Depressive Symptoms in Subjects With Diagnosed and Undiagnosed Type 2 Diabetes

Mirjam J. Knol, MSc, Eibert R. Heerdink, PhD, Antoine C. G. Egberts, PharmD, PhD, Mirjam I. Geerlings, PhD, Kees J. Gorter, MD, PhD, Mattijs E. Numans, MD, PhD, Diederick E. Grobbee, MD, PhD, Olaf H. Klungel, PharmD, PhD, and Huibert Burger, MD, PhD

Objective: To investigate if disturbed glucose homeostasis or known diagnosis of diabetes was associated with depressive symptoms. The reason for the increased prevalence of depression in patients with Type 2 diabetes mellitus (DM2) is unknown. **Methods:** Within the Utrecht Health Project, an ongoing longitudinal study among inhabitants of a residential area of a large city in The Netherlands, 4747 subjects (age: 39.4 ± 12.5 years) were classified into four mutually exclusive categories: normal fasting plasma glucose (FPG) (<5.6 mmol/l), impaired FPG (≥5.6 and <7.0 mmol/l), undiagnosed DM2 (FPG ≥7.0 mmol/l), and diagnosed DM2. Presence of depressive symptoms was defined as a score of ≥25 on the depression subscale of the Symptom Check List (SCL-90) or self-reported use of antidepressants. **Results:** Diagnosed DM2 was associated with an increased risk of depressive symptoms (odds ratio (OR) = 1.69; 95% confidence interval (CI) 1.06–2.72) after adjustment for demographic and lifestyle variables. Additional adjustment for number of chronic diseases reduced the OR to 1.36 (95% CI 0.83–2.23). Impaired fasting glucose and undiagnosed DM2 were not associated with depressive symptoms. **Conclusions:** Our findings suggest that disturbed glucose homeostasis is not associated with depressive symptoms. The increased prevalence of depressive symptoms among patients with *diagnosed* DM2 suggests that depressive symptoms might be a consequence of the burden of diabetes. The number of chronic diseases seems to explain part of the association between DM2 and depressive symptoms. **Key words:** depressive symptoms, diabetes, blood glucose, burden.

DM2 = Type 2 diabetes mellitus; **CI** = confidence interval; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, fourth revision; **FPG** = fasting plasma glucose; **OR** = odds ratio; **SCID** = Structured Clinical Interview for DSM-IV; **SCL-90** = Symptom Checklist; **SD** = standard deviation; **SPSS** = Statistical Package for the Social Sciences; **UHP** = Utrecht Health Project.

INTRODUCTION

Diabetes and depression are both common conditions in today's society. There are about 200 million people with diabetes worldwide (1) and an estimated 121 million people currently suffer from depression (2). Diabetes and depression are also often comorbid conditions. A recent meta-analysis showed that the prevalence of depression is doubled in patients with Type 2 diabetes compared with subjects without diabetes (3). However, the reason for the increased prevalence among patients with diabetes is unknown. Also, the direction of the association between Type 2 diabetes and depression is not known. Recently, a meta-analysis of longitudinal studies suggested that depression is a small risk factor for the onset of Type 2 diabetes (4). However, depression is also often seen as a consequence of Type 2 diabetes (5). In this paper, we will focus on the latter.

There are two possible mechanisms underlying the association between Type 2 diabetes and the onset of depression. First, biochemical changes associated with diabetes could account for the increased risk of depression (5). For example, hyperglycemia and hyperinsulinemia increase the activity of the hypothalamic-pituitary-adrenal axis, inducing arousal of the nervous system, which in turn may promote depression (6,7). Second, depression in patients with diabetes may be viewed as the result of the burden of the disease (5,8). This is supported by the finding that when the burden of diabetes increases, the probability of mood symptoms increases as well (9). Furthermore, an increased prevalence of depression is also seen in patients with chronic diseases other than diabetes (10).

The aim of the present study was to investigate if disturbed glucose homeostasis is associated with depressive symptoms or if a known diagnosis of diabetes is associated with depressive symptoms. We compared the prevalence of depressive symptoms in four groups: subjects with normal fasting glucose level; subjects with prediabetes, i.e., impaired fasting glucose level; subjects who did not know they had Type 2 diabetes, but whose fasting plasma glucose (FPG) level indicated the presence of diabetes; and subjects who know they had Type 2 diabetes because their doctor diagnosed them.

PATIENTS AND METHODS

Study Population

The Utrecht Health Project (UHP) was a data source for this study (11). The UHP is an ongoing longitudinal study, set up in 2000, among all inhabitants of a new residential area of Utrecht, a large city in The Netherlands. Each new inhabitant who registered with a general practitioner (GP) was invited by mail to participate in the study. In the Dutch healthcare system, access to pharmacy care or secondary care is only possible via the GP. Therefore, almost all inhabitants of The Netherlands are registered with a GP. At baseline, an individual health profile is made for every participant that includes an interview-assisted questionnaire, physical examination, and a blood sample. The questionnaire includes questions about demographic factors, lifestyle factors, current health status, quality of life, psychopathology, and disability. Physical examination includes measurements of weight, height, and blood pressure. Blood assessment includes FPG and cholesterol level

From the Julius Center for Health Sciences and Primary Care (M.J.K., M.I.G., M.E.N., D.E.G., H.B.), University Medical Center Utrecht, Netherlands; Department of Pharmacoepidemiology and Pharmacotherapy (M.J.K., E.R.H., A.C.G.E., O.H.K.), Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Netherlands; Department of Psychiatry and Department of Epidemiology (H.B.), University Medical Center Groningen, Netherlands.

Address correspondence and reprint requests to M. J. Knol, Julius Center for Health Sciences and Primary Care, UMC Utrecht, Utrecht, Netherlands. E-mail: m.j.knol@umcutrecht.nl

Received for publication July 7, 2006; revision received January 22, 2007.

This study was supported by an unrestricted grant from Novo Nordisk and the Scientific Institute of Dutch Pharmacists (WINAp). The Utrecht Health Project (LRGP) received grants from the Ministry of Health, Welfare, and Sports (VWS), the University of Utrecht, the Province of Utrecht, the Dutch Organisation of Care Research (ZON), the University Medical Center Utrecht (UMC Utrecht) and the Dutch College of Healthcare Insurance Companies (CVZ).

DOI: 10.1097/PSY.0b013e31805f48b9

0033-3174/07/6904-0300

measurements. In the future, follow-up data on morbidity, medication, and referrals will be obtained through the automated registry of all GPs and pharmacists in the area.

The Medical Ethics Committee of the University Medical Center Utrecht in The Netherlands approved the UHP. The UHP started to recruit participants in 2001 and, since then, response has been steadily increasing. By January 2005, 13,128 inhabitants were invited, of whom 6755 (51.4%) gave informed consent. Baseline data were complete for 6304 (48.0%) participants, of whom 4950 were aged ≥18 years. Nonresponders were more often male (51.5% versus 45.9%) and nonresponders were younger than responders (mean age (SD): 36.5 years (12) versus 38.7 years (13)). Reasons for not participating in the study were a) not interested in the study (44%); b) no recognition of personal advantage in participating (26%); and c) too busy (14%). A small group did not want to participate in scientific research from conviction (2%); others had practical reasons for not participating (14%).

The current analysis is based on baseline data of 4950 subjects aged ≥18 years.

FPG and Diabetes

First, subjects who reported having been diagnosed with diabetes by a physician were classified as having "diagnosed diabetes." Second, the remaining subjects were, according to the latest American Diabetes Association criteria (12), categorized based on their FPG concentration into a) normal FPG (<5.6 mmol/l); b) impaired FPG (≥5.6 and <7.0 mmol/l); and c) undiagnosed diabetes (≥7.0 mmol/l). Fasting glucose values were obtained from a venous blood sample. In 178 subjects, a finger prick sample was obtained instead of a venous blood sample, producing whole blood glucose values. These whole blood values were converted into venous values by multiplying with factor 1.11 (13). Some patients were not fasting when the blood sample was obtained. If subjects had a nonfasting blood glucose value which was increased (≥5.6 mmol/l), they were excluded from further analyses ($n = 22$). Patients with diagnosed diabetes who used insulin and no oral hypoglycemic agents were defined as having Type 1 diabetes and were excluded ($n = 14$) from the study.

Depressive Symptoms

Depressive symptoms were assessed with a psychopathology questionnaire, the Symptom Check List (SCL-90) (14,15). The SCL-90, a self-rated scale, consists of eight psychiatric symptom domains, including a 16-item depression subscale. Each item is scored on a 5-point scale. In this study, the presence of depressive symptoms was defined as a score of ≥25 on the depression subscale. A validation study showed that this cut-off point was the optimal cut-off point with a sensitivity of 88.5 and a specificity of 60.7 when compared with the depression section of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (SCID) (16). Another study showed that a cut-off point of 25 gave a sensitivity of 95.5 and a specificity of 74.0 for major depression 1 month after a myocardial infarction, also with the SCID as the gold standard (17).

In addition, subjects reporting use of antidepressants were classified as having depressive symptoms irrespective of their score on the SCL-90. Subjects who used antidepressants for a nonpsychiatric indication ($n = 3$), such as pain and incontinence, were recoded as "not using antidepressants."

Covariates

Before performing the analyses, we selected gender, age, education level, body mass index, smoking, alcohol consumption, physical activity, and the number of chronic diseases as potential confounders. Information on gender, age, highest attained education level, smoking, alcohol consumption, physical activity (number of days for ≥30 minutes), and chronic diseases was collected with a self-report questionnaire. We categorized education level as follows: a) low (no education, primary school, or lower vocational training); b) intermediate (general secondary school or intermediate vocational training); and c) high (higher vocational training or university). Smoking was categorized as never, current, and former smoking. Alcohol consumption was assessed with number, frequency, and type of alcoholic drinks. Alcohol consumption was categorized as 0 glasses per day, 1 to 2 glasses per day, and >2 glasses per day. To assess the level of physical activity, the number of days with at least half an hour of physical activity (including cycling, gardening, or sports) in leisure time was used.

Chronic diseases that were present during the last year and diagnosed by a physician included asthma, chronic obstructive pulmonary disease, severe heart disease, myocardial infarction, stroke, cancer, osteoarthritis, and rheumatoid arthritis. Weight and height were measured and body mass index was calculated.

Data Analysis

Relative risks of depressive symptoms for subjects with impaired FPG concentrations, undiagnosed, and diagnosed Type 2 diabetes were estimated using logistic regression and were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Model 0 shows the crude ORs. In model 1, we adjusted for gender, age, and education level. In model 2, we added body mass index, smoking status (never, current, former), alcohol consumption, and physical activity to the model. In model 3, the number of chronic diseases, other than diabetes, was added to the model. These covariates were selected before the analyses. Gender, education level, smoking status, and alcohol consumption were included as categorical covariates. Age, body mass index, physical activity, and number of chronic diseases were included as continuous covariates. We performed the goodness-of-fit test as a measure of model fit.

Only 2.3% of the data we used was missing. However, if we performed complete case analysis, we lost 1168 (24.6%) subjects, as these subjects had missing values on ≥1 variables. Missing data can severely affect the power of statistical analyses because patients with incomplete data are typically excluded. Furthermore, complete case analysis can give biased results because nonresponse is usually selective. Therefore, in the present study, multiple imputation (18) was used to fill in missing values under the assumption that these values only depend on observed values (missing at random). Five complete datasets were created, using the library Multivariate Imputation by Chained Equations (19) in the statistical package S-PLUS 2000. Although it depends on the percentage of missing data as to how many datasets should be created, in many applications three to five imputations are sufficient to obtain excellent results (20). Subsequently, logistic regression modeling was performed on each dataset, and the regression coefficients of the five models were pooled.

We reasoned that adjusting for cardiovascular disease in the model might not be appropriate because a cardiovascular condition could, in part, be an intermediate factor in the association between Type 2 diabetes and depressive symptoms. Therefore, we performed an additional analysis in which we excluded 79 subjects who reported severe heart disease, myocardial infarction, or stroke.

All analyses were performed with SPSS version 12.0 (SPSS Inc., Chicago, IL) or S-PLUS 6.2 (Insightful Corp., Seattle, WA).

RESULTS

The source population consisted of 4950 subjects aged ≥18 years. Questionnaire data were completely missing from 167 subjects and these subjects were excluded (mean age: 35.4 years (SD = 11) and 46.7% male subjects). Twenty-two subjects with only nonfasting plasma glucose concentration available and 14 subjects with Type 1 diabetes were excluded, leaving 4747 subjects in the study population. Of these subjects, 2121 (44.7%) were male and 2626 (55.3%) were female; they had a mean age of 39.4 (SD = 12.5) years. In this population, the prevalence (95% CI) of impaired fasting glucose, undiagnosed, and diagnosed Type 2 diabetes was 15.5% (14.4%–16.6%), 1.3% (0.96%–1.6%), and 2.4% (1.9%–2.9%), respectively. The overall prevalence (95% CI) of depressive symptoms (including antidepressant use) was 19.3% (18.2%–20.4%). These percentages are the observed prevalences, i.e., before imputation.

Table 1 presents the subject characteristics in the four subgroups before multiple imputation was performed and the

TABLE 1. Characteristics of the Study Population (Observed Data, Before Multiple Imputation)

	Normal FPG (<5.6)	Impaired FPG (≥5.6 and <7.0)	Undiagnosed DM2 (FPG ≥7.0)	Diagnosed DM2
N	3499	671	55	102
Gender, % male	40.4	63.6	43.6	52.9
n missing	0	0	0	0
Age, mean ± SD	37.7 ± 11.3	46.7 ± 13.9	56.9 ± 12.7	55.8 ± 14.4
n missing	0	0	0	0
Education				
% low	17.1	28.5	51.9	44.9
% middle	42.9	43.9	34.6	40.8
% high	40.0	27.6	13.5	14.3
n missing	114	19	3	4
BMI (kg/m^2), mean ± SD	24.9 ± 4.0	27.7 ± 4.3	29.2 ± 6.1	28.1 ± 4.6
n missing	6	1	0	0
Smoking				
% current	23.5	26.8	16.4	20.6
% former	28.1	37.3	58.2	41.2
n missing	36	7	0	0
Alcohol use, %				
0 glasses/day	23.5	21.4	33.3	42.9
% 1–2 glasses/day	60.5	53.9	43.1	38.8
% >2 glasses/day	15.9	24.7	23.5	18.4
n missing	106	35	4	4
Physical activity (days/week), mean ± SD	3.2 ± 2	3.2 ± 2	3.3 ± 3	3.3 ± 2
n missing	255	61	4	12
Asthma/COPD, %	8.8	12.5	3.6	17.8
n missing	42	5	0	1
Severe heart disease or MI, %	0.6	2.4	3.6	9.8
n missing	41	7	1	5
Stroke, %	0.4	0.9	0.0	6.1
n missing	40	4	0	3
Cancer, %	0.5	2.0	1.8	5.9
n missing	38	10	0	1
Osteoarthritis, %	6.0	14.0	27.3	29.9
n missing	57	7	0	5
Arthritis, %	3.9	6.1	9.1	17.7
n missing	85	13	0	6
Depressive symptom score, mean ± SD	21.0 ± 7.2	20.8 ± 7.1	20.9 ± 6.3	23.0 ± 9.2
Median (range)	18.0 (16–77)	18.0 (16–62)	19.0 (16–46)	19.0 (16–64)
n missing	52	10	0	1
Use of antidepressants, %	2.5	3.6	3.6	2.0
n missing	19	6	0	0
Depressive symptoms,[a] %	19.4	17.5	20.0	29.7
n missing	63	13	0	1
Fasting plasma glucose, mean ± SD	4.9 ± 0.4	5.9 ± 0.3	8.3 ± 2.1	8.3 ± 3.3
n missing	0	0	0	7

[a] Defined as score of ≥25 on depression subscale of SCL-90 and/or self-reported use of antidepressants.
FPG = fasting plasma glucose; DM2 = Type 2 diabetes mellitus; SD = standard deviation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction.

numbers of missing values. In 385 subjects, information on FPG concentration and diagnosed diabetes was missing and, in 77 subjects, depressive symptom score or information on antidepressant use was missing. Gender ratio, age, education level, and body mass index differed considerably among the four subgroups. All chronic diseases were most prevalent in the patients with diagnosed Type 2 diabetes. Mean depressive symptom score was highest in the group with diagnosed diabetes, whereas the percentage of subjects who used antidepressants was lowest in this group. The prevalence of depressive symptoms, defined as a score of ≥25 on the depression subscale of the SCL-90, use of antidepressants, or both, was 20.0% in the patients with undiagnosed diabetes and 29.7% in the patients with diagnosed Type 2 diabetes. Mean FPG levels were similar in the undiagnosed patients as well as the patients with diagnosed Type 2 diabetes, although the variance was higher in the patients with diagnosed diabetes.

Table 2 presents the crude and adjusted ORs and 95% CIs of depressive symptoms for impaired FPG concentration and undiagnosed and diagnosed Type 2 diabetes. These are the effect estimates after multiple imputation was performed. Therefore, the numbers of subjects in the exposure groups are

TABLE 2. Association of Impaired Fasting Plasma Glucose Concentration, Undiagnosed, and Diagnosed Type 2 Diabetes With Depressive Symptoms, Expressed as Crude and Adjusted Odds Ratio (95% Confidence Interval) (After Multiple Imputation)

	Normal FPG (<5.6; *N* = 3853)	Impaired FPG (≥5.6 and <7.0; *N* = 732)	Undiagnosed DM2 (FPG ≥7.0; *N* = 58)	Diagnosed DM2 (*N* = 104)
Model 0[a]	1.00	0.90 (0.72–1.12)	1.00 (0.51–1.96)	1.79 (1.17–2.75)
Model 1[b]	1.00	1.03 (0.81–1.31)	0.84 (0.42–1.69)	1.70 (1.07–2.70)
Model 2[c]	1.00	1.01 (0.78–1.29)	0.82 (0.40–1.68)	1.69 (1.06–2.72)
Model 3[d]	1.00	0.99 (0.77–1.27)	0.86 (0.42–1.77)	1.36 (0.83–2.23)

[a] Reference category.
[b] Adjusted for gender, age, and education.
[c] Adjusted for gender, age, education, body mass index, current and former smoking, alcohol consumption, and physical activity.
[d] Adjusted for gender, age, education, body mass index, current and former smoking, alcohol consumption, physical activity, and number of chronic diseases.
FPG = fasting plasma glucose; DM2 = Type 2 diabetes mellitus.

higher than the numbers presented in Table 1. Compared with the normal glucose group, the odds of depressive symptoms was not higher in the impaired glucose group (OR = 0.90 (0.72–1.12)) and the patients with undiagnosed Type 2 diabetes (OR = 1.00 (0.51–1.96)) (model 0). Adjustment for demographic, lifestyle variables, and the number of chronic diseases did not change this finding. In the diagnosed Type 2 diabetes group, however, the odds of depressive symptoms was increased (OR = 1.79 (1.17–2.75); model 0). Adjustment for gender, age, education level, body mass index, smoking status, alcohol consumption, and physical activity did not change this risk estimate (model 2). Adding the number of chronic diseases to the model lowered the OR for diagnosed Type 2 diabetes (OR = 1.36 (0.83–2.23); model 3). The model adjusted for all demographic and lifestyle variables (model 2) and the model additionally adjusted for the number of chronic diseases (model 3) showed no deviance of goodness-of-fit with p values of .47 and .29, respectively. Model 1 did show deviance of goodness-of-fit with $p = .01$, but we considered this less relevant as this was not our primary model of interest.

When excluding 79 subjects with cardiovascular disease, the ORs for the impaired fasting glucose group and the patients with undiagnosed diabetes were comparable with those presented in Table 2 (data not shown). For the patients with diagnosed Type 2 diabetes, the ORs were slightly higher than when subjects with cardiovascular disease were not excluded: when adjusting for gender, age, and education (model 1), the OR for patients with diagnosed Type 2 diabetes was 1.92 (95% CI = 1.17–3.14). Additional adjustment for lifestyle factors (model 2) resulted in an OR of 1.95 (95% CI = 1.18–3.22). The OR was 1.77 (95% CI = 1.06–2.96) when adjusting for the number of (other) chronic diseases (model 3).

In the results presented above, we categorized the FPG levels into three groups, which reflect clinical practice. We performed a post hoc analysis where we included FPG level as a continuous variable and diagnosis of diabetes as a dichotomous variable into the model. The crude OR (95% CI) for continuous FPG (per 1 mmol/l increase) was 0.91 (0.83–1.01) and the crude OR for a diagnosis of diabetes was 2.38 (95% CI = 1.43–3.95). Adjusting for age, gender, and education level (model 1) changed the OR into 0.98 (95% CI = 0.89–1.07) and 1.79 (95% CI = 1.07–3.01). Additional adjustment for lifestyle factors and the number of chronic diseases (model 3) resulted in an OR for fasting plasma glucose level of 0.99 (95% CI = 0.90–1.09) and for a diagnosis of diabetes of 1.40 (95% CI = 0.81–2.41). Again, models 2 and 3 did not show deviance of goodness-of-fit and model 1 showed deviance of goodness-of-fit. These results are similar to the results described above; namely, having a diagnosis of diabetes increased the risk of depressive symptoms whereas no association was seen between FPG and depressive symptoms.

DISCUSSION

In the present study, subjects with impaired FPG concentration and undiagnosed Type 2 diabetes did not have an increased risk of depressive symptoms. Patients with diagnosed Type 2 diabetes had a 1.7 times increased risk of depressive symptoms compared with subjects with normal glucose concentrations after adjustment for demographic and lifestyle variables. After additional adjustment for number of chronic diseases, the risk of depressive symptoms was no longer significantly increased in patients with diagnosed diabetes.

These results suggest that disturbed glucose homeostasis is not associated with depressive symptoms. As subjects aware of their diabetes had an increased risk of depressive symptoms and subjects unaware of their diabetes had not, the increased risk of depressive symptoms in diabetes might be a consequence of its burden rather than a consequence of high glucose levels. The number of comorbid chronic diseases explains part of the increased prevalence seen in patients with diagnosed Type 2 diabetes.

Depressive symptoms might be a consequence of diagnosed diabetes. However, as this study has a cross-sectional design, we cannot distinguish between causes and consequences. Diagnosed diabetes can also be a consequence of having depressive symptoms. This may occur if subjects with depressive symptoms are more likely to be diagnosed with Type 2 diabetes because they more often consult a physician, i.e., detection bias.

It is possible that we found a high prevalence of depressive symptoms in the patients with diagnosed Type 2 diabetes and

not in subjects in earlier stages of diabetes because patients with diagnosed diabetes have a higher level and longer duration of disturbed glucose homeostasis. Although, if this were the case, we would expect to see a trend between increasing glucose levels and depressive symptoms, which we did not.

Our findings support those of Palinkas et al. (21), who showed an increased prevalence of depression in patients with previously diagnosed Type 2 diabetes and no increased prevalence in patients unaware of their diabetes, suggesting that depression develops after a diagnosis of diabetes. The almost two-fold increased prevalence of depressive symptoms we observed in patients with diagnosed Type 2 diabetes is also in accordance with the results of a meta-analysis, showing an OR of 2 when pooling 20 cross-sectional studies (3). Further, our finding of the absence of an association between fasting glucose concentrations and depressive symptoms is not inconsistent with the results of two recent studies showing a negative (22) and a positive association (23) between insulin resistance and depression. Also, in a recent prospective study on insulin resistance and depressive symptoms in middle aged men, no association was found (24). However, in that study, no association between clinically manifest diabetes and depressive symptoms was found either. Another prospective study showed no association between patients with diagnosed diabetes and those with depressive symptoms (25).

Two recent studies on factors associated with depression in Type 2 diabetes showed that patients with diabetes and comorbid chronic somatic diseases had an increased prevalence of depression, whereas those without diabetes did not (26,27). In our study, the number of chronic diseases also explained part of the increased prevalence of depressive symptoms in patients with diagnosed Type 2 diabetes. Interestingly, a prospective study showed no increased risk of developing depression in patients with diabetes compared with those with osteoarthritis (28). This suggests nonspecificity of diabetes as a risk factor for depression and is consistent with our finding that depression in patients with diabetes may be a consequence of the burden of the disease rather than a result of physiologic changes due to high glucose levels.

Some limitations of our study need to be addressed. First, we used self-report to define diagnosis of Type 2 diabetes. It is possible that some misclassification occurred in that patients with diagnosed diabetes misclassified themselves as not diagnosed. Yet, a Dutch validation study showed that self-reported diagnosis of diabetes is in good agreement with a physician diagnosis (29). Furthermore, if misclassification was random, the relative risk of depressive symptoms in patients with diagnosed diabetes we estimated is an underestimation. Type 1 diabetes was defined as use of insulin and no use of oral hypoglycemic agents; we excluded 14 subjects based on this definition. It is possible that some of these subjects were patients with Type 2 diabetes after all. An additional analysis showed that including or excluding these subjects did not change the association between diagnosed diabetes and depressive symptoms.

Second, we did not use a diagnostic interview to confirm depression according to the DSM-IV criteria. However, our aim was to compare different groups regarding depressive symptom level and not to obtain precise estimates of the prevalence of depression in these groups. Analyzing the depression score continuously might have given more power to detect an association. However, we used the validated cut-off point of 25 described in the literature (16,17). Also, two practical reasons to dichotomize the depressive symptom score were that the variable was not normally distributed, which could not be solved by several transformations, and that we also included users of antidepressant medication into the depressive symptom group. Regarding the cut-off point of 25, one study also suggested a cut-off point of 27 for major and minor depression with a sensitivity of 81.1 and a specificity of 83.5 (17). Use of this more conservative cut-off point did not change our findings.

Third, antidepressant use is not solely prescribed for depression but also for other psychiatric problems such as anxiety and panic disorders; this prescription practice may have confound our results. However, in our study, only 5.9% of the subjects with depressive symptoms were defined as such based on antidepressant use. Excluding subjects who used antidepressants resulted in a slightly higher OR in the group with diagnosed Type 2 diabetes. In addition, analyzing antidepressant use as a covariate, instead of as an indicator of depression on the dependent variable side, did not change our conclusion.

Fourth, as the response rate of the study was about 50%, selection bias could have occurred. Nonresponders were more often male and were younger than responders, which may have influenced the prevalence of diabetes and depressive symptoms but most likely not the association between diabetes and depressive symptoms (30). Potential selection bias through missing data was minimized because we performed multiple imputation to impute missing values. Multiple imputation is the preferred method to deal with missing values because it leads to unbiased estimates and correct standard errors as opposed to complete case analysis or single imputation techniques (31). Because our study population was young, the number of patients with undiagnosed and diagnosed Type 2 diabetes was relatively low. Therefore, the study may have had limited power. Regarding generalizability, our results may not apply to an elderly population because of our relatively young study population.

A strong aspect of our study is that we used a large sample from the general population. Second, we adjusted for the most important factors known from the literature that could disturb the association between Type 2 diabetes and depressive symptoms. Third, the design of the UHP made it possible to compare subjects who were unaware of their diabetes with subjects who were aware of their diabetes within a single population; therefore, we could make some inferences about the reason for the increased prevalence of depressive symptoms in patients with Type 2 diabetes.

In conclusion, the results of the present study suggest that disturbed glucose homeostasis is not associated with depressive symptoms. The association we found between diagnosed

diabetes and depressive symptoms suggests that the increased prevalence of depressive symptoms in patients with Type 2 diabetes is a consequence of the burden of the disease. Furthermore, the number of chronic diseases seems to partly explain the association between diagnosed Type 2 diabetes and depressive symptoms.

More research is needed to confirm the association between Type 2 diabetes and depressive symptoms. Instead of cross-sectional studies, longitudinal studies should be performed to investigate if diabetes is an independent risk factor for the onset of depressive symptoms. In these studies, the influence of a history of depression and the influence of comorbid chronic diseases should be taken into account. Furthermore, future research should clarify if the onset of depressive symptoms is specific for Type 2 diabetes or if it is also present in other chronic diseases. Finally, the mechanisms underlying the association between diabetes and depression should be investigated.

We acknowledge the participating inhabitants of Leidsche Rijn, Utrecht, The Netherlands, and the GPs working in this area for providing research data from their routine care. We also want to acknowledge the biostatistician, W. B. Busschers, from the Centre of Biostatistics of Utrecht University, for his help with multiple imputation.

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–53.
2. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. Lancet 1997;349:1498–504.
3. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001;24:1069–78.
4. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 2006;49:837–45.
5. Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults: is there a link? Diabetes Care 2000;23:1556–62.
6. Cameron OG, Kronfol Z, Greden JF, Carroll BJ. Hypothalamic-pituitary-adrenocortical activity in patients with diabetes mellitus. Arch Gen Psychiatry 1984;41:1090–5.
7. Chan O, Inouye K, Riddell MC, Vranic M, Matthews SG. Diabetes and the hypothalamo-pituitary-adrenal (HPA) axis. Minerva Endocrinol 2003;28:87–102.
8. Musselman DL, Betan E, Larsen H, Phillips LS. Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. Biol Psychiatry 2003;54:317–29.
9. Peyrot M, Rubin RR. Persistence of depressive symptoms in diabetic adults. Diabetes Care 1999;22:448–52.
10. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry 2003;54:216–26.
11. Grobbee DE, Hoes AW, Verheij TJ, Schrijvers AJ, van Ameijden EJ, Numans ME. The Utrecht health project: optimization of routine health-care data for research. Eur J Epidemiol 2005;20:285–7.
12. Diagnosis and classification of diabetes mellitus. Diabetes Care 2005;28:S37–S42.
13. Stahl M, Brandslund I, Jorgensen LG, Hyltoft PP, Borch-Johnsen K, de Fine ON. Can capillary whole blood glucose and venous plasma glucose measurements be used interchangeably in diagnosis of diabetes mellitus? Scand J Clin Lab Invest 2002;62:159–66.
14. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale—preliminary report. Psychopharmacol Bull 1973;9:13–28.
15. Arrindell WA, Ettema JHM. Dimensionele structuur, betrouwbaarhied en validiteit van de Nederlandse bewerking van de Symptom Checklist (SCL-90). Nederlands Tijdschrift Psychologie 1981;43:381–7.
16. Aben I, Verhey F, Lousberg R, Lodder J, Honig A. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and Hamilton depression rating scale as screening instruments for depression in stroke patients. Psychosomatics 2002;43:386–93.
17. Strik JJ, Honig A, Lousberg R, Denollet J. Sensitivity and specificity of observer and self-report questionnaires in major and minor depression following myocardial infarction. Psychosomatics 2001;42:423–8.
18. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med 1991;10:585–98.
19. Buuren van S, Oudshoorn K. Flexible multivariate imputation by MICE. Leiden: TNO Prevention and Health; 1999.
20. Schafer JL, Olsen MK. Multiple imputation for multivariate missing-data problems: a data analyst's perspective. Multivariate Behavioral Research 1998;33:545–71.
21. Palinkas LA, Barrett-Connor E, Wingard DL. Type 2 diabetes and depressive symptoms in older adults: a population-based study. Diabet Med 1991;8:532–9.
22. Lawlor DA, Smith GD, Ebrahim S. Association of insulin resistance with depression: cross sectional findings from the British women's heart and health study. BMJ 2003;327:1383–4.
23. Timonen M, Laakso M, Jokelainen J, Rajala U, Meyer-Rochow VB, Keinanen-Kiukaanniemi S. Insulin resistance and depression: cross sectional study. BMJ 2005;330:17–8.
24. Lawlor DA, Ben Shlomo Y, Ebrahim S, Davey SG, Stansfeld SA, Yarnell JW, Gallacher JE. Insulin resistance and depressive symptoms in middle aged men: findings from the Caerphilly prospective cohort study. BMJ 2005;330:705–6.
25. Palinkas LA, Lee PP, Barrett-Connor E. A prospective study of type 2 diabetes and depressive symptoms in the elderly: the Rancho Bernardo study. Diabet Med 2004;21:1185–91.
26. Engum A, Mykletun A, Midthjell K, Holen A, Dahl AA. Depression and diabetes: a large population-based study of sociodemographic, lifestyle, and clinical factors associated with depression in type 1 and type 2 diabetes. Diabetes Care 2005;28:1904–9.
27. Pouwer F, Beekman AT, Nijpels G, Dekker JM, Snoek FJ, Kostense PJ, Heine RJ, Deeg DJ. Rates and risks for co-morbid depression in patients with type 2 diabetes mellitus: results from a community-based study. Diabetologia 2003;46:892–8.
28. Kessing LV, Nilsson FM, Siersma V, Andersen PK. No increased risk of developing depression in diabetes compared to other chronic illness. Diabetes Res Clin Pract 2003;62:113–21.
29. Klungel OH, de Boer A, Paes AH, Seidell JC, Bakker A. Cardiovascular diseases and risk factors in a population-based study in the Netherlands: agreement between questionnaire information and medical records. Neth J Med 1999;55:177–83.
30. Van Loon AJ, Tijhuis M, Picavet HS, Surtees PG, Ormel J. Survey non-response in the Netherlands: effects on prevalence estimates and associations. Ann Epidemiol 2003;13:105–10.
31. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087–91.