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Somatic depression in the picture

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Chapter 2

Association of depressive and anxiety disorders with diagnosed versus undiagnosed diabetes: an epidemiological study of 90,686 participants

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Abstract

Objective: To compare the odds of depressive and anxiety disorders for participants with diagnosed diabetes, participants with diabetes but unaware of this, and participants without diabetes. Such knowledge might improve etiological insight into psychopathology in diabetes.

Methods: Data of 90,686 participants (mean age: 45; 59% female) was used from LifeLines. Depressive and anxiety disorders were assessed by the mini-international neuropsychiatric interview (MINI). Odds of depression and anxiety were assessed for 3 groups: 1) diagnosed diabetes: diabetes medication use and/or self-reported “diabetes”; 2) undiagnosed diabetes: fasting blood glucose (FBG) ≥ 7.0 mmol/l, but no diabetes medication use and self-reported “no diabetes”; 3) no diabetes: FBG < 7.0 mmol/l and self-reported “no diabetes”. Logistic regression was performed to compare the odds of depression and anxiety in these groups, adjusting for age, sex, diabetes-related diseases, comorbid depressive or anxiety disorders, and HbA1C.

Results: 3002 (3.3%) participants were diagnosed with depression and 9018 (9.9%) with anxiety; 1781 (2.0%) had diagnosed and 786 (0.9%) had undiagnosed diabetes. Both diagnosed (OR=1.4: 1.1-1.8; $p=.006$) and undiagnosed (OR=1.8: 1.3-2.6; $p=.001$) diabetes were independently associated with depression. Odds of depression did not differ between diagnosed and undiagnosed diabetes (OR=0.7; $p=.17$). Diagnosed diabetes was independently associated with anxiety (OR=1.4: 1.2-1.7; $p<.001$), but undiagnosed diabetes was not (OR=0.8: 0.6-1.1; $p=.20$). Odds of anxiety were significantly higher in diagnosed compared to undiagnosed diabetes (1.68: 1.23-2.31; $p=.001$).

Conclusions: Depression was more prevalent in participants with diagnosed as well as undiagnosed diabetes, whereas anxiety was more prevalent only in participants who were aware of their diabetes. Longitudinal research is needed to assess whether these associations are causal or consequential.

Introduction

Depression and anxiety are more prevalent among participants with diabetes compared to the general population.^{1,2} Moreover, participants with diabetes in combination with depressive disorders are at increased risk for an adverse medical prognosis, such as diabetes complications and mortality.^{3,4} There still exists debate whether increased risks for these disorders might be dependent on the awareness of having a diagnosis of diabetes, or might already exist in undiagnosed cases. Such knowledge could improve insight into the etiology of psychopathology in patients with diabetes, and could result in improved treatment or prevention of depression and anxiety in these patients.

Several relatively small studies have compared depression prevalence in patients with diagnosed and undiagnosed diabetes. A meta-analysis on these studies found that participants with diagnosed diabetes had an increased prevalence of depression compared to undiagnosed diabetes.⁵ Depression prevalence in undiagnosed diabetes was not higher compared to participants without diabetes, suggesting that the psychological impact of the diabetes diagnosis underlies the increased risk for depression in patients with diabetes.⁵ However, analyses were not adjusted for underlying disease severity indicators such as severity of impaired glucose metabolism and somatic comorbidity, which could explain the higher depression prevalence in participants with diagnosed compared to undiagnosed diabetes.^{6,9} In addition, only one study in this meta-analysis used a diagnostic interview to assess depressive disorder; all other studies used questionnaires to assess depressive symptoms.

Recently, a study on a large Chinese cohort was published, which compared the prevalence of both depression and generalized anxiety disorder (GAD) for diagnosed and undiagnosed diabetes relative to participants without diabetes.¹⁰ This study also concluded that diagnosed, but not undiagnosed diabetes is associated with depression. Diagnosed diabetes was associated with GAD and undiagnosed diabetes was marginally associated with GAD.¹⁰ However, as in the meta-analysis, this study did not adjust for underlying diabetes severity factors. In addition, diagnosed and undiagnosed diabetes were not directly compared to each other, but only indirectly through a control group without diabetes. Further, only the anxiety disorder GAD was taken into account and analyses were not adjusted for comorbid mental disorders. Because anxiety and depression are highly comorbid, this could hamper the comparison between increased risks of these disorders.

The aim of the current study was to directly compare diagnosed and undiagnosed diabetes for the odds of depressive and anxiety disorders assessed by a systematic diagnostic interview, while adjusting for the severity indicators HbA1c and diabetes-related somatic comorbidity, and co-morbid anxiety and

depression. For this purpose, a large population-based sample consisting of 90,686 participants was used.

Methods

Design and participants

We used data from LifeLines, a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 participants living in the North East region of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics.¹¹ Baseline data was recruited between 2006 and 2013.¹² Participants receive a questionnaire every 1,5 year and a basic medical examination every 5 years. The aim is to follow participants for at least 30 years with extensive standardized measurements. After complete description of the study to the subjects, written informed consent was obtained.

The total LifeLines sample available for this study consisted of 95,433 participants. When participants had a Mini-Mental State Examination score <26 (indicating poor cognitive function) or were unable to fill out questionnaires, they did not get a psychiatric interview and were therefore excluded from our analyses (N=2396). In addition, the first 2351 participants of Lifelines did not receive a psychiatric interview for current diagnoses of depressive and anxiety disorders and were excluded as well, leaving 90,686 participants (59% female) to be included in this study, aged 18-93 years (mean: 45).

Assessment of diagnosed and previously undiagnosed diabetes

Fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) were measured in venous blood. Questionnaires about somatic diagnoses and current medication use were used to assess diabetes and somatic comorbidities associated with diabetes. Participants were classified as diagnosed diabetes if they reported medication for diabetes on a medication list, or if they brought drug containers including diabetes medication, or if they reported a diagnosis of diabetes and treatment for diabetes on a questionnaire on history of medical illnesses. Medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system. When patients only used tablets (ATC-code A10B) or diet for their diabetes, they were classified as type 2 diabetes. When patients used insulin (ATC-code A10A), type of diabetes was based on self-report of type 1 diabetes or type 2 diabetes. In case this variable was missing, or patients reported not to know the type, we assessed whether insulin use started within (type 1

diabetes) or after (type 2 diabetes) one year after the diagnosis. Participants were classified as undiagnosed diabetes if they had a FBG ≥ 7.0 mmol/l and did not receive treatment for diabetes. Participants were classified as no diabetes if they had a FBG < 7.0 mmol/l and did not receive treatment for diabetes.

Assessment of depressive and anxiety disorders

The presence of a current (past 2 weeks) depression (major depressive episode or dysthymic mood) and anxiety (panic disorder, agoraphobia, social anxiety disorder, and GAD) was assessed according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria. Post-traumatic stress disorder and specific phobia were not assessed in Lifelines. A systematic diagnostic interview, the Mini-international neuropsychiatric interview (MINI 5.0.0), was performed by trained research assistants. Previous studies suggested acceptable validity and reliability of the MINI.¹³ The MINI assessment took place during the baseline visit. At the time of the interview, participants were not yet informed on the outcome of the diabetes screening.

Analyses

Baseline characteristics were compared according to diabetes state using F-tests and chi-square. Participants with diagnosed diabetes, undiagnosed diabetes, and no diabetes were compared on the presence of depressive and anxiety disorders, unadjusted for any confounders. Participants with and without missing data were compared with respect to baseline characteristics. Logistic regression analyses were performed to test whether diagnosed and undiagnosed diabetes were associated with increased odds of depression and anxiety relative to no diabetes. For this purpose, two dummy variables of diabetes were added to the models, with 'no diabetes' as reference category. In addition, we directly compared the odds of depressive and anxiety disorders between diagnosed and undiagnosed diabetes, using two dummy variables of diabetes with 'diagnosed diabetes' as reference category. The analyses were performed in three models. In model 1, analyses were adjusted for age and sex. In model 2, analyses were additionally adjusted for self-reported current presence of the following diabetes-related diseases: CHD (previous MI, coronary artery bypass graft (CABG) surgery, or percutaneous coronary intervention (PCI)), stroke, and impaired renal function, which were assessed by a questionnaire on history of medical illnesses. Furthermore, this model was adjusted for comorbid anxiety and depression. In model 3, analyses were additionally adjusted for HbA1c. Model 3 was only performed for the diagnosed versus undiagnosed diabetes groups, as participants without diabetes have no marked impaired glucose regulation.

In addition to our main analyses, we performed a sensitivity analysis in which we only took type 2 diabetes into account. Participants with undiagnosed

diabetes were over 18 years and therefore more likely to suffer from type 2 diabetes, which may be physiologically different from type 1 diabetes. Thus, this sensitivity analysis was performed to analyze the possibility that differences between diagnosed and undiagnosed diabetes were due to the presence of type 1 diabetes in the diagnosed but not the undiagnosed group.

For all analyses, SPSS 20 was used and significance level was set at 0.05, two-tailed.

Results

Sample characteristics

The sample for the current study consisted of 90,686 participants, of which 573 (0.6%) participants did not have a MINI assessment for depressive disorders and 85 (0.1%) for anxiety disorders. Participants without a depression assessment differed from participants with this assessment in that they were more likely to have diagnosed diabetes (3.7% vs. 2.0%; $p=0.004$), to have a higher HbA1c (5.66 vs. 5.57; $p<.001$), and to have somatic comorbidity (5.9% vs. 3.0%; $p<.001$). There was no difference with respect to age and sex. Participants without an anxiety

Table 1: Characteristics of participants according to total sample and diabetes status

Characteristics	Total sample N=90,686		No DM N=87,876		UDM N=769		DDM N=1,811		p^a	p	p
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	UDM vs. no DM	DDM vs. no DM	DDM vs. UDM
Age (years)	45.5	75	45.2	76	53.1	12	55.8	12	.004	<.001	<.001
Female	53,306	59%	51,934	59%	303	39%	927	51%	<.001	<.001	<.001
BMI (kg/m ²)	26.1	4.3	26.0	4.2	30.1	5.3	30.1	5.6	<.001	<.001	.90
Comorbidity ^b	2,738	3.0%	2,414	2.7%	53	6.9%	265	14.6%	<.001	<.001	<.001
Any DEP disorder	3,002	3.3%	2,858	3.3%	34	4.5%	90	5.0%	.067	<.001	.54
MDD	2,059	2.3%	1,947	2.2%	24	3.1%	73	4.0%	.090	<.001	.27
Dysthymia	943	1.0%	911	1.1%	10	1.4%	17	1.0%	.45	.76	.43
Any ANX disorder	9,018	9.9%	8,669	9.9%	66	8.6%	244	13.5%	.24	<.001	<.001
GAD	3,894	4.3%	3,739	4.3%	25	3.3%	110	6.1%	.17	<.001	.003
Social phobia	823	0.9%	788	0.9%	10	1.3%	24	1.3%	.24	.056	.96
PD-Agoraphobia	2,067	2.3%	2,012	2.3%	12	1.6%	36	2.0%	.18	.40	.46
PD+Agoraphobia	714	0.8%	682	0.8%	4	0.5%	27	1.5%	.42	.001	.038
Agoraphobia-PD	3,079	3.4%	2,940	3.3%	29	3.8%	95	5.3%	.51	<.001	.11
FBG (mmol/L)	5.01	0.82	4.93	0.50	8.38	2.3	7.82	2.5	<.001	<.001	<.001
HbA1c (%)	5.57	0.43	5.53	0.31	6.76	1.5	7.00	1.06	<.001	<.001	<.001

DM = diabetes mellitus; UDM = undiagnosed diabetes mellitus ; DDM = diagnosed diabetes mellitus; BMI = body mass index; DEP = depressive disorder; MDD = major depression disorder; ANX = anxiety disorder; GAD = generalized anxiety disorder; PD = panic disorder; FBG = fasting blood glucose

^a P-values are based on F-test and chi square.

^b Comorbidity = at least one of the following DM-related conditions: coronary heart disease, stroke and impaired renal function.

assessment only differed from participants with this assessment with respect to HbA1c (5.71% vs. 5.57%; $p=.002$).

Prevalence of depression, anxiety and diabetes

Of the total sample, 3002 (3.3%) were diagnosed with any depressive disorder and 9018 (9.9%) with any anxiety disorder; these numbers include 1866 (2.1%) fulfilling the criteria for both conditions. There were 1811 (2.0%) participants with diagnosed diabetes and 769 (0.85%) with undiagnosed diabetes. In table 1, baseline characteristics were pairwise compared according to diabetes status.

Diabetes status and odds of depression and anxiety

The results of the multivariable logistic regression analyses for depression and anxiety are depicted in tables 2 and 3 respectively.

Both diagnosed (OR=1.8: 1.5-2.3) and undiagnosed (OR=1.7: 1.2-2.4) diabetes were significantly associated with higher odds of depression compared to no diabetes. No differences in odds of depression between undiagnosed and diagnosed diabetes were observed (OR=1.09: 0.7-1.6). These findings apply to both before and after additional adjustment for covariates, namely anxiety and somatic comorbidity (model 2) and HbA1c (model 3) (table 2).

Table 2: Logistic regression analyses predicting depressive disorders.

	Model 1^b OR (95% CI)	Model 2^c OR (95% CI)	Model 3^d OR (95% CI)
Undiagnosed DM vs. no DM	1.69 (1.19-2.39)**	1.79 (1.23-2.61)**	
Diagnosed DM vs. no DM	1.84 (1.48-2.28)***	1.39(1.10-1.76)**	
Diagnosed DM vs. Undiagnosed DM	1.09 (0.73-1.63)	0.78 (0.50-1.20)	0.75 (0.48-1.16)
<i>Covariates:</i>			
Age (per year)	0.990 (0.987-0.993)***	0.989 (0.986-0.992)***	0.987 (0.984-0.991)***
Female gender	1.73 (1.60-1.88)***	1.34 (1.23-1.46)***	1.34 (1.23-1.46)***
Comorbidity ^a (0 vs. >1)		2.07 (1.72-2.50)***	2.04 (1.69-2.46)***
Any anxiety disorder		18.2 (16.8-19.7)***	18.1 (16.8-19.6)***
HbA1c			1.23 (1.12-1.35)***

OR = odds ratio; CI = confidence interval; DM = diabetes mellitus. * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

^a Comorbidity = at least one of the following DM-related conditions: coronary heart disease, stroke and impaired renal function

^b Model 1 is adjusted for age and sex

^c Model 2 is additionally adjusted for comorbidity and anxiety disorder

^d Model 3 is additionally adjusted for HbA1c; NB: Model 3 was only performed for the diagnosed versus undiagnosed DM group, as participants without DM have no impaired glucose regulation.

Only diagnosed (OR=1.6: 1.4-1.8), but not undiagnosed (OR=1.0: 0.8-1.3) diabetes was associated with higher odds of anxiety compared to no diabetes. In addition, odds of anxiety were significantly higher for diagnosed compared to undiagnosed diabetes (OR=1.6: 1.2-2.1). These findings apply to both before and after adjustment for depression and somatic comorbidity (model 2) and HbA1c (model 3) (table 3).

Post hoc, a sensitivity analysis was performed in which we only took diagnosed type 2 diabetes (N=1580) into account. This sensitivity analysis was performed to analyze the possibility that differences between diagnosed and undiagnosed diabetes were due to the presence of type 1 diabetes (N=230) in the diagnosed but not the undiagnosed group. This did not change the results (data not shown).

Because undiagnosed diabetes was associated with higher odds of depression compared to no diabetes, we post hoc tested whether undiagnosed pre-diabetes was also associated with higher odds of depression. Results, adjusted for age, sex, anxiety and somatic comorbidity, showed that pre-diabetes was also associated with higher odds of depression compared to no diabetes (pre-diabetes defined by the American Diabetes Association(ADA): FBG: 5.6-6.9 mmol/l; N=9,123; OR=1.2: 1.0-1.3; p=.014; pre-diabetes defined by World Health Organization (WHO): FBG: 6.1-6.9 mmol/l N=2,458; OR=1.6:1.3-2.0; p<.001).

Table 3: Logistic regression analyses predicting anxiety disorders.

	Model 1^b OR (95% CI)	Model 2^c OR (95% CI)	Model 3^d OR (95% CI)
Undiagnosed DM vs. no DM	1.0 (0.78-1.30)	0.86 (0.65-1.14)	
Diagnosed DM vs. no DM	1.58 (1.38-1.82)***	1.42(1.22-1.65)***	
Diagnosed DM vs. Undiagnosed DM	1.57 (1.18-2.10)**	1.65 (1.21-2.27)**	1.64 (1.19-2.25)**
<i>Covariates:</i>			
Age (per year)	0.995 (0.993-0.997)***	0.996 (0.994-0.998)***	0.996 (0.994-0.998)***
Female gender	1.81 (1.72-1.90)***	1.74 (1.66-1.83)***	1.75 (1.66-1.84)***
Comorbidity ^a (0 vs. >1)		1.17 (1.02-1.34)*	1.17 (1.02-1.34)*
Any depressive disorder		18.2 (16.8-19.7)***	18.1 (16.7-19.6)***
HbA1c			1.02 (0.95-1.09)

OR = odds ratio; CI = confidence interval; DM = diabetes mellitus. *p<0.05; **p<0.01; ***p<0.001.

^a Comorbidity = at least one of the following DM-related conditions: coronary heart disease, stroke and impaired renal function

^b Model 1 is adjusted for age and sex

^c Model 2 is additionally adjusted for comorbidity and depressive disorder

^d Model 3 is additionally adjusted for HbA1c; NB: Model 3 was only performed for the diagnosed versus undiagnosed DM group, as participants without DM have no impaired glucose regulation.

Discussion

This cross-sectional study in a population-based sample of 90,686 participants revealed that current depressive disorder was more prevalent in participants who were aware as well as participants who were unaware of their diabetes, while current anxiety disorder was only associated with diabetes when participants were aware of their diabetes.

To our knowledge, only two previous studies examined the prevalence of anxiety in diagnosed and undiagnosed diabetes.^{10,14} One study of a Chinese cohort found higher odds of GAD in diagnosed and undiagnosed diabetes, although the association with undiagnosed diabetes was marginally significant.¹⁰ In contrast, the other study did not find any increased odds of elevated anxiety symptoms, neither for impaired glucose metabolism (IGM), nor for diagnosed diabetes.¹⁴ In the current study we found that the odds of anxiety disorder were only higher for diagnosed diabetes.

Our results regarding depression are different from a meta-analysis and the recent Chinese study, which found that only participants with diagnosed diabetes, but not participants with undiagnosed diabetes, had higher odds of depression compared to participants without diabetes.^{5,10} Associations between diabetes and depression and anxiety may be different in Asian populations compared to western populations.¹⁰ In addition, a limitation of the Chinese study is that the authors did not directly compare diagnosed versus undiagnosed diabetes. However, the meta-analysis found a significantly higher depression prevalence in diagnosed diabetes compared to undiagnosed diabetes.⁵ These previous findings may suggest that the awareness of diabetes explains the higher risk of depression in participants with diabetes. However, these previous studies did not adjust for comorbid anxiety disorders and for important factors indicating diabetes disease severity, which could explain a higher depression prevalence in diagnosed versus undiagnosed diabetes.^{6,9} Nevertheless, some of the included studies in the meta-analysis did adjust for number of chronic diseases or (risk factors of) CHD, which in general attenuated the odds ratios in these studies,¹⁴⁻¹⁸ indicating that adjustment for potential confounders is important. In addition, in our unadjusted analysis we only found a trend for a difference in depression prevalence between participants with undiagnosed diabetes and no diabetes (table 1), which became significant after adjustment for confounders. Furthermore, in the current study, participants with diagnosed diabetes had more impaired glucose metabolism, more somatic comorbidity, and more anxiety compared to participants with undiagnosed diabetes. Moreover, these factors were significantly associated with depression. However, also in our analyses without adjustment for disease severity indicators and anxiety, there were no significant differences between depression odds for diagnosed and undiagnosed diabetes. Possible other explanations for the inconsistencies with the meta-analysis may be that most studies included in

the meta-analysis used depression questionnaires.⁵ Questionnaires, more than diagnostic interviews, may reflect diabetes distress¹⁹ and can pick up somatic complaints reflecting the severity of diabetes instead of depression.²⁰ Therefore, depression prevalence in diagnosed diabetes may be over-estimated when using a questionnaire, which may explain the different findings for studies using either questionnaires or diagnostic interviews to measure anxiety and depression. More research is required to unravel the inconsistencies in the literature, in which analyses should be adjusted for diabetes severity indicators and comorbid depression and anxiety.

Interestingly, despite the fact that anxiety and depression are highly comorbid disorders,²¹ the current results may suggest a different etiology of the two disorders in the context of diabetes. Although in this cross-sectional study we cannot determine causal mechanisms, we can speculate that a physiological process might play a more profound role in increased depression prevalence, while a psychological process might be particularly responsible for increased anxiety prevalence. How could this be explained? Previous studies proposed several physiological mechanisms that might explain why diabetes patients are at increased risk for depression. Diabetes and depression are both associated with increased inflammatory activity and increased HPA-axis activity, which are thought to link diabetes and depression in a bi-directional way.^{22,23} In addition, insulin deficiency has been found to have a direct impact on neurotransmitter metabolism and is associated with decreased serotonin production in the brain, which is associated with depression.^{8,24-28} Furthermore, our results show a relation between worse glycemic control (as reflected in HbA1c) and depression, an association that has been reported before.⁶⁻⁸ We did not find this relation for anxiety. Alternatively, it could also be that depression preceded the onset of diabetes and therefore prevalence of depression is similar in undiagnosed and diagnosed diabetes. This would be in line with a previous meta-analysis showing that depression predicts the onset of diabetes.¹ Depression is associated with increased sympathetic and hypothalamic-pituitary-adrenal axis activity and pro-inflammatory cytokines, which can induce insulin resistance and thereby increase the risk of diabetes.²² Also, depression is associated with poor health behaviors (e.g. smoking, high fat diet, and low physical activity) that could increase risk of diabetes.²⁹ Prospective studies, addressing biological and behavioral measures relevant to diabetes and depression, are needed to examine whether depression predisposes to diabetes onset and vice versa.

Post-hoc tests showed that undiagnosed pre-diabetes was also associated with higher odds of depression, compared to no diabetes. Interestingly, odds of depression were higher using the more conservative threshold of pre-diabetes defined by the WHO (6.1-6.9 mmol/l), than using the more liberal threshold of the ADA (5.6-6.9 mmol/l). This renders support for the speculation that there is a physiological etiology for depression in participants with diabetes. In this light,

it could be that some symptoms of depression are a direct result of physiological mechanisms associated with diabetes. Worse glycemic control is associated with symptoms such as fatigue, sleeping problems, and concentration problems.^{6,30} In addition, eating disorders are common among participants with diabetes, and insulin treatment can be associated with weight gain.³¹

The question arises why awareness of a diabetes diagnosis might be more of influence on anxiety than depression. The need for monitoring ones blood glucose and increased risk for future medical complications or related diseases may induce anxiety in participants with diabetes.³² In addition, the treatment of diabetes may increase anxiety.³³⁻³⁵ An alternative explanation could be help seeking behavior. Participants with anxiety might go to the general practitioner at an earlier stage in which case they are more likely to be classified as diagnosed diabetes. Because this was a cross-sectional study, this could not be investigated. Finally, it cannot be excluded that unmeasured confounding, due to factors associated with diabetes and depressive, but not anxiety disorders, explains the increased depression prevalence in undiagnosed diabetes. However, given the overlap between anxiety and depression, it is difficult to think of a non-physiological risk factor shared between diabetes and depressive disorders specifically.

A strength of this study is that, to our knowledge, this is the first study comparing the prevalence of both the major anxiety and depressive disorders in diagnosed and undiagnosed diabetes. In addition, we adjusted analyses for underlying diabetes severity indicators, including HbA1c and diabetes-related somatic comorbidity, and for comorbid anxiety and depressive disorders. Another strength of this study is that it was performed in a large sample including 90,686 participants, who were all assessed for current depressive and anxiety disorders using a diagnostic interview.

It is important to note that the LifeLines study is not a representative sample of the general population. The percentages for depressive and anxiety disorders³⁶ and those for diagnosed and undiagnosed diabetes³⁷ are slightly lower in LifeLines than previously reported. The lower percentages for psychopathology³⁶ might also be explained by the fact that we used current diagnoses (past 2 weeks) of psychopathology, while earlier reports used past year diagnoses. We should acknowledge that using a current diagnosis of MDD, with no information on history of MDD, increased the chance of including false positive as well as false negative cases of MDD in the analyses. Nevertheless, it is not likely that these differences will importantly influence the reported associations of diabetes with depression and anxiety. Furthermore, as poor glycemic control can produce symptoms that overlap with depressive symptoms, such as sleep disruption, fatigue and concentration difficulties, we could have identified persons as having MDD when in fact their symptoms are a result of their (un)diagnosed diabetes. Another limitation is that FBG was measured only once, while according to the WHO guidelines, in asymptomatic patients this must be confirmed by at least one

further measure on a subsequent day. Consequently, in the current study some participants with undiagnosed diabetes might have been incorrectly classified as such, as result of a chance finding. This could have led to an underestimation of the odds of psychopathology for undiagnosed diabetes.

Furthermore, there was no information available for microvascular complications of diabetes, such as retinopathy, neuropathy, and impotence. Therefore, only macro-vascular comorbidities (stroke, CHD and renal disease) could be taken into account in order to adjust for markers of disease severity in the analyses, thus ignoring effects of potentially disabling diabetes complications. As participants with undiagnosed diabetes were over 18 years, we assumed - in the sensitivity analysis - that the participants with undiagnosed diabetes suffered from type 2 diabetes. However, we could not preclude that some of these participants had type 1 diabetes, which is an additional limitation of this study. Finally, as our study was based on cross-sectional data, causality could not be determined. However, a cross-sectional design is appropriate in order to examine the current research question whether awareness of the diagnosis is associated with the presence of psychopathology.

Thus, although we are aware that we cannot determine causality with this cross-sectional design, our results suggest that physiological factors increase the risk for depressive disorders, while the psychological impact of diabetes increases risk for anxiety disorders. This potential difference may have important treatment and research implications. Adherence to diet advices and medication is not only important for the physical health of depressed diabetes patients, but could potentially also improve their mental health. It is advisable to treat physiological and psychological factors simultaneously. A randomized controlled trial in patients with diabetes and depression showed that an intervention that addressed both medical risk factors and depressive symptoms, improved control of medical disease and reduced depressive symptoms.³⁵

For anxiety, it might be more important to pay attention to the patient's coping with the diabetes diagnosis. Unfortunately, effective treatment programs are largely lacking. A review that evaluated effectiveness of some interventions for anxiety in diabetes patients revealed that only 2 out of 7 interventions studies found a positive effect.³⁸ One of these interventions was a psychological stress management intervention and the other was an education program. However, anxiety in the context of medical comorbidities has not been studied a lot.³⁹ Therefore, further research is needed to assess whether an intervention focused on a patient's coping with the diabetes diagnosis will improve anxiety symptoms in the context of diabetes. Also, because of inconsistent results in the literature, this study should be replicated in other cohorts. Finally, the question arises whether differences in odds of depression and anxiety are also present when comparing other diagnosed and undiagnosed chronic medical conditions. This would be interesting to examine in future research.

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