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Original Article: Education and psychological aspects

Predictors of incident major depression in diabetic outpatients with subthreshold depression

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Abstract

Aims The objective of the study was to determine rates and risks of major depression in diabetes outpatients with subthreshold depression.

Methods This study is based on data of a stepped care-based intervention study in which diabetic patients with subthreshold depression were randomly allocated to low-intensity stepped care, aimed at reducing depressive symptoms, or to care as usual. Patients had a baseline Center for Epidemiologic Studies Depression Scale (CES-D) score ≥ 16 , but no baseline major depression according to the Mini International Neuropsychiatric Interview (MINI). Demographic, biological and psychological characteristics were collected at baseline. The MINI was used to determine whether participants had major depression during 2 year follow-up. Predictors of major depression were studied using logistic regression models.

Results Of the 114 patients included at baseline, 73 patients were available at 2 year follow-up. The 2 year incidence of major depression was 42% ($n = 31$). Higher baseline anxiety levels [odds ratio (OR) = 1.25; 95% confidence interval (CI), 1.04–1.50; $P = 0.018$] and depression severity levels (OR = 1.09; 95% CI, 1.00–1.18; $P = 0.045$) were predictors of incident major depression. Stepped care allocation was not related to incident major depression. In multivariable models, similar results were found.

Conclusions Having a higher baseline level of anxiety and depression appeared to be related to incident major depression during 2 year follow-up in diabetic patients with subthreshold depression. A stepped care intervention aimed at depression alone did not prevent the onset of depression in these patients. Besides level of depression, anxiety might be taken into account in the prevention of major depression in diabetic patients with subthreshold depression.

Diabet. Med. 27, 1295–1301 (2010)

Keywords diabetes mellitus, incidence, major depression, subthreshold depression

Abbreviations CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; EPQ-N, Eysenck Personality Questionnaire – Neuroticism; HADS(-A), Hospital Anxiety and Depression Scale (Anxiety subscale); HbA_{1c}, glycated haemoglobin; ICD-10, International Classification of Diseases, Tenth Revision; MINI, Mini International Neuropsychiatric Interview; OR, odds ratio; PAID, Problem Areas in Diabetes scale; STEPPED, Stepped Treatment of Emotional Problems in Patients with Established Diabetes

Introduction

Major depression is a common, burdensome disease in patients with diabetes [1,2]. Among patients with diabetes, depression is associated with less optimal glycaemic control, more diabetes complications, reduced quality of life and increased mortality

[3–6]. Although subthreshold depression is a significant risk factor for major depression in the general population [7,8], not all persons with subthreshold depression will develop a full-blown depression. It is useful to know which characteristics of persons are associated with incident major depression in order to target preventive interventions. Until now, most studies focusing on risk factors for depression in diabetic patients had a cross-sectional design and relied on self-reported measures of depression. For instance, it was demonstrated that female sex, younger age, low education, being unmarried, high body mass

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index, smoking, higher co-morbidity and treatment with insulin were associated with depressive symptoms in diabetic patients [9]. Only a handful of longitudinal studies have investigated persistent or incident depression in diabetic patients. Accumulating evidence suggests that persistent depression is frequently observed in diabetic patients [10,11], in particular in patients who have more diabetes complications, are not treated with insulin and are less educated [11]. Pibernik-Okanovic *et al.* [12] showed that emotional factors were better predictors for 1 year persistence of depression in diabetic patients than demographic or diabetes-related variables. They found that clinical depression at baseline, diabetes-related distress and social and physical quality of life aspects predicted the existence of depression after 1 year in diabetic patients with subthreshold depression [12]. However, little is known about the risk factors that predispose diabetic patients with subthreshold depression to a major depression.

The goal of the present study was twofold: (1) to explore the risk factors for incident clinical major depression during a 2 year follow-up period in diabetic patients with subthreshold depression; and (2) to evaluate whether a relatively simple, stepped care intervention focused on depressive symptoms alone would affect this risk.

Patients and methods

Patients and setting

The present study was part of the Stepped Treatment of Emotional Problems in Patients with Established Diabetes (STEPPED). STEPPED is a randomized controlled trial testing the effects of a stepped care intervention for diabetic patients with elevated depressive symptoms vs. care as usual. Participants of STEPPED were recruited from May 2004 until August 2005 from the following four diabetes outpatients clinics in the north of the Netherlands: Academic Hospital of Groningen, Groningen; Martini Hospital, Groningen; Wilhelmina Hospital, Assen; and Medical Centre Leeuwarden Zuid, Leeuwarden. Inclusion criteria for participation in STEPPED were age ≥ 55 years, diabetes (Type 1 or Type 2) and a score of ≥ 16 on the Center for Epidemiologic Studies Depression Scale (CES-D). Exclusion criteria were insufficient mastery of the Dutch language, currently receiving psychiatric treatment and having a life expectancy of < 1 year.

Potential participants were mailed an invitation letter for the study. The CES-D [13] was mailed to participants to assess self-reported symptoms of depression. One hundred and thirty-one participants met the inclusion criteria of the study and agreed to participate. All participants gave written informed consent. Patients were followed up for 2 years. For this study, we aimed to explore predictors of incident major depression during 2 year follow-up. Therefore, we excluded all participants with a major depression at baseline ($n = 9$) and those whose clinical status of major depression could not be determined ($n = 8$). Baseline major depression was assessed with a face-to-face Mini

International Neuropsychiatric Interview (MINI) [14]. The MINI is a brief and reliable structured diagnostic instrument based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and the International Classification of Diseases, Tenth Revision ICD-10, with an administration time of approximately 15 min [14].

Measures

Outcome measure

The primary outcome measure of the study was the incidence of major depression during 2 year follow-up. First, this was determined with the MINI at 2 year follow-up [14], which was administered by telephone. For the purpose of the present study, an adaptation of the MINI was made so that the presence of major depression could be determined in the time frame of 2 years, using the Life Chart method as developed by Lyketsos *et al.* [15].

Secondly, depression severity after 2 years was assessed with the CES-D questionnaire [13], assessing depressive symptoms in the previous week. A total score between 0 and 60 can be obtained. Higher scores reflect higher depressive symptom severity. The questionnaire has good psychometric properties, also in older persons [16].

Independent variables

The selection of the potential predictors was based on the literature and availability in the study. At baseline, demographic, biological and psychosocial predictors were measured. Age, sex, educational level, marital and cohabitation status, nationality and type of diabetes were obtained during an interview. Blood was sampled at baseline to assess glycated haemoglobin (HbA_{1c}). Furthermore, participants received a questionnaire to be completed at home. Apart from age and sex, the following measures were included as possible predictors of incident depression.

Stressful life events were measured with a list of 16 threatening events based on the List of Threatening Events [17]. Participants were asked which events they experienced in the last year. The number of life events in the last year was summed and categorized into 0, 1 and ≥ 2 life events.

Co-morbid chronic illness(es) were determined by self-report, using a list developed by the Dutch National Institute of Statistics (Statistics Netherlands), comprising the 25 most prevalent chronic illnesses. Patients were asked whether they had the chronic disease in the last year. The total number of chronic co-morbidities was calculated and classified into < 3 co-morbidities and ≥ 3 co-morbidities.

Depression severity was assessed at baseline with the CES-D [13].

Anxiety was assessed with the seven-item Hospital Anxiety and Depression Scale Anxiety subscale (HADS-A) [18]. The HADS-A is suitable for use in patients with a chronic disease. This instrument has been developed to measure cognitive symptoms of anxiety, as somatic symptoms of anxiety such as trembling can overlap with symptoms of a concurrent medical problem (e.g. hypoglycaemia) [18]. A score of 0–21 can be

obtained. Higher scores reflect more anxiety symptoms. Anxiety was used as a continuous measure and as a dichotomized variable (≥ 11) to indicate probable anxiety pathology, based on previously determined criteria [18].

Diabetes-specific emotional distress was assessed with the 20-item Problem Areas In Diabetes scale (PAID) [19]. Scores on the PAID items were summed and transformed to a 0–100 scale, with higher scores indicating higher levels of diabetes-specific emotional distress.

Neuroticism or emotional instability was assessed with the 12-item neuroticism subscale of the Revised Eysenck Personality Questionnaire (EPQ-N) [20]. The total score reflects the patient tendency to personality trait of neuroticism, which is considered to signal a person's vulnerability to internalizing mental disorders, including anxiety and depression [21].

Intervention vs. care as usual

We also investigated whether the intervention of the randomized controlled trial influenced depression outcome. Participants of STEPPED were randomly assigned to either stepped care or care as usual. Participants assigned to the intervention group entered a stepped care intervention, based on their initial level of depression according to the MINI. Patients with symptomatic depression (no depression diagnosis on the MINI) entered the programme at step 1 (watchful waiting/bibliotherapy), patients with minor depression on the MINI entered the programme at step 2 (cognitive behavioural interventions by a non-specialist). Patients with major depression entered the programme at step 3 (mental health specialist intervention), but were excluded from the present analyses because we investigated the incidence of major depression. Each step lasted 12 weeks. When no improvement was observed (CES-D score ≥ 16 or did not decrease at least 5 points), the patient entered a higher step for another 12 weeks, until improvement was observed. The control group received care as usual during the study, in which antidepressants or psychotherapy were treatment possibilities. To take possible effects of the intervention on incident major depression into account, we included the intervention allocation as a predictor.

Statistical analysis

We compared the baseline characteristics of patients whose major depression status could be determined after 2 years and the drop-outs using Student's *t*-tests and χ^2 tests. Predictors of incident major depression during 2 year follow-up were tested in univariable and multivariable (adjusted for age and sex) logistic regression analyses. The following baseline predictors were tested: sex, age, type of intervention (stepped care intervention vs. care as usual), number of co-morbid chronic diseases, number of stressful life events, HbA_{1c}, depression severity, anxiety severity, diabetes-specific emotional distress and neuroticism. The assumption that continuous variables are linearly related to the logit was checked with the Box–Tidell transformation [22] and met for each continuous variable, except for age. Therefore, age was categorized into tertiles (55–59, 60–66 and 67–88 years).

Furthermore, we conducted univariable and multivariable (adjusted for age and sex) linear regression analyses with the CES-D score at 2 year follow-up as dependent outcome. The independent variables used in these analyses were similar to the independent variables in the logistic regression analyses. The statistical assumptions for linear regression were checked and were met for all models. All the data were analysed using SPSS version 17 (SPSS Inc., Chicago, IL, USA). The *P*-value for statistical significance was set at 0.05.

Results

For the present study, 114 patients were eligible at baseline. Table 1 presents baseline characteristics of these patients. The average age was 65 years, and 54% were male. Most patients (81%) had Type 2 diabetes. Although the patients described in Table 1 did not fulfil the criteria for major depression, the average CES-D score was relatively high (mean score 24; SD 8). The majority of the patients assigned to the stepped care intervention started with watchful waiting ($n = 48$, 83%). The baseline characteristics shown in Table 1 did not differ between the intervention and care as usual group.

Of the 114 persons available at baseline, 73 were available at 2 year follow-up (64%). Twenty-four patients could not be reached, 14 participants refused further participation, and three participants died during the follow-up. Persons who dropped out were on average older and had more often a low education level. For the other variables presented in Table 1, no differences were observed between those who dropped out and those who did not.

Incidence of major depression

The incidence of major depression during 2 year follow-up was 42% ($n = 31$). In the univariable logistic regression models (Table 2), baseline depression severity was related to the onset of major depression [odds ratio (OR) = 1.08; 95% confidence interval (CI), 1.00–1.18; $P = 0.05$]. In addition, both continuous and dichotomized baseline anxiety scores were significant predictors of incident major depression (OR = 1.25; 95% CI, 1.04–1.50; $P = 0.02$; and OR = 5.50; 95% CI, 1.48–20.39; $P = 0.01$, respectively). Type of intervention (stepped care or care as usual) was not related to the incidence of major depression during 2 year follow-up (OR = 1.25; 95% CI, 0.49–3.18; $P = 0.64$). Furthermore, sex, age, number of co-morbidities, number of stressful life events, HbA_{1c}, diabetes-specific emotional distress score and neuroticism score did not significantly predict the incidence of major depression during 2 year follow-up. After adjustment for age and sex in multivariable models, similar results were found (Table 3).

Additional analyses

To investigate the possibility of a differential effect of the intervention on major depression for persons with high levels of

Table 1 Baseline characteristics of the diabetic patients with subthreshold depression who participated in the randomized clinical trial ($n = 114$)

	n^*	Percentage
Female	52/114	46
Male	62/114	54
Intervention	58/114	51
Care as usual	56/114	49
Educational level		
Primary school	18/111	16
Secondary (vocational) education	74/111	67
Higher education (college/university)	19/111	17
Marital status		
Married or living together	72/111	65
Never married	6/111	5
Divorced	12/111	11
Widow	21/111	19
Dutch nationality	111/111	100
Diabetes Type 1	20/105	19
Diabetes Type 2	85/105	81
Co-morbidities†		
0	4/90	4
1	12/90	13
2	13/90	14
≥ 3	61/90	68
Stressful life events		
0	27/74	37
1	24/74	32
≥ 2	23/74	31
Probable anxiety (HADS-A score ≥ 11)	22/91	24
Increased diabetes-specific related distress (PAID score ≥ 40)	22/75	29
	n	Mean (SD)
Age	114	65.3 (8.2)
Depression severity (CES-D score)	114	24.5 (6.8)
Glycated haemoglobin	101	7.5 (1.1)
Depression severity (HADS-Depression score)	91	8.1 (4.0)
Anxiety level (HADS-A score)	91	8.3 (3.4)
Diabetes-specific related distress (PAID score)	75	29.4 (19.0)
Neuroticism (EPQ-N score)	89	5.9 (2.8)

*The first number denotes the number of participants in the category; the second number denotes the total response on the variable.

†Based on 25 common chronic diseases in adults.

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; EPQ-N, Eysenck Personality Questionnaire – Neuroticism; HADS, Hospital Anxiety and Depression Scale; and PAID, Problem Areas in Diabetes scale.

anxiety and depression, we first compared the baseline levels of anxiety and depression of the two groups, and second included the interaction term of Anxiety*Randomization and Depression*Randomization, respectively, in the logistic regression model. Baseline anxiety and depression scores did not

significantly differ between the intervention and care as usual group. No significant interaction was observed between level of anxiety and intervention and depression and intervention for incident major depression.

Depression severity

For 57 persons (50% of the eligible study population at baseline), the CES-D score for depression severity at 2 year follow-up was available. The onset of major depression during 2 year follow-up and the CES-D score at 2 year follow-up were correlated (Pearsons' $r = 0.48$, $P < 0.001$). Table 4 shows the results of the univariable linear regression analysis for predictors of the CES-D score at 2 year follow-up. Again, anxiety was a significant predictor of depression severity either as a continuous variable (regression coefficient = 1.16; 95% CI, 0.38–1.93; $P = 0.004$) or as dichotomized variable (regression coefficient = 7.07; 95% CI, 1.42–12.71; $P = 0.015$). Intervention allocation was not associated with depressive symptoms at 2 year follow-up (regression coefficient = 1.78; 95% CI, –2.61 to 6.17; $P = 0.42$). Similar associations were found in multivariable analyses (Table 5). In addition, neuroticism score became a statistically significant predictor.

Discussion

This explorative, longitudinal study showed that more than 40% of the diabetic patients with co-morbid subthreshold depression developed a major depression during a 2 year follow-up period. Besides depression severity, higher levels of anxiety appeared to be a significant predictor for the onset of major depression during 2 year follow-up. In additional analyses, with depression severity score after 2 years as outcome measure, anxiety remained significantly related to depression. Whether patients were allocated to a low-intensity stepped care intervention aimed at reducing depressive symptoms or to care as usual was not predictive of incident major depression during 2 year follow-up.

Overall, few studies have investigated risk factors for incident major depression longitudinally. Cuijpers *et al.* [23] studied risk factors for the onset of depression in non-diabetic participants with a subthreshold depression in the primary care. A family history of depression and the presence of chronic illness were related to incident major depression in persons with subthreshold depression, after adjusting for potential confounders [23]. In addition, higher depression symptomatology and neuroticism were associated with increased incident depression in univariable analyses. In our sample we also observed that higher depression severity was a risk factor for subsequent major depression.

In contrast to Cuijpers *et al.* [23], all participants in our study had a chronic disease (diabetes). No significant relationship between additional co-morbid chronic illnesses and incident major depression was observed. Possibly, the existence of a chronic illness is more important than the number of chronic illnesses, but our lack of association might also be related to the small amount of variation on this variable combined with a small

Table 2 Univariable logistic regression with baseline predictors for clinical major depression during 2 year follow-up according to the MINI

	<i>n</i>	Wald	OR*	95% CI	<i>P</i> -value	<i>r</i> ² (Nagelkerke)
Female	73	0.11	1.17	0.46–2.97	0.74	0.002
Middle tertile age (60–66 years)†	73	2.83	2.67	0.85–8.37	0.09	0.118
Highest tertile age (67–88 years)†	73	0.70	0.59	0.17–2.04	0.40	0.118
Intervention vs. care as usual	73	0.22	1.25	0.49–3.18	0.64	0.004
≥ 3 vs. < 3 co-morbidities	62	0.22	1.29	0.44–3.78	0.64	0.005
1 vs. 0 stressful life events	50	0.01	1.05	0.28–3.92	0.94	0.006
≥ 2 vs. 0 stressful life events	50	0.16	0.75	0.19–3.03	0.69	0.006
Glycated haemoglobin (%)	66	0.40	0.86	0.54–1.37	0.53	0.008
Depression severity (CES-D score)	73	4.01	1.08	1.00–1.18	0.045	0.079
Anxiety severity (HADS-A score)	62	5.60	1.25	1.04–1.50	0.018	0.131
Probable anxiety (HADS-A ≥ 11)	62	6.50	5.50	1.48–20.39	0.011	0.149
Diabetes-specific emotional distress score (PAID)	52	1.92	1.02	0.99–1.05	0.17	0.050
Increased diabetes-specific emotional distress score (PAID ≥ 40)	52	0.77	1.69	0.52–5.43	0.38	0.020
Neuroticism score (EPQ-N)	61	1.41	1.07	0.88–1.31	0.48	0.011

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; EPQ-N, Eysenck Personality Questionnaire – Neuroticism; HADS-A, Hospital Anxiety and Depression Scale, anxiety subscale; OR, odds ratio; and PAID, Problem Areas in Diabetes scale. The statistically significant relationships ($P < 0.05$) are printed in bold.

*Owing to the relatively high incidence in our sample, odds ratios should not be interpreted as relative risks.

†Reference is the lowest age tertile: 55–59 years.

Table 3 Multivariable logistic regression (adjusted for sex and age) with baseline predictors for clinical major depression during 2 year follow-up according to the MINI

	<i>n</i>	Wald	OR*	95% CI	<i>P</i> -value	<i>r</i> ² (Nagelkerke)
≥ 3 vs. < 3 co-morbidities	62	0.37	1.42	0.46–4.41	0.55	0.100
1 vs. 0 stressful life events	50	0.82	2.04	0.44–9.51	0.37	0.174
≥ 2 vs. 0 stressful life events	50	0.02	0.90	0.20–4.16	0.89	0.174
Glycated haemoglobin (%)	66	0.14	0.91	0.54–1.51	0.71	0.186
Depression severity (CES-D score)	73	3.88	1.09	1.00–1.19	0.049	0.198
Anxiety severity (HADS-A score)	62	6.23	1.28	1.05–1.56	0.013	0.242
Probable Anxiety (HADS-A ≥ 11)	62	5.79	5.44	1.37–21.6	0.016	0.228
Diabetes-specific emotional distress score (PAID)	52	3.15	1.03	1.00–1.06	0.08	0.151
Increased diabetes-specific emotional distress score (PAID ≥ 40)	52	1.28	2.05	0.59–7.11	0.26	0.103
Neuroticism score (EPQ-N)	61	0.40	1.07	0.87–1.32	0.53	0.105

Abbreviations are as for Table 2.

The statistically significant relationships ($P < 0.05$) are printed in bold.

*Owing to the relatively high incidence in our sample, odds ratios should not be interpreted as relative risks.

sample size; the majority of the participants had several co-morbid illnesses.

In a sample of diabetic patients studied by Pibernik-Okanovic *et al.* [12], clinical depression at baseline, diabetes-related distress and social and physical quality of life aspects were related to depression after 1 year in diabetic patients with subthreshold depression. Anxiety was not included as a possible predictor. In the study of Cuijpers *et al.* [23], 18% of the persons with subthreshold depression developed a major depression during 1 year follow-up. In our study in diabetic patients, this percentage was strikingly high (42%) during 2 year follow-up. Thus, many patients who eventually developed major depression were detected with the CES-D. However, simply screening for depression may not be sufficient to improve outcomes [24].

Instead, embedding screening and monitoring in routine care might be more effective. For example, monitoring and discussing psychological wellbeing by a diabetes nurse specialist as part of standard diabetes care significantly improved mood in diabetic outpatients [25]. Furthermore, the stepped care intervention in this study was not sufficient to prevent incident major depression. This result could be biased due to the relatively large number of patients lost to follow-up. However, it can also be related to the limited monitoring of depression during the follow-up period, or to the focus of the intervention, which was merely on the reduction of depressive symptoms. De Jonge *et al.* recently observed that a multifaceted nurse-led intervention reduced major depression in diabetes outpatients with a high risk for depression [26]. This intervention consisted of the

Table 4 Univariable linear regression models for depression severity score (CES-D) after 2 year follow-up

Variable	<i>n</i>	<i>t</i>	B	95% CI B	<i>P</i> -value
Female	57	1.74	3.74	−0.57 to 8.04	0.09
Age (years)	57	1.14	0.17	−0.13 to 0.47	0.26
Intervention vs. care as usual	57	0.81	1.78	−2.61 to 6.17	0.42
≥ 3 vs. < 3 co-morbidities	50	0.73	1.90	−3.32 to 7.11	0.47
1 vs. 0 stressful life events	40	−0.62	−2.14	−9.08 to 4.78	0.54
≥ 2 vs. 0 stressful life events	40	−0.17	−0.58	−7.74 to 6.57	0.87
Glycated haemoglobin (%)	51	0.92	1.01	−1.19 to 3.20	0.36
Depression severity score (CES-D)	57	1.83	0.39	−0.04 to 0.81	0.07
Anxiety severity score (HADS-A)	50	2.99	1.16	0.38–1.93	0.004
Probable anxiety (HADS-A ≥ 11)	50	2.52	7.07	1.42–12.71	0.015
Diabetes-specific emotional distress score (PAID)	41	1.87	0.12	−0.01 to 0.25	0.07
Increased diabetes-specific emotional distress score (PAID ≥ 40)	41	0.57	1.63	−4.19 to 7.44	0.57
Neuroticism score (EPQ-N)	49	1.93	0.91	−0.04 to 1.85	0.06

Abbreviations are as for Table 2. In addition, *t* refers to *t* statistic, and B refers to the regression coefficient. The statistically significant relationships ($P < 0.05$) are printed in bold.

Table 5 Multivariable linear regression models (adjusted for sex and age) for depression severity score (CES-D) after 2 year follow-up

Variable	<i>n</i>	<i>t</i>	B	95% CI B	<i>P</i>
≥ 3 vs. < 3 co-morbidities	50	0.50	1.32	−3.98 to 6.62	0.62
1 vs. 0 stressful life events	40	−0.19	−0.70	−8.30 to 6.90	0.85
≥ 2 vs. 0 stressful life events	40	−0.16	−0.56	−7.85 to 6.72	0.88
Glycated haemoglobin (%)	51	0.66	0.72	−1.49 to 2.94	0.51
Depression severity score (CES-D)	57	1.45	0.31	−0.12 to 0.75	0.15
Anxiety severity score (HADS-A)	50	3.10	1.19	0.42–1.96	0.003
Probable anxiety (HADS-A ≥ 11)	50	2.76	7.62	2.07–13.18	0.008
Diabetes-specific emotional distress score (PAID)	41	1.67	0.12	−0.02 to 0.26	0.10
Increased diabetes-specific emotional distress score (PAID ≥ 40)	41	0.38	1.13	−4.95 to 7.20	0.71
Neuroticism score (EPQ-N)	49	2.44	1.16	0.20–2.12	0.020

Abbreviations are as for Table 2. In addition, *t* refers to *t* statistic, and B refers to the regression coefficient. The statistically significant relationships ($P < 0.05$) are printed in bold.

following single or combined treatments: counselling, focusing on coping with disease and compliance with treatment; referral to a liaison psychiatrist; or organization of a multidisciplinary case conference attended by the treating physicians, nurses and a liaison psychiatrist [26]. Therefore, a multifaceted intervention might be more effective in the prevention of depression than an intervention merely focused on depression.

Furthermore, we observed that anxiety was a strong risk factor for incident major depression. This complies with studies in the general population showing that an anxiety disorder often precedes a major depressive episode [27,28]. Based on our results, a targeted prevention of major depression should probably also focus on anxiety. Anxiety symptoms are prevalent among diabetic patients [29]. Although treatment for anxiety is not well studied in diabetic patients, both psychological and pharmacological treatments can be considered as treatment [30].

An important strength of our study is the use of the MINI, which can be used to diagnose major depression. Furthermore, in contrast to most research on risk factors for depression in

diabetes, our study had a longitudinal design. This provides more information concerning the direction of the relationship. However, causality cannot be inferred from this cohort study because data prior to the study period are lacking. Furthermore, there is always the possibility of residual confounding. The results of our study should be considered in light of several limitations. First, our explorative study was based on data of a randomized controlled study that was designed to investigate the effect of a stepped care intervention compared with care as usual. To study the relationship of possible predictors and incident major depression was a secondary aim. Second, we could not rely on complete data for all participants. There were missing data for the predictor variables because not all baseline questionnaires were completed and returned. In addition, there was a considerable loss to follow-up from baseline to 2 year follow-up (36%). Due to the small sample size, we were not able to test multivariable models extensively. Although some differences existed between those available for follow-up and those who were not (age and education level), we do not know the impact on the relationship studied. Third, we do not have information about

treatment of depression during the follow-up. Fourth, information about previous depressive episodes was lacking, while it is likely that this will influence the onset of major depression.

As our study is explorative, our results should be interpreted as preliminary. Further research on predictors of incident major depression in patients with diabetes is warranted and should include larger study samples.

In summary, more than 40% of the diabetic patients with subthreshold depression developed a major depression during 2 year follow-up. Both baseline depression and anxiety levels were related to the onset of major depression.

Competing interests

Nothing to declare.

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