Association of Depression and Diabetes Complications: A Meta-Analysis

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Objective: The objective of this study was to examine the strength and consistency of the relationship between depression and diabetes complications in studies of type 1 and type 2 adult patients with diabetes. **Method:** MEDLINE and PsycINFO databases were searched for articles examining depression and diabetes complications in type 1 and type 2 diabetes samples published between 1975 and 1999. Meta-analytic procedures were used. Studies were reviewed for diabetes type, sample size, statistical tests, and measures of diabetes complications and depression. Significance values, weighted effect sizes *r*, 95% confidence intervals (CI), and tests of homogeneity of variance were calculated for the overall sample (k = 27) and for subsets of interest. **Results:** A total of 27 studies (total combined $N = 5374$) met the inclusion criteria. A significant association was found between depression and complications of diabetes ($p < .00001$, $z = 5.94$). A moderate and significant weighted effect size ($r = 0.25$; 95% CI: 0.22–0.28) was calculated for all studies reporting sufficient data (k = 22). Depression was significantly associated with a variety of diabetes complications (diabetic retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction). Effect sizes were in the small to moderate range ($r = 0.17$ to 0.32). **Conclusions:** These findings demonstrate a significant and consistent association of diabetes complications and depressive symptoms. Prospective, longitudinal studies are needed to identify the pathways that mediate this association. **Key words:** depression, diabetes mellitus, meta-analysis.

CI = Confidence Interval; ES = Effect Size; BDI = Beck Depression Inventory; SCID = Structured Clinical Interview for the DSM; SCL-90 R = Symptom Checklist 90-Item Version, Depression Subscale; DIS = Diagnostic Interview for the DSM; Zung = Zung Depression Scale; KDS-1 = Kupffer-Detre Depression Scale, Form 1; PSE = Present State Exam; CES-D = Center for Epidemiologic Studies Depression Inventory.

Diabetes doubles the likelihood of comorbid depression, which is present in approximately 30% of patients with type 1 or type 2 diabetes (1). A recent meta-analysis of 27 studies found a statistically significant association between depression and hyperglycemia in both type 1 and type 2 diabetes (2). In a randomized, controlled trial of antidepressant treatment in 68 patients with type 1 and type 2 diabetes, improvements in depressive symptoms predicted improved glycemic control after controlling for the independent contribution of nortriptyline (3). A separate, randomized, controlled trial of cognitive behavior therapy for depression demonstrated that improvement in depression scores corresponded with improvement in glycemic control (4). Other randomized controlled studies have observed that improvements in glycemic control are correlated with improvements in depressive symptoms (5, 6).

Chronic hyperglycemia is a well-established predictor of the onset and exacerbation of diabetes complications in both type 1 (eg (7),) and type 2 diabetes (8). If depression is associated with hyperglycemia and hyperglycemia is associated with diabetes complications, it follows that depression may also be associated with diabetes complications. Previous studies have correlated depression with a variety of diabetes complications such as diabetic neuropathy (9) and cardiovascular disease (10), yet others have failed to find an association between depression and diabetic retinopathy (11) or other complications such as nephropathy (12). Although a number of studies have examined this relationship, none have systematically reviewed the literature to assess the magnitude and consistency of the association. The demonstration of a consistent relationship is important because it lays the groundwork for exploring the pathways between depression as a psychological variable and complications as medical variables.

The purpose of the current investigation was to determine whether a consistent relationship between depression and diabetes complications among type 1 and type 2 diabetes patient samples could be established using meta-analytic techniques. We were interested in determining: 1) whether there is an association; 2) its direction, if found; and 3) whether the relationship differs among specific diabetes complications.

METHODS

Literature searches were conducted using the MEDLINE and PsycINFO databases for all articles using the keywords "diabetes" or "diabetes mellitus" and "depression" or "depressive disorder." Ar-

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ticles meeting the following criteria were included in the searches: 1) studies involving human subjects published in English language journals between 1975 and 1999, 2) sample sizes of at least 25 subjects, 3) only adult samples (age 18 or older), and 4) evaluation of the relationship between current or recent depression and at least one complication of type 1 and/or type 2 diabetes. Studies that focused primarily on gestational diabetes, impaired glucose tolerance, or borderline diabetes were excluded. The diabetes-specific complications of interest include: diabetic retinopathy, diabetic neuropathy, diabetic nephropathy or end stage renal disease (ESRD), macrovascular complications such as coronary artery disease (CAD), and sexual dysfunction. Studies reporting associations of complications to both lifetime and current depression were included, although only analyses of the relationship of complications with current depression were used in the meta-analysis.

Statistical Analyses

Meta-analysis was developed by Glass (13), Hedges and Olkin (14), and Rosenthal (15) to estimate effect sizes across multiple studies. Effect size, the measure of the magnitude of association between two variables, may be calculated from test statistics, variance estimates, or significance values (eg, *p* values, odds ratios). A variety of ES indices may be used to estimate the magnitude of an effect (16). In the current study, the Pearson correlation coefficient *r* was used as the ES estimator. Rosenthal (15) and Cohen (16) note that *r* is a robust estimator that reflects the proportion of common elements between two variables. The random effects model was used to estimate effect sizes. This conservative model was chosen to reduce overestimation of effect sizes in light of the correlational nature of the studies available in the literature.

Meta-analytic techniques for data collection, aggregation, and analysis were based on the procedures recommended by Rosenthal (15). For each study meeting the inclusion criteria, the following information was gathered: sample size, diabetes type, duration of diabetes, sample source, method of depression assessment, method of diabetes complication assessment, test statistics, and statistical significance values for the association between depression and complications, and if available, effect sizes. Depression assessment methods varied from self-report symptom inventories (eg, Beck Depression Inventory (17)) to diagnostic interview protocols (eg, Diagnostic Interview Schedule (18)), as did the definition of depression (eg, depressive symptoms vs. major depression). Diabetes complication assessment methodologies varied from patient self-report symptom inventories to physiologic test protocols (eg, biothesiometers used to measure nerve conductance). Likewise, the sources of complication data varied across studies (eg, protocol evaluations vs. medical chart data).

Published test statistics, significance values and effect sizes from each contributing study were used to calculate estimates of effect sizes and combined *p* values. Meta-analytic software (19) was used to perform these calculations.

ES estimates were calculated using standard formulas (15) from the following source data: test statistics; means, standard deviations, and sample sizes; or *p* values. For studies in which ES could be derived from more than one method, test statistic values took precedence. In the case of articles that reported only nonsignificant *p* values and did not provide enough information to replicate test statistics, *r* values were set as missing and omitted from further analyses. Once calculated, effect size *r* values were converted to Fisher's Z_r.

To estimate the combined effect size, weighted and unweighted effect sizes *r* were calculated for each data aggregation. Weighted effect sizes were calculated by multiplying the Fisher's Z_r values by the respective sample size weights and dividing the sum by the sum of the sample sizes. Confidence intervals were calculated from residual variation of the effect sizes. CI represent the range of variance in the sample of effect sizes with a value of zero or less in the lower bound indicating statistical nonsignificance.

Combined *p* values were also calculated to estimate the probability of the null hypothesis (ie, the likelihood that the association of depression and complications is a chance occurrence) in an aggregation of studies. While combined *p* values provide less specific information about the magnitude of effects within a given study, they provide an estimate of the overall significance of findings. In order to evaluate all studies in the same metric, significance values for two-tailed tests were divided by two to yield one-tailed *p* values. Several papers referred to nonsignificant test results in the text but did not provide specific *p* values. In these cases, a *p* value of .50 was assigned. The *p* values were then transformed into *z* scores. In studies that contributed more than one significance test, the *z* scores were averaged and backtransformed to obtain the average *p* value. To calculate the combined *p* value, *z* scores from each study were multiplied by their respective sample sizes, summed, and divided by the square root of the sum of the squared sample sizes.

Homogeneity of variance concerns the degree of variability in the effect sizes in an aggregation of studies. The random effects model assumes that effect sizes are sample estimates of a true population parameter. Consequently, ES are subject to sampling error. Homogeneity of variance is estimated to measure the degree of variability associated with the effect size estimate. The homogeneity hypothesis was tested for each grouping of studies. Three tests of homogeneity of variance were calculated: residual variation, proportion of variance observed, and chi-square. The presence of heterogeneity of variance suggests that there may be other sources of systematic variance (moderator variables) in the relationship between two variables. It may also suggest the presence of "noise" or measurement error in aggregations of studies.

Finally, the Fail Safe N was calculated for each sample grouping. As noted by Rosenthal and others (15), a common criticism of meta-analysis is the "file drawer problem" or the extent to which nonsignificant results are disproportionately excluded from publication. Fail Safe N indicates the number of unpublished studies with negative findings that would be required to reduce the effect size to the $r = 0.05$ level (19). An effect size level of $r = 0.05$ was chosen as an ES approximating zero.

RESULTS

Twenty-seven of the studies identified by the literature search met our inclusion criteria. The characteristics and findings of these studies are summarized in Table 1. The studies varied considerably with respect to depression assessment methods, diabetes type, mean duration of illness, and diabetes complications. Twenty of the studies used data from self-report measures or inventories to examine the relationship of depressive symptoms to complications, while seven used diagnostic interviews based on the DSM criteria (20). Ten studies examined only type 1 diabetes, and five studies examined only type 2. One study (21) examined type 1 and type 2 patient samples separately, so the results from this study were included in aggregations of both type 1 and type 2 diabetes sam-

TABLE 1. Depression and Diabetes Complications Studies 1975–1999 ($N = 27$)

Study	Diabetes Type (*N*)	Duration of Diabetes (yrs) Mean (SD)	Gender Male/Female	Setting	Depression Assessment Method[a]	Complication: Assessment Method	Statistical Tests	*p* Value	Z_p[b]	*r*	Fisher's Z_r
Erbey et al. (26) 1998	Type 1 (658)	Presence of complications: 30.7 (.7) Absence of complications: 23.9 (.3)	333/325	Diabetes registry	BDI	CAD: Medical history and clinical examination. Diagnosis of angina or confirmed myocardial infarction using electrocardiogram & blood pressure measures.	*T*-test: Presence vs. absence of CAD & BDI score. $t = 7.97$ $p < .001$	.001	3.30	.30	.31
Cohen et al. (25) 1997	Type 1 (49)	No Psych Hx: 17.2 (2.9) MDD: 16.3 (4.7)	22/27	Outpatient diabetes clinic	SCID	Retinopathy: Stereo fundus photography.	*T*-test: Major depression vs. no psychiatric history & ETDRS step score. $t = 1.91$ $p = .07$.	.07	1.48	.38	.40
Karlson and Agardh (11) 1997	Type 1 (155)	17.8	87/68	Outpatient diabetes clinic	SCL-90-R Depression subscale	Retinopathy: medical record.	Spearman correlation of complication categories & depression scores:				
						Nephropathy: medical record (incipient: urinary albumin 30–300 mg 1; or clinical: urinary albumin > 300 mg l) and/or serum creatinine levels > 116 $mMol^{-1}$ for men, >100 $mMol^{-1}$ for women.	Retinopathy: No signs $r = -.10$; p = NS; Proliferative $r = -.03$; p = NS Nephropathy: No signs $r = -.04$; p = NS Clinical signs $r = -.07$; p = NS	NS NS NS NS	0.00 0.00 0.00 0.00	−.10 .03 −.04 .07	−.10 .03 −.04 .07
Lloyd et al. (27) 1996	Type 1 (634)	No CAD: 18.5 (7.5) CAD: 26.3 (5.3)	322/312	Diabetes registry	BDI	CAD: Medical record. Diagnosis of angina, history of MI (confirmed by electrocardiogram or chart note), or CAD death.	*T*-tests: Absence vs. presence and BDI: Men BDI scores: $t = -.99$, p = NS. Women $t = -3.29$ $p < .001$.	.50 .001	0.00 3.30	.06 .19	.06 .19
Lloyd et al. (10) 1997	Type 1 (610)	20.0	NA[c]	Diabetes registry	BDI	Coronary heart disease: No information provided.	*T*-tests: Presence/absence of CHD and BDI: Men t = NA, $p < .001$ Women t = NA, $p < .01$	.001 .01	2.58 3.30		
Lloyd et al. (22) 1992	Type 1 (175)	>25.0	88/87	Diabetes registry	BDI	Nephropathy: renal failure (serum creatinine levels > 442 mMol, dialysis, or renal transplant), or AER > 200 μg/min in 2 or 3 timed urine samples, serum creatinine levels > 176.8 mMol). Neuropathy: distal symmetrical polyneuropathy symptoms (patient self-report, decreased tendon reflector sensory loss). Retinopathy: stereo fundus photography. Peripheral vascular disease: ankle-arm blood pressure ratio < .8 or history of amputation. Cardiovascular disease: electrocardiogram or documented MI.	*T*-tests: Absence vs. presence complication & BDI scores: Retinopathy: $t = -.66$ p = NS Neuropathy: $t = -1.47$ p = NS Nephropathy: $t = -1.13$ p = NS Macrovascular (PVD and/or CVD): $t = -2.42$ $p < .05$ One complication vs. None: $t = -1.03$, p = NS Two complications vs. none: $t = 1.03$, p = NS Three complications vs. none: $t = -1.67$ $p < .05$ Four complications vs. none: $t = -3.41$ $p < .001$.	.50 .50 .50 .05 .50 .50 .05 .001	0.00 0.00 0.00 1.96 0.00 0.00 1.96 3.30	.06 .13 .12 .25 .16 −.12 .22 .50	.06 .13 .12 .25 .16 −.12 .22 .55

TABLE 1. (*Continued*)

Study	Diabetes Type (*N*)	Duration of Diabetes (yrs) Mean (SD)	Gender Male/Female	Setting	Depression Assessment Method[a]	Complication: Assessment Method	Statistical Tests	*p* Value	Z_p[b]	*r*	Fisher's Z_r
Winocour et al. (28) 1990	Type 1 (130)	14.0	83/47	Outpatient diabetes clinic	Zung	Ischaemic heart disease: physical exam. History of MI, typical angina or pronounced Q wave abnormalities or T wave inversion and ST segment depression. Peripheral vascular disease: physical exam. History of intermittent claudication with one or more absent foot pulses. Peripheral neuropathy: loss of sensation, ankle jerks and patient self-report. Retinopathy: proliferative retinopathy confirmed by fluorescein angiography. Impotence: continued difficulty achieving and maintaining penile erection.	*T*-tests: Presence vs. absence of complication & Zung score: Retinopathy: t = NA, p = NS Neuropathy: t = NA, $p < .01$ Ischaemic heart disease: t = NA, $p < .02$. Peripheral vascular disease: t = NA, $p < .05$ Impotence: Pearson correlation $r = .28$, $p < .01$.	.50 .01 .02 .05 .01	0.00 2.57 2.33 1.96 2.33	 .27 .20 .17 .28	 .28 .20 .24 .29
Popkin et al. (29) 1988	Type 1 (75)	20.0	27/48	Pancreas transplant candidates	DIS	No information available.	Statistical test values unavailable. Retinopathy: p = NS Neuropathy: p = NS Impairment of vision: p = NS	 .50 .50 .50	 0.00 0.00 0.00		
Stone et al. (30) 1984	Type 1 (57)	18.7 (7.3)	25/32	Community sample	BDI	Patient self-report questionnaire to assess presence and functional impact.	Pearson correlations between depression symptoms and complication impact score. Neuropathy: $r = .54$, $p < .001$ Impotence: $r = .30$, $p = .01$ Number of complications: $r = .36$, $p = .004$ Severity of complications: $r = .36$, $p = .004$	 .001 .01 .004 .004	 3.09 2.33 2.65 2.65	 .54 .30 .36 .36	 .60 .31 .38 .38
Turkington (9) 1980	Type 1 (59)	10.8	27/32	Outpatient diabetes clinic	KDS-1	Neuropathy: Patient sensory report, nerve conduction velocities.	*T*-test: Neuropathy: with and without leg pain compared with controls on KDS-1 scores. $t = 3.94$, $p < .001$	.001	3.30	.41	.44
Miyaoka et al. (31) 1997	Type 2 (151)	6.4 (7.2)	93/58	Outpatient diabetes clinic	Zung	Retinopathy: clinical exam. Neuropathy: clinical exam & motor neuron conduction velocity < 45 m/s in ulnar nerve media and 40 m/s in tibial and peroneal nerve. Nephropathy: presence of albuminuria.	*T*-test: Presence vs. absence and BDI scores. Retinopathy: $t = -2.76$ $p < .01$ Neuropathy: $t = -1.71$ p = NS Nephropathy: $t = -2.70$ $p < .05$ Number of Complications (1 + vs. None): t = NA, $p < .01$	 .01 .50 .05 .01	 2.58 0.00 1.96 2.58	 .22 .14 .22 .19	 .22 .14 .22 .19

TABLE 1. (*Continued*)

Study	Diabetes Type (*N*)	Duration of Diabetes (yrs) Mean (SD)	Gender Male/Female	Setting	Depression Assessment Method[a]	Complication: Assessment Method	Statistical Tests	*p* Value	Z_p[b]	*r*	Fisher's Z_r
Viinamäki et al. (32) 1995	Type 2 (82)	10.0	44/38	Community sample	Zung	Neuropathy: medical record and interview.	Chi-square: Proportion of sample with complication by depression caseness:				
						Artherosclerotic vascular disease: hospital-verified MI or stroke or major Q-QS (1.1–2) ECG abnormalities.	Neuropathy: chi-square = 17.31 $p < .001$	.001	3.10	.42	.44
							Artherosclerotic vascular disease: chi-square = 3.25, p = NS	NS	0.00	.20	.20
Leedom et al. (23) 1991	Type 2 (71)	No complications: 6.0 (1.1) Complications: 12.0 (1.5)	21/50	Outpatient diabetes clinic	BDI Zung	Peripheral Neuropathy: physical and neurological exams. Degree of pain assessed by patient self-report (0–10 scale)	Pearson correlations and *t*-tests: Peripheral neuropathy (severity) Pearson correlation: Self-rated pain & BDI score: $r = -.05$, p = NS.	.50	0.00	−.05	−.05
						Impotence: patient self-report (0–10 scale).	Impotence and BDI score: Female: $r = .47$, $p < .01$	.01	2.33	.47	.47
							Male: $r = .26$, p = NS	.50	0.00	.26	.26
							Presence vs. absence of complications & BDI score. $t = 5.57$ $p < .001$.	.001	3.30	.56	.63
Naliboff and Rosenthal (33) 1989	Type 2 (102)	13.7	102/0	Outpatient diabetes clinic	BDI MMPI-D	Peripheral neuropathy: clinical judgement 0–1 scale; Autonomic neuropathy: 0–2 scale; Ischaemic heart disease: medical record. Retinopathy: ophthalmoscopy after pupillary dilation.	*T*-tests: Complication scores and BDI or MMPI-D subscale scores. Peripheral neuropathy: t = NA, p = NS	.50	0.00		
							Autonomic neuropathy: t = NA, p = NS	.50	0.00		
							Retinopathy: t = NA, p = NS	.50	0.00		
Geringer et al. (34) 1988	Type 2 (64)	NA	0/64	Outpatient diabetes clinic	Zung	Peripheral neuropathy: vibratory threshold over medial malleolus using biothesiometer and patient self-report about pain severity.	*T*-test: Depressed vs. nondepressed and biothesiometer score (neuropathy severity). t = .32, p = NS	.50	0.00	.04	.04
							Pearson correlation: depressed sample and biothesiometer score. $r = .71$, $p < .01$	.01	2.33	.71	.89
							Pearson correlation: nondepressed sample and biothesiometer score. r = NA, p = NS	.50	0.00		
							Chi-square: Absence vs. presence of PVD by depressed vs. nondepressed. Chi-square = 1.14, p = NS	.50	0.00	.13	.14
Black (35) 1999	Type 1 and Type 2 (636)	NA	266/370	Mexican-American Community sample	CES-D	Presence/absence of complications: patient self-report phone survey.	Proportion of depressed vs. nondepressed and absence/presence.				
							Eye Problems: Chi-square = NA, $p < .001$	.001	3.10	.20	.20
							Circulation Problems: Chi-square = NA, $p < .05$	.05	1.65	.15	.15
							Kidney Problems: Chi-square = NA, $p < .001$	.001	3.10	.34	.35
							Amputation: Chi-square: NA, p = NS	.50	0.00		

TABLE 1. (*Continued*)

Study	Diabetes Type (*N*)	Duration of Diabetes (yrs) Mean (SD)	Gender Male/ Female	Setting	Depression Assessment Method[a]	Complication: Assessment Method	Statistical Tests	*p* Value	Z_p[b]	*r*	Fisher's Z_r
Jacobson et al. (21) 1997	Type 1 and Type 2 (143)	15.4 (10.3)	78/65	Outpatient diabetes clinic	SCID	Number of complications: medical record.	Chi-square: Proportion of sample Major Depression vs. no psychiatric history and number of complications: Type 1: Chi square = NA, p = NS Type 2: Chi square = NA, p = NS	.50 .50	0.00 0.00		
Peyrot and Rubin (36) 1997	Type 1 and Type 2 (634)	Range: 0–30+	257/374	Outpatient diabetes clinic	CES-D&Zung	Presence of complications: medical record.	Chi-square: Proportion of depression cases and number of complications: No values specified. p = NS	.50	0.00		
Bailey (37) 1996	Type 1 and Type 2 (180)	NA	72/108	Community sample	CES-D	Number of complications: patient self-report.	Regression analysis: number of complications predicting CES-D score: standardized Beta = .37, $p \leq .05$	.05	1.65	.37	.39
Padgett (38) 1993	Type 1 and Type 2 (180)	7.8	92/88	Outpatient diabetes clinic Zagreb, Croatia	Zung	Presence of complications: medical record.	*T*-test: Presence vs. Absence of complications t = NA, $p < .05$. Pearson correlation: Presence of complications correlated with Zung scores $r = .21$, $p < .01$	.05 .01	1.96 2.33	.15 .21	.15 .21
Carney et al. (24) 1994	Type 1 and Type 2 (70)	NA	16/54	Diabetes registry	DIS	Coronary artery disease: medical record. Exercise stress test and diagnosis of ischaemic heart disease; angiogram and CAD; confirmed myocardial infarction; or sudden cardiac death.	Proportion of depressed vs. nondepressed with and without CAD: Chi-square = 4.14 p = .04	.04	1.75	.23	.24
Haire-Joshu et al. (39) 1994	Type 1 and Type 2 (186)	Non-smokers: 15.0 (8.6) Smokers: 14.0 (9.5)	84/102	Diabetes registry & outpatient diabetes clinic	BDI	Patient self-report validated by medical record.	Pearson correlation. Number of complications and BDI score: $r = .43$, $p < .01$	.01	2.33	.43	.46
Lustman and Clouse (40) 1990	Type 1 and Type 2 (37)	14.9 (13.1)	37/0	Community sample	DIS	Impotence: clinical interview. Recurrent failure to maintain an erection sufficient for orgasm.	*T*-test: Presence and absence of impotence and BDI score: t = NA $p < .01$	.01	2.58	.42	.45
Bernbaum et al. (41) 1988	Type 1 and Type 2 (29)	22.0 (2.0)	11/18	Community sample	Zung	Visual impairment: corrected visual acuity < 20/100. Stable: 20/300 to complete vision loss. Fluctuating: laser photocoagulation or vitrectomy.	*T*-test: Stable vs. Fluctuating vision and Zung score: $t = 3.57$; $p < .01$	.01	2.58	.57	.65
Lustman et al. (12) 1988	Type 1 and Type 2 (48)	Index timepoint IDDM/ NIDDM: 16.0 (8.8)/ 12.4 (7.8) Follow-up timepoint IDDM/ NIDDM: 21.7	NA	Outpatient diabetes clinic	DIS	Neuropathy: nerve conduction studies. Retinopathy: steroescopic fundus photography Nephropathy: 24 hr. urinary protein excretion and serum creatinine.	Chi-square: Proportion of complications (present/ absent) and depressed group vs. comparison group: Retinopathy: chi-square = NA, $p > .15$ Neuropathy: chi-square = NA, $p > .15$ Nephropathy: chi-square = NA, $p > .15$	 .15 .15 .15	 1.04 1.04 1.04	 .20 .20 .20	 .20 .20 .20

TABLE 1. (*Continued*)

Study	Diabetes Type (*N*)	Duration of Diabetes (yrs) Mean (SD)	Gender Male/Female	Setting	Depression Assessment Method[a]	Complication: Assessment Method	Statistical Tests	*p* Value	Z_p[b]	*r*	Fisher's Z_r
Robinson et al. (42) 1988	Type 1 and Type 2 (N = 130)	Range: 0–10+	72/58	Outpatient diabetes clinic	PSE	Presence/absence of complications: clinical exam. CHD, angina and MI: WHO Chest Pain Questionnaire. ECG, abnormal Q/QS waves, S-T depression; T wave inversion or flattening; or left bundle branch block. Retinopathy: direct fundoscopy.	Chi-square: Proportion of depression 'cases' and Presence vs. absence of complications: chi-square = 2.9, p = NS	.50	0.00	.16	.16
							Proportion of depression cases and macrovascular complications vs. none: chi-square = 4.68, $p < .05$	.05	1.65	.20	.21
Takahashi and Hirata (43) 1983	Type 1 and Type 2 (N = 37)	8.2	25/12	Outpatient diabetes clinic	Zung	Neuropathy: Patellar and axillary tendon reflex; ulnar and peroneal motor conduction velocity; ulnar and sural sensory nerve conduction velocity.	*T*-test: Painful vs. nonpainful neuropathy and BDI: $t = 6.41$ $p < .001$	.001	3.30	.73	.93

[a] BDI = Beck Depression Inventory; SCID = Structured Clinical Interview for the DSM; SCL-90 R = Symptom Checklist 90-Item Version, Depression Subscale; DIS = Diagnostic Interview for the DSM; Zung = Zung Depression Scale; KDS-1 = Kupfer-Detre Depression Scale, Form 1; PSE = Present State Exam; CES-D = Center for Epidemiologic Studies Depression Inventory.
[b] *Z* transformed one-tailed *p* value.
[c] NA = Information not provided by authors.

ples. The remaining 11 studies used mixed type 1 and type 2 diabetes samples.

As shown in Table 2, meta-analytic statistics for the entire sample of studies were calculated for all complications and diabetes types combined. The combined *p* value was significant ($p < .00001$, $z = 5.94$). The weighted effect size among studies for which sufficient information was available (k = 22) was $r = 0.25$ (95% CI: 0.22–0.28), indicating a moderate ES (16). The total aggregation of studies was heterogeneous according to all three tests of homogeneity of variance.

The heterogeneity of variance in the effect sizes among these studies suggested that moderator variables may be present. Consequently, the studies were divided into subgroups by type and measure of complications (absence/presence or numeric count of complications) and diabetes type. Meta-analyses were then performed on each subgroup. The results of the subgroup analyses are displayed in Tables 2 and 3.

Studies were aggregated that compared depression ratings of patients with any complication to those without complications. The three studies that examined the presence or absence of complications yielded a significant combined *p* value ($p = .004$, $z = 2.59$) with a moderate effect size (weighted $r = 0.25$; 95% CI: 0.16–0.35). Similar results were found for studies that compared the number of complications present ($p = .05$, $z = 1.67$). In these studies, higher levels of depression were associated with increasing numbers of complications. As shown in Table 2, both of these data aggregations yielded heterogeneous variability estimates.

To examine whether the association between depression and diabetes complications differs by diabetes type, studies were aggregated by type of diabetes irrespective of complications. As shown in Table 2, the aggregations yielded significant combined *p* values with weighted effect sizes ranging from $r = 0.21$ to $r = 0.30$ (95% CI range: 0.17–0.34). These findings indicate consistent and moderate effect sizes in the relationships between depression and complications in both type 1 and type 2 diabetes. ES and CI were similar for studies of type 1 and type 2 patient samples. Tests of homogeneity of variance indicated that the type 1 and mixed samples data aggregations were heterogeneous, suggesting the possible presence of moderator variables. Type 2 study aggregations, however, were homogeneous.

Finally, the studies were aggregated by specific diabetes complications. Studies reporting analyses for depression and several separate diabetes complications were entered into each diabetes complication aggregation for which results were available. As shown in Table 3, the specific diabetes complications represented in this literature included diabetic retinopathy (k = 10), neuropathy

TABLE 2. Depression and Diabetes Complications: Total Sample and Subgroup Meta-Analysis Results

Study Aggregations	Combined Weighted *p* and *z* Values	Weighted *r* Value	95% Confidence Interval	Unweighted *r* Value	95% Confidence Interval	Tests of Homogeneity[a]	Fail Safe N ($r = .05$)
All studies/all complications combined	$p < .00001$ (k = 27)[b] $z = 5.94$	.25 (k = 22)[c]	.22–.28	31 (k = 22)	.24 –.37	Heterogeneous Res SD = .10 % Obs Var = 34.1% Chi-square = 64.2 ($p < .0001$)	89
Presence vs. absence of any complications	$p = .004$ (k = 3) $z = 2.59$	.25 (k = 3)	.16–.35	.30 (k = 3)	.09 –.51	Heterogeneous Res SD = .13 Obs Var = 29.6% Chi-square = 10.1 ($p < .006$)	12
Number of complications	$p = .05$ (k = 6) $z = 1.67$	.29 (k = 4)	.22–.37	.30 (k = 4)	.19 –.40	Heterogeneous Res SD = .08 % Obs Var = 47.6% Chi-square = 8.3 ($p = .04$)	19
All complications							
Type 1 samples	$p < .00001$ (k = 11) $z = 4.68$	.21 (k = 8)	.17–.25	.25 (k = 8)	.14 –.35	Heterogeneous Res SD = .10 % Obs Var = 27.0% Chi-square = 29.5 ($p = .0001$)	26
Type 2 samples	$p = .01$ (k = 6) $z = 2.27$	.27 (k = 4)	.17–.37	.30 (k = 4)	.23 –.36	Homogeneous Res SD = .0000 % Obs Var = 100% Chi-square = 2.08 ($p = .55$)	18
Type 1 and type 2 mixed samples	$p = .0006$ (k = 11) $z = 3.29$	.30 (k = 10)	.25–.34	.36 (k = 10)	.25 –.46	Heterogeneous Res SD = .09 % Obs Var = 37.9% Chi-square = 26.0 ($p = .002$)	49

[a] Three tests of homogeneity of variance were performed. Res SD = Residual standard deviation. % Obs Var = proportion of observed variance.
[b] Number of studies included in the analysis.
[c] Some studies did not provide enough information to calculate effect size *r*. These studies were omitted from effect size *r* analysis.

(k = 12), nephropathy (k = 5), sexual dysfunction (k = 4), and macrovascular complications (k = 10).

The ten studies that examined relationships between depressive symptoms and diabetic retinopathy yielded a significant combined *p* value ($p < .0001$; $z = 3.84$) and a small to moderate effect size ($r = 0.17$; 95% CI: 0.11–0.22; k = 7). Five studies examined nephropathy and yielded a significant combined *p* value ($p = .0002$; $z = 3.51$) and moderate effect size ($r = .25$; 95% CI: .19–.30; k = 5). Similar findings were obtained for the subsets of studies examining diabetic neuropathy ($p = .0002$; $z = 3.57$; $r = .28$; 95% CI: .22–.34; k = 10) and sexual dysfunction ($p < .0001$; $z = 3.77$; $r = .32$; 95% CI: .22–.42; k = 4).

Ten studies examined the association between depressive symptoms and macrovascular complications (eg, coronary artery disease, peripheral vascular disease, coronary vascular disease, ischemic heart disease, arthrosclerotic vascular disease). These studies were aggregated to form a general "macrovascular" disease category. The combined *p* value was significant ($p < .0001$; $z = 5.42$) and there was a moderate effect size ($r = .20$; 95% CI: .16–.24; k = 9).

Tests of homogeneity of variance indicated that all of the subgroups except sexual dysfunction and type 2 diabetes were heterogeneous. This suggests that additional sources of variability exist in these study aggregations.

Fail Safe N values were calculated for each data aggregation. The numbers of unpublished studies with negative findings that would be required to reduce the effect sizes to the $r = .05$ level are shown in Tables 2 and 3.

Effect sizes *r* and 95% confidence intervals are graphically represented in Figure 1 for all study aggre-

TABLE 3. Depression and Specific Diabetes Complications: Meta-Analytic Results

Study Aggregations	Combined Weighted *p* and *z* Values	Weighted *r* Value	95% Confidence Interval	Unweighted *r* Value	95% Confidence Interval	Tests of Homogeneity[a]	Fail Safe N ($r = .05$)
Retinopathy	$p < .00006$ (k = 10)[b] $z = 3.84$	.17 (k = 7)[c]	.11–.22	.21 (k = 7)	.40–.60	Heterogeneous Res. SD = .10 % Obs Var = 33.8% Chi-square = 20.7 ($p = .002$)	17
Nephropathy	$p < .0002$ (k = 5) $z = 3.51$	.25 (k = 5)	.19–.30	.17 (k = 5)	.05–.29	Heterogeneous Res. SD = .14 % Obs Var = 16.9% Chi-square = 29.4 ($p < .0001$)	20
Neuropathy	$p = .0002$ (k = 12) $z = 3.57$	.28 (k = 10)	.22–.34	.32 (k = 10)	.19–.46	Heterogeneous Res SD = .16 % Obs Var = 26.7% Chi-square = 37.1 ($p < .0001$)	46
Sexual dysfunction	$p < .00001$ (k = 4) $z = 3.77$	.32 (k = 4)	.22–.42	.34 (k = 4)	.29–.40	Homogeneous Res SD = 0.0000 % Obs Var = 100% Chi-square = 1.03 ($p = .79$)	22
Macrovascular complications	$p < .00001$ (k = 10) $z = 5.42$	.20 (k = 9)	.16–.24	.20 (k = 9)	.16–.23	Homogeneous (2/3) Res. SD = .04 % Obs Var = 71.5% Chi-square = 12.6 ($p = .12$)	28

[a] Three tests of homogeneity of variance were performed. Res SD = Residual standard deviation. % Obs Var = proportion of observed variance.
[b] Number of studies included in the analysis.
[c] Some studies did not provide enough information to calculate effect size *r*. These studies were omitted from effect size *r* analysis.

gations. The associations between depression and diabetes complications were consistently positive. That is, increased depression was associated with increased numbers, severity, or ratings of complications. The lower 95% confidence limits did not cross zero in any of the aggregations, indicating statistically significant effect size estimates.

DISCUSSION

The results of this meta-analysis revealed a consistent, statistically significant relationship between depression and a variety of diabetes complications. The overall effect size ($r = .25$) was statistically significant and in the small-to-moderate range as defined by Cohen (16). ES for individual diabetes complication subgroups were similar to the overall finding, ranging from small (eg, retinopathy $r = .17$) to moderate effects (eg, sexual dysfunction $r = .32$). None of the confidence intervals for the effect sizes included zero, indicating statistical significance.

The findings are noteworthy for their consistency. In all subgroup aggregations, the association between depressive symptoms and specific complications was statistically significant. In addition, effect sizes were similar across physiologically diverse complications such as retinopathy, nephropathy, and sexual dysfunction. It is reasonable to expect that the course and patient experience of diabetic retinopathy, for example, might differ considerably from that of macrovascular complications. Likewise, depression might be expected to have a different relationship with neuropathy, than with nephropathy. Yet, the results within these aggregations indicated that depression was consistently associated with increased severity of diabetes complications. Likewise, there was similarity in effect size in type 1 and type 2 study samples. Type 1 and type 2 diabetes are etiologically distinct diseases, with differing ages of onset, courses of illness, and treatment regimens. This consistency suggests that there may be common pathways that support the association between depression and type 1 and type 2 diabetes.

Each of these analyses indicated a positive direction of association. An increase in depressive symptoms was

associated with an increase in the severity or number of diabetes complications. As shown in Table 1, 89% of all studies showed significant, positive correlations. The three exceptions to this trend reported statistically nonsignificant inverse relationships (range: −.04 to −.12) between self-report depression scores and complications (11, 22, 23). The consistency of the positive association increases confidence that these findings are replicable.

The meta-analysis has several limitations. First, a limited sample of studies were available for the analysis, which yielded small numbers of studies in each of the subgroup analyses. This may have contributed to the effect size variance found within most of the study aggregations. Second, the Fail Safe N values indicate that additional studies are needed to confidently reject the "file drawer problem" for some of the data aggregations (eg, presence/absence of complications, number of complications, type 2 samples, and retinopathy). Third, all of the studies available for analysis used cross-sectional designs, rather than prospective longitudinal approaches. Caution should be used in interpreting the strength of the association in light of the correlational nature of these studies. Finally, as noted in Tables 2 and 3, calculation of the ES in the majority of data aggregations yielded heterogeneous variance estimates indicating the possible presence of moderator variables. Heterogeneity of variance remained after studies were subdivided into logical aggregations (eg, specific complications, diabetes type). This suggests that additional variables not disclosed by the source studies may be important contributors to the association.

At this stage in the development of the literature, it is not possible to determine causal directions or mechanisms to explain the association between depression and complications due to the correlational nature of many of the contributing studies. Depression may precede and/or follow the onset of diabetes complications depending on the individual or course of disease. Depression, once established, may affect the course of complication development, promoting the onset of some, intensifying others. Depression may have an impact on some complications (eg, macrovascular disease) but little impact on the course of other complications (eg, nephropathy). It would be reasonable to speculate that underlying mechanisms linking depression and diabetes complications are a function of biological, social, and psychological variables that may interact with depression in differing ways to produce similar interactions with complications. In order to better characterize the relationship between depression and diabetes complications, three issues require further investigation: temporal relationships between depression and diabetes complications, the role of glycemic control as a potential mediating variable between depression and complications, and whether depression may accelerate the onset or progression of complications.

Temporal relationships between depressive symptoms and complications warrant clarification. The development of depression has often been considered a secondary response to the onset of complications but depression might also play a primary role in the development or exacerbation of diabetes complications. Which comes first? For whom? Are there differences in these relationships by type of diabetes? Do these relationships differ by diabetes complication? What role does duration of diabetes play in the development of depression? The majority of studies evaluated mean duration of diabetes, but no studies have used this variable as a covariate in analyses of the association

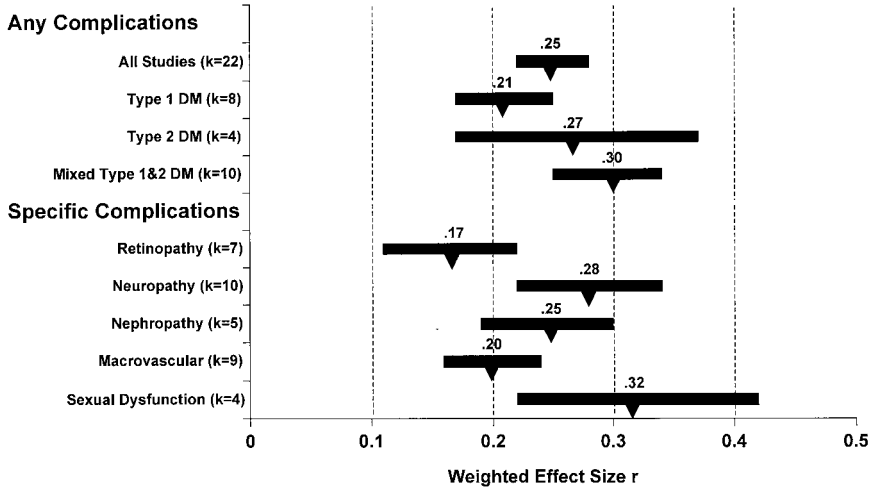

FIGURE 1. Weighted effect sizes and 95% confidence intervals for study aggregations. All combined p values were statistically significant ($p < .05$). k indicates number of studies for which sufficient data were available for use in the effect size calculation.

between depression and complications. Precise characterization of the timing and predictors of this interrelationship is needed.

Second, the role of glycemic control as a mediating variable is suggested by the recent review by Lustman and colleagues (2). Depression has been found to be associated with worsened glycemic control. Further work is needed to identify the mechanisms underlying the association between glycemic control and depression and what predicts the onset of depression in some individuals with hyperglycemia but not in others.

Finally, further investigation is needed to establish the role depression may play in the exacerbation of diabetes complications, that is, hastening the onset or progression of complications. In a longitudinal study of 114 patients over a ten-year period, Carney and colleagues (24) found a three-fold increased likelihood of developing coronary artery disease in patients with depression. Cohen and colleagues (25) reported that patients with a lifetime history of any affective disorder had greater progression of retinopathy than patients with no psychiatric history. Findings from these two studies lend support to the hypothesis that depression may accelerate the development of diabetes complications.

Prospective longitudinal studies are needed to explore these hypotheses. Such studies would require use of control samples, stratification of samples by diabetes type and disease duration, and precision in the documentation of diabetes complication trajectories. In addition, use of standardized interview protocols and diagnostic standards would be essential to documenting the existence of depressive syndromes, episodes, and disorders.

In conclusion, this meta-analysis documents consistent and significant associations between depression and a variety diabetes complications in both type 1 and type 2 diabetes. Well-designed, longitudinal studies are needed to pinpoint depression and complication trajectories and the mechanisms that link these diseases (26–43).

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