Recurrent Subthreshold Depression in Type 2 Diabetes: An Important Risk Factor for Poor Health Outcomes

Norbert Schmitz,[1,2,3,4] Geneviève Gariépy,[2,3] Kimberley J. Smith,[1,2] Matthew Clyde,[1,2] Ashok Malla,[1,2,3] Richard Boyer,[5] Irene Strychar,[4,6] Alain Lesage,[5] and JianLi Wang[7]

OBJECTIVE

To evaluate the association between recurrent subthreshold depressive episodes and functioning in a prospective community sample of people with type 2 diabetes.

RESEARCH DESIGN AND METHODS

A prospective community study in Quebec, Canada, was carried out between 2008 and 2013 (n = 1,064). Five yearly follow-up assessments (telephone interviews) were conducted. Baseline and the first three follow-up assessments were used to identify recurrent subthreshold depressive episodes (Patient Health Questionnaire [PHQ]-9). Functioning (World Health Organization Disability Assessment Schedule II [WHODAS-II]) and health-related quality of life (Centers for Disease Control and Prevention [CDC] unhealthy days) at 4- and 5-year follow-up assessments were the outcome measures.

RESULTS

Nearly half of the participants suffered from at least one episode of subthreshold depressive symptoms. After adjusting for potentially confounding factors, the risk of poor functioning/impaired health–related quality of life was nearly three times higher (relative risk = 2.86) for participants with four subthreshold depressive episodes compared with participants with no/minimal depression. Results suggest a dose-response relationship: the risk of poor functioning/impaired health–related quality of life increased with the number of recurrent subthreshold depressive episodes even after controlling for potentially confounding variables (significant linear trend, $P < 0.001$).

CONCLUSIONS

Recurrent subthreshold depressive symptoms might be an important risk factor for poor health outcomes in type 2 diabetes. Early identification, monitoring, and treatment of recurrent subthreshold depressive symptoms might improve functioning and quality of life in people with type 2 diabetes.

Diabetes Care 2014;37:970–978 | DOI: 10.2337/dc13-1832

[1]*Department of Psychiatry, McGill University, Montreal, Quebec, Canada*
[2]*Douglas Mental Health University Institute, Montreal, Quebec, Canada*
[3]*Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada*
[4]*Montreal Diabetes Research Centre, Montreal, Quebec, Canada*
[5]*Centre de Recherche Fernand Seguin, Hôpital Louis-H. Lafontaine, University of Montreal, Montreal, Quebec, Canada*
[6]*Department of Nutrition, Faculty of Medicine, University of Montreal, and the Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada*
[7]*Departments of Psychiatry and Community Health Sciences, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada*

Corresponding author: Norbert Schmitz, norbert.schmitz@mcgill.ca.

Received 3 August 2013 and accepted 29 October 2013.

Depression is a common comorbidity in type 2 diabetes, affecting 10–30% of people with diabetes (1). The prevalence rate of depression is nearly twice as high in people with type 2 diabetes compared with those without (1). There is evidence from both clinical and epidemiological studies that depressive symptoms are linked to poor outcomes in diabetes (2,3). For example, Scott et al. (4), using data from the World Mental Health Survey, found that the proportion of severe disability among those with both diabetes and comorbid depression was much higher than the sum of the proportions for the single conditions. Compared with adults with diabetes alone, adults with diabetes and depression have been shown to have more difficulties with diabetes self-management (e.g., following a healthy diet, not smoking, engaging in exercise, medication adherence, and blood glucose monitoring) (5), which, in turn, increases the risk of the development of macro- and microvascular complications (6).

Most of the current evidence on the diabetes-depression–functioning relationship is based on cross-sectional studies. So far, only a few population-based longitudinal studies have examined the effect of depression on functioning in diabetes (7–11), and these studies have mainly focused on major depression or clinically relevant levels of depressive symptoms. There is some evidence that subthreshold depressive symptoms have an impact on health outcomes in diabetes, too. Von Korff et al. (12) found in a cross-sectional study that adults with diabetes and minor depression had a twofold increase in risk of work disability compared with those without depression. Black et al. (10) found that mild depressive symptoms were associated with a small increased risk of functional disability in a prospective study of Mexican Americans aged 65 years and older with type 2 diabetes. Minor depression was also associated with increased mortality in a community sample of people with type 2 diabetes (major depression: hazard ratios = 2.30 and minor depression: hazard ratios = 1.67) in this study.

Depression is often a recurrent condition. General population studies have shown that 50% of people with depression experience symptoms that are recurrent or persistent (13). A single subthreshold depressive episode might reflect a situational response to life/disease circumstances and have a weak long-term effect on health, but persistent or recurrent subthreshold depressive episodes might have a significant long-term impact on health. Recurrent (moderate) depressive symptoms may produce an allostatic load (14), which increases the probability of developing worse health outcomes (15). Chronic subthreshold depressive symptoms might also affect the energy and ability for people to self-manage their diabetes, which might lead to health and functional problems later on.

The primary aim of this study was to evaluate the association between recurrent subthreshold depressive episodes and functioning in a prospective community sample of people with type 2 diabetes. We hypothesized that recurrent subthreshold depressive episodes would be associated with a higher risk of poor functioning and impaired health–related quality of life than a single subthreshold depressive episode. We expected a dose-response relationship between the frequencies of recurrent subthreshold depressive episodes and poor functioning and impaired health–related quality of life. A secondary aim was to investigate the depression treatment given to those with subthreshold depressive episodes.

RESEARCH DESIGN AND METHODS

Data from the Montreal Diabetes Health and Well-Being Study (DHS) were used for the current study. The DHS is a community-based telephone survey of adults with diabetes in Quebec, Canada. Participants were recruited in winter/spring 2008 through random digit dialing. Eligible participants were individuals who were between 18 and 80 years of age and had a diagnosis of diabetes. Five follow-up interviews were conducted approximately 12, 24, 36, 48, and 60 months after baseline interview (late winter/early spring). All participants were interviewed by a recognized polling firm (Bureau d'intervieweurs professionnels, Montreal, Quebec, Canada). Telephone interviews rather than mail surveys were conducted to achieve appropriate response rates. More details are reported elsewhere (16–18). Respondents who gave verbal informed consent to participate were administered the survey. The Douglas Mental Health University Institute ethics board approved the consent procedures and the study protocol.

Results reported in this article are for individuals with type 2 diabetes. Participants <30 years at diagnosis who commenced insulin therapy immediately after diagnosis were epidemiologically classified as having type 1 diabetes and were excluded from the analysis.

The Patient Health Questionnaire (PHQ)-9 (19) was used to assess depressive symptoms. The PHQ-9 is a brief instrument based on the diagnostic criteria for major depressive disorder, as defined in the DSM-IV. The nine items assess symptoms that have occurred during the last 2 weeks. Each of the items is scored from 0 (not at all) to 3 (nearly every day) and the sum of the PHQ-9 item scores (range 0–27) is an indicator of depression severity. The PHQ-9 is widely accepted as a valid measure of depression severity in medical settings (20). PHQ-9 scores of 0–4, 5–9, 10–14, 15–19, and 20–27 represent no/minimal, mild, moderate, moderately severe, and severe depression categories, respectively (19). For the present analysis we defined three categories: PHQ-9 scores between 0 and 4 were labeled as no/minimal depressive symptoms, scores between 5 and 14 were labeled as subthreshold depressive symptoms, and scores of 15 and higher were labeled as severe depressive symptoms. In additional sensitivity analyses, we considered different cutoff points for the classification of subthreshold depression (PHQ-9 scores 6–14, 6–15, 5–13, and 4–13). We considered also an alternative classification for subthreshold depression: a PHQ-9 score between 5 and 14 and a positive

response (score of 1 or higher) to one of the first two stem PHQ-9 items (little interest or pleasure in doing things and feeling down, depressed, or hopeless). This classification excludes participants who only score positive on the somatic items of the PHQ-9 (sleep, fatigue, and appetite).

Global functioning was assessed using the 12-item version of the World Health Organization (WHO) Disability Assessment Schedule II (WHODAS II) (21,22). The WHODAS II assesses functioning during the past 30 days in domains defined by the WHO International Classification of Functioning, Disability and Health (ICF): mobility, work and domestic responsibilities, self-care, understanding and communication, interpersonal relations, and participation in community activities. The WHODAS II summary scores were transformed to percent scores (0–100%), with higher scores reflecting greater disability. Andrews et al. (23) suggested that a WHODAS II score of 21 or greater indicates clinically significant level of poor functioning.

Unhealthy days as an indicator for impaired health–related quality of life were used as an additional outcome measure. The number of unhealthy days in the past month was assessed by the two questions: "Now thinking about your physical health, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good?" and "Now thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?" Overall unhealthy days were calculated, which is the sum of each respondent's physically and mentally unhealthy days, with a maximum of 30 unhealthy days. These questions are part of the standard 4-item set of the Centers for Disease Control and Prevention's (CDC) health–related quality-of-life instrument (24) and have been used as outcome measure in surveys (25–27). The unhealthy days measures have been validated in both general and disabled populations and have good construct and acceptable criterion validity (24,28). A total of 14 or more unhealthy days is often considered as a meaningful cut point for participants reporting substantially impaired health–related quality of life (29). This corresponds empirically to the upper 10–15% of the general population in the U.S. Behavioral Risk Factor Surveillance System (BRFSS) (25).

The DHS collected data on sociodemographic characteristics, including age, sex, marital status, ethnicity, and educational level. Participants were asked about their smoking status (current smoker, former smoker, and never smoker) and to provide the number of days they exercised or participated in sports activity for at least 15 min in the last month. The latter was collapsed into three categories: inactive (0 day), moderately active (1–12 days), and active ($>$12 days). BMI was calculated based on self-reported weight and height. Participants were asked whether they suffered from various chronic health conditions (asthma, high blood pressure, heart disease, stomach or intestinal ulcers, arthritis/rheumatism, migraine headaches, cancer, kidney disease, and back problems).

Diabetes complications were assessed using the 17-item Diabetes Complications Severity Index (DCI) (30). The DCI assesses diabetes complications on the basis of patient self-report (retinopathy, neuropathy, large-vessel atherosclerotic disease, peripheral vascular disease, cerebrovascular disease, and foot problems). Duration of diabetes was calculated based on the age at which participants were first diagnosed with diabetes.

In addition, participants were asked if they had *1*) outpatient visits with any type of physician who prescribed either an antidepressant or mood stabilizer for a minimum of 30 days in the last year and *2*) outpatient visits with any professional in the specialty mental health sector for psychotherapy for depression lasting at least 30 min in the last year.

Statistical Analyses

Baseline and the first three follow-up assessments were used to identify recurrent subthreshold depressive episodes. We considered six categories for depression status (1): no/minimal depression, participants with PHQ-9 scores of 4 or less at all four assessments (2); one subthreshold episode, participants with PHQ-9 scores between 5 and 14 at one assessment and lower scores at the other assessments (3); two subthreshold episodes, participants with PHQ-9 scores between 5 and 14 at two assessments and lower scores at the other assessments (4); three subthreshold episodes, participants with PHQ-9 scores between 5 and 14 at three assessments and a lower score at the other assessment (5); four subthreshold episodes, participants with PHQ-9 scores between 5 and 14 at all four assessments; and (6) severe depression episode, participants with PHQ-9 scores of 15 or higher during at least one assessment. Depression status of participants who did not drop out of the study but who missed one or two of the first four follow-up assessments was classified as no/minimal depression. In sensitivity analyses, we repeated our analyses for participants with complete depression information at the first four follow-up assessments.

The outcome variables were clinically significant functioning impairment and impaired health–related quality of life at the fourth and fifth follow-up assessments. Participants with a WHODAS II score of 21 or greater at 4- or 5-year follow-up assessment were classified as having a clinically significant level of poor functioning, while participants with 14 more unhealthy days at 4- or 5-year follow-up assessment were classified as having impaired health–related quality of life.

Participants with a WHODAS II score of 21 or greater at one of the four previous assessments were classified as having a history of poor functioning, while a history of impaired health–related quality of life was defined as 14 or more unhealthy days in one of the first four assessments. We controlled for these two variables in multivariate analysis.

We compared prevalence of sociodemographic variables, health characteristics, and depression treatment by depression status (χ^2 tests and general linear models were used for

categorical and continuous variables, respectively). Poisson regression was used to calculate the relative risks (RRs) and adjusted RRs and 95% CIs of depression status at the first four assessments and functioning and impaired health–related quality of life at the fifth and sixth assessment while controlling for potential confounding variables (sex, age, education, diabetes-specific complications, smoking, physical activity, BMI, chronic conditions, duration of diabetes, and history of poor functioning/impaired health–related quality of life, antidepressant treatment, and psychotherapy). Potential interactions between sex and depression status were evaluated. Linear trends in RRs were determined from unadjusted and adjusted models. In addition, contrast analysis was conducted to test whether a single subthreshold depressive episode had similar association with functioning and impaired health–related quality of life than two, three, or four subthreshold depressive episodes.

Due to the missing data for the confounders at follow-up assessments, we generated multiple imputed values for the missing data from the variables used in the analysis (PROC MI and PROC MIANALYSE in SAS 9.3).

RESULTS

A total of 2,003 individuals with diabetes participated in the DHS at baseline (53% female). After excluding those who refused to participate in a follow-up interview (n = 246), who had type 1 diabetes (n = 125), or unknown type of diabetes (n = 4), 1,628 individuals formed the baseline sample for the longitudinal cohort. A total of 519 individuals did not participate in the 4- or 5-year follow-up assessment (dropped out, were unavailable, refused, or deceased) and additional 45 individuals were excluded because they had a complete depression assessment at only one of the four interviews, resulting in a final sample size of 1,064 participants for the current study.

Participants who dropped out were older, had more diabetes-specific complications, poorer functioning status, and suffered more often from severe depressive symptoms at baseline than those who did not drop out (Table 1).

A total of 405 participants had no/minimal depressive symptoms at the first four assessments, while 524 participants had subthreshold depressive symptoms (two times, n = 156; three times, n = 85; and four times, n = 69) and 135 participants had severe depressive symptoms.

Sociodemographic and clinical baseline characteristics with respect to depression status are presented in Table 2. There were important differences between the six groups: those with no or minimal depressive symptoms during the first four assessments were more often male, more often married, had better education, better physical health (less diabetes complications, chronic conditions, obesity, better functioning and less impaired health–related quality of life), and were less often physically inactive compared with those with one or more depressive episodes. The number of depressive episodes was positively associated with diabetes-specific complications, poor functioning, impaired health–related quality of life, obesity, and physical inactivity at baseline (Table 2).

The proportion of participants with an antidepressant prescription (1 year before baseline to 3-year follow-up) was 4, 11, 13, 14, and 20% for those with no, one, two, three, and four subthreshold depressive episodes, respectively. Nearly 40% of those with at least one severe depression episode reported an antidepressant treatment. A similar association was observed for psychotherapy.

There was a strong dose-response relationship between the number of subthreshold depressive episodes at the first four assessments and poor functioning and impaired health–related quality of life at the fifth and sixth assessment: the prevalence of poor functioning/impaired health-related quality increased with the number of depressive episodes (Fig. 1). Table 3 presents the results of the regression analysis for the association between depression status and poor functioning/impaired health–related quality of life. The number of subthreshold depressive episodes was associated with an increased risk of poor functioning/impaired health–related quality of life (significant linear trend, $P < 0.001$). After adjusting for potentially confounding factors, the risk of poor functioning was more than two times higher (RR = 2.14) for participants with three subthreshold depressive episodes and nearly three times higher (RR = 2.86) for participants with four subthreshold depressive episodes compared with participants with no/minimal depression. The risk of poor functioning was similar for participants with four subthreshold depressive

Table 1—Baseline characteristics of participants and nonparticipants

Baseline characteristics	Participants (n = 1,064)	Nonparticipants (n = 564)	P
Sex, % women	54.4	51.8	0.309
Age, mean (SD)	59.2 (10.5)	60.6 (12.2)	0.014
Education, %			0.293
Secondary school	27.8	28.4	
>Secondary school	31.7	27.3	
Ethnicity, % white	91.7	89.5	0.138
Diabetes duration (years), mean (SD)	10.3 (10.2)	11.8 (11.8)	0.006
Diabetes-specific complications, %			<0.001
1 complication	29.6	26.4	
2 and more complications	38.3	49.2	
WHODAS II >20, %	20.8	30.8	<0.001
Disability days per month, % 15 or more days	12.1	18.8	0.001
Depression status, %			<0.001
Subthreshold depressive symptoms	34.3	39.9	
Severe depressive symptoms	5.2	10.9	

Table 2—Baseline characteristics among 1,064 people with type 2 diabetes, stratified by depression status

Baseline characteristics	No/minimal depression (*n* = 405)	One subthreshold depression episode (*n* = 214)	Two subthreshold depression episodes (*n* = 156)	Three subthreshold depression episodes (*n* = 85)	Four subthreshold depression episodes (*n* = 69)	One or more severe depression episodes (*n* = 135)	*P*
Sex, % women	47.2	53.3	57.1	58.8	76.8	60.7	<0.001
Age, mean (SD)	59.9 (9.9)	59.5 (10.6)	59.9 (10.7)	59.6 (11.9)	57.4 (11.2)	56.1 (10.5)	<0.001
Education, %							<0.001
<Secondary school	34.6	44.3	43.2	32.9	39.7	54.8	
Secondary school	32.1	24.3	21.3	25.9	36.8	24.4	
>Secondary school	33.3	31.4	35.5	41.2	23.5	20.7	
Marital status, %							<0.001
Married/living as married	71.8	68.7	65.2	67.1	45.6	51.9	
Divorced/ separated/ widowed	11.1	12.2	13.6	10.6	17.7	23.0	
Single	17.1	19.2	21.3	22.4	36.8	25.2	
Diabetes duration (years), mean (SD)	9.8 (9.6)	9.0 (9.9)	12.5 (12.7)	11.9 (11.0)	11.5 (10.5)	9.5 (8.1)	0.683
Diabetes-specific complications (DCI), %							<0.001
1	30.1	30.0	32.7	31.7	37.5	18.0	
2 and more	25.8	31.5	45.3	51.9	56.3	64.1	
BMI, %							0.009
Overweight	38.9	33.8	31.5	34.2	26.6	31.2	
Obese	37.9	46.0	50.0	55.3	57.8	50.0	
Smoking, %							0.066
Current smoker	15.8	17.8	17.3	11.8	23.2	27.4	
Former smoker	42.7	45.8	49.4	49.4	46.4	37.8	
Physical activity, % inactive	17.0	23.9	27.9	31.3	42.0	45.5	<0.001
Chronic conditions, %							<0.001
1	35.8	31.9	25.8	16.9	24.2	16.5	
2 and more	35.8	48.8	62.9	75.9	66.7	71.0	
WHODAS II ≥21, %	6.4	13.6	24.4	32.9	46.4	51.3	<0.001
Unhealthy days Past months (CDC), % 15 or more days	3.8	9.8	9.5	20.8	33.9	37.4	<0.001
Depression treatment, %							<0.001
Antidepressant medication	4.2	11.2	12.8	14.1	20.3	39.6	
Psychotherapy	0.7	3.7	2.6	4.7	7.3	19.3	

episodes compared with those with at least on severe depressive episode. Participants with two to four recurrent subthreshold depressive episodes were at higher risk for poor functioning than those with one recurrent subthreshold depressive episode ($P = 0.034$).

A similar dose-response relationship was observed between depression status and impaired health–related quality. There was a similar risk of impaired health–related quality for people with four subthreshold depressive episodes and people with at least one severe depressive episode.

In sensitivity analyses, these findings remained largely unchanged. In these analyses, the adjusted RRs were similar for the different cutoff points. The adjusted RRs did not differ systematically when we used the alternative classification of subthreshold depression (PHQ-9 score between 5 and 14 and a positive response to one of the first two PHQ-9 items). A similar association between depression status and poor functioning/ impaired health–related quality was observed when we repeated our analyses for those with complete data only and when we used different cutoff points for the classification of depression status (results not shown).

There was no significant depression status by sex interaction for the two outcome measures.

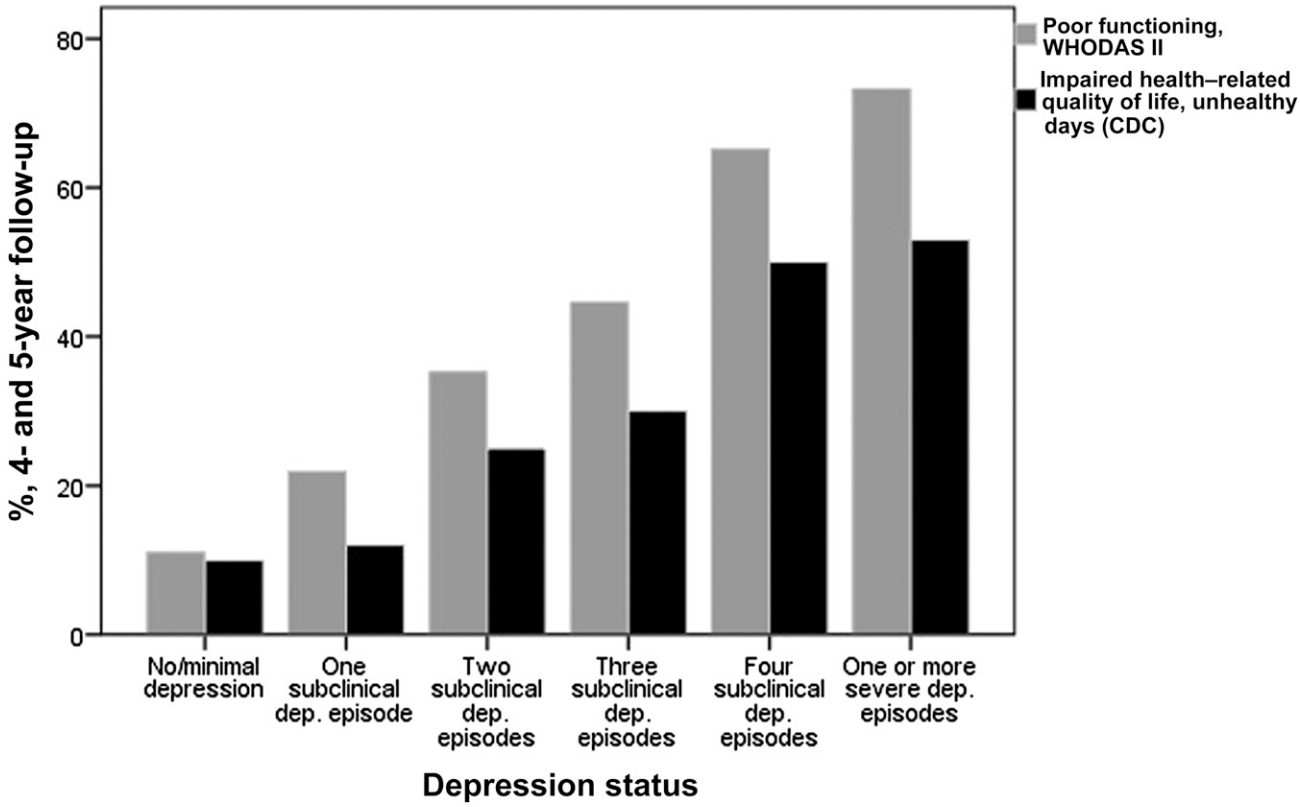

Figure 1—Association between depression status and poor functioning and impaired health–related quality of life. Dep., depression.

CONCLUSIONS

In this prospective community study of 1,064 people with type 2 diabetes who were followed for 5 years, we have evaluated the impact of recurrent subthreshold depressive symptoms on functioning. Nearly half of the participants did not suffer from severe depressive symptoms but suffered from subthreshold depressive symptoms during at least one of the four assessments, while approximately 13% suffered from severe depressive symptoms during at least one of the four assessments. We found a dose-response relationship between the number of recurrent subthreshold depressive episodes and increased risk of poor functioning and impaired health–related quality: the risk of poor functioning/impaired health–related

Table 3—Risk for poor functioning and impaired health–related quality of life at 4- or 5-year follow-up assessment

	Poor functioning WHODAS II[a]		Impaired health–related quality of life, unhealthy days (CDC)[b]	
Baseline characteristics	RR (95% CI)	Adjusted[c] RR (95% CI)	RR (95% CI)	Adjusted[d] RR (95% CI)
No/minimal depression	1	1	1	1
One subthreshold depression episode	1.98 (1.36–2.87)	1.53 (1.07–2.19)	1.29 (0.83–2.02)	1.07 (0.69–1.67)
Two subthreshold depression episodes	3.17 (2.24–4.49)	1.93 (1.36–2.73)	2.44 (1.64–3.63)	1.68 (1.11–2.53)
Three subthreshold depression episodes	4.02 (2.80–5.78)	2.14 (1.48–3.09)	2.99 (1.93–4.62)	1.86 (1.18–2.91)
Four subthreshold depression episodes	5.87 (4.24–8.12)	2.86 (1.98–4.13)	4.89 (3.35–7.14)	2.45 (1.59–3.78)
One or more severe depression episodes	6.60 (4.92–8.85)	2.77 (1.95–3.96)	5.18 (3.71–7.24)	2.27 (1.48–3.49)
P for trend	<0.001	<0.001	<0.001	<0.001
P for contrast: one subthreshold depression episode vs. two, three, or four subthreshold depression episodes	<0.001	<0.034	<0.001	0.016

RRs and 95% CIs were computed using Poisson regression for binary outcomes. [a]WHODAS II score ≥21 vs. WHODAS II score <21. [b]Fourteen and more unhealthy days vs. 13 and fewer unhealthy days. [c]Adjusted for sex, age, education, diabetes-specific complications, smoking, physical activity, BMI, chronic conditions, duration of diabetes, history of poor functioning, antidepressant treatment, and psychotherapy. [d]Adjusted for sex, age, education, diabetes-specific complications, smoking, physical activity, BMI, chronic conditions, duration of diabetes, history of impaired health–related quality of life, antidepressant treatment, and psychotherapy.

quality increased with the number of recurrent subthreshold depressive episodes even after controlling for poor functioning history/impaired health–related quality and other potentially confounding variables.

Our results confirm previous findings that even subthreshold depressive symptoms are associated with an increased risk of poor health outcomes and that a severe depression episode is a strong risk factor for poor health outcomes. What our study adds to the current literature is the important role of recurrent subthreshold depressive episodes on functioning and impaired health–related quality of life. The risk of poor functioning and impaired health–related quality of life was much higher for those with recurrent subthreshold depressive episodes than for those with a single subthreshold depressive episode. Participants with four recurrent subthreshold depressive episodes had a similar risk of poor functioning and impaired health–related quality of life than participants with one or more severe depressive episodes.

There are at least two ways in which recurrent subthreshold depressive symptoms can affect functioning outcomes. First, recurrent depressive symptoms, especially if combined with stressful life circumstances, may produce an allostatic load (14). The human body is in a state of dynamic equilibrium, or homeostasis. The allostatic systems (e.g., the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis) act adaptively to external challenges such as stress to maintain homeostasis and health (31). Prolonged adverse exposures, such as chronic stress or recurrent depression, might influence allostatic load, leading to an adverse impact on organ systems and functioning. Second, recurrent depressive symptoms might affect self-care behaviors, which, in turn, increase the risk of diabetes complications and poor functioning. To prevent diabetes-specific complications, diabetes treatment requires active self-care behaviors in multiple domains, including diet, smoking, physical activity, medication adherence, treatment-seeking behavior, and symptom monitoring. Depression might impede those demanding self-management behaviors through a decrease in energy and/or motivation to maintain behaviors that are protective against poor health outcomes (32). There is evidence that both minor and major depression are associated with decreased self-care behaviors in diabetes, and it is likely that recurrent subthreshold depression might have a stronger impact on self-care behaviors than a single minor or subthreshold depression episode (33).

Furthermore, it is likely that depressive symptoms and somatic symptoms/poor self-care behaviors interact with each other in a dynamic way: depressive symptoms can stop people from managing their diabetes as effectively as they need to, which can lead to complications and somatic symptoms, which, in turn, can result in more depressive symptoms (a vicious cycle).

Depression in people with type 2 diabetes is often undiagnosed and untreated. Li et al. (34), using data from 2006 BRFSS, found that nearly half of the adult diabetes patients with depression were undiagnosed. This rate was much higher for people with minor depression. Similar results have been reported from WHO Collaborative Study on Psychological Problems in General Health Care in 14 countries (35) and from the Pathways Study (36). In our study, approximately one-third of participants with three or four recurrent subthreshold depressive episodes received some form of depression treatment during the 4-year period with either antidepressant medication or psychotherapy treatment. This number is very low and depression treatment might not have been adequate or evidence-based for some of those participants. Early identification and treatment of recurrent subthreshold depression might be an important step in improving health outcomes. However, this is not an easy task: some somatic symptoms of subthreshold depression like lack of energy might be due to the diabetes-related problems and might not be an indicator of depression, which might result in a misclassification of depression. Diagnostic assessments should be conducted in people with (recurrent) subthreshold depression to minimize misdiagnosis or overdiagnosis of depression. Current evidence suggests that antidepressant drugs are ineffective in patients with mild and subthreshold depression when compared with placebo (37). The National Institute for Health and Care Excellence (NICE) in the U.K. suggests that antidepressant drugs should not routinely be used to treat subthreshold depression, but to consider those drugs in patients with subthreshold depressive symptoms who have either a past history of moderate or severe depression or a history of persistent subthreshold depressive symptoms (at least 2 years) (38). Active monitoring of (recurrent) depressive symptoms, psychoeducation, psychosocial interventions, and collaborative care (39) might be important treatment strategies in people with subthreshold depressive symptoms.

The strengths of the study were the cohort design, population-based sampling, large sample size, two different outcome measures, and repeated yearly assessment over 5 years. Some limitations, however, also need to be considered. The PHQ-9 is a brief questionnaire for the assessment of depression and is based on depressive symptoms in the last 2 weeks according to DSM-IV criteria, but it is not a clinical interview designed to diagnose depression. It is possible that some of the participants with recurrent subthreshold depressive episodes might have suffered from dysthymia rather than subthreshold depression. We have no information whether individuals suffered from depression before the baseline assessment and between the individual assessments, since the PHQ-9 focuses on depressive symptoms in the last 2 weeks. Some participants with no/minor depressive episodes in our study might have had recurrent depressive episodes before they started the study. The 12-item WHODAS II questionnaire was used for the assessment of functioning. Functioning is a complex, multidimensional phenomenon and a global self-report instrument might not cover all aspects of functioning. Unhealthy days are a very general

indicator of health-related quality of life. Another limitation is that our other study variables were self-reported, and that those measures may not fully capture a person's lifetime experiences. The sampling frame was limited to landline telephones, which might result in selection bias. Attrition might be another source of bias: those who dropped out had a poorer health status at baseline and a higher rate of severe depression. Finally, our findings may not be valid for people with undiagnosed diabetes.

In conclusion, our study conducted in a community-based sample of people with type 2 diabetes highlights a potential role of recurrent subthreshold depressive symptoms as an important risk factor for poor health outcomes in type 2 diabetes. Early identification, monitoring, and treatment of recurrent subthreshold depressive symptoms might improve functioning and quality of life in people with type 2 diabetes.

Funding. This work was supported by Operating Grant MOP-84574 from the Canadian Institutes of Health Research.

The funding agencies had no role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. N.S., A.M., R.B., I.S., A.L., and J.W. were responsible for the study concept and design. G.G. and M.C. were responsible for the acquisition of data. N.S., G.G., K.J.S., A.M., R.B., I.S., A.L., and J.W. analyzed and interpreted the data. N.S. drafted the manuscript. N.S., G.G., K.J.S., M.C., A.M., R.B., I.S., A.L., and J.W. critically revised the manuscript for important intellectual content. N.S., G.G., and M.C. were responsible for statistical analyses. N.S., A.M., R.B., I.S., A.L., and J.W. obtained funding. N.S. supervised the study. N.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord 2012;142(Suppl.):S8–S21
2. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 2007;370:851–858
3. Schram MT, Baan CA, Pouwer F. Depression and quality of life in patients with diabetes: a systematic review from the European depression in diabetes (EDID) research consortium. Curr Diabetes Rev 2009;5:112–119
4. Scott KM, Von Korff M, Alonso J, et al. Mental-physical co-morbidity and its relationship with disability: results from the World Mental Health Surveys. Psychol Med 2009;39:33–43
5. Gonzalez JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes Care 2008;31:2398–2403
6. Lin EHB, Rutter CM, Katon W, et al. Depression and advanced complications of diabetes: a prospective cohort study. Diabetes Care 2010;33:264–269
7. Goldney RD, Phillips PJ, Fisher LJ, Wilson DH. Diabetes, depression, and quality of life: a population study. Diabetes Care 2004;27:1066–1070
8. Egede LE. Diabetes, major depression, and functional disability among U.S. adults. Diabetes Care 2004;27:421–428
9. Egede LE. Effects of depression on work loss and disability bed days in individuals with diabetes. Diabetes Care 2004;27:1751–1753
10. Black SA, Markides KS, Ray LA. Depression predicts increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes. Diabetes Care 2003;26:2822–2828
11. Huang H, Russo J, Von Korff M, et al. The effect of changes in depressive symptoms on disability status in patients with diabetes. Psychosomatics 2012;53:21–29
12. Von Korff M, Katon W, Lin EHB, et al. Potentially modifiable factors associated with disability among people with diabetes. Psychosom Med 2005;67:233–240
13. Hardeveld F, Spijker J, De Graaf R, Nolen WA, Beekman ATF. Prevalence and predictors of recurrence of major depressive disorder in the adult population. Acta Psychiatr Scand 2010; 122:184–191
14. McEwen BS. Mood disorders and allostatic load. Biol Psychiatry 2003;54:200–207
15. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci USA 2001;98:4770–4775
16. Schmitz N, Nitka D, Gariepy G, et al. Association between neighborhood-level deprivation and disability in a community sample of people with diabetes. Diabetes Care 2009;32:1998–2004
17. Badawi G, Gariépy G, Pagé V, Schmitz N. Indicators of self-rated health in the Canadian population with diabetes. Diabet Med 2012;29:1021–1028
18. Schmitz N, Gariépy G, Smith KJ, et al. The pattern of depressive symptoms in people with type 2 diabetes: a prospective community study. J Psychosom Res 2013; 74:128–134
19. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001; 16:606–613
20. Gilbody S, Richards D, Brealey S, Hewitt C. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. J Gen Intern Med 2007;22:1596–1602
21. Chwastiak LA, Von Korff M. Disability in depression and back pain: evaluation of the World Health Organization Disability Assessment Schedule (WHO DAS II) in a primary care setting. J Clin Epidemiol 2003; 56:507–514
22. Von Korff M, Katon W, Lin EH, et al. Work disability among individuals with diabetes. Diabetes Care 2005;28:1326–1332
23. Andrews G, Kemp A, Sunderland M, Von Korff M, Ustun TB. Normative data for the 12 item WHO Disability Assessment Schedule 2.0. PLoS One 2009;4:e8343
24. Moriarty DG, Zack MM, Kobau R. The Centers for Disease Control and Prevention's Healthy Days Measures—population tracking of perceived physical and mental health over time. Health Qual Life Outcomes 2003;1:37
25. Okoro CA, Strine TW, Balluz LS, et al. Serious psychological distress among adults with and without disabilities. Int J Public Health 2009;54(Suppl. 1):52–60
26. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being—A World Health Organization study in primary care. JAMA 1998;280:147–151
27. Li CY, Ford ES, Mokdad AH, Jiles R, Giles WH. Clustering of multiple healthy lifestyle habits and health-related quality of life among U.S. adults with diabetes. Diabetes Care 2007;30:1770–1776
28. Ounpuu S, Chambers LW, Chan D, Yusuf S. Validity of the US Behavioral Risk Factor Surveillance System's health related quality of life survey tool in a group of older Canadians. Chronic Dis Can 2001;22:93–101
29. Brown DW, Brown DR, Heath GW, et al. Associations between physical activity dose and health-related quality of life. Med Sci Sports Exerc 2004;36:890–896
30. Fincke BG, Clark JA, Linzer M, et al. Assessment of long-term complications due to type 2 diabetes using patient self-report: the diabetes complications index. J Ambul Care Manage 2005;28:262–273
31. McEwen BS, Seeman T. Protective and damaging effects of mediators of stress—elaborating and testing the

concepts of allostasis and allostatic load. In *Socioeconomic Status and Health in Industrial Nations: Social, Psychological, and Biological Pathways*. Adler NE, Ed. New York, New York Academy of Sciences, 1999, p. 30–47

32. Egede LE. Effect of depression on self-management behaviors and health outcomes in adults with type 2 diabetes. Curr Diabetes Rev 2005;1:235–243
33. Egede LE, Ellis C, Grubaugh AL. The effect of depression on self-care behaviors and quality of care in a national sample of adults with diabetes. Gen Hosp Psychiatry 2009; 31:422–427
34. Li CY, Ford ES, Zhao GX, Ahluwalia IB, Pearson WS, Mokdad AH. Prevalence and correlates of undiagnosed depression among U.S. adults with diabetes: the Behavioral Risk Factor Surveillance System, 2006. Diabetes Res Clin Pract 2009;83:268–279
35. Lecrubier Y. Widespread underrecognition and undertreatment of anxiety and mood disorders: results from 3 European studies. J Clin Psychiatry 2007;68(Suppl. 2):36–41
36. Katon WJ, Simon G, Russo J, et al. Quality of depression care in a population-based sample of patients with diabetes and major depression. Med Care 2004;42:1222–1229
37. Baumeister H. Inappropriate prescriptions of antidepressant drugs in patients with subthreshold to mild depression: time for the evidence to become practice. J Affect Disord 2012;139:240–243
38. Depression: the treatment and management of depression in adults (NICE clinical guideline 90) [article online], 2009. Available from http://guidance.nice.org.uk/CG90.
39. Katon WJ, Lin EHB, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. N Engl J Med 2010;363:2611–2620