by reduced adherence to medical prescriptions, both for nonpharmacologic and pharmacologic treatments, which could contribute to an increased risk of diabetes in subjects at risk.[9] Other potential mechanisms also underlie the association of depression with diabetes; those include hyperactivity of stress-related hormonal systems (eg, cortisol) and hyperproduction of proinflammatory cytokines, which interfere with glucose metabolism.[6,7,11,12] The investigation of those putative pathogenetic mechanisms, which deserve further exploration, is beyond the aim of epidemiologic studies.

In conclusion, depressed mood is associated with increased risk of diabetes. Such association is not entirely mediated by weight gain, and it does not appear to be due only to the effects of antidepressant drugs. The American Diabetes Association[39] recommends diabetes screening every 3 years in all subjects above 45 years of age; an earlier and more intensive testing is advised in overweight persons with other risk factors (eg, physical inactivity, family history of diabetes, previous gestational diabetes, hypertension, hypertriglyceridemia, polycystic ovary syndrome). On the basis of the results of available studies, depression fully deserves to be included among the risk factors that should drive diabetes screening.

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