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Psychosocial factors contributing to persistent depressive symptoms in type 2 diabetic patients: A Croatian survey from the European Depression in Diabetes (EDID) Research Consortium

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Abstract

Objective: The study was aimed at exploring a one-year course of depression in persons with type 2 diabetes and analysing demographic, disease-related and psychological variables that may predict persistent depressive symptoms. **Patients and methods:** One hundred patients from a randomly selected sample of 470 outpatients were found to be suffering from severe depressive symptoms. They were followed and re-examined for depression after one year. Baseline depression was assessed by the Center for Epidemiologic Studies-Depression scale (CES-D) and a face-to-face diagnostic interview relying on the DSM-IV. Non-parametric tests for between-group differences were used to compare patients who recovered from depression with those who still suffered from severe depressive symptoms. Multiple logistic regression was used to determine predictors of depression persistence. **Results:** Seventy-nine of 100 patients with baseline depression scores indicative of severe depression were reached at one-year follow-up. Among them, 53% were shown to have improved depressive symptoms to CES-D <16, while 47% continued to suffer from severe depressive disturbances (CES-D≥16). Logistic regression analysis indicated that psychosocial variables predicted persistently elevated depressive symptoms better than demographic and diabetes-related ones. Clinical depression at baseline (OR =3.8 /CI 1.31-10.98/ p=0.01), diabetes-related distress (OR=3.3 /CI 1.01-10.98/ p=0.05), and social and physical quality of life aspects (OR=0.92 /CI 0.88-0.97/ p=0.0005 and OR=0.94 /CI 0.90-0.98/ p=0.002 respectively) were shown to be independent predictors of one-year depression outcomes. **Conclusions:** Severity of baseline depression, a degree to which depression disrupted the patients' quality of life, and concomitant emotional problems related to diabetes were shown to be associated with persistently elevated depressive symptoms.

Key words: depressive symptoms, type 2 diabetes, diabetes-related distress, quality of life, persistence of depression

1. Introduction

There is a growing body of research on the relationship between diabetes mellitus and mood disorders aimed at understanding the interplay of somatic and psychological processes, and hypothesizing mechanisms that may explain it. It has been supposed that diabetes-depression comorbidity may be due to the psychosocial burden of diabetes, biochemical changes related to diabetes and its treatment, or to a coincident occurrence of two highly prevalent diseases (Lustman et al., 1992) A rewiev article by Talbot et al. (2000) indicated that psychosocial burden of having diabetes is a plausible explanation of the relationship between diabetes and depression, although this relationship may be bidirectional as well. A meta-analysis of longitudinal studies on depression as a risk factor for the onset of type 2 diabetes (Knol et al., 2006) has indicated that depressed adults have a 37 percent increased risk of developing diabetes.The underlying pathophysiological mechanisms remain to be determined. Examining independent factors associated with depressive disorders in diabetes Egede et al. (2003) have found that perceptions about the effect of diabetes on overall health seem to play an important role in the etiology of depression in addition to other psychosocial factors such as age, gender, education and socioeconomic status. Perceived lack of control and illness intrusiveness have also been found to be associated with the development of depression in diabetic patients (Talbot et al., 1999).

The analysis of predictors of depression in a randomly selected sample of Croatian diabetic patients has shown that psychological factors are more strongly associated with the development of depressive symptoms than the disease-related variables. The psychological factors comprised variables referring to psychological well-being, subjective limitations due to emotional problems, and experienced social support (Pibernik-Okanovic et al., 2005).

Research has shown that the prevalence of clinical depression in diabetic patients is approximately twice as high as in the general population (Anderson et al., 2001). Women, minorities and patients with lower socioeconomic status or physical disability are particularly at risk (Fisher et al., 2001). In persons with diabetes depression has been shown to be associated with poor self-care (Ciechanowsky et al., 2000) and increased risk of developing diabetes complications, including heart disease and cerebral infarction (De Groot et al., 2001). Comorbid depression in diabetic patients increases the risk of developing physical diseases, the need for health care and corresponding health care costs (Penninx et al., 1998; Greenberg et al., 1993).

Once diagnosed, depression was shown to be recurrent in persons with diabetes (Lustman et al., 1988; Peyrot et al., 1997). Patients with more diabetes-related complications, non-insulin treated and less educated ones are more likely to suffer from persistent depressive disturbances (Peyrot et al., 1999).

In addition to demographic and disease-related variables psychological factors may also be hypothesized to affect the course of depression in diabetic patients. A recent cross-cultural study by Pouwer et al. (2005) demonstrated that diabetes-specific emotional problems as measured by the Problem Areas in Diabetes scale (Welch et al., 1997) are particularly prevalent in depressed diabetic patients, suggesting possible interaction between depression and diabetes-related emotional distress. Whether specific vulnerabilities to the stress of living with diabetes affect long-term outcomes of depression remains to be determined.

This study was aimed at: 1) exploring one-year depression outcomes in patients found to be depressed by a random screening procedure for depression, and 2) determining predictors of persistent depressive symptoms at one-year follow-up.

2. Patients and methods

An observational study design with a one-year follow-up was used. The study was carried out at the Vuk Vrhovac University Clinic, a referral center for the registration, treatment and follow-up of patients with diabetes mellitus in Croatia.

The examined sample was found to be depressed among randomly selected diabetic outpatients (total number = 470) attending their regular check-ups. Patient records were marked one day prior to their scheduled appointment, at which patients' consent was requested. Psychological anamnesis and data on current life circumstances were collected by a semi-structured interview. Questionnaires assessing depressive symptoms (CES-D), problem areas in diabetes (PAID) and health-related quality of life (SF-12) were used to gain insight into the individuals' experience in living with their disease. Patients with CES-D scores ≥16 were invited for a psychiatric interview relying on Axis I disorders of the DSM-IV (SCID) to establish the clinical significance of their symptoms. If not already treated, clinically depressed patients with confirmed diagnosis of either major depressive episode or dysthymic disorder were informed about the importance and the possibilities of depression treatment. Patients with CES-D scores≥16, but not confirmed by SCID, were considered as subclinically depressed and advised to seek treatment if their symptoms were subjectively intolerable or got worse.

All patients with CES-D scores ≥16 were contacted by phone at 3-month intervals in order to check their current state and treatment seeking behavior, and re-examined for depression after one year. The retest CES-D scores <16 were considered indicative of improvement.

The participant flow diagram is presented in Figure 1.

Disease-related data were collected from the patients' files.

The study was approved by the Clinic's Ethics committee.

2.1. Measures

Depressive symptoms were measured by Center for Epidemiological Studies Depression (CES-D) scale (Radloff et al., 1986). This is a 20-item, self-report scale that asks respondents to indicate the frequency of experiencing each of the 20 symptoms over the previous week. The instrument uses a 4-point response scale ranging from «rarely or none of the time» to «most or all of the time» with total scores ranging from 0 to 60. Higher scores indicate more severe depressive symptoms. A cut-point of ≥16 was considered indicative of severe depression.

Diabetes-related emotional distress was assessed by the Problem Areas in Diabetes (PAID) questionnaire (Welch et al., 1997). This is a 20-item, self-report scale that asks respondents to rate how much of a problem they find each of the 20 diabetes-related issues. The answers are given on a 5-point scale ranging from 0 («not a problem») to 4 («serious problem»). The PAID scores are summed (with total scores ranging from 0 to 80) and transformed to a 0-100 scale with higher scores indicating more diabetes-related distress. Scores > 40 were considered indicative of high distress.

The PAID scale was translated to Croatian in accordance with the generally accepted rules (translating, backtranslating, piloting) prior to the study and applied to 157 patients with different disease characteristics. The performed psychometric analysis indicated the translated scale's good internal consistency and construct validity, as well as factor loadings comparable to the original scale (Cronbach's alpha=0.926; 3 factors explaining 42.6%, 6.6% and 6.1% of the variance, respectively).

Health-related quality of life was assessed by the SF-12 v2 questionnaire which comprises self-assessments of general health, physical functioning, physical roles, bodily pain, vitality, social functioning, emotional roles and mental health. The raw scores for particular subscales are transformed to a 0-100 scale with higher scores indicating better health-related quality of life (Ware te al., 1996).

Clinical significance of depressive symptoms detected by the questionnaire was determined by structured clinical interview for DSM-IV Axis I Disorders – Clinician Version (SCID-CV) (First et al., 2000) conducted by a psychiatrist.

HbA_{1c} was determined by an automated immunoturbidimetric method using Bayer reagents (Tarrytown, Il, USA) on Olympus AU600 analyser (Olympus Optical Co., Tokyo, Japan) with a normal range from 3.5 to 5.7% (Vucic et al., 1999).

2.2. Statistical analysis

Subgroups of patients with and without severe depressive symptoms at follow-up were compared using the Mann-Whitney U test. Predictors of depression were determined by using multiple logistic regression with retest CES-D score <16 vs ≥16 as a dependent variable, and demographic (gender, age, education, economic status), disease-related (diabetes therapy, body mass index, glycemic regulation, concomitant diseases, presence/absence of a clinical diagnosis of depression at baseline) and psychological variables (quality of life and diabetes-related distress) as independent variables. Three subsequent models of hypothetical predictors were tested: Model 1 containing demographic and disease-related variables, i.e. gender, age, insulin therapy, BMI, concomitant diseases, glycemic control, education, economic status and baseline severity of depression; Model 2 comprising variables included in Model 1+PAID scores ; and Model 3 including Model 1+SF-12 scores. The last model was tested by adding SF-12 subscales to variables from Model 1 one at a time. Social functioning and Role physical subscales were observed as having the highest predictive value and were for this reason analysed in Model 3. The underlying rationale for using three different models was to a) check predictive value of demographic and disease-related factors known from the literature (Model 1), b) examine a hypothetical contribution of diabetes-specific distress to

persistent depressive symptoms (Model 2), and c) examine a hypothetical contribution of diabetes non-specific quality of life to persistently elevated depressive symptoms (Model 3).

3. Results

Seventy-nine patients with baseline CES-D scores ≥16 were reached at one-year follow-up. The attenders did not differ from non-attenders with respect to gender, age, education, duration of diabetes, diabetes therapy, body mass index, glycemic control and baseline CES-D scores (all $P>.05$).

As presented in Table 1, 53% (N=42) of the initially depressed patients reached at follow-up improved their depressive symptoms, while 47% (N=37) remained above the cut-off. Patients who recovered from severe depressive symptoms and those still severely depressed were of comparable age (p=0.73), sex distribution (p=0.38), education (p=0.53), diabetes duration (p=0.91) and insulin treatment (p=0.93). They did not differ in the number of concomitant diseases (p=0.39), BMI (p=0.30), HbA_{1c} (p=0.96), and the presence of cardiopathy (p=0.91), neuropathy (p=0.80) and retinopathy (p=0.87). Comparable proportions of patients from the two groups reported previous psychological problems (p=0.36). There was no significant difference in proportions of patients from the two groups who were treated for psychological problems at baseline (p=0.22) and during the follow-up period (p=0.27). A tendency towards poorer economic status was indicated in the group with persistent depression, but was not statistically significant (p=0.07).

The patients with persistent symptoms had higher baseline CES-D scores (p<0.001), were more frequently classified as clinically depressed (p<0.01), and had lower baseline scores at all SF-12 subscales excepting Mental health subscale (Physical functioning p= 0.001; Role physical p=0.0001; Bodily pain p=0.01; General health p=0.005; Vitality p=0.04; Social functioning p=0.0005; Role emotional p=0.02; Mental health p=0.16). Although a higher

level of diabetes-related distress was observed in the group with persistent depressive symptoms, a statistical significance was not reached (p=0.20). However, the proportion of patients with baseline PAID scores above the median of the entire group was significantly higher in the persistently depressed group (p=0.05).

As presented in Table 2, Model 1 including demographic and disease-related variables was not shown to predict one-year depression outcomes as a whole (χ^2=10.8 p= 0.37 Nagelkerke R^2= 0.167). However, baseline severity of depression, defined as either the presence or absence of clinical diagnosis of depression, independently predicted persistence of or recovery from depressive symptoms (Wald's χ^2=6.32 p=0.01 OR =3.8 CI 1.31-10.98). More severe baseline depressive symptoms, i.e. a clinical diagnosis of either major depressive episode or dysthymia was shown to increase the possibility of persistent depressive symptoms after a one-year follow-up.

Model 2, integrating demographic and disease-related variables with the PAID scores, did not reach statistical significance as a whole. Nevertheless, the variance it explained increased in comparison with Model 1 (χ^2= 14.9 p= 0.19 Nagelkerke R^2=0.229). PAID scores above the median of the whole group were shown to independently predict persistent depressive symptoms (Wald's χ^2= 3.9 p=0.05 OR=3.3 CI 1.01-10.98), indicating that very severe diabetes-related distress in addition to depression increased the likelihood of suffering from persistent depressive disturbances.

Model 3, integrating demographic and disease-related variables with social and physical quality of life scores, was shown to significantly predict one-year outcomes, i.e. persistent vs improved depressive symptoms (χ^2= 47.25 p<0.00001 Nagelkerke R^2= 0.499). Both Social functioning and Role physical subscales independently predicted persistently elevated depressive symptoms (OR= 0.92; CI 0.88-0.97 p=0.0005 and OR= 0.94 CI 0.90-0.98

p=0.002, respectively), indicating that better diabetes non-specific quality of life was shown to have a protective role and diminished the likelihood of persistent depressive symptoms.

4. Discussion

The obtained data demonstrated that depressive mood was persistent in a considerable proportion of the examined sample – approximately half of patients found to be depressed at baseline had CES-D scores indicative of pervasive depression at the one-year follow-up. Even the patients who improved depressive symptoms scoring to less than 16 at the follow-up CES-D scale may be considered to have residual symptoms that include an increased risk from depression recurrence (Keller, M.B., 2004).

The obtained indicators of persistent depressive symptomatology are in accordance with other published data suggesting that depression is an ongoing disease in patients with diabetes. The study by Lustman et al. (1997) has demonstrated that patients diagnosed with major depression had an average of 5 episodes during a 5-year follow-up period. The recurrence rate in the first year was high even in patients who improved their mood during a placebo controlled trial of nortriptilyne. Persistence of depressive symptoms was also found in a substantial proportion of subclinically depressed patients, accompanied by a slight tendency to adversely affect glycemic control (Hermanns et al., 2004).

The study by Peyrot et al. (1999) has demonstrated that 13% of the examined adults with diabetes were persistently depressed at three time points during a six-month follow-up period. This relatively small proportion could be due to the coping skills training the examined patients received as part of the psychoeducational intervention.

Twenty-four percent of patients who improved their depressive symptoms and 38% of those with persistent severe symptoms were treated by antidepressant therapy between the baseline and the follow-up assessment. The small proportion of treated patients may suggest that patients' readiness to accept treatment recommended at baseline was relatively low. Since not

all, but only clinically depressed patients were encouraged to engage in depression therapy, the compliance rate is actually higher – approximately 60% of the patients accepted recommended treatment, while some of the subclinically depressed patients sought professional help on their own. This suggests that screening patients for depression and encouraging them to take care of it may increase the currently low response rates to depression treatment in diabetic population (Rubin et al., 2004).

Persistent depression in the examined sample was not shown to be associated with demographic and disease-related variables (gender, age, education, economic status, duration of diabetes, diabetes treatment, glycemic control, presence of diabetes complications and concomitant diseases), all of which were comparable in both patients who recovered from depression and those who persisted in severe depressive symptoms. This is not quite in accordance with the previously reported findings indicating that poorly educated patients, those with more than two complications and non-insulin treated ones were more likely to persist in depressive symptoms (Peyrot et al., 1999). In the intervention study by Lustman et al., (1998), nonremission of depression was associated with lower compliance with blood glucose monitoring, higher glycated hemoglobin, higher weight and a history of depression. However, diabetes control and psychological anamnesis were not shown to be discriminative in our subgroups with different outcomes. What did count in the one-year course of depression was the baseline severity of depression defined in terms of clinical diagnosis, emotional problems due to diabetes, and the extent to which depression ruined the individuals' quality of life, particularly their physical and social functioning.

Perceived health-related quality of life varies in patients with comparable health conditions. Published results have indicated that depression is significantly related to self-reported quality of life even when differences in physical health and age have been statistically controlled for (Kohen et al., 1998). Our results have shown that the interaction between depression and

quality of life in patients with diabetes can be hypothesized to be associated with persistence of depression as well. Perceived quality of life seems to have a protective role with respect to depression persistence. Persisent symptoms seemed less likely in individuals whose subjective quality of life was less disrupted by depressive symptoms than in those with more negative depression : quality of life interaction. This particularly referred to the individuals' social functioning, and the degree to which they perceived their physical roles as being limited. The groups' comparability regarding both diabetes- and concomitant diseases' status suggests that subjective rather than objective health status may play a role in experiencing a long time depression.

Baseline severity of depression defined either as clinical diagnosis of depression or subclinical depressive symptoms was shown to predict the persistence of depression as well. Clinical cases are more likely to suffer from prolonged depressive symptoms than the subclinical ones. Suprisingly, one-year depression outcomes were not associated with depresion treatment. Patients found to be clinically depressed at baseline were encouraged to engage in depression therapy. Approximately 60% of them accepted the recommendation and were pharmacologically treated during the follow-up period. Probably due to the small number of patients in the two groups (15 treated vs 11 not treated), the treated patients did not reveal significantly better outcomes, although a tendency towards an improvement was indicated in the treated individuals.

Diabetes-related distress was shown to be associated with long-term depression outcomes in addition to its baseline severity and impact on quality of life. Depressed patients are generally more likely to experience serious diabetes-related emotional problems (Pouwer et al., 2005). Whether diabetes-related distress increases the possibility to develop depressive symptoms, or depressive mood makes individuals more vulnerable to such a distress remains unanswered. Very likely, a two-way relationship between the two disturbances may be hypothesized.

Certainly, when present in depressed patients as a concomitant condition, diabetes-related emotional problems in addition to the severity of depression and subjectively perceived quality of life predict the course of depressive symptoms and are associated with long-term patients' outcomes.

In conclusion, the obtained results suggest that psychological factors are associated with the course of depressive symptoms in type 2 diabetic patients by making the symptoms persistent. This is especially true for factors that are connected with the examined individuals' subjective experience of diabetes and overall health condition,.

From a clinical point of view, these findings suggest that increased attention should be given to patients whose depressive disturbances are combined with serious emotional problems related to diabetes. Assessing diabetes-related distress in addition to assessing depressive symptoms may be recommended in order to better understand patients' needs and provide them with appropriate treatment. Depression treatment addressing specific diabetes-related problems may be expected to improve the outcomes.

The limitations of this study are a relatively small number of patients, and the fact that not all of them could be reached at the one-year follow-up. However, a random sampling procedure among patients regularly attending their outpatient visits, and the fact that patients who were not available at follow-up did not differ from the attenders, may support the validity of these findings.

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Figure 1: Participant flow diagram

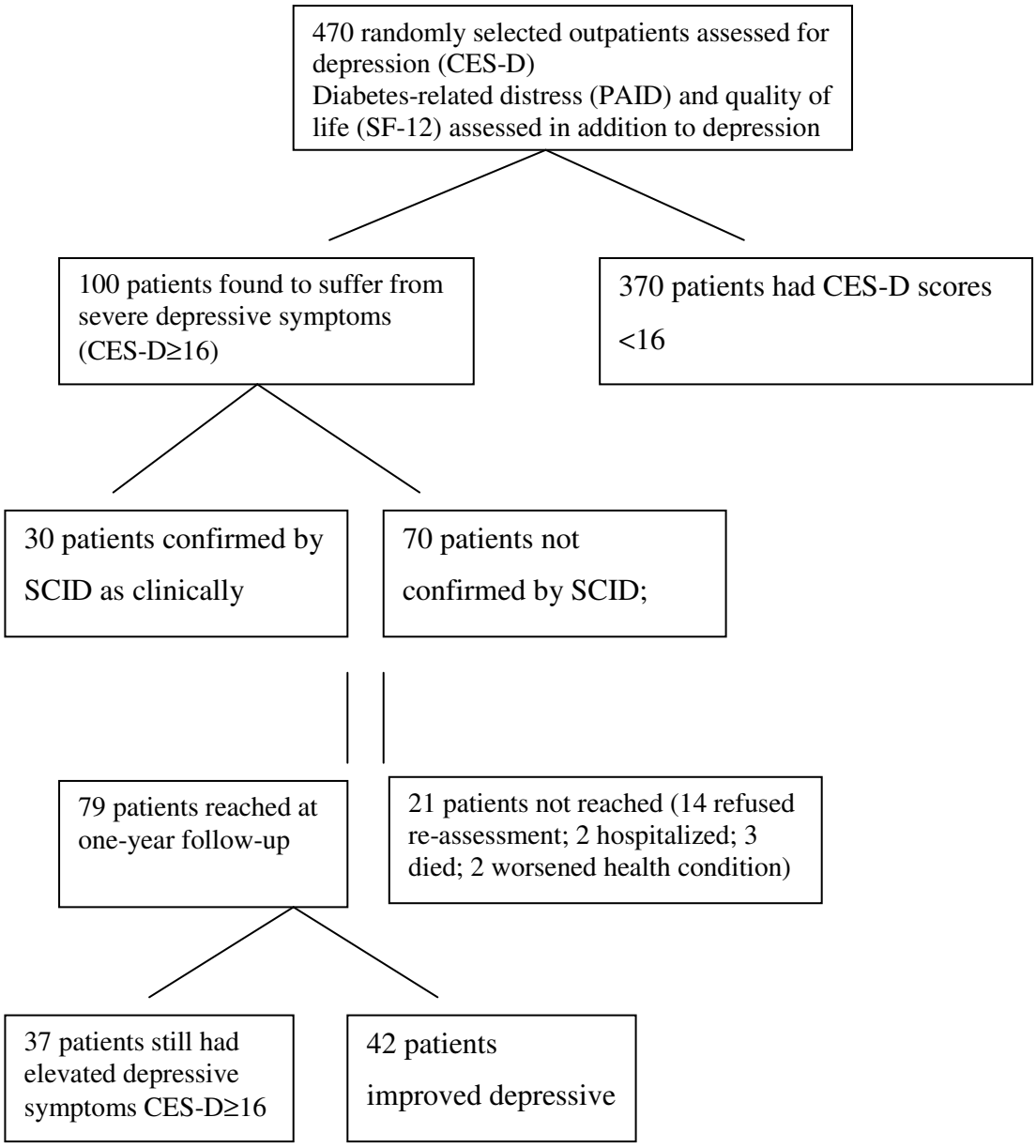

Table 1: **Comparisons between the group with depressive symptoms improved to CES-D<16 and the group with persistent CES-D scores ≥ 16**

	CES-D<16 n=42	CES-D≥16 n=37	*P*
% female	71	62	.38
Age	55 (50-63)	57 (53-61)	.73
Education (yrs)	11 (8-12)	11 (8-12)	.53
Socioeconomic status (% very poor)	21	41	.07
Duration of diabetes	9.5 (5-12)	9 (4-14)	.91
% insulin treated	52	51	.93
HbA1C at baseline	7.9 (7.2-8.9)	7.6 (6.8-9.4)	.73
HbA1C at follow-up	7.8 (6.8-8.4)	7.5 (6.7-9.4)	.96
Body mass index (kg/m^2)	29.2 (26.7-32.6)	28 (26-31)	.30
% with cardiopathy	29	30	.91
% with neuropathy	40	43	.80
% with retinopathy	28	27	.87
% with more than one concomitant disease	66	57	.39
% with previous psychological problems	60	70	.36
% receiving psychopharmaceuticals at baseline (not exclusively for depression)	43	57	.22
Baseline CES-D score	19 (16-26)	25 (22-35)	.0001**
% clinically depressed (SCID)	18	48	.001**
% treated for depression during the follow-up	24	38	.27
PAID scores	49 (35-62)	56 (36-68)	.20

% with PAID scores above 49 (the entire group's median)	21	29	.05*
Physical functioning (SF-12)	50 (50-75)	50 (25-50)	.001**
Role physical (SF-12)	50 (50-75)	50 (25-50)	.0001**
Bodily pain (SF-12)	75 (25-75)	25 (25-50)	.01**
General health (SF-12)	25 (25-61)	25 (0-25)	.005**
Vitality (SF-12)	50 (25-50)	25 (25-50)	.04*
Social functioning (SF-12)	75 (50-75)	50 (25-50)	.0005**
Role emotional (SF-12)	75 (50-75)	50 (38-50)	.02*
Mental health (SF-12)	50 (38-50)	38 (25-50)	.16
CES-D at follow-up	10 (7-13)	24 (19-31)	.0001**

Data are expressed as medians (interquartile range) or frequences. P values refer to either Mann-Whitney U test or χ^2 test.

Table 2: Logistic regression analysis of one-year depression outcomes: persistent vs improved depressive symptoms

Model 1	Coeff.	Standard error	Wald's χ^2	p value	Odds ratio	95% CI
Gender	-0.40	0.58	0.47	0.49	0.67	0.21-2.12
Age	0.0003	0.03	0.0001	0.99	1.00	0.94-1.06
Education	-0.04	0.09	0.20	0.66	0.96	0.80-1.15
Socioeconomic status	0.13	0.39	0.11	0.74	1.14	0.53-2.45
Insulin therapy	-0.12	0.29	0.16	0.69	0.89	0.50-1.58
Body mass index	-0.07	0.06	1.31	0.25	0.89	0.50-1.58
Concomitant diseases	0.36	0.42	0.74	0.39	1.43	0.62-3.29
HbA1C	0.12	0.24	0.24	0.62	1.12	0.70-1.80
Baseline severity of depression	**1.34**	**0.53**	**6.32**	**0.01**	**3.80**	**1.31-10.98**

The entire model's χ^2=10.8 p= 0.37 Nagelkerke R^2=.167

Model 2	Coeff.	Standard error	Wald's χ^2	p value	Odds ratio	95% CI
Gender	-0.53	0.60	0.78	0.38	0.59	0.18-1.96
Age	0.001	0.03	0.001	0.97	1.00	0.94-1.07
Education	-0.03	0.09	0.13	0.72	0.97	0.80-1.16
Socioeconomic status	-0.11	0.41	0.08	0.78	0.89	0.39-2.03
Insulin therapy	-0.18	0.31	0.35	0.56	0.84	0.45-1.54
Body mass index	-0.88	0.07	1.72	0.19	0.92	0.80-1.05
Concomitant diseases	0.34	0.43	0.61	0.43	1.40	0.59-3.32
HbA1C	0.14	0.24	0.33	0.57	1.15	0.71-1.88
Baseline severity of depression	**1.26**	**0.54**	**5.42**	**0.02**	**3.54**	**1.20-10.45**
PAID scores >49	**1.19**	**0.61**	**3.89**	**0.05**	**3.28**	**1.01-10.98**

The entire model's χ^2=14.86 p=0.19 Nagelkerke R^2=.229

Model 3	Coeff.	Standard error	Wald's χ^2	p value	Odds ratio	95% CI
Gender	-0.90	0.67	1.78	0.18	0.41	0.11-1.56
Age	0.05	0.05	1.41	0.23	1.06	0.96-1.16
Education	-0.22	0.13	2.81	0.09	0.80	0.61-1.04
Socioeconomic status	-0.71	0.55	1.65	0.20	0.49	0.16-1.49
Insulin therapy	-0.63	0.39	2.54	0.11	0.54	0.24-1.17
Body mass index	-0.11	0.08	2.24	0.13	0.89	0.77-1.04
Concomitant diseases	0.41	0.48	0.72	0.40	1.51	0.57-3.94
HbA1C	0.49	0.31	2.48	0.12	1.64	0.88-3.08
Baseline severity of depression	1.18	0.73	2.60	0.11	3.25	0.75-14.00
Role physical (SF- 12)	**-0.06**	**0.02**	**9.20**	**0.002**	**0.94**	**0.90-0.98**
Social functioning (SF-12)	**-0.08**	**0.02**	**11.87**	**0.0005**	**0.92**	**0.88-0.97**

The entire model's χ^2=47.25 p<0.000001 Nagelkerke R^2=.499

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