

Depression and Poor Glycemic Control

A meta-analytic review of the literature

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OBJECTIVE — Depression is common among patients with diabetes, but its relationship to glycemic control has not been systematically reviewed. Our objective was to determine whether depression is associated with poor glycemic control.

RESEARCH DESIGN AND METHODS — Medline and PsycINFO databases and published reference lists were used to identify studies that measured the association of depression with glycemic control. Meta-analytic procedures were used to convert the findings to a common metric, calculate effect sizes (ESs), and statistically analyze the collective data.

RESULTS — A total of 24 studies satisfied the inclusion and exclusion criteria for the meta-analysis. Depression was significantly associated with hyperglycemia ($Z = 5.4, P < 0.0001$). The standardized ES was in the small-to-moderate range (0.17) and was consistent, as the 95% CI was narrow (0.13–0.21). The ES was similar in studies of either type 1 or type 2 diabetes (ES 0.19 vs. 0.16) and larger when standardized interviews and diagnostic criteria rather than self-report questionnaires were used to assess depression (ES 0.28 vs. 0.15).

CONCLUSIONS — Depression is associated with hyperglycemia in patients with type 1 or type 2 diabetes. Additional studies are needed to establish the directional nature of this relationship and to determine the effects of depression treatment on glycemic control and the long-term course of diabetes.

Diabetes Care 23:934–942, 2000

Hyperglycemia has been linked to the development of diabetic complications (1). Treatments that lower blood glucose levels reduce the risks of retinopathy, neuropathy, and nephropathy in patients with type 1 (2,3) or type 2 (4,5) diabetes. Accordingly, maintenance of good glycemic control is the focus of diabetes therapy, and the importance of other clinical factors is judged largely in relation to their effects on this parameter.

Clinical and subclinical expressions of depression are present in >25% of patients

with type 1 or type 2 diabetes (6–14) and have adverse effects on functioning and quality of life (15,16). The existing literature is not consistent and clear with regard to the association between depression and poor glycemic control. Such an association would suggest the possibility that depression treatment might have favorable effects on diabetic outcomes. We surveyed the scientific literature, identified studies that measured the association of depression (either by symptoms or the diagnosis) with glycemic control, and performed a meta-

analysis to assess the reliability and strength of any association.

RESEARCH DESIGN AND METHODS — Medline and PsycINFO were used to locate studies published in the last 25 years (1975–1999) that reported the association of depression with glycemic control in adult diabetic subjects. The reference lists of these articles were examined to identify additional studies, and this led to the consideration of several unpublished papers and manuscripts.

Inclusion and exclusion criteria

Studies were limited to adult participants (≥ 18 years of age), to those that assessed glycemic control using a measure of glycohemoglobin (denoted as GHb within this article) (17,18), and to those that measured depression and GHb coincident to the study evaluation. Studies with <25 patients, those neither published nor available in English, and those that ascertained only a history of depression were excluded. Subjects in the included studies were patients diagnosed with type 1 or type 2 diabetes; studies of subjects with impaired glucose tolerance, borderline diabetes, or gestational diabetes were not considered. Studies were included without regard to the way the depression–glycemic control association was tested. In some studies, depression was the independent variable and glycemic control the dependent variable. Other studies used the reverse approach, and some reported only the correlation between the 2 variables.

Study procedures and statistical analysis

Study characteristics were recorded, and the studies were categorized by methodology. Type of diabetes and method of depression assessment were recorded, and effect sizes (ESs) were examined in relation to these factors. The diagnosis of depression (major depressive disorder) was established by using structured or semistructured clinical interviews and the diagnostic criteria in use at the time of the study (e.g., American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* [19,20] or the Research Diagnostic Criteria [21]).

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Received for publication 20 December 1999 and accepted in revised form 4 April 2000.

Abbreviations: BESD, binomial effect size display; ES, effect size; RCT, randomized clinical trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Depression and glycemic control articles: 1975–1999

Study (ref.)	Subjects		Depression assessment	Statistical tests	P	Z _p	ES r	Fisher's Z _t *
	Type of diabetes	Sex (M/F)						
Berlin et al. (53)	Type 1	102 56/46	MADRS	Recalculated <i>t</i> test: IV: GHb groups; DV: MADRS	<0.10	1.29	0.15	0.15
Karlson et al. (54)	Type 1	155 87/68	SCL-90R-D	Pearson correlation: SCL-90R-D and GHb	0.06	1.56	0.15	0.15
Songar et al. (55)	Type 1	60 19/41	BDI SCL-90R-D	Pearson correlations: BDI and GHb SCL-90R-D and GHb	NS	0.00	0.19	0.19
Eaton et al. (13)	Type 1	127 50/71‡	CES-D	Average values† Pearson correlation: CES-D and GHb	NS	0.00	0.19	0.19
Wrigley et al. (56)	Type 1	178 86/92	POMS PSE and Bedford College criteria	<i>t</i> test: admissions vs. controls per POMS depression subscale.	<0.01	2.33	0.18	0.18
Winocour et al. (57)	Type 1	130 NV	Zung	No specific information provided.	NS	0.00	NV	NV
Niemcrynck et al. (58)	Type 1	48 30/18	CES-D	Pearson correlation: CES-D and GHb	NS	0.00	0.15	0.15
Karlsson et al. (59)	Type 1	53 26/27	SCL-90R-D	ANOVA: IV: GHb groups; DV: SCL-90R-D	<0.02	2.06	0.28	0.29
Mazze et al. (28)	Type 1	84 25/59	Zung	ANOVA: IV: GHb groups; DV: Zung Pearson correlation: Change in GHb and change in depression 0-36 weeks.	<0.001	3.10	0.46	0.48
SurrIDGE et al. (60)	Type 1	50 27/23	BDI HDRS	Average values No specific information provided	0.005 NS	2.58 0.00	0.36 NV	0.37 NV
Miyaoka et al. (61)	Type 2	151 93/58	Zung	Pearson correlation: Zung and GHb Recalculated ANOVA: IV: GHb groups; DV: Zung	NS NS	0.00 0.00	NV 0.20	NV 0.20
Van der Does et al. (62)	Type 2	188 85/103	POMS	Average values Spearman rank correlation: POMS and GHb	NS <0.05	0.00 1.65	0.20 0.16	0.20 0.16
Pibernik-Okanovic et al. (63)	Type 2	88 36/52	BDI	Kendall's τ -B: BDI and GHb	NS	0.00	0.07	0.07
Connell et al. (64)	Type 2	191 81/110	Zung	Regression analyses: GHb predicts Zung Zung predicts GHb	<0.10 <0.10	2.33 2.33	0.13 0.18	0.13 0.18
Geringer et al. (65)	Type 2	64 0/64	Zung	Average values <i>t</i> test: IV: Zung; DV: GHb	0.10 NS	2.33 0.00	0.16 0.02	0.16 0.02
Biglan et al. (66)	Type 2	184 61/123	SADS and RDC BDI CES-D	Correlations: Depression diagnosis and GHb BDI and GHb CES-D and GHb	<0.01 NS NS	2.33 0.00 0.00	0.28 0.03 0.08	0.29 0.03 0.08
de Groot et al. (67)	Type 1 Type 2	33 40/32 39	SCID and DSM (current diagnosis only)	Average values <i>t</i> tests: Type 1: IV: depression diagnosis; DV: GHb Type 2: IV: depression diagnosis; DV: GHb	0.22 <0.09 <0.06	0.78 1.35 1.56	0.13 0.43 0.33	0.13 0.46 0.34
Bailey et al. (68)	Type 1 and 2 (Mixed)	180 NV	CES-D	Average values Pearson correlation: CES-D and GHb	0.07 NS	1.46 0.00	0.38 0.10	0.40 0.10
Lee et al. (69)	Type 1 and 2 (Mixed)	93 39/54	Symptom checklist devised from the DSM-III	Average values <i>t</i> test: IV: GHb groups; DV: number of depressive symptoms	0.07 <0.02	1.46 2.06	0.38 0.21	0.40 0.21
Haire-Joshu et al. (70)	Type 1 Type 2	163 84/102 23	BDI	Pearson correlation: BDI and GHb Regression analysis: GHb predicts BDI	<0.01 <0.05	2.33 1.65	0.19 0.04	0.19 0.04
Padgett et al. (71)	Type 1 Type 2	33 92/88 147	Zung	Average values Pearson correlation: Zung and GHb	0.02 NS	1.99 0.00	0.12 0.04	0.12 0.04
Von Dras et al. (72)	Type 1 Type 2	66 55/61 50	Zung	Pearson correlation: Zung and GHb Regression analysis: GHb predicts Zung	<0.0001 <0.0001	3.70 3.70	0.36 0.28	0.38 0.29

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Table 1—Continued

Study (ref.)	Subjects		Depression assessment	Statistical tests	P	Z _p	ES r	Fisher's Z _r *	
	Type of diabetes	Sex (M/F)							
Von Dras et al. (72) (continued)				Average values	0.0001	3.70	0.33	0.34	
Lustman et al. (73)	Type 1 Type 2	57 57	38/76	DIS and DSM	t test: IV: Depression diagnosis; DV: GHb	<0.01	2.33	0.36	0.38
Robinson et al. (74)	Type 1 Type 2	60 70	71/59	PSE and Bedford College criteria	t test: IV: Depression caseness; DV: GHb	NS	0.00	0.08	0.08
Lustman et al. (37)	Type 1	12	11/14	DIS and DSM BDI	t test: IV: Depression diagnosis; DV: GHb	0.03	1.89	0.41	0.44
Lustman et al. (36)	Type 2 Type 1 and 2 (Mixed)	13 48	NV	DIS and DSM BDI	t test: IV: Depression diagnosis; DV: GHb	0.025	1.96	0.29	0.30

n = 26 Cross-sectional studies. ANOVA, analysis of variance; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies-Depression Scale; DIS, Diagnostic Interview Schedule for the DSM-III-R; DSM, DSM-III-R criteria; DV, dependent or outcome variable; HDRS, Hamilton Psychiatric Rating Scale for Depression; IV, independent or grouping variable; MADRS, Montgomery-Asberg Depression Rating Scale; NV, authors did not provide sufficient information; POMS, Profile of Mood States; PSE, Present State Examination; SADS, Schedule for Affective Disorder and Schizophrenia; SCID, Structured Clinical Interview for the DSM-III-R; SCL-90R, Symptom Check List-Revised; Zung, Zung Self-Rating Depression Scale. *ES r were converted to Fisher's Z scores. Fisher Z scores were averaged in studies that reported more than one ES. †Average values indicates the mean P value, Z_p, ES r, and Z_r used in analyses. ‡Author did not specify sex of n = 6 subjects who did not complete study protocol.

Depression was quantified using self-report instruments that measure the severity of recent depression symptoms. These instruments (e.g., the Beck Depression Inventory [22] or the Center for Epidemiological Studies-Depression Scale [23]) provided interval data on depression severity. Pearson's r was calculated to determine the correlation between depression severity and GHb. In some studies, threshold scores on these instruments were also used to identify categories of depression severity (mild, moderate, severe) or depression caseness (absent/present) that were studied in relation to glycemic control. In a similar fashion, glycemic control was sometimes used as the independent or grouping variable (e.g., a mean split of the GHb observations), and the groups were statistically compared for differences in the frequency or severity of depression. Lastly, studies were included that reported, in the context of a randomized clinical trial (RCT), the pretreatment association of depression with glycemic control and/or the correlation of pre- to posttreatment change in depression or GHb levels with, respectively, pre- to posttreatment change in GHb or depression levels.

Meta-analytic procedures were used to transform the findings of each study into a common metric that permitted statistical analysis of the outcomes collectively as well as within logical subsets of the data (e.g., type 1 or type 2 diabetes). The procedures followed the meta-analytic approach

described by Hunter et al. (24). For each study, a single measure of ES r was calculated that was equal to the reported Pearson product-moment correlation coefficient r or was transformed from t, F, or P values using standard formulas (25,26). In studies that reported statistically significant associations but did not provide the means, standard deviations, actual ES, or test statistic value, the P value was used to calculate r. In studies that reported nonsignificant associations and did not provide means, standard deviations, actual ES, or obtained P values, P was set equal to 0.50 and then transformed to z. Studies that did not report specific P values and provided neither a test statistic nor information sufficient to calculate a test statistic (e.g., t, F, χ^2) were excluded from ES r calculations.

Each study contributed only 1 ES per outcome to maintain the independence of effects central to meta-analytic procedures, except when the data allowed for separate ES calculations within aggregations of interest (e.g., type 1 versus type 2 diabetes) (26,27). When >1 association was reported, the associations were converted to standardized Z scores and averaged to form a single ES. The study by Mazze et al. (28) counted as 2 independent studies because it reported the cross-sectional (pretreatment) correlation of depression with GHb as well as the longitudinal correlation of pre- to posttreatment change in GHb with change in depression.

Two estimators of the population ES were calculated, the unweighted r and the weighted r. The unweighted r was calculated by transforming the individual r values into Fisher's z, averaging the individual Z values, and then backtransforming the average Z into r. The weighted r was calculated by transforming the individual r values into Fisher's z, multiplying these Z values by the observed sample size, summing across all studies in a category, and dividing the sum by the square root of the sum of the squared weights. The weighted Z was then backtransformed into r (26). The weighted r is generally considered the best estimate of the population ES, and the meta-analysis and ESs were based on this statistic. An ES is considered statistically significant if the 95% CI around the effect does not include 0 or if the P value associated with the size of the Z statistic is <0.05 (27). Both the weighted and unweighted r's are provided in tables for comparison purposes. Large differences in the findings among the studies decrease confidence in the results of a meta-analysis (26). Thus, the individual ESs were statistically checked for heterogeneity against the summary estimate of effect. The principal meta-analysis was restricted to a homogenous aggregation of the data.

Meta-analytic software (META, Version 5.3) (29) was used to calculate average z-scores and P values, weighted and unweighted ESs r, and the 95% CI around

Table 2—Results of meta-analyses of study subsets

Grouping of studies	k	Weighted P and Z	Weighted r	95% CI	Unweighted r	95% CI	Tests of homogeneity	Fail-safe N	BESD
All	30	P = 0.00001 Z = 5.44	0.16 (k = 28)	0.13–0.20	0.20 (k = 28)	0.16–0.24	Heterogeneous (RSD = 0.05, %OV = 77.7, $\chi^2 = 35.9$ [P = 0.11])	63	0.42–0.58
Cross-sectional	26	P = 0.00001 Z = 5.43	0.17 (k = 24)	0.13–0.21	0.19 (k = 24)	0.16–0.23	Homogeneous	58	0.41–0.59
Depression per symptom scales	21	P < 0.00001 Z = 4.52	0.15 (k = 19)	0.11–0.19	0.16 (k = 19)	0.12–0.19	Homogeneous	37	0.43–0.57
Depression per diagnostic criteria	6	P < 0.00002 Z = 3.51	0.28 (k = 6)	0.20–0.36	0.30 (k = 6)	0.22–0.38	Homogeneous	28	0.36–0.64
Type 1 sample	11	P = 0.0002 Z = 3.7	0.19 (k = 9)	0.12–0.25	0.21 (k = 9)	0.15–0.28	Homogeneous	24	0.41–0.59
Type 2 sample	7	P = 0.005 Z = 2.76	0.16 (k = 7)	0.09–0.22	0.16 (k = 7)	0.09–0.22	Homogeneous	15	0.42–0.58
Mixed type 1 and type 2 sample	9	P = 0.00001 Z = 3.56	0.17 (k = 9)	0.11–0.23	0.22 (k = 9)	0.16–0.28	Heterogeneous (RSD = 0.08, %OV = 58.2, $\chi^2 = 15.4$ [P = 0.05])	22	0.41–0.59
Depression is the IV	7	P = 0.003 Z = 2.70	0.22 (k = 7)	0.14–0.29	0.25 (k = 7)	0.18–0.32	Heterogeneous (RSD = 0.08, %OV = 59.2, $\chi^2 = 11.8$ [P = 0.07])	24	0.39–0.61
HbA _{1c} is the IV	6	P = 0.00001 Z = 4.05	0.18 (k = 6)	0.11–0.25	0.20 (k = 6)	0.13–0.27	Homogeneous	16	0.41–0.59

k, Number of studies. N, number of unpublished studies (having $r = 0$) that would be needed to lower the mean effect size to 0.05. IV, independent variable; RSD, residual standard deviation; %OV, percent of observed variance.

the collective ES values. The software calculated 3 tests of interstudy heterogeneity (residual standard deviation, percentage of observed variance accounted for by sampling error, and χ^2). It also calculated the

binomial effect size display (BESD) and the fail-safe N. These measures are often used to aid interpretation of the weighted effect r . The BESD was developed to illustrate the practical importance of the estimated ES in

a way that is not easily discerned from common ES estimators (e.g., r^2 , ω^2 , ϵ^2). The BESD is equivalent to the standardized ES r but is displayed as the increase in the success rate of the particular treatment or predictor variable under study (30). The fail-safe N provides an estimate of the potential for publication bias and is expressed as the number of studies with ESs of 0 that are required to bring the mean ES down to a defined level (30,31). Publication bias threatens the validity of the results and exists to the extent that the studies included in the meta-analysis (i.e., published studies) are not representative of the population of such studies. Although the concept of publication bias is well accepted, the methods for calculating it are not (32), and thus statistics like the fail-safe N should be interpreted cautiously.

RESULTS — A total of 30 studies were identified that measured the association of depression with glycemic control. Of these studies, 28 provided information sufficient to calculate the study r ; the remaining 2 did not. These 2 studies contributed only to the calculation of the overall P . Meta-analysis revealed a significant association of depression with hyperglycemia ($Z = 5.3$, $P < 0.0001$) and a small-to-moderate standard-

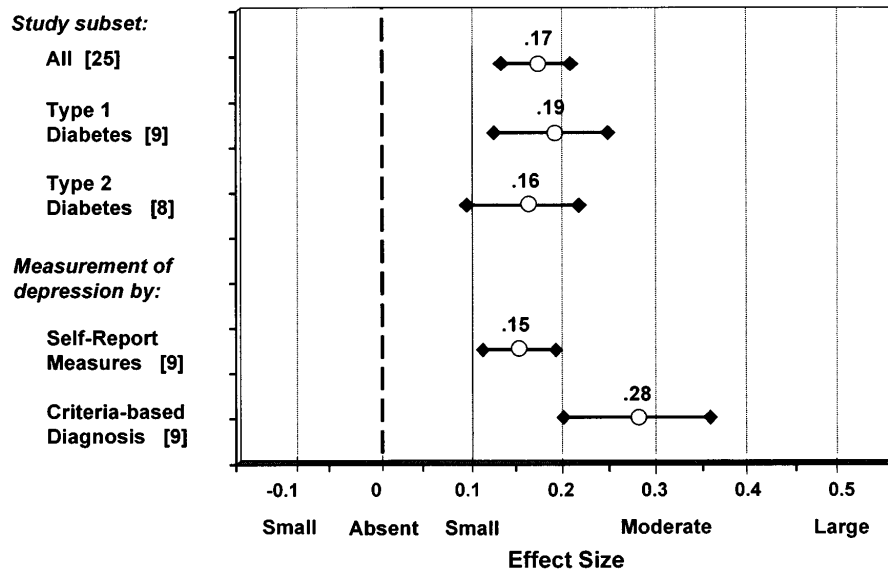


Figure 1—ESs and 95% CIs for homogenous aggregations of the 25 studies included in the meta-analysis. All ESs were statistically significant, $P < 0.05$. Numbers in brackets indicate the number of studies used in the calculation.

Table 3—RCT studies

Study	Subjects		Depression assessment	Independent variable	Dependent variable	Statistical tests	P	Z _p	ES	r	Fisher's Z _r *
	Type of diabetes	n									
Depression treatment											
Lustman et al. (33)	Type 2	42	17/25	DIS and DSM BDI	Responders vs. nonresponders per posttreatment BDI	GHb	t test	0.003	2.75	0.51	0.56
					Responders vs. nonresponders per follow-up BDI	GHb		0.006	2.51	0.47	0.51
							Average values†	0.004	2.63	0.49	0.53
Lustman et al. (35)	Type 1 and 2	54	17/37	DIS and DSM BDI HDRS	Fluoxetine vs. placebo	Change in GHb over time.	t test	0.13	1.13	0.16	0.16
					Responders vs. nonresponders per HDRS	GHb	t test	0.60	0.00	NV ⁴	NV
					Responders vs. nonresponders per BDI	GHb	t test	0.90	0.00	NV	NV
							Average values ANCOVA	0.35	0.37	0.16	0.16
Lustman et al. (34)	Type 1 and 2	68	33/35	DIS and DSM BDI	Remitted vs. nonremitted depression per BDI	GHb	ANCOVA	NS	0.00	NV	NV
					Nortriptyline vs. placebo	GHb	ANCOVA	0.07	1.48	0.28	0.29
							Path analysis: change in BDI predicts change in GHb	<0.05	1.65	0.20	0.20
							Average values	0.15	1.04	0.25	0.25
Diabetes treatment											
Mazze et al. (28)	Type 1	84	25/59	Zung			Pearson correlation: change in GHb and change in Zung 0–36 weeks	0.001	3.10	0.46	0.50
Testa et al. (38)	Type 2	569	320/249	Depression subscale embedded in QOL measure			Change in depression following Glipizide treatment	0.05	1.65	0.07	0.07

n = 5. *Studies with multiple effect sizes were converted to Fisher Z scores and averaged. Average Z scores were then reconverted to r values for inclusion in meta-analysis software program. †Average values indicates the mean P value, Z_p, ES, r, and Z_r used in analyses. ANCOVA, analysis of covariance; BDI, Beck Depression Inventory; DSM, Diagnostic Interview Schedule and DSM-III-R criteria; HDRS, Hamilton Psychiatric Rating Scale for Depression; NV, authors did not provide enough information to calculate r; Zung, Zung Self-Rating Depression Scale.

ized ES (0.16; 95% CI 0.13–0.20). However, the residual standard deviation test of interstudy variance was statistically significant, indicating heterogeneity of variance in this aggregation of studies. This finding was not surprising given that studies with distinctly different designs and methods were included. Consequently, the studies were divided into cross-sectional (n = 26) and RCT (n = 5) subsets. The RCT subset was heterogeneous by all 3 tests of interstudy ES variance, and these studies were therefore not subjected to meta-analysis. The tests uniformly indicated that the cross-sectional

subset was homogeneous. The characteristics of these 26 studies are described in Table 1. Weighted and unweighted ESs, BESDs, fail-safe N's, and tests of ES variance are reported in Table 2 for all and for subsets of the cross-sectional studies.

Meta-analysis of the cross-sectional studies

Of the 26 cross-sectional studies, 10 (38.5%) examined the association of depression with GHb in patients with type 1 diabetes, 6 (23.1%) involved only patients with type 2 diabetes, and 10 (38.5%)

included a mixed sample of patients with type 1 or type 2 diabetes. Of the 26 studies, 20 (76.9%) used self-report questionnaires to assess depression, 5 (19.2%) used a structured diagnostic interview, and 1 (3.8%) used both methods. The mean sample size in the studies of type 1 patients was smaller but not statistically different from that in the studies of type 2 patients (93 vs. 144, P > 0.2), and neither of these were statistically different from the mean sample size (119) of the studies of subjects with either type 1 or type 2 diabetes. In these mixed-sample studies, roughly equal pro-

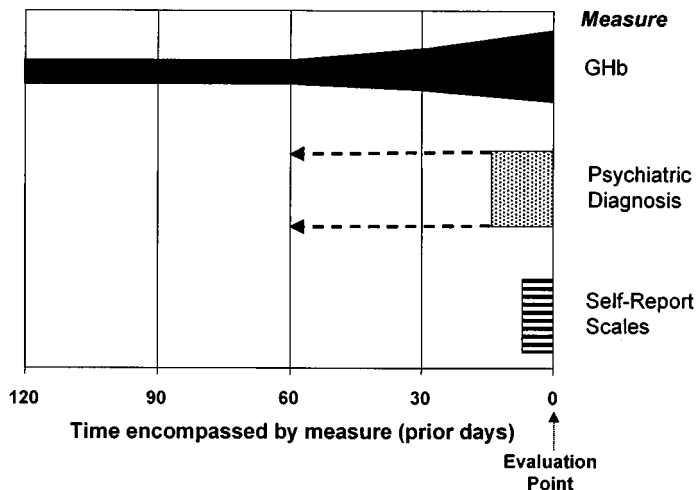


Figure 2—Time interval encompassed by a measure of glycemic control (GHb) in relationship to that of 2 depression assessment methods, psychiatric diagnosis and self-report inventories. GHb level is an integrated measure of glucose behavior over the previous 120 days, with the 60 days proximate to testing accounting for 75% of the variance in the measure. The criteria for the diagnosis of depression require that symptoms be present for no less than 14 days, and patients diagnosed with depression usually have had symptoms over a considerably longer interval, as depicted by the dotted arrows. Paper-and-pencil self-report measures usually assess the severity of depression symptoms over the preceding week.

portions of the subjects had type 1 versus type 2 diabetes (50.4 vs. 49.6%).

Twenty-four (92.3%) of the 26 cross-sectional studies provided enough information to calculate the individual ES. These 24 studies had a total of 2,817 subjects. The combined effect showed that depression was significantly associated with hyperglycemia ($Z = 5.4$, $P < 0.0001$). The standardized ES was small to moderate (0.17) and statistically significant (95% CI 0.13–0.21). ESs for the overall group and for homogeneous subsets are displayed in Fig. 1. The ES was similar in studies of type 1 compared with type 2 diabetes (ES: 0.19 vs. 0.16) and greater in studies that used interview-based diagnoses rather than self-report measures of symptom severity to assess depression (ES 0.28 vs. 0.15).

RCTs

Five studies were identified that measured the covariation over time of depression and glycemic control (33–37) with experimental perturbation of 1 of the variables. Although these studies did not meet the meta-analytic requirement of homogeneity, they provided additional data reflecting on the character of the depression–hyperglycemia association. The findings of the 5 studies are summarized in Table 3. Three of the RCTs were studies of psychological (cognitive behavior therapy) or psy-

chopharmacological (nortriptyline, fluoxetine) treatments for depression in adults with diabetes (33–35). In all 3 of these trials, the active treatment was significantly more effective than the control treatment in relieving depression. Treatment-related improvements in glycemic control were noted in 2 of the studies (33,35), and 2 of 3 studies reported that reduction in depression severity was directly associated with significant reductions in GHb (33,34).

The other 2 RCTs assessed the comparative efficacy of 2 diabetes interventions. In both trials, glycemic control was the primary dependent variable, and depression was a secondary (28) or ancillary (38) outcome measure. The first trial found no differences in GHb level between treatments (28). However, pre- to posttreatment changes in GHb and depression severity were correlated ($r = 0.46$, $P = 0.001$), showing that as metabolic control improved, so did depression, or vice versa. In the second study (38), participants were randomized to diet titration with either glipizide or placebo for 12 weeks. Glipizide-treated patients had significantly better glycemic control and less depression compared with placebo-treated patients ($P < 0.05$).

CONCLUSIONS—Belief in mind–body, or psychosomatic, associations is widespread. Many medical problems are

attributed by patients and physicians alike to mental stress or other psychosocial phenomena, but few of these relationships have been confirmed by rigorous scientific research. When an empirical association is reported, the psychosocial factor is usually related to a general medical outcome (e.g., depression and mortality from acquired immunodeficiency syndrome [39], hostility with increased risk of heart disease [40], and depression following myocardial infarction with increased morbidity and mortality [41–43]). When the association is made with a potential physiological mechanism (e.g., stress with natural killer cell toxicity, T-cell responses, and antibody production [44,45]), the ESs have been moderate, but perhaps more importantly, have often been difficult to interpret clinically (44).

Our meta-analysis used a specific physiological measure (GHb) as the marker of the somatic component. GHb is accepted as the best measure of recent glycemic control and is used to guide clinical management (46). Its relevance to the course of diabetes is well established (1). Small, persistent elevations in GHb significantly increase the risk of major complications of diabetes (2,47). The effect is most evident at the hyperglycemic range of possible glucose values. For example, a decrease in GHb of ~1.0% (from 9.5 to 8.5%) is associated with nearly a 33% reduction in the progression rate of retinopathy (48). Our meta-analysis indicates that depression is associated with higher GHb, i.e., with hyperglycemia. Although the ES of 0.17 demonstrates that depression accounts for a small amount (3%) of the variance in GHb, this is not trivial in practice. The BESD is a method for translating ES into useful clinical information. For example, extrapolated to the treatment of depression in a diabetic population, our meta-analysis suggests that treatment of depression could potentially increase the proportion of subjects in good control from 41 to 58% in a diabetic population (30).

The ES was greater in studies that assessed depression using standardized interviews and criteria-based diagnoses rather than self-report measures of symptom severity, perhaps because the relationship may be stronger in patients with clinical than with subclinical depression. Self-report inventories are also less specific measures of depression, as elevated scores may be produced not only by depression but also by anxiety, general emotional distress, or medical illness. The difference may

also reflect better synchrony in the intervals assessed by the measures of depression and glycemic control (Fig. 2). GHb is a temporally weighted measure of mean blood glucose over the preceding 120-day period (49,17). In contrast, the diagnosis of major depression requires that symptoms be present and severe over at least the previous 14 days, and self-report depression measures typically assess mood state over the previous 7 days (50). The reliability of self-report measures over a 120-day interval is low, particularly in psychiatric samples (51).

This meta-analysis confirms the association of depression with hyperglycemia but reveals neither the mechanism nor the direction of the association. Depression may be a cause or a consequence of hyperglycemia; the causal mechanisms underlying these pathways may or may not be the same; and both the direction and the mechanism may vary over time, between episodes, and both between and within individuals. Cross-sectional studies are not methodologically capable of establishing directional effects. The RCTs are potentially more informative. Within these trials, 1 variable (depression or glycemic control) is experimentally perturbed through treatment, and effects on the other variable may be studied as a function of treatment or in relation to change in the variable that is the primary target of treatment.

In 2 of the 3 antidepressant trials, improvement (reduction) in depression was significantly associated with improvement (reduction) in GHb (33,34). In the third trial, treatment with fluoxetine (35) had beneficial effects on GHb, but these effects were independent of changes in depression. In both trials of antihyperglycemic agents, treatment-related improvements in glycemic control were paralleled by improvements in depression (38,28). These findings support the hypothesis of a reciprocal interaction between depression and glycemic control wherein depression may produce hyperglycemia and hyperglycemia provoke depression. Further studies are needed that test this hypothesis more directly.

Publication bias is a threat to the generalizability of meta-analytic reviews and exists if the outcome of recovered studies differs from unpublished reports because results had affected the likelihood of publication (52). The fail-safe *N* was 57, and thus the possibility of some publication bias could not be excluded (27). The likelihood of bias was perhaps diminished because many of the studies were not dri-

ven specifically by a depression-glycemic control hypothesis. In most of the studies, depression was only 1 of a number of psychosocial and behavioral variables studied in relation to glycemic control.

Because the meta-analysis demonstrates that depression is associated with hyperglycemia, a claim is supported that psychosomatic interactions are at work in patients with type 1 or type 2 diabetes. The ES was modest, consistent, and clinically important. Data from the clinical trials support the depression-hyperglycemia association, highlight the possibility of their reciprocal interaction, and suggest that treatment of major depression may be beneficial to both mood and glycemic control. Additional studies are needed to determine the actual gain in medical outcome that can be attained through long-term depression management in diabetes.

Acknowledgments — This study was supported in part by grants from the National Institutes of Health, DK 36452 and DK 553060 from the National Institute of Diabetes and Digestive and Kidney Diseases, and 5 T32 HL07456-18 from the National Heart, Lung, and Blood Institute.

The authors thank Joseph Rossi, PhD, for providing consultation on meta-analysis procedures and Ralf Schwarzer for making his software for meta-analysis available without cost via the Internet at: http://www.yorku.ca/faculty/academic/schwarze/meta_e.htm.

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