Diabetes and emotional distress

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CHAPTER 1

General introduction

Growing number of people with diabetes

The general term "diabetes mellitus" subsumes several metabolic conditions characterized by hyperglycemia (high blood glucose levels), resulting from insufficient action of the hormone insulin on peripheral target tissues in the body or from an absolute deficiency of insulin secretion [1]. Diabetes is affecting a growing number of people worldwide. Global prevalence estimates are projected to rise from 171 million in 2000 to 366 million in 2030 [2]. Given the associated increased risk of disability [3, 4] and mortality [5], diabetes is considered one of the main threats to human health of the 21st century [6]. Moreover, due to a relatively long asymptomatic phase between the onset of hyperglycemia and an actual clinical diagnosis in most individuals with type 2 diabetes, almost half of the total diabetes population is unaware of their disease status [7]. In The Netherlands, the scope of the problem is similar to these global trends, with approximately one million people having diabetes [8]. Early epidemiological studies estimated that up to 50% of all Dutch people with diabetes were undiagnosed [9], but more recent figures suggest that the number of Dutch people with undiagnosed type 2 diabetes has decreased to approximately one quarter of the total diabetes population [8]. This may be due to an increased awareness among citizens and health care providers, improvements in screening and early diagnosis [8].

Diabetes mellitus: pathophysiology

There are two main forms of diabetes, which differ markedly in etiology and clinical presentation. Type 1 diabetes (5 – 10% of those with diabetes) is due to autoimmune destruction of the insulin producing ß-cells of the pancreas, which leads to an absolute deficiency of insulin secretion [10]. This condition commonly develops in children and young adults, but can occur at any age, even in the elderly [10]. It often presents with acute diabetes symptoms and markedly elevated blood glucose levels, and most people are diagnosed soon after the onset of hyperglycemia [10]. In type 2 diabetes, which accounts for about 90% of all diabetes cases in high-income countries [7], hyperglycemia is caused by a diminished response to insulin by peripheral target tissues in the body and abnormal insulin secretion, either of which may predominate [6, 10]. The risk of developing type 2 diabetes is most likely an interaction between genetic predisposition, demographic factors (e.g. age, race / ethnicity), and lifestyle-related influences such as unhealthy dietary behaviors (e.g. high intake of saturated fats and a high caloric diet), obesity and lack of physical activity [10]. As hyperglycemia tends to develop more gradually and symptoms are often not noticed in the earlier stages of the disease, type 2 diabetes may go undiagnosed for many years [10]. Although most people develop type 2 diabetes in middle age or later, it is now being increasingly diagnosed in young adults and children as well, paralleling the escalating rates of obesity across all age categories in the Western world [6].

Living with diabetes

Leading a fulfilling and enjoyable life while having diabetes is certainly possible for many people but, for others, coping with the condition, its management and its complications can be both demanding and challenging. For example, diabetes can be accompanied by acute short-term complications, such as hypoglycaemia and ketoacidosis, and by long-term micro-vascular complications (e.g. retinopathy, neuropathy and nephropathy) and macro-vascular disease (e.g. heart disease, stroke and peripheral arterial disease) [11]. To date, diabetes remains a predominant cause of vision loss, renal failure and lower extremity amputations in developed countries [12]. A large-scaled study among over 7,000 people with type 2 diabetes in eight European countries concluded that approximately 72% of the participants had at least one complication, while 24% of the total study group had both micro- and macrovascular complications [3]. Vascular complications are common in type 1 diabetes as well, with a recent study reporting a 30-year cumulative incidence of proliferative retinopathy, nephropathy, and cardiovascular disease of 50%, 25%, and 14%, respectively [13]. From previous landmark studies such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), we know that these vascular conditions can be prevented or delayed through optimal management of blood glucose levels and other cardiovascular risk factors such as blood pressure and cholesterol [14-18]. The importance of daily self-management is therefore unquestionable; yet, diabetes self-care can place a heavy burden on individuals. Self-management encompasses a wide range of activities, including daily oral medication and / or insulin use, blood glucose monitoring, foot care, healthy eating (and, for some, carbohydrate counting), and engaging in regular physical activity. Unsurprisingly, having diabetes (and its complications) can have a serious negative impact on the emotional well-being and quality of life of people living with this condition [19-22]. In turn, emotional distress may hamper self-care behaviors and increase the risk of adverse diabetes outcomes [23, 24].

Depression is common in diabetes

Depression can be considered as a common complication of diabetes, affecting 10 – 30% of people with diabetes [19]. Major depressive disorder is a psychiatric condition characterized by at least one of two core symptoms: depressed mood (dysphoria) and a markedly diminished interest or pleasure in all, or almost all, activities (anhedonia) [25]. Additional symptoms may include significant weight loss or weight gain / decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate / indecisiveness, and recurrent thoughts of death and suicide [25]. Rather than encompassing a homogenous condition, depression is characterized by a variety of symptoms and subtypes, which do not all have to be present in any particular individual with depression [26]. Self-

report questionnaires are often utilized to determine the presence of elevated depressive symptoms, but a syndromal diagnosis of major or minor depression can only be ascertained using a standardized diagnostic interview [25]. A meta-analysis of 42 studies concluded that the prevalence of depression in diabetes was significantly higher when assessed by self-report questionnaires (31%) than by standardized diagnostic interviews (11%) [19].

Depression appears to be nearly twice as common in people with type 2 diabetes compared with those without (18% vs. 10%, OR = 1.6, 95% CI 1.5 – 1.7) [27], but a reliable comparison across studies with regard to the assessment method used to define depression could not be given due to the small number of controlled studies using a diagnostic interview. A systematic review published in 2006 suggested that it would be premature to conclude that the prevalence of depression is elevated in type 1 diabetes [28], but a more recent study showed that adults with type 1 diabetes were twice as likely to report symptoms of depression and / or use antidepressant medication, compared to age- and sex-matched individuals without diabetes [29]. In outpatient settings, about one-third of people with type 1 or type 2 diabetes report depression [30], while lower prevalence estimates (15 – 20%) have been found for type 2 diabetes in population-based studies [31, 32]. Furthermore, the prevalence of depression appears to be increased among people with diabetes and (multiple) co-morbid medical conditions [31, 33, 34]. It is important to distinguish depression from diabetes-specific emotional distress, which concerns negative emotions specifically related to living with diabetes and its self-management [21, 35], although these diabetes-specific emotional problems appear to be particularly common in people with diabetes and depression [36-38].

The complex interplay between diabetes and depression

A close link between depression and diabetes has been acknowledged for many years, but the exact nature of this relationship remains unclear [39]. For example, for type 2 diabetes, there is convincing evidence that the relation with depression is bidirectional. Several meta-analyses have identified depression as a risk factor for the development of type 2 diabetes [40, 41] and the presence of type 2 diabetes may contribute to the onset of depression [40, 42]. Any prospective association between depression and the onset of type 1 diabetes is yet to be established.

The adverse consequences of depression in people with diabetes

Co-morbid depression in diabetes not only has a profound negative impact on patient-reported health outcomes such as quality of life [43], but may also be related to other poor health outcomes. A growing number of studies suggest that depression may predict the development of macrovascular disease and microvascular complications [24, 44-50], although most work to date has exclusively used data from samples from the USA. Several prospective

studies have shown that people with diabetes and co-morbid depression are more likely to die earlier than their non-depressed counterparts [51-55], where mortality risks appear to extend beyond cardiovascular-related causes [54]. Moreover, having both diabetes and depression appears to have an association with health beyond that due to having either diabetes or depression alone [44, 51]. Findings regarding the association between depression and suboptimal glycemic control are less consistent. A meta-analysis of 24 cross-sectional studies published up until 1999 concluded that depression was significantly associated with higher glycated hemoglobin (HbA_{1c}) concentrations in people with type 1 and type 2 diabetes (standardized effect size 0.17, 95% CI 0.13 – 0.21) [56], but subsequent studies have yielded mixed results [57].

Aims and outline of thesis

While our understanding of the relation between diabetes and emotional distress has increased in the past twenty years [58], many important issues remain to be elucidated. The present thesis will address the following main questions:

- Does hyperglycemia and / or the burden of living with diabetes explain the high prevalence of depression in diabetes?
- What is the course of depression in type 2 diabetes?
- Is depression associated with timing of insulin therapy in type 2 diabetes?
- Are symptom-clusters related to the two core features of depression (dysphoria, anhedonia) differentially associated with health-outcomes in people with type 2 diabetes, and are there symptom-specific mechanisms in play?
- What is the role of other, more chronic forms of emotional distress in diabetes?

Understanding the high prevalence of depression in diabetes

Although the precise reasons for the higher prevalence rates of depression in people with diabetes are not fully understood, there are two dominant hypotheses focusing on the initial onset of depression in this group [59]. The “emotional burden hypothesis” states that the higher rate of depression in people with diabetes results from the burden of having to manage a chronic condition on a daily basis and / or having to cope with its short- or long term complications [59]. Alternatively, depression may be provoked by biochemical changes directly due to diabetes [59] such as hyperglycemia. One (indirect) way to study whether hyperglycemia affects mood would be to compare the prevalence of depression in people with normal glucose metabolism with the rate of depression in people who, by definition, have higher levels of blood glucose (those with impaired glucose metabolism or undetected type 2 diabetes). Additional support for the emotional burden hypothesis is found when people with known type 2 diabetes are more likely to report depression than people with undiagnosed type 2 diabetes or impaired glucose metabolism, who do not have the

emotional distress of being diagnosed with or having to self-manage a chronic condition. Therefore, **Chapter 2** will examine whether the prevalence of depression in people with impaired glucose metabolism or undiagnosed diabetes is elevated relative to individuals with normal glucose metabolism or decreased relative to those with previously diagnosed type 2 diabetes by reviewing the literature and conducting a meta-analysis of studies on this topic.

The course of depression in people with diabetes

Previous research among people with diabetes has mainly focused on prevalence estimates of depression in cross-sectional studies [19, 27, 28]. Of the longitudinal studies that have been conducted, most have examined incident depression [42]. However, few have taken history of depression before study onset into account, and should therefore be interpreted cautiously with respect to incident depression in the strictest sense (i.e. first occurrence) [42]. Longitudinal studies in general community and primary care samples have provided ample evidence that depression (either measured with an interview or questionnaire) can be regarded as a chronic and recurrent condition for many people, with approximately 20 – 30% showing persistent depression and up to 50% experiencing residual symptoms or recurrences [60-62]. Much less is known about the course of depression in people with diabetes. An early, highly cited study suggests that the natural course of major depression in diabetes is malevolent, perhaps even more so than in depressed people who are otherwise medically well [63]. Subsequent studies have mostly focused on elevated depressive symptoms rather than clinical diagnoses of depression, showing that approximately half of all people experiencing depressive symptoms at baseline also reported depression 1 to 5 years later [64, 65]. While fluctuating course types are best studied in designs with at least three measurements [62], only two studies have examined the course of depressive symptoms over more than two assessments. However, one did not provide strictly observational findings, as depression was assessed in the framework of a psycho-educational program [66] and the other did not allow an evaluation of specific course patterns as persistence estimates were combined across study waves [67]. In addition, little is known about which factors predict recurrent or persistent depression among people with diabetes. Previous studies have generally reported inconsistent results, finding a role for general risk factors such as low education and history of depression and diabetes-specific factors including the presence of multiple complications and emotional problems due to diabetes [64-66].

More insights with respect to the course of depression and the health risks associated with emotional distress may come from the DiaDDZoB (*Dia*betes, *D*epression, Type *D* personality *Z*uid*o*ost-*B*rabant) Study. **Chapter 3** describes the rationale and design of this prospective cohort study among people with type 2 diabetes in primary care. Using data from this

study, the aim of **Chapter 4** is to gain more insight in the course (incidence, recurrence / persistence) of depression in people with type 2 diabetes, and the demographic, medical and psychological factors predicting these different course patterns.

Depression and insulin initiation

As type 1 diabetes is characterized by an absolute deficiency of insulin secretion [10], insulin suppletion therapy needs to be introduced immediately after diagnosis in order to effectively lower blood glucose levels. In the etiology of type 2 diabetes insulin resistance and abnormal insulin secretion may both play a role and therefore, the management of hyperglycemia in type 2 diabetes often follows a stepwise strategy [68-70]. Unless significant hyperglycemia symptoms and / or high plasma glucose concentrations are present at diagnosis, glycemic management normally starts with diet and exercise recommendations, in combination with or followed by the prescription of an oral agent [68-70]. Partly due to progressive loss of beta-cell function, glycemic control gradually deteriorates over time [71] and pharmacological monotherapy no longer suffices to attain target values for HbA_{1c} [72]. Combination therapy with an additional oral or injectable agent may have merit, but ultimately a substantial number of people will need the addition of insulin therapy to obtain an HbA_{1c} level below 7% (53 mmol / mol) [70, 72].

Several recent cross-sectional studies in insulin-naïve people with type 2 diabetes have shown an association between higher levels of depression and a more negative appraisal of insulin therapy [73-75]. The motivational aspects of depression – including fatigue or loss of energy, low self-esteem, and a diminished ability to think, concentrate or make decisions [25] – may underlie a more general reluctance to start insulin, which in turn could translate into a later initiation of insulin therapy [74]. On the other hand, the association between depression and difficulties with diabetes self-care activities [76] and its ensuing negative impact on glycemic control may accelerate introduction of insulin therapy. At present, however, it is unclear whether depression actually plays a role in the timing of insulin therapy. Therefore, **Chapter 5** focuses on the longitudinal association between depression and insulin initiation in people with type 2 diabetes, using data from the DiaDDZoB cohort.

The heterogeneity of depression and its implications for people with diabetes

In general psychiatry and cardiology, increased attention has focused on the heterogeneity of depression and its implications for health [77]. One potentially relevant distinction centers around the two core features of depression, dysphoria and anhedonia [25]. Dysphoria comprises negative emotions such as feelings of sadness and emptiness, while anhedonia is often conceptualized as a condition in which positive affect is reduced [78]. Anhedonia – or low positive affect – has been shown to predict cardiovascular conditions and mortality

in community-dwelling elderly and people with established coronary artery disease [79-84], and all-cause mortality in people with diabetes [85]. A small study in older women without diabetes found a negative association between positive affect and HbA_{1c} levels [86]. The relative importance of anhedonia and dysphoria in the association with health among people with diabetes is an underresearched area.

Therefore, in **Chapter 6** cross-sectional baseline data from a dynamic cohort study of people with type 2 diabetes in primary care are used to explore whether depression symptom clusters (dysphoria and anhedonia) are differentially associated with suboptimal glycemic control. **Chapter 7** prospectively examines whether elevated depressive symptoms are associated with hospitalization for cardiovascular disease and all-cause mortality in the DiaDDZoB cohort, and whether symptoms of dysphoria and anhedonia are differentially associated with these end points. Furthermore, this chapter explores whether there are symptom-specific behavioral or pathophysiological mechanisms in play. The behavioral or physiological pathways through which depression may increase the risk of cardiovascular disease and mortality remain unclear. Suboptimal diabetes self-care behaviors may be one pathway [76]. Depressed people with diabetes are less likely to engage in a range of self-care activities, including eating a healthy diet, physical activity and medication taking [76], and even low levels of depressive symptoms have been associated with suboptimal self-care activities in type 2 diabetes [23]. Moreover, depression has been linked to other risk factors for macrovascular disease, including smoking and high body mass index [87, 88]. The association between depression and (cardio)vascular risk factors such as cholesterol and blood pressure is less clear in people with diabetes [88] and has mostly been limited to HbA_{1c} levels [56]. Whether there are symptom-specific mechanisms in play is yet to be determined.

Type D "distressed" personality

Depression has been associated with the development of microvascular complications and macrovascular disease in people with diabetes [24, 44]. However, measures of depression usually relate to the previous 1 – 2 weeks, while complications might take several years to develop. Little is known about the risk imposed by more chronic forms of distress, for example those that are related to individual differences in personality [89]. In recent years, the Type D or "distressed" personality has emerged in cardiovascular research as a risk factor for adverse health outcomes in people with a cardiovascular condition, including non-fatal myocardial infarction, revascularization and (cardiac) mortality [89-91]. Individuals with a Type D personality tend to experience negative emotions across time and situations (Negative Affectivity; NA), but are inclined to inhibit self-expression in order to avoid disapproval or rejection by others (Social Inhibition; SI) [92]. The Type D scale (DS14) is a brief self-report measure of Type D personality that has been shown to possess adequate psychometric

properties in people with a cardiac condition [92-96], but has not been validated in people with diabetes. Therefore, **Chapter 8** examines the psychometric properties and clinical correlates of the Type D personality construct and its assessment in people with type 2 diabetes from the DiaDDZoB cohort.

One potential mechanism through which Type D personality might exert a negative influence on health includes suboptimal self-care behavior. The studies conducted so far have involved a variety of populations (healthy young adults, community samples, and people at high risk of cardiovascular conditions or those with established cardiac disease), and indicate that individuals with a Type D personality are less like to engage in physical activity and healthy eating, less likely to follow recommended medication regimens, and are less likely to seek consultations with health professionals when needed [97-102]. Type D personality has also been associated with anxiety, depression and other indicators of suboptimal mental health in people with cardiovascular and non-cardiovascular conditions and individuals from the general population [89, 103, 104]. Type D personality may indirectly increase cardiovascular risk through its association with these negative emotional states. To date, no studies have examined the clinical correlates of Type D personality in people with diabetes. **Chapter 9** aims to establish whether Type D personality and its two constituent components – NA and SI – are differentially associated with three potential cardiovascular risk mechanisms in people with type 1 or type 2 diabetes participating in Diabetes MILES – The Netherlands, a national online cross-sectional observational study among people with diabetes in The Netherlands.

Chapter 10 concludes with a summary and a general discussion of methodological and clinical considerations, and future directions.

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CHAPTER 2

Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: a systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium

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ABSTRACT

Objective: Meta-analyses have shown that the risk for depression is elevated in type 2 diabetes. Whether this risk in individuals with impaired glucose metabolism (IGM) or undiagnosed diabetes (UDD) is elevated relative to normal glucose metabolism (NGM) or decreased relative to previously diagnosed type 2 diabetes (PDD) has not been the subject of a systematic review / meta-analysis. This study examined the prevalence of depression in IGM and UDD subjects relative to each other and to NGM and PDD subjects by reviewing the literature and conducting a meta-analysis of studies on this topic.

Research design and methods: EMBASE and MEDLINE databases were searched for articles published up to May 2010. All studies that compared the prevalence of depression in subjects with IGM and UDD were included. Odds ratios (ORs) were calculated using fixed and random-effects models.

Results: The meta-analysis showed that the risk for depression was not increased in IGM versus NGM subjects (OR 0.96, 95% CI 0.85 – 1.08). Risk for depression did not differ between individuals with UDD and individuals with either NGM (OR 0.94, 95% CI 0.71 – 1.25) or IGM (OR 1.16, 95% CI 0.88 – 1.54). Finally, individuals with IGM or UDD both had a significantly lower risk of depression than individuals with PDD (OR 0.59, 95% CI 0.48 – 0.73 and OR 0.57, 95% CI 0.45 – 0.74, respectively).

Conclusions: Results of this meta-analysis show that the risk of depression is similar for NGM, IGM and UDD subjects. PDD subjects have an increased risk of depression relative to IGM and UDD subjects.

INTRODUCTION

Several meta-analyses have shown that the risk of elevated levels of depression and the risk of incident depression are increased in people diagnosed with type 2 diabetes compared with nondiabetic control subjects [1, 2]. Comorbid depression in people with diabetes forms a serious threat to quality of life [3]. Moreover, people with both depression and diabetes have been found to be at increased risk for the development of cardiovascular complications of diabetes and to have increased mortality rates and higher health care costs [4-6].

The reasons for the high prevalence of depression in type 2 diabetes remain unclear, although it is likely that the burden resulting from having a chronic disease and / or its associated complications plays an important role [7, 8]. It is also possible that increased levels of blood glucose are implicated, although the exact nature of the relationship between hyperglycemia and depression remains unclear [9].

Hyperglycemia (and insulin resistance) may contribute to depression by two mechanisms: *1)* through its impact on symptoms, such as fatigue and difficulty concentrating [10], complications, and fear of complications [11], and *2)* through physiological pathways, including inflammatory processes, and reductions in neurotrophic function [12-14], which in turn may lead to reduced plasticity of neuronal networks and subsequently depression [15].

It is worth noting that depression is a common disorder in the general population and is not only increased in people with diabetes [1, 2], but also in people with other physical health problems, such as chronic pain, asthma, and heart disease [16]. This would suggest that elevated blood glucose levels are not a necessary condition for developing depression.

One way to study whether elevated blood glucose levels affect mood is to investigate the prevalence of depression in people with impaired glucose metabolism (IGM) or undetected type 2 diabetes (UDD) and compare these to prevalence rates of depression in people with normal glucose metabolism (NGM) and people with previously diagnosed type 2 diabetes (PDD). Although people with IGM and people with UDD have, by definition, elevated blood glucose levels compared with individuals with NGM, the level of glucose impairment varies, ranging from NGM to IGM to full blown type 2 diabetes. Moreover, people with IGM or UDD differ from people with PDD, because they do not have the psychological burden of being diagnosed with the condition or having to self-manage it.

As the prevalence of depression in people with UDD or IGM has not been evaluated in a systematic review and meta-analysis, this report examines the relationship between these categories of glycemic dysregulation and risk of depression. We examined the combined

prevalence of depression in samples of people with NGM, IGM, UDD, or PDD by conducting a meta-analysis of studies published on this subject in the peer-reviewed literature.

RESEARCH DESIGN AND METHODS

Retrieval of studies

To identify the studies of interest, MEDLINE (1950 to May 2010) and EMBASE (1947 to May 2010) databases were searched. The search terms are shown in Supplementary Table 1. Titles and abstracts of the retrieved studies were scanned by two authors (A.N. reviewed all abstracts, and the second reviews were divided among coauthors) to exclude studies that were clearly irrelevant. The full text of the remaining studies was then read by three authors (A.N., G.N., and F.P.) to determine whether the studies met our inclusion criteria. Furthermore, the reference lists of articles that studied our topic of interest were scanned to check for additional publications.

Inclusion / exclusion criteria

In this systematic review and meta-analysis, we included all studies that examined the prevalence of depression either in UDD or IGM subjects, also defined as impaired glucose tolerance, impaired fasting glucose, and impaired glucose resistance, comparing these rates to those in NGM and / or PDD subjects.

Data extraction

Three authors (A.N., G.N., and F.P.) independently extracted data from the studies, in particular regarding *1*) name of first author, *2*) publication year, *3*) study design, *4*) number of participants by category of glycemic (dys)regulation, *5*) sex of participants, *6*) age of participants, *7*) method and criteria for depression assessment, *8*) methods of diabetes and / or pre-diabetic state assessment, *9*) number and percentage of case subjects with depression, *10*) fasting plasma glucose, and *11*) unadjusted and adjusted odds ratios (ORs) and 95% CIs. This allowed comparison of IGM with NGM and PDD and comparison of UDD with NGM, IGM, and PDD.

In the included studies, method of depression assessment could be either *1*) a diagnosis of depression assessed by a diagnostic psychiatric interview, *2*) assessment of depressive symptoms by a self-report questionnaire, *3*) a diagnosis by a physician, or *4*) in combination with a prescription of antidepressant medication.

Statistical analysis

The odds of depression in each category (UDD or IGM) were compared with the odds of depression in NGM or PDD to calculate the unadjusted OR. From these, pooled ORs were estimated. Both the fixed-effects model and the random-effects model were used. The fixed-effects model assumes that variability between studies is exclusively due to random variation, and individual studies are simply weighted by their precision. The random-effects model assumes that a different true effect size exists for at least one study and takes this into consideration as an additional source of variation. A random-effects meta-analysis is more conservative than a fixed-effects meta-analysis, since it may give wider CIs around the point estimate and is recommended when it is suspected that individual studies may not be estimating the same true effect size [17]. A forest plot was made to show the OR and 95% CI of each study and the pooled OR and 95% CI.

We followed recommendations in the Cochrane Handbook [17] for investigating reporting bias; these recommendations advise that Harbord's statistical test for small study bias is appropriate when the outcome statistic is an OR and the number of studies is at least 10 to avoid false-positive results in the presence of study heterogeneity. Forest plots were used to visually assess homogeneity of the studies. This was also tested with the Cochran's Q test and the I-squared statistic. All statistical analyses were performed using STATA 10.0 (STATA Corporation, College Station, TX).

RESULTS

The MEDLINE search (1950 to May 2010) identified 3,357 articles, of which 12 met our inclusion criteria and were subsequently included in the systematic review and meta-analysis. The search in EMBASE (1947 to May 2010, total number of studies 4,337, excluding duplicates) identified one additional study meeting the selection criteria. Thus, a total of 13 studies were included in the meta-analysis. The characteristics and the extracted data of the 13 included studies are presented in Table 1 and, for the (un)adjusted odds ratios, in Supplementary Table 2.

In total, the included studies identified 1,483 case subjects with UDD, 6,236 case subjects with IGM, and 2,121 case subjects with PDD. However, because the number of studies varied for each comparison, numbers of cases may differ.

Table 1 Characteristics and results of the 13 studies included in the meta-analysis

Study	Design	Number of participants	Age (years)		*n* Male (%)	Criteria for depression	Assessment of DM2 / IGM	Fasting plasma glucose (mmol / l) (SD)	Cases of depression	Methodological issues
			Mean (SD)	Range						
U.S.: Palinkas et al., 1991 [29]	Population-based study	NGM: 1,284 (81%) UDD: 209 (13%) PDD: 93 (6%)	NGM: 69 (10) UDD: 74 (8) PDD: 72 (9)	≥ 50	NGM: 584 (46%) UDD: 101 (48%) PDD: 56 (60%)	Beck Depression Inventory ≥ 13	WHO 1985 (OGTT, FPG) Self-reported diabetes diagnosis by physician Current use of diabetes medication	NGM: 4.8 (0.5) UDD: 5.9 (1.5) PDD: 7.1 (2.6)	NGM: 58 (5%) UDD: 8 (4%) PDD: 10 (11%)	Excluded participants: - IGT and no personal diabetes history or current use of diabetes medication (n = 559) - Using insulin (n = 6) - Failed to fast for 12h or missing glucose results (n = 106)
Finland: Hiltunen et al., 1996 [19]	Population-based study	NGT: 149 (40%) IGT: 122 (33%) UDD: 33 (9%) PDD: 65 (18%)	NGT: M 74; W 75 IGT: M 76; W 76 UDD: M 74; W 78 PDD: M 73; W 79 (median)	70 – 92	NGT: 63 (42%) IGT: 43 (35%) UDD: 12 (36%) PDD: 19 (29%)	Short Zung SDS score ≥ 28	WHO 1985 (OGTT) Previous diabetes diagnosis Receiving oral drug, insulin, or diet treatment	NA	NGT: 26 (17%) IGT: 19 (15%) UDD: 6 (18%) PDD: 9 (14%) [a]	Small sample
Finland: Rajala et al., 1997 [18]	Population-based study	NGM: 480 (65%) IGT: 192 (26%) UDD: 26 (4%) PDD: 36 (5%)	NGM: 55 IGT: 55 UDD: 55 PDD: 55	55	NGM: 199 (41%) IGT: 85 (44%) UDD: 13 (50%) PDD: 24 (67%)	Zung SDS score ≥ 45	WHO 1985 (OGTT) Self-reported diabetes diagnosis by physician In patients with random blood glucose value ≥ 8 2x FG or two FG values ≥ 6.7 mmol / l	NA	NGM: 56 (12%) IGT: 24 (13%) UDD: 3 (12%) PDD: 9 (25%)	Small sample PDD treatment: diet only, 22 (54%); oral agents, 11 (27%); oral agents and insulin, three (7%); insulin, five (12%) Median diabetes duration 5 years (range 1 – 40)
U.S.: Yaffe et al., 2004 [20]	Intervention multisite (n = 180) multicountry (n = 25) study	NGM: 6,463 (92%) IFG: 297 (4%) PDD: 267 (4%)	NGM: 66 (7) IFG: 68 (7) PDD: 68 (6)	NA	0 (0%)	15-item Geriatric Depression Scale ≥ 6	FG Self-reported pre-existing diabetes Currently using hypoglycemic medication	NGM: 5.0 (0.4) IFG: 6.4 (0.2) PDD: 8.5 (2.7)	NGM: 142 (2%) IFG: 10 (3%) PDD: 11 (4%) [b]	Postmenopausal women only Of 267 women with diabetes, 184 (69%) reported having diabetes by history, 198 (74%) had FG level ≥ 7 mmol / l, and 111 (42%) reported using hypoglycemic medication

Table 1 (continued)

Study	Design	Number of participants	Age (years) Mean (SD)	Age (years) Range	*n* Male (%)	Criteria for depression	Assessment of DM2 / IGM	Fasting plasma glucose (mmol / l) (SD)	Cases of depression	Methodological issues
The Netherlands: Knol et al., 2007 [21]	Population-based study	NFG: 3,499 (81%) IFG: 671 (16%) UDD: 55 (1%) PDD: 102 (2%) [c]	NFG: 38 (11) IFG: 47 (14) UDD: 57 (13) PDD: 56 (14) [c]	≥ 18	NFG: 1,414 (40%) IFG: 427 (64%) UDD: 24 (44%) PDD: 54 (53%) [c]	Symptom Checklist-90 depression subscale ≥ 25 *and / or* self- reported antidepressant use	ADA 2005 (FPG) Self-reported diabetes diagnosis by physician	NFG: 4.9 (0.4) IFG: 5.9 (0.3) UDD: 8.3 (2.1) PDD: 8.3 (3.3) [c]	NFG: 667 (19%) IFG: 115 (18%) UDD: 11 (20%) PDD: 30 (30%) [c]	Patients with diagnosed diabetes who used insulin and no oral hypoglycemic agents were defined as having type 1 diabetes and were excluded (n = 14)
U.S.: Golden et al., 2007 [22]	Population-based study	NGM: 3,911 (58%) IFG: 1,879 (28%) UDD: 292 (4%) PDD: 672 (10%)	Depressed: 61 (10) Non-depressed: 62 (10)	45 – 84	3,186 (47%)	CES-D ≥ 16 *and / or* self-reported use of antidepressant medication	ADA 2003 (FG) Use of hypoglycemic medication (oral agents and / or insulin)	NGM: 5.0 (0.3) IFG: 5.9 (0.3) UDD: 9.0 (3.0) PDD: 8.5 (3.1) [d,e]	NGM: 721 (18%) IFG: 304 (16%) UDD: 46 (16%) PDD: 153 (23%)	UDD defined as "untreated diabetes" PDD defined as "treated diabetes" Among 292 individuals with untreated diabetes, 50 (17%) were aware of diagnosis CES-D scores of two groups were not significantly different ($p = 0.28$)
Germany: Icks et al., 2008 [30]	Population-based study	NGM: 3,995 (87%) UDD: 248 (5%) PDD: 352 (8%)	NGM: M: 59 (8) W: 59 (8) UDD: M: 60 (7) W: 62 (8) PDD: M: 63 (7) W: 64 (7)	45 – 75	NGM: 1,905 (48%) UDD: 175 (71%) PDD: 214 (61%)	CES-D short form ≥ 15	FG, random blood glucose Self-reported diabetes diagnosis by physician Taking glucose-lowering medication	NGM: 5.8 (0.5) UDD: 8.0 (1.9) PDD: 8.8 (2.5) [e]	NGM: 557 (14%) UDD: 15 (6%) PDD: 47 (13%)	
U.S.: Rhee et al., 2008 [24]	Adult volunteer subjects who were not known to have diabetes	NGT: 642 (61%) Pre-PDD: 352 (34%) UDD: 53 (5%)	NGT: 46 (12) Pre-PDD: 52 (10) UDD: 55 (10)	NA	NGT: 186 (29%) Pre-PDD: 180 (51%) UDD: 24 (45%)	Patient Health Questionnaire-9 ≥ 10	ADA 2007 (OGTT, FPG)	NGT: 4.9 (0.4) Pre-PDD: 5.7 (0.1) UDD: 6.9 (0.9) [d,e]	NGT: 45 (7%) Pre-PDD: 25 (7%) UDD: 6 (11%)	Pre-PDD: IFG and / or IGT Ethnicity (% black): NGT 55%; Pre-PDD 51%; UDD 62% Past / current depression treatment: NGT: 11% / 10% Pre-PDD: 11% / 10% UDD: 4% / 13%
The Netherlands: Adriaanse et al., 2008 [23]	Population-based study	NGM: 260 (47%) IGM: 164 (30%) PDD: 126 (23%)	NGM: 69 (6) IGM: 70 (6) PDD: 71 (7)	60 – 87	NGM: 130 (50%) IGM: 86 (52%) PDD: 60 (48%)	CES-D ≥ 16	WHO 1999 (OGTT, FPG)	NGM: 5.4 (0.4) IGM: 6.1 (0.5) PDD: 7.9 (2.1) [e]	NGM: 20 (8%) IGM: 24 (15%) PDD: 22 (17%)	IGM: IGT or IFG

Table 1 (continued)

Study	Design	Number of participants	Age (years) Mean (SD)	Age (years) Range	*n* Male (%)	Criteria for depression	Assessment of DM2 / IGM	Fasting plasma glucose (mmol / l) (SD)	Cases of depression	Methodological issues
U.K.: Holt et al., 2009 [25]	Population-based study	NGM: 1,568 (52%) IFG: 298 (10%) IGT: 698 (23%) UDD: 249 (8%) PDD: 182 (6%)	Total: 66 M: 66 (3) W: 67 (3)	59 – 73	NGM: 830 (53%) IFG: 207 (69%) IGT: 309 (44%) UDD: 124 (50%) PDD: 108 (59%)	Hospital Anxiety and Depression Scale depression subscale ≥ 11: probable depression	WHO (year not specified) (OGTT, FPG) Self-reported previous diabetes diagnosis	NGM: NA IGT: 5.9 (1.1) UDD: 7.2 (1.2)[e] PDD: NA	NGM: 19 (1%) IGT/IFG: 8 (1%) UDD: 6 (2%) PDD: 4 (2%)	Exact number of participants with NGM is unknown
U.K.: Aujla et al., 2009 [26]	Population-based study	NGT: 4,956 (82%) IGR: 855 (14%) UDD: 198 (3%)	58 (10)	40 – 75	2,849 (47%)	WHO-5 ≤ 13	WHO 2006 (OGTT, FG)	NGT: 5.0 (0.4) IGR: 5.7 (0.7) UDD: 8.1 (3.0) [e]	NGT: 1,035 (25%) IGR: 167 (26%) UDD: 29 (21%)	IGR: IFG and / or IGT WHO-5 is not a measure of depression 2% of participants had pre-existing history of depression Overall sample: 4,682 (78%) white European; 1,327 (22%) South Asian
U.S.: Gale et al., 2010 [27]	Ex-military personnel randomly drawn from records of U.S. veterans	NFG: 3,573 (83%) IFG: 492 (11%) UDD:182 (4%) PDD: 46 (1%)	NFG: 38 (3) IFG: 39 (2) UDD: 39 (2) PDD: 40 (2)		4,293 (100%)	Diagnostic Interview Schedule major depression	Fasting serum glucose Self-reported diabetes diagnosis by physician Use of diabetes medication	NFG: 5.0 (0.3) IFG: 5.8 (0.1) UDD: 7.0 (2.2) PDD: 9.4 (4.3) [e,f]	NFG: 227 (6%) IFG: 25 (5%) UDD: 16 (9%) PDD: 8 (17%)	Random sample of 15,288 veterans of telephone survey Diagnosis of depression Relatively young sample UDD
The Netherlands: Bouwman et al., 2010 [28]	Population-based study	NGM: 2,061 (77%) IGM: 425 (16%) PDD: 181 (7%)	NGM: 53 (7) IGM: 55 (6) PDD: 56 (6)	40 – 65	NGM: 923 (45%) IGM: 241 (57%) PDD: 97 (54%)	CES-D ≥ 16	WHO 2006 (OGTT, FPG)	NGM: 5.3 (0.4) IGM: 6.0 (0.5) PDD: 7.8 (2.2)	NGM: 258 (13%) IGM: 52 (12%) PDD: 38 (21%)	

All values are rounded to the nearest integer. Abbreviations: ADA, American Diabetes Association; CES-D, Center for Epidemiologic Studies Depresion Scale; FG, fasting glucose; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGM, impaired glucose metabolism; IGR, impaired glucose regulation; IGT, impaired glucose tolerance; M, men; NFG, normal fasting glucose; NGM, normal glucose metabolism; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PDD, Previously diagnosed type 2 diabetes; UDD, Undiagnosed type 2 diabetes; W, women; WHO, World Health Organization; WHO-5, World Health Organization-5 Wellbeing Index; Zung SDS, Zung Self-Rating Depression Scale; [a] % unadjusted for age and sex; [b] % differ from reported % in article; presence of missing values or calculation errors unclear; [c] Values reported before multiple imputation; [d] Converted from mg / dl to mmol / l; [e] Data obtained through correspondence with the authors; [f] The FG differed significantly between the UDD and PDD groups ($p < 0.001$).

Depression in individuals with impaired glucose metabolism

Eleven studies [18-28] compared the prevalence of depression in individuals with IGM relative to individuals with NGM. The forest plot (Figure 1) clearly shows that, compared with people with normal glucose regulation, the prevalence of depression is not increased in patients with IGM (fixed-effects OR 0.94, 95% CI 0.86 – 1.02; random-effects OR 0.96, 0.85 – 1.08). Harbord's test for reporting bias was negative (p = 0.2). Nine studies reported data on the prevalence of depression in individuals with IGM compared with individuals with PDD [18-23, 25, 27, 28]. Compared with individuals with PDD, people with IGM had an almost 40% lower risk of depression (fixed-effects OR 0.61, 95% CI 0.52 – 0.71; random-effects OR 0.59, 0.48 – 0.73). In both analyses, the I-squared value was low, suggesting that the results of the fixed-effects model may be appropriate for these comparisons. Because of ambiguities in two studies, we conducted sensitivity analyses to determine whether our analytic decisions affected the results. In one study [20], there appeared to be a discrepancy between the reported number of people with depressive symptoms (n = 10) and the percentage of participants with depressive symptoms (2.2%). Therefore, we compared the results with the raw numbers and the recalculated data based on the reported percentages. Another study [21] reported the total number of participants and ORs based on imputed data; therefore, we compared the results with the total number of participants and with ORs based on imputed data. Results of these sensitivity analyses showed that in both cases, using alternative data did not change the overall results.

Depression in undiagnosed type 2 diabetes

Three comparisons were carried out for the prevalence of depression in UDD: 10 studies [18, 19, 21, 22, 24-27, 29, 30] comparing with NGM, eight studies [18, 19, 21, 22, 24-27] comparing with IGM, and eight studies [18, 19, 21, 22, 25, 27, 29, 30] comparing with PDD. The I-squared statistic was moderately large for the comparison of UDD versus NGM (I-squared = 49.0%; p = 0.039 for the Cochran's Q test for heterogeneity), suggesting that the random-effects model was the most appropriate for this comparison. However, a single study [30] accounted for all heterogeneity beyond that due to chance, and when this study was omitted from the analysis, the I-squared statistic diminished to 0% and the fixed- and random-effects pooled estimates became 0.98 (95% CI 0.81 – 1.19). Harbord's test for reporting bias just reached statistical significance (p = 0.03). For consistency, only the random-effects models for each comparison were considered.

The forest plots of the ORs and 95% CI of each study and the pooled OR for comparisons of UDD versus NGM are shown in Figure 2: the pooled OR of 0.94 (95% CI 0.71 – 1.25) indicated that the risk for being depressed was not significantly different. Furthermore, the odds of depression did not differ significantly between UDD versus IGM (OR 1.16, 95% CI 0.88 – 1.54). Finally, the risk of depression was significantly lower in individuals with UDD versus PDD (OR 0.57, 95% CI 0.45 – 0.74).

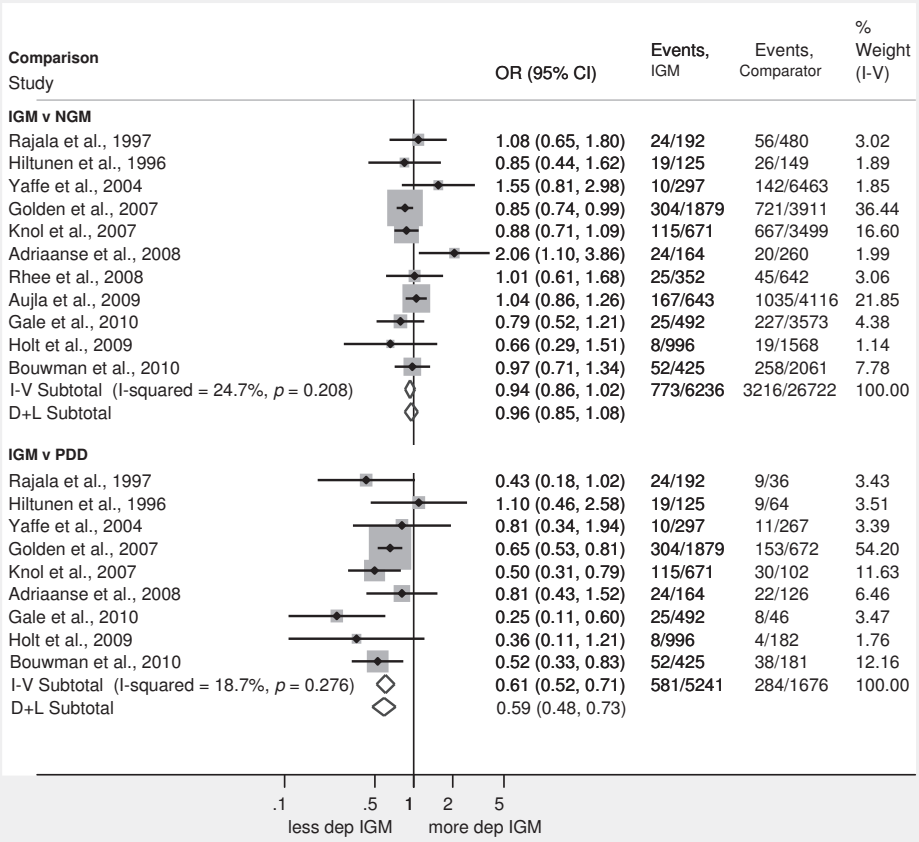

Figure 1 Forest plots showing the OR and 95% CI of depression in IGM compared with NGM and PDD. I-V, fixed-effects estimate (inverse variance method); D+L, random-effects estimate (Der Simonian and Laird method)

Sensitivity analyses

We conducted sensitivity analyses to determine whether using OR controlled for demographic factors affected the results. In all the studies that provided adjusted OR, NGM was always the reference; thus, we were not able to conduct sensitivity analyses for comparisons of IGM or UDD with PDD or IGM with UDD. Results did not change in the sensitivity analyses. A pooled OR of 0.93 (95% CI 0.85 – 1.04) was obtained for the comparison of IGM versus NGM [21-23, 26-28] and an OR of 1.04 (95% CI 0.85 – 1.28) for the comparison of UDD versus NGM [21, 22, 26, 27, 30].

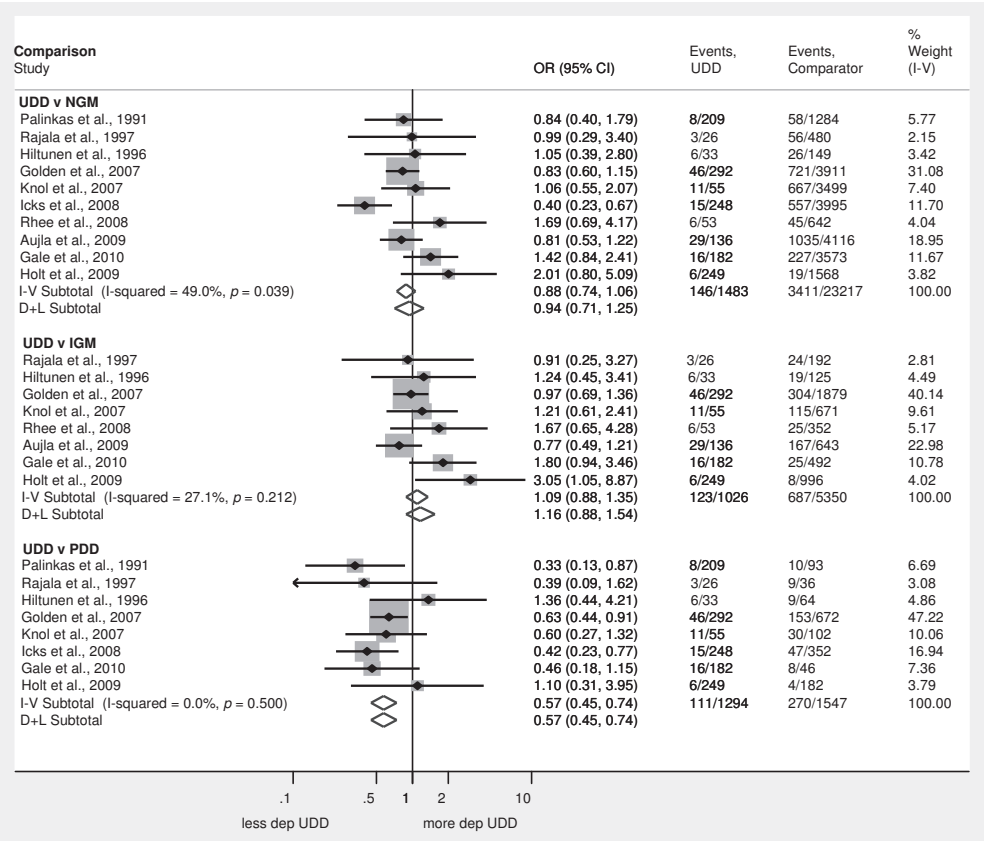

Figure 2 Forest plots showing the OR and 95% CI of depression in UDD compared with NGM, IGM, and PDD. I-V, fixed-effects estimate (inverse variance method); D+L, random-effects estimate (Der Simonian and Laird method)

CONCLUSIONS

The results of the present meta-analysis clearly show that people who have impaired glucose metabolism or undiagnosed type 2 diabetes are not at increased risk for depression compared with people in the general population or people with normal glucose metabolism. When compared with people with known type 2 diabetes, individuals with impaired glucose metabolism or unknown diabetes have significantly lower risk of having depressive symptoms. This result could be regarded as support for the "psychological burden hypothesis" [31], which states that the burden of knowing that you have diabetes and having a chronic illness to manage, or complications to cope with contributes to higher levels of depression. By definition, people with IGM and undiagnosed diabetes have both higher levels of blood glucose than people with normal glucose metabolism or people in the

general population. Results of the present meta-analysis indicate that higher blood glucose levels per se in the prediabetic or early diabetes stages are not associated with an increased level of depressive symptoms.

One explanation for the lower risk of depression in UDD compared with PDD might relate to differences in the number of complications between people with UDD and people with PDD. Although diabetes complications can occur in people with undiagnosed diabetes, these are more likely to be found in people with longstanding diabetes [32, 33]. The results of the current meta-analysis would then concur with a large cross-sectional population-based study that showed that, compared with healthy control subjects, diabetes alone did not increase the chances of depressive symptoms but having diabetes and diabetes complications did [34]. However, a recent study showed that the risk of depressive disorder is increased in the 2 years after diagnosis of type 2 diabetes in the absence of diabetes complications [35]. In another study, it was found that diabetes distress did not become associated with depressive symptoms until after 1 year of living with diabetes [36]. In yet another study, people who were prescribed a more intensive treatment developed more depressive symptoms in the first 3 years after detection of type 2 diabetes than individuals on less intensive treatment [37]. These studies suggest that factors other than diabetes complications (e.g., fear of complications, burden of treatment) may increase the risk of depressive symptoms. However, because none of the studies included in the meta-analysis assessed diabetes complications, it was not possible to refute or support this argument. Future studies into depression and undiagnosed diabetes should assess diabetes complications in these groups.

There are several limitations to this study. First, the number of people with undiagnosed diabetes in the included investigations was quite small despite the fact that many were large-scale population-based studies. Second, the meta-analysis draws on observational cohort studies, and it is appropriate to analyze adjusted rather than unadjusted effect estimates. However, because only half of the studies provided adjusted effect estimates and controlled for important demographic confounders, we used the unadjusted ORs in our analyses. However, when calculating pooled ORs based on the studies that did provide ORs controlled for demographics, the outcome did not change. Given these results and the low heterogeneity, we are confident that the results in the current study are reliable. Third, although in all studies oral glucose tolerance tests were used to establish participants' glucose metabolism classification, it is possible that unmeasured differences in blood glucose level between the previously diagnosed and undiagnosed diabetes groups may explain their differences in depression. Because these data were not routinely available in the published reports, we contacted authors of the more recent articles to obtain these data and used them to calculate weighted pooled mean blood glucose levels for each group.

Whereas blood glucose levels did not differ between NGM (mean 5.1, 95% CI 3.9 – 6.3) and IGM (5.8, 4.6 – 7.0) and between UDD (8.8, 7.6 – 10.0) and PDD (8.3, 7.1 – 9.5), differences between the diabetes groups (UDD and PDD) and individuals without diabetes (NGM and IGM) were significant. These results suggest that despite differences in depression between those with versus those without diabetes, blood glucose levels did not differ within these broader categories. Fourth, the possibility of reporting bias cannot be ruled out. There was weak evidence of reporting bias for the comparison of undiagnosed diabetes versus normal glucose metabolism, but the number of studies here, as for other comparisons, was too low for strong inference.

The relatively low level of heterogeneity observed in most comparisons (I-squared ranging from 0 to 27%) was not amenable to productive exploration using meta-regression; this was because it is recommended that at least 10 studies per study level variable explored are required if spurious associations are to be avoided, and a complete set of data for this number of studies was unfortunately not available for study level variables of interest (e.g., age, sex, fasting plasma glucose).

Fifth, the studies in this meta-analysis used cross-sectional data and therefore do not provide evidence regarding the time frame in which depression develops after the diagnosis of type 2 diabetes. A recent study reported that antidepressant medication use showed a temporary peak during the year of diagnosis of type 2 diabetes, suggesting that the risk of depressive symptoms is increased soon after diagnosis and recedes thereafter in the absence of another incident risk factor [38].

Finally, only one of the included studies [27] used diagnostic criteria to determine depression status. In this study, the prevalence of depression was particularly increased in people with previously diagnosed diabetes (compared with NGM) and in people with undiagnosed diabetes, although for the latter, this failed to reach significance. IGM was not significantly associated with the increased prevalence of major depressive disorder. These findings suggest that diabetes, but not IGM, is associated with increased prevalence of major depressive disorder. However, the numbers in this study were small, and further research is needed.

Overall, the results of this meta-analysis show that the risk of depression is not directly related to elevated blood glucose levels. One conclusion, in line with the results of the current meta-analysis, is that the burden of diabetes and its complications are the main determinants of depressive symptoms in individuals with diabetes [16]. Future research should examine the constituents of this burden.

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Supplementary Table 1 Search terms

1. exp Depression/ or depression.mp.
2. depressive disorder$.mp. or exp Depressive Disorder/
3. mood disorder$.mp. or exp Mood Disorders/
4. dysthmic disorder$.mp.
5. (depress$ adj3 (disorder$ or symptom$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
6. or/1-4
7. (impaired glucose adj3 (tolera$ or metaboli$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8. diabetes mellitus.mp. or exp Diabetes Mellitus/
9. glucose intolerance.mp. or exp Glucose Intolerance/
10. or/7-9
11. 6 and 10

Supplementary Table 2 Unadjusted and adjusted odds ratios for depression, comparing IGM / UDD / PDD with NGM

Study		Outcome unadjusted OR (95% CI) [a]					Outcome adjusted OR (95% CI)		
		IGM vs. NGM*	UDD vs. NGM*	PDD vs. NGM*			IGM vs. NGM*	UDD vs. NGM*	PDD vs. NGM*
Palinkas et al., 1991		n/a	n/a	n/a			n/a	n/a	n/a
Hiltunen et al., 1996		n/a	n/a	n/a			n/a	n/a	n/a
Rajala et al., 1997		RR = 1.1 (0.7-1.7)	RR = 1.0 (0.3-2.9)	RR = 2.1 (1.2-4.0)			n/a	n/a	n/a
Yaffe et al., 2004		n/a	n/a	n/a			n/a	n/a	n/a
Knol et al., 2007 [b]		0.90 (0.72-1.12)	1.00 (0.51-1.96)	1.79 (1.17-2.75)	Model 1 [c]		1.03 (0.81-1.31)	0.84 (0.42-1.69)	1.70 (1.07-2.70)
					Model 2 [d]		1.01 (0.78-1.29)	0.82 (0.40-1.68)	1.69 (1.06-2.72)
					Model 3 [e]		0.99 (0.77-1.27)	0.86 (0.42-1.77)	1.36 (0.83-2.23)
Golden et al., 2007		n/a	n/a	n/a	Model 1 [f]		1.01 (0.87-1.18)	1.03 (0.74-1.45)	1.57 (1.27-1.96)
					Model 2 [g]		1.01 (0.86-1.18)	0.98 (0.69-1.39)	1.52 (1.22-1.90)
					Model 3 [h]		1.01 (0.86-1.18)	1.05 (0.72-1.45)	1.54 (1.23-1.93)
					Model 4 [i]		1.02 (0.87-1.19)	0.96 (0.67-1.37)	1.53 (1.21-1.92)
					Model 5 [j]		1.00 (0.84-1.78)	1.02 (0.71-1.47)	1.48 (1.16-1.88)
					Model 6 [k]		1.00 (0.85-1.17)	0.92 (0.64-1.32)	1.47 (1.17-1.95)
Icks et al., 2008		n/a	n/a	n/a	Model 1 [l]	M	n/a	0.30 (0.13-0.70)	0.62 (0.35-1.09)
						W	n/a	0.67 (0.33-1.36)	1.48 (0.98-2.24)
					Model 2 [m]	M	n/a	0.28 (0.12-0.65)	0.55 (0.31-0.98)
						W	n/a	0.63 (0.31-1.30)	1.34 (0.88-2.04)
					Model 3 [n]	M	n/a	0.22 (0.09-0.54)	0.50 (0.27-0.91)
						W	n/a	0.60 (0.29-1.24)	1.14 (0.73-1.76)
Rhee et al., 2008		n/a	n/a	n/a			n/a	n/a	n/a
Adriaanse et al., 2008	M	0.90 (0.32-2.57)	n/a	2.04 (0.76-5.49)	Model 1 [o]	M	0.90 (0.31-2.58)	n/a	1.95 (0.71-5.34)
	W	3.60 (1.57-8.28)	n/a	3.18 (1.31-7.74)		W	3.04 (1.28-7.21)	n/a	3.18 (1.26-8.02)
					Model 2 [p]	M	0.78 (0.26-2.35)	n/a	1.05 (0.32-3.39)
						W	2.55 (1.00-6.49)	n/a	2.52 (0.86-7.33)
					Model 3 [q]	M	0.83 (0.23-2.95)	n/a	1.26 (0.36-4.43)
						W	3.48 (1.35-8.95)	n/a	2.83 (0.93-8.61)
					Model 4 [r]	M	0.89 (0.28-2.90)	n/a	1.52 (0.47-4.94)
						W	2.21 (0.87-5.60)	n/a	2.76 (1.01-7.50)

Supplementary Table 2 (continued)

Study	Outcome unadjusted OR (95% CI) [a]				Outcome adjusted OR (95% CI)		
	IGM vs. NGM*	UDD vs. NGM*	PDD vs. NGM*		IGM vs. NGM*	UDD vs. NGM*	PDD vs. NGM*
Holt et al., 2009	n/a	n/a	n/a		n/a	n/a	n/a
Aujla et al., 2009	1.04 (0.86-1.26)	0.81 (0.53-1.22)	n/a	Model 2 [s]	1.17 (0.96-1.42)	0.95 (0.62-1.45)	n/a
				Model 3 [t]	1.10 (0.89-1.36)	0.74 (0.44-1.23)	n/a
Gale et al., 2010	n/a	n/a	n/a	Model 1 [u]	0.82 (0.54-1.26)	1.67 (0.99-2.81)	3.39 (1.54-7.43)
				Model 2 [v]	0.90 (0.58-1.40)	1.80 (1.01-3.19)	3.83 (1.72-8.54)
				Model 3 [w]	0.90 (0.58-1.40)	1.80 (1.01-3.22)	3.82(1.68-8.70)
Bouwman et al., 2010	0.97 (0.71-1.34)	n/a	1.86 (1.27-2.72)	Model 2 [x]	1.13 (0.81-1.57)	n/a	2.02 (1.35-3.04)
				Model 3 [y]	1.09 (0.78-1.54)	n/a	1.77 (1.13-2.78)

* Denotes reference category. M: men; W: women.
[a] Values are OR (95% CI), unless otherwise specified
[b] After multiple imputation
[c] Knol et al. Model 1: adjusted for demographics (gender, age, education)
[d] Knol et al. Model 2: adjusted for Model 1 + BMI + health behaviors (smoking, alcohol consumption, physical activity)
[e] Knol et al. Model 3: adjusted for Model 2 + number of chronic diseases (present during last year and diagnosed by physician: asthma, chronic obstructive pulmonary disease, severe heart disease, myocardial infarction, stroke, cancer, osteoarthritis, rheumatoid arthritis)
[f] Golden et al. Model 1: adjusted for demographics (age, sex, race/ethnicity) + research site
[g] Golden et al. Model 2: adjusted for Model 1 + BMI
[h] Golden et al. Model 3: adjusted for Model 2 + metabolic variables (log-transformed triglycerides, HDL cholesterol, LDL cholesterol)
[i] Golden et al. Model 4: adjusted for Model 2 + inflammatory variables (IL-6, CRP)
[j] Golden et al. Model 5: adjusted for Model 2 + lifestyle variables (daily caloric intake, smoking status)
[k] Golden et al. Model 6: adjusted for Model 2 + socioeconomic status (education status, annual household income)
[l] Icks et al. Model 1: adjusted for age
[m] Icks et al. Model 2: adjusted for Model 1 + number of co-morbidities (none, one, two or more of the following: myocardial infarction, heart failure, peripheral arterial disease, stroke, emphysema, asthma, cancer, rheumatism, slipped disk, migraine)
[n] Icks et al. Model 3: adjusted for Model 2 + intake of depression-inducing medication, BMI, activity level, smoking, living without a partner, educational level
[o] Adriaanse et al. Model 1: adjusted for demographics (age, low education)
[p] Adriaanse et al. Model 2: adjusted for Model 1 + cardiovascular risk factors (triglycerides, HDL cholesterol, total cholesterol, waist circumference, hypertension, smoking)
[q] Adriaanse et al. Model 3: adjusted for Model 1 + cardiovascular diseases (carotid intima-media thickness, ischaemic heart disease)
[r] Adriaanse et al. Model 4: adjusted for Model 1 + diabetes symptoms (hyperglycemic, cardiovascular, neuropathic pain, sensibility, ophthalmological)
[s] Aujla et al. Model 2: adjusted for demographics (age, sex, ethnicity)
[t] Aujla et al. Model 3: adjusted for Model 2 + clinical characteristics (waist circumference, BMI) + health behaviors (moderate exercise, vigorous exercise, smoking) + deprivation (IMD score)
[u] Gale et al. Model 1: adjusted for demographics (age, ethnicity)
[v] Gale et al. Model 2: adjusted for Model 1 + clinical characteristics (BMI, triglycerides, HDL cholesterol, cortisol, systolic and diastolic blood pressure) + health behaviors (smoking, alcohol consumption)
[w] Gale et al. Model 3: adjusted for Model 2 + intelligence, educational attainment, household income
[x] Bouwman et al. Model 2: adjusted for demographics (sex, age, education, family history DM2)
[y] Bouwman et al. Model 3: adjusted for Model 2 + cardiovascular risk factors (triglycerides, HDL cholesterol, total cholesterol, hypertension, smoking, waist circumference)

CHAPTER 3

Psychological risk factors of micro- and macrovascular outcomes in primary care patients with type 2 diabetes: rationale and design of the DiaDDZoB Study

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ABSTRACT

Background: Depression is a common psychiatric complication of diabetes, but little is known about the natural course and the consequences of depressive symptoms in primary care patients with type 2 diabetes. While depression has been related to poor glycemic control and increased risk for macrovascular disease, its association with microvascular complications remains understudied. The predictive role of other psychological risk factors such as Type D (distressed) personality and the mechanisms that possibly link depression and Type D personality with poor vascular outcomes are also still unclear.

Methods / Design: This prospective cohort study will examine: (1) the course of depressive symptoms in primary care patients with type 2 diabetes; (2) whether depressive symptoms and Type D personality are associated with the development of microvascular and/or macrovascular complications and with the risk of all-cause or vascular mortality; and (3) the behavioral and physiological mechanisms that may mediate these associations. The DiaDDZoB Study is embedded within the larger DIAZOB Primary Care Diabetes study, which covers a comprehensive cohort of type 2 diabetes patients treated by over 200 primary care physicians in South-East Brabant, The Netherlands. These patients will be followed during their lifetime and are assessed annually for demographic, clinical, lifestyle and psychosocial factors. Measurements include an interviewer-administered and self-report questionnaire, regular care laboratory tests and physical examinations, and pharmacy medication records. The DiaDDZoB Study uses data that have been collected during the original baseline assessment in 2005 (M_0; N = 2,460) and the 2007 (M_1; N = 2,225) and 2008 (M_2; N = 2,032) follow-up assessments.

Discussion: The DiaDDZoB Study is expected to contribute to the current understanding of the course of depression in primary care patients with type 2 diabetes and will also test whether depressed patients or those with Type D personality are at increased risk for (further) development of micro- and cardiovascular disease. More knowledge about the mechanisms behind this association is needed to guide new intervention studies.

BACKGROUND

The number of people with diabetes mellitus is increasing rapidly worldwide. Based on aging and other demographic changes, prevalence estimates of this chronic metabolic disease are projected to rise from 171 million in 2000 to 366 million in 2030 [1]. As the disease progresses, diabetes patients are often confronted with long-term vascular complications. While premature cardiovascular disease (including coronary artery disease, stroke and peripheral arterial disease) accounts for considerable morbidity and mortality, complications of microvascular origin also contribute significantly to adverse health outcomes [2]. To date, diabetes remains a predominant cause of vision loss, renal failure and lower extremity amputations in developed countries [3]. A large-scaled study among over 7,000 patients with type 2 diabetes in eight European countries concluded that approximately 72% of the participants had at least one complication, while 24% of the total study group had both micro- and macrovascular complications [4]. Not surprisingly, the presence of these vascular conditions has a substantial negative impact on both overall healthcare expenditures [4] and patients' quality of life [5].

Depression is common in type 2 diabetes

Depression is another common and burdensome complication of type 2 diabetes. A recent meta-analysis of ten controlled studies showed that the prevalence of depression was significantly higher in patients with type 2 diabetes compared with non-diabetic controls (18 vs. 10%, OR = 1.6, 95% CI 1.2 – 2.0) [6]. Even though depression is a common co-morbidity in diabetes, little longitudinal research has been undertaken with respect to its natural course in type 2 diabetes [7]. A meta-analysis of seven prospective studies by Mezuk et al., all excluding prevalent cases of depression at baseline, concluded that the association between type 2 diabetes and the incidence of depression is only modest (RR = 1.15, 95% CI 1.02 – 1.30) [8]. However, a negative depression screening score at study entry cannot rule out a history of depression and therefore the conclusion by Mezuk et al., about the role of diabetes as a risk factor for "new" cases of depression, might be premature [9]. Two meta-analyses showed that the reversed association, with depression as a risk factor for the onset of type 2 diabetes, is stronger. Depressed adults have a 30-60% increased risk of developing type 2 diabetes [8, 10].

There is abundant evidence showing that depression can be regarded as a chronic condition for many patients, with periods of (partial) remission and relapse in community [11] and primary care [12] samples. Although the existing literature suggests that depression is even more persistent in diabetes patients, these studies are hampered by relatively small numbers of type 2 diabetes patients [7, 13], the inclusion of selected populations from specialised clinics [14] and the measurement of depression in a selected sample of patients who have participated in an antidepressant drug trial [13] or diabetes education programme [7, 15]. A large

study examining different aspects of the natural course (incidence, remission, recurrence) of depression in a representative sample of primary care patients with type 2 diabetes is currently lacking.

Depression is associated with poor disease outcomes

Depression in diabetes was found to be associated with poor glycemic control [16], a higher number of cardiovascular risk factors [17], micro- and macrovascular complications [18], and an increased mortality risk [19-22]. Meta-analyses of prospective studies suggest that depression is associated with the onset or progression of cardiovascular disease in primary care and community samples [23] and post-myocardial infarction patients [24]. An important limitation of the current diabetes literature is that most studies on the association between depression and vascular conditions used cross-sectional data [18], hence precluding any inferences about possible causal pathways. In recent years, a limited number of prospective studies have been published. While depression predicted the incidence of vascular complications [19, 25] and greater all-cause mortality [19-22], its effect on mortality due to vascular causes still is unclear [20, 26]. So far, the emphasis in these studies has been on macrovascular outcomes, in particular coronary heart disease. Only two large longitudinal studies have considered the association between depression and the incidence of microvascular conditions. One of these was conducted in a sample of elderly Mexican-Americans and used self-report to ascertain the presence of complications [19], while the other only examined advanced complications, including end-stage renal disease, low vision or blindness, and amputations [27].

Type D personality and cardiovascular disease

Most research on the psychological aspects of diabetes has focused on depression, leaving the role of other dimensions of emotional distress, such as anxiety and more stable emotional traits, as understudied areas. An emerging risk factor in the cardiovascular research domain is “Type D (distressed) personality”, which is defined by the two stable personality traits “negative affectivity” and “social inhibition” [28]. Individuals with this personality type tend to experience negative emotions across time and situations, but are inclined to inhibit the expression of emotions and behaviors in order to avoid disapproval or rejection [28, 29]. Type D personality is relatively common, with prevalence estimates ranging from 21% in the general population to 28% in coronary heart disease patients and 53% in hypertensives [28]. Accumulating evidence suggests that having a Type D personality is associated with a 2 to 5-fold increased risk of adverse prognosis, impaired quality of life and emotional distress across cardiovascular patient groups, independent of standard biomedical risk factors [29, 30]. No studies to date have been undertaken to examine the impact of Type D personality on disease-related outcomes in patients with type 2 diabetes, although vascular disease is relatively common in this group.

Mechanisms that could link depression and Type D with poor outcomes

Several plausible mechanisms have been hypothesized to mediate the association between emotional distress (depression, Type D) and poor vascular outcomes. Potential mediators include health behaviors, such as smoking, alcohol consumption and physical inactivity, and biomedical factors (e.g. underlying cardiac disease severity, an unfavorable cardiovascular risk profile / the "metabolic syndrome", immune processes) [31-33]. In the Heart and Soul Study, a cohort of more than 1,000 outpatients with stable coronary heart disease, the association between depressive symptoms and adverse cardiovascular events was largely explained by behavioral factors, in particular physical inactivity (32% change in effect size) [33]. The extent to which these mechanisms account for the increased risk of vascular complications in distressed diabetes patients, should this association exist, is still unclear.

Innovative aspects of the DiaDDZoB Study

To summarize: (1) While there are numerous studies that aimed to determine the prevalence of depression in type 2 diabetes patients, little is known about the natural course of depression in diabetes (incidence, recurrence, remission). (2) The majority of studies examining the association between emotional distress and vascular disease had a cross-sectional design, focused on depression and had macrovascular disease as outcome. The role of other aspects of emotional distress and the association with common microvascular complications is therefore still unclear. (3) It is unknown which behavioral and / or biomedical mechanisms may account for the hypothesized associations between emotional distress and vascular conditions. The DiaDDZoB Study (**Dia**betes, **D**epression, Type **D** Personality **Z**uid**o**ost-**B**rabant) will examine the abovementioned issues in a cohort of primary care patients with type 2 diabetes.

METHODS / DESIGN

Aims and hypotheses

The DiaDDZoB Study was designed as a prospective cohort study and aims to address the following main research questions:

1. What is the natural course (prevalence, incidence, recurrence, remission) of depressive symptoms in a sample of primary care patients with type 2 diabetes?
2. Do patients with type 2 diabetes and co-morbid emotional distress (as evidenced by an increased level of depressive symptoms and / or Type D personality) have an increased risk for the onset / progression of micro- and macrovascular complications?
3. Do these types of emotional distress also increase the risk of all-cause or vascular mortality?
4. When a significant relation is found in (2) or (3): which factors mediate the association between emotional distress and diabetes outcomes?

Based on the current literature, we hypothesize the following: Approximately one fifth of our sample will have an increased level of depressive symptoms at each separate measurement occasion (prevalence). In the group of patients without a self-reported history of depression, incident depression will be low (< 5%). In the patients with a history of depression, recurrence rates will be relatively high (at least 25%). Significant risk factors for depression most likely will be: (1) psychosocial factors such as stressful life events and loneliness and (2) the presence (onset or progression) of vascular complications. We also hypothesize that patients with co-morbid distress (either depressive symptoms or Type D) will be at increased risk for the development of micro- and macrovascular conditions and both all-cause and vascular mortality; these associations are (partly) explained by behavioral (smoking behavior, alcohol consumption, physical inactivity) and biomedical (cardiovascular disease history, characteristics of the metabolic syndrome) mechanisms.

Study design

From 2005 onwards, data for the DiaDDZoB Study have been collected within the framework of the DIAZOB (Diabetes care Zuidoost-Brabant) project, a large-scale diabetes management programme for primary care patients with type 2 diabetes. To evaluate the implementation of this standard diabetes care programme in daily practice, an observational cohort study (the DIAZOB Primary Care Diabetes study) was designed, including annual assessments of a broad range of demographic, medical, lifestyle and psychosocial factors [34, 35]. Follow-up surveys of the total DIAZOB population (N ≈ 12,000) are planned for the upcoming years. The DiaDDZoB Study builds upon data from three completed measurement occasions. The original baseline measurement (M_0) took place in the second half of 2005. Follow-up assessments were realized in 2007 (M_1) and 2008 (M_2).

Subjects

The ongoing assessment of the DIAZOB-cohort is conducted in collaboration with over 200 general practitioners who are currently allied to PoZoB (Praktijkondersteuning Zuidoost Brabant), a large managed care organisation responsible for the implementation of the DIAZOB standard care programme. The practices are located in the South-Eastern area of The Netherlands, mainly in the region south of the city of Eindhoven. The patient population is residing in rural and suburban areas. To be included in the DIAZOB Primary Care Diabetes study, the patient had to be formally diagnosed with type 2 diabetes according to the guidelines of the Dutch College of General Practitioners (as evidenced by either a fasting glucose concentration of > 6.9 mmol / l in venous plasma or > 6.0 mmol / l in capillary blood on two separate days or an arbitrary glucose level > 11.0 mmol / l in the presence of the classic hyperglycemia symptoms [36]. These criteria are comparable to the recommendations of the American Diabetes Association [37]. Other inclusion criteria were: the patient was

receiving treatment for diabetes in the DIAZOB diabetes care programme, had the primary care practice nurse as his / her main health care provider for diabetes issues, was at least 18 years old (with no upper age limit) and had sufficient mastery of the Dutch language. Patients were excluded if they had a treatment or condition other than type 2 diabetes as the primary cause of the hyperglycemia and / or were physically / mentally incapable of completing a questionnaire (e.g. co-morbid dementia, terminal cancer), as judged by the primary care practice nurse.

Recruitment of patients

From 2005 onward, patients were invited by their primary care practice nurse to participate in the DIAZOB standard care project. In the period of April (pilot) and June - December 2005, the DIAZOB patients were informed of the evaluation study and received a detailed description of its practical and scientific aim. Patients who were willing to participate were asked to sign an informed consent form. Consent was sought for (a) using the anonymised data (questionnaire and medical information) for reports and scientific publications; requesting information from the patient's (b) pharmacist and (c) specialist; and (d) informing the general practitioner or primary care practice nurse of study results, if necessary.

Participant drop-out

In the beginning of 2005, the total number of type 2 diabetes patients in the area covered by the participating general practitioners at that time was estimated at 3,000 to 3,500. During the baseline inclusion period, 3,017 patients were considered for participation in the study. A detailed overview of the study's participation and drop-out rate can be found in Figure 1. Reasons for baseline non-response could be grouped into "patient characteristics" (e.g. not meeting inclusion criteria / screening positive on exclusion criteria, refusing to participate, not showing up at the baseline interview) and "practice nurse characteristics" (lack of time, omitting to invite newly diagnosed or insulin-using patients). Of the resulting 2,460 patients, 2,448 (99.5%) attended the interview and 1,850 (75.2%) returned the self-report questionnaire that had to be filled in at home. For the M_1 and M_2 assessments, 2,225 and 2,032 patients were available, respectively.

Measures used in the DiaDDZoB Study

The DIAZOB Primary Care Diabetes study measurements include an interviewer-administered and self-report questionnaire, results from regular care laboratory tests and physical examinations, and pharmacy medication records. An overview of the variables that were used for the DiaDDZoB Study can be found in Table 1.

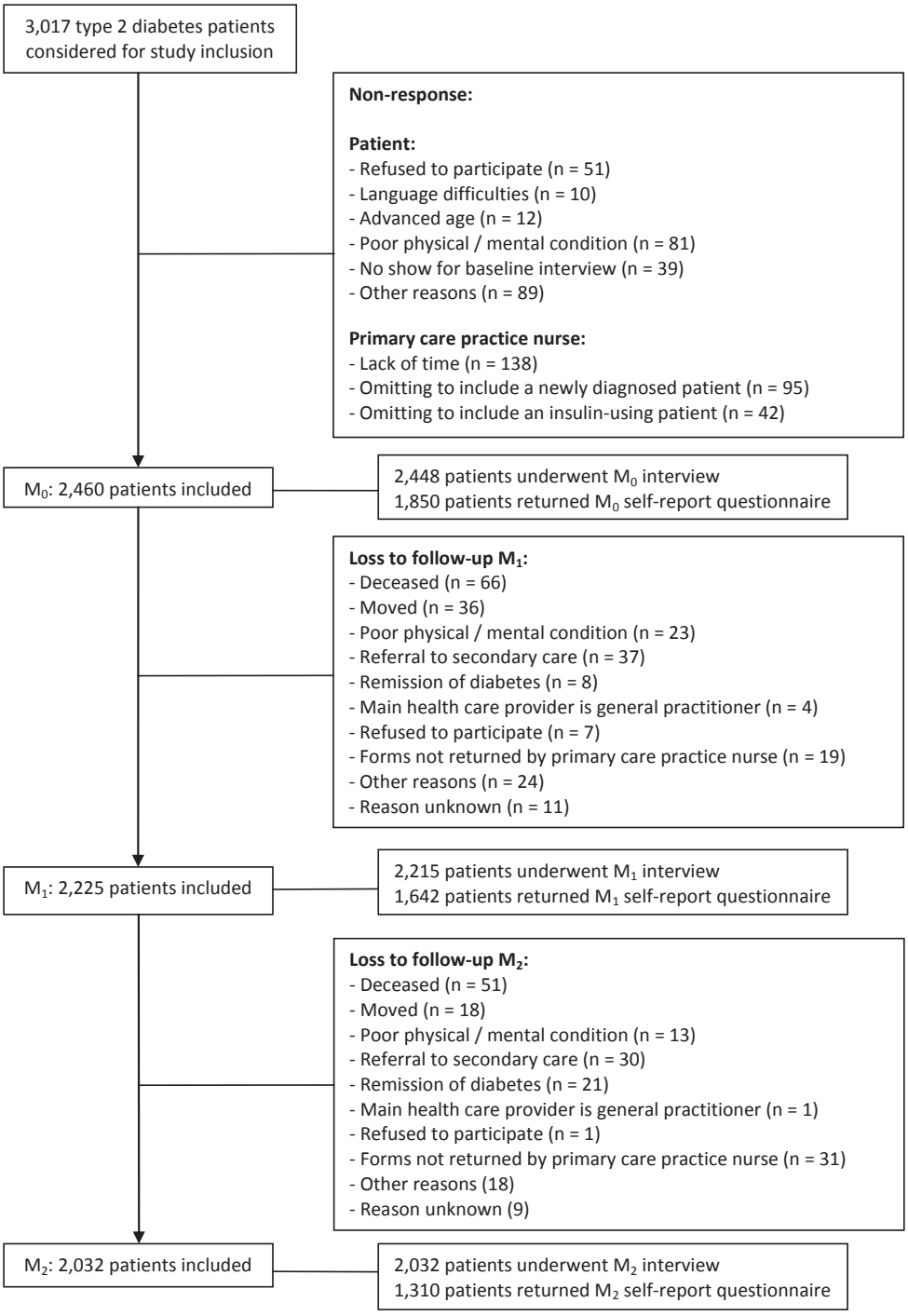

Figure 1 Flow chart of the original DIAZOB cohort

Data acquired during an interview with the primary care practice nurse
The interview-administered questionnaire was filled out by the practice nurse along with the patient during regular diabetes check-up and included questions about demographic factors, clinical parameters, hyperglycemia treatment and health behaviors.

Demographics
Information was gathered about age, gender and ethnicity.

Clinical parameters
At baseline, the primary care practice nurse recorded the number of months / years since diabetes diagnosis and took a basic medical history, including self-reported history of depression. Self-reported medical diagnoses were verified through inspection of the medical record. At follow-up, onset and / or progression of vascular complications and other conditions was recorded, as was mortality date and cause of death for those patients who deceased during the study.

Hyperglycemia treatment
At each measurement occasion, the practice nurse documented whether patients were currently treated for their hyperglycemia by diet, oral agents, insulin or a combination of these treatment modalities.

Health behaviors / Lifestyle
A basic overview of current and former smoking behavior and alcohol consumption was collected at the baseline assessment. Changes to this baseline pattern were recorded during follow-up. Physical activity was assessed by means of two items. Patients had to indicate how many hours per week they spent on (a) “active” (all physical activities other than practicing sports, e.g. gardening, walking, cycling, climbing stairs) and (b) “sportive” physical activities (e.g. sports, fitness).

Data acquired using self-report questionnaires
A second questionnaire was completed by the patient at home and addressed several additional demographic variables and psychosocial factors. For practical purposes, the questions about health behaviors were transferred from the interview-administered to the self-report questionnaire for the follow-up measurements.

Demographics
The demographic measures included marital status (dichotomized as being single versus having a partner), living situation (independent versus dependent of others), employment status (paid employment versus no paid employment / unemployed / disabled / retired) and educational level (low education versus middle / high education).

Depressive symptoms

Depressive symptoms during the last seven days were assessed using a validated Dutch version of the Edinburgh Depression Scale (EDS) [38]. This is a 10-item self-rating scale in which each item is scored on a four-point scale. Total scores range from 0 to 30 points. The EDS was originally developed to measure post partum depression [39], but has later been validated in non-postnatal women [40], women around menopausal age [41], men [42] and community samples [43]. Although cut-off points for predicting a diagnosis of clinical depression vary [44], a cut-off score of 12 or more seems to have satisfactory sensitivity and specificity [41, 43].

Type D personality

Type D personality was assessed using the Type D Scale-14 [28]. This questionnaire consists of 14 items, which are scored on a five-point rating scale ranging from 0 = "false" to 4 = "true". The DS14 comprises two scales, one measuring level of negative affectivity (NA) and the other social inhibition (SI). Subjects who obtain a score of ten or more on both scales are considered to have a Type D personality [28]. Both scales have been shown to be internally consistent (Cronbach's α = 0.88 for the NA scale and 0.86 for the SI scale), stable over an 18-month period [45] and are independent of mood and health status [28, 45].

Other psychosocial factors

Social support was measured using O'Hara's modified Social Support Scale [46], comprising three items. Answer categories range from 0 to 4 points, with 0 indicating "no social support at all" and 4 indicating "extensive social support". The total social support score is obtained by adding scores on all three items. A single item was used to measure feelings of loneliness in the past 12 months, which were scored on a scale from 1 to 10 points, with a score of 1 meaning "I never felt lonely" and a score of 10, "I always felt lonely". To account for non-diabetes related stressors, respondents were asked if they had experienced a stressful life event in the previous 12 months (e.g. loss of a loved one, a break-in, relationship problems, loss of work, serious financial problems, physical / mental abuse).

Laboratory tests and physical examinations

Biomedical parameters were derived from standard care laboratory tests and physical examinations carried out by the Diagnostic Centre Eindhoven, a primary care institution where biological records of the regional diabetes population are filed after each regular care check-up appointment. For the DIAZOB project, blood was drawn annually to determine glycemic control (glycosylated hemoglobin or HbA_{1C} levels, fasting glucose), creatinin, the MDRD clearance (only at follow-up) and cholesterol values (total, LDL, HDL, triglycerides); urine samples were taken to assess albumin and the albumin-to-creatinin ratio. As for the physical examination, blood pressure measurements (systolic and diastolic), body mass index (BMI; weight in kilograms / length in metres^2), and fundus photography and foot screening results were provided. To diagnose retinopathy, digital fundus photography was carried out by a biometrist and interpreted by an ophthalmologist. Foot screening included

a neurological and vascular examination (Doppler test), and inspection of feet and shoes by a podotherapist or a biometrist under supervision. For the baseline measurement, only the presence of abnormalities to the feet was recorded. During follow-up testing, the lower extremities were assessed for neuropathy, ischemia, wounds / ulcers and excessive coldness.

Pharmacy medication records

With the patient's consent, information regarding prescribed medication was obtained from local pharmacists. In addition to the medication applied for the management of hyperglycemia, the use of cardiovascular agents (including several antihypertensives and a class of cholesterol-lowering drugs) was registered.

Table 1 Measurements included in the DiaDDZoB Study

Variable	Categories	Measurement occasion
Demographic factors		
Age		M_0
Gender	Male, female	M_0
Ethnicity	Dutch, other Caucasian (white Western) groups, other (Asian, black, Turkish / Moroccan)	M_0
Marital status	Married / living together, single, LAT relationship, divorced / separated, widowed	M_0, M_1, M_2
Living situation	Independent, residing with family / friends, residing in a nursing home	M_0, M_1, M_2
Employment status	Paid employment, unemployed, disabled, no paid employment, retired	M_0, M_1, M_2
Education level	Primary school, primary vocational education, secondary school, secondary vocational education, higher vocational education, university	M_0
Medical history		
Disease duration	Months / years since diabetes diagnosis	M_0, M_1
Medical history	M_0: lifetime history: arterial disease, bypass / angioplasty, myocardial infarction, stroke, angina pectoris, high cholesterol, kidney disease, asthma / COPD, cancer, rheumatic disorder, depression, burn-out M_1 and M_2: during last 12 months: arterial disease, bypass / angioplasty, myocardial infarction, stroke, angina pectoris, high cholesterol, asthma / COPD, osteoporosis, depression, kidney disease	M_0, M_1, M_2
Treatment		
Current hyperglycemia treatment modality	None, diet, diet / oral agents, diet / insulin, diet / oral agents / insulin, other	M_0, M_1, M_2
Medication use	ACE inhibitors, β-blockers, calcium antagonists, diuretics, other antihypertensive agents, statins	M_0, M_1, M_2

Table 1 (continued)

Variable	Categories	Measurement occasion
Laboratory tests		
HbA_{1c}		M_0, M_1, M_2
Fasting glucose		M_0, M_1, M_2
Cholesterol	Total cholesterol	M_0, M_1, M_2
	LDL-cholesterol	M_0, M_1, M_2
	HDL-cholesterol	M_0, M_1, M_2
	Triglycerides	M_0, M_1, M_2
Protein levels	Albumin	M_0, M_1, M_2
	Creatinin	M_0, M_1, M_2
	Albumin-to-creatinin ratio	M_0, M_1, M_2
	MDRD clearance	M_1, M_2
Physical examination		
Length	Length in metres	M_0, M_1, M_2
Weight	Weight in kilograms	M_0, M_1, M_2
Body Mass Index (BMI)	Weight in kilograms / (length in metres)^2	
Blood pressure	Systolic	M_0, M_1, M_2
	Diastolic	M_0, M_1, M_2
Fundus photography	Unassessable, normal, retinopathy	M_0, M_1, M_2
Foot examination	M_0: Normal, abnormal M_1 and M_2: Normal, neuropathy, ischemia, wound / ulcer, excessive coldness	M_0, M_1, M_2
Lifestyle indicators		
Smoking behavior	Current smoking: yes / no, number of cigarettes per day Additional for M_0: smoking history	M_0, M_1, M_2
Alcohol consumption	Current alcohol consumption: yes / no, number of consumptions per week Additional for M_0: history of alcohol consumption	M_0, M_1, M_2
Physical activity	Hours per week of active physical activity	M_0, M_1, M_2
	Hours per week of sportive physical activity	M_0, M_1, M_2
Psychological factors		
Depressive symptoms	Edinburgh Depression Scale (EDS)	M_0, M_1, M_2
Type D personality	Type D Scale-14 (DS14)	M_1, M_2
Social support	O'Hara's modified Social Support Scale	M_0, M_1, M_2
Loneliness	Single item concerning feelings of loneliness in the past 12 months	M_0, M_1, M_2
Stressful life events	Single item concerning stressful life event(s) in the past 12 months	M_0, M_1, M_2

Ethical principles

This study was planned and conducted in accordance with the medical professional codex and the Helsinki Declaration of 1996 [47]. Written informed consent was obtained from all participants. The study protocol of the DiaDDZoB Study was approved by the medical research ethics committee of a local hospital, the Máxima Medical Centre in Veldhoven (NL27239.015.09).

Planned statistic analyses

Statistical analyses will be performed using the latest version of the Statistical Package for Social Sciences (SPSS). A $p < 0.05$ significance level will be adopted in all statistical tests. As the number of previous studies on these research topics is limited, we choose to use two-sided tests in all analyses.

Frequencies will be provided for (1) the prevalence, (2) incidence (with / without self-reported history of depression), (3) recurrence (high score across two or three assessments) and (4) other patterns of relapse and remission of high depressive symptoms (EDS-score of 12 or more). In addition, logistic regression analyses will be used to determine significant predictors of these different course patterns. Baseline characteristics of patients with / without high depressive symptoms (EDS-score of 12 or more) and with / without a Type D personality will be compared using independent-samples t-tests and X^2 tests. To evaluate the vascular risk associated with increased levels of emotional distress, we will perform logistic regression analyses for (1) the development of each separate micro- and macrovascular complication and (2) a composite measure of vascular disease (the development of any vascular condition) during the two year follow-up period, with either depression or Type D personality as the independent variable. The group of participants with low depressive symptoms or no Type D personality, respectively, will be used as the reference category. Analogous analyses will be used for mortality, with the dependent variable defined as (1) all-cause mortality or (2) (cardio)vascular mortality, as registered in primary care medical records up until December 2008. Before proceeding to the multivariate statistics, several study variables will be evaluated for their potential as confounders or mediators in the association between emotional distress and disease outcomes (the onset / progression of micro- and macrovascular complications, all-cause and vascular mortality). In line with the methods used in a study by Whooley et al. [33], we will adopt a > 5% change in the effect size (odds ratio) for emotional distress before and after adjustment for the variable in question as the criterion to identify suitable mediating or confounding factors. All variables satisfying these conditions will be included in the final logistic regression models. In addition, we will look at mediating variables more closely using one of the statistical methods described in the recent article by MacKinnon, Fairchild and Fritz [48].

Power calculation

The sample size was determined using PASS 2008 [49] and was based on the logistic regression analyses for the main research question ("Do patients with type 2 diabetes and co-morbid emotional distress have an increased risk for the onset / progression of micro- and macrovascular complications?"). Assuming a power of 0.80, an alpha level of 0.05, two-sided testing, and a baseline prevalence rate of 20% for the binary independent variable (either high levels of depressive symptoms or Type D personality), we calculated the sample size for a range of scenarios. Based on earlier primary care and community studies [19, 27] and on known characteristics of the DIAZOB population, we expect a two-year cumulative event rate (the development of any vascular complication) of 10 - 15%. In psychological research, R^2 (achieved when emotional distress is regressed on the other independent variables) usually ranges from 0.20 - 0.30. Assuming equivalence between OR / RR / HR due to the relatively low event rate of vascular outcomes, the majority of earlier studies on the risk of vascular disease in diabetes patients, primary care / community samples and post-myocardial infarction patients has found an effect size for depression of approximately 1.5 - 2.0 [23, 24, 27]. Therefore, the entered values were either 0.10, 0.125 or 0.15 for P_0 (the probability that a participant develops any vascular complication during the two year follow-up period, given that he / she has a low level of depressive symptoms or no Type D personality at baseline), 0.20, 0.25 or 0.30 for R^2, and 1.5, 1.75 or 2.0 for the OR. Sample sizes ranged from 3905 in the most conservative scenario (P_0 = 0.10, R^2 = 0.30 and OR = 1.5) to 764 in the least restricted scenario (P_0 = 0.15, R^2 = 0.20 and OR = 2.0). When positing a middle-ground scenario (P_0 = 0.125; R^2 = 0.25 and OR = 1.75), the study needs a total of 1499 participants to detect an OR of 1.75. Anticipating an annual 10% loss to follow-up (death, serious illness, moving), we need to include approximately 1850 patients at baseline. As we expect a 40% non-response / exclusion rate, we will consider for eligibility the total patient group (n ≈ 3000).

DISCUSSION

As the prevalence of type 2 diabetes is high and the absolute numbers of patients with both diabetes and depression will continue to rise considerably in the next decades, it has become even more essential to further increase our understanding of the associations between diabetes and depression. Currently, our knowledge about this area is still limited. The present paper gives an outline of the theoretical background and methodology of the DiaDDZoB Study, a Dutch prospective cohort study in primary diabetes care, which aims to answer several key research questions regarding the course and vascular impact of depression and Type D personality in patients with type 2 diabetes.

The major strengths of the DiaDDZoB Study include its longitudinal design and relatively large sample size, its focus on type 2 diabetes patients who are being treated in a primary care setting, the wealth of detailed patient information that is available, and the policy to verify self-reported disease by inspection of medical records. The results of this study may lead to the identification of high risk patients and could guide the development of future intervention studies.

While the DIAZOB Primary Care Diabetes study aims to include a relatively unselected patient population, depressive symptoms (including a depressed mood or markedly diminished interest, loss of energy and a diminished ability to think or concentrate) could have negatively affected the initial decision to participate in those patients who would otherwise have screened positive for depression on the EDS. In a similar vein, as the nurse-led interview required a certain amount of openness and direct communication with a health provider about disease and concurrent complaints, social inhibition might have deterred patients with a Type D personality. In a study of 178 patients with chronic heart failure, patients with a Type D personality not only experienced and worried more about cardiac symptoms, they also were less likely to report these symptoms to their cardiologist or nurse [50].

The sharp rise in the number of patients with type 2 diabetes has resulted in a gradual shift from secondary to primary care, thereby placing considerable demands on primary health care teams [51]. Secondary care consultations or referrals are indicated in case of more complex disease management, e.g. in the presence of complications or poorly regulated blood glucose levels [52, 53]. Seeing that approximately 3% (67 / 2,460) of all patients participating in the baseline assessment dropped out of the study after a secondary care referral, future assessments should be planned and carried out in close cooperation with hospital practitioners to keep the cohort intact. To alleviate some of the workload for general practitioners, the primary care nurse specialist has been introduced as the main care-provider for patients with type 2 diabetes in family practice [54]. Since nurse practitioners generally provide longer consultations and are trained to focus on the medical, practical as well as the emotional aspects of diabetes [55], depression prevalence estimates could have been lowered with more adequate detection and subsequent treatment of depression. Unfortunately, earlier work has shown that the reverse is probably true, i.e. the presence of emotional problems was recorded in the medical chart in only 20 – 30% of diabetes patients with high scores on questionnaires measuring emotional distress [55].

Although a recent cohort study has investigated whether depression runs a chronic course with high rates of recurrence in primary care [12], there is a paucity of research on the trajectory of emotional distress in specific chronic diseases. While our annual screening

method most likely will identify a subsample with recurrent, high levels of depressive symptoms, a prospective design with yearly follow-up assessments will by definition miss some patients with a relapsing-remitting symptom profile who happen to be in complete or partial remission at the assessment occasion. While an in-depth characterization of short-term fluctuations in emotional distress goes beyond the initial goals of the DIAZOB project, a similar model offers interesting research perspectives for future studies.

A structured psychiatric interview using DSM-IV criteria is considered the gold standard for diagnosing clinical depression [56]. While self-report questionnaires were originally developed to quantify the severity of depression, they are often adopted as time-efficient case-finding instruments in large samples [57]. However, depression is not the only common emotional problem in diabetes patients [58, 59]. Depression questionnaires may detect some [56], but certainly not all [58] components of distress. Given the tendency of psychosocial factors to cluster together within individuals [60, 61], the simultaneous assessment of multiple distress types seems justified to obtain a more precise risk stratification [60]. Other studies have emphasized the importance of examining both episodic emotional states and more chronic psychosocial factors [60, 62]. By extending the focus of our research from a cross-sectional assessment of depressive symptoms to repeated measurements of not only depression, but also Type D personality, we intend to take a step in this direction.

Several other study limitations need to be mentioned. First, while laboratory determinations and physical examinations are part of regular care protocols and therefore did not impose an extra burden on the participating patients, we cannot avoid that for some patients these tests were scheduled several months before or after the official measurement occasion in question. In these cases, we used the test results that were the closest in time to the rest of the data. Secondly, although the prescription of antihyperglycemic and cardiovascular agents was documented relatively well, information on the concurrent use of psychotropic medication is lacking. Earlier studies have suggested that different classes of antidepressant drugs may exert a clinically relevant positive or negative effect on glucose-insulin homeostasis [63]. Requesting pharmacy information from large databases of pharmacy dispensing records [64] might improve the accuracy of medication registration. Finally, although we aim to elucidate the mechanisms responsible for the adverse effect of emotional distress on vascular outcomes, no information was available on several interesting candidate mechanisms, including dysfunctional activity of the hypothalamic-pituitary-adrenal axis, neurotransmitter function or inflammatory processes [31-33].

General practice settings offer relatively favorable conditions for conducting longitudinal research, as the Dutch health care system is characterized by a high level of care continuity

between patients and family physicians [65]. In enhancing the quality of longitudinal data collection, it is essential to ensure the provision of solid research facilities, standardization of data between practices and over time, and integration of scientific and patient care data collection in a clinician-friendly manner [65]. Planning and conducting longer term epidemiologic studies considerably challenges the motivation and benevolence of participating health care providers. Apart from central coordination of the DIAZOB research infrastructure, PoZoB also contributes to a clinical translation of scientific findings by organising feedback meetings and training programmes, thus enabling an ongoing research commitment of general practitioners and their staff [65]. Keeping an eye on the needs and developments in primary care daily practice, the collaboration between PoZoB and C*o*RPS, Tilburg University, will provide an excellent framework to explore the wealth of information already available and at the same time ensure a continuing qualitative and innovative development of primary care diabetes research.

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CHAPTER 4

The course of depressive symptoms in primary care patients with type 2 diabetes: results from the Diabetes, Depression, Type D personality Zuidoost-Brabant (DiaDDZoB) Study

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ABSTRACT

Aims / hypothesis: The aim of the study was to examine the course (incidence, recurrence / persistence) of depressive symptoms in primary care patients with type 2 diabetes and to identify significant predictors of these different course patterns.

Methods: A cohort of 2460 primary care patients with type 2 diabetes was assessed for demographic, clinical and psychological factors in 2005 and followed-up in 2007 and 2008. Depression was defined as a score of ≥ 12 on the Edinburgh Depression Scale. Multivariate logistic regression analyses were used to determine whether several depression-course patterns could be predicted by means of demographics, medical co-morbidities and psychological factors.

Results: A total of 630 patients (26%) met the criterion for depression at one or more assessments. In the subgroup with no baseline depression, incident depression at follow-up was present in 14% (n = 310), while recurrence / persistence in those with baseline depression was found in 66% (n = 212).The presence of any depression was associated with being female, low education, non-cardiovascular chronic diseases, stressful life events and a self-reported history of depression. Incident depression was predicted by female sex, low education and depression history, while patients with a history of depression had a 2.5-fold increased odds of recurrent / persistent depression.

Conclusions / interpretation: Depression is common in primary care patients with type 2 diabetes, with one in seven patients reporting incident depression during a 2.5 year period. Once present, depression often becomes a chronic / recurrent condition in this group. In order to identify patients who are vulnerable to depression, clinicians can use questionnaire data and / or information about the history of depression.

INTRODUCTION

Compared with controls without diabetes, the risk of depression is nearly doubled in individuals with type 2 diabetes, affecting approximately one in every five patients [1]. A recent meta-analysis has shown that individuals with previously diagnosed diabetes have an increased risk of depression relative to those with impaired glucose metabolism or undiagnosed diabetes [2]. Co-morbid depression not only has a profound negative impact on patients' quality of life [3], but is also related to worse glycaemic control [4], the development of macro- and microvascular complications [5, 6] and a higher mortality risk [7]. Despite the growing body of literature demonstrating the harmful effects of depression in this patient group, the course of depression in type 2 diabetes has received relatively little research attention.

Previous cross-sectional research has mainly focused on prevalence estimates of depression, finding particularly high rates in women, patients treated in specialist settings and those with co-morbid medical conditions [1, 8-11]. Furthermore, the longitudinal studies that have been conducted have mainly focused on incident depression in type 2 diabetes. A recent meta-analysis of 11 studies concluded that people with type 2 diabetes have a 24% increased odds of incident depression compared with people without diabetes [12]. However, as only one of the studies excluded people with a history of depression in the years before study onset, the results of this study are likely to overestimate the risk for incident depression in the strictest sense (i.e. first occurrence) [12]. Although a few studies have examined the course of depression once symptoms were present (recurrence / persistence, remission), most had considerable limitations: for example, a small sample size ($n < 175$) [13-15], recruitment from specialist settings [15] or only two assessments of depression [15, 16]. Two studies did not provide strictly observational findings as they assessed depression in the framework of an intervention study [13, 14]. One observational study of 506 patients with type 2 diabetes assessed depression three times over a period of 18 months (with 9 month intervals) [17]. However, the authors combined persistence estimates into the categories "condition at only a single wave", "condition at any two waves" and "condition at all three waves", thereby impeding an evaluation of specific course patterns.

To our knowledge, a large study simultaneously addressing different aspects of the course of depression in primary care patients with type 2 diabetes is currently lacking. Therefore, the main aim of the present study was to examine several course trajectories of depressive symptoms (incidence, recurrence / persistence) using data from three separate assessments during a 2.5 year period and to gain insight in the demographic, medical and psychological risk factors predicting these different course patterns.

METHODS

Methods and response rates of the Diabetes, Depression, Type D *["distressed"]* Personality Zuidoost-Brabant (DiaDDZoB) Study have been described in detail elsewhere [18]. In short, 2460 patients with type 2 diabetes (82% of those considered for study inclusion) treated within 77 primary care practices in South-East Brabant, The Netherlands, were recruited at the baseline assessment in the second half of 2005 (M_0). Of these patients, nearly all (2448) attended a baseline nurse-led interview, while 75% (1850) returned the self-report questionnaire that had to be completed at home. This cohort was re-contacted for follow-up assessments in 2007 (M_1) and 2008 (M_2), and included 2225 and 2032 participants, respectively. The study protocol of the DiaDDZoB Study was approved by the medical research ethics committee of a local hospital, the Máxima Medical Centre in Veldhoven (NL27239.015.09). Written informed consent was obtained from all participants.

Assessment of depression

Symptoms of depression during the last 7 days were assessed using a validated Dutch version of the Edinburgh Depression Scale (EDS) [19]. The EDS was originally designed to assess postpartum depression [20], but has now been validated in non-postnatal women [21], women around menopausal age [22], men [23], community samples [24] and primary care patients with type 2 diabetes [25]. The EDS is a ten-item self-report questionnaire, in which each item is scored on a four-point scale. Total EDS scores are determined by summing the scores of all ten individual items (total score range 0 – 30), with higher scores indicating higher levels of depressive symptoms. A total score of 12 or more is commonly used to identify patients with depression [24]. Using this cut-off, we calculated dichotomised depression scores (no depression / depression) for all three measurements. Patients were considered to suffer from "any depression" if they obtained an EDS score ≥ 12 during at least one of the three measurement occasions. To specify the course trajectory of these depressive symptoms, we split the total sample into two groups based on the baseline (M_0) EDS score. "Incident depression" was determined in the subgroup with an EDS score < 12 at M_0 (no baseline depression). Patients in this group who obtained an EDS score ≥ 12 at M_1 and / or M_2 were considered incident cases. Rates of "recurrence / persistence" were examined in the remaining group of participants who had an EDS score ≥ 12 at M_0 (baseline depression). Depression was labelled "recurrent / persistent" if patients had at least one other high EDS score at M_1 or M_2.

Baseline demographic, medical and psychological predictors

Baseline demographic data included sex, age, marital status (having a partner vs being single) and educational level (middle / high vs low), and were acquired during a patient interview led by the primary care practice nurse and also by means of a self-report questionnaire.

The primary care practice nurse took a medical history, after which all self-reported medical diagnoses were verified through inspection of the medical record. Indicators of microvascular disease were derived from standard-care laboratory tests and physical examinations carried out by the Diagnostic Centre Eindhoven, a primary care diagnostic institute. The results from patients' yearly digital fundus photography were available to ascertain retinopathy (yes / no), while albumin level in a random urine sample was used as a proxy of nephropathy [26]. Macro- and microalbuminuria were defined as urine albumin concentrations > 200 and 20 – 200 mg / l, respectively. All medical co-morbidities were combined into three composite disease measures, i.e. cardiovascular diseases (myocardial infarction, bypass / angioplasty, stroke and / or arterial disease), microvascular complications (retinopathy and / or micro- / macroalbuminuria) and other chronic conditions (kidney disease, asthma / chronic obstructive pulmonary disease [COPD], cancer, arthrosis and / or rheumatoid arthritis). In addition, patients were asked if they had ever suffered from depression. Non-diabetes-related stressful life-events in the previous 12 months (e.g. loss of a loved one, burglary, relationship problems) were assessed by means of a single questionnaire item.

Other patient characteristics

The interview included one question regarding ethnicity (white vs non-white). Baseline treatment for diabetes and diabetes duration were documented by the primary care practice nurse. Standard-care determinations of HbA_{1c} concentrations and BMI were provided by the Diagnostic Centre Eindhoven.

Statistical analyses

Baseline sample characteristics and descriptive statistics for the EDS data at all three measurement occasions were calculated. To compare differences between men and women, X^2 tests were used for categorical data and independent samples t-tests for continuous data. Of all demographic, clinical and psychological data needed for the analyses, 27% was missing. As complete case analysis would restrict the sample to 511 patients (21%), multivariate imputation by chained equations was applied to impute missing values (Electronic supplementary material [ESM] Table 1), using the package MICE V2.0 [27] and the software program R [28]. Adequate results can generally be obtained by creating five to ten imputed datasets, retaining final imputations per dataset after ten iterations [27, 29]. For the present study, 20 imputed datasets were generated, allowing ten iterations per set.

Following imputation, depression prevalence rates and estimates for any, incident and recurrent / persistent depression were calculated, pooling the results over the 20 individual datasets. Multivariate logistic regression analyses were used to determine whether these different depression course trajectories could be predicted by means of: (1) demographics

(female sex, age, low education, being single); (2) medical co-morbidities (prior cardiovascular disease, the presence of microvascular complications, other co-morbid conditions); (3) stressful life events; and (4) self-reported history of depression. As missing EDS baseline data were also imputed, the number of individuals classified in either the "incident depression" or "recurrent / persistent depression" subgroup varied slightly per individual imputed dataset. Therefore, in addition to reporting the pooled results of the regression analyses for incident and recurrent / persistent depression, the range of n across all 20 individual imputed datasets was provided. With the exception of the multiple imputation procedure, all analyses were performed using PASW Statistics version 17.0 (IBM SPSS Statistics, Somers, NY, USA). A *p*-value < 0.05 was considered to be statistically significant.

RESULTS

Baseline sample characteristics

Table 1 presents the characteristics of the total DiaDDZoB sample before multiple imputation (n = 2460, 49% men, mean age 67 years) and the number of missing values per variable. Overall, participants were in relatively good glycaemic control (mean HbA_{1c} 6.7% [50 mmol / mol]), and the majority were being treated with a combination of diet and oral glucose-lowering agents. Co-morbid diseases were common, with vascular disease and other major (chronic) medical conditions being present in one-third and one-half of all patients, respectively. Advanced microvascular complications, including retinopathy and macroalbuminuria, were relatively rare. However, almost one in four patients had microalbuminuria. When examining results separately for men and women, women were shown to be significantly older, more commonly had a low educational level and were more likely to be single. Myocardial infarction, bypass / angioplasty procedures and albuminuria were more prevalent in men, while the medical history of women included more diagnoses of cancer, arthrosis and rheumatoid arthritis. Furthermore, women were more likely to report a history of depression and at least one stressful life event in the past year.

Table 1 Baseline characteristics before multiple imputation

	All (n = 2460)	*n* missing	Men (n = 1192)	Women (n = 1268)	*P* value
Demographics					
Age (years)	67 (11)	5	66 (11)	68 (11)	<0.001
Non-white	3% (78/2424)	36	3% (36/1174)	3% (42/1250)	0.68
Low education level	64% (1140/1770)	690	53% (459/866)	75% (681/904)	<0.001
Being single	25% (455/1831)	629	16% (144/893)	33% (311/938)	<0.001
Medical history					
Cardiovascular disease	36% (842/2368)	92	40% (458/1157)	32% (384/1211)	<0.001
Myocardial infarction	12% (280/2353)	107	16% (188/1149)	8% (92/1204)	<0.001
Bypass / angioplasty	13% (312/2358)	102	18% (207/1153)	9% (105/1205)	<0.001
Stroke	7% (164/2360)	100	8% (88/1154)	6% (76/1206)	0.21
Arterial disease	24% (559/2349)	111	25% (287/1142)	23% (272/1207)	0.14
Microvascular disease	35% (612/1769)	691	38% (334/886)	32% (278/883)	0.006
Retinopathy	5% (86/1767)	693	4% (37/878)	6% (49/889)	0.21
Microalbuminuria [a]	23% (477/2077)	383	26% (264/1003)	20% (213/1074)	<0.001
Macroalbuminuria [b]	4% (72/2077)		5% (46/1003)	2% (26/1074)	
Other chronic conditions	50% (1184/2377)	83	44% (510/1157)	55% (674/1220)	<0.001
Kidney disease	4% (95/2339)	121	4% (47/1144)	4% (48/1195)	0.91
Asthma / COPD	13% (315/2360)	100	13% (153/1147)	13% (162/1213)	0.99
Cancer	9% (222/2351)	109	8% (90/1144)	11% (132/1207)	0.01
Arthrosis	34% (793/2365)	95	27% (309/1152)	40% (484/1213)	<0.001
Rheumatoid arthritis	7% (161/2352)	108	4% (44/1146)	10% (117/1206)	<0.001
Clinical values					
Hyperglycaemia treatment					
No treatment	1% (19/2422)	38	1% (9/1179)	1% (10/1243)	0.04
Diet only	18% (432/2422)		19% (219/1179)	17% (213/1243)	
Diet, oral agents	75% (1821/2422)		76% (892/1179)	75% (929/1243)	
Diet, oral agents, insulin	5% (114/2422)		4% (46/1179)	6% (68/1243)	
Diet, insulin	1% (33/2422)		1% (10/1179)	2% (23/1243)	
Other	0% (3/2422)		0% (3/1179)	0% (0/1243)	
Diabetes duration ≥3 years	61% (1467/2424)	36	59% (697/1175)	62% (770/1249)	0.24
HbA_{1c} %; mmol / mol	6.7 (0.9); 50 (10)	61	6.7 (0.8); 50 (9)	6.7 (0.9); 50 (10)	0.28
BMI (kg / m^2)	29 (5)	234	28 (4)	30 (5)	<0.001
Psychosocial factors					
History of depression	11% (248/2345)	115	9% (97/1146)	13% (151/1199)	0.001
Stressful life event(s)	35% (635/1800)	660	32% (280/881)	39% (355/919)	0.002
M_0 depressive symptoms					
EDS total score	6 (5)	715	5 (4)	7 (5)	<0.001
EDS score ≥ 12	12% (216/1745)		8% (70/861)	17% (146/884)	<0.001
M_1 depressive symptoms					
EDS total score	6 (5)	918	5 (4)	7 (5)	<0.001
EDS score ≥ 12	14% (210/1542)		9% (66/741)	18% (144/801)	<0.001
M_2 depressive symptoms					
EDS total score	6 (5)	1226	5 (5)	7 (5)	<0.001
EDS score ≥ 12	15% (188/1234)		10% (60/580)	20% (128/654)	<0.001

Values are mean (standard deviation), unless otherwise specified; [a] Albumin concentration of 20 - 200 mg / l; [b] Albumin concentration of > 200 mg / l

Prevalence of depression

Figure 1 shows the number of patients with depression (EDS score ≥ 12) at the baseline assessment in 2005 (M_0) and the two follow-up occasions (M_1 and M_2), after multiple imputation. Depression slowly increased from 13% (M_0) to 14% (M_1) to 16% (M_2). This pattern was evident for both men and women after splitting by sex. Compared with men, the prevalence of depression was twice as high for women at each assessment.

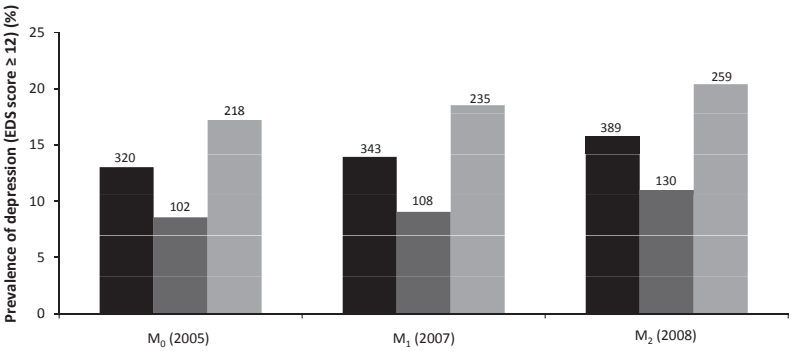

Figure 1 Prevalence of depression (EDS score ≥ 12) at baseline (M_0) and the two follow-up assessments (M_1, M_2) for the total sample (n = 2460) and examined separately for men (n = 1192) and women (n = 1268). Bars represent total group (black), men (dark grey) and women (light grey); the number shown above each bar represents the number with depression in that group. $p < 0.001$ for men vs women for all three assessments

Any depression, incidence and recurrence / persistence

After multiple imputation, 26% of the total sample (n = 630) reported an EDS score ≥ 12 at M_0, M_1 and / or M_2 ("any depression"). The presence of any depression was significantly more likely in women compared with men (32%, n = 412 vs 18%, n = 218; $p < 0.001$). In the subgroup of patients with an M_0 EDS score < 12 (no depression; n = 2140), incident depression at M_1 or M_2 was present in 310 individuals (14%), with a higher rate for women (18%, n = 193 vs 11%, n = 116; $p < 0.001$). An additional X^2 analysis showed that participants who were not depressed at baseline but did have a self-reported history of depression were significantly more likely to experience incident depression during follow-up than those without such a history (33%, n = 52 vs 13%, n = 257; $p < 0.001$). Of the 320 patients with an EDS score of ≥ 12 at M_0, 66% also met the criterion for depression at M_1 and / or M_2 and were therefore considered to be recurrently / persistently depressed. The rate of recurrence / persistence was similar for female and male patients (69%, n = 151 vs 60%, n = 61; $p = 0.09$), but was significantly higher in those with a self-reported history of depression (79%, n = 79 vs 60%, n = 133; $p = 0.001$). When considering specific patterns of remission and relapse, 34% (n = 109) of all initially depressed patients at M_0 recovered and remained below the EDS score cut-off at M_1 and M_2, 15% (n = 47) relapsed at M_2 and 38% (n = 123) were still depressed at both follow-ups.

Baseline risk factors predicting any depression

Table 2 shows the pooled effect estimates of a multivariate logistic regression analysis predicting the presence of any depression (EDS score ≥ 12 at M_0, M_1 and / or M_2) by several baseline characteristics. In the first step, female sex and low education were the only significant demographic predictors. In the second step, having co-morbid chronic medical conditions was positively associated with depression, while the presence of cardiovascular disease and microvascular complications also increased the odds of depression but did not reach statistical significance (p = 0.27 and p = 0.09, respectively). In the third step, having experienced stressful life events during the past year nearly doubled the odds for depression, while in the final step participants with a history of depression had an almost fivefold increased odds of reporting depression during at least one assessment occasion.

In order to test whether sex was an effect modifier, the same regression analysis (excluding sex in the first step) was conducted for women (n = 1268) and men (n = 1192) separately. After entry of all variables in the model, low educational level (fully adjusted OR = 1.93, 95% CI 1.24, 3.01 in women vs OR = 1.56, 95% CI 1.02, 2.39 in men), stressful life events (OR = 1.90, 95% CI 1.40, 2.59 vs OR = 1.83, 95% CI 1.25, 2.68) and a history of depression (OR = 4.53, 95% CI 2.95, 6.95 vs OR = 5.52, 95% CI 3.38, 9.01) were significantly associated with depression for both sexes. In addition, the non-cardiovascular chronic medical conditions played a significant role in the model for women (OR = 1.51, 95% CI 1.12, 2.03), while for men no other significant predictors were found (ESM Table 2).

Table 2 Multivariate logistic regression analysis predicting any depression (EDS score ≥ 12 at M_0, M_1 and / or M_2) by baseline demographic factors, medical co-morbidities, stressful life events and self-reported history of depression (n = 2460)

	Model 1	Model 2	Model 3	Model 4
1. Demographic factors				
Female sex	1.86 (1.51, 2.29)	1.87 (1.51, 2.31)	1.82 (1.47, 2.25)	1.74 (1.39, 2.17)
Age	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Low education level	1.66 (1.25, 2.22)	1.65 (1.24, 2.19)	1.66 (1.24, 2.23)	1.75 (1.28, 2.38)
Being single	1.28 (0.98, 1.68)	1.27 (0.97, 1.68)	1.19 (0.90, 1.57)	1.18 (0.88, 1.56)
2. Medical co-morbidities				
Cardiovascular disease [a]		1.13 (0.91, 1.40)	1.12 (0.90, 1.39)	1.10 (0.88, 1.38)
Microvascular disease [b]		1.25 (0.97, 1.60)	1.24 (0.96, 1.60)	1.25 (0.96, 1.62)
Other chronic conditions [c]		1.50 (1.19, 1.87)	1.44 (1.15, 1.82)	1.36 (1.07, 1.73)
3. Stressful life events			1.90 (1.51, 2.40)	1.86 (1.46, 2.38)
4. History of depression				4.90 (3.53, 6.82)

Values are OR (95% CI)

[a] Myocardial infarction, bypass / angioplasty, stroke and / or arterial disease; [b] Retinopathy and / or micro- / macroalbuminuria; [c] Kidney disease, asthma / COPD, cancer, arthrosis and / or rheumatoid arthritis

Model 1: demographic factors; Model 2: model 1 + medical co-morbidities; Model 3: model 2 + stressful life events; Model 4: model 3 + history of depression

Additional analyses in the total sample examining depression risk for each medical co-morbidity separately revealed that after correction for demographics, arthrosis (OR = 1.57, 95% CI 1.26, 1.96) and rheumatoid arthritis (OR = 1.57, 95% CI 1.04, 2.39) were the only significant predictors (ESM Table 3).

Table 3 Multivariate logistic regression analysis predicting incident depression by baseline demographic factors, medical co-morbidities, stressful life events and self-reported history of depression, examined separately for men and women

	Model 1	Model 2	Model 3	Model 4
MEN (range n = 1081 – 1096)				
1. Demographic factors				
Age	1.01 (0.99, 1.03)	1.00 (0.98, 1.02)	1.00 (0.98, 1.03)	1.00 (0.98, 1.03)
Low education level	1.56 (0.96, 2.54)	1.51 (0.92, 2.48)	1.54 (0.93, 2.54)	1.56 (0.94, 2.60)
Being single	1.11 (0.58, 2.14)	1.11 (0.57, 2.13)	1.08 (0.56, 2.07)	0.99 (0.50, 1.95)
2. Medical co-morbidities				
Cardiovascular disease [a]		1.42 (0.87, 2.31)	1.42 (0.87, 2.31)	1.43 (0.87, 2.34)
Microvascular disease [b]		1.30 (0.79, 2.12)	1.30 (0.80, 2.14)	1.35 (0.82, 2.20)
Other chronic conditions [c]		1.28 (0.76, 2.15)	1.24 (0.74, 2.09)	1.20 (0.71, 2.04)
3. Stressful life events			1.40 (0.82, 2.39)	1.38 (0.81, 2.36)
4. History of depression				3.99 (1.98, 8.04)
WOMEN (range n = 1042 – 1064)				
1. Demographic factors				
Age	1.01 (0.99, 1.03)	1.01 (0.98, 1.03)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
Low education level	1.59 (0.95, 2.68)	1.59 (0.94, 2.68)	1.59 (0.94, 2.68)	1.69 (0.99, 2.88)
Being single	1.14 (0.75, 1.74)	1.12 (0.73, 1.72)	1.10 (0.71, 1.69)	1.11 (0.72, 1.70)
2. Medical co-morbidities				
Cardiovascular disease [a]		0.92 (0.61, 1.39)	0.92 (0.61, 1.38)	0.91 (0.60, 1.37)
Microvascular disease [b]		1.35 (0.83, 2.19)	1.34 (0.82, 2.19)	1.34 (0.81, 2.20)
Other chronic conditions [c]		1.35 (0.94, 1.93)	1.34 (0.93, 1.92)	1.27 (0.88, 1.84)
3. Stressful life events			1.24 (0.83, 1.86)	1.24 (0.82, 1.88)
4. History of depression				2.93 (1.64, 5.26)

Values are OR (95% CI)

[a] Myocardial infarction, bypass / angioplasty, stroke and / or arterial disease; [b] Retinopathy and / or micro- / macroalbuminuria; [c] Kidney disease, asthma / COPD, cancer, arthrosis and / or rheumatoid arthritis

Model 1: demographic factors; Model 2: model 1 + medical co-morbidities; Model 3: model 2 + stressful life events; Model 4: model 3 + history of depression

Baseline risk factors predicting incident and recurrent / persistent depression

A multivariate logistic regression analysis identical to the model described in Table 2 was conducted to predict incident depression (range of n over all 20 datasets, 2131 – 2156; ESM Table 4). In the last step, female sex (OR = 1.63, 95% CI 1.20, 2.21), low education (OR = 1.62, 95% CI 1.12, 2.36) and self-reported history of depression (OR = 3.27, 95% CI 2.05, 5.22) were all associated with incident depression, while microvascular disease, other chronic conditions and stressful life events increased the odds of depression by 25 – 33%, but did not reach statistical significance (p = 0.14, 0.18 and 0.14, respectively). Repeating the analysis (excluding entry of history of depression in the last step) in the group of patients reporting no history of depression and no M_0 depression (range of n, 1967 – 1992) yielded similar results (data not shown). After splitting by sex, self-reported history of depression was associated with a three- to four-fold increased odds of incident depression in both men and women (Table 3). Low education increased the odds, but was not significant (p = 0.09 and 0.06 in men and women, respectively).

Self-reported history of depression was the only significant predictor of recurrent / persistent depression (range of n, 304 – 329; OR = 2.54, 95% CI 1.23, 5.23). Similar results were found when examining results separately for men and women (women: OR = 2.69, 95% CI 1.06, 6.82; men: OR = 2.76, 95% CI 0.64, 11.88), but failed to reach statistical significance in men (p = 0.18; ESM Tables 5 and 6).

DISCUSSION

Depression (defined as a high level of depressive symptoms) appeared to be a common co-morbid health problem in primary care patients with type 2 diabetes, with one in four patients suffering from depression at least once during a 2.5 year period. New occurrences of depressive symptoms were frequently observed among those with no symptoms at baseline (14%). Once present, depressive symptoms tended to be recurrent / persistent over time in two-thirds of all cases.

The cross-sectional prevalence estimates of our study (13 – 16%) were slightly lower than the figure reported in a previous meta-analysis (18%) [1], but did slowly increase over time. This may reflect cohort aging and the ensuing development of additional co-morbidities and accompanying functional limitations. In line with the results of a previous study [17], expanding the time frame from cross-sectional analyses (point prevalence) to a total estimate across successive assessments (“any depression”) revealed a higher prevalence rate in a 2.5 year period, suggesting that prevalence estimates taken at one point in time underestimate the true scope of the problem.

The onset of depression in diabetes has been examined several times before, but most of these studies (including ours) have defined incident depression as the presence of depression at a distinct follow-up time point in those without baseline depression, rather than also taking incident cases during the whole follow-up period into account [12]. This definition does not allow for a correction for variable follow-up length across studies by calculating annual incidence rates, as studies with longer follow-up periods are likely to miss more incident cases and as a consequence would substantially underestimate true yearly incidence rates.

Our finding that depressive symptoms have a high rate of recurrence and chronicity in diabetes patients is in line with previous research showing that approximately half of all patients experiencing depressive symptoms at baseline also reported depression 1 to 5 years later [15, 16]. Furthermore, over 40% of diabetes patients with elevated depressive symptoms appear to develop major depression within 2 years [30]. However, to our knowledge, only two previous studies have examined the course of depressive symptoms over more than two assessments. In one study, 20% of all participants obtained scores ≥ 16 on the Center for Epidemiological Studies – Depression questionnaire at least twice [17]. A second study among 245 diabetes patients (65% with type 2 diabetes) measured depressive symptoms at the beginning and end of a 1 week diabetes education programme and at 6 month follow-up. While the authors concluded that only 13% of their total sample was persistently depressed (i.e. exceeded the criterion for depression symptoms at all three time points), recurrent depression (depressed at least once during follow-up) was found in two-thirds of the patients depressed before the start of the programme [14]. Even though this study included a psycho-educational intervention programme incorporating coping skills training, the results were roughly comparable with those from our study.

With regard to prognostic factors, female sex, a low educational level, non-cardiovascular chronic medical conditions, stressful life events and a self-reported history of depression were associated with the presence of any depression. Previous cross-sectional studies have shown an association between prevalent depression and the presence of co-morbid chronic diseases in diabetes patients [8, 9] and have suggested that a large number of general life stressors, in addition to more diabetes-specific distress, can contribute to depressive symptoms [8]. However, the logistic regression analysis predicting incident depression in the subgroup with no baseline depression limited the results to female sex, low education and history of depression, while recurrent / persistent depression in those patients with baseline depression left only depression history as a significant predictor in the model.

Two previous studies aiming to identify baseline predictors of “persistent” depressive symptoms reported conflicting results. In one study, low level of education, the presence

of multiple complications and a treatment without insulin significantly predicted persistent depression [14], while the other described an important role for more psychologically orientated factors, including baseline severity of depression, emotional problems due to diabetes and the extent to which depression disrupted the patient's quality of life [15]. Even though vascular complications are often cited as an important determinant of disease burden in diabetes, macro- and microvascular conditions were not associated with depression in any of the present analyses. One possible explanation may lie in the fact that our study focused on baseline and pre-baseline factors as potential predictors of depression. However, the onset or progression of medical conditions and cardiovascular procedures during follow-up are likely candidates to trigger new cases of depression or hamper recovery from already existing emotional problems. This hypothesis is partly supported by a study in which coronary procedures during follow-up (but not incident macro- and microvascular complications) were associated with major depression at the 5 year follow-up [16]. Alternatively, rather than examining the mere presence of any macro- or microvascular conditions, it could be that having multiple (vascular) co-morbidities (and probably accompanying functional limitations) is what particularly increases the odds of depression [8-10].

Self-reported history of depression was the only factor that consistently identified those individuals who had increased odds of experiencing any kind of depression during a period of 2.5 years, even after controlling for demographics, medical co-morbidities and stressful life events. These results are valuable for primary care, as they clearly show that a simple self-report question is highly predictive of future depression. Additional monitoring may be required in patients who report a history of depression.

Some limitations of the present study need to be mentioned. First, depression was assessed by means of a self-report questionnaire, while the gold standard for a diagnosis of depression is a standardised psychiatric diagnostic interview. Although 30 – 40% of patients with an increased level of depressive symptoms are clinically depressed [11, 31], self-reported depressive symptoms have been shown to predict the development of major depression [30] and adverse health outcomes [5] in diabetes patients. Second, a more accurate measurement of incident depression can be achieved in studies also covering the time period(s) between separate measurement occasions, for example by using handheld computers for the assessment of depression. In case researchers do not want or are not able to use these devices, other authors have argued that fluctuating course types are best studied in designs with at least three measurements [32]. Third, although we aimed to study the course of depression in this cohort, no information was available on either pharmacological or psychotherapeutic treatment of depression during the study. However, this potential source of bias is most likely restricted to a minority, as depression often goes unrecognised and untreated in

patients with diabetes [33]. Fourth, while interpreting our results, it has to be borne in mind that 27% of all demographic, clinical and psychological data needed for the analyses were missing and imputed using multivariate imputation techniques. However, several authors have argued that multiple imputation is preferred over other missing data approaches, including complete case analysis, in the case of complex incomplete data problems [27, 29]. Finally, the vast majority of individuals in our sample (97%) were white, which may not be representative of other diabetes populations. The strengths of the study include the large sample of primary care patients with type 2 diabetes, the prospective observational design with multiple depression assessments and the policy to verify self-reported medical diagnoses by inspection of medical records.

In sum, our results show that as many as one in four primary care patients with type 2 diabetes are confronted with depression during a 2.5 year period. Once present, depression often becomes a chronic / recurrent condition in this group. Monitoring of emotional well-being / depression seems warranted and does not necessarily have to be very elaborate, but should be embedded in collaborative care approaches [34]. Moreover, given that a considerable number of patients do not benefit from the current pharmacological and psychotherapeutic treatment modalities, future research efforts are required to further optimise depression outcomes for depressed patients with type 2 diabetes [34]. Web-based treatment of depression in diabetes appears to be effective and can be employed to help to battle this common problem in patients with diabetes with low costs [35].

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ESM Table 1 Overview of all variables included in the imputation process

Variables used in subsequent regression analyses [a]
All ten individual baseline (M_0) EDS items (5 response categories)
All ten individual follow-up 1 (M_1) EDS items (5 response categories)
All ten individual follow-up 2 (M_2) EDS items (5 response categories)
Sex (men vs women)
Age (continuous)
Educational level (middle / high vs low educational level)
Marital status (having a partner vs being single)
Myocardial infarction (no vs yes)
Bypass / angioplasty (no vs yes)
Stroke (no vs yes)
Arterial disease (no vs yes)
Results of fundus screening (normal vs retinopathy)
Albuminuria (continuous)
History of kidney disease (no vs yes)
Asthma / COPD (no vs yes)
Cancer (no vs yes)
Arthrosis (no vs yes)
Rheumatoid arthritis (no vs yes)
Stressful life event(s) in past year (no vs yes)
History of depression (no vs yes)
Auxiliary variables [b]
Ethnicity (white vs non-white)
Hyperglycaemia treatment (6 response categories)
Diabetes duration (< 3 years vs ≥ 3 years)
HbA_{1c} (continuous)
BMI (continuous)

[a] For the subsequent regression analyses, several imputed variables are redefined into summary or composite variables (see main manuscript text); [b] Variables not used in subsequent analyses, but used to improve imputations

ESM Table 2 Multivariate logistic regression analysis predicting any depression (EDS score ≥ 12 at M_0, M_1 and/or M_2) by baseline demographic factors, medical co-morbidities, stressful life events and self-reported history of depression, examined separately for men and women

	Model 1	Model 2	Model 3	Model 4
MEN (n = 1192)				
1. Demographic factors				
Age	1.00 (0.99, 1.02)	1.00 (0.98, 1.01)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
Low education level	1.53 (1.03, 2.26)	1.49 (1.01, 2.20)	1.52 (1.02, 2.27)	1.56 (1.02, 2.39)
Being single	1.52 (0.98, 2.34)	1.51 (0.98, 2.32)	1.43 (0.92, 2.22)	1.36 (0.85, 2.16)
2. Medical co-morbidities				
Cardiovascular disease [a]		1.33 (0.94, 1.88)	1.33 (0.93, 1.89)	1.30 (0.90, 1.86)
Microvascular disease [b]		1.18 (0.83, 1.69)	1.19 (0.83, 1.69)	1.21 (0.85, 1.72)
Other chronic conditions [c]		1.30 (0.91, 1.86)	1.23 (0.85, 1.77)	1.17 (0.80, 1.72)
3. Stressful life events			1.89 (1.30, 2.75)	1.83 (1.25, 2.68)
4. History of depression				5.52 (3.38, 9.01)
WOMEN (n = 1268)				
1. Demographic factors				
Age	1.00 (0.98, 1.01)	0.99 (0.98, 1.01)	1.00 (0.98, 1.01)	1.00 (0.98, 1.02)
Low education level	1.80 (1.20, 2.71)	1.81 (1.20, 2.74)	1.81 (1.19, 2.73)	1.93 (1.24, 3.01)
Being single	1.20 (0.85, 1.70)	1.19 (0.83, 1.69)	1.09 (0.76, 1.57)	1.08 (0.75, 1.56)
2. Medical co-morbidities				
Cardiovascular disease [a]		1.01 (0.76, 1.34)	0.99 (0.74, 1.32)	0.98 (0.73, 1.32)
Microvascular disease [b]		1.29 (0.93, 1.80)	1.28 (0.90, 1.81)	1.29 (0.90, 1.84)
Other chronic conditions [c]		1.64 (1.24, 2.18)	1.61 (1.21, 2.14)	1.51 (1.12, 2.03)
3. Stressful life events			1.93 (1.44, 2.59)	1.90 (1.40, 2.59)
4. History of depression				4.53 (2.95, 6.95)

Values are OR (95% CI)

[a] Myocardial infarction, bypass / angioplasty, stroke and / or arterial disease; [b] Retinopathy and / or micro- / macroalbuminuria; [c] Kidney disease, asthma / COPD, cancer, arthrosis and / or rheumatoid arthritis

Model 1: demographic factors; Model 2: model 1 + medical co-morbidities; Model 3: model 2 + stressful life events; Model 4: model 3 + history of depression

ESM Table 3 Association between specific medical co-morbidities and any depression (adjusted for demographics [a])

Medical co-morbidity (n = 2460)	OR (95% CI)
Myocardial infarction	1.30 (0.91, 1.84)
Bypass / angioplasty	1.35 (0.99, 1.85)
Stroke	1.29 (0.86, 1.92)
Arterial disease	1.12 (0.88, 1.44)
Retinopathy	1.26 (0.67, 2.37)
Micro- / macroalbuminuria	1.24 (0.97, 1.59)
Kidney disease	0.89 (0.48, 1.65)
Asthma / COPD	1.24 (0.93, 1.67)
Cancer	0.96 (0.67, 1.38)
Arthrosis	1.57 (1.26, 1.96)
Rheumatoid arthritis	1.57 (1.04, 2.39)

[a] Sex, age, educational level and marital status

ESM Table 4 Multivariate logistic regression analysis predicting incident depression by baseline demographic factors, medical co-morbidities, stressful life events and self-reported history of depression (range n = 2131 – 2156)

	Model 1	Model 2	Model 3	Model 4
1. Demographic factors				
Female sex	1.65 (1.23, 2.21)	1.69 (1.25, 2.29)	1.68 (1.24, 2.27)	1.63 (1.20, 2.21)
Age	1.01 (0.99, 1.02)	1.00 (0.99, 1.02)	1.01 (0.99, 1.02)	1.01 (0.99, 1.03)
Low education level	1.57 (1.10, 2.26)	1.55 (1.08, 2.23)	1.56 (1.08, 2.26)	1.62 (1.12, 2.36)
Being single	1.13 (0.80, 1.59)	1.13 (0.80, 1.59)	1.10 (0.78, 1.55)	1.09 (0.77, 1.54)
2. Medical co-morbidities				
Cardiovascular disease [a]		1.11 (0.80, 1.52)	1.10 (0.80, 1.51)	1.10 (0.80, 1.51)
Microvascular disease [b]		1.32 (0.91, 1.93)	1.32 (0.90, 1.92)	1.33 (0.91, 1.95)
Other chronic conditions [c]		1.32 (0.96, 1.81)	1.30 (0.95, 1.78)	1.25 (0.91, 1.72)
3. Stressful life events			1.30 (0.93, 1.82)	1.30 (0.92, 1.83)
4. History of depression				3.27 (2.05, 5.22)

Values are OR (95% CI)

[a] Myocardial infarction, bypass / angioplasty, stroke and / or arterial disease; [b] Retinopathy and / or micro- / macroalbuminuria; [c] Kidney disease, asthma / COPD, cancer, arthrosis and / or rheumatoid arthritis

Model 1: demographic factors; Model 2: model 1 + medical co-morbidities; Model 3: model 2 + stressful life events; Model 4: model 3 + history of depression

ESM Table 5 Multivariate logistic regression analysis predicting recurrent / persistent depression by baseline demographic factors, medical co-morbidities, stressful life events and self-reported history of depression (range n = 304 – 329)

	Model 1	Model 2	Model 3	Model 4
1. Demographic factors				
Female sex	1.43 (0.80, 2.55)	1.40 (0.77, 2.53)	1.39 (0.77, 2.51)	1.36 (0.74, 2.50)
Age	1.00 (0.97, 1.03)	0.99 (0.96, 1.02)	1.00 (0.96, 1.03)	1.00 (0.97, 1.03)
Low education level	1.28 (0.64, 2.56)	1.28 (0.63, 2.57)	1.25 (0.61, 2.55)	1.30 (0.63, 2.66)
Being single	1.19 (0.66, 2.16)	1.17 (0.64, 2.13)	1.13 (0.61, 2.09)	1.15 (0.61, 2.16)
2. Medical co-morbidities				
Cardiovascular disease [a]		1.15 (0.62, 2.13)	1.14 (0.62, 2.11)	1.10 (0.59, 2.04)
Microvascular disease [b]		1.03 (0.49, 2.15)	1.03 (0.49, 2.16)	1.01 (0.48, 2.12)
Other chronic conditions [c]		1.37 (0.71, 2.64)	1.36 (0.70, 2.62)	1.33 (0.68, 2.58)
3. Stressful life events			1.26 (0.68, 2.35)	1.26 (0.66, 2.41)
4. History of depression				2.54 (1.23, 5.23)

Values are OR (95% CI)

[a] Myocardial infarction, bypass / angioplasty, stroke and / or arterial disease; [b] Retinopathy and / or micro- / macroalbuminuria; [c] Kidney disease, asthma / COPD, cancer, arthrosis and / or rheumatoid arthritis

Model 1: demographic factors; Model 2: model 1 + medical co-morbidities; Model 3: model 2 + stressful life events; Model 4: model 3 + history of depression

ESM Table 6 Multivariate logistic regression analysis predicting recurrent / persistent depression by baseline demographic factors, medical co-morbidities, stressful life events and self-reported history of depression, examined separately for men and women

	Model 1	Model 2	Model 3	Model 4
MEN (range n = 96 – 111)				
1. Demographic factors				
Age	1.00 (0.95, 1.06)	1.00 (0.95, 1.05)	1.01 (0.95, 1.06)	1.01 (0.96, 1.07)
Low education level	1.96 (0.68, 5.65)	2.00 (0.66, 6.00)	1.79 (0.55, 5.82)	2.04 (0.60, 6.92)
Being single	1.35 (0.44, 4.12)	1.35 (0.42, 4.35)	1.32 (0.40, 4.33)	1.54 (0.43, 5.51)
2. Medical co-morbidities				
Cardiovascular disease [a]		1.71 (0.63, 4.61)	1.73 (0.62, 4.85)	1.55 (0.52, 4.62)
Microvascular disease [b]		1.01 (0.33, 3.09)	0.94 (0.30, 2.92)	0.85 (0.26, 2.79)
Other chronic conditions [c]		0.77 (0.28, 2.12)	0.71 (0.25, 2.05)	0.65 (0.23, 1.90)
3. Stressful life events			1.71 (0.54, 5.35)	1.68 (0.51, 5.51)
4. History of depression				2.76 (0.64, 11.88)
WOMEN (range n = 204 – 226)				
1. Demographic factors				
Age	0.99 (0.96, 1.03)	0.99 (0.95, 1.03)	0.99 (0.95, 1.03)	1.00 (0.95, 1.04)
Low education level	0.88 (0.30, 2.59)	0.90 (0.31, 2.62)	0.91 (0.31, 2.62)	0.90 (0.31, 2.61)
Being single	1.20 (0.55, 2.58)	1.14 (0.51, 2.54)	1.11 (0.49, 2.56)	1.08 (0.45, 2.57)
2. Medical co-morbidities				
Cardiovascular disease [a]		0.96 (0.44, 2.06)	0.95 (0.44, 2.04)	0.94 (0.44, 2.02)
Microvascular disease [b]		0.99 (0.36, 2.73)	1.00 (0.36, 2.75)	1.01 (0.37, 2.79)
Other chronic conditions [c]		1.76 (0.76, 4.06)	1.77 (0.77, 4.10)	1.79 (0.77, 4.19)
3. Stressful life events			1.13 (0.52, 2.45)	1.14 (0.51, 2.55)
4. History of depression				2.69 (1.06, 6.82)

Values are OR (95% CI)

[a] Myocardial infarction, bypass / angioplasty, stroke and / or arterial disease; [b] Retinopathy and / or micro- / macroalbuminuria; [c] Kidney disease, asthma / COPD, cancer, arthrosis and / or rheumatoid arthritis

Model 1: demographic factors; Model 2: model 1 + medical co-morbidities; Model 3: model 2 + stressful life events; Model 4: model 3 + history of depression

CHAPTER 5

The longitudinal association between depressive symptoms and initiation of insulin therapy in people with type 2 diabetes in primary care

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ABSTRACT

Objective: To examine whether depressive symptoms are associated with time to insulin initiation in people with type 2 diabetes in primary care.

Research design and methods: 1,389 insulin-naïve people with type 2 diabetes completed the Edinburgh Depression Scale (EDS) in 2005 and were followed until: 1) insulin therapy was started, 2) death, 3) an oral antihyperglycemic drug (OAD) prescription gap > 1 year, 4) last OAD prescription in 2010 or 5) the end of the study period (December 31, 2010). Cox regression analyses were used to determine whether there was a difference in time to insulin initiation between people with a low versus a high depression score at baseline, adjusting for potential demographic and clinical confounders, including HbA_{1c} levels.

Results: The prevalence of depression (EDS ≥ 12) was 12% (n = 168). After a mean follow-up of 1,597 ± 537 days, 253 (18%) participants had started insulin therapy. The rate of insulin initiation did not differ between depressed and non-depressed participants. People with depression were not more likely to start insulin therapy earlier or later than their non-depressed counterparts (HR = 0.98, 95% CI 0.66 – 1.45), also after adjustment for sex and age (HR = 0.95, 0.64 – 1.42). Adding individual candidate confounders to the age- and sex-adjusted base model did not change the HR by more than 4% and the association remained non-significant. Similar results were found for continuous depression scores.

Conclusions: In the present study, depression was not associated with time to insulin initiation. The hypothesis that depression is associated with delayed initiation of insulin therapy merits more thorough testing, preferably in studies where more information is available about patient-, provider- and health care system factors that may influence the decision to initiate insulin.

INTRODUCTION

Results from the United Kingdom Prospective Diabetes Study (UKPDS) have shown that improved glycemic control can prevent or delay diabetes complications, in particular those of microvascular origin, in people with type 2 diabetes [1, 2]. Since these landmark findings were published, optimal management of blood glucose levels has become one of the top priorities in diabetes care [3]. The management of hyperglycemia in type 2 diabetes often follows a stepwise strategy, starting with diet and exercise recommendations and followed by the prescription of oral agents [3-5]. Partly due to progressive loss of beta-cell function, glycemic control gradually deteriorates over time [6] and pharmacological monotherapy no longer suffices to attain target values for HbA_{1c} [7]. Eventually, even treatment with a combination of oral antidiabetics increased to their maximum doses will fail in most people and the majority will require insulin therapy [7]. Approximately 5 – 10% of people initially treated with oral antihyperglycemic therapy switch to insulin on a yearly basis [8].

Although national and international guidelines and treatment algorithms advocate rapid treatment modifications when target glycemic goals are not achieved or sustained [3-5], several studies have shown a delay in insulin initiation of up to five years after failure of oral glucose-lowering agents [9, 10]. While provider attitudes and aspects of the health system are likely to be implicated [11, 12], a reluctance to start insulin therapy has been shown to occur in at least one-quarter of insulin-naïve people with type 2 diabetes [13]. This phenomenon is often termed “psychological insulin resistance” and may encompass a range of negative attitudes towards insulin, including weight concerns, needle phobia and the belief that initiation of insulin therapy signifies failure to self-manage diabetes [14].

A factor that might be of particular relevance in this context is depression. Comorbid depression is present in approximately 20% of people with type 2 diabetes [15] and is associated with worse quality of life [16], suboptimal glycemic control [17], an increased risk for the development of vascular complications [18, 19] and a higher mortality risk [20]. Several recent studies have suggested that in insulin-naïve people with type 2 diabetes, higher levels of depression are associated with a more negative appraisal of insulin therapy [21-23]. Depression is often characterized by fatigue or loss of energy, low self-esteem and a diminished ability to think, concentrate or make decisions [24]. These motivational aspects may underlie a general reluctance to start insulin, which in turn could translate into a later initiation of insulin therapy [22]. However, preliminary results from a small Dutch primary care study (n = 152) suggest that people who switch over to insulin therapy due to secondary failure more frequently suffer from depression [25]. Hence, the association between depression and difficulties with diabetes self-care activities [26], and its ensuing impact on glycemic control may be implicated in this process.

To our knowledge, the role of depressive symptoms in the timing of insulin therapy has not been examined in a large-scale study. Therefore, the primary aim of the present study was to establish whether depressive symptoms are associated with time to insulin initiation in a sample of people with type 2 diabetes in primary care. In addition, we sought to identify demographic and clinical confounders of this relation.

METHODS

Procedure

The DiaDDZoB (Diabetes, Depression, Type D personality Zuidoost-Brabant) Study was designed as a prospective cohort study among people with type 2 diabetes in primary care in South-East Brabant, The Netherlands [27]. A total of 2,460 individuals (82% of those considered for study inclusion) participated in the 2005 baseline assessment, consisting of a nurse-led interview and the completion of a self-report questionnaire. To increase the accuracy of prescription data, record linkage was sought with the PHARMO Database Network [28], a population-based patient-centric data tracking system which started in 1986 that includes high quality and complete information of patient demographics, drug dispensings, hospitalizations, clinical laboratory, pathology and general practitioner information of 3.2 million community-dwelling inhabitants of 65 municipal areas in The Netherlands. As both the DiaDDZoB and PHARMO databases only contain de-identified patient information, record linkage was realized based on the combination of date of birth, sex, first initial, first letter of family name, first letter of marital name (women only) and zip code. This procedure resulted in successful record linkage for 81% (n=1,982) of the original DiaDDZoB cohort.

Participants

The present sample (n = 1,389) includes all DiaDDZoB participants for whom linkage with the PHARMO Database Network could be realized, who completed at least nine items of the EDS during the 2005 baseline assessment, and who had not been prescribed insulin in the six-month period leading up to the baseline assessment. These individuals did not differ significantly from the rest of the DiaDDZoB cohort (n = 1,071) with respect to sex, age, educational level, the presence of chronic co-morbidities (other than cardiovascular disease) or body mass index. However, they were somewhat less likely to have a non-Western ethnicity (2% vs. 5%, $p = 0.001$), to be single (23% vs. 29%, $p = 0.01$), or to have a diabetes duration of more than three years (59% vs. 63%, $p = 0.02$). In addition, they had a slightly lower mean HbA_{1c} level (6.7% vs. 6.8%, $p = 0.003$) and were less likely to have a history of cardiovascular disease (33% vs. 39%, $p = 0.005$), in particular arterial disease (22% vs. 27%, $p = 0.002$), or to have microvascular complications (32% vs. 38%, $p = 0.02$), which was mainly driven by differences in the presence of micro- and / or macroalbuminuria (25% vs. 29%, $p =$

0.03). All 1,389 participants were followed from the baseline assessment in 2005 to the date on which insulin was added to the treatment regimen (end point), date of death, date of last OAD prescription in 2010 or, for those without any prescription of oral antihyperglycemic drugs (OADs) during follow-up, the end of the study period (December 31, 2010), whichever occurred first. To correct for the possibility that peoples' OAD prescriptions might have been (temporarily) transferred to a pharmacy not included in the PHARMO registry, individuals who were initially prescribed OADs but who showed a period of more than twelve months without any OAD prescription or initiation of insulin were censored on the day of the last OAD prescription before the prescription gap. The DiaDDZoB study protocol was approved by the medical research ethics committee of a local hospital, the Máxima Medical Centre in Veldhoven (NL27239.015.09). Written informed consent was obtained from all participants. The PHARMO compliance committee gave permission to establish the link between the DiaDDZoB cohort and the PHARMO Database Network.

Assessment of depression

Symptoms of depression during the last seven days were assessed using a validated Dutch version of the Edinburgh Depression Scale (EDS) [29]. Originally designed to assess postpartum depression [30], this questionnaire has now been validated in several other (male and female) strata, including people with type 2 diabetes from a primary care setting [31]. Total EDS scores are determined by summing the scores of all ten individual items (four-point scale for each item, total score range 0 – 30), with higher scores indicating higher levels of depressive symptoms. A total score of 12 or more is commonly used to identify people with depression [32]. For participants who only completed 9 items, we replaced the missing value with the mean of the remaining items before calculating the total EDS score.

Antihyperglycemic medication

All dispensed drugs registered in the PHARMO outpatient pharmacy database are coded according to the Anatomical Therapeutic Chemical Classification (www.whocc.no). Baseline hyperglycemia treatment was determined from dispensing records in the six-month period leading up to the baseline assessment and – based on the sample at hand – subdivided into the general categories lifestyle recommendations only, metformin monotherapy, monotherapy with an agent from a different OAD class, combination of metformin and sulfonylurea, other combination of agents from two OAD classes, and combination of metformin with agents from two or three different OAD classes. We did not differentiate between a switch in OAD classes or add-on therapy, but summarized the classes that were used in the six-month period. The first appearance of the A10A* code (insulin and analogues) in the dispensing records was taken to signify the initiation of insulin therapy, irrespective of (dis)continuation of OAD therapy.

Baseline demographics, medical history and clinical values

Information regarding sex, age, ethnicity ([white] western vs. non-[white] western), educational level (middle / high vs. low), marital status (having a partner vs. being single) and diabetes duration (less than three years vs. three years or more) was obtained during an interview with participants by the primary care practice nurse or was part of the questionnaire booklet that had to be filled in at home. The primary care practice nurse took a medical history, after which all self-reported medical diagnoses were verified through inspection of the medical record. The Diagnostic Centre Eindhoven, a primary care diagnostic institute, provided results from standard care laboratory tests (HbA_{1c} and albumin levels) and physical examinations (body mass index, eye screening). The results from yearly digital fundus photography were available to ascertain retinopathy (no / yes), while albumin level in a random urine sample was used as a proxy for nephropathy [33]. Micro- and macroalbuminuria were defined as urine albumin concentrations 20 – 200 and > 200 mg / l, respectively. Additional medical co-morbidities included cardiovascular disease (myocardial infarction, bypass / angioplasty, stroke and / or arterial disease) and other chronic conditions (kidney disease, asthma / chronic obstructive pulmonary disease [COPD], cancer, arthrosis and / or rheumatoid arthritis).

Statistical analyses

Baseline differences in demographic and clinical characteristics between people with and without high depressive symptoms were examined using independent samples t-tests for continuous data and X^2 tests for categorical data. For both groups, time to insulin initiation was visualized by means of Kaplan-Meier curves, using the log-rank test to compare the two survival curves. A univariable Cox regression analysis was used to provide an effect size for the association between depression and time to insulin initiation, reporting the hazard ratio with corresponding 95% confidence interval. The proportional hazards assumption was checked by visual inspection of the Kaplan-Meier survival curves, Cox regression with a time-dependent covariate and the Harrel and Lee test based on the Schoenfeld residuals. To evaluate whether the association between depression and time to insulin initiation was confounded by specific demographic or clinical factors, we first calculated the percentage change in effect size (HR) for depression before and after adjustment for sex, and repeated this procedure for age. In a next step, we constructed a sex- and age-adjusted base model of the association between depression and time to insulin initiation and examined the percentage change in HR when individual candidate confounders were introduced to this base model. Meaningful confounding was defined as a more than 5% change in effect size [34]. All analyses were performed using PASW Statistics version 19 (IBM SPSS Statistics, Somers, NY, USA). A p-value < 0.05 was considered to be statistically significant.

RESULTS

The total sample consisted of 1,389 participants (50% female), with a mean age of 67 ± 10 years (range 35 - 91), mostly self-identifying as (white) western. Overall, participants were in relatively good glycemic control (mean HbA_{1c} 6.7%, 49 mmol / mol), and the majority were being treated with lifestyle recommendations only (27%), metformin monotherapy (20%), monotherapy with an agent from a different OAD class (17%; sulfonylurea derivative, thiazolidinedione or repaglinide), or a combination of metformin and sulfonylurea derivative(s) (31%). Co-morbidities were common, with vascular disease and other major (chronic) medical conditions being present in one-third and one-half of all participants, respectively. Twelve percent (n = 168) had an EDS-score ≥ 12, indicating depression. Compared with those with an EDS-score < 12, participants with depression were more likely to be female, to have a non-western ethnicity, a low educational level and no partner. Furthermore, their medical history was more likely to include a diagnosis of a chronic medical condition (other than cardiovascular), in particular asthma / COPD and arthrosis (Table 1).

During a mean follow-up period of 1,597 ± 537 days (range 17 – 1,964), 253 (18%) participants added insulin to their treatment regimen. The rate of insulin initiation did not differ between people with and without high depressive symptoms (17%, n = 28 vs. 18%, n = 225; p = 0.58). When examining the Kaplan-Meier curves, we also did not observe a difference in time to insulin initiation for both groups (log-rank test $X^2[1] = 0.01$, p = 0.92), with a mean time to event of 1,783 (95% CI 1,758 – 1,807) and 1,749 (95% CI 1,671 – 1,828) for those without and with depression, respectively (Figure 1). As only 18% of the total sample switched to insulin therapy in the follow-up period, median survival times could not be reported. In univariable Cox regression analysis (n = 1,387; two cases censored before the earliest event in stratum), we found a non-significant HR of insulin initiation (0.98, 95% CI 0.66 – 1.45, p = 0.92).

Table 1 Baseline demographic and clinical characteristics (n = 1,389), stratified by EDS total score

	N missing	Total	EDS score < 12 (n = 1,221)	EDS score ≥ 12 (n = 168)	*P* value
Demographics					
Female sex	0	50% (699/1389)	48% (590/1221)	65% (109/168)	<0.001
Age, years	0	67 ± 10	67 ± 10	67 ± 10	0.81
Non-western ethnicity	15	2% (30/1374)	2% (20/1207)	6% (10/167)	<0.001
Low educational level	65	64% (843/1324)	62% (723/1167)	76% (120/157)	<0.001
Being single	15	23% (321/1374)	22% (271/1208)	30% (50/166)	0.03
Medical history					
Diabetes duration ≥ 3 years	13	59% (805/1376)	58% (703/1209)	61% (102/167)	0.47
Cardiovascular disease	24	33% (453/1365)	33% (391/1198)	37% (62/167)	0.25
Myocardial infarction	27	11% (153/1362)	11% (135/1195)	11% (18/167)	0.84
Bypass / angioplasty	22	13% (178/1367)	13% (152/1200)	16% (26/167)	0.30
Stroke	21	7% (94/1368)	7% (79/1200)	9% (15/168)	0.26
Arterial disease	29	22% (292/1360)	21% (252/1193)	24% (40/167)	0.40
Microvascular disease	363	32% (332/1026)	32% (286/906)	38% (46/120)	0.14
Retinopathy	368	5% (46/1021)	4% (38/903)	7% (8/118)	0.21
Micro- and / or macroalbuminuria	171	25% (301/1218)	24% (261/1072)	27% (40/146)	0.42
Other chronic conditions	17	48% (661/1372)	47% (565/1205)	58% (96/167)	0.01
Kidney disease	30	3% (46/1359)	3% (40/1192)	4% (6/167)	0.87
Asthma / COPD	23	12% (168/1366)	11% (137/1199)	19% (31/167)	0.009
Cancer	27	9% (123/1362)	9% (106/1195)	10% (17/167)	0.58
Arthrosis	17	32% (440/1372)	31% (372/1205)	41% (68/167)	0.01
Rheumatoid arthritis	21	7% (95/1368)	7% (78/1200)	10% (17/168)	0.08
Hyperglycemia treatment					
Number of OAD classes	0	1 ± 0.8	1 ± 0.8	1 ± 0.8	0.26
Lifestyle only		27% (368/1389)	27% (329/1221)	23% (39/168)	
Monotherapy metformin		20% (277/1389)	20% (243/1221)	20% (34/168)	
Monotherapy other OAD class		17% (238/1389)	17% (208/1221)	18% (30/168)	
Metformin + SU derivative(s)	0	31% (424/1389)	31% (373/1221)	30% (51/168)	0.70
Other combination of two OAD classes		4% (51/1389)	4% (43/1221)	5% (8/168)	
Metformin + two or three different OAD classes		2% (31/1389)	2% (25/1221)	4% (6/168)	
Clinical values					
HbA_{1c}, % (mmol / mol)	21	6.7 ± 0.8 (49 ± 9)	6.7 ± 0.8 (49 ± 9)	6.6 ± 0.8 (49 ± 8)	0.64
Body Mass Index (kg / m^2)	105	29 ± 5	29 ± 5	29 ± 5	0.88

Values are mean ± standard deviation, unless otherwise specified; COPD = chronic obstructive pulmonary disease; OAD = oral antihyperglycemic drug; SU derivative = sulfonylurea derivative

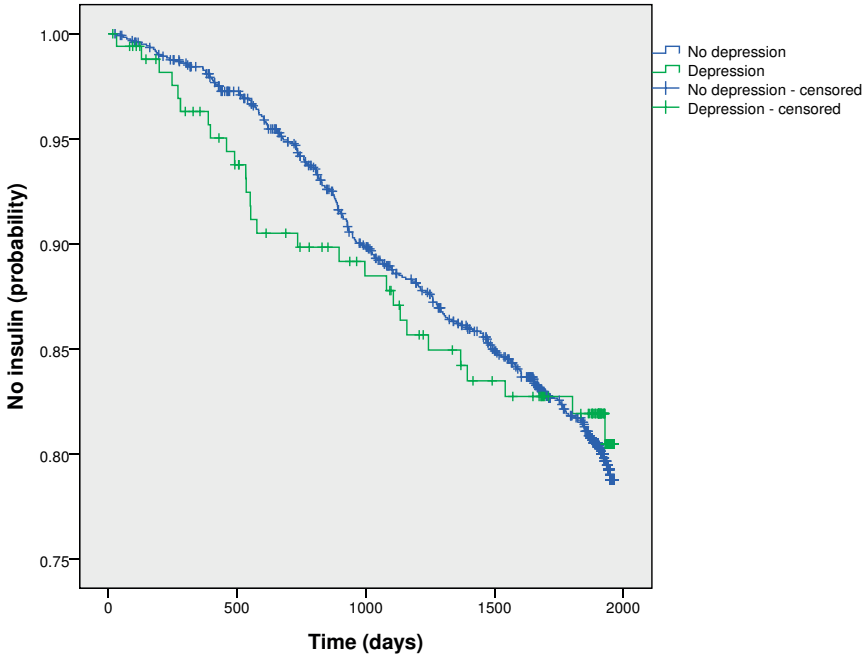

Figure 1 Kaplan-Meier curves EDS score < 12 vs. EDS score ≥ 12

To check the assumption of proportional hazards, we first examined the Kaplain-Meier curves for people with and without depression (Figure 1). Although the curve for the depression group followed a marginally lower course overall before converging with the non-depressed group at the end of follow-up, both lines appeared to converge briefly at 1000 days. Therefore, we conducted a Cox regression with a time-dependent covariate (splitting the follow-up period in the period before and after 1000 days). When added to the unadjusted regression model, the interaction term of this dichotomous time indicator and depression was not significant (p = 0.25), suggesting that the proportional hazard assumption was not violated. The correlation between the Schoenfeld residuals and ranked survival time was significant, but marginal in magnitude (r = -0.15, p = 0.01).

In the univariable Cox regression analysis, unadjusted confounding could have obscured the association between depression and time to insulin initiation. Therefore, in a next step, potential demographic and clinical confounders were taken into account. Examined separately, neither sex nor age changed the HR of the association between depression and time to insulin initiation by more than 2%. After simultaneous adjustment for sex and age, the association remained non-significant (HR 0.95, 95% CI 0.64 – 1.42, p = 0.81). None of the demographic and clinical factors that were introduced individually to the sex- and age

adjusted base model changed the strength of the association between depression and time to insulin initiation by more than 4% (Table 2). For none of the candidate confounders, adjustment produced a statistically significant association between depression and time to insulin initiation.

Similar results were found when examining the association between the continuous EDS total score and time to insulin initiation, with an unadjusted HR of 1.01 (95% CI 0.98 – 1.03, $p = 0.68$) and a sex- and age adjusted HR of 1.00 (95% CI 0.98 – 1.03, $p = 0.81$). None of the selected demographic and clinical candidate confounders changed the HR by more than 0.5%, and in all models the association between depressive symptoms and time to insulin initiation stayed non-significant.

DISCUSSION

In a sample of 1,389 people with type 2 diabetes, depression (defined as a high level of depressive symptoms) was not associated with an earlier or later start of insulin therapy over a mean follow-up period of 1,597 ± 537 days. After adjustment for potential demographic and clinical confounders, including baseline HbA_{1c} levels, people with depression still did not differ from their non-depressed counterparts with respect to the time before insulin was introduced to their diabetes management.

Although the present study did not find support for an association between depression and treatment intensification with insulin, we believe that further examination of this relation in other samples is warranted, for several reasons. With respect to the sample at hand, relatively few participants (18%) started insulin therapy during the study's five year follow-up. This was presumably linked to the fact that, at baseline, most participants had HbA_{1c} levels well within the optimal range and one-fourth were managing their blood glucose levels with lifestyle recommendations only. Moreover, in the present sample, few participants (12%) had elevated depression scores [15, 35]. Taking these factors into account, five years of follow-up might not have been long enough to detect any meaningful differences in time to insulin initiation between those with and without depression.

The management of hyperglycemia in type 2 diabetes can be complex for people with diabetes and health care providers alike, as the benefits of optimizing glycemic control through treatment intensification need to be balanced with the needs, preferences and drug tolerances of each individual person [3-5]. Ultimately, the decision to initiate or refrain from insulin therapy stems from a combination of individual patient and provider factors and characteristics of the health care system, and depression may feed into these processes in a myriad number of ways.

Table 2 Percent change in the strength of the association between depression and time to insulin initiation, after adjustment for potential confounders

Potential confounder	N [a]	*P* value before	*P* value after	HR (95% CI) before adjustment	HR (95% CI) after adjustment	Change in HR (%)
Female sex	1387	0.92	0.86	0.980 (0.662-1.452)	0.964 (0.649-1.431)	-1.6
Age	1387	0.92	0.90	0.980 (0.662-1.452)	0.976 (0.659-1.445)	-0.4
Base model (adjusted for sex and age)	1387	0.92	0.81	0.980 (0.662-1.452)	0.953 (0.642-1.415)	-2.8
Base + non-western ethnicity	1372	0.84	0.86	0.961 (0.647-1.427)	0.964 (0.647-1.435)	0.3
Base + low education level	1322	0.52	0.46	0.871 (0.570-1.331)	0.850 (0.555-1.302)	-2.4
Base + being single	1372	0.73	0.73	0.931 (0.623-1.392)	0.931 (0.622-1.391)	0.0
Base + diabetes duration ≥ 3 years	1374	0.88	0.74	0.970 (0.653-1.441)	0.935 (0.629-1.391)	-3.6
Base + any cardiovascular disease	1363	0.83	0.74	0.957 (0.644-1.422)	0.934 (0.629-1.388)	-2.4
Base + myocardial infarction	1360	0.86	0.80	0.966 (0.650-1.435)	0.950 (0.639-1.412)	-1.7
Base + bypass / angioplasty	1365	0.83	0.70	0.958 (0.645-1.423)	0.926 (0.623-1.376)	-3.3
Base + stroke	1366	0.84	0.84	0.961 (0.646-1.427)	0.959 (0.646-1.426)	-0.2
Base + arterial disease	1358	0.84	0.82	0.959 (0.645-1.425)	0.955 (0.643-1.418)	-0.4
Base + any microvascular complication	1024	0.31	0.26	0.779 (0.479-1.267)	0.754 (0.463-1.228)	-3.2
Base + retinopathy	1019	0.19	0.20	0.707 (0.423-1.183)	0.715 (0.427-1.195)	1.1
Base + micro- and / or macroalbuminuria	1216	0.68	0.59	0.913 (0.597-1.397)	0.890 (0.581-1.364)	-2.5
Base + any other chronic medical condition	1370	0.80	0.75	0.950 (0.640-1.411)	0.937 (0.630-1.392)	-1.4
Base + kidney disease	1357	0.81	0.80	0.952 (0.641-1.415)	0.951 (0.640-1.413)	-0.1
Base + asthma / COPD	1364	0.67	0.62	0.917 (0.614-1.371)	0.903 (0.603-1.351)	-1.5
Base + cancer	1360	0.80	0.80	0.951 (0.640-1.413)	0.949 (0.639-1.410)	-0.2
Base + arthrosis	1370	0.81	0.80	0.952 (0.641-1.414)	0.951 (0.640-1.413)	-0.1
Base + rheumatoid arthritis	1366	0.80	0.81	0.950 (0.639-1.411)	0.952 (0.641-1.414)	0.2
Base + number of OAD classes	1387	0.81	0.77	0.953 (0.642-1.415)	0.942 (0.634-1.401)	-1.2
Base + HbA_{1c}	1366	0.83	0.80	0.957 (0.644-1.422)	0.949 (0.640-1.409)	-0.8
Base + Body Mass Index	1282	0.66	0.65	0.910 (0.599-1.381)	0.909 (0.599-1.380)	-0.1

[a] N varies due to exclusion of cases censored before the earliest event in a stratum (n = 2) and missing values for the candidate confounder at hand

If depression systematically leads to an earlier start of insulin therapy in some people but to later insulin commencement in others, these opposite effects may cancel each other out when averaged at the group level. Therefore, it may be hard to characterize the association between depression and insulin initiation, without knowing more about the driving factors behind these treatment decisions. Furthermore, depression itself is a heterogeneous condition, both in terms of severity and subtypes [24]. It is possible that there is a relation between depression and insulin initiation, but only when certain depression characteristics are present, e.g. fatigue or loss of energy, low self-esteem and / or diminished ability to think, concentrate or make decisions.

From the patient perspective, we know that at least one in four insulin-naïve people with type 2 diabetes is reluctant to start insulin therapy [13] and that this process of psychological insulin resistance is associated with the presence of depressive symptoms [21-23]. Whether there only is a relation with a later start of insulin therapy in those people for whom the motivational aspects of depression cause a general reluctance to start insulin, is yet to be determined in a prospective study. Importantly, these studies should also clarify the context of insulin timing, as a later start can either signify an inappropriate delay of insulin therapy or a longer period of optimal glucose control. Although negative appraisals of insulin therapy do not by definition lead to a delay of insulin therapy, it would be interesting to see if an inappropriate delay of insulin therapy is among the factors that explain why depression is a risk factor for adverse outcomes such as the development of vascular complications and mortality in people with diabetes [19, 20].

Given its close relation with suboptimal glycemic control [17], depression may also be related to an earlier start of insulin therapy. Although time to insulin initiation was not taken into account, a small primary care study (n = 152) suggested that people with type 2 diabetes switching to insulin therapy were 14-times more likely to have co-morbid depression than those individuals who did not start insulin [25]. However, the wide 95% confidence interval around this estimate (2.7 – 74.9) hints to a relatively small number of individuals with depression in this sample and consequently, this study does not allow any firm inferences about the association between insulin use and depression. We do know, however, that depression is associated with suboptimal medication taking across a range of chronic diseases [36] and that problems with self-management appear to figure prominently in providers' considerations when choosing antihyperglycemic medications [11, 37, 38]. Perceived problems with self-management on the part of the person with diabetes have been identified as a significant barrier to insulin initiation for health care providers [37, 38], but providers also appear to be more willing to delay insulin initiation if they perceive people with diabetes as more adherent to their medication or appointment regimens [11].

Consultation practices may also play a role in the relation between depression and insulin initiation. Co-morbid depression in diabetes has been associated with increased health care use, including a higher number of ambulatory visits [39]. As a result of this higher contact frequency, physicians may have more opportunities to introduce insulin to the hyperglycemia treatment of depressed people with diabetes. On the other hand, competing demands during care contacts may decrease the likelihood of treatment intensification [40]. In people with diabetes and co-morbid depression, priority might be given to more urgent mood problems.

Recent guidelines and treatment algorithms emphasize the need for early addition of insulin therapy in people who do not meet target goals, in order to reduce the time people are exposed to hyperglycemia [3]. However, previous work suggests that a substantial number of health providers delay insulin therapy until absolutely necessary [11] and there appears to be a tendency to postpone insulin treatment if it is possible to add other oral agents [12]. Of course, there are legitimate clinical reasons to refrain from initiating insulin therapy, including decreased life expectancy and incapacitating comorbidities [3, 4]. Knowing that depression is also more common in people with type 2 diabetes who have co-morbid chronic conditions [41], studies examining the association between depression and insulin initiation should take the potential confounding role of these co-morbid conditions into account. Although we did examine medical history in terms of cardiovascular disease, microvascular complications and the presence of several non-cardiovascular chronic conditions, we were unable to verify the burden of these conditions at baseline.

Several additional study limitations need to be mentioned. First, we used a self-report questionnaire assessing depressive symptoms, while the gold standard for a clinical diagnosis of depression is a structured psychiatric diagnostic interview. In addition, we only focused on baseline depression, while participants' depression status may have changed over the follow-up period. In a similar vein, by only examining the role of baseline HbA_{1c} levels, we might have missed clinically relevant changes in average blood glucose levels during follow-up that could have shed more light on the association between depression and insulin initiation. Second, the exact reason(s) for insulin initiation were unknown. In some instances insulin is prescribed on a temporary basis, for example in case of corticosteroid use or acute illness such as infections [4]. By focusing solely on community pharmacy dispensings and not including prescriptions from the (inpatient) hospital pharmacy during hospital admissions, we have tried to cancel out some of this confounding. For people who do initiate insulin therapy during a hospital stay as part of their regular hyperglycemia treatment, prescriptions will be transferred to the community pharmacy once they are discharged, thereby introducing only a minor distortion in insulin therapy start date. Third, we cannot rule out that some

participants have used insulin in the past. Although we have excluded all people who were prescribed insulin in the six-month period leading up to the baseline assessment, initial insulin therapy may have been withdrawn for some obese individuals due to significant weight loss before that time. Furthermore, insulin may be the first agent prescribed to newly diagnosed individuals with severely uncontrolled diabetes [3, 4]. Fourth, our analyses were based on pharmacy prescriptions, which may not represent actual medication taking. In addition, pharmacy prescriptions only record the start of insulin therapy, and do not provide information about the date on which insulin therapy was first offered to a participant. Fifth, it is unclear whether the introduction of new blood glucose lowering drugs, such as glucagon-like peptide-1 receptor agonists, during follow-up may have influenced insulin initiation. Finally, we cannot rule out that a small minority of our sample have latent auto-immune diabetes of adulthood rather than type 2 diabetes.

Strengths of the study include the large sample of people with type 2 diabetes from a primary care setting, and the detailed medication dispensing data available in the PHARMO Database Network. In The Netherlands, the dispensing records of community pharmacies generally provide an accurate account of all outpatient drug prescriptions. Missing outpatient prescription data (an estimated 5% or less of all outpatient records) are mostly covered by dispensings of antibiotics and analgesics from emergency pharmacies. Furthermore, Dutch community pharmacies dispense the vast majority of outpatient drug prescriptions from both general practitioners and specialists. Therefore, it is unlikely that we would have missed the initiation of insulin therapy due to a referral from primary to secondary care.

In sum, the results of the first longitudinal study examining the role of depressive symptoms in the timing of insulin therapy showed that depression was not associated with time to insulin initiation. Additional studies in other samples, preferable incorporating more information about the decision making process behind insulin initiation, are needed to further elucidate whether or not depression is associated with initiation of insulin therapy. These studies may also explore the role of other psychological or behavioral factors.

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CHAPTER 6

Suboptimal glycemic control in type 2 diabetes: a key role for anhedonia?

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ABSTRACT

Recent studies examining the relationship between depression and glycosylated hemoglobin (HbA_{1c}) concentrations in patients with type 2 diabetes have yielded mixed findings. One explanation may lie in the heterogeneity of depression. Therefore, we examined whether distinct features of depression were differentially associated with suboptimal glycemic control. Cross-sectional baseline data from a dynamic cohort study of primary care patients with type 2 diabetes from the Eindhoven region, The Netherlands, were analyzed. A total of 5772 individuals completed baseline measurements of demographic, clinical, lifestyle and psychological factors between 2005 and 2009. The Edinburgh Depression Scale was used to assess symptoms of depressed mood, anhedonia and anxiety. Suboptimal glycemic control was defined as HbA_{1c} values ≥ 7%, with 29.8% of the sample (n = 1718) scoring above this cut-off. In univariate logistic regression analyses, anhedonia was significantly associated with suboptimal glycemic control (OR 1.29, 95% CI 1.09 – 1.52), while both depressed mood (OR 1.04, 0.88 – 1.22) and anxiety (OR 0.99, 0.83 – 1.19) were not. The association between anhedonia and glycemic control remained after adjustment for the other depression measures (OR 1.33, 1.11 – 1.59). Alcohol consumption and physical activity met criteria for mediation, but did not attenuate the association between anhedonia and glycemic control by more than 5%. Although diabetes duration was identified as a confounder and controlled for, the association was still significant (OR 1.20, 1.01 – 1.43). Studying different symptoms of depression, in particular anhedonia, may add to a better understanding of the relationship between depression and glycemic control.

INTRODUCTION

Depressive symptoms are common among individuals with type 2 diabetes, affecting up to 30% of patients [1]. A growing number of studies indicate that depressed diabetes patients are at increased risk for various adverse health outcomes, including the development of macro- and microvascular complications and higher mortality rates [2, 3]. Findings regarding the association between depression and glycemic control are less consistent. Although a meta-analysis based on 24 cross-sectional studies published up until 1999 concluded that depression was significantly associated with higher glycosylated hemoglobin (HbA_{1c}) concentrations (effect size 0.17, 95% CI 0.13 – 0.21) [4], subsequent studies in patients with type 2 diabetes have yielded mixed results [5].

One explanation may lie in the heterogeneity of depression. Rather than encompassing a homogeneous condition, depression is characterized by a variety of symptoms and subtypes, which do not all have to be present in individual patients [6]. Core characteristics range from depressed mood (dysphoria) to a loss of interest or pleasure (anhedonia), and additional symptoms may even include anxiety [7]. While dysphoria comprises negative emotions such as feelings of sadness and emptiness, anhedonia is often conceptualized as a condition in which positive affect is reduced [8]. Low positive affect has been associated with a higher risk of cardiovascular conditions and mortality in community-dwelling elderly and patients with established coronary artery disease [9-13] and was found to predict all-cause mortality in people with diabetes [14]. A small study in older women without diabetes showed an adverse effect of low positive affect on HbA_{1c} levels [15], but this association has not been examined in patients who already have diabetes.

Therefore, the primary aim of this study was to explore whether the two core features of depression – dysphoria and anhedonia – are differentially associated with suboptimal glycemic control. Knowing that anxiety symptoms may figure prominently in depression and appear to adversely affect patient outcomes [16], anxiety was included in the analyses as a second measure of negative affect. As the mechanisms behind the association between emotional distress and glycemic control are still unclear but likely include less adequate self-care behaviors [17], we also examined the role of body mass index and several health behaviors as potential mediators of these associations.

MATERIALS AND METHODS

Study sample

The DIAZOB Primary Care Diabetes study is an ongoing dynamic cohort study in primary care patients with type 2 diabetes and is conducted in collaboration with over 200 general practitioners from the Eindhoven region (The Netherlands). Measurements include the annual assessment of a broad range of demographic, medical, lifestyle and psychosocial factors and are performed within the framework of the DIAZOB (Diabetes care Zuidoost-Brabant) standard care project, a diabetes management programme for patients with type 2 diabetes in which a primary care practice nurse provides regular diabetes care. Within DIAZOB, diabetes is diagnosed according to the guidelines of the Dutch College of General Practitioners. These criteria are comparable to the current recommendations of the American Diabetes Association. A more detailed description of the DIAZOB Primary Care Diabetes study and related projects can be found elsewhere [18]. The present study includes cross-sectional baseline data from 5772 patients with type 2 diabetes who joined DIAZOB between April 2005 and January 2009 and had complete data regarding gender, age, HbA_{1c} and depressive symptoms. These patients did not differ significantly from those with missing depression data (n = 6405) with respect to gender (48.6% versus 50.3% women, $p = 0.060$), but were somewhat older (mean age 66.8 versus 66.4 years, $p = 0.045$) and had a clinically irrelevant, slightly lower mean HbA_{1c} (6.72 versus 6.75, $p = 0.044$). The study was approved by the medical research ethics committee of a local hospital, the Máxima Medical Center Veldhoven. Written informed consent was obtained from all participants.

Suboptimal glycemic control

Suboptimal glycemic control was defined as HbA_{1c} values ≥ 7%, in line with the Dutch Primary Care Guidelines for type 2 diabetes. HbA_{1c} was assessed at the Diagnostic Center Eindhoven (a primary care diagnostic laboratory), the Elkerliek Hospital Deurne / Helmond and the St. Anna Hospital Geldrop, using ion-exchange high performance liquid chromatography.

Depressive symptoms

Presence of the two key elements of depression (dysphoria, anhedonia) and additional symptoms of anxiety during the last seven days was assessed using a validated Dutch version of the Edinburgh Depression Scale (EDS) [19]. The EDS is a 10-item self-rating scale in which each item is scored on a four-point scale, with total scores ranging from 0 to 30 points. Even though the EDS was originally designed to assess postpartum depression, later evidence showed that it is also valid for use in other (male and female) strata [20-23]. It has become clear that the EDS actually measures three different symptom dimensions: depressed mood (4 items: e.g. “I have felt sad or miserable”, “I have been so unhappy that I have been crying”), anhedonia (2 items: “I have been able to laugh and see the funny side of things”, “I have

looked forward with enjoyment to things"), and anxiety (3 items: e.g. "I have been anxious or worried for no good reason", "I have felt scared or panicky for no very good reason") [24]. In the present study, the Cronbach's alpha of the different subscales was 0.76, 0.78 and 0.70, respectively. As the previously published cut-off values of the ten-item EDS (usually ≥ 12) [20, 21, 23] generally correspond to the upper 90th percentile score, high scores on its subscales were also defined using the 90th percentile cut-off (depressed mood ≥ 4, anhedonia ≥ 3, anxiety ≥ 6) in this study.

Potential demographic, clinical and lifestyle-related confounding or mediating factors

Information regarding age, sex, ethnicity (Caucasian versus non-Caucasian), educational level (middle/high versus low education), diabetes duration (less than three years versus three years or more) and health behaviors was obtained by a nurse-led interview and a self-report questionnaire. Lifestyle factors included smoking status (no versus one or more cigarettes / day), alcohol intake (14 or less versus more than 14 drinks / week) and physical activity as defined by hours of "active" (daily activities including gardening, walking, climbing stairs) and "sportive" activities (e.g., sports, fitness) per week. Patients' body mass index (BMI; weight in kilograms / length in metres^2) was derived from standard care physical examinations. BMI was dichotomized into BMI < 30 versus ≥ 30 kg / m^2. Dichotomization of variables was employed to improve clinical interpretability by allowing a comparison of low-medium versus high risk groups based on several Dutch and international health care guidelines [25-27].

Statistical analyses

A confirmatory factor analysis was used to examine the fit of the three factor EDS structure (depressed mood, anhedonia, anxiety) to our data. Demographic, clinical and lifestyle characteristics of patients with and without high levels of symptoms on the three subscales of the EDS were compared using X^2 tests (dichotomous variables) and independent samples t-tests (continuous variables). To test whether the EDS subscales were associated with suboptimal HbA_{1c}, univariate logistic regression analyses were performed, followed by a multivariate model in which all measures of emotional distress were entered simultaneously. In case we found a significant association between an EDS subscale and HbA_{1c}, several candidate confounders or mediators were examined.

To establish mediation, selected variables (BMI, smoking, alcohol consumption and the two measures of physical activity) had to meet the four mediation criteria formulated by Baron and Kenny [28]. To this end, a series of logistic regression analyses was conducted. In a first step, the independent variable had to be associated with the mediator (regressing the candidate mediator on the EDS subscale). Second, the independent variable had to be

associated with the dependent variable (as was done in the previously mentioned univariate analyses, by regressing glycemic control on the EDS subscales). Third, the mediator had to be associated with the dependent variable, after controlling for the independent variable (regressing glycemic control on both the mediator and the EDS subscale). Finally, the effect of the independent variable on the dependent variable in regression 3 had to be smaller than in step two. When a candidate variable met all four criteria, we evaluated the plausibility of the mediator by examining the magnitude of the change in a last step. To do so, we determined the percentage change in the effect size (odds ratio) of the association between the EDS subscale and suboptimal glycemic control before and after adjustment for the potential mediator using hierarchical regression analyses, in line with the methods used in the Heart and Soul Study [29]. If a variable resulted in a more than 5% change [29] and fulfilled all four criteria by Baron and Kenny [28], it was marked as a mediator. The (Aroian) Sobel method was used as a test of significance for the indirect effect of the independent variable on the dependent variable via the mediator [28]. As our mediation analyses involved a dichotomous outcome variable and candidate mediators, we made the regression coefficients comparable across the equations using the computational model by Herr [30] before entering coefficients and standard errors into the commonly used Sobel test calculation tool by Preacher and Leonardelli [31]. However, in light of clinical considerations, a significant mediation effect accompanied by a marginal change in effect size (≤ 5%) was not taken to signify meaningful mediation.

Variables that did not meet the assumptions for mediation were then evaluated as potential confounding factors, along with several other variables (gender, age, ethnicity, education, diabetes duration). A variable was considered to meaningfully confound the association between an EDS subscale and glycemic control when it changed this association by more than 5%, following the previously mentioned statistical procedure by Whooley et al. [29]. All confounders and mediators fulfilling these criteria were included in a final multivariate model.

AMOS 19.0 was used for the confirmatory factor analysis (Amos Development Corporation, Meadville, Pennsylvania, USA); all other analyses were performed using PASW Statistics 17.0 (IBM SPSS Statistics, Somers, New York, USA). For all analyses, a two-tailed $P < 0.05$ significance level was adopted. If applicable, 95% confidence intervals were reported.

RESULTS

Characteristics of the total sample are described in Table 1. The overall sample was in relatively good glycemic control (HbA_{1c} mean 6.72, SD 0.82, range 4.70 – 14.90); however, 29.8% of patients (1718 / 5772) had an $HbA_{1c} \geq 7$ %. A confirmatory factor analysis confirmed adequate fit of the three factor EDS structure (depressed mood, anhedonia, anxiety) to our own data, with $X^2(24) = 229$, $p < 0.001$ (likely due to the large sample size), RMSEA 0.04 (90% CI 0.03 – 0.04), CFI = 0.99 and TLI = 0.98. All symptoms of emotional distress were significantly correlated, with Pearson's $r = 0.53$ for depression and anhedonia, 0.60 for depression and anxiety and 0.32 for anhedonia and anxiety (all $p < 0.001$). A high depressed mood score was present in 13.7% (793 / 5772), anhedonia in 12.7% (735 / 5772) and anxiety in 10.6% (614 / 5772) of the patients. While the majority reported symptoms from only one category (n = 857), 573 individuals experienced co-morbid emotional distress. Compared to their counterparts with low emotional distress, patients with a high depression, anhedonia or anxiety score were significantly more likely to be women, to have a low educational level and to have a higher (continuous) BMI score, while they tended to consume fewer alcoholic beverages and engaged less in activities requiring mild to moderate physical activity (Table 1). Additionally, those reporting high symptom levels of depressed mood were significantly more likely to be non-Caucasian, to have a diabetes duration of at least three years and to smoke. The same significant results were found for those with anhedonia, while these patients were also slightly older and less likely to be in optimal glycemic control or to engage in sportive physical activities. The relation between anhedonia and BMI was no longer significant when BMI values were dichotomized to differentiate obese individuals (BMI ≥ 30) from those with lower body mass index.

Univariate logistic regression analyses showed that only anhedonia significantly predicted suboptimal HbA_{1c} (OR 1.29, 95% CI 1.09 – 1.52), while both anxiety (OR 0.99, 95% CI 0.83 – 1.19) and depressed mood (OR 1.04, 95% CI 0.88 – 1.22) did not. The odds ratio for the association between anhedonia and suboptimal glycemic control increased when using higher cut-off values for suboptimal HbA_{1c}: $HbA_{1c} > 7.5\%$: OR 1.70 (95% CI 1.38 – 2.09), $HbA_{1c} > 8\%$: OR 1.57 (95% CI 1.18 – 2.09) and $HbA_{1c} > 8.5\%$: OR 1.72 (95% CI 1.18 – 2.52). Anhedonia remained a significant predictor of suboptimal glycemic control (OR 1.33, 95% CI 1.11 – 1.59) after adjustment for symptoms of anxiety and depressed mood.

Table 1 Characteristics of 5772 type 2 diabetes patients with complete data on gender, age and the main study variables (HbA_{1c}, EDS), stratified by depressed mood, anhedonia and anxiety

	All (n = 5772)	Low depression (n = 4979)	High depression (n = 793)	*P* value	Low anhedonia (n = 5037)	High anhedonia (n = 735)	*P* value	Low anxiety (n = 5158)	High anxiety (n = 614)	*P* value
Mean HbA_{1c} (SD)	6.7 (0.8)	6.7 (0.8)	6.7 (0.8)	0.43	6.7 (0.8)	6.9 (1.0)	<0.001	6.7 (0.8)	6.7 (0.9)	0.89
HbA_{1c} ≥ 7	29.8% (1718 / 5772)	29.7% (1477 / 4979)	30.4% (241 / 793)	0.71	29.1% (1464 / 5037)	34.6% (254 / 735)	0.003	29.8% (1536 / 5158)	29.6% (182 / 614)	.98
Potential confounders and / or mediators										
Mean age (SD), years	66.8 (10.5)	66.8 (10.4)	67.0 (10.6)	0.59	66.6 (10.4)	67.7 (10.7)	0.009	66.8 (10.5)	66.8 (10.5)	0.93
Female sex	48.6% (2805 / 5772)	45.7% (2277 / 4979)	66.6% (528 / 793)	<0.001	47.3% (2384 / 5037)	57.3% (421 / 735)	<0.001	46.5% (2401 / 5158)	65.8% (404 / 614)	<0.001
Non-Caucasian	2.5% (143 / 5719)	1.9% (95 / 4938)	6.1% (48 / 781)	<0.001	2.2% (111 / 4996)	4.4% (32 / 723)	0.001	2.4% (122/5118)	3.5% (21 / 601)	0.13
Low educational level	59.8% (3318 / 5553)	57.8% (2772 / 4800)	72.5% (546 / 753)	<0.001	58.0% (2814 / 4854)	72.1% (504 / 699)	<0.001	58.6% (2906 / 4958)	69.2% (412 / 595)	<0.001
Diabetes duration ≥ 3 years	59.2% (3202 / 5413)	58.4% (2743 / 4696)	64.0% (459 / 717)	0.005	58.1% (2750 / 4735)	66.7% (452 / 678)	<0.001	59.0% (2864 / 4855)	60.6% (338 / 558)	0.50
Mean BMI (SD)	29.6 (5.0) (n = 4722)	29.5 (5.0) (n = 4095)	30.4 (5.5) (n = 627)	<0.001	29.5 (4.9) (n = 4147)	30.1 (5.8) (n = 575)	0.03	29.5 (5.0) (n = 4233)	30.0 (5.6) (n = 489)	0.04
BMI ≥ 30	42.5% (2008 / 4722)	41.5% (1699 / 4095)	49.3% (309 / 627)	<0.001	42.2% (1752 / 4147)	44.5% (256 / 575)	0.32	41.9% (1773 / 4233)	48.1% (235 / 489)	0.01
Smoking [a]	13.7% (782 / 5709)	13.3% (655 / 4930)	16.3% (127 / 779)	0.03	13.2% (658 / 4990)	17.2% (124 / 719)	0.004	13.5% (691 / 5110)	15.2% (91 / 599)	0.29
High alcohol intake [b]	7.0% (395 / 5667)	7.5% (366 / 4888)	3.7% (29 / 779)	<0.001	7.3% (359 / 4945)	5.0% (36 / 722)	0.03	7.5% (378 / 5068)	2.8% (17 / 599)	<0.001
"Active" physical activity [c]	74.8% (4278 / 5717)	76.8% (3793 / 4937)	62.2% (485 / 780)	<0.001	77.2% (3859 / 4997)	58.2% (419 / 720)	<0.001	75.6% (3869 / 5118)	68.3% (409 / 599)	<0.001
"Sportive" physical activity [d]	39.5% (2236 / 5665)	40.0% (1954 / 4890)	36.4% (282 / 775)	.06	40.8% (2020 / 4948)	30.1% (216 / 717)	<0.001	39.3% (1993 / 5066)	40.6% (243 / 599)	0.59

The continuity correction was applied in the computation of X^2 for all 2 x 2 tables; [a] ≥ 1 cigarette / day; [b] > 14 consumptions / week; [c] At least 2 hours of "active" physical activity a week; [d] At least 1 hour of "sportive" physical activity a week

In a next step, potential confounding or mediating factors of the association between anhedonia and suboptimal glycemic control were examined. Of the selected candidate mediators, only alcohol consumption and the two measures of physical activity met both criterium 1 (anhedonia had to be associated with the mediator) and criterium 3 (the mediator had to be associated with glycemic control, adjusted for anhedonia) of the mediation model (Table 2).

Table 2 Criteria 1 and 3 of the mediation model

	n	Step 1 [a]	*P* value	Step 3 [b]	*P* value
Potential mediators					
BMI	4722	1.10 (0.92 – 1.31)	0.30	1.28 (1.13 – 1.45)	<0.001
Smoking	5709	1.37 (1.11 – 1.69)	0.003	1.06 (0.90 – 1.24)	0.51
High alcohol intake	5667	0.67 (0.47 – 0.95)	0.03	0.76 (0.60 – 0.96)	0.02
Active physical activity	5717	0.41 (0.35 – 0.48)	<0.001	0.78 (0.69 – 0.89)	<0.001
Sportive physical activity	5665	0.63 (0.53 – 0.74)	<0.001	0.82 (0.73 – 0.92)	0.001

[a] Regressing the mediator on the independent variable (anhedonia);
[b] Regressing the dependent variable (HbA_{1c}) on the mediator, controlled for anhedonia

Although the Sobel test was in fact significant for active and sportive physical activity, none of the variables changed the strength of the association between anhedonia and suboptimal HbA_{1c} by more than 5% (Table 3). Adjustment for active and sportive physical activity had the largest effect, reducing the effect size by 4.7 and 2.1%, respectively. When considering potential confounding factors, only diabetes duration changed the effect size for anhedonia by more than 5% (Table 3). Even though correction for diabetes duration reduced the strength of the association, anhedonia remained an independent predictor of suboptimal glycemic control (OR 1.20, 95% CI 1.01 – 1.43; $p = 0.036$).

Table 3 Percent change in the strength of the association (OR) between anhedonia and suboptimal glycemic control (HbA_{1c} ≥ 7) after adjustment for potential confounders and mediators

	n	*P* value	OR (95% CI)	Change in OR (%)	Sobel test [a]
POTENTIAL CONFOUNDERS					
Demographic variables					
Female gender	5,772				
Before		0.002	1.289 (1.094 – 1.518)	-0.5	-
After		0.003	1.282 (1.088 – 1.511)		
Age	5,772				
Before		0.002	1.289 (1.094 – 1.518)	-0.1	-
After		0.002	1.288 (1.094 – 1.518)		
Non-Caucasian	5,719				
Before		0.004	1.276 (1.082 – 1.505)	-1.2	-
After		0.006	1.261 (1.069 – 1.488)		
Low education	5,553				
Before		0.007	1.259 (1.064 – 1.489)	+0.3	-
After		0.007	1.263 (1.067 – 1.496)		
Clinical values					
Diabetes duration ≥ 3 years	5,413				
Before		0.005	1.274 (1.074 – 1.511)	-5.6	-
After		0.036	1.203 (1.012 – 1.431)		
POTENTIAL CONFOUNDERS / MEDIATORS					
Clinical values					
BMI (≥ 30)	4,722				
Before		0.02	1.247 (1.036 – 1.500)	-0.6	0.33
After		0.02	1.240 (1.031 – 1.493)		
Health behaviors					
Smoking	5,709				
Before		0.002	1.303 (1.105 – 1.537)	-0.2	0.54
After		0.002	1.300 (1.102 – 1.534)		
Alcohol intake	5,667				
Before		0.003	1.280 (1.085 – 1.510)	-0.5	0.13
After		0.004	1.273 (1.079 – 1.502)		
Active physical activity	5,717				
Before		0.003	1.286 (1.090 – 1.517)	-4.7	<0.001
After		0.02	1.226 (1.037 – 1.449)		
Sportive physical activity	5,665				
Before		0.003	1.290 (1.093 – 1.522)	-2.1	0.005
After		0.006	1.263 (1.070 – 1.492)		

[a] Not restricted to the anhedonia data reported in the nested models displayed in the columns to the left, but using anhedonia data of total sample (n=5,772)

DISCUSSION

In the present large sample of primary care patients with type 2 diabetes, preliminary evidence was found that within the spectrum of depression, particularly symptoms with an emphasis on reduced positive affect (anhedonia) are associated with suboptimal glycemic control, while symptoms focusing on negative emotions (dysphoria, anxiety) are not. Even after controlling for these negative emotions, diabetes patients with high levels of anhedonia had a 30% increased odds of having an $HbA_{1c} \geq 7$. Even though these findings are preliminary, they are consistent with the results of a previous study in which positive affect was identified as an independent inverse correlate of HbA_{1c} levels in older women without diabetes [15] and add to a broader body of literature suggesting that (reduced) positive affect is associated with clinical outcomes above and beyond the presence of negative emotions [9-14].

The association between anhedonia and suboptimal glycemic control persisted after adjustment for potential demographic and clinical confounders, although it was somewhat attenuated when controlling for diabetes duration. Moreover, none of the selected health behaviors (physical activity, smoking, alcohol consumption) had a substantial mediating effect, suggesting that other, unmeasured factors may play a mediating role. As for physiological pathways, previous studies have postulated that the two core elements of depression may have distinct neurochemical correlates, relating dysphoria and anhedonia to dysfunctions of the serotonin and dopamine systems, respectively [32]. Even though poorly understood, dopamine appears to play an important role in the regulation of glucose homeostasis. However, as the activation of dopamine D2-like receptors expressed by pancreatic beta cells has been shown to inhibit glucose-stimulated insulin secretion [33], it is unlikely that the hypofunction of the dopaminergic system associated with anhedonia [32] has a direct hyperglycemic effect. An alternative mechanism relates to dopaminergic involvement in the brain reward system and its ensuing impact on health behaviors. While we did not find a noteworthy mediating role for smoking, alcohol consumption and physical activity, there are several other diabetes self-care activities closely related to glycemic control that were not examined in the present study, including healthy eating, medication taking and self-monitoring of blood glucose levels [34]. Eating behavior is of special interest to future research, as opioid and dopamine neurotransmitter systems have been implicated in reward processes surrounding food consumption [35]. Consumption of palatable foods (e.g. high-fat, high-sugar) can improve mood and mitigate the effects of stress [35]. Anhedonic individuals, who by definition have a decreased ability to experience pleasure, may be more dependent upon so-called “comfort foods” (rich in fat and carbohydrates) to raise hedonic tone [35]. Consistent with this hypothesis, anhedonic individuals have been shown to be more prone to relapse after smoking cessation, most likely because they are more susceptible to the effects of tobacco deprivation on hedonic states [36].

Non-adherence to treatment may represent an important pathway between emotional distress and poor diabetes outcomes [17]. As anhedonia has been related to dysfunctions of the brain reward system and is usually characterized by an impaired responsiveness to rewarding stimuli [32], it may be that anhedonic patients are less likely to experience satisfaction or pleasure from achieving and maintaining adequate or good glycemic control. As a result, one can expect that these patients will be less likely to engage in adequate diabetes self-care behaviors. More studies are needed to understand the exact physiological and behavioral mechanisms in play.

Several study limitations need to be acknowledged. First, the study's cross-sectional design prohibits any conclusions regarding causality, as anhedonia may also be the result of suboptimal glycemic control. Poor metabolic control can directly exacerbate mood symptoms or may contribute to patient burden and poor well-being by increasing an individual's risk of developing micro- and macrovascular complications [37, 38]. The latter hypothesis may also explain why higher diabetes duration was found to attenuate the association between anhedonia and glycemic control. Unfortunately, no data were available to examine the potential confounding role of medical co-morbidities. Secondly, in the operationalization of anhedonia we have mainly focused on the affective component of this construct (reduced positive affect), while we have not directly measured its behavioral correlates including neglect of pleasurable avocations and social withdrawal [7]. Thirdly, we were not able to test potential mediation by physiological pathways, although these are likely to be implicated in anhedonia's detrimental effect on health. Fourthly, measuring depressive symptomatology by means of a self-report questionnaire could have obscured the association between glycemic control and negative affect. A meta-analysis including 11 studies published prior to 2002 only found a significant association with hyperglycemia in studies that determined anxiety from diagnostic interviews [39], while results for depression also appear to be more pronounced when standardized interviews and diagnostic criteria rather than self-report questionnaires are used [4]. Finally, although the present study is the first to address which features of depression are particularly associated with suboptimal glycemic control, no information was available regarding concurrent somatic or cognitive symptoms. As anhedonia is part of a "melancholic" symptom cluster that also includes diurnal variation of mood, early morning awakening, marked psychomotor retardation or agitation, significant anorexia or weight loss and excessive or inappropriate guilt [7], future studies examining the association between depression and glucose control should also incorporate a focus on depression subtypes, including melancholic and atypical depression. While focusing on symptom clusters is one way of examining the heterogeneity of depression, the course trajectory of these symptoms could be equally relevant for future research, as incident, relapsing-remitting and persistent depression subtypes may each be differently associated

with health outcomes. Strengths of the present study include the use of a validated measure to study the associations between distinctly different features of depression and glycemic control, and the inclusion of a large sample of primary care patients with type 2 diabetes.

In conclusion, we found clinical evidence that on a symptom level, anhedonia (or the reduced capacity to experience positive affect) rather than measures of negative affect appears to be associated with suboptimal glycemic control. Studying different symptoms and subtypes of depression, in particular anhedonia, may add to a better understanding of the relationship between depression and glycemic control. A focus on different depressive symptoms and subtypes fits well with research trends in psychiatry and cardiology, to "dismantle" depression into the elements that are adversely affecting health [40, 41]. Prospective studies are needed to clarify the directional nature of this relationship and to test mediation through other behavioral or physiological pathways. Given that a substantial proportion of depressed diabetes patients does not benefit from the current pharmacological and psychotherapeutic treatment modalities, future research should also examine whether tailoring depression treatment to a patient's specific symptom profile might not only improve mood, but also glycemic outcomes.

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CHAPTER 7

Depressive symptoms, cardiovascular disease and all-cause mortality in people with type 2 diabetes: a focus on depression symptom clusters and potential mechanisms

Nefs G, Pouwer F, Denollet J, Pop V

Original text

ABSTRACT

Background: Depression has been associated with the development of cardiovascular disease and all-cause mortality in people with type 2 diabetes. We examined whether symptoms related to the two core features of depression – dysphoria and anhedonia – and anxiety are differentially associated with these end points and whether there are symptom-specific behavioral or pathophysiological mechanisms in play.

Methods: 1,465 people completed the Edinburgh Depression Scale (EDS – including subscales measuring dysphoria, anhedonia and anxiety) in 2005 and were followed until first cardiovascular hospitalization during follow-up, death, or the end of the study period (December 31, 2010). Cox regression analyses were used to determine whether there was a difference in time to hospitalization for a cardiovascular event or to all-cause mortality between people with a low versus a high dysphoria / anhedonia / anxiety score at baseline (adjusting for meaningful demographic and clinical confounders) and to identify mediating mechanisms.

Results: The prevalence of depression (EDS ≥ 12) was 12% (n = 182). At the end of follow-up, 191 people had experienced a hospitalization for a cardiovascular event and 139 had died. Depression was associated with survival time (adjusted HR = 1.93, 95% CI 1.10 – 3.41), but not with time to first cardiovascular hospitalization. Dysphoria predicted a shorter time to first cardiovascular hospitalization during follow-up in univariable analysis only (unadjusted HR = 1.49, 1.02 – 2.17), while anxiety was associated with a longer time to event in the multivariable model (adjusted HR = 0.52, 0.29 – 0.92). Dysphoria and anxiety were not associated with survival time. However, at all time points people with anhedonia had an almost 2-fold increased risk to die compared to their counterparts without anhedonia, also after taking potential confounders into account. Physical activity met criteria for mediation, attenuating the HR for anhedonia by approximately 20%.

Conclusions: Symptom-clusters of negative emotions predicted time to first hospitalization for a cardiovascular event during follow-up, while symptoms of anhedonia were associated with shorter survival time. Mechanistic pathways, in particular physical activity, should be explored further.

INTRODUCTION

Depression and diabetes are closely linked, with depression being a risk factor for the development of type 2 diabetes and the presence of type 2 diabetes contributing to the onset of depression [1, 2]. The prevalence of depression is significantly higher in people with type 2 diabetes compared with those without (18% vs. 10%, OR = 1.6, 95% CI 1.2 – 2.0) [3]. Individuals with previously diagnosed diabetes have an increased risk of depression relative to those with impaired glucose metabolism or undiagnosed diabetes [4]. Moreover, depression (defined as a high level of depressive symptoms) appeared to be recurrent / persistent during a 2.5 year period in 66% of people with diabetes with a high baseline depression score [5].

Importantly, co-morbid depression in diabetes not only poses a significant threat to quality of life [6], but is also related to other health outcomes. A recent meta-analysis and systematic review based on 16 longitudinal studies concluded that depression was associated with a shorter survival time in people with diabetes (HR of all-cause mortality = 1.46, 95% CI 1.29 – 1.66) [7]. Although based on only 5 studies, similar results were found for cardiovascular mortality (HR = 1.39, 95% CI = 1.11 – 1.73) [7]. A growing number of studies also suggest that depression may predict the development of both macrovascular and microvascular complications [8-15], with a research emphasis on more advanced conditions such as myocardial infarction, stroke and amputations and most studies covering samples from the United States of America.

In both psychiatry and cardiology, increased attention has focused on the heterogeneity of depression and its implications for health [16]. Depression is characterized by a range of symptoms and different symptom clusters [17]. Identification of symptom clusters or subtypes of depression that are associated with the greatest risk of morbidity and mortality would facilitate both risk stratification in clinical practice and the design of effective treatments [18]. One potentially relevant distinction centers around the two core features of depression, namely dysphoria (depressed mood) and anhedonia (loss of interest or pleasure) [19]. While dysphoria subsumes negative emotions including feelings of sadness or emptiness, anhedonia can be conceptualized as a condition in which positive affect is reduced [20]. Anhedonia – or low positive affect – has been shown to predict cardiovascular conditions and mortality in community-dwelling elderly and people with established heart disease, even after taking the presence of negative emotions into account [21-26]. Similar results for all-cause mortality have been found in people with diabetes using data from the National Health and Nutrition Examination Study I Epidemiologic Follow-Up Study [27]. To date, the relative importance of anhedonia and dysphoria in predicting the development of vascular disease has not been studied among people with diabetes.

In addition, the behavioral or pathophysiological pathways through which depression increases the risk of vascular morbidity and mortality remain unclear. Candidate mechanisms include suboptimal self-care behaviors and other (cardio)vascular risk factors such as obesity, hyperglycemia, hypertension, and high cholesterol [28-31]. Which factors may underlie the development of cardiovascular disease in depressed people with diabetes and whether there are symptom-specific mechanisms in play is yet to be determined.

The aims of the present study were threefold. First, we examined whether depression was associated with hospitalization for cardiovascular disease and all-cause mortality in a large cohort of people with type 2 diabetes from The Netherlands. Second, we explored whether the two core features of depression – dysphoria and anhedonia – were differentially associated with these two end points. Knowing that anxiety symptoms may figure prominently in depression and appear to adversely affect patient outcomes [32], anxiety was included in the analyses as another measure of negative affect. Where previous studies have mainly focused on advanced diabetes complications, we have also included "milder" conditions, such as angina pectoris. Third, in case of a significant association between depression symptom clusters and cardiovascular disease and mortality, we sought to determine which behavioral or pathophysiological mechanisms might be involved in mediating any symptom-specific association(s) with adverse health outcomes.

METHODS

The DiaDDZoB (Diabetes, Depression, Type D personality Zuidoost-Brabant) Study was designed as a prospective cohort study among people with type 2 diabetes from primary care practices in South-East Brabant, The Netherlands [33]. A total of 2,460 individuals (82% of those considered for study inclusion) participated in the 2005 baseline assessment, consisting of a nurse-led interview and the completion of a self-report questionnaire. To increase the accuracy of cardiovascular diagnoses and mortality records, record linkage was sought with the PHARMO Database Network [34], a population-based patient-centric data tracking system which started in 1986 that includes high quality and complete information of patient demographics, drug dispensings, hospitalizations, clinical laboratory, pathology and general practitioner information of 3.2 million community-dwelling inhabitants of 65 municipal areas in The Netherlands. As both the DiaDDZoB and PHARMO databases only contain deidentified patient information, record linkage was realized based on the combination of date of birth, sex, first initial, first letter of family name, first letter of marital name (women only) and zip code. This procedure resulted in successful record linkage for 81% (n = 1,982) of the original DiaDDZoB cohort.

The present sample (n = 1,465) includes all DiaDDZoB participants for whom linkage with the PHARMO Database Network could be realized and who completed at least nine items of the EDS during the 2005 baseline assessment. These people did not differ significantly from the rest of the DiaDDZoB cohort (n = 995) with respect to sex, age, educational level, the presence of microvascular complications, diabetes duration, HbA_{1c} and fasting glucose, body mass index, HDL cholesterol, systolic and diastolic blood pressure, time spent in activities requiring mild to moderate physical activity, or alcohol consumption. However, they were somewhat less likely to have a non-western ethnicity (2% vs. 5%, $p = 0.001$), to be single (24% vs. 30%, $p = 0.02$), to engage in sportive physical activity (32% vs. 28%, $p = 0.03$), to smoke (14% vs. 19%, $p = 0.003$), to have kidney disease (3% vs. 5%, $p = 0.047$), or to have a history of cardiovascular disease (33% vs. 39%, $p = 0.003$), in particular arterial disease (21% vs. 28%, $p < 0.001$). In addition, they had slightly lower mean levels of total cholesterol (4.5 vs. 4.7 mmol / l, $p = 0.003$) and LDL cholesterol (2.6 vs 2.7 mmol / l, $p = 0.006$). In the analyses relating to cardiovascular disease, participants were followed from the baseline assessment in 2005 to the date of the first cardiovascular hospitalization during follow-up, date of death, or the end of the study period (December 31, 2010), whichever occurred first. As for all-cause mortality, follow-up extended to either date of death or the end of the study period (December 31, 2010). The DiaDDZoB study protocol was approved by the medical research ethics committee of a local hospital, the Máxima Medical Centre in Veldhoven (NL27239.015.09). Written informed consent was obtained from all participants. The PHARMO compliance committee gave permission to establish the link between the DiaDDZoB cohort and the PHARMO Database Network.

Assessment of depression

Symptoms of depression during the last seven days were assessed using the Dutch version of the Edinburgh Depression Scale (EDS) [35]. Originally designed to assess postpartum depression [36], this questionnaire has now been validated in several other (male and female) strata, including people with type 2 diabetes in primary care [37]. Total EDS scores are determined by summing the scores of all ten individual items (four-point scale for each item, total score range 0 – 30), with higher scores indicating higher levels of depressive symptoms. A total score of 12 or more is commonly used to identify people with depression [38]. In the present study, total EDS scores were only calculated when at least 9 items were completed, replacing the missing value with the mean of the remaining items. Three different EDS symptom dimensions have been identified: depressed mood or dysphoria (4 items; e.g. “I have felt sad or miserable”), anhedonia (2 items; e.g. “I have looked forward with enjoyment to things”), and anxiety (3 items; e.g. “I have been anxious or worried for no good reason”) [39]. In the present study, Cronbach’s alpha for the subscales was 0.72, 0.81 and 0.66, respectively. As the cut-off of the ten-item EDS generally corresponds to the upper 90th percentile score, high scores on its subscales were also defined using the 90th percentile cut-off (dysphoria ≥ 4, anhedonia ≥ 3, anxiety ≥ 6) in this study.

Cardiovascular hospitalization and all-cause mortality

Date of death was established using the PHARMO Database Network and records provided by general practitioners / primary care practice nurses participating in the DiaDDZoB Study. The first cardiovascular event during follow-up was identified using PHARMO's hospitalization database (Dutch Hospital Data: LMR, available at http://www.dutchhospitaldata.nl), which includes detailed information concerning the primary (mandatory) and secondary (optional) discharge diagnoses, procedures and dates of hospital admission and discharge for admissions for more than 24 hours and admissions for less than 24 hours for which a bed is required. Descriptions and diagnostic codes (International Classification of Diseases, 9th edition) of the conditions that were included in the composite cardiovascular hospitalization endpoint can be found in Online Appendix Table 1.

Baseline demographics, medical history, clinical values and health behaviors

Information regarding sex, age, ethnicity ([white] western vs. non-[white] western), educational level (middle / high vs. low), marital status (having a partner vs. being single) and diabetes duration (less than three years vs. three years or more) was obtained during an interview with the person with diabetes by the primary care practice nurse or was part of the questionnaire booklet that had to be filled in at home. The primary care practice nurse took a medical history, after which all self-reported medical diagnoses were verified through inspection of the medical record. Hyperglycemia treatment was determined from dispensing records in the six-month period leading up to the baseline assessment, using the community pharmacy drug dispensing records from the PHARMO Database Network. The Diagnostic Centre Eindhoven, a primary care diagnostic institute, provided results from standard care laboratory tests (fasting glucose, HbA_{1c}, cholesterol, and albumin levels) and physical examinations (blood pressure, body mass index, eye screening). The results from yearly digital fundus photopgraphy were available to ascertain retinopathy (no / yes), while albumin level in a random urine sample was used as a proxy for nephropathy [40]. Micro- and macroalbuminuria were defined as urine albumin concentrations 20 – 200 and > 200 mg / l, respectively. Additional medical co-morbidities included cardiovascular disease (myocardial infarction, bypass / angioplasty, stroke and / or arterial disease) and other chronic conditions (kidney disease, asthma / chronic obstructive pulmonary disease [COPD], cancer, arthrosis and / or rheumatoid arthritis). Health behaviors included smoking (no vs. one or more cigarettes / day), alcohol intake (≤ 14 vs. > 14 drinks / week), and physical activity, defined by hours of "active" (daily activities including gardening, walking, climbing stairs) and "sportive" activities (e.g. sports, fitness) per week.

Statistical analyses

Baseline differences in demographics, medical history, clinical characteristics and health behaviors between people with and without high depressive symptoms were examined using independent samples t-tests for continuous data and X^2 or Fisher's exact tests for categorical data, as appropriate. For both groups, time to first hospitalization for a cardiovascular event during follow-up and survival time were visualized by means of Kaplan-Meier curves, using the log-rank test to compare the two survival curves. A univariable Cox regression analysis was used to provide an effect size for the association between depression and time to cardiovascular hospitalization / death, reporting the hazard ratio with corresponding 95% confidence interval. The proportional hazards assumption was checked by visual inspection of the Kaplan-Meier survival curves (using Cox regression with a time-dependent covariate only when these suggested violation), and the Harrel and Lee test based on the Schoenfeld residuals. To evaluate whether the association between depression and time to cardiovascular hospitalization / all-cause mortality was confounded by specific demographic or clinical factors, we calculated the percentage change in the regression coefficient for depression before and after adjustment for individual candidate confounders [41]. All variables resulting in a more than 10% change in the regression coefficient were considered to be meaningful confounders [41] and were included in a multivariable-adjusted model.

For all associations that became / remained significant after taking confounding factors into account, potential pathophysiological and behavioral mediators were examined. To establish (plausible) mediation, candidate mediators had to meet the four mediation criteria formulated by Baron and Kenny [42]. To this end, a series of linear, logistic and Cox regression analyses were conducted. In a first step, the independent variable had to be associated with the mediator (regressing the candidate mediator on depression). Second, the independent variable had to be associated with the dependent variable (as was done in the previously mentioned univariable Cox regression analysis, by regressing time to event on depression). Third, the mediator had to be associated with the dependent variable, after adjusting for the independent variable (regressing time to event on both the mediator and depression). Finally, the effect of the independent variable on the dependent variable in regression 3 had to be smaller than in step two. When a candidate variable met all four criteria, we evaluated the plausibility of the mediator by examining the magnitude of the change in a last step. To do so, we determined the percentage change in the effect size (HR) of the association between depression and time to event before and after adjustment for the potential mediator [43]. If a variable resulted in a more than 5% change [43] and fulfilled all four criteria by Baron and Kenny [42], it was marked as a plausible mediator. We repeated these analyses comparing people scoring low vs. high on dysphoria, anhedonia and anxiety, respectively. All analyses were performed using PASW Statistics version 19 (IBM SPSS Statistics, Somers, NY, USA). A p-value < 0.05 was considered to be statistically significant.

RESULTS

Baseline demographics, clinical factors and health behaviors of the total sample (n = 1,465) are shown in Table 1. Twelve percent (n = 182) had an EDS-score ≥ 12. Compared with their non-depressed counterparts, participants with depression were more likely to be female, to have a non-western ethnicity, a low educational level and no partner. In addition, their medical history was more likely to include a diagnosis of a non-cardiovascular chronic medical condition, in particular asthma / COPD, arthrosis and rheumatoid arthritis. With respect to health behaviors, they were less likely to engage in activities requiring mild to moderate physical activity and more likely to smoke.

Depression and cardiovascular hospitalization

During a mean follow-up period of 1,762 ± 470 days (range 14 – 1,964), 191 participants (13%) were hospitalized for cardiovascular disease. The most common cardiovascular hospitalization during follow-up was linked to a cardiac condition, most notably coronary atherosclerosis and heart failure (Table 2). No differences were found between people with and without depression with respect to the hospitalization rate of cardiovascular disease in general or specific diagnoses. When examining the Kaplan-Meier curves, we also did not observe a difference in time to first cardiovascular hospitalization during follow-up for both groups (log-rank test $X^2[1] = 0.03$, $p = 0.86$), with a mean time to event of 1,823 (95% CI 1,800 – 1,845) and 1,815 (95% CI 1,752 – 1,877) days for those without and with depression, respectively (Figure 1a). Neither the Kaplan-Meier plots nor the correlation between the Schoenfeld residuals and ranked survival time ($r = -0.02$, $p = 0.80$) suggested violation of the proportional hazards assumption. In univariable Cox regression analysis, the HR of a cardiovascular hospitalization was 1.04 (95% CI 0.68 – 1.59, $p = 0.86$). All selected demographical and clinical variables changed the regression coefficient for depression by more than 10% (Table 3), but none of these meaningful confounders yielded a significant association between depression and time to cardiovascular hospitalization. After simultaneous adjustment for all confounding factors in a multivariable model, the HR of cardiovascular hospitalization remained non-significant (0.84, 95% CI 0.48 – 1.47, $p = 0.54$).

Depression and all-cause mortality

At the end of the five-and-a-half year study period (mean follow-up 1,878 ± 306 days, range 26 – 1,964), there were 114 (9%) deaths in people without depression compared to 25 deaths (14%) in people with depression ($p = 0.04$). Depressed individuals had a 1.5 to 2-fold increased odds of all-cause mortality, also after adjustment for sex, age and cardiovascular disease history (Table 2). The survival curves for both groups also differed significantly (log-rank test $X^2(1) = 4.64$, $p = 0.03$), where people with depression had a shorter mean time to event than those without depression (1,886, 95% CI 1,870 – 1,902 vs. 1,825, 95% CI 1,767 – 1,882 days; Figure 1b). Again, the proportional hazards assumption was satisfied (correlation between Schoenfeld residuals and ranked survival time $r = -0.09$, $p = 0.30$).

Table 1 Baseline demographic and clinical characteristics (n=1,465), stratified by EDS total score

	N missing	Total (n = 1,465)	EDS score < 12 (n = 1,283)	EDS score ≥ 12 (n = 182)	*P* value
Demographics					
Female sex	0	51% (743/1465)	49% (622/1283)	67% (121/182)	<0.001
Age, years	0	67 ± 10	67 ± 10	67 ± 10	0.88
Non-western ethnicity	17	2% (32/1448)	2% (21/1267)	6% (11/181)	<0.001
Low educational level	65	64% (889/1400)	62% (757/1229)	77% (132/171)	<0.001
Being single	15	24% (342/1450)	23% (287/1270)	31% (55/180)	0.02
Medical history					
Cardiovascular disease	26	33% (478/1439)	33% (411/1259)	37% (67/180)	0.22
Myocardial infarction	29	11% (160/1436)	11% (139/1255)	12% (21/181)	0.83
Bypass / angioplasty	23	13% (190/1442)	13% (162/1261)	16% (28/181)	0.33
Stroke	23	7% (97/1442)	6% (81/1261)	9% (16/181)	0.23
Arterial disease	31	21% (306/1434)	21% (264/1254)	23% (42/180)	0.49
Microvascular disease	386	33% (358/1079)	32% (308/951)	39% (50/128)	0.13
Retinopathy	397	5% (54/1068)	5% (46/944)	7% (8/124)	0.45
Micro- and / or macroalbuminuria	186	25% (321/1279)	25% (277/1121)	28% (44/158)	0.39
Other chronic conditions	18	48% (699/1447)	47% (592/1266)	59% (107/181)	0.002
Kidney disease	31	3% (49/1434)	3% (43/1253)	3% (6/181)	0.94
Asthma / COPD	25	12% (177/1440)	11% (144/1260)	18% (33/180)	0.008
Cancer	29	9% (133/1436)	9% (112/1256)	12% (21/180)	0.23
Arthrosis	19	32% (466/1446)	31% (390/1265)	42% (76/181)	0.003
Rheumatoid arthritis	22	7% (102/1443)	7% (82/1261)	11% (20/182)	0.03
Clinical values					
Hyperglycemia treatment	0				0.16
Lifestyle only		25% (368/1465)	26% (329/1283)	21% (39/182)	
Oral agents, without insulin		70% (1021/1465)	70% (892/1283)	71% (129/182)	
Insulin (with or without oral agents)		5% (76/1465)	5% (62/1283)	8% (14/182)	
Diabetes duration ≥ 3 years	17	60% (870/1448)	60% (756/1268)	63% (114/180)	0.34
HbA_{1c}, % (mmol / mol)	26	6.7 ± 0.8 (50 ± 9)	6.7 ± 0.8 (50 ± 9)	6.7 ± 0.8 (49 ± 9)	0.75
Fasting glucose (mmol / l)	26	7.1 ± 1.6	7.2 ± 1.6	7.0 ± 1.5	0.20
Body Mass Index (kg / m^2)	116	28.8 ± 4.7	28.8 ± 4.6	29.0 ± 5.0	0.56
Total cholesterol (mmol / l)	60	4.5 ± 1.0	4.5 ± 1.0	4.5 ± 1.1	0.75
LDL cholesterol (mmol / l)	84	2.6 ± 0.8	2.6 ± 0.8	2.5 ± 0.8	0.75
HDL cholesterol (mmol / l)	86	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.3	0.75
Systolic blood pressure (mmHg)	59	141.7 ± 18.4	141.9 ± 18.4	140.2 ± 18.1	0.25
Diastolic blood pressure (mmHg)	59	78.1 ± 9.5	78.2 ± 9.4	77.7 ± 9.8	0.55
Health behaviors					
"Active" physical activity	5	85% (1237/1460)	86% (1103/1279)	74% (134/181)	<0.001
"Sportive" physical activity	21	32% (465/1444)	33% (416/1265)	27% (49/179)	0.14
Current smoking	4	14% (211/1461)	14% (174/1280)	20% (37/181)	0.01
Alcohol consumption	10	8% (116/1455)	9% (108/1274)	4% (8/181)	0.06

Values are mean ± standard deviation, unless otherwise specified; COPD = chronic obstructive pulmonary disease

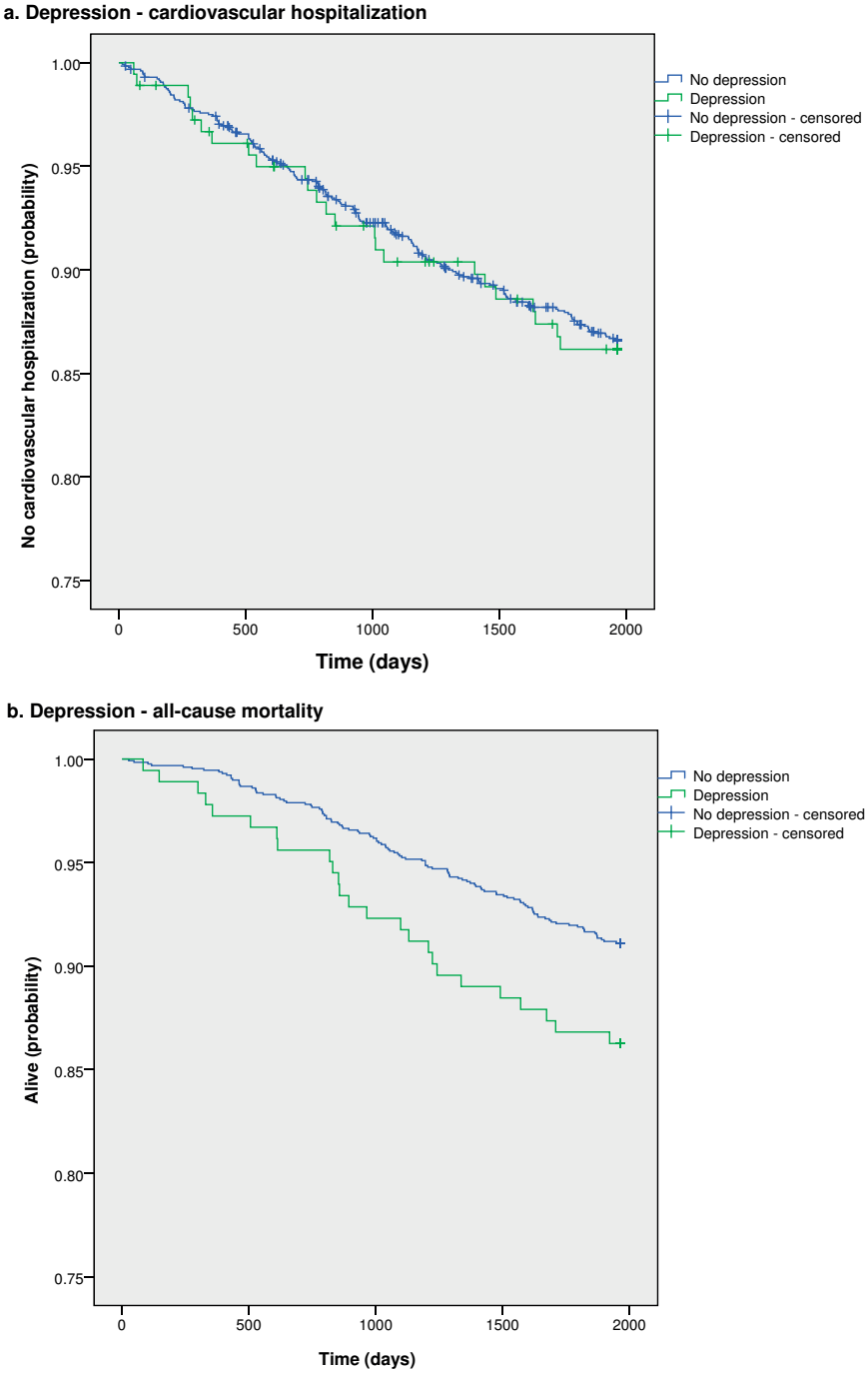

Figure 1 Kaplan-Meier curves EDS score < 12 vs. EDS score ≥ 12

Table 2 Number of deaths and number of people hospitalized for a cardiovascular event during follow-up, stratified by depression

	Total	EDS score < 12 (n = 1,283)	EDS score ≥ 12 (n = 182)	*P* value	Unadjusted OR (95% CI)	Adjusted [a] OR (95% CI)
All-cause mortality	10% (139/1465)	9% (114/1283)	14% (25/182)	0.04	1.63 (1.03-2.60)	1.92 (1.16-3.20)
Any cardiovascular hospitalization	13% (191/1465)	13% (167/1283)	13% (24/182)	0.95	1.02 (0.64-1.61)	0.98 (0.61-1.59)
Cardiovascular hospitalization during follow-up [c]						
Heart disease	10% (148/1465)	10% (131/1283)	9% (17/182)	0.72	[b]	[b]
Acute myocardial infarction	2% (24/1465)	2% (22/1283)	1% (2/182)	0.76	[b]	[b]
Intermediate coronary syndrome	3% (41/1465)	3% (35/1283)	3% (6/182)	0.66	[b]	[b]
Other and unspecified angina pectoris	3% (36/1465)	2% (28/1283)	4% (8/182)	0.08	[b]	[b]
Coronary atherosclerosis	4% (57/1465)	4% (52/1283)	3% (5/182)	0.39	[b]	[b]
Other specified forms of chronic ischemic heart disease	0.1% (1/1465)	0.1% (1/1283)	0% (0/182)	1.00	[b]	[b]
Heart failure	3% (48/1465)	3% (42/1283)	3% (6/182)	0.99	[b]	[b]
Event related to brain	2% (35/1465)	2% (29/1283)	3% (6/182)	0.43	[b]	[b]
Peripheral arterial disease	1% (20/1465)	1% (18/1283)	1% (2/182)	1.00	[b]	[b]

OR = odds ratio. [a] Adjusted for sex, age and history of cardiovascular disease (no / yes); [b] Logistic regression could not be run due to low number of people with events in depression group; [c] List of conditions included in the composite cardiovascular disease hospitalization end point can be found in Online Appendix Table 1

At any given time during the follow-up period, depressed individuals had a 1.6-fold increased risk to die compared to their non-depressed counterparts (95% CI 1.04 – 2.47, p = 0.03). Although sex and age were identified as meaningful confounders (Table 3), the association between depression and survival time remained significant after their individual influences were taken into account. However, the association was no longer significant when adjusting for educational level (HR = 1.55, 95% CI 0.98 – 2.44, p = 0.06), marital status (HR = 1.54, 95% CI 1.00 – 2.38, p = 0.05), the presence of microvascular disease (HR = 1.53, 95% CI 0.89 – 2.62, p = 0.12) or a history of non-cardiovascular chronic medical conditions (HR = 1.49, 95% CI 0.97 – 2.31, p = 0.07). When entering all meaningful confounders at the same time in a multivariable Cox regression analysis, depression was significantly associated with survival time (HR = 1.93, 95% CI 1.10 – 3.41, p = 0.02).

Table 3 Percent change in the regression coefficient for depression in the association with time to cardiovascular hospitalization and survival time, after adjustment for potential confounders

	Depressive symptoms (dichotomous)		Dysphoria (dichotomous)		Anhedonia (dichotomous)		Anxiety (dichotomous)	
	CVD	MORT	CVD	MORT	CVD	MORT	CVD	MORT
Demographics								
Female sex	+71.1%	+17.4%	+9.6%	+32.6%	+9.1%	10.9%	-8.4%	+34.0%
Age, years	+89.5%	+11.5%	+5.8%	+3.7%	-14.3%	-10.0%	-0.8%	+11.9%
Low educational level	+690.0%	-10.8%	-18.6%	-24.8%	-22.8%	-7.6%	+13.3%	-15.0%
Being single	+300.0%	-12.0%	-10.3%	-41.9%	-11.7%	-13.6%	0%	-1.1%
Medical history								
Cardiovascular disease	-69.8%	-6.3%	-4.7%	-11.2%	-32.6%	-8.3%	-8.9%	+7.4%
Microvascular disease	+361.5%	-12.2%	-12.8%	-34.9%	-136.4%	-5.7%	-4.7%	+6.3%
Other chronic conditions	-48.8%	-15.2%	-6.5%	-33.6%	-2.6%	-4.8%	+1.6%	-9.8%
Diabetes duration ≥ 3 years	-100.0%	-3.7%	-2.3%	-8.3%	-7.4%	-8.0%	-1.1%	+3.3%
Dysphoria	-	-	-	-	-56.2%	-2.3%	+72.5%	-22.1%
Anhedonia	-	-	-10.8%	-86.1%	-	-	+17.5%	-36.4%
Anxiety	-	-	+49.9%	-37.1%	+24.9%	-6.5%	-	-

Ethnicity was not examined as a potential confouder, as only four people in the non-western group had a cardiovascular hospitalization and none died; CVD = hospitalization for cardiovascular disease; MORT = all-cause mortality

Symptom clusters

All symptom clusters were significantly correlated, with Pearson's r = 0.54 for dysphoria and anhedonia, 0.59 for dysphoria and anxiety and 0.32 for anhedonia and anxiety (all p < 0.001). A high dysphoria score was present in 13% (n = 188), anhedonia in 12% (n = 170) and anxiety in 10% (n = 152) of the participants. While the majority reported symptoms from only one category (n = 211), 131 individuals experienced symptoms from two or three clusters.

People with a high dysphoria score were significantly more likely to be hospitalized for cardiovascular disease, compared to their counterparts with low dysphoria symptoms (Table 4). Dysphoria remained significantly associated with increased odds of being hospitalized for a cardiovascular condition after adjustment for symptoms of anhedonia and anxiety, sex, age and cardiovascular disease history. Although no significant univariable association was found, anxiety was associated with 0.48-fold decreased odds of cardiovascular hospitalization in the multivariable model. Anhedonia was the only dimension of depression that predicted all-cause mortality, in both unadjusted and adjusted analyses.

After inspection of the Kaplan-Meier curves for cardiovascular hospitalization and all-cause mortality (Figure 2 a – f) and examination of the correlation between the Schoenfeld residuals and ranked survival time (with *r* ranging between -0.09 and 0.01, all non-significant), the proportional hazards assumption was verified for all three symptom clusters. There was no difference in time to first cardiovascular hospitalization during follow-up between people with and without anhedonia or between people with and without anxiety (Figure 2 a, c, e), but individuals reporting high dysphoria did have a shorter mean time to event than those without high dysphoria (1,758 [95% CI 1,687 – 1,830] vs. 1,831 [95% CI 1,809 – 1,853] days). When adjusting for the other two symptom clusters, similar results were found for dysphoria (HR = 1.73, 95% CI 1.12 – 2.66, $p = 0.01$) and anhedonia (HR = 1.15, 95% CI 0.73 – 1.79, $p = 0.55$). However, the association between anxiety and time to cardiovascular hospitalization became significant (HR = 0.52, 95% CI 0.29 – 0.92, $p = 0.03$). After adjustment for all meaningful confounding factors (Table 3), neither anhedonia (HR = 0.83, 95% CI 0.47 – 1.48, $p = 0.53$) nor dysphoria (HR = 1.55, 95% CI 0.91 – 2.64, $p = 0.11$) were significantly associated with time to cardiovascular hospitalization. Anxiety did remain associated with a longer time to cardiovascular hospitalization (HR = 0.49, 95% CI 0.27 – 0.89, $p = 0.02$).

With respect to all-cause mortality, only anhedonia was significantly associated with survival time in univariable analysis (Figure 2 b, d, f). People with a high score on the subscale measuring anhedonia had a shorter mean time to event (1,823 days, 95% CI 1,763 – 1,882) than those with low anhedonia-scores (1,886 days, 95% CI 1,870 – 1,901). Anhedonia remained a significant predictor of survival time (HR = 1.78, 95% CI 1.11 – 2.84, $p = 0.02$), after adjustment for symptoms of anxiety (HR = 1.26, 95% CI 0.74 – 2.15, $p = 0.40$) and dysphoria (HR = 0.96, 95% CI 0.56 – 1.64, $p = 0.87$). Controlling for meaningful confounding factors (Table 3) attenuated the HR for anhedonia only slightly (HR = 1.72, 95% CI 1.11 – 2.65, $p = 0.02$). In these multivariable models, no significant association was found for anxiety (HR = 1.44, 95% CI 0.83 – 2.51, $p = 0.20$) or dysphoria (HR = 0.61, 95% CI 0.30 – 1.24, $p = 0.17$).

Table 4 Number of deaths and number of people hospitalized for a cardiovascular event during follow-up, stratified by dysphoria, anhedonia and anxiety

	Low EDS subscale score	High EDS subscale score	P value	Unadjusted OR (95% CI)	Adjusted [a] OR (95% CI)
Dysphoria					
Any cardiovascular hospitalization	12% (158/1277)	18% (33/188)	0.049	1.51 (1.00-2.27)	1.91 (1.15-3.15)
All-cause mortality	9% (117/1277)	12% (22/188)	0.27	1.31 (0.81-2.13)	0.97 (0.52-1.80)
Anhedonia					
Any cardiovascular hospitalization	13% (164/1295)	16% (27/170)	0.24	1.30 (0.84-2.03)	1.01(0.61-1.67)
All-cause mortality	9% (113/1295)	15% (26/170)	0.006	1.89 (1.19-2.99)	1.84 (1.07-3.17)
Anxiety					
Any cardiovascular hospitalization	14% (177/1313)	9% (14/152)	0.14	0.65 (0.37-1.15)	0.48 (0.25-0.91)
All-cause mortality	9% (120/1313)	13% (19/152)	0.18	1.42 (0.85-2.38)	1.51 (0.81-2.82)

[a] Adjusted for sex, age, history of cardiovascular disease, and the other two symptom clusters

Mediating mechanisms

When examining the association between depression (EDS score ≥ 12) and all-cause mortality (Table 5), only "active" physical activity met both criterion 1 (depression had to be associated with the mediator) and criterion 3 (the mediator had to be associated with survival time, adjusted for depression) of the mediation model. Adjustment for active physical activity reduced the strength of the association between depression and survival time by almost 15% (adjusted HR = 1.38, 95% CI 0.89 – 2.14, p = 0.15). Addition of physical activity to the confounder-adjusted model for depression showed similar results (adjusted HR = 1.58, 95% CI 0.89 – 2.82, p = 0.12, reduction in HR of 18%). With respect to the symptom clusters, none of the selected pathophysiological and behavioral factors qualified as a mediator for the (adjusted) association between anxiety and time to cardiovascular hospitalization. For the association between anhedonia and all-cause mortality, both measures of physical activity met the criteria for mediation. While active physical activity changed the strength of the association between anhedonia and survival time by 23% (adjusted HR = 1.42, 95% CI 0.92 – 2.20, p = 0.12), adjustment for sportive physical activity only resulted in a 6% lower and still significant HR for anhedonia (1.77, 95% CI 1.15 – 2.71, p = 0.009). Repeating the mediation analysis for the confounder-adjusted anhedonia model resulted in a 19% reduction in effect size when active physical activity was added to the model (HR = 1.41, 95% CI 0.90 – 2.20, p = 0.14).

DISCUSSION

In a sample of 1,465 people with type 2 diabetes, depression (defined as a high level of depressive symptoms) was not associated with time to cardiovascular hospitalization over a follow-up period of five-and-a-half years, but did predict survival time. After adjustment for demographic and clinical confounders, depressed individuals still had an almost 2-fold increased risk to die from all-causes at any moment during follow-up compared to their non-depressed counterparts. With regard to different symptoms of depression, symptom clusters focusing on negative emotions predicted time to first cardiovascular hospitalization during follow-up. Dysphoria was associated with a shorter time to event, but this relation was no longer significant after taking confounding factors into account. The presence of anxiety symptoms was associated with a longer time to event, but only when adjusting for confounders. Reduced positive affect (anhedonia) was consistently associated with shorter time to death of all-causes. Mild to moderate physical activity was identified as a mediating mechanism in the association of depression in general and anhedonia, with survival time.

Previous studies have shown that depression is implicated in the onset or progression of cardiovascular conditions in healthy individuals [31] and people with established heart disease [44].

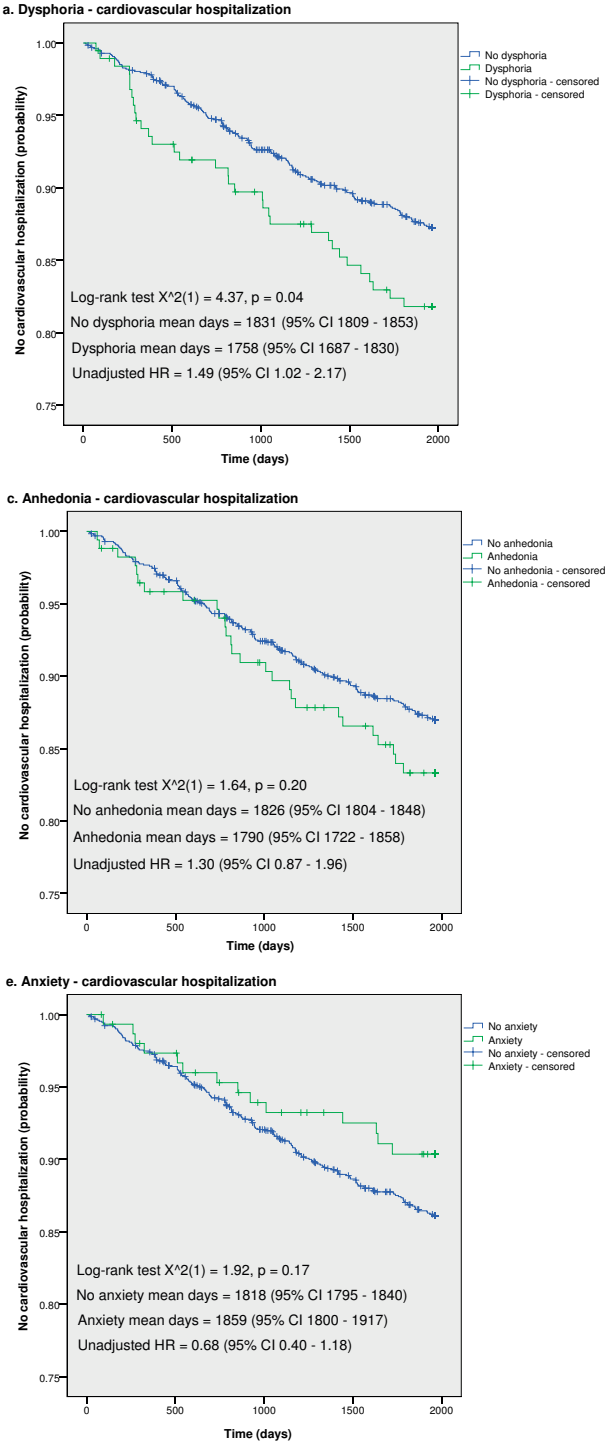

Figure 2 Kaplan-Meier curves low vs. high dysphoria, anhedonia, anxiety

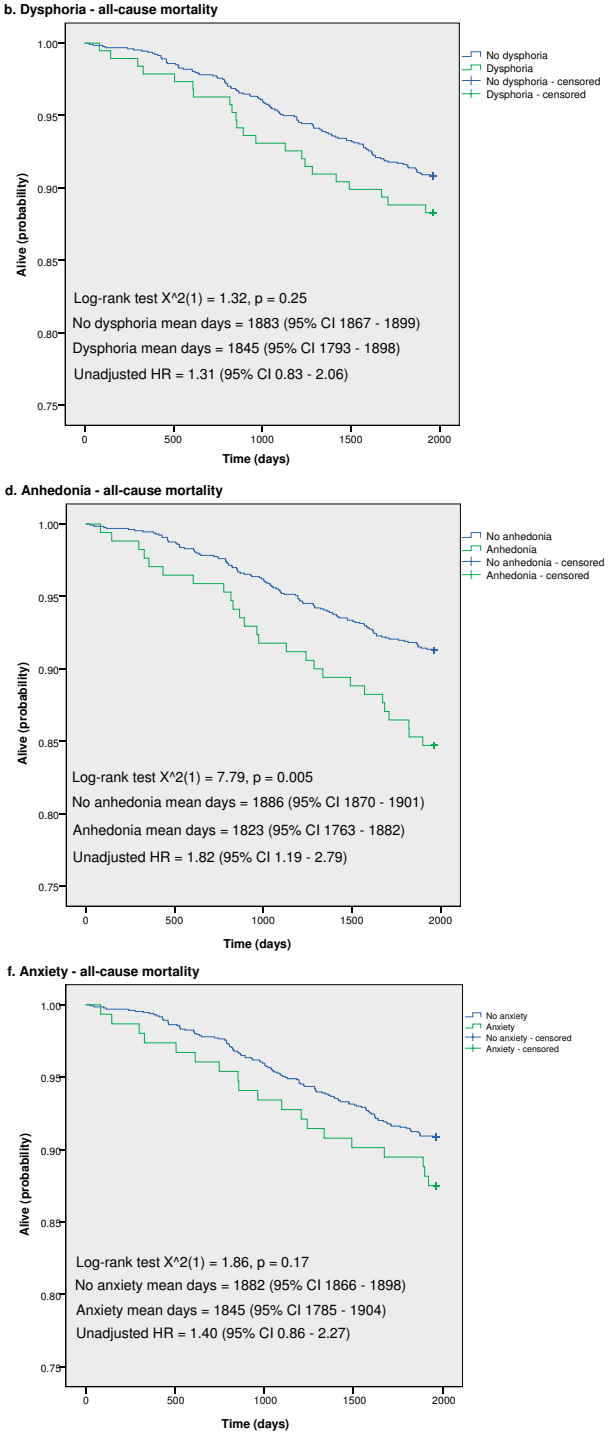

Figure 2 (continued) Kaplan-Meier curves low vs. high dysphoria, anhedonia, anxiety

Table 5 Criteria 1 and 3 of the mediation model, and percent change in the strength of the association (HR) between EDS subscales and outcome measures, after adjustment for potential mediators

	Step 1 [a] OR (95% CI), *p* value – or – B, *p* value	Step 3 [b] (HR)	HR (95% CI, *p*-value) before adjustment	HR (95% CI, *p*-value) after adjustment	Change in HR (%)
Depression (EDS ≥ 12) & mortality					
Alcohol intake	0.50 (0.24-1.04), *p*=0.06	0.93 (0.49-1.76), *p*=0.82	1.616 (1.048-2.492), *p*=0.03	1.611 (1.044-2.486), *p*=0.03	-0.3%
Smoking	1.63 (1.10-2.42), *p*=0.02	1.47 (0.97-2.22), *p*=0.07	1.608 (1.043-2.479), *p*=0.03	1.553 (1.006-2.400), *p*=0.047	-3.4%
"Active" physical activity	0.46 (0.32-0.66), *p*<0.001	0.32 (0.22-0.46), *p*<0.001	1.622 (1.052-2.502), *p*=0.03	1.381 (0.892-2.139), *p*=0.15	-14.9%
"Sportive" physical activity	0.77 (0.54-1.09), *p*=0.14	0.40 (0.25-0.63), *p*<0.001	1.652 (1.071-2.550), *p*=0.02	1.587 (1.028-2.450), *p*=0.04	-3.9%
Body Mass Index	0.23, *p*=0.56	0.94 (0.90-0.99), *p*=0.009	1.494 (0.924-2.414), *p*=0.10	1.518 (0.939-2.453), *p*=0.09	+1.6%
Fasting glucose	-0.16, *p*=0.20	0.78 (0.69-0.88), *p*<0.001	1.659 (1.075-2.560), *p*=0.02	1.643 (1.064-2.535), *p*=0.03	-1.0%
HbA_{1c}	-0.02, *p*=0.75	1.15 (0.97-1.36), *p*=0.11	1.647 (1.067-2.542), *p*=0.02	1.655 (1.072-2.554), *p*=0.02	+0.5%
Total cholesterol	0.03, *p*=0.75	0.89 (0.74-1.06), *p*=0.18	1.671 (1.073-2.604), *p*=0.02	1.670 (1.072-2.601), *p*=0.02	-0.1%
HDL cholesterol	0.009, *p*=0.75	1.00 (0.61-1.64), *p*=0.98	1.653 (1.052-2.598), *p*=0.03	1.653 (1.052-2.598), *p*=0.03	0%
LDL cholesterol	-0.02, *p*=0.75	0.90 (0.73-1.12), *p*=0.34	1.612 (1.026-2.531), *p*=0.04	1.606 (1.022-2.521), *p*=0.04	-0.4%
Systolic blood pressure	-1.72, *p*=0.25	1.00 (0.99-1.01), *p*=0.86	1.626 (1.046-2.528), *p*=0.03	1.624 (1.045-2.526), *p*=0.03	-0.1%
Diastolic blood pressure	-0.47, *p*=0.55	0.96 (0.94-0.98), *p*<0.001	1.638 (1.054-2.546), *p*=0.03	1.601 (1.029-2.489), *p*=0.04	-2.3%
Anxiety & cardiovascular hospitalization [c]					
Alcohol intake	0.53 (0.24-1.16), *p*=0.11	0.89 (0.52-1.53), *p*=0.67	0.490 (0.269-0.892), *p*=0.02	0.491 (0.269-0.893), *p*=0.02	+0.2%
Smoking	1.39 (0.90-2.16), *p*=0.14	0.96 (0.64-1.46), *p*=0.86	0.489 (0.269-0.890), *p*=0.02	0.490 (0.269-0.892), *p*=0.02	+0.2%
"Active" physical activity	0.64 (0.42-0.98), *p*=0.04	0.79 (0.54-1.15), *p*=0.21	0.491 (0.270-0.893), *p*=0.02	0.491 (0.270-0.893), *p*=0.02	0%
"Sportive" physical activity	1.14 (0.80-1.63), *p*=0.46	0.78 (0.56-1.07), *p*=0.12	0.493 (0.271-0.898), *p*=0.02	0.499 (0.274-0.909), *p*=0.02	+1.2%
Body Mass Index	0.12, *p*=0.78	0.98 (0.95-1.02), *p*=0.33	0.486 (0.255-0.928), *p*=0.03	0.486 (0.255-0.927), *p*=0.03	0%
Fasting glucose	-0.10, *p*=0.47	0.99 (0.90-1.08), *p*=0.78	0.505 (0.278-0.919), *p*=0.03	0.505 (0.277-0.919), *p*=0.03	0%
HbA_{1c}	-0.01, *p*=0.87	1.07 (0.91-1.25), *p*=0.43	0.493 (0.271-0.899), *p*=0.02	0.492 (0.270-0.897), *p*=0.02	-0.2%
Total cholesterol	0.10, *p*=0.26	0.79 (0.68-0.92), *p*=0.003	0.455 (0.244-0.847), *p*=0.01	0.445 (0.239-0.829), *p*=0.01	-2.2%
HDL cholesterol	0.04, *p*=0.26	0.68 (0.43-1.05), *p*=0.08	0.434 (0.228-0.829), *p*=0.01	0.441 (0.231-0.842), *p*=0.01	+1.6%
LDL cholesterol	0.05, *p*=0.50	0.82 (0.69-0.99), *p*=0.04	0.424 (0.222-0.809), *p*=0.009	0.417 (0.219-0.797), *p*=0.008	-1.7%
Systolic blood pressure	0.72, *p*=0.66	1.01 (1.01-1.02), *p*=0.009	0.439 (0.231-0.833), *p*=0.01	0.419 (0.220-0.797), *p*=0.008	-4.6%
Diastolic blood pressure	-0.43, *p*=0.61	0.97 (0.95-0.98), *p*<0.001	0.441 (0.233-0.837), *p*=0.01	0.434 (0.229-0.823), *p*=0.01	-1.6%

Table 5 (continued)

	Step 1 [a] OR (95% CI), *p* value – or – B, *p* value	Step 3 [b] (HR)	HR (95% CI, *p*-value) before adjustment	HR (95% CI, *p*-value) after adjustment	Change in HR (%)
Anhedonia & mortality					
Alcohol intake	0.79 (0.42-1.50), *p*=0.47	0.91 (0.48-1.74), *p*=0.78	1.848 (1.206-2.832), *p*=0.005	1.846 (1.204-2.828), *p*=0.005	-0.1%
Smoking	1.52 (1.01-2.29), *p*=0.047	1.47 (0.97-2.22), *p*=0.07	1.826 (1.192-2.797), *p*=0.006	1.777 (1.158-2.725), *p*=0.008	-2.7%
"Active" physical activity	0.31 (0.22-0.45), *p*<0.001	0.33 (0.23-0.47), *p*<0.001	1.842 (1.203-2.823), *p*=0.005	1.422 (0.918-2.202), *p*=0.12	-22.8%
"Sportive" physical activity	0.66 (0.45-0.95), *p*=0.03	0.40 (0.26-0.64), *p*<0.001	1.878 (1.225-2.879), *p*=0.004	1.767 (1.152-2.712), *p*=0.009	-5.9%
Body Mass Index	-0.03, *p*=0.93	0.95 (0.91-0.99), *p*=0.01	1.571 (0.972-2.539), *p*=0.07	1.551 (0.959-2.508), *p*=0.07	-1.3%
Fasting glucose	0.14, *p*=0.27	0.78 (0.68-0.88), *p*<0.001	1.773 (1.149-2.737), *p*=0.01	1.848 (1.197-2.853), *p*=0.006	+4.2%
HbA_{1c}	0.18, *p*=0.01	1.12 (0.95-1.33), *p*=0.18	1.773 (1.149-2.737), *p*=0.01	1.728 (1.117-2.673), *p*=0.01	-2.5%
Total cholesterol	0.002, *p*=0.98	0.89 (0.74-1.06), *p*=0.19	1.749 (1.114-2.745), *p*=0.02	1.747 (1.113-2.741), *p*=0.02	-0.1%
HDL cholesterol	-0.004, *p*=0.90	1.00 (0.61-1.64), *p*=1.00	1.692 (1.068-2.680), *p*=0.03	1.692 (1.068-2.680), *p*=0.03	0%
LDL cholesterol	-0.09, *p*=0.21	0.91 (0.73-1.12), *p*=0.37	1.687 (1.066-2.671), *p*=0.03	1.672 (1.056-2.647), *p*=0.03	-0.9%
Systolic blood pressure	-0.10, *p*=0.95	1.00 (0.99-1.01), *p*=0.81	1.717 (1.105-2.669), *p*=0.02	1.718 (1.105-2.671), *p*=0.02	+0.1%
Diastolic blood pressure	0.32, *p*=0.69	0.96 (0.94-0.98), *p*<0.001	1.717 (1.105-2.669), *p*=0.02	1.725 (1.110-2.682, *p*=0.02	+0.5%

[a] Regressing the mediator on the independent variable; [b] Regressing the dependent variable on the mediator, controlled for the independent variable; [c] For the association between anxiety and cardiovascular hospitalization, the confounder-adjusted model was used to calculate the percent change in the effect size

While ours is not the first study that did not confirm a positive assocation between depression and the development of cardiovascular disease in people with type 2 diabetes [45], other studies do provide evidence for this link [8, 10]. Differences in study population and methodology may help to explain some discrepancies in findings. For example, apart from diverging length of follow-up and confounder adjustment, we studied a predominantly white-western population who were treated in primary care practices and were in relatively good health. In addition, we identified cardiovascular events by using diagnostic codes linked to hospitalizations, while other studies have relied on medical record review and death certificate data [10] or self-report [8]. By relying on hospital data only, we may have missed fatal cardiovascular events outside the hospital or cardiovascular events for which hospital admission (more than 24 hours or less than 24 hours for which a bed is required) was not necessary. Previous work has focused mostly on composite endpoints including advanced cardiovascular disease, such as a combination of cardio- and cerebrovacular disease [8, 45] or a more comprehensive combination of myocardial infarction, stroke, congestive heart failure, cardiovascular procedures, revascularization of the lower extremities and deaths due to coronary, cerebrovascular, or peripheral arterial disease [10]. Apart from these "more advanced" events, we also included "milder" diagnoses such as transient ischemic attacks and angina pectoris that were serious enough to warrant hospital admission. Using a composite end point to capture the development of cardiovascular disease may increase the event rate and thus reduce sample size requirements, but can be difficult to interpret [46]. The magnitude of the association may differ markedly across individual components of composite cardiovascular outcomes, and results may be misleading if most events belong to a certain category [46]. The number of people with specific cardiovascular hospitalizations was too small to examine the association between depression and specific CVD outcomes, such as "acute" and more chronic cardiac conditions, peripheral arterial disease and atherosclerotic processes affecting the brain. Preliminary findings from a small study among women with diabetes suggested that the development of coronary heart disease was significantly more rapid in participants with depression, but depression did not predict the development of clinically apparent peripheral or cerebrovascular disease [9]. However, these results need to be interpreted with caution, as the analyses may have been unstable due to small sample sizes and numbers of outcome events [9]. A study among more than 300,000 people free of cardiovascular disease at baseline concluded that people with type 2 diabetes alone and people with major depression alone were at approximately 30% increased risk for MI, while people with both type 2 diabetes and major depression were at 82% increased risk for MI [13].

In line with previous studies in the general population [47], people with established heart disease [44], and people with diabetes [7], we did see a clear association between depression and all-cause mortality, even when confounders such as sex, age and co-morbidities were

taken into account. It is hard to interpret these findings, as the cause of death was unknown. Premature cardiovascular and microvacular conditions represent the most common cause of morbidity and mortality in people with diabetes [48], but diabetes is associated with a higher risk of death for many diseases, including several specific forms of cancer [49]. Likewise, depression is a risk factor for all major disease-related causes of death [50]. While depression has been associated with cardiovascular mortality in people with diabetes in some but not all studies [7], it may also play a role in deaths not caused by cancer or atherosclerotic cardiovascular disease [51].

When examining the potential role of specific symptom clusters (anxiety, anhedonia, and dysphoria), only anhedonia was consistently associated with survival time, but not with time to first cardiovascular hospitalization during follow-up. Even though these findings are preliminary, similar relations with all-cause mortality have been found in a community sample of older adults [22] and people with diabetes [27], even after adjustment for negative emotions. A population-based study among older adults also found an inverse association between positive affect and the incidence of stroke [21]. Research in people with established cardiovascular disease also suggests an association of anhedonia with adverse clinical outcomes [23-25]. However, these studies have used composite endpoints including both mortality and major adverse cardiac events and therefore, it is hard to disentangle whether the association with anhedonia holds for mortality only or also for the development of cardiovascular disease in these groups. When anhedonia, dysphoria and anxiety were considered simultaneously, only the two measures of negative affect showed an association with time to cardiovascular hospitalization. After including meaningful confounders in the model, the association for dysphoria was no longer significant. Research examining the association between anxiety and health is scarce. In the present study, anxiety was associated with a longer time to cardiovascular event, while studies in healthy individuals and people with established heart disease have suggested the opposite [52, 53]. However, depending on the individual, anxiety can either operate as a health-promoting factor by increasing the number of health visits or as a health-compromising factor by promoting more avoidant coping strategies [54, 55].

The association between depression in general and anhedonia, and subsequent all-cause mortality was largely explained by physical inactivity, in particular relating to daily activities of mild to moderate intensity. Interestingly, none of the pathophysiological cardiovascular risk factors appeared to play a mediating role. Likewise, in the Heart and Soul Study, a cohort of more than 1,000 people with stable coronary heart disease, the association between depressive symptoms and a composite cardiovascular outcome measure (heart failure, myocardial infarction, stroke, transient ischemic attack and death) was also largely explained

by physical activity, while a range of pathophysiological factors (heart rate variability, norepinephrine and cortisol excretion, serotonin levels, C-reactive protein level, and levels of omega-3 fatty acids) only accounted for a small or negligible part of the association [43]. Although mediation was not directly tested, the association between depression and adverse cardiovascular events – including deaths due to coronary, cerebrovascular, or peripheral arterial disease – in people with diabetes was somewhat attenuated after simultaneous addition of body mass index, smoking, limited physical activity and HbA_{1c} [10]. While these factors appeared to be particularly important in cardiovascular-related mortality among persons with diabetes, they did not fully explain the association with all-cause mortality [51]. Other potential mediating mechanisms – not necessarily restricted to cardiovascular disease - may also underlie the link between depression and excess mortality in diabetes [51], including other health behaviors such as medication taking and healthy diet and dysregulations of the hypothalamic-pituitary-adrenal-axis, sympathetic nervous system and inflammation [51, 56].

Research focusing on the associations between symptom clusters or depression subtypes, adverse health outcomes and potential mediating mechanisms is still within its early phases [57]. As for anhedonia, our results suggest that health behaviors – in particular physical activity – are an important element of future research and a target of new interventions. By definition, people with anhedonia display decreased interest and pleasure [19], elements that may tap into motivation for diabetes self-care. Anhedonia has been related to dysfunctions of the brain reward system and is usually characterized by an impaired responsiveness to rewarding stimuli [58]. It may be that anhedonic individuals are less likely to experience satisfaction or pleasure from achieving or maintaining optimal diabetes self-management, and may therefore be less likely to engage in these self-care behaviors [59]. The biological correlates of positive affect are only beginning to be described, but pathophysiological pathways may include the autonomic nervous system, the hypothalamus-pituitary-adrenal axis and the immune system [60].

Distinguishing between symptoms of dysphoria and anhedonia appears to be a promising avenue for future research examining the heterogeneity of depression, but there might be more. Although current findings are inconsistent, risk stratification based on persistence / recurrence and timing of onset of depressive symptoms has been marked a promising line of research in the field of cardiac psychology [18]. In the present study, we focused on the predictive power of baseline anhedonia and dysphoria, irrespective of the course pattern of these symptoms. It makes sense to expect a greater health risk for those being exposed to depression over longer periods of time. However, it is also very well possible that depression is a factor predisposing an individual to the onset of vascular complications, without being the factor that maintains the development of these conditions once the

relevant pathophysiological processes have been activated [57]. Other potentially relevant classifications include "cognitive" versus "somatic" symptoms of depression and depression subtypes such as melancholic and atypical depression [18, 59].

Apart from those already mentioned, several study limitations need to be acknowledged. First, dysphoria and anhedonia were derived from a self-report questionnaire measuring depressive symptoms and not based on a diagnostic psychiatric interview, which is considered the gold standard. Second, depressive symptoms and the potential behavioral and pathophysiological mediating factors were measured at the same point in time. Therefore, we cannot rule out the possibility that depression was caused by these factors or that they changed over the follow-up period. Strengths of the study include the large sample of people with type 2 diabetes, the longitudinal design, the innovative focus on symptom clusters within depression, the examination of both behavioral and pathophysiological candidate mediators, and our policy to examine cardiovascular hospitalization and all-cause mortality as separate endpoints.

Although both psychotherapeutic and pharmacological intervention strategies appear to be moderately effective in reducing depressive symptoms in people with diabetes [61, 62], compelling evidence showing that the risk of vascular events and mortality can be reduced by treating depression is currently lacking. One randomized controlled trial in depressed older adults with diabetes based in primary care suggested that participation in a depression management program was associated with a decreased 5-year mortality risk (adjusted HR = 0.49, 95% CI 0.24 – 0.98) [63], but this study has been heavily criticized based on methodological grounds [64]. Depression intervention trials in people with established heart disease have not led to lower rates of recurrent cardiovascular events or death either [65].

Our findings add to a growing body of literature demonstrating a link between depression and adverse outcomes in people with diabetes, and suggest that studying different symptom clusters of depression may add to a better understanding of the relationship between depression, cardiovascular disease and mortality. In turn, these findings may have important implications for clinical practice. The treatment studies that have been done have not taken into account that depression is a highly heterogeneous condition and that different symptoms of depression may have diverging effects on (diabetes) prognosis. By tailoring depression treatment to an individual's predominant symptom cluster and related risk profile and by directly targeting the underlying (vasculo)toxic mechanisms, we might optimize our current treatment protocols and not only improve mood, but also diabetes outcomes. For example, preliminary evidence suggests that antidepressants enhancing dopaminergic and noradrenergic activity may offer a therapeutic advantage over serotonergic antidepressants

in the treatment of symptoms associated with low positive affect [20]. In addition, as the behavioral correlates of anhedonia include neglect of pleasurable avocations and social withdrawal [19], a renewal of interest and pleasure in these activities through behavioral activation may be of benefit to daily self-care behavior as well. Interventions that integrate efforts to improve diabetes management with strategies aimed at decreasing depressive symptoms in people with diabetes and co-morbid depression appear to be most promising [61, 62].

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Online Appendix Table 1 Descriptions and ICD-9 diagnostic codes of all conditions included in the composite cardiovascular disease hospitalization end point

Diagnosis	ICD-9 code
HEART	
Acute myocardial infarction	410.xx
Intermediate coronary syndrome	411.1
Other acute and subacute forms of ischemic heart disease	411.8x
Old myocardial infarction	412
Other and unspecified angina pectoris	413.9
Coronary atherosclerosis	414.0x
Chronic total occlusion of coronary artery	414.2
Coronary atherosclerosis due to lipid rich plaque	414.3
Coronary atherosclerosis due to calcified coronary lesion	414.4
Other specified forms of chronic ischemic heart disease	414.8
Chronic ischemic heart disease, unspecified	414.9
Heart failure	428.xx
BRAIN	
Occlusion and stenosis of precerebral arteries	433.xx
Occlusion of cerebral arteries	434.xx
Transient cerebral ischemia	435.xx
Other and ill-defined cerebrovascular disease	437.0, 437.1
PERIPHERAL ARTERIES (LOWER EXTREMETIES)	
Peripheral arterial disease	250.70, 250.72, 440.2x, 440.3x, 440.4, 444.22, 444.81

CHAPTER 8

Type D (distressed) personality in primary care patients with type 2 diabetes: validation and clinical correlates of the DS14 assessment

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ABSTRACT

Objective: In cardiovascular research, Type D personality (high negative affectivity and social inhibition) has been associated with a more than 3-fold increased risk of adverse health outcomes. This study examined the validity and clinical correlates of the Type D construct as assessed by the Type D Scale-14 (DS14) in type 2 diabetes patients.

Methods: 1553 primary care patients with type 2 diabetes were assessed for demographic, clinical, lifestyle and psychological characteristics in 2007. A subgroup (n = 1012) completed the DS14 again 1 year later.

Results: The two-factor model of the Type D construct was confirmed in exploratory and confirmatory factor analyses; results were stable across gender. The Negative Affectivity (NA) and Social Inhibition (SI) subscales had adequate reliability in both men and women, as measured by Cronbach's alpha (NA = 0.87, SI = 0.83), lambda2 (NA = 0.87 / 0.88, SI = 0.84), corrected item-total correlations (NA 0.47 – 0.77, SI 0.34 – 0.72) and mean inter-item correlations (NA = 0.50 / 0.51, SI = 0.42). One year test-retest reliability using intraclass correlation coefficients was 0.64 / 0.63 for NA and 0.73 / 0.65 for SI. Type D and non-Type D patients did not differ in vascular history or physiological risk factors, but Type D women had a more sedentary lifestyle ($p = 0.003$). Type D patients experienced less social support and more stressful life events, loneliness, and more depressed mood, anhedonia and anxiety ($p < 0.001$ for most variables). These differences were clinically significant (Cohen's $d > 0.60$ for most variables).

Conclusion: Type D personality can be reliably assessed in primary care patients with type 2 diabetes, and is associated with increased loneliness, stress and emotional distress in these patients.

INTRODUCTION

Premature cardiovascular and microvascular conditions represent the most common cause of morbidity and mortality in diabetes patients, while these individuals are also frequently confronted with emotional problems, including depression and anxiety [1]. Several recent meta-analyses have demonstrated that negative emotions are implicated in the onset of cardiovascular conditions in healthy subjects [2, 3] and predict adverse cardiac outcomes in patients with established heart disease [2, 4]. Most research has focused on depression, with several studies showing that depressed diabetes patients are at increased risk for the development of micro- and macrovascular complications and mortality as well [5, 6]. Less is known about the risk imposed by more general forms of psychological distress [7].

Recently, the Type D or "distressed" personality has emerged as a risk factor for poor psychological and medical outcomes in cardiovascular [7] and other [8] patient populations. Type D is defined as the combination of two stable personality traits, i.e. "Negative Affectivity" and "Social Inhibition". Individuals with a Type D personality tend to experience negative emotions across time and situations, but are inclined to inhibit self-expression in order to avoid disapproval or rejection by others [9]. While general negative affect has been shown to contribute to cardiovascular risk [10], social inhibition appears to potentiate the adverse effect of negative emotions [11]. Type D personality has been associated with a more than 3-fold increased risk of adverse events, including myocardial infarction, revascularization and (cardiac) death among individuals with cardiovascular disease [7]. Since diabetes is associated with a high risk of cardiovascular complications [12], Type D personality might also predict the risk of cardiovascular conditions in people with diabetes. In other patient populations, Type D personality has also been associated with depression, anxiety and poor mental health [7, 8], and diabetes patients with Type D personality may also represent a group at high risk for long-term emotional distress. However, no studies to date have examined the potential role of Type D personality in patients with diabetes.

The Type D scale (DS14) is a brief self-report measure of Type D personality that has been shown to possess adequate psychometric properties in cardiac patients [9, 13-16], but has not been validated in patients with diabetes. Therefore, the primary aim of the present study was to examine the validity of the Type D personality construct and its assessment in a sample of primary care patients with type 2 diabetes. The second aim was to examine the clinical correlates of the Type D personality construct in this patient population. Based on the literature, we expected that individuals with Type D personality would be more likely to report poor mental health [7, 8, 17] and less likely to engage in adequate self-care activities, particularly in terms of physical activity [18-20]. Previous studies reported inconsistent findings with respect to traditional cardiovascular risk factors. Some studies found that Type D was related to blood pressure, cholesterol levels and obesity [18-20], while other studies have failed to establish this

association [21, 22]. The third aim was to examine whether the Type D personality model would apply across men and women with diabetes [23]. Preliminary evidence suggests that there might be gender differences with respect to the health correlates of Type D personality [18].

METHOD

Participants

The DiaDDZoB (*Dia*betes, *D*epression, Type *D* personality *Z*uid*oo*st-*B*rabant) Study was designed as a prospective cohort study among primary care patients with type 2 diabetes in South-East Brabant, The Netherlands [24]. A total of 2460 patients (82% of those considered for study inclusion) participated in the 2005 baseline assessment, consisting of a nurse-led interview and the completion of a self-report questionnaire. During follow-up waves in 2007 (n = 2225) and 2008 (n = 2032), the DS14 was added to the standard assessment battery. The present sample includes all participants who completed the 14-item Type D scale (DS14) [9] during the 2007 follow-up assessment (n = 1553). The study protocol was approved by the medical research ethics committee of a local hospital, the Máxima Medical Centre in Veldhoven (NL27239.015.09). Written informed consent was obtained from all participants.

Type D personality

Type D personality was assessed using the DS14 [9], consisting of two seven-item subscales of Negative Affectivity (NA) and Social inhibition (SI). The NA dimension comprises three lower-order traits, including dysphoria (items 4, 7, 13), worry (items 2, 12) and irritability (items 5, 9). The SI dimension also includes three lower-order traits: discomfort in social interactions (items 6, 8, 14), reticence (items 10, 11) and social poise (items 1, 3) [9]. Items are scored on a five-point rating scale ranging from 0 (“false”) to 4 (“true”) (total score range 0 – 28 for each subscale). Individuals who obtain a score of ten or more on both scales are classified as Type D [9], with Item Response Theory analyses showing that all items have highest measurement precision around this cut-off and that DS14 measurements are equivalent across the general population and clinical groups [25]. The DS14 has adequate psychometric qualities, is stable over time and is independent of mood and health status [9, 13-16, 21, 26]. In the present study, a total of 1450 participants completed all DS14 items, while an additional 158 patients had 1 to 13 missing values. The distribution of missing responses was fairly equal across all items, ranging from 2% for item 14 “When socializing, I don’t find the right things to talk about” to 3% for item 5 “I am often irritated”. One exception was the first item of the questionnaire “I make contact easily when I meet people”, with only 0.6% not completing this particular item. Total scores on the NA and SI subscales were only calculated when at least 6 out of 7 subscale items were present. For cases with one missing DS14 item on either the NA or SI subscale, the missing value was replaced with the mean of the remaining six subscale items (n = 103), resulting in the final sample size of 1553.

Depression, anhedonia and anxiety

Depressive symptoms during the last 7 days were assessed using the Dutch version of the Edinburgh Depression Scale (EDS) [27], a 10-item self-rating scale in which each item is scored on a four-point scale (total score range 0 – 30, with higher scores indicating higher levels of depressive symptoms). Total EDS scores were calculated for patients completing at least 9 items. The EDS subscales "depressed mood", "anhedonia" and "anxiety" (four, two and three EDS items, respectively) [28] were used as separate measures of emotional distress.

Social support and loneliness

Social support was measured using O'Hara's modified Social Support Scale [29], comprising three items ranging from 0 ("no support at all") to 4 ("extensive support"). A single item was used to measure feelings of loneliness in the past 12 months (ranging from 1 "I never felt lonely" to 10 "I always felt lonely"). Additionally, patients were asked if they had experienced a stressful life event in the previous 12 months (e.g. loss of a loved one, financial problems, physical/mental abuse).

Demographic and clinical characteristics

Sex, age, ethnicity, education level, marital status, cardiovascular disease history, current hyperglycemia treatment, diabetes duration and health behaviors were measured during an interview with the patient by the primary care nurse practitioner or were part of the questionnaire booklet that had to be filled in at home. The results from standard care laboratory tests (including urinary albumin levels, HbA_{1c}, fasting glucose, cholesterol) and physical examinations (blood pressure, body mass index, foot and eye screening) were provided by the Diagnostic Centre Eindhoven, a primary care diagnostic institute [24].

Statistical analyses

Sex differences in demographic, clinical and psychological characteristics in the total sample were examined using X^2 tests (categorical data) and independent samples t-tests (continuous variables). Following a cross-validation design, both men (n = 745) and women (n=808) were randomly divided in two groups of equal size to create separate samples for an exploratory (EFA) and confirmatory factor analysis (CFA): (A) men EFA (n = 372), (B) men CFA (n = 373), (C) women EFA (n = 404), (D) women CFA (n = 404). In groups A and C, exploratory factor analysis with principal axis factor extraction was used to examine the structural validity of the DS14. The decision about the number of factors to retain was guided by the eigenvalues from the unreduced correlation matrix, using the Kaiser-Guttman rule (eigenvalues > 1) and scree plot criterion. As the factors of the DS14 were expected to be moderately correlated [13, 14, 26], oblique rotation of the initial factor solution was applied to facilitate interpretation of the factor structure. Items loading > |0.40| on one factor and < |0.30| on any other factor after rotation were considered to meet criteria for simple structure [30].

In groups B and D, both the factor solution derived from the exploratory factor analysis and the previously defined two-factor structure [9] were tested using confirmatory factor analysis. Maximum likelihood estimation was employed to estimate all models. Although X^2 is frequently used as a goodness-of-fit index to determine overall model fit, this measure often leads to an incorrect rejection of model fit in larger samples [30]. Therefore, additional fit statistics were examined, including the Root Mean Square Error of Approximation (RMSEA, 90% confidence interval), the comparative fit index (CFI) and the Tucker-Lewis index (TLI). Acceptable model fit was defined as RMSEA < 0.08, CFI ≥ 0.90 and TLI ≥ 0.90 [30]. In all models, DS14 factors were allowed to covary; error-terms were correlated based on the previously hypothesized lower order constructs of the two DS14 subscales (Online Appendix Figure 1) [9].

For convenience of data presentation in Table 2, reliability of the DS14 subscales was examined using the data of groups A and C (EFA groups), and included Cronbach's alpha, Guttmans lambda2, mean inter-item correlations and corrected item-total correlations. Optimal values were ≥ 0.80 for Cronbach's alpha, 0.20 – 0.50 for mean inter-item correlations and > 0.20 for item-total correlations [26, 31]. To examine the temporal stability of the Negative Affectivity and Social Inhibition subscales and Type D status (≥ 10 on both subscales) [9], intraclass correlation coefficients using 2-way random effect models and the consistency definition [32, 33] and X^2 tests were calculated. To assess the clinical correlates of Type D personality (defined as a score of ≥ 10 on both the Negative Affectivity and Social Inhibition subscale of the DS14 [9]) in the total sample, demographic, clinical, lifestyle and psychological characteristics of patients with and without Type D personality were compared using X^2 tests (categorical variables) and independent samples t-tests (continuous variables). Cohen's *d* was used as an index of effect size. AMOS 18.0 was used for the confirmatory factor analyses; all other analyses were performed using PASW Statistics 17.0 (IBM SPSS Statistics, Somers, New York). Unless otherwise specified, p-values <0.05 were considered statistically significant.

RESULTS

Sample characteristics

The total sample consisted of 1553 patients (48% male), with a mean age of 68.6 ± 10.2 years (range 33.8 – 101.5), the majority (98%) was Caucasian. Most patients were treated with diet and oral antihyperglycemic agents (n = 1165, 76%) and were in relatively good glycemic control (mean HbA_{1c} 6.8 ± 0.8), with a mean diabetes duration of 6.2 ± 4.9 years. Female participants were slightly older and were more likely to have a low education, no partner and a higher mean BMI (Table 1). Women also reported more loneliness and emotional distress (depressed mood, anhedonia and anxiety) and were more likely to have experienced a stressful life event during the past year. Microalbuminuria and a history of adverse cardiac events were more common in men.

Table 1 Characteristics of the total sample, stratified by gender

	Men (n = 745)	Women (n = 808)	*P* value
Demographics			
Age (years)	67.3 (10.0)	69.8 (10.2)	<0.001
Non-Caucasian	2.2% (16/735)	2.6% (21/801)	0.69
Low educational level	52.6% (319/606)	75.4% (482/639)	<0.001
Being single	16.8% (125/743)	36.0% (290/806)	<0.001
Medical history			
Macrovascular disease			
Myocardial infarction	16.4% (115/700)	9.1% (69/757)	<0.001
Bypass / angioplasty	20.0%(140/701)	10.6% (80/757)	<0.001
Stroke	8.6% (60/699)	7.4% (56/756)	0.47
Arterial disease	33.8% (235/695)	32.8% (248/757)	0.71
Angina pectoris	16.2% (112/691)	11.9% (88/740)	0.02
Microvascular disease			
Retinopathy	4.0% (21/520)	3.0% (15/508)	0.44
Neuropathy	23.7% (154/651)	24.1% (162/671)	
Ischemia	1.5% (10/651)	0.9% (6/671)	
Wounds / ulcers	0.8% (5/651)	0.6% (4/671)	
Excessive coldness	1.4% (9/651)	0.3% (2/671)	0.20
Microalbuminuria [a]	29.4% (151/514)	20.4% (98/480)	
Macroalbuminuria [b]	2.9% (15/514)	2.7% (13/480)	0.004
Clinical values			
Hyperglycemia treatment			
No treatment	0.4% (3/740)	0.8% (6/800)	
Diet only	16.2% (120/740)	13.9% (111/800)	
Diet, oral agents	76.4% (565/740)	75.0% (600/800)	
Diet, oral agents, insulin	6.5% (48/740)	9.0% (72/800)	
Diet, insulin	0.4% (3/740)	1.4% (11/800)	
Other	0.1% (1/740)	0.0% (0/800)	0.06
Diabetes duration (years)	6.2 (4.7)	6.3 (5.0)	0.73
HbA_{1c} (%)	6.7 (0.8)	6.8 (0.8)	0.76
Body Mass Index	28.6 (4.0)	30.5 (5.2)	<0.001
Psychological factors			
Negative Affectivity	5.6 (5.4)	6.5 (5.8)	0.002
Social Inhibition	7.6 (5.5)	8.0 (5.7)	0.19
Type D	13.8% (103/745)	19.9% (161/808)	0.002
Total EDS depression score	5.0 (4.4)	6.9 (5.2)	<0.001
Depressed mood (EDS)	1.1 (1.5)	1.8 (2.0)	<0.001
Anhedonia (EDS)	0.7 (1.3)	1.0 (1.5)	0.001
Anxiety (EDS)	2.4 (1.9)	3.2 (2.1)	<0.001
Social support	7.0 (3.8)	7.9 (3.8)	<0.001
Loneliness	2.3 (1.9)	2.9 (2.1)	<0.001
Stressful life event(s)	26.3% (193/733)	34.2% (271/793)	0.001

All values are mean (standard deviation), unless otherwise specified. Yates' Correction for Continuity was applied in the computation of X^2 for all 2 x 2 tables. [a] Albumin concentration of 20 - 200 mg / l; [b] Albumin concentration of > 200 mg / l

Exploratory factor analysis

Both the Kaiser-Meyer-Olkin measure of sampling adequacy (men 0.90, women 0.91) and Bartlett's test of sphericity ($p < 0.001$) verified the appropriateness of using factor analysis in groups A and C. For men, EFA yielded two factors with initial eigenvalue > 1 (5.9 and 1.8, respectively), accounting for 42% and 13% of the total item variance. The scree plot also indicated a last substantial drop and subsequent leveling of the curve after the second factor, justifying the retention of two factors. After rotation, all NA and SI items loaded between 0.48 and 0.80 on their corresponding factor, with trivial cross-loadings (Table 2). In women, Kaiser's criterion (initial eigenvalues 6.2 and 1.7; 45% and 12% explained variance) and scree plot (marked elbow after the second factor) also indicated a two-factor structure. Inspection of the factor loadings after rotation (Table 2) confirmed the presence of a "Negative Affectivity" and "Social Inhibition" subscale, although item 6 ("I often feel inhibited in social interactions") revealed a significant cross-factor loading (0.44 for NA, 0.38 for SI).

Confirmatory factor analysis

As the two-factor solution derived from the EFA for men was shown to correspond to the DS14 structure described in earlier studies, only the original model was cross-validated using CFA in group B. Fit statistics indicated acceptable or close to acceptable fit, $X^2(66) = 200$, $p < 0.001$, RMSEA 0.07, 0.06 – 0.09, CFI = 0.94 and TLI = 0.92. Unstandardized / standardized parameter estimates and squared multiple correlations can be found in Online Appendix Table 1. All freely estimated regression weights and variances ($p< 0.001$) and the covariances for NA / SI, e2 / e12, e1 / e3 ($p < 0.001$) and e10 / e11 ($p = 0.01$) reached statistical significance. Each DS14 item loaded strongly on its designated factor, with standardized factor loadings ranging from 0.54 to 0.82 for NA and 0.35 to 0.78 for SI. Squared multiple correlations indicated that most items were meaningfully related to their respective DS14 factor (R^2 range 0.29 – 0.68), although explained variance was somewhat lower for item 3 ("I often talk to strangers"; 12%). The correlation between the factors "Negative Affectivity" and "Social Inhibition" was 0.62.

In group D (CFA women), both the original two-factor model [9] and an adjusted model based on EFA results (exclusion of item 6) were tested. The fit indices of the original two-factor model confirmed acceptable fit, with $X^2(66) = 130$, $p < 0.001$, RMSEA 0.05 (0.04 – 0.06), CFI = 0.97 and TLI = 0.96. Although the X^2 difference test ($X^2_{diff}(10) = 19$, $p = 0.04$) indicated a somewhat better fit for the adjusted model (deletion of item 6), fit indices were highly similar (RMSEA = 0.05 (0.04 – 0.06), CFI = 0.97, TLI = 0.96). Therefore, item 6 was retained in the CFA model. Similar to the results in group B, statistical significance among the freely estimated unstandardized parameters was found for all regression weights and variances in the theoretical model (Online Appendix Table 1). In addition to significant results for the covariances between NA / SI, e2 / e12, e1 / e3 and e10 / e11 (all $p < 0.001$), a p value of 0.001 was found for e5 / e9 and e8 / e14. With the exception of item 3 (0.20), all standardized factor loadings were high (range 0.43 – 0.81). Explained variance was promising for the majority of items (R^2 range 0.19 – 0.66), although the value for item 3 (4%) was considerably lower. "Negative Affectivity" and "Social Inhibition" correlated 0.76.

Table 2 Structural validity and reliability of the DS14, stratified by gender

		Men (n = 372)			Women (n = 404)		
		Factor I	Factor II	Corrected item-total correlations	Factor I	Factor II	Corrected item-total correlations
Negative Affectivity							
2	I often make a fuss about unimportant things	**0.55**	-0.07	0.48	**0.52**	-0.05	0.47
4	I often feel unhappy	**0.68**	-0.02	0.63	**0.74**	-0.06	0.64
5	I am often irritated	**0.63**	0.04	0.60	**0.80**	-0.03	0.72
7	I take a gloomy view of things	**0.80**	0.05	0.76	**0.76**	0.05	0.73
9	I am often in a bad mood	**0.69**	0.07	0.66	**0.65**	0.13	0.64
12	I often find myself worrying about something	**0.76**	0.02	0.71	**0.64**	0.10	0.67
13	I am often down in the dumps	**0.77**	0.07	0.73	**0.82**	0.03	0.77
				Cronbach's α = 0.87			Cronbach's α = 0.87
				Lambda2 = 0.87			Lambda2 = 0.88
				MIIC = 0.50			MIIC = 0.51
Social Inhibition							
1	I make contact easily when I meet people (R)	0.01	**0.63**	0.57	-0.03	**0.64**	0.56
3	I often talk to strangers (R)	-0.16	**0.58**	0.43	-0.14	**0.50**	0.34
6	I often feel inhibited in social interactions	0.29	**0.48**	0.57	**0.44**	**0.38**	0.58
8	I find it hard to start a conversation	0.02	**0.70**	0.63	0.26	**0.56**	0.65
10	I am a closed kind of person	0.27	**0.51**	0.60	0.14	**0.65**	0.65
11	I would rather keep other people at a distance	0.27	**0.53**	0.62	0.17	**0.58**	0.62
14	When socializing, I don't find the right things to talk about	0.09	**0.71**	0.68	0.26	**0.63**	0.72
				Cronbach's α = 0.83			Cronbach's α = 0.83
				Lambda2 = 0.84			Lambda2 = 0.84
				MIIC = 0.42			MIIC = 0.42

MIIC = mean inter-item correlation; (R) = reverse coded; Bold = factor loadings ≥ |0.30|

Table 3 Sample characteristics, stratified by gender and Type D status

	Men			Women		
	Non-Type D (n = 642)	Type D (n = 103)	*P* value	Non-Type D (n = 647)	Type D (n = 161)	*P* value
Demographics						
Age (years)	67.5 (9.9)	66.1 (10.8)	0.18	70.0 (10.0)	68.7 (11.3)	0.16
Non-Caucasian	1.7% (11/634)	5.0% (5/101)	0.09	2.3% (15/641)	3.8% (6/160)	0.47
Low educational level	51.3% (269/524)	61.0% (50/82)	0.13	74.6% (384/515)	79.0% (98/124)	0.36
Being single	16.6% (106/640)	18.4% (19/103)	0.74	36.0% (232/645)	36.0% (58/161)	1.00
Medical history						
Macrovascular disease						
Myocardial infarction	16.0% (97/605)	18.9% (18/95)	0.57	9.1% (55/605)	9.2% (14/152)	1.00
Bypass / angioplasty	19.4% (117/604)	23.7% (23/97)	0.39	11.4% (69/605)	7.2% (11/152)	0.18
Stroke	8.6% (52/603)	8.3% (8/96)	1.00	7.1% (43/603)	8.5% (13/153)	0.69
Arterial disease	34.2% (205/600)	31.6% (30/95)	0.71	34.1% (206/604)	27.5% (42/153)	0.14
Angina pectoris	16.9% (101/597)	11.7% (11/94)	0.26	12.0% (71/590)	11.3% (17/150)	0.92
Microvascular disease						
Retinopathy	4.0% (18/451)	4.3% (3/69)	1.00	3.2% (13/403)	1.9% (2/105)	0.70
Neuropathy	24.1% (135/561)	21.1% (19/90)		23.5% (124/528)	26.6% (38/143)	
Ischemia	1.6% (9/561)	1.1% (1/90)		0.9% (5/528)	0.7% (1/143)	
Wounds / ulcers	0.9% (5/561)	0.0% (0/90)		0.8% (4/528)	0.0% (0/143)	
Excessive coldness	1.6% (9/561)	0.0% (0/90)	0.55	0.4% (2/528)	0.0% (0/143)	0.70
Microalbuminuria [a]	29.2% (130/445)	30.4% (21/69)		21.1% (81/384)	17.7% (17/96)	
Macroalbuminuria [b]	3.4% (15/445)	0.0% (0/69)	0.30	1.8% (7/384)	6.3% (6/96)	0.05
Clinical values						
Hyperglycemia treatment						
No treatment	0.5% (3/638)	0.0% (0/102)		0.9% (6/640)	0.0% (0/160)	
Diet only	16.0% (102/638)	17.6% (18/102)		13.1% (84/640)	16.9% (27/160)	
Diet, oral agents	76.6% (489/638)	74.5% (76/102)		75.3% (482/640)	73.8% (118/160)	
Diet, oral agents, insulin	6.3% (40/638)	7.8% (8/102)		9.7% (62/640)	6.3% (10/160)	
Diet, insulin	0.5% (3/638)	0.0% (0/102)		0.9% (6/640)	3.1% (5/160)	
Other	0.2% (1/638)	0.0% (0/102)	0.89	0.0% (0/640)	0.0% (0/160)	0.06

Table 3 (continued)

	Men			Women		
	Non-Type D (n = 642)	Type D (n = 103)	*P* value	Non-Type D (n = 647)	Type D (n = 161)	*P* value
Diabetes duration (years)	6.3 (4.7)	5.9 (5.0)	0.51	6.3 (5.2)	6.4 (4.1)	0.66
HbA_{1c} (%)	6.7 (0.8)	6.7 (0.7)	0.79	6.8 (0.8)	6.7 (0.7)	0.19
Fasting glucose	7.9 (1.7)	7.6 (1.7)	0.14	7.7 (1.8)	7.6 (1.8)	0.44
Body Mass Index	28.5 (3.9)	29.3 (4.7)	0.10	30.6 (5.2)	30.0 (5.1)	0.18
Total cholesterol	4.0 (0.8)	4.1 (0.9)	0.50	4.4 (0.9)	4.3 (0.9)	0.36
LDL cholesterol	2.4 (0.7)	2.5 (0.8)	0.52	2.6 (0.8)	2.6 (0.8)	0.57
HDL cholesterol	1.1 (0.3)	1.0 (0.2)	0.22	1.2 (0.3)	1.2 (0.3)	0.17
Triglycerides	1.5 (0.9)	1.6 (0.8)	0.22	1.5 (0.7)	1.6 (0.8)	0.51
Systolic blood pressure	148.2 (19.3)	146.7 (20.8)	0.47	148.0 (20.6)	146.4 (20.4)	0.39
Diastolic blood pressure	78.4 (10.5)	79.7 (9.4)	0.24	77.3 (10.8)	76.7 (11.0)	0.55
Health behaviors						
"Active" physical activity [c]	79.3% (505/637)	72.8% (75/103)	0.18	74.0% (470/635)	61.9% (99/160)	0.003
"Sportive" physical activity [d]	43.0% (272/632)	37.6% (38/101)	0.36	45.2% (283/626)	45.6% (72/158)	1.00
Current smoking	13.7% (87/635)	16.5% (17/103)	0.54	11.0% (71/643)	13.7% (22/161)	0.43
Alcohol consumption [e]	10.2% (64/630)	6.1% (6/99)	0.27	1.1% (7/636)	2.5% (4/161)	0.33
Psychological factors						
Total EDS depression score	4.3 (3.7)	9.7 (5.2)	<0.001	5.7 (4.5)	11.8 (5.0)	<0.001
Depressed mood (EDS)	0.9 (1.3)	2.6 (1.9)	<0.001	1.4 (1.7)	3.5 (2.2)	<0.001
Anhedonia (EDS)	0.6 (1.2)	1.5 (1.7)	<0.001	0.7 (1.3)	1.9 (1.9)	<0.001
Anxiety (EDS)	2.2 (1.7)	4.2 (2.0)	<0.001	2.7 (2.0)	4.9 (1.8)	<0.001
Social support	7.2 (3.9)	6.0 (3.1)	0.001	8.1 (3.9)	7.5 (3.3)	0.07
Loneliness	2.0 (1.6)	4.1 (2.1)	<0.001	2.6 (2.0)	4.0 (2.3)	<0.001
Stressful life event(s)	25.0% (158/632)	34.7% (35/101)	0.05	30.8% (196/637)	48.1% (75/156)	<0.001

All values are mean (standard deviation), unless otherwise specified. Yates' Correction for Continuity was applied in the computation of X^2 for all 2 x 2 tables. [a] Albumin concentration of 20 - 200 mg / l; [b] Albumin concentration of > 200 mg / l; [c] At least 2 hours of "active" physical activity a week (daily activities of mild to moderate intensity, including gardening, walking, climbing stairs); [d] At least 1 hour of "sportive" physical activity a week (e.g. sports, fitness); [e] > 14 consumptions / week

Internal consistency and homogeneity

Reliability estimates for groups A and C were similar to the values found in the total samples of men and women (n = 745 and n = 808, respectively; data for total groups not shown). Cronbach's alpha values for both DS14 subscales were high and stable across gender (0.87 for NA, 0.83 for SI); lambda2 produced identical or only slightly higher values (Table 2). All corrected item-total correlations ranged from 0.34 to 0.77 and the mean inter-item correlations were within or just above the optimal range of 0.20 – 0.50. Dropping item 6 from the Social Inhibition subscale for women slightly lowered Cronbach's alpha and lambda2 (0.81 and 0.82, respectively) and overall produced minor changes in the corrected item-total correlations (range 0.37 – 0.69), but did not change the mean inter-item correlation.

Temporal stability

Of the 1553 patients with valid DS14 data in 2007, 65% (n = 1012; 47% men) completed the questionnaire a second time 1 year later. Intraclass correlation coefficients for the DS14 subscales were 0.64 (95% CI 0.58 – 0.69) and 0.63 (95% CI 0.57 – 0.68) for NA, and 0.73 (95% CI 0.68 – 0.77) and 0.65 (95% CI 0.60 – 0.69) for SI in men and women, respectively. Examination of individual Type D / non-Type D classification revealed that 88% of all male patients remained in the same category (n = 39 for Type D, n = 379 for non-Type D). As for the women, Type D / non-Type D classification was confirmed 1 year later in 51 and 390 patients, respectively (82%).

Clinical correlates of Type D personality

A total of 264 patients (17%) were classified as Type D (score of ≥ 10 on both the NA and SI subscale), with a higher rate for women than for men (20% vs 14%, $p = 0.002$). Patients with a Type D personality did not differ from their non-Type D counterparts with respect to diabetes duration, cardiovascular disease history, current microvascular complications or physiological cardiovascular risk factors, including glycemic control, cholesterol and blood pressure (Table 3). While there were no significant differences in health behaviors for men, women with a Type D personality were significantly less likely to engage in activities requiring mild to moderate physical activity (62% versus 74%, $p = 0.003$; Table 3).

Concerning psychological functioning, patients with a Type D personality reported more loneliness and emotional distress, including symptoms of depressed mood, anhedonia and anxiety (Table 3). Type D patients also experienced lower levels of social support, although results failed to reach statistical significance in women ($p = 0.07$). The effect size of the difference in psychological functioning between men / women with and without a Type D personality was moderate to large (> |0.50|), with the exception of low social support (Cohen's $d = 0.32$ for men and 0.15 for women; Figure 1). Finally, those with a Type D personality were more likely to have experienced a stressful life event in the past year (35% versus 25%, $p = 0.05$ in men; 48% versus 31%, $p < 0.001$ in women).

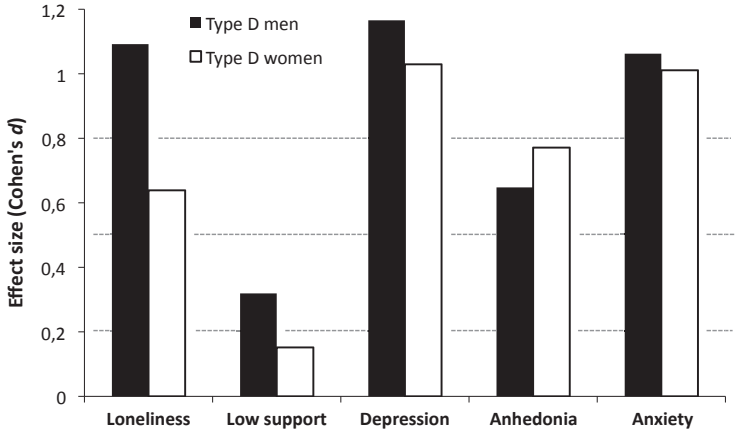

Figure 1 The effect size of the difference in psychological functioning associated with Type D personality in men and women

Note. Cohen's *d* was calculated using *d* = (mean variable Type D – mean variable non-Type D) / standard deviation total group. 0.20 = small effect, 0.50 = moderate effect, 0.80 = large effect.

DISCUSSION

The present study is the first to evaluate the validity of the Type D construct in patients with type 2 diabetes. The two-factor model of the DS14 measure was confirmed in both exploratory and confirmatory factor analyses, with the individual subscales Negative Affectivity and Social Inhibition showing adequate reliability in terms of internal consistency, homogeneity and one-year temporal stability.

These findings correspond to the results of previous validation studies in healthy populations and populations with cardiovascular disorder [9, 13-16, 26]. The prevalence of Type D found in our sample (17.0%) was relatively low compared to the rates generally found in patients with cardiovascular disorders and the general population (approximately 20 – 35%), although similar estimates have been reported [7, 17]. The only other study examining Type D prevalence in diabetes patients (33%) was conducted in a younger sample (mean age 60.5) of patients with more advanced disease as evidenced by the presence of diabetic foot syndrome [34].

Our finding that Type D personality is strongly related to psychological distress is in line with the results from a recent meta-analysis and two systematic reviews, indicating that Type D personality is associated with anxiety, depression and other symptoms of poor mental health in cardiovascular and non-cardiovascular patient groups and individuals from the general population [7, 8, 17]. Even though Type D personality appears to identify those patients who are likely to experience emotional problems, Type D personality remains an independent predictor of clinical events in cardiovascular patients after adjustment for co-occurring symptoms of depression [7].

One potential mechanism through which Type D might exert a negative influence on health includes inadequate self-care behavior. In the present study, women with a Type D personality were significantly less likely to engage in day-to-day activities of light to moderate intensity. Other studies indicate that individuals with a Type D personality are less likely to exercise, follow a healthy diet or adhere to medication regimens than their non-Type D counterparts [18-20, 35, 36]. Moreover, preliminary evidence suggests that healthy young adults and cardiac patients are less likely to get a regular medical checkup or to consult health practitioners in case of cardiac symptoms, respectively [35, 37]. In addition, social inhibition may impede effective communication with health care providers and subsequently hinder the detection of health risk behaviors and potentially harmful disease symptoms.

While these behavioral mechanisms may add to a better understanding of the relation between Type D personality and adverse clinical prognosis, postulated differences in self-care activities between Type D and non-Type D patients were not reflected in a less optimal cardiovascular risk profile in terms of glycemic control, cholesterol levels, blood pressure or vascular disease history in the present study. The low prevalence rate (17%) of Type D personality found in this sample may be one explanation. As there is no information available about the Type D status of non-participants, we cannot rule out the possibility that patients with a Type D personality were less inclined to participate. Even though the study's self-report questionnaire was anonymous, the face-to-face interview with the primary care nurse practitioner could have been a social situation that was too discomforting for those with a Type D personality. A systematic opting-out of study participation by patients with a Type D personality could have diluted possible associations with traditional cardiovascular risk factors. In addition, this sample was in relatively good health, particularly in terms of glycemic control and cholesterol levels, making it more difficult to detect any meaningful differences in physical health between those with and without a Type D personality. The fact that we did not find any differences in cardiovascular disease history, the presence of microvascular conditions or physiological parameters between Type D and non-Type D patients does not preclude Type D as a risk marker for poor vascular outcomes in diabetes patients, however. Previous work in cardiovascular patients has shown that Type D is not confounded by disease severity or traditional physiological cardiovascular risk factors [16, 21, 22], suggesting that other pathways may be implicated, including dysfunctions of the autonomic nervous system, hypothalamic-pituitary-adrenal axis and immune system [7, 38].

Several methodological study limitations also need to be acknowledged. First, the present findings indicate that the DS14 can be administered in its original two-factor format in diabetes patients, but not all error covariances in the CFA models reached statistical significance. Reverse-wording (items 1 and 3) and very similarly worded items (e.g. item 10 "I am a closed kind of person" and item 11 "I would rather keep other people at a distance")

are known reasons for correlated errors [30]. However, this cannot explain why some other closely related items did not covary (e.g. items 4 and 13). Our final RMSEA values (0.07 for men, 0.05 for women) indicate that more parsimonious solutions might be achieved when corrections are based on post hoc model modifications, although these should also have a theoretical justification. Second, the one year stability of Type D status was high (approximately 85%), but we had no data on temporal changes over shorter or substantially longer time spans. While other studies support the notion that both the Type D classification and the two separate subscales are stable over periods from 3 weeks up to 18 months [9, 13, 21, 26], the test-retest reliability of Negative Affectivity and Social Inhibition in the present study was somewhat lower than found in studies with shorter follow-up periods [9, 13, 26]. Finally, our study only included type 2 diabetes patients who were treated in primary care settings. As these patients are usually in somewhat better glycemic control than outpatients with type 2 diabetes and have different demographic and disease characteristics than those with type 1 diabetes, our validation results might not generalize to the total population of diabetes patients.

Strengths of our study include the large number of participants that allowed detailed testing of the psychometric characteristics of the DS14, using a cross-validation design for both sexes. Other strong points are the wealth of detailed patient information that is available and the presence of longitudinal data to examine the temporal stability of Type D personality.

In conclusion, the DS14 is a valid and a reliable measure of Type D personality in both male and female primary care patients with type 2 diabetes mellitus, and is associated with loneliness and stressful life events, low social support and symptoms of depression, anhedonia and anxiety. As accumulating evidence endorses the negative impact of Type D personality on disease prognosis and psychological functioning in cardiovascular populations [7], prospective studies are now warranted to examine whether Type D personality is independently associated with adverse health outcomes in patients with diabetes as well. The prevention or delay of vascular complications constitutes the main goal of diabetes treatment, and self-care activities in terms of adherence to dietary, exercise and medication regimens play a crucial role in the successful management of this disease. However, no studies to date have addressed the health risks of Type D personality in diabetes populations. Although its clinical relevance for diabetes patients is yet to be determined, the assessment of Type D personality poses minimal burden to patients. This study shows that the DS14 may serve as a screening tool to identify those patients who require more clinical attention due to a clustering of psychological risk factors [9].

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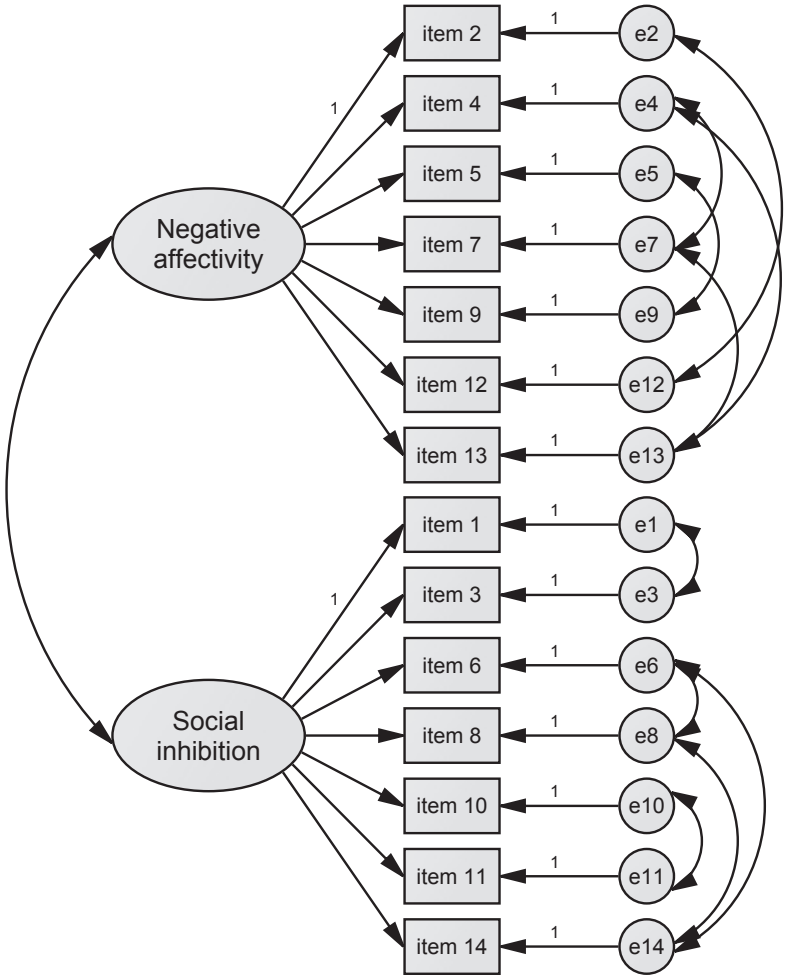
Online Appendix Table 1 Estimated unstandardized / standardized regression weights, covariances, correlations, variances and squared multiple correlations for the final CFA models with correlated error terms in men and women

	Men (n = 373)					Women (n = 404)				
	Unstandardized estimate	**SE**	***P* value**	**Standardized estimate**	**Squared multiple correlation**	**Unstandardized estimate**	**SE**	***P* value**	**Standardized estimate**	**Squared multiple correlation**
Negative Affectivity										
Item 2	1.000	-	-	0.536	0.287	1.000	-	-	0.524	0.275
Item 4	0.987	0.110	<0.001	0.677	0.458	1.164	0.122	<0.001	0.745	0.555
Item 5	1.131	0.122	<0.001	0.666	0.443	0.971	0.110	<0.001	0.593	0.352
Item 7	1.219	0.125	<0.001	0.781	0.609	1.341	0.134	<0.001	0.811	0.658
Item 9	0.909	0.098	<0.001	0.669	0.447	0.944	0.099	<0.001	0.678	0.459
Item 12	1.253	0.112	<0.001	0.765	0.586	1.281	0.122	<0.001	0.660	0.435
Item 13	1.042	0.104	<0.001	0.822	0.676	1.197	0.120	<0.001	0.811	0.659
Social Inhibition										
Item 1	1.000	-	-	0.595	0.354	1.000	-	-	0.432	0.187
Item 3	0.738	0.101	<0.001	0.345	0.119	0.531	0.126	<0.001	0.197	0.039
Item 6	1.296	0.137	<0.001	0.697	0.486	1.745	0.229	<0.001	0.732	0.536
Item 8	1.515	0.149	<0.001	0.773	0.598	1.702	0.230	<0.001	0.685	0.469
Item 10	1.433	0.139	<0.001	0.681	0.464	1.497	0.202	<0.001	0.632	0.399
Item 11	1.105	0.118	<0.001	0.597	0.365	1.444	0.194	<0.001	0.639	0.408
Item 14	1.485	0.145	<0.001	0.778	0.605	1.579	0.213	<0.001	0.682	0.465
	Covariances			**Correlations**		**Covariances**			**Correlations**	
	Estimate	**SE**	***P* value**	**Estimate**		**Estimate**	**SE**	***P* value**	**Estimate**	
NA, SI	0.236	0.038	<0.001	0.620		0.256	0.044	<0.001	0.764	
e4, e7	0.009	0.034	0.790	0.020		-0.012	0.037	0.755	-0.026	
e4, e13	0.005	0.027	0.861	0.014		0.023	0.034	0.490	0.059	
e7, e13	-0.036	0.027	0.174	-0.118		0.025	0.035	0.474	0.068	
e2, e12	0.164	0.046	<0.001	0.226		0.217	0.060	<0.001	0.206	
e5, e9	0.055	0.034	0.104	0.099		0.113	0.035	0.001	0.189	
e6, e8	-0.118	0.048	0.013	-0.214		0.059	0.060	0.321	0.080	
e6, e14	-0.086	0.047	0.066	-0.162		-0.037	0.054	0.498	-0.053	
e8, e14	0.020	0.050	0.692	0.040		0.198	0.061	0.001	0.254	
e10, e11	0.125	0.049	0.011	0.164		0.211	0.053	<0.001	0.261	
e1, e3	0.387	0.054	<0.001	0.429		0.710	0.081	<0.001	0.508	

Online Appendix Table 1 (continued)

	Variances			Variances		
	Estimate	**SE**	***P* value**	**Estimate**	**SE**	***P* value**
NA	0.437	0.083	<0.001	0.443	0.084	<0.001
SI	0.332	0.056	<0.001	0.253	0.061	<0.001
e2	1.085	0.085	<0.001	1.171	0.087	<0.001
e4	0.503	0.046	<0.001	0.481	0.049	<0.001
e5	0.702	0.058	<0.001	0.769	0.059	<0.001
e7	0.417	0.045	<0.001	0.415	0.050	<0.001
e9	0.445	0.037	<0.001	0.466	0.038	<0.001
e12	0.485	0.045	<0.001	0.945	0.075	<0.001
e13	0.228	0.028	<0.001	0.329	0.040	<0.001
e1	0.606	0.049	<0.001	1.104	0.082	<0.001
e3	1.345	0.101	<0.001	1.770	0.126	<0.001
e6	0.591	0.063	<0.001	0.668	0.073	<0.001
e8	0.513	0.065	<0.001	0.832	0.083	<0.001
e10	0.788	0.070	<0.001	0.856	0.073	<0.001
e11	0.732	0.060	<0.001	0.766	0.065	<0.001
e14	0.479	0.062	<0.001	0.727	0.072	<0.001



Online Appendix Figure 1 Original CFA model with correlated error terms

CHAPTER 9

Type D personality, suboptimal health behaviors and emotional distress in people with diabetes: Diabetes MILES – The Netherlands

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ABSTRACT

Objective: In cardiovascular research, Type D personality – high negative affectivity (NA) and social inhibition (SI) – has been associated with a 2 to 3-fold increased risk of adverse prognosis. We examined the differential associations of Type D personality and its two constituent components with three potential risk mechanisms in people with diabetes: health behaviors, emotional distress and physiological factors.

Methods: 3,314 Dutch individuals with self-reported type 1 or type 2 diabetes completed an online survey, including the Type D Scale-14 and several measures of health-related behavior, emotional distress and physiological factors (HbA_{1c}, high blood pressure, high cholesterol).

Results: Type D individuals were less likely to follow a healthy diet or to consult health professional(s) in case of problems with diabetes management than those scoring high on neither or only one component. They also reported more: barriers surrounding medication use, diabetes-specific social anxiety, loneliness and symptoms of depression and anxiety. The relation between Type D and infrequent exercise appeared to be driven by NA, while suboptimal foot inspection was linked to SI. No relevant differences were found with respect to other self-care measures or physiological risk factors. In multivariable logistic regression analyses, Type D personality was associated with a 2 to 3-fold increased odds of several suboptimal health-behaviors and related cognitions and a more than 15-fold increased odds of experiencing general emotional distress, after adjustment for demographics, clinical variables and the individual Type D components.

Conclusions: Although not specific for diabetes, the joint presence of NA and SI is particularly associated with several behavioral and emotional adversities in people with diabetes.

INTRODUCTION

Several studies have shown that specific negative emotions such as depression and anxiety are implicated in the onset or progression of vascular conditions in healthy individuals [1, 2], people with established heart disease [3, 4] and with type 1 or type 2 diabetes [5, 6]. Previous research has suggested that a more general disposition toward negative affectivity (NA) may also affect cardiovascular outcome [7]. This risk appears to be especially pronounced in individuals who are also high in social inhibition (SI) [8]. The combined tendency to experience negative emotions across time and situations (high NA) and to inhibit self-expression when with others (high SI) is termed Type D or "distressed" personality [9]. Type D has been associated with a two- to three-fold increased risk of adverse health outcomes in people with a cardiovascular condition, including non-fatal myocardial infarction, revascularization and (cardiac) mortality [10, 11]. To date, no studies have examined the health risks of Type D personality in people with diabetes, although premature cardiovascular and microvascular conditions represent the most common cause of morbidity and mortality in this group [12].

One potential mechanism through which Type D personality might exert a negative influence on health includes suboptimal self-care behavior. A growing number of studies indicate that healthy individuals and people with a cardiac condition who have a Type D personality are less likely to exercise, follow a healthy diet or to take medication according to recommendations than their non-Type D counterparts [13-19]. Moreover, preliminary evidence suggests that those with a Type D personality are less likely to get a regular medical checkup or to consult health practitioners in case of cardiac symptoms [13, 20]. A primary care study among over 1,500 people with type 2 diabetes concluded that participants with and without Type D personality did not differ with respect to cardiovascular risk factors, but Type D women did have a more sedentary lifestyle [21].

Type D personality has also been associated with anxiety, depression and other indicators of suboptimal mental health in people with cardiovascular and non-cardiovascular conditions and individuals from the general population [10, 22, 23]. A German study found significant correlations between the two individual Type D components and measures of depression, anxiety and diabetes-related distress in a small group of people with diabetic foot problems [24]. In type 2 diabetes, the combination of NA and SI has been related to lower levels of perceived social support and more: stressful life events, loneliness and symptoms of depressed mood, anhedonia and anxiety [21]. Type D personality may indirectly increase cardiovascular risk through its association with these negative emotional states.

However, it is unclear whether the combination of NA and SI is most strongly related to these measures or whether associations are mainly driven by one Type D component only.

Therefore, the aim of the present study was to explore whether Type D personality and its two constituent components – NA and SI – are differentially associated with three potential cardiovascular risk mechanisms in people with type 1 or type 2 diabetes: health behaviors, physiological risk factors and emotional distress.

METHODS

Data were collected within the framework of Diabetes MILES - The Netherlands, a national online cross-sectional observational study among people with diabetes in The Netherlands [25]. Following the example of Diabetes MILES (Management and Impact for Long-term Empowerment and Success) - Australia [26], the primary aim of the Dutch study was to examine the psychosocial aspects of living with diabetes. In close cooperation with the Dutch Diabetes Association (Diabetesvereniging Nederland), all Dutch individuals having self-reported diabetes of any type aged ≥ 19 years were given the opportunity to participate in the online questionnaire survey in September – October 2011. Of the 4,590 individuals who had registered for participation at the study's website, 3,960 (86%) opened the survey web application of whom 84% (n = 3,332) completed the entire survey. The present sample included all participants with self-reported type 1 or type 2 diabetes who completed the 14-item Type D scale (DS14). The study protocol of Diabetes MILES – The Netherlands was approved by the Psychological Research Ethics Committee of Tilburg University, The Netherlands (EC-2011 5). As the study was web-based, digital informed consent was obtained from all participants.

Demographic and clinical characteristics

Self-reported demographic and clinical characteristics included sex, age, ethnic background, educational level, marital status, type of diabetes, diabetes duration, current hyperglycemia treatment, and physician diagnosed micro- and macrovascular complications. Participants were also asked to indicate whether a physician had diagnosed them with high blood pressure or high cholesterol. In addition, they had to specify their most recent HbA_{1c} and their height / weight in order to calculate their Body Mass Index (BMI).

Type D personality

Type D personality was assessed using the DS14 [9], consisting of two seven-item subscales measuring NA and SI. Items are scored on a five-point rating scale ranging from 0 ("false") to 4 ("true"), with total subscale scores between 0 – 28. Individuals scoring ten or more on both scales are classified as having Type D personality [9]. The DS14 has been shown to possess adequate psychometric properties in several populations, including people with type 2 diabetes [9, 21].

Health behaviors

Diabetes-related self-care was examined using the Diabetes Self Care Inventory-Revised, a newly designed questionnaire covering the frequency of a broad range of diabetes self-care activities [25, 26]. Topics included taking the required number of insulin injections, adjusting insulin dosage / units for special occasions, taking the prescribed number of tablets to lower blood glucose level / cholesterol / blood pressure, following a healthy diet, meeting the national norm for healthy exercise (all measured using a Likert-scale ranging from 0 "Never" to 4 "[Almost] always"), monitoring of blood glucose levels, inspection of feet (times per week), and whether individuals were trying to achieve or maintain a healthy weight (yes / no). In line with Diabetes MILES – Australia, we added smoking behavior to the list. The number of alcohol consumptions per week was measured using a single question.

Barriers to medication adherence and adherence-related behavior were assessed using the 12-item Adherence Starts with Knowledge questionnaire (ASK-12) [27]. Dietary habits were measured using a purpose-designed food frequency questionnaire, asking participants to report the number of days per week (measured using a Likert-scale with 0 = 0 days, 1 = 1 – 3 days, 2 = 4 – 5 days and 3 = 6 – 7 days) they generally consumed specific products, including ≥ 2 pieces of fruit, ≥ 200 grams of vegetables, whole grain products, fatty fish, full-fat milk products, full-fat cheese, non-lean meat, fried products, salt and sweets. The Dutch Eating Behavior Questionnaire (DEBQ) was used to measure habitual eating style, with 13 items covering emotional eating (eating in response to emotional arousal), 10 items covering external eating (eating in response to external food cues, such as taste and smell) and 10 items covering restrained eating (attempts to refrain from eating) [28]. Physical activity levels in the last seven days (expressed as metabolic equivalent of task-minutes / week) were assessed using the International Physical Activity Questionnaire short form (IPAQ-short) [29].

Medical appointment attendance rates were examined by adjusting the self-reported number of cancelled care appointments with diabetes and non-diabetes specific healthcare providers in the previous twelve months for the total number of care appointments in this period. Consultation behavior was assessed using ten newly designed questions, asking participants to rate on a 5-point scale (scored 0 ["Not true"] to 4 ["True"]) how likely it was that they would act or feel in a certain way in several scenarios involving contact with diabetes health care professional(s). Exploratory factor analysis showed a two-factor structure (Online Appendix Table 1). Four items appeared to represent suboptimal consultation behavior in case of problems with (the management of) diabetes, while four other items seemed to reflect diabetes-specific social anxiety. Based on these findings, we created two consultation behavior subscales by summing the scores on the items concerned (total score range 0 – 16), with higher scores indicating more suboptimal consultation behavior and more diabetes-specific social anxiety, respectively.

General and diabetes-specific emotional distress

Symptoms of depression and anxiety during the previous two weeks were measured using the 9-item Patient Health Questionnaire (PHQ-9) [30] and the 7-item General Anxiety Disorder questionnaire [31], respectively. A single item was used to measure feelings of loneliness in the past 12 months (ranging from 1 "I never felt lonely" to 10 "I always felt lonely"). The 20-item Problem Areas in Diabetes (PAID) scale was included to assess diabetes-related distress [32]. The Consequences dimension of the Brief Illness Perception Questionnaire (BIPQ; "How much does your illness affect your life?") was used to examine whether participants viewed their diabetes as having major consequences on their lives, with response options ranging from 0 ("no effect at all") to 10 ("severely affects my life") [33]. As the BIPQ and the DEBQ were included in only two of five complementary questionnaire modules that were randomly assigned to subgroups of the total sample [25], results for these two measures could only be reported for 40%.

Statistical analyses

To examine whether Type D personality and its individual components NA and SI were differentially related to demographical and clinical characteristics, health behaviors, physiological risk factors and emotional distress, participants were classified into one of four subgroups based on their DS14 scores: (i) those scoring low on both Type D components (NA- / SI-); (ii) those scoring high on SI only (NA- / SI+); (iii) those scoring high on NA only (NA+ / SI-); (iv) those scoring high on both NA and SI (Type D). Comparisons between these four subgroups were made using one-way between-groups ANOVAs (continuous variables) and X^2 tests (categorical variables). An ANCOVA was applied for the number of cancelled care appointments during the previous twelve months, in order to adjust for the total number of care appointments in this period. To account for the number of individual statistical tests needed to analyze the ten DSCI-R items, a more stringent α level was used for the overall difference per item (Bonferroni correction 0.05 / 10 = 0.005). This procedure was also followed for the ten eating pattern questions. Three planned comparisons were specified (Type D vs. NA- / SI-, Type D vs. NA- / SI+, Type D vs. NA+ / SI-), using a Bonferroni adjusted α level of 0.05 / 3 ≈ 0.0167. Cohen's *d* was used as an index of effect size for significant planned comparisons and was calculated by subtracting the mean of a certain variable for the comparison group of interest from the mean for the Type D group and dividing this number by the standard deviation of the two groups combined (with 0.20, 0.50 and 0.80 indicating a small, moderate and large effect, respectively).

For those variables showing a unique contribution of NA+ / SI+ in the univariable group comparisons, multivariable logistic regression analyses were used to determine whether the association for Type D personality held when using the NA- / SI- as the reference group

and adjusting for demographics (sex, age, educational level, being single), clinical factors (diabetes duration, the presence of diabetes complications) and the two individual Type D components. Dichotomization based on pre-defined cut-off points, content of response categories and tertiles was employed to improve clinical interpretability, by allowing a comparison of low – medium versus high risk groups. All analyses were performed using SPSS Version 19 (IBM SPSS Statistics, Somers, New York). Unless otherwise specified, statistical significance was taken at $p < 0.05$.

RESULTS

The total sample consisted of 3,314 people (53% women, mean age 55 ± 14 years, age range 19 – 90), of whom 43% had type 1 diabetes. Approximately half of the participants with type 1 diabetes (690 / 1,422) reported to use an insulin pump as their primary hyperglycemia treatment and 53% (993 / 1,890) of those with type 2 diabetes were managing their condition with insulin in general (pump and / or injections). Twenty-nine per cent of the sample (n = 952) was categorized as having Type D personality, while SI only and NA only were present in 17% (n = 562) and 15% (n = 492), respectively. These prevalence estimates did not differ when stratifying by diabetes type ($p = 0.78$). When comparing the four NA / SI groups with respect to demographics and clinical characteristics (Table 1), significant overall differences were found for sex, age, partner status, diabetes duration, HbA_{1c} level, BMI and the presence of high cholesterol. Planned comparisons indicated that Type D individuals were somewhat younger than the other three groups and were less likely to have a partner. Compared to the reference group and the SI only group, Type D individuals had a higher mean BMI and were more likely to be female. Type D individuals were more likely to report high cholesterol than the reference group and had had diabetes for a significantly shorter period of time than the SI only group. With respect to HbA_{1c} level, the planned contrasts did not yield any significant results for the comparisons of interest. Results for Type D personality in relation to self-care behaviors and emotional distress were similar when stratifying by diabetes type (data not shown), and are therefore reported for the total sample.

Table 1 Demographic and clinical characteristics of study sample (n = 3,314), stratified by the four NA / SI groups

	N missing	ALL	REFERENCE GROUP NA- / SI- (n = 1,308)	ONLY ONE TYPE D COMPONENT NA- / SI+ (n = 562)	ONLY ONE TYPE D COMPONENT NA+ / SI- (n = 492)	TYPE D PERSONALITY NA+ / SI+ (n = 952)	Overall *p* value	TYPE D *versus* NA- / SI-	TYPE D *versus* NA- / SI+	TYPE D *versus* NA+ / SI-
Female sex	1	1770 (53)	647 (50)	231 (41)	301 (61)	591 (62)	<0.001	<0.001 [b]	<0.001 [b]	0.74
Age, years	48	55 ± 14	57 ± 14	57 ± 14	55 ± 14	52 ± 15	<0.001	<0.001 [b]	<0.001 [b]	0.003 [b]
(Non-Dutch) ethnic minority	0	84 (3)	31 (2)	14 (3)	9 (2)	30 (3)	0.46	-	-	-
Low educational level	7	855 (26)	325 (25)	130 (23)	138 (28)	262 (28)	0.14	-	-	-
Being single	0	675 (20)	215 (16)	119 (21)	94 (19)	247 (26)	<0.001	<0.001 [b]	0.04	0.004 [b]
Type 2 diabetes	0	1892 (57)	757 (58)	318 (57)	285 (58)	532 (56)	0.78	-	-	-
Diabetes duration, years	3	16 ± 13	17 ± 13	17 ± 13	16 ± 13	15 ± 13	0.04	0.02	0.01 [b]	0.44
Primary treatment	2						0.33	-	-	-
Insulin pump		798 (24)	298 (23)	120 (21)	136 (28)	244 (26)				
Insulin injections		1617 (49)	646 (49)	284 (51)	234 (48)	453 (48)				
GLP-1 injections		33 (1)	13 (1)	5 (1)	8 (2)	7 (1)				
Blood glucose lowering tablets		775 (23)	314 (24)	141 (25)	103 (21)	217 (23)				
Lifestyle		89 (3)	37 (3)	12 (2)	11(2)	29 (3)				
≥ 1 diabetes complication(s) [a]	0	1041 (31)	390 (30)	173 (31)	166 (34)	312 (33)	0.30	-	-	-
HbA_{1c}, mmol / mol (%)	886	56 ± 12 (7.3 ± 1.1)	55 ± 11 (7.2 ± 1.1)	55 ± 11 (7.2 ± 1.1)	58 ± 13 (7.4 ± 1.2)	57 ± 13 (7.3 ± 1.2)	0.002	0.04	0.03	0.17
Body Mass Index	32	28 ± 6	27 ± 5	27 ± 5	29 ± 6	29 ± 7	<0.001	<0.001 [b]	<0.001 [b]	0.58
High blood pressure	0	1,280 (39)	468 (36)	227 (40)	205 (42)	380 (40)	0.05	-	-	-
High cholesterol	0	1,155 (35)	418 (32)	208 (37)	178 (36)	351 (37)	0.045	0.015 [b]	0.96	0.80

Values are n (%) or mean ± SD.

[a] At least one of the following: self-reported myocardial infarction, stroke, peripheral arterial disease, nephropathy, retinopathy, neuropathy, foot condition due to diabetes; [b] Significant contrast when using Bonferroni-adjusted α level 0.05 / 3 ≈ 0.0167

Self-care behaviors

The four groups did not differ with respect to their self-reported use of insulin, oral hypoglycemic tablets, and cholesterol or blood pressure lowering agents (Table 2). However, Type D individuals reported significantly more barriers to taking medications (overall $p < 0.001$; contrast Type D vs. SI only $p < 0.001$ and Cohen's $d = 0.44$; contrast Type D vs. NA only $p = 0.001$ and Cohen's $d = 0.18$). No association was found with insulin adjustments, blood glucose monitoring, alcohol consumption or trying to achieve or maintain a healthy weight. Type D personality was related to less frequent inspection of feet (with a non-significant difference between the SI only and Type D group and an effect size of $d = -0.16$ for the Type D vs. NA only contrast at $p = 0.005$). Furthermore, Type D individuals were somewhat more likely to smoke than the SI only group (11% vs. 6%, $p = 0.005$), but not when compared to the reference group ($p = 0.22$) or NA only group ($p = 0.62$).

Individuals with a Type D personality were less likely to follow a healthy diet (Table 2; overall $p < 0.001$; all planned comparisons $p < 0.001$; Cohen's $d = -0.47$, -0.26 and -0.20 for the contrast with the reference, SI only and NA only group, respectively). Significant overall group differences were found for several specific dietary habits (Online Appendix Table 2), with Type D individuals being less likely to consume healthy foods (fruit, vegetables, whole grain products, fatty fish) and more likely to consume less healthy foods (non-lean meat, fried products, sweets). Contrasts with the other three groups were either non-significant or of fairly minor effect size (range Cohen's d $|0.13 – 0.29|$). In the subsample completing the three DEBQ eating style subscales (n = 1,312 / 1,332), we found a significant difference in emotional ($p < 0.001$), external ($p < 0.001$) and restraint eating ($p = 0.001$) average scale scores for the four NA / SI groups. Type D individuals were more inclined to eat in response to emotional arousal or to external food cues than the reference group (both p-values < 0.001, Cohen's $d = 0.80$ / 0.51) and SI only group (both p-values < 0.001, Cohen's $d = 0.62$ / 0.32). For restrained eating, only the Type D vs. SI only contrast was significant ($p = 0.01$, Cohen's $d = 0.22$).

There was a significant overall group difference in physical activity (Table 2; $p < 0.001$). Type D individuals were less likely to meet the national norm for healthy exercise when compared to the reference and SI only group (both p-values < 0.001, Cohen's $d = -0.30$ / -0.26), but there was no significant difference with the NA only group. When examining physical activity levels more closely using the IPAQ short form, the overall group effect ($p < 0.001$) was only reflected in a significant difference between Type D and the reference group ($p < 0.001$, Cohen's $d = -0.21$).

Table 2 Self-reported self-care behaviors, stratified by the four NA / SI groups

	N missing	REFERENCE GROUP NA- / SI-	ONLY ONE TYPE D COMPONENT NA- / SI+	ONLY ONE TYPE D COMPONENT NA+ / SI-	TYPE D PERSONALITY NA+ / SI+	Overall *p* value
Diabetes Self-Care Inventory - Revised						
Taking the number of insulin injections you require each day [a]	6	3.9 ± 0.4	3.9 ± 0.3	3.9 ± 0.5	3.9 ± 0.5	0.06
Adjusting insulin dosage / units for special occasions (illness, travel, parties) [b]	0	2.3 ± 1.4	2.3 ± 1.4	2.3 ± 1.4	2.3 ± 1.4	0.98
Taking prescribed number of tablets to lower blood glucose level [c]	2	3.9 ± 0.5	3.9 ± 0.4	3.9 ± 0.4	3.9 ± 0.5	0.47
Taking prescribed dosage of cholesterol-lowering medication [d]	2	3.8 ± 0.8	3.8 ± 0.7	3.7 ± 0.9	3.7 ± 1.0	0.01
Taking prescribed dosage of blood pressure-lowering medication [e]	1	3.9 ± 0.4	4.0 ± 0.3	3.8 ± 0.6	3.9 ± 0.5	0.006
Number of blood glucose measurements / week [f]	4	18.6 ± 16.3	18.4 ± 16.3	19.4 ± 16.4	19.5 ± 16.4	0.50
Number of feet inspections / week	2	3.0 ± 2.7	2.5 ± 2.7	2.9 ± 2.9	2.5 ± 2.7	<0.001 § [g,i]
Following healthy diet	0	3.3 ± 0.8	3.1 ± 0.9	3.0 ± 0.9	2.8 ± 1.0	<0.001 § [g,h,i]
Meeting norm for healthy exercise	1	2.5 ± 1.3	2.4 ± 1.3	2.2 ± 1.3	2.1 ± 1.3	<0.001 § [g,h]
Trying to achieve / maintain healthy weight (yes)	0	1104 (84)	461 (82)	424 (86)	812 (85)	0.25
Daily smoker	5	117 (9)	35 (6)	56 (11)	100 (11)	0.01 [h]
Alcohol: >14 consumptions / week	0	100 (8)	49 (9)	28 (6)	66 (7)	0.27
Barriers to medication taking (ASK-12 total score)	116	19.8 ± 5.4	21.0 ± 5.0	22.5 ± 5.5	23.5 ± 6.0	<0.001 [g,h,i]
Physical activity (IPAQ total score)	366	3205 ± 3093	2926 ± 2669	2888 ± 2809	2593 ± 2552	<0.001 [g]
Eating style (DEBQ subscale scores) [j]						
Emotional eating average scale score	20	1.8 ± 0.7	1.9 ± 0.8	2.3 ± 0.9	2.5 ± 1.0	<0.001 [g,h]
External eating average scale score	20	2.4 ± 0.6	2.5 ± 0.6	2.6 ± 0.6	2.7 ± 0.6	<0.001 [g,h]
Restraint eating average scale score	20	2.8 ± 0.8	2.6 ± 0.8	2.9 ± 0.8	2.8 ± 0.7	0.001 [h]
Consultation behavior						
Subscale suboptimal consultation behavior total score	0	1.9 ± 2.6	2.5 ± 2.8	2.2 ± 2.7	3.0 ± 3.0	<0.001 [g,h,i]
Subscale diabetes-specific social anxiety total score	0	1.9 ± 2.4	2.2 ± 2.5	3.2 ± 3.0	3.8 ± 3.3	<0.001 [g,h,i]

Values are n (%) or mean ± SD.

[a] Question posed to people using insulin injections, irrespective of pump (n = 1,636 / 3,312); [b] Question posed to people using insulin pump and/or insulin injections (n = 2,415 / 3,312); [c] Question posed to people using blood glucose lowering tablets (n = 1,551 / 3,312); [d] Question posed to people using cholesterol-lowering medication (n = 1,924 / 3,313); [e] Question posed to people using blood pressure-lowering medication (n = 1,668 / 3,314); [f] Question posed to people indicating to have a blood glucose meter (n = 3,090 / 3,314); [g] Significant Type D vs. NA- / SI- contrast when using Bonferroni-adjusted α level 0.05 / 3 ≈ 0.0167; [h] Significant Type D vs. NA- / SI+ contrast when using Bonferroni-adjusted α level 0.05 / 3 ≈ 0.0167; [i] Significant Type D vs. NA+ / SI- contrast when using Bonferroni-adjusted α level 0.05 / 3 ≈ 0.0167; § Significant overall group difference when using Bonferroni-adjusted α level 0.05 / 10 = 0.005 for individual DSCI items; [j] Question posed to subsample only (n = 1,332)

Type D individuals indicated they were less inclined to consult health professional(s) in case of problems with diabetes management (overall $p < 0.001$; contrast Type D vs. reference group $p < 0.001$ and Cohen's $d = 0.40$; Type D vs. SI only $p = 0.001$ and Cohen's $d = 0.18$; Type D vs. NA only $p < 0.001$ and Cohen's $d = 0.27$). They also reported more diabetes-specific social anxiety (overall $p < 0.001$; all contrasts $p < 0.001$, with Cohen's $d = 0.66$, 0.52 and 0.21 for the comparison with the reference, SI only and NA only group, respectively). There was a small but significant difference between the four groups in the mean number of cancelled care appointments during the previous twelve months, after adjusting for the total number of care appointments in this period (n = 3,261; $p < 0.001$, partial η^2=0.005). The mean number of cancellations was significantly higher in Type D individuals (adjusted mean [standard error] = 0.44 [0.03]) compared to the reference category (0.33 [0.03], $p = 0.01$) and the SI only group (0.24 [0.04], $p < 0.001$), but not to the NA only group (0.45 [0.05], $p = 0.92$).

Emotional distress

Type D individuals reported more loneliness, and symptoms of depression and anxiety than the other three groups (Table 3; $p < 0.001$). Large effect sizes were found for the comparison with the reference group (Cohen's $d = 1.17$ / 1.14 / 1.16, respectively) and the SI only group (Cohen's $d = 0.84$ / 0.95 / 0.99) and small to moderate effect sizes for the difference with the NA only group (Cohen's $d = 0.40$ / 0.20 / 0.13). With respect to diabetes-specific distress, significant overall differences were found in mean scores on the PAID and the consequences item of the B-IPQ (both overall $p < 0.001$). Type D individuals experienced more negative emotions related to living with diabetes and endorsed a larger impact of this condition on their life when compared with the reference group (Cohen's $d = 1.01$ / 0.57) and the SI only group (Cohen's $d = 0.85$ / 0.47), but not with the NA only group.

Multivariable analyses

We dichotomized the PHQ-9 and GAD-7 scores using the validated cut-off of ≥ 10. For the DSCI-R healthy eating item, this division was based on the response categories (0=Regularly, often, [almost] always, 1 = Sometimes, never). The split for the remaining variables was based on a comparison between the lowest and middle tertile (0 = no problems) and the highest tertile (1 = problems) of total scores. After adjustment for demographics, clinical factors, NA only and SI only, Type D individuals had a more than 15-fold increased odds of reporting loneliness (OR = 15.32, 95% CI 11.95 – 19.64) and high depressive symptoms (OR = 28.99, 95% CI 17.03 – 49.34) when compared with the reference category. SI only and NA only were also associated with these emotional distress measures, with an adjusted OR of 3.04 (2.26 – 4.09) and 7.70 (5.81 – 10.19) for loneliness, and 2.16 (1.03 – 4.51) and 21.71 (12.44 – 37.88) for depressive symptoms. As only three people in the reference and SI only group had a high GAD-7 score, the analysis for anxiety could not be run.

Table 3 Emotional functioning, stratified by the four NA / SI groups

	N missing	REFERENCE GROUP NA- / SI-	ONLY ONE TYPE D COMPONENT NA- / SI+	ONLY ONE TYPE D COMPONENT NA+ / SI-	TYPE D PERSONALITY NA+ / SI+	Overall *p* value	TYPE D *versus* NA- / SI-	TYPE D *versus* NA- / SI+	TYPE D *versus* NA+ / SI-
Depressive symptoms (PHQ-9 total score)	3	2.0 ± 2.3	2.5 ± 2.6	6.4 ± 4.9	7.4 ± 5.4	<0.001	<0.001 [b]	<0.001 [b]	<0.001 [b]
Symptoms of anxiety (GAD-7 total score)	9	1.0 ± 1.5	1.2 ± 1.9	4.9 ± 3.8	5.4 ± 4.4	<0.001	<0.001 [b]	<0.001 [b]	0.016 [b]
Diabetes-specific distress (PAID total score)	0	12.0 ± 12.4	14.1 ± 13.4	29.8 ± 20.1	31.8 ± 21.5	<0.001	<0.001 [b]	<0.001 [b]	0.08
Impact of diabetes (consequences B-IPQ) [a]	21	5.3 ± 2.7	5.7 ± 2.4	7.1 ± 2.0	6.8 ± 2.3	<0.001	<0.001 [b]	<0.001 [b]	0.13
Feelings of loneliness	2	1.9 ± 1.3	2.5 ± 1.7	3.6 ± 2.3	4.5 ± 2.4	<0.001	<0.001 [b]	<0.001 [b]	<0.001 [b]

[a] Question posed to subsample only (n = 1,332)

[b] Significant contrast when using Bonferroni-adjusted α level 0.05 / 3 ≈ 0.0167

In the multivariable models, Type D personality remained significantly associated with suboptimal consultation behavior (OR = 2.03, 1.69 – 2.44), diabetes-specific social anxiety (OR = 2.85, 2.35 – 3.45), the presence of barriers to medication taking (OR = 2.86, 2.36 – 3.47), and suboptimal healthy eating (OR = 2.96, 95% CI 1.94 – 4.52). The two individual Type D components also significantly increased the odds of these suboptimal health behaviors (range of ORs 1.35 – 1.85 for SI only and 1.36 – 2.38 for NA only), but the combination of NA and SI in Type D individuals consistently showed the strongest independent association with all outcomes of interest (Figure 1).

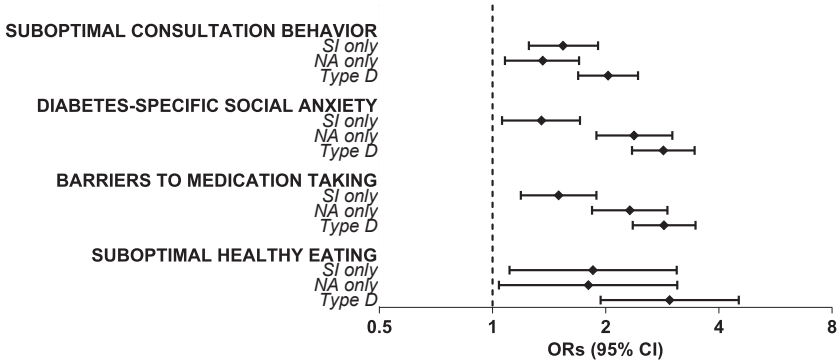

Figure 1 Odds of suboptimal health behaviors as a function of personality

Note. Multivariable logistic regression analyses, displaying the odds of experiencing several suboptimal health behaviors for individuals with SI only, NA only and Type D personality (compared to the reference category), after adjustment for demographics and clinical factors. All personality variables were entered simultaneously in the regression models. Cut-off was ≥ 3 for the suboptimal consultation behavior subscale, ≥ 4 for the diabetes-specific social anxiety subscale, and ≥ 24 for the ASK-12.

DISCUSSION

In this large sample of people with type 1 or type 2 diabetes, Type D personality (the combination of NA and SI) was present in 29%. This estimate did not differ across diabetes type and is comparable to prevalence rates reported for the general population and people with cardiovascular and non-cardiovascular conditions [10, 22, 23], and for a sample of people who were hospitalized for diabetic foot problems [24]. However, it is higher than the prevalence found in a study among people with type 2 diabetes in primary care (17%) [21], although similar estimates have been reported previously [10, 23]. Compared to those scoring high on neither or only one component, people with diabetes and Type D personality tended to have a less healthy diet, were less likely to consult their health professional(s), experienced more barriers regarding medication use, and reported more loneliness, more diabetes-specific social anxiety, and more symptoms of anxiety and depression in general. NA (with or without SI) was associated with infrequent exercise, emotional and external eating style,

and diabetes-specific distress, and SI (with or without NA) with suboptimal inspection of feet. No relevant differences were found with respect to physiological risk factors, in line with the results from a study among people with type 2 diabetes where participants with and without Type D personality did not differ with respect to glycemic control, cholesterol levels and blood pressure [21]. Previous research concluded that Type D is not confounded by traditional cardiovascular risk factors [10], suggesting that other pathways may be implicated. Extending earlier findings comparing people with and without Type D personality [10, 13-19, 22, 23], our results confirm that behavioral and emotional factors are viable candidates.

Previous efforts to relate personality dispositions to the consumption of specific dietary components such as fat and salt have generally produced inconsistent results [34]. However, neuroticism has been positively related to skipping breakfast, dieting to lose weight, and unwillingness to try new foods, and negatively related to consumption of vegetables, fruit and brown bread [34]. In the present study, the NA+ / SI+ (Type D) group was the least likely to follow a healthy diet on a regular basis. A strong tendency to eat in response to emotions or external cues was found in both Type D individuals and in those with NA only.

With respect to physical activity, NA was more prominent in explaining exercise behavior than SI. Both neuroticism and introversion have been related to lower levels of exercise [35, 36]. The need to socialize and meeting people is a prominent exercise motive along the introversion-extraversion dimension, but neuroticism has been associated with a range of exercise barriers, including lack of motivation / desire, lack of energy and embarrassment at having a fitness evaluation [35]. The passive stance enclosed in most of these barriers may be a stronger determinant of physical activity than social considerations and could be the main driving factor in the association between Type D personality and exercise documented in previous studies [15, 16, 18].

A recent study among individuals who were hospitalized for myocardial infarction concluded that the constituent components of Type D do interact to predict medication adherence, after controlling for the effects of each component separately [17]. However, data from a sample with acute coronary syndrome attenuated this conclusion by suggesting the primacy of NA over the Type D personality construct in predicting medication adherence [37]. Our results may add yet another dimension to this discussion by suggesting that it might not be the actual frequency of medication taking that is at stake for individuals with Type D personality, but their tendency to perceive more (potential) barriers to medication taking. Similar perceptual differences have been found in people with obstructive sleep apnea who were using continuous positive airway pressure (CPAP) treatment. Type D individuals reported a significantly higher frequency of side effects from the CPAP treatment, but also experienced the side effects as more troublesome [38].

Building upon previous studies reporting a relation between Type D personality and suboptimal consultation behavior [20, 39], our results suggest it is in fact the combination of NA and SI that bears the strongest association with the tendency not to consult health professionals in case of problems with diabetes management and diabetes-specific social anxiety related to the health care contact. Coupled with an inhibited interpersonal style, people with a Type D personality may be particularly inclined not to address topics that carry a high risk of negative evaluation by health professionals, e.g. whether one is successfully managing his / her diabetes and health, and to enter the health care contact anticipating direct or indirect judgmental interactions. They appear less likely to actively address any problems that arise and characteristically cope by using avoidance strategies such as resignation and withdrawal [40]. In addition, they are more likely to endorse statements such as "One can do little or nothing for maintaining and improving one's health status" [41].

The joint presence of NA and SI showed the strongest association with mental health status in the present study. Type D personality has previously been associated with depression, anxiety, loneliness, inadequate social support, and stressful life events [10, 21-23, 40, 41]. We extend these findings by showing that higher symptom reports of general emotional distress in individuals with Type D personality are not fully explained by trait NA alone. People high on NA are quite likely to discuss their own thoughts, feelings and behaviors with other people [42]. Individuals with Type D personality may feel a similar need to express themselves, but they are held back by social evaluation concerns which may add to their overall distress levels. Most strikingly, individuals with a Type D personality had a 15-fold increased odds of experiencing loneliness, even after adjustment for partner status and the two individual Type D components. Previous studies have linked Type D personality to self-reported social isolation [41] and lower levels of perceived social support [13, 40].

Of note, people with Type D personality and those with NA alone did not differ with respect to diabetes-specific distress. In Type D research, few studies have focused on emotional functioning related directly to the medical condition itself. Type D personality has been associated with more negative illness perceptions in people with myocardial infarction and colorectal cancer [43, 44]. However, most of these cognitive and emotional representations of illness appear to be driven by NA, irrespective of standing on SI [44]. One tentative hypothesis would be that, from the perspective of an individual having a Type D personality, the distress directly linked to a concrete medical condition is somehow more socially acceptable than less tangible symptoms of depression or anxiety. While we did see a clear relation between Type D and diabetes-specific social anxiety, this only bore on the diabetes-related medical setting.

Limitations of the present study are its cross-sectional design, the use of self-report measures, a definition of optimal health-promoting behavior that did not account for maladaptive, hyper vigilant behavior (e.g. checking blood glucose levels significantly more often than needed), and the representativeness of the sample for the diabetes population at large. As described elsewhere [25], the Diabetes MILES – The Netherlands sample underrepresented people with type 2 diabetes managing their condition with a combination of lifestyle modifications and blood glucose lowering tablets, those from ethnic minority groups, and people with co-morbid vascular conditions. Strengths of the study include the large number of participants, the wide variety of health behavior and emotional distress measures, and the four-group stratification which allowed a more detailed analysis of the unique and shared health correlates of NA and SI.

In conclusion, people with diabetes and Type D personality appear to be less likely to eat healthy, are more likely to report barriers surrounding medication use, loneliness and symptoms of depression and anxiety, and are more reserved and anxious when it comes to health care contacts. Combined with a tendency to exercise infrequently and to eat in response to emotions and external stimuli, Type D delineates a group of people who may require special clinical attention. Further study is warranted to test the clinical relevance of Type D personality for people with diabetes in terms of clinical prognosis. Our study suggests that there are important individual differences in the way people perceive and manage their health. NA and SI do not cover all personality dimensions relevant to health, but their combination may help to identify those individuals who are at increased risk of suboptimal health behaviors and emotional distress and at the same time less likely to address these and other issues during medical visits. These individuals might benefit from a more patient-tailored care approach, where health care providers are sensitive to their tendency to keep worries and problems to themselves.

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Online Appendix Table 1 Structural validity and reliability of the purpose-designed consultation behavior questionnaire

		Factor I	Factor II	Corrected item-total correlations
Suboptimal consultation behavior in case of problems				
1	If new symptoms develop that worry me, I contact a health professional (R)	**0.77**	-0.11	0.49
2	If existing symptoms get worse, I contact a health professional (R)	**0.77**	-0.09	0.50
8	If I find it difficult to take my diabetes medication in the correct way, I disucss this with a health professional (R)	**0.42**	0.13	0.45
9	If I find it difficult to lead a healthier lifestyle (e.g. exercise more, eat healthier, quit smoking), I discuss this with a health professional (R)	**0.40**	0.16	0.43
				Cronbach's α = 0.67
				Lambda2 = 0.68
				MICC = 0.36
Diabetes-specific social anxiety				
3	If I share my concerns about my diabetes with a health professional, he / she will think I am exaggerating	0.09	**0.45**	0.36
4	At a meeting with a health professional or a check-up, I am afraid to receive bad news about my diabetes	-0.11	**0.49**	0.34
7	If my blood glucose is often too high, I rather not tell a health professional	0.05	**0.52**	0.40
10	When things are not going well with my diabetes, a health professional will blame me	-0.01	**0.57**	0.41
				Cronbach's α = 0.59
				Lambda2 = 0.59
				MICC = 0.27
5	If I don't understand what a health professional is saying, I ask for clarification (R)	0.25	0.25	
6	If I disagree with a health professional, I will stand up for myself (R)	0.20	**0.33**	

MIIC = mean inter-item correlation; (R) = reverse coded; Bold: factor loadings ≥|0.30|
Simple structure: items loading >|0.40| on one factor and <|0.30| on any other factor after rotation
Exploratory factor analysis (principal axis factor extraction, oblimin rotation) yielded three factors with initial eigenvalue > 1 (2.9, 1.4 and 1.02, respectively). However, as the scree plot showed a marked elbow after the second factor, two factors were retained. Kaiser-Meyer-Olkin measure of sampling adequacy = 0.76; Bartlett's test of sphericity $p < 0.001$; cumulative explained variance 43%.

Online Appendix Table 2 Eating patterns, stratified by the four NA / SI groups (n = 3,314)

	REFERENCE GROUP	ONLY ONE TYPE D COMPONENT		TYPE D PERSONALITY	Overall *p*	TYPE D *versus*	TYPE D *versus*	TYPE D *versus*
	NA- / SI-	NA- / SI+	NA+ / SI-	NA+ / SI+	value	NA- / SI-	NA- / SI+	NA+ / SI-
Fruit (≥ 2 pieces)	2.1 ± 1.0	1.9 ± 1.0	1.9 ± 1.0	1.8 ± 1.1	<0.001 §	<0.001 [a]	0.002 [a]	0.05
Vegetables (≥ 200 gram)	2.4 ± 0.8	2.3 ± 0.8	2.3 ± 0.8	2.2 ± 0.8	<0.001 §	<0.001 [a]	0.01 [a]	0.003 [a]
Whole grain products	2.6 ± 0.9	2.6 ± 0.9	2.5 ± 1.0	2.4 ± 1.0	0.001 §	<0.001 [a]	0.005 [a]	0.62
Fatty fish	0.7 ± 0.5	0.7 ± 0.5	0.7 ± 0.5	0.6 ± 0.5	<0.001 §	<0.001 [a]	0.09	<0.001 [a]
Full-fat milk products	0.4 ± 0.8	0.4 ± 0.8	0.5 ± 0.8	0.4 ± 0.8	0.17	-	-	-
Full-fat cheese	0.9 ± 1.0	1.0 ± 1.0	1.0 ± 1.0	0.9 ± 1.0	0.24	-	-	-
Non-lean meat	0.8 ± 0.6	0.8 ± 0.6	0.8 ± 0.6	0.9 ± 0.6	0.001 §	<0.001 [a]	0.09	0.12
Fried products	0.7 ± 0.5	0.7 ± 0.5	0.7 ± 0.5	0.7 ± 0.5	0.004 §	0.002 [a]	0.008 [a]	0.68
Salt intake	1.3 ± 1.2	1.3 ± 1.2	1.3 ± 1.2	1.3 ± 1.2	0.83	-	-	-
Sweets	0.9 ± 0.8	1.0 ± 0.8	1.0 ± 0.8	1.1 ± 0.8	<0.001 §	<0.001 [a]	0.16	0.09

§ Significant overall group difference when using Bonferroni-adjusted α level 0.05 / 10 = 0.005 for individual items

[a] Significant contrast when using Bonferroni-adjusted α level 0.05 / 3 ≈ 0.0167

CHAPTER 10

Summary and general discussion

In the present Chapter, the main findings of this thesis are summarized. This is followed by a discussion of methodological and conceptual considerations, clinical implications, and suggestions for future directions.

OVERVIEW OF MAIN FINDINGS

In **Chapter 2**, we examined the prevalence of depression in people with impaired glucose metabolism and undiagnosed diabetes relative to each other and to individuals with normal glucose metabolism and with previously diagnosed type 2 diabetes by reviewing the literature and conducting a meta-analysis of studies on this topic. The meta-analysis showed that the odds of depression was not increased in people with impaired glucose metabolism versus those with normal glucose metabolism (OR = 0.96, 95% CI 0.85 – 1.08). The odds of depression did not differ between people with undiagnosed diabetes and those with either normal glucose metabolism (OR = 0.94, 95% CI 0.71 – 1.25) or impaired glucose metabolism (OR = 1.16, 95% CI 0.88 – 1.54). Finally, people with impaired glucose metabolism or undiagnosed diabetes both had a significantly lower odds of depression compared with people with previously diagnosed type 2 diabetes (OR = 0.59, 95% CI 0.48 – 0.73 and OR = 0.57, 95% CI 0.45 – 0.74, respectively). These results indicate that higher blood glucose levels per se in the prediabetes or early diabetes stages are not associated with a higher prevalence of depression. Furthermore, they provide support for the "emotional burden hypothesis", which states that the burden of knowing that you have diabetes and having a chronic condition that you have to manage or complications to cope with contribute to higher levels of depression.

In **Chapter 3**, we described the rationale and design of the DiaDDZoB (*Dia*betes, *D*epression, Type *D* personality *Z*uid*o*ost-*B*rabant) Study. This prospective cohort study aimed to examine: (1) the course of depression (defined as a score of ≥ 12 on the Edinburgh Depression Scale) in people with type 2 diabetes in primary care; (2) whether depression and Type D personality were associated with the development of microvascular complications and / or macrovascular disease and with mortality; and (3) the behavioral and pathophysiological mechanisms that may mediate these associations. The baseline assessment took place in 2005 (n = 2,460) and follow-up waves were realized in 2007 (n = 2,225) and 2008 (n = 2,032). Measurements included a nurse-led interview, a self-report questionnaire and the results from regular care laboratory tests and physical examinations.

Chapter 4 examined the course (incidence, recurrence / persistence) of depression in people with type 2 diabetes, using data from the DiaDDZoB cohort, with three separate assessments during a 2.5 year period. In addition, we tried to identify demographic, medical

and psychological risk factors predicting these different course patterns. A total of 630 participants (26%) met the criterion for depression at one or more assessments. In the subgroup with no baseline depression, incident depression at follow-up was present in 14% (n = 310), while recurrence / persistence in those with baseline depression was found in 66% (n = 212). The presence of any depression was significantly associated with being female, low education, non-cardiovascular chronic diseases, stressful life events and a self-reported history of depression. Incident depression was predicted by female sex, low education and depression history, while people with a history of depression had a 2.5-fold increased odds of recurrent / persistent depression. Depression appears to be an important co-morbid health problem in people with type 2 diabetes, with one in seven people reporting incident depression during a 2.5 year period. Once present, depression often becomes a chronic / recurrent condition in this group. Self-reported history of depression was the only factor that consistently identified those individuals who had increased odds of experiencing any kind of depression during the study, even after taking demographics, medical co-morbidities and stressful life events into account.

In **Chapter 5**, we examined whether depression (Edinburgh Depression Scale total score ≥ 12) was associated with time to insulin initiation in insulin-naïve people with type 2 diabetes from the DiaDDZoB cohort. The prevalence of depression was 12% (n = 168), and 253 (18%) participants had started insulin therapy over a mean follow-up period of 1,597 ± 537 days. People with depression were not more likely to start insulin therapy earlier or later than their non-depressed counterparts (HR = 0.98, 95% CI 0.66 – 1.45), also after adjustment for sex and age (HR = 0.95, 95% CI 0.64 – 1.42). Adding individual candidate confounders to the age- and sex-adjusted base model did not change the HR by more than 4% and the association remained non-significant. Additional studies in other samples, preferable incorporating more information about the decision making process behind insulin initiation, are needed to further elucidate whether or not depression is associated with (delayed) initiation of insulin therapy.

In **Chapter 6**, we used cross-sectional baseline data from the DIAZOB Primary Care Diabetes study, a dynamic cohort study of people with type 2 diabetes in primary care, to explore whether symptom clusters relating to the two core features of depression – dysphoria and anhedonia – were differentially associated with suboptimal glycemic control (HbA_{1c} values ≥ 7%; 53 mmol / mol). In univariable logistic regression analyses, anhedonia was significantly associated with suboptimal glycemic control (OR = 1.29, 95% CI 1.09 – 1.52), while both dysphoria (OR = 1.04, 95% CI 0.88 – 1.22) and anxiety (OR = 0.99, 95% CI 0.83 – 1.19) were not. The association between anhedonia and glycemic control remained significant after adjustment for dysphoria and anxiety (OR = 1.33, 95% CI 1.11 – 1.59). Alcohol consumption

and physical activity met criteria for mediation, but did not change the strength of the association between anhedonia and glycemic control by more than 5%. Adjustment for diabetes duration attenuated the association, but the association was still significant (OR = 1.20, 95% CI 1.01 – 1.43). Studying different symptom clusters of depression, in particular anhedonia, may add to a better understanding of a possible relationship between depression and glycemic control.

Chapter 7 examined whether depression was associated with hospitalization for cardiovascular disease and all-cause mortality in the DiaDDZoB Study, and whether symptom clusters related to dysphoria, anhedonia and anxiety were differentially associated with these end points. In addition, we sought to determine whether there were symptom-specific behavioral or pathophysiological mechanisms in play. The prevalence of depression (Edinburgh Depression Scale total score ≥ 12) was 12% (n = 182). At the end of the five-and-a-half year follow-up, 191 people had experienced a cardiovascular hospitalization and 139 had died. Depression was associated with survival time (adjusted HR = 1.93, 95% CI 1.10 – 3.41), but did not predict time to cardiovascular hospitalization. After adjustment for meaningful demographic and clinical confounders, depressed individuals still had an almost 2-fold increased risk to die from all-causes at any moment during follow-up compared with their non-depressed counterparts. With regard to different (depression) symptom clusters, symptom clusters focusing on negative emotions predicted time to first cardiovascular hospitalization during follow-up. Dysphoria was associated with a shorter time to event (unadjusted HR = 1.49, 95% CI 1.02 – 2.17), but this relation was no longer significant after taking confounding factors into account. The presence of anxiety symptoms was associated with a longer time to event, but only when adjusting for confounders (adjusted HR = 0.52, 95% CI 0.29 – 0.92). Symptoms of anhedonia were consistently associated with shorter time to death of all-causes (adjusted HR = 1.72, 95% CI 1.11 – 2.65). Physical activity met criteria for mediation, attenuating the HR for anhedonia by approximately 20%. Symptom-specific associations with health outcomes and mechanistic pathways deserve further exploration in other studies.

In **Chapter 8**, we examined the validity / reliability and clinical correlates of the Type D personality construct and its assessment in people with type 2 diabetes from the DiaDDZoB cohort. The 2-factor model of the Type D construct was confirmed in exploratory and confirmatory factor analyses; results were stable across gender. The Negative Affectivity (NA) and Social Inhibition (SI) subscales had adequate reliability in both men and women, as measured by Cronbach's alpha (NA = 0.87, SI = 0.83), lambda2 (NA = 0.87 / 0.88, SI = 0.84), corrected item-total correlations (NA 0.47 – 0.77, SI 0.34 – 0.72) and mean inter-item correlations (NA = 0.50 / 0.51, SI = 0.42). One year test–retest reliability using intraclass

correlation coefficients was 0.64 / 0.63 for NA and 0.73 / 0.65 for SI. Type D and non-Type D individuals did not differ in vascular history or physiological risk factors, but Type D women had a more sedentary lifestyle ($p = 0.003$). Type D individuals experienced less social support and more stressful life events, loneliness, and more depressed mood, anhedonia and anxiety ($p < 0.001$ for most variables). These differences were clinically relevant (Cohen's $d > 0.60$ for most variables, indicating moderate to large effect sizes). Type D personality can be reliably assessed in people with type 2 diabetes, and is associated with increased loneliness, stress and emotional distress in this group.

Chapter 9 aimed to explore whether Type D personality and its two constituent components – NA and SI – were differentially associated with three potential mechanisms that could link Type D personality with poor health outcomes (health behaviors, emotional distress, and pathophysiological factors) in people with type 1 or type 2 diabetes, using data from Diabetes MILES – The Netherlands. Compared with those scoring high on neither or only one component, people with diabetes and Type D personality tended to have a less healthy diet, were less likely to consult their health professional(s) in case of problems with diabetes management, experienced more barriers regarding medication use, and reported more loneliness, more diabetes-specific social anxiety, and more symptoms of anxiety and depression in general. NA (with or without SI) was associated with less frequent exercise, emotional and external eating style, and diabetes-specific distress, and SI (with or without NA) with suboptimal inspection of feet. No relevant differences were found with respect to other self-care measures or pathophysiological risk factors. In multivariable logistic regression analyses, Type D personality was associated with a 2 to 3-fold increased odds of several suboptimal health-behaviors and related cognitions and a more than 15-fold increased odds of experiencing general emotional distress, after adjustment for demographics, clinical variables and the individual Type D components. Assessing the joint presence of NA and SI may help to identify those individuals who are at increased risk of suboptimal health behaviors and emotional distress and at the same time less likely to address these and other issues during medical visits.

METHODOLOGICAL AND CLINICAL CONSIDERATIONS

Study design

All studies included in this thesis were based on cross-sectional or longitudinal observational data. Cross-sectional studies prohibit definite conclusions regarding causality. Prospective studies may give more insight in certain relations over time, but still do not provide conclusive proof for causality. Randomized controlled trials and experiments are currently the best way to study causal relationships, but may not always be feasible or ethical in clinical settings [1].

With respect to potential confounders, we have examined a range of demographic, medical and psychosocial factors. However, there always is the possibility of residual confounding by unmeasured or imperfectly measured factors, for example with respect to disease characteristics. Concerning the overall research paradigm, the associations of interest in the present thesis have all been studied at group level. While this approach may provide general insights into presumed relations, it may not always adequately reflect the reality for individuals. When trying to understand complex phenomena such as the decision (not) to initiate insulin, where a multitude of individual patient-, provider- and health-care system factors play a role, more ideographic study designs may be of additional value.

Study setting

The majority of studies in this thesis were based on data from a cohort of people with type 2 diabetes, who were being treated in primary care practices. While this group covers the majority of people currently living with diabetes, it may be premature to generalize findings in this group to the diabetes population at large. Dutch secondary care settings predominantly focus on people with type 1 diabetes or more complex type 2 diabetes, e.g. in case of multiple long-term vascular complications or problematic diabetes regulation, or when intensive blood glucose lowering regimens are required. Most people with type 2 diabetes seen in primary care are in optimal glycemic control and manage their diabetes with oral agents and lifestyle recommendations only. The prevalence of elevated depressive symptoms in chapter 4 (13 – 16%) was lower than previously found in outpatient settings [2], but comparable to figures reported in population-based studies [3, 4].

Compared with the rates generally found in people with cardiovascular disease and the general population (approximately 20 – 35%) [5, 6], the prevalence of Type D personality found in the DiaDDZoB Study (17%; chapter 8) was relatively low, but similar estimates have been reported [5, 6]. A previous study among people who were hospitalized for diabetic foot problems found a prevalence of 33%, but they were younger than the DiaDDZoB subsample (mean age 61 years vs. 69 years) and it was unclear whether they were normally seen in primary or secondary care. Chapter 9 found a similar rate of Type D personality for people with type 1 or type 2 diabetes (29%), but as primary health care setting was not measured reliably in Diabetes MILES – The Netherlands, a comparison by primary / secondary care for the type 2 subsample could not be made.

Diabetes type

While most studies examined people with type 2 diabetes in primary care, one chapter provided information about people with type 1 and type 2 diabetes, participating in a national online survey. Type 1 and type 2 diabetes differ on several important aspects,

including etiology, clinical presentation and self-management activities, and at this stage it is unclear whether this is any different for the etiology and presentation of depression in both groups. Where possible, studies are advised to stratify results by diabetes type. The clinical correlates of Type D personality (chapter 9) were combined across diabetes type, but only after establishing that results were similar for type 1 and type 2 diabetes. Apart from chapter 9, diabetes status was based on diagnoses made in clinical practice. While this will be reliable for most individuals, there is always the possibility that less common diabetes types, such as latent auto-immune diabetes of adulthood, are misdiagnosed. Although the scope of this problem is not entirely clear, in a population-based sample of 2,350 Dutch individuals aged 50 – 74 years it was found that about 4% of people with known diabetes appear to have antibodies to GAD65 [7]. In studies where diabetes type is determined through self-report, such as in chapter 9, a certain margin of error cannot be ruled out either. For example, some people with type 2 diabetes using insulin treatment may have self-identified as having type 1 diabetes.

Co-morbidities, complications and mortality

Problems relating to self-report of diabetes type apply to complications and co-morbidities as well, as some people may not be aware of specific diagnoses. In some of the studies included in the present thesis, we have addressed these issues by verifying self-reported diagnoses in the medical chart or by using data from a national hospital registry. However, even in these cases, researchers are dependent on the quality of diagnostics and registration inherent to these systems. A similar line of reasoning goes for the mortality data in chapter 7, where (all-cause) mortality data were available from a range of different sources.

The problem of overfitting in regression analyses

In several of the chapters in the present thesis, we have used logistic regression or survival analyses to examine correlates / predictors of binary outcomes or time-to-event data. An issue that needs to be considered when using these statistical methods is the problem of overfitting, i.e. capitalizing on the idiosyncrasies of the sample at hand [8]. Overfitted models may ask too much from the available data and generally occur when a model is too complex, consequently yielding overly optimistic results [8]. Simulation studies have suggested that logistic regression and survival analyses will produce relatively unbiased estimates if the minimum number of events per predictor is approximately 10 [9, 10]. While this guideline does not appear to be violated in the chapters concerned, we have tried to interpret our results in cautious language where appropriate [8]. Babyak (2004) has suggested several strategies to avoid or minimize overfitting [8]. One option would be to increase a study's follow-up time or to recruit more participants, in order to include more events in the planned regression analyses. Alternatively, the number of predictor variables in the model could be reduced by

combining theoretically related predictors into a single composite measure, as was done in Chapter 4 and 7 for microvascular complications, cardiovascular disease, and other (chronic) medical conditions. While this approach preserves degrees of freedom in the model, this comes at a trade-off, as specific information about the individual components of the composite measure is lost [8].

Measuring mediation

Central to the definition of a mediating variable is that it is in the causal pathway between the independent variable and the outcome of interest [11]. As noted before, causality cannot be inferred from observational studies, although time-varying factors are useful in this context [11]. Many observational studies (including chapter 6 and 7) examine potential mediating factors that are measured at the same point in time as the independent variable, making the relation even more unclear. Despite these limitations, it may be informative to examine some basic relations between the variables of interest to get a first glance of mediation [12], as was done in these chapters. These procedures are to be preferred over strategies where all potential mediators are included in a multivariable model at the same time, as they may obscure an association that is actually present. However, studying potential behavioral and pathophysiological mediating mechanisms in isolation ignores the fact that these factors are often interrelated and interdependent [13]. Advanced computational models may provide one way of dealing with this complexity, but they are beyond the scope of regular medical statistics [13] and may require a more ideographic approach before being used in large cohort studies.

Measuring emotional distress in people with diabetes

The predominant conceptual model for understanding the problem of depression in people with diabetes is the syndromal diagnosis of major depressive disorder [14]. However, in terms of research, the vast majority of studies examining depression in diabetes – including the studies in the present thesis – have relied on self-report questionnaires that assess symptoms of depression or distress [14]. Most self-report measures contain some items that could be confounded with symptoms of suboptimal diabetes management, including fatigue, sleeping difficulties and appetite changes [15] and, thus, are not necessarily related to depression. At present, it is also unclear whether specific depressive symptoms are more strongly related to adverse health outcomes in people with diabetes. Finally, self-report questionnaires of depression may also tap into a broader spectrum of emotional problems [16] and may reflect other types of distress including more general forms of distress [14, 16, 17].

Type D personality refers to a general form of distress that is defined by the tendency to experience negative emotions (Negative Affectivity or NA) and to inhibit self-expression

(Social Inhibition or SI) [5, 6], and that is assessed by an elevated score (≥ 10) on both the NA and SI subscales of the DS14 [18]. By comparing Type D individuals (NA+ / SI+) with an undifferentiated combination of the three non-Type D groups (NA- / SI+, NA+ / SI-, NA- / SI-), it is assumed that these three groups all have similar levels of risk [19]. However, a significant Type D versus non-Type D group comparison could also be due to other patterns, for example when a high risk in one of the three non-Type D groups is averaged with a low risk in the other two groups [19]. Chapter 9 explored this issue by comparing clinical correlates across all four NA / SI groups, and found significant differences between the Type D group and the other three groups with respect to several health behaviors and emotional distress measures. However, it still remains unclear whether the health risks associated with Type D are due to the addition of individual effects for NA and SI, or whether there is a synergy between both subcomponents.

Given the construct and measurement overlap that has been identified across specific negative emotions such as depression and anxiety [20], there has been considerable debate as to whether it might be more appropriate to study a more general disposition toward negative affectivity when it comes to understanding the health risks of emotional distress [21]. There appears to be merit to both approaches, as previous work has suggested that there are both unique and shared effects of these negative emotions on the risk of incident coronary heart disease [21]. The results of the present thesis imply that examining symptom clusters related to specific negative emotions does have additional value in understanding why some people are more likely to experience adverse health outcomes than others, as long as (the absence of) positive emotion is also taken into account. At the same time, our findings support previous assertions that symptoms of depression / anxiety may not only reflect episodic distress but also a more ingrained tendency to experience distress [5], which may partly account for the health risks ascribed to specific types of distress. Therefore, it appears best not to consider specific (e.g. dysphoria, anhedonia, anxiety) and general (e.g. Type D personality) approaches to distress as incompatible, but rather as representing complementary perspectives to understand emotional functioning and health outcomes [5].

Treatment of depression in people with diabetes

Depression is recognized and treated appropriately in fewer than half of depressed people with diabetes in primary care [22, 23]. This may be due to an overlap among ''somatic'' depression symptoms and symptoms of diabetes [15] or an overlap with symptoms that are related to increasing age. People with diabetes may also be reluctant to discuss emotional distress during routine care consultation [24]. The results from chapter 4 suggest that a simple question about history of depression may help clinicians to identify those individuals who have an increased risk for depressive symptoms later on. However, case-finding alone does

not necessarily improve the management of depression [25], also in people with diabetes [26], indicating the need for additional care. A recent meta-analysis showed that pharmacological treatment, psychotherapeutic interventions and diabetes self-management education improve mental health in people with diabetes who are emotionally distressed [27]. Some authors have suggested that we may maximize the effect of treatment in people with diabetes by combining treatment for depression with interventions focusing on diabetes management [28, 29]. For example, a nurse-led care-management intervention integrating the management of medical and psychological conditions improved both medical outcomes and depression in depressed people with diabetes, heart disease, or both [30]. One area where such an integration of depression and self-care interventions might be easily achieved is behavioral activation through exercise [29], as there is evidence supporting the benefits of exercise for improving both diabetes [31, 32] and mood [33, 34].

Personalized approach

A personalized approach to intervention should also consider individual differences in the various determinants of emotional distress among people with diabetes. Understanding the diabetes-related factors that drive the experience of distress in people with diabetes is crucial to the development of appropriate interventions, and in many cases interventions that focus on addressing both distress and diabetes management are likely to have the strongest effect [14]. Apart from diabetes related-factors, individual differences in personality should also be considered as a determinant of distress. Type D personality may help to identify those individuals who are at increased risk of emotional distress or suboptimal health behaviors while, at the same time, being less likely to address these issues during medical visits. Findings from chapter 8 and 9 are consistent with previous studies [5, 35], suggesting that the NA and SI do signal important individual differences in the way people with diabetes perceive and manage their health. The fact that Type D refers to a personality construct does not necessarily imply that interventions in Type D individuals may not be beneficial [35]. People with Type D personality can learn new strategies to reduce their level of general distress [36]. For example, mindfulness-based stress reduction may reduce the negative affectivity and social inhibition components of Type D [37], and has also been shown to improve health-related quality of life and mental health in adults with diabetes [38]. The variety of interventions delivered over the internet is growing rapidly, and e-health may also be an appropriate way to address the emotional problems of people with Type D personality. These interventions may not only reduce general emotional distress but also diabetes-specific distress when the content of web-based interventions are being modified and tailored towards the specific experiences and needs of people with diabetes [39].

FUTURE DIRECTIONS

The temporal architecture of depression and diabetes

One of the issues that remain to be resolved is related to the temporal architecture of depression. Chapter 4 indicated that self-reported history of depression was the only factor that consistently identified those individuals who had increased odds of experiencing any kind of depression later on, even after controlling for demographics, medical co-morbidities, and stressful life events in the previous year. Knowing that depression may predate and even predict the onset of type 2 diabetes [40, 41], it may be worthwhile to explore the relation between depression and diabetes from a lifetime perspective. Although time- and resource intensive, important new insights might come from a study where a cohort of people without diabetes and without depression is followed over a longer period of time. By tracking the course of depression in terms of remission, relapse, recovery and recurrence [42] and by examining the timing of diabetes onset in this process, we may learn whether depression in diabetes represents an independent new episode or relapse of the initial episode that prompted the development of diabetes. Furthermore, such a study may shed more light on whether the onset and the course of depression in diabetes are predicted by the same factors as in the general population, or whether diabetes-specific factors are more important.

Although such a design may be easier to implement for type 2 diabetes than for type 1 diabetes due to its onset later in life, it is important to focus on depression in type 1 diabetes as well. There is a disconcerting shortage of published data available on the prevalence and treatment of depression and other types of emotional distress in type 1 diabetes [27, 43], and with the escalating rates of obesity found across all age groups [44], younger people with type 2 diabetes may also become a special group of interest. Type 1 and type 2 diabetes differ on several important aspects, including etiology, clinical presentation and self-management activities, and it is premature to conclude at this stage that this is different for the etiology and presentation of depression in both groups.

The heterogeneity of emotional distress in diabetes

More randomized controlled trials are needed to test collaborative care approaches that have a broader focus than just major depression, and offer suitable treatment for anxiety and diabetes-specific distress [45] as well as subclinical depressive symptoms. These studies may also determine whether screening is a necessary component of these enhanced care strategies [25], and whether stepped-care approaches in which individuals receive different types and intensities of services tailored to their observed outcomes [46] are the most effective and cost-efficient way of obtaining results. Given the low figures of emotional distress reported in the present thesis for people with type 2 diabetes in primary care, we may need to reconsider whether such resource-intensive approaches are suitable for all clinical settings.

Improving clinical outcomes and treatment for people with diabetes and depression

Given that a considerable number of people with diabetes do not respond to the current depression treatment modalities, future research efforts are required to optimize depression outcomes in this group [45]. Distinguishing major depression from other types of emotional distress may be one step, but the heterogeneity within depression should also be taken into account. Focusing treatments on the predominant symptomatology of an individual may improve the success rates of depression interventions [47], and could potentially also improve the increased risk of adverse events that has been observed among depressed people with diabetes [48, 49]. Findings from the present thesis have suggested that different symptom clusters may be differentially related to health outcomes in people with diabetes. These preliminary findings merit further exploration in other diabetes cohorts. If different symptoms of depression indeed prove to have divergent associations with (diabetes) prognosis, we might optimize outcomes for depressed people with diabetes by directly targeting the underlying (vasculo)toxic mechanisms as well.

The potential mechanisms that may explain a link between depression (subtypes) and adverse health outcomes are generally divided into behavioral and pathophysiological pathways. Chapter 7 identified an important role for physical activity in explaining all-cause mortality, which was not the case for other (cardio)vascular risk factors such as blood glucose, cholesterol and blood pressure. Because depression has been associated with a wide spectrum of mortality causes [50, 51], the mechanisms underlying the association between depression and excess mortality may not be restricted to cardiovascular disease. Other candidate pathways that were not addressed in the present thesis, but that may also link depression to mortality across different conditions, include medication taking, dysregulations of the HPA-axis and the autonomic nervous system, and inflammatory processes [13, 51]. By supplementing our current cohort studies with paradigms encompassing comprehensive study of depression subtypes and their health outcomes in small groups of well-selected individuals may provide a plethora of relevant new insights that could inform the design of new cohort and treatment studies.

Screening and treatment: who are we missing?

In order to put findings relating to screening and treatment for emotional problems in the right perspective, we need to know more about the people who are not participating in screening procedures. Preliminary findings suggest that the group who is missed by screening have higher HbA_{1c} values, are younger, are more likely to smoke and show a high rate of not showing up at the outpatient clinic for their appointment with the physician, characteristics that have all been related to depression [52]. If we are systematically missing those people who may need our help most, we may need to rethink ways of reaching them.

Discrepancies between screening-results and the need for / acceptance of professional help
While the high prevalence of undertreatment may partly be due to the low recognition rates of mental health problems in people with diabetes [53], not all people who score positive on screening instruments will need or accept professional help. In a Dutch diabetes outpatient clinic, only one third of all people with elevated depressive symptoms and / or diabetes-related distress indicated an unmet need for which they would like a referral for additional psychosocial care [52]. The remaining group was either not interested in additional care, indicated that they had already received help, or could not be reached [52]. In a Croatian study among people with type 2 diabetes treated at a university clinic for diabetes, 77% of the participants reporting at least one elevated depressive symptom on a postal screening indicated a need for professional help [54]. The reasons to decline help were unknown, although the authors speculated that these individuals may already receive treatment [54]. Almost one-third of the participants who were deemed eligible for a behavioral treatment of subsyndromal depression declined participation, most frequently reporting competing priorities such as professional and family obligations or lack of time as reasons for nonparticipation [54]. Comparing characteristics of people with and without an agreed referral for elevated depressive symptoms and / or diabetes-related distress in the MIND study showed that the first group was more likely to have a lower educational level, diabetes complications and higher HbA_{1c} values [55].

Why people may refuse professional help
As the number of people with screen-detected emotional problems accepting professional care is generally low, it would be interesting to explore the reasons behind this refusal in more detail. Emotional problems as measured with screening questionnaires may not always be severe enough to seriously disrupt daily life, and people may have other, sufficient resources available to cope with their emotional problems, including high levels of social support. Alternatively, people may be reluctant to seek or accept professional help because they minimize problems that are profoundly affecting them or their close ones due to pride or fear of stigma, or because they want to avoid shameful and sometimes confusing feelings. Where there is a clear need for professional care, we need to be sensitive to these potential barriers and think about other paradigms to make this care available. Although certainly not a treatment option for all problems, web-based interventions – where feedback is given in an indirect way - may help to remove some of the reservations people might have in accepting professional help.

Type D personality and health outcomes in people with diabetes

Chapter 8 and 9 have suggested that Type D personality may be related to suboptimal self-care behaviors and emotional distress in people with diabetes. Further study is warranted to determine the clinical relevance of Type D personality for people with diabetes in terms of clinical prognosis. These prospective studies are advised to focus on other potential risk mechanisms as well, including dysregulations of the hypothalamic-pituitary-adrenal axis, sympathetic nervous system and immune processes [56], and to examine whether any risks associated with Type D personality are driven by its NA or SI subcomponent only, or whether it is the combination of the two that poses a risk to health. In the upcoming years, the DiaDDZoB Study will provide some preliminary results with respect to these questions in a cohort of people with type 2 diabetes in primary care. Importantly, these associations should be addressed in other diabetes cohorts as well. Although earlier findings have been reasonably consistent [5, 57], several recent studies have failed to establish a relation between Type D personality and all-cause mortality [58-61]. These later studies mostly focused on people with chronic heart failure, who are generally somewhat older than the samples with coronary artery disease examined in previous studies [57]. Interestingly, depression and anxiety did not predict mortality in these studies either [58-61]. It may be difficult to establish a specific role of psychosocial factors in predicting mortality in older populations, because these individuals often have numerous co-morbid chronic medical conditions that may be implicated.

CONCLUDING REMARKS

By acknowledging the heterogeneity of emotional distress in people with diabetes, we acknowledge that current clinical practice and research might benefit from a more personalized approach. This may mean that we need to learn more about the usefulness of specific interventions and adjust our treatments for different subgroups of people with diabetes [62], in order to successfully improve both emotional distress and diabetes outcomes. This paradigm shift may start small, by reconsidering the potential importance of emotional problems in standard diabetes care. By emphasizing that emotional distress is common in people with diabetes – without overpathologizing problems – and by establishing a working relation where people feel safe to discuss their concerns, health providers may encourage greater willingness to discuss emotional problems and to accept appropriate referral when needed.

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CHAPTER 11

Nederlandse samenvatting (Summary in Dutch)
Dankwoord (Acknowledgements)
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Nederlandse samenvatting (Summary in Dutch)

Inleiding

Leven met diabetes

Wereldwijd krijgt een groeiend aantal mensen te maken met diabetes, een chronische stofwisselingsziekte waarbij sprake is van verhoogde bloedsuikerwaardes als gevolg van een tekort en / of een verminderde werkzaamheid van insuline. In Nederland zijn er ongeveer één miljoen mensen met diabetes, van wie een kwart niet weet dat ze deze aandoening hebben. Er bestaan verschillende vormen van diabetes, die vaak een verschillende oorzaak en presentatie hebben. Bij ongeveer 90% van de mensen met diabetes is sprake van diabetes type 2. Deze vorm van diabetes ontstaat vaak op middelbare of oudere leeftijd, maar wordt vanwege zijn samenhang met overgewicht steeds vaker vastgesteld bij jongvolwassen en kinderen. Een andere belangrijke vorm is diabetes type 1 (5 – 10%), veroorzaakt door vernietiging van cellen in de alvleesklier die verantwoordelijk zijn voor de aanmaak van insuline. Deze aandoening ontwikkelt zich over het algemeen bij kinderen en jongvolwassenen, maar kan in principe op alle leeftijden ontstaan.

De meeste mensen zijn in staat om met diabetes een prettig leven te leiden, maar voor een aantal kan het soms moeilijk zijn om te gaan met de diagnose, de zelfzorg en de (dreiging van) complicaties van de diabetes. Zo kunnen mensen op korte termijn te maken krijgen met te lage (hypo's) of te hoge (hypers) waardes van de bloedsuikers. Op langere termijn kunnen hart- en vaatziekten en beschadigingen aan de kleine bloedvaatjes van bijvoorbeeld de ogen, nieren en zenuwen (microvasculaire complicaties) ontstaan. Het is mogelijk om deze vaataandoeningen te voorkomen of te vertragen door het nastreven van een zo optimaal mogelijke regeling van bloedsuikerwaardes en andere risicofactoren voor hart- en vaatziekten, zoals bloeddruk en cholesterol. De hieruit voortkomende zelfzorg voor de diabetes bestaat uit verschillende activiteiten, waaronder het dagelijks gebruik van tabletten en / of insuline, het regelmatig meten van bloedsuikerwaardes, voetzorg, gezond eetgedrag (en voor sommigen het tellen van koolhydraten) en voldoende lichaamsbeweging. Het is dan ook niet verwonderlijk dat diabetes en de complicaties van diabetes een negatieve invloed kunnen hebben op het emotioneel welbevinden en de kwaliteit van leven van mensen die met deze aandoening leven. Op hun beurt kunnen emotionele problemen de zelfzorg voor de diabetes behoorlijk bemoeilijken en de kans op negatieve gezondheidsuitkomsten verhogen.

Depressie komt vaak voor bij mensen met diabetes

Depressie komt voor bij 10 – 30% van de mensen met diabetes, ongeveer tweemaal zo vaak als bij mensen zonder deze aandoening. Vaak wordt gebruik gemaakt van vragenlijsten om de aanwezigheid van verhoogde depressieve symptomen in kaart te brengen, maar een depressieve stoornis kan alleen vastgesteld worden met een diagnostisch interview. Studies

die depressie meten aan de hand van een vragenlijst vinden vaak hogere percentages sombere deelnemers dan studies die gebruik hebben gemaakt van een interview. Bij mensen met diabetes hangt depressie niet alleen samen met zogenoemde “patiënt-gerapporteerde uitkomstmaten” als kwaliteit van leven, maar er lijkt ook een link te zijn met andere negatieve gezondheidsuitkomsten. Zo zijn er studies die een relatie hebben gevonden tussen depressie en verhoogde bloedsuikerwaardes, de ontwikkeling van microvasculaire complicaties en hart- en vaatziekte, en vroegtijdige sterfte.

Doel van dit proefschrift

In de afgelopen twintig jaar zijn we veel te weten gekomen over de relatie tussen diabetes en emotionele problemen. Er zijn echter nog verschillende vragen onbeantwoord gebleven. Dit proefschrift gaat in op de volgende vragen:

- Kunnen hoge bloedsuikerwaardes en / of de last van het leven met diabetes het grote aantal mensen met diabetes en depressie verklaren?
- Wat is het verloop van depressie bij mensen met diabetes type 2?
- Hangt depressie samen met het moment waarop met insulinetherapie wordt gestart bij mensen met diabetes type 2?
- Hangen symptomen die te maken hebben met de twee hoofdkenmerken van depressie (dysforie, anhedonie) op een andere manier samen met gezondheidsuitkomsten bij mensen met diabetes type 2? Spelen gezondheidsgedrag en verstoorde lichaamsfuncties als hoge bloedsuikerwaardes, verhoogd cholesterol, en hoge bloeddruk hierbij een rol?
- Wat is de rol van andere, meer chronische emotionele problemen bij mensen met diabetes?

Beter begrijpen van het grote aantal mensen met diabetes en depressie

Momenteel begrijpen we nog niet precies waarom depressie vaker voorkomt bij mensen met diabetes dan bij mensen zonder deze chronische aandoening. Een mogelijke reden zou kunnen zijn dat mensen met diabetes eerder depressief raken, omdat zij iedere dag rekening moeten houden met hun aandoening en om moeten gaan met (de dreiging van) complicaties van de diabetes. In dat geval zou depressie vaker moeten voorkomen bij mensen bij wie diabetes type 2 is vastgesteld dan bij mensen die niet weten dat ze diabetes type 2 hebben of bij mensen bij wie sprake is van een voorstadium van diabetes type 2 (pre-diabetes). Deze twee laatste groepen hoeven immers (nog) niet om te gaan met het feit dat ze een chronische aandoening hebben die dagelijkse zelfzorg vereist. Een andere mogelijkheid is dat depressie direct voortkomt uit lichamelijke veranderingen door de diabetes, zoals hoge bloedsuikers. Als hoge bloedsuikers inderdaad direct de stemming beïnvloeden, dan verwachten we dat mensen met een normale suikerstofwisseling minder vaak depressieve

klachten rapporteren dan mensen die hogere bloedsuikers hebben, zoals mensen met pre-diabetes en mensen met nog niet ontdekte diabetes type 2.

Om deze twee mogelijke verklaringen verder te onderzoeken, hebben we in **Hoofdstuk 2** alle bestaande studies in kaart gebracht die hebben gekeken naar het voorkomen van depressie bij mensen met pre-diabetes of ongediagnosticeerde diabetes ten opzichte van mensen met een normale suikerstofwisseling of mensen met eerder vastgestelde diabetes type 2. Uit dit literatuuronderzoek bleek dat depressie niet vaker voorkwam bij mensen met pre-diabetes of met ongediagnosticeerde diabetes in vergelijking met mensen met een normale suikerstofwisseling. Bij deze twee groepen was echter minder vaak sprake van depressie dan bij mensen die eerder de diagnose diabetes type 2 hadden gekregen. Het lijkt er dus op dat depressie niet zozeer samenhangt met de hoogte van de bloedsuikers op zich, maar meer met de emotionele last die de diagnose en zelfzorg van diabetes met zich meebrengen.

Het verloop van depressieve symptomen bij mensen met diabetes
Studies in de algemene bevolking en in de eerste lijn hebben laten zien dat depressie (gemeten met een diagnostisch interview of een vragenlijst) voor veel mensen een chronische en terugkerende aandoening is. Over het verloop van depressie bij mensen met diabetes is veel minder bekend. De studies die zijn verricht suggereren dat depressie in deze groep ook een ongunstig beloop kent, maar hebben verschillende tekortkomingen. Zo onderzochten ze meestal maar een klein aantal mensen met diabetes, hadden ze vaak maar twee momenten waarop depressie werd gemeten, of brachten ze het verloop van de problemen in kaart bij mensen die deelnamen aan een interventie die de klachten mogelijk kon beïnvloeden. Ook over de factoren die het verloop van depressie kunnen voorspellen, weten we maar weinig.

Meer informatie over het beloop van depressie en de gezondheidsrisico's van emotionele problemen komt mogelijk voort uit de DiaDDZoB (*Dia*betes, *De*pression, Type *D* personality Zuid*o*ost-*B*rabant) Studie. In **Hoofdstuk 3** beschrijven we het idee achter en het ontwerp van deze studie die een grote groep mensen met diabetes type 2 in de eerste lijn volgt in de tijd. De belangrijkste doelen van de studie waren (1) het in kaart brengen van het verloop van depressie, gemeten met een vragenlijst, in deze groep; (2) te onderzoeken of depressie en Type D persoonlijkheid samenhangen met de ontwikkeling van microvasculaire complicaties en hart- en vaatziekten, en met vroegtijdig overlijden; en (3) te kijken of gezondheidsgedrag en verstoringen in normale lichaamsfuncties daarbij een mogelijke verklaring vormen. De eerste meting vond plaats in 2005 (2460 deelnemers) en vervolgmetingen werden gerealiseerd in 2007 (2225 deelnemers) en 2008 (2032 deelnemers). Er werd gebruik gemaakt van een interview door de praktijkondersteuner, een vragenlijst die de persoon

zelf moest invullen, en de resultaten van laboratoriumonderzoek en lichamelijk onderzoek dat binnen de normale zorg werd uitgevoerd.

Gebruikmakend van informatie die binnen de DiaDDZoB Studie tijdens drie meetmomenten in een periode van 2 ½ jaar is verzameld, beschrijft **Hoofdstuk 4** het verloop van depressie bij mensen met diabetes type 2. In totaal had één op de vier deelnemers ten minste één keer een verhoogde score op de gebruikte depressievragenlijst. In de groep die bij start van de studie geen depressieve symptomen rapporteerde, was op een later meetmoment bij 14% wel sprake van depressieve symptomen. Twee-derde van de deelnemers die bij aanvang van de studie depressieve symptomen rapporteerden, had later in de studie ook een verhoogde score op de depressievragenlijst. Depressie, gemeten met een vragenlijst, lijkt dus regelmatig voor te komen bij mensen met diabetes type 2 en is vaak chronisch / terugkerend in deze groep. Het rapporteren van eerdere depressie(s) was de enige factor die consistent voorspelde wie tijdens de studie met depressie te maken kreeg, zelfs als rekening gehouden werd met leeftijd, geslacht, opleiding, burgerlijke status, de aanwezigheid van andere medische aandoeningen, en stressvolle gebeurtenissen in het afgelopen jaar.

Depressie en start met insulinetherapie
Omdat er bij diabetes type 1 sprake is van een absoluut tekort aan insuline, moet er meteen na de diagnose begonnen worden met extra toediening van insuline. Bij diabetes type 2 spelen een verminderde gevoeligheid voor insuline in het lichaam en een abnormale afscheiding van insuline een rol. Hierbij kan vaak eerst geprobeerd worden de bloedsuikers omlaag te krijgen met een gezonde leefstijl of tabletten die de bloedsuikers verlagen. Een groot aantal mensen met diabetes type 2 zal uiteindelijk toch insuline moeten gaan gebruiken om de bloedsuikerwaardes te reguleren. Momenteel is het onduidelijk of depressie een rol speelt bij het bepalen van het moment waarop gestart wordt met insulinetherapie. Er zijn aanwijzingen dat de aanwezigheid van depressieve symptomen bij mensen met diabetes type 2 die nog geen insuline gebruiken samenhangt met een negatievere kijk op insulinetherapie. Dit zou ervoor kunnen zorgen dat mensen die depressieve klachten rapporteren de start met insulinetherapie proberen uit te stellen. Het is ook mogelijk dat depressie een eerdere start met insulinetherapie nodig maakt, omdat het samenhangt met een minder optimale zelfzorg en hogere bloedsuikerwaardes.

In **Hoofdstuk 5** is daarom gekeken of depressie, gemeten met een vragenlijst, samenhangt met een eerdere start van insulinetherapie bij mensen met diabetes type 2 die nog geen insuline gebruiken. Naast informatie uit de DiaDDZoB Studie werd hierbij gebruik gemaakt van medicatievoorschriften uit een grote landelijke database (PHARMO Database Network). In een periode van 5 ½ jaar startte 18% van de deelnemers met insulinetherapie. Mensen

met een verhoogde score op de depressievragenlijst startten niet vroeger of later met insulinetherapie dan mensen die geen verhoogde score lieten zien, zelfs niet als rekening gehouden werd met geslacht, leeftijd, bloedsuikerspiegels en andere factoren die mogelijk een rol zouden kunnen spelen bij het besluit te starten met insuline. Er is meer informatie nodig over het beslisproces rondom de start met insuline (zowel wat betreft de persoon met diabetes zelf, de zorgverlener en het zorgsysteem) om met meer zekerheid vast te stellen of depressie inderdaad niet samenhangt met het moment waarop met insulinetherapie wordt begonnen.

De diversiteit van depressie en de gevolgen daarvan voor mensen met diabetes
Naast een per persoon wisselende combinatie van problemen op het gebied van eetlust / gewicht, slaap, concentratie, vermoeidheid, traagheid / onrust, waardeloosheid / schuld, of gedachten aan (zelf)dood is er bij een depressieve stoornis altijd sprake van ten minste één van twee kernsymptomen: een depressieve stemming (ook wel dysforie genoemd) en / of een duidelijk verminderde interesse of plezier in activiteiten (anhedonie). Dysforie omvat negatieve emoties zoals gevoelens van droefheid en leegheid, terwijl het bij anhedonie eerder lijkt te gaan om de afwezigheid van positieve emoties. Er zijn aanwijzingen dat symptomen die samenhangen met anhedonie een sterkere samenhang vertonen met gezondheid dan symptomen die betrekking hebben op dysforie. Zo is bij ouderen uit de algemene bevolking en mensen met hartaandoeningen gevonden dat de afwezigheid van positieve emoties samenhangt met de ontwikkeling van cardiovasculaire aandoeningen en met vroegtijdig overlijden. Over het belang van dysforie en anhedonie voor de gezondheid van mensen met diabetes is nog weinig bekend.

In **Hoofdstuk 6** werd daarom gebruik gemaakt van data uit de DIAZOB Primary Care Diabetes studie, een studie in de eerste lijn die een grote groep mensen met diabetes type 2 over de tijd volgt, om te bekijken of symptomen die betrekking hebben op dysforie op een andere manier samenhangen met een minder optimale instelling van de diabetes, gemeten met behulp van het HbA_{1c}, dan symptomen van anhedonie. Hierbij bleek dat alleen anhedonie – en niet dysforie of angst – samenhing met een minder optimaal HbA_{1c}. Alcoholgebruik, lichaamsbeweging en de duur van de diabetes leken hierbij een mogelijke rol te spelen, maar vormden geen van allen een afdoende en overtuigende verklaring voor de gevonden relatie tussen anhedonie en HbA_{1c}.

Hoofdstuk 7 onderzocht vervolgens of dysforie, anhedonie en angst ziekenhuisopnames voor hart- en vaatziekte en sterfte konden voorspellen in de DiaDDZoB Studie. Ook hier werd gebruik gemaakt van informatie die beschikbaar was in het PHARMO Database Network, ditmaal met betrekking tot ziekenhuisopnames en overlijden. Na 5 ½ jaar was 13% van de

deelnemers ten minste één keer in het ziekenhuis opgenomen geweest vanwege hart- en vaatziekte en 10% van de deelnemers bleek overleden te zijn. Dysforie hing samen met een kortere tijd tot de eerste ziekenhuisopname, maar deze relatie bleek niet overeind te blijven als rekening werd gehouden met demografische en medische factoren. In dat geval bleek angst wel samen te hangen met een langere tijd tot de eerste ziekenhuisopname. In alle scenario's voorspelden symptomen van anhedonie vroegtijdig overlijden. Lichaamsbeweging leek hierbij een belangrijke verklarende rol te spelen.

Type D persoonlijkheid ("binnenvetters")
Een aantal recente studies heeft laten zien dat depressie de ontwikkeling van microvasculaire complicaties en hart- en vaatziekte kan voorspellen bij mensen met diabetes. Meetinstrumenten die gebruikt worden om depressie in kaart te brengen hebben echter vaak betrekking op de afgelopen 1 – 2 weken, terwijl het vaak jaren duurt voordat complicaties zich aandienen. We weten weinig over de gezondheidsrisico's van langer durende emotionele problemen, bijvoorbeeld die te maken hebben met individuele verschillen in persoonlijkheid. In de afgelopen jaren zijn er verschillende studies verschenen die hebben laten zien dat mensen met een hart- en vaatziekte en een zogenaamde Type D persoonlijkheid een groter risico lopen op bijvoorbeeld het doormaken van een hartinfarct, het moeten ondergaan van medische ingrepen om de bloedcirculatie te herstellen, en vroegtijdig overlijden. Mensen met Type D persoonlijkheid ervaren veel negatieve emoties (negatieve affectiviteit), maar zijn tegelijkertijd geneigd deze emoties niet te uiten (sociale inhibitie) uit angst voor kritiek of afwijzing van anderen. Type D persoonlijkheid wordt meestal gemeten met de Type D schaal (DS14), maar we weten niet of we dit instrument zonder meer ook bij mensen met diabetes kunnen toepassen.

Hoofdstuk 8 onderzocht daarom de validiteit (meet de vragenlijst wat hij zou moeten meten) en de betrouwbaarheid (is de vragenlijst consistent) van de DS14 bij mensen met diabetes type 2 uit de DiaDDZoB Studie. De vragenlijst bleek inderdaad twee verschillende factoren te meten, te weten negatieve affectiviteit en sociale inhibitie. De betrouwbaarheid van deze twee schalen was voldoende, ook als de vragenlijst na een jaar opnieuw werd ingevuld. Deze resultaten werden gevonden voor zowel mannen als vrouwen en suggereren dat de DS14 inderdaad toegepast kan worden bij mensen met diabetes. In een volgende stap werd gekeken of mensen met Type D persoonlijkheid verschilden van mensen zonder Type D persoonlijkheid wat betreft demografische en klinische kenmerken. Er bleken geen verschillen te bestaan tussen deelnemers met en zonder Type D persoonlijkheid wat betreft de aanwezigheid van hart- en vaatziekte of risicofactoren voor vataandoeningen, zoals bloeddruk, cholesterol en bloedsuikers. Wel waren vrouwen met een Type D persoonlijkheid minder vaak lichamelijk actief. Deelnemers met een Type D persoonlijkheid rapporteerden

verder minder sociale steun en meer stressvolle gebeurtenissen, eenzaamheid, en meer dysforie, anhedonie en angst.

Een mogelijke weg waarlangs Type D persoonlijkheid de gezondheid negatief zou kunnen beïnvloeden, is minder optimaal gezondheidsgedrag. Eerder onderzoek onder verschillende groepen (gezonde jongvolwassenen, algemene bevolking, mensen die een hoog risico lopen op het ontwikkelen van hart- en vaatziekte, mensen met bestaande hart- en vaatziekte) suggereert dat mensen met Type D persoonlijkheid minder vaak lichamelijk actief zijn en gezond eten, minder vaak adviezen van zorgverleners met betrekking tot medicatie opvolgen, en minder vaak contact opnemen met zorgverleners als daar een goede reden voor is. Type D persoonlijkheid lijkt ook samen te hangen met angst, depressie en andere emotionele problemen, en zou via deze negatieve emoties ook indirect van invloed kunnen zijn op de gezondheid. Het is echter onduidelijk of het hierbij gaat om de combinatie van negatieve affectiviteit en sociale inhibitie, of dat slechts één van de onderdelen van Type D persoonlijkheid een rol speelt.

In **Hoofdstuk 9** werd daarom gekeken of Type D persoonlijkheid en diens twee onderdelen – negatieve affectiviteit en sociale inhibitie – op een andere manier samenhangen met gezondheidsgedrag, emotionele problemen en verstoorde lichaamsfuncties als hoge bloeddruk, verhoogd cholesterol en hoge bloedsuikers bij mensen met diabetes type 1 of type 2. Hierbij werd gebruik gemaakt van gegevens uit Diabetes MILES – The Netherlands, een landelijk online vragenlijstonderzoek onder volwassen Nederlanders met diabetes. In vergelijking met mensen die op geen of slechts één onderdeel hoog scoorden, aten deelnemers met Type D persoonlijkheid minder vaak gezond, waren ze minder geneigd contact op te nemen met zorgverleners als er problemen rondom de zelfzorg waren, ervoeren ze meer problemen rondom het gebruik van medicatie, en rapporteerden ze meer eenzaamheid, diabetes-specifieke sociale angst en symptomen van angst en depressie in het algemeen. Negatieve affectiviteit (met of zonder de aanwezigheid van sociale inhibitie) hing samen met minder lichaamsbeweging, de neiging te eten bij emoties of prikkels van buitenaf, en zorgen rondom de diabetes. Sociale inhibitie (met of zonder negatieve affectiviteit) hing op zijn beurt samen met een minder frequente controle van de voeten. Er werden geen verschillen gevonden wat betreft ander gezondheidsgedrag of verstoorde lichaamsfuncties. Door te kijken naar de aanwezigheid van zowel negatieve affectiviteit als sociale inhibitie kunnen we mogelijk mensen herkennen die eerder te maken krijgen met minder optimaal gezondheidsgedrag en emotionele problemen, en tegelijkertijd minder snel geneigd zijn deze issues te bespreken met zorgverleners.

Discussie

De belangrijkste bevindingen van dit proefschrift suggereren dat er voor mensen met diabetes en emotionele problemen op zowel lichamelijk als geestelijk gebied nog de nodige gezondheidswinst te behalen valt. Zorgverleners kunnen hierbij meer aandacht geven aan de diversiteit van symptomen binnen depressie en tegelijkertijd breder kijken dan depressie op zich, door ook rekening te houden met eerder doorgemaakte depressieve episodes en persoonlijkheid. Een aanzienlijk aantal mensen met diabetes heeft momenteel niet of onvoldoende baat bij de huidige behandelingen voor depressie. Op de juiste manier onderscheid maken tussen een depressieve stoornis en andere vormen van emotionele problemen bij mensen met diabetes lijkt een goede eerste stap om hier verbetering in te brengen, maar er moet ook rekening gehouden worden met de diversiteit binnen depressie zelf. Door de behandeling te richten op de meest op de voorgrond staande symptomen van een persoon zouden we de succespercentages van depressie-interventies kunnen verbeteren, en mogelijk ook een deel van het gezondheidsrisico wegnemen dat aan depressie kleeft. Een persoonsgerichte aanpak wat betreft de keuze van interventies dient ook rekening te houden met individuele verschillen in de factoren die een rol spelen bij het ontstaan en voortduren van emotionele problemen bij mensen met diabetes. Omdat diabetes en emotionele problemen zo nauw met elkaar samenhangen, lijkt het zinvol om interventies die zich richten op emotionele problemen te combineren met interventies die focussen op zelfzorg voor de diabetes.

Individuele verschillen in persoonlijkheid kunnen een andere leidraad vormen bij de keuze voor geschikte interventies. Zo kan Type D persoonlijkheid helpen om personen op te sporen die een grote kans hebben om emotionele problemen te ervaren en problemen te hebben met de zelfzorg, terwijl ze minder geneigd zijn deze problemen te bespreken met hun zorgverlener. Als zorgverleners moeten we oog hebben voor deze mogelijke barrières en nadenken over andere vormen waarop we onze zorg toch beschikbaar kunnen stellen. Het bieden van de mogelijkheid een interventie te volgen via het internet, waarbij er op afstand toch feedback wordt gegeven, zou een deel van de terughoudendheid in het accepteren van hulp kunnen wegnemen. Een eerste verandering ligt echter in de aandacht die we binnen de standaardzorg voor diabetes aan emotionele problemen geven. Door te benadrukken dat emotionele problemen regelmatig voorkomen bij mensen met diabetes – zonder dat we deze groter maken dan ze zijn – en door te investeren in een werkrelatie waarin mensen zich veilig voelen hun zorgen te bespreken, kunnen we als zorgverleners een grotere bereidheid bereiken tot het bespreken van emotionele problemen en het accepteren van hulp.

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List of publications

Manuscripts included in thesis:

Nouwen A, **Nefs G**, Caramlau I, Connock M, Winkley K, Lloyd C, Peyrot M, Pouwer F. Prevalence of depression in inidividuals with impaired glucose metabolism or undiagnosed diabetes: a systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium. Diabetes Care 2011;34:752-62

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Nefs G, Pop V, Denollet J, Pouwer F. The longitudinal association between depressive symptoms and initiation of insulin therapy in people with type 2 diabetes in primary care. *Submitted for publication*

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De Cock E, Emons W, **Nefs G**, Pop V, Pouwer F. Dimensionality and scale properties of the Edinburgh Depression Scale (EDS) in patients with type 2 diabetes mellitus: the DiaDDZoB Study. BMC Psychiatry 2011;11:141

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About the author

Giesje Nefs was born on January 3, 1985 in Halsteren, The Netherlands. In 2003, she completed her pre-university education (VWO) at the Mollerlyceum in Bergen op Zoom. Subsequently, she obtained her Bachelor's degree in Psychology and Health (2006; summa cum laude) and her Master's degree in Medical Psychology (2008; cum laude) at Tilburg University. After working as a psychologist at the Medical Psychology department of the St. Elisabeth Hospital in Tilburg, she started her PhD project focusing on emotional distress and diabetes at Tilburg University in 2009. During her PhD research, she visited the research group of Prof. Jane Speight at the Australian Centre for Behavioural Research in Diabetes in Melbourne, Australia, and Dr. Marjolein Iversen at Bergen University College, Norway. She has given oral presentations about her work at several international diabetes conferences, including the American Diabetes Association's Scientific Sessions, the European Association for the Study of Diabetes Annual Meeting, and the Psychosocial Aspects of Diabetes (PSAD) Spring Meeting. In 2010 she received the Prof. Dr. J. Terpstra Young Investigator Award of the Dutch Association for Diabetes Research (NVDO) and Lilly Diabetes. This award has supported Diabetes MILES – The Netherlands, a national online observational study among adults with diabetes. In 2012 she won the PSAD / Novo Nordisk Science Award for a paper published in Diabetologia. Furthermore, she has obtained the University Teaching Qualification (Basiskwalificatie Onderwijs) at Tilburg University. Since 2012, she is Honorary Secretary of the Psychosocial Aspects of Diabetes (PSAD) Study Group. In the upcoming two years, Giesje will continue her research into the psychosocial aspects of living with diabetes as a post-doctoral researcher at the Center of Research on Psychology in Somatic diseases (C*o*RPS) at Tilburg University.