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and concomitant emotional distress?

Jenny van Son

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Is mindfulness valuable for people with diabetes and concomitant emotional distress?

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Voor mijn opa's

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Chapter 1

General introduction

In this introductory chapter an overview is provided on the content of the present thesis. In general, this thesis concerns the relationship between mindfulness and psychological/physiological functioning in people with diabetes. More specifically, an important part of the thesis consists of a randomized controlled trial, testing the effectiveness of Mindfulness-Based Cognitive Therapy (MBCT) in reducing elevated levels of emotional distress in people with diabetes. In the present introductory chapter of this thesis, first, background information is provided about diabetes and the role of emotional problems in people with diabetes. Second, the concept of mindfulness is explained and a rationale is provided for the investigation of its relationship with psychological and physiological functioning in people with diabetes. Finally, the specific aims and outline of this thesis are discussed.

DIABETES MELLITUS

To date, diabetes mellitus (or simply diabetes) is one of the major health problems worldwide. It has been estimated that worldwide, approximately 366 million persons have diabetes and this number is expected to rise to 552 million by 2030. This sharp increase in prevalence is partly due to the ageing of the population and the increase in the number of people being overweight and physically inactive.[1] Diabetes is a chronic disease characterized by high levels of blood glucose resulting from a deficit in the secretion of the hormone insulin (absolute insulin deficiency: type 1 diabetes), or insufficient insulin action (insulin resistance) and a failure of the beta-cells to produce enough insulin, i.e. beta-cell dysfunction (type 2 diabetes). Type 2 diabetes is the most common form, affecting approximately 90-95% of the cases.[2] For all people with diabetes, good glycemic control by means of adequate self-management is required in order to prevent or delay the development or progression of diabetes complications.[3] Long-term complications of diabetes include microvascular complications (i.e., nephropathy, retinopathy, and neuropathy) and macrovascular complications (i.e., cardiovascular, peripheral arterial, and cerebrovascular disease).[2] The diabetes self-management consists, for example, of a healthy diet, physical exercise, frequent assessment of the blood glucose levels, and (in many cases) the use of medication to control the blood glucose (an oral hypoglycemic agent and/or insulin).[3]

Diabetes and emotional problems

The majority of people with diabetes live “happy lives”: they have a satisfactory emotional well-being and are able to adequately cope with their chronic disease. Nonetheless, a substantial proportion of the people with diabetes (20-40%) experience emotional problems, which vary from general symptoms of distress, anxiety and depression to more disease-specific worries, such as worries about complications or fear of hypo’s (Box 1).[4-6]

The prevalence of depression is even estimated to be around twice to three-times higher in people with diabetes compared to those without diabetes (ranges: 6-43% vs. 3-19%).[7] In turn, emotional problems often result in lower quality of life.[8] In addition, depression is associated with suboptimal self-care behaviors,[9] suboptimal glycemic control,[10] adverse cardiovascular outcomes, and even higher mortality rates.[11, 12] From this, it is clear that addressing emotional distress is important. This opinion is shared by the American Diabetes Association, and as such, they recommend to screen for psychosocial problems in routine care and to refer individuals to mental health care services (i.e., psychological intervention) if necessary.[13]

Box 1 | Emotional distress in people with diabetes

General emotional distress

- *Depressive symptoms*
- *Anxiety* [21]
- *General perceived stress*

Diabetes-specific distress

- *Worries about future complications*
- *Not accepting diabetes*
- *Feelings of guilt or shame (e.g., related to overweight, inadequate self-management and/or suboptimal glycemic control)*
- *Concerns about food*
- *Distressing social interactions related to diabetes* [21]
- *Fear of hypo's*
- *Fear of injections*

Interventions for people with diabetes and co-morbid emotional distress

Research evaluating the effectiveness of interventions in reducing emotional distress in people with diabetes is limited, especially regarding anxiety and (diabetes-specific) distress. Previous research has shown that antidepressant medication and Cognitive Behavioral Therapy (CBT) might be effective treatments for emotional distress in this population.[14-18] However, the use of antidepressant medication is often accompanied with serious side effects, such as sexual dysfunction and significant weight gain,[19] and non-adherence and discontinuation rates are high.[20] In addition, still a substantial percentage of the patients (approximately 30-45%) do not respond to pharmacological or traditional psychological treatment or relapse.[21]

Taking this into account, it is worthwhile to evaluate alternative interventions. An alternative psychological intervention that could be of interest is a program based on the cultiva-

tion of mindfulness. For several reasons this particular intervention could be regarded as promising in this patient population. First, mindfulness-based interventions have shown to be effective in reducing emotional distress in other populations with a chronic physical disease (e.g., chronic pain or cancer).[22] Second, regarding risk of relapse, the effects of Mindfulness-Based Cognitive Therapy appear to be comparable to a maintenance dose of anti-depressant medication [23] and is currently the recommended approach in the prevention of relapse from recurrent depression.[24] This suggests that mindfulness may be of added value regarding the specific problem of relapse. Finally, mindfulness involves a different psychological approach compared to the more traditional CBT, which may be of benefit to people having a chronic disease, such as diabetes. Instead of altering thoughts and subsequent experience, an important aspect of the mindfulness approach involves a nonjudgmental acceptance of the present experience whatever there is,[25] as is explained below in more detail.

MINDFULNESS

"This is the only way, monks, for the purification of beings, for the overcoming of sorrow and lamentation, for the destruction of pain and grief… namely the four foundations of mindfulness"
Satipatthāna Sutta (an ancient Buddhist text)[26]

The concept of mindfulness

Mindfulness is a concept that originally stems from Buddhist tradition (Sati), in which it may be defined as "the clear and single-minded awareness of what actually happens to us and in us, at the successive moments of perception".[26] Buddhism is essentially concerned with identifying the inner causes of human suffering and the means to realize freedom from this suffering.[27] From a Buddhist perspective, human suffering (which constitutes emotional distress also) is inherent to a human life and mainly caused by internal processes, such as the desire to want things to be different than they are. However, according to Buddhist tradition, emotional well-being can be improved by (amongst other things) mental training of mindfulness.[26] In this context, the practice of mindfulness has become of interest to Western psychology.

In Western scientific literature, mindfulness is mainly defined as a mode of awareness that involves the giving of purposeful, non-judgmental attention to all experiences in the present moment.[25, 28] In this definition, mindfulness consists of three aspects: intention (purposeful or single-minded), attention, and attitude (non-judgmental).[29] In addition to a

mode of awareness, mindfulness is also viewed as a human trait and a trainable skill,[28, 30] which however are not mutually exclusive. In this thesis, mindfulness is viewed as (i) a mode of awareness (see definition above); (ii) people have naturally to a larger or lesser extent access to this mode and make to a larger or lesser extent use of this mode in daily life; (iii) access to and use of this mode of awareness can be improved by training.
Concerning the latter, mindfulness can be cultivated by the practice of mindfulness meditation. The instruction in most of these meditation practices is to bring the attention to an object (e.g., your breathing) and try to notice when attention is distracted from it, to become aware of the distracter (e.g., name it), and subsequently to bring attention back to the meditation object. This process is called mindfulness meditation.[25] This is also the main practice in mindfulness-based psychological interventions. Next to a non-judgmental attitude, a number of other attitudes are considered to be helpful during mindfulness practice, some of which are related to the non-judgmental attitude, namely: curiosity, non-striving, acceptance, letting-go, a beginner's mind, patience, and trust.[25]

Mindfulness and emotional well-being

According to Buddhist tradition, mindfulness might improve emotional well-being by the following mechanism.[31] From Buddhist perspective, humans habitually react to feelings or situations with a pursuing of those that are pleasant (attachment) and an avoidance of those that are unpleasant (aversion). Attachment and aversion, in their turn, lead to mental proliferation (the production of additional mental events triggered by the initial feeling in order to gain the pleasant or avoid the unpleasant; also called perseverative thinking). In addition, according to Buddhist theory, this process never leads to enduring satisfaction and usually even results in feelings of frustration, anxiety, or depression due to the impermanent nature of all phenomena, including pleasant states, and continuous threat of a) loosing the pleasant; and b) experiencing something unpleasant. Mindfulness is thought to result in less emotional distress by reducing these habitual reactions and resulting mental proliferation. It does so by allowing all feelings and thoughts to naturally come up and go away, without the subsequent cognitive processing that arises from attachment and aversion. While mindful, feelings can still be experienced as pleasant or unpleasant, but if there is no attachment, aversion and subsequently no mental proliferation, these feelings do not lead to emotional distress.[31]

Since the last decades, scientific research on mindfulness has expanded vastly: A search in Pubmed on the appearance of the term "mindfulness" in the title of scientific articles gave 7 hits in 1990, while it now shows approximately 1000 hits. This research generally supports the Buddhist view of the existence of a relationship between mindfulness and emotional well-being. Several studies have shown that people naturally differ in their

level of mindfulness (dispositional mindfulness) and that this is associated with emotional well-being.[30, 32-34] For example, two studies in student samples found that mindfulness was negatively correlated with anxiety and depressive symptoms and positively with positive affect and life satisfaction.[30, 32] However, more direct evidence for a positive influence of mindfulness on emotional well-being comes from intervention studies.

Mindfulness as a psychological intervention

In the past two decades there is a fast growing interest in the use of mindfulness-based interventions (MBIs) as a psychological intervention, aimed at reduction of emotional distress and physical symptoms in both mental and somatic health care. A pioneer in this field has been Jon Kabat-Zinn, who developed the Mindfulness-Based Stress Reduction (MBSR) program in the Medical Centre of the University of Massachusetts around 1980.[25, 35] Around the early 1990s, three psychologists (Zindel Segal, Mark Williams, and John Teasdale) adjusted the original MBSR program by incorporating elements of cognitive therapy into it, to make it suitable for the prevention of relapse from depression and named it Mindfulness-Based Cognitive Therapy (MBCT).[36] Independently from these interventions, other MBIs have been developed, including Acceptance and Commitment Therapy (ACT),[37] and Dialectical Behavior Therapy.[38] Together with MBSR and MBCT, these interventions are also referred to as the "Third Wave Cognitive Therapies".[39] The focus of this thesis is on MBCT and to a lesser extent on MBSR.

The central aspect of the MBCT/MBSR program is the cultivation of mindfulness (or the increase of one's capacity to remain in a mindful mental state[40]). Although the construct of mindfulness has its roots in Buddhism, the program is not bound to a certain religion or cultural view.[25] The standard MBCT/MBSR program is a group program and consists of eight weekly sessions of two and a half hours plus a six-hour session on a weekend day during the sixth week. During the sessions the participants practice several meditation exercises, like sitting meditation, walking meditation, and the mindful body scan, as well as a number of mindful yoga exercises (Box 2). In addition, participants are asked to practice both these formal practices and informal practice (i.e. trying to bring mindfulness into normal daily activities) at home. The formal practice is originally performed half an hour to three quarters of an hour six days per week.[25, 36]

The original focus of the research on MBSR encompassed pain, stress, and coping.[41] However, during the last two decades this focus has been extended. To date, mindfulness programs have been developed for a broad range of medical and psychiatric conditions, ranging from cancer [42] to autism.[43] Most MBI effectiveness studies have however focused on the effect on anxiety and depressive symptoms. A comprehensive general

Box 2 | Examples of mindfulness meditation practices	
Sitting meditation *(e.g., attention to breathing)*	*People sit in an up straight position and focus on the sensations of their breathing (e.g., the belly, the chest, or the nostrils)*
Walking meditation	*People focus on the sensations in their body (often leg and feet) while walking back and forth or in a circle (e.g., the sensations as one lift one's feet and leg, the movement of one's leg as it swings through the air, and then the contact of the foot on the ground).*
Mindful body scan	*People 'travel' through their body, attending to bodily sensations in each part of their body.*
Mindful yoga exercises	*People do simple body movements while attending to their bodily sensations.*
	During all practices, an important part is to try to become aware of mind-wandering, drifting of attention away to thoughts, sounds, or other phenomena, and gently bringing the attention back to the focus of attention.

meta-analysis found small to medium effect sizes concerning the effect on anxiety and depressive symptoms (Hedge's g = 0.33 and 0.41 respectively for controlled studies),[22] while a meta-analysis on studies in people with anxiety disorders [44] yielded large effect sizes for both anxiety and depressive symptoms (Hedge's g = 0.83 and 0.72 respectively for controlled studies). In addition, in people with recurrent depression, MBCT was effective in the prevention of relapse of depression (reduction risk ratio of 0.66).[23] Moreover, a recent meta-analysis showed that the effect of MBIs did not differ from traditional CBT and behavioral therapies (Hedge's g =-0.07) or pharmacological treatments (Hedge's g = 0.13).[45]

In people with a chronic disease, positive effects of MBIs on emotional well-being have been reported also. Randomized controlled trials yielded positive findings in diverse medical samples, including people with cardiac disease,[46] rheumatic disease,[47] and asthma;[48] just as meta-analyses on studies in people with cancer [49-51] and somatization disorders.[52] However, research have not been univocal as there have been studies showing no effect on mental well-being also, including a randomized trial in people with traumatic brain injury,[53] and chronic low back pain.[54] Improving emotional well-being was however not a central focus in these former studies.

As stated above, studies generally showed the effectiveness of MBIs in reducing emotional distress in diverse samples, however there are still a number of gaps in MBI research. First, most of the research has focused on short-term effects of mindfulness-based interven-

tions. Though, the results of studies examining longer-term effects are promising. A recent meta-analysis, revealed that follow-up results were largely similar to results obtained immediate after the intervention (Hedge's g = 0.43 for n = 17 controlled studies). However, the specific follow-up effect sizes regarding emotional well-being were not specified.[45] Second, the general effectiveness of MBIs in reducing emotional distress in various samples does not imply that the intervention is effective for each individual. Hence, from a clinical and financial point of view, it is valuable to get insight into which person characteristics predict benefit from mindfulness interventions. Research into these so-called moderators of MBI effect is still limited.

Mindfulness for people with diabetes

The importance of research on psychological interventions aimed at reducing emotional distress in people with diabetes is already discussed. In addition, it is explained that mindfulness is associated with emotional well-being and that MBIs seem to be effective in the reduction of emotional distress. From this, it is arguable that MBCT might be a suitable intervention for reducing emotional distress in people with diabetes who experience levels of anxiety, depression, general or diabetes-specific distress. Next to the reduction of emotional distress, MBCT might also be effective in terms of improvement in physical parameters important in people with diabetes, such as glycemic control and blood pressure.

It is known that episodic or chronic emotional distress can increase blood pressure.[55] This is unfavorable for people with diabetes, as the prevalence of high blood pressure in people with diabetes is approximately twice as high compared to the general population [56] and both diabetes and high blood pressure are important risk factors for cardiovascular disease.[56] To date, studies that have examined the influence of MBIs on blood pressure are limited but show promising results.[57-61] In people with diabetes, two prior studies have examined the effect of MBSR on blood pressure, with an uncontrolled study finding a reduction in mean arterial pressure at one month follow-up,[60] and a randomized controlled trial showing a reduction in diastolic blood pressure at one year follow-up.[61] It would be valuable for people with diabetes and co-morbid emotional problems if MBCT would have a positive effect on both emotional distress and high blood pressure.

Regarding glycemic control, as mentioned before, it is important to adequately control the blood glucose levels in order to prevent the development of diabetes complications. In addition, it is known that depressive symptoms are associated with suboptimal glycemic control.[10] Hence, if an MBI would lead to a reduction in depressive symptoms, potentially

the intervention could also have a positive influence on HbA_{1c}. Results of a number of studies supporting this notion are discussed below.

To date, there are two studies that have examined the impact of MBSR on emotional distress in people with diabetes.[60, 61] In one uncontrolled study, the mindfulness group showed a significant decrease in depressive symptoms at post intervention (Cohen's *d* = 0.86) and in HbA_{1c} and mean arterial pressure at one month follow-up (Cohen's *d* = 0.88 and 0.48, respectively).[60] In the other study, there were no significant effects directly after the intervention, but significant improvements in depressive symptoms and mental health status were reported at one year follow-up (Cohen's *d* = 0.71 and 0.54 respectively).[61] Another study examined the effect of ACT (a related MBI), finding improvements in self-care behaviors (Cohen's *d* = 0.68) and decreased HbA_{1c} values (Cohen's *d* = 0.35).[62]

The results of these studies are in line with the notion that a mindfulness program could be an adequate intervention for people with diabetes and emotional problems for reducing emotional distress and potentially improving HbA_{1c} and blood pressure. However, in all studies the presence of emotional distress was not an inclusion criterion and only two of the studies were randomized controlled trials.[61, 62] In addition, studies testing the effectiveness of MBIs in outpatients with type 1 diabetes are still lacking. Therefore, there is a clear need for randomized controlled studies in this area, examining the potential benefits of mindfulness interventions on emotional well-being in people with diabetes.

AIMS AND OUTLINE OF THIS THESIS

The first aim of the current thesis was to gain more insight into the relationship between mindfulness and emotional well-being in people with diabetes. The second and main aim of this thesis was to evaluate the short-term and longer term (six months) effectiveness of MBCT for people with diabetes who are experiencing mild to moderate emotional problems. For this aim, an RCT was set up and conducted: the Diabetes and Mindfulness (DiaMind) randomized controlled trial. In this context, a final objective was to examine which person characteristics (i.e., clinical, demographic, personality, mindfulness) would predict benefit from MBCT.

As previously outlined, the extent to which people are mindful has been associated with their level of emotional well-being, with more mindful people experiencing a higher emotional well-being than less mindful people.[30, 32-34] In **chapter 2**, this association is investigated in people with diabetes using the data of a large scale online survey, called

the Diabetes Miles (Management and Impact for Long-term Empowerment and Success) Study - The Netherlands. In addition, in this chapter, the question is explored whether dispositional mindfulness could serve as a potential buffer against the negative influence of co-morbid conditions and stressful life situations on emotional well-being. In chapter 3 to chapter 7, the design and different results of the DiaMind trial are described and discussed. The design of the DiaMind study is described in **chapter 3**. The short-term results on the primary outcome emotional distress and on outcome emotional distress and on glycemic control and health status were examined in **chapter 4**. In addition, **chapter 5** discusses the effect of the mindfulness intervention on blood pressure in participants who had an elevated blood pressure during the intake interview at baseline. Subsequently, six months follow-up findings on the primary outcomes primary outcomes and glycemic control are described in **chapter 6**. Moreover, the research question 'which person characteristics (i.e., demographic, personality, mindfulness) predict which persons most likely benefit from the intervention' is examined in **chapter 7**. Finally, in **chapter 8,** the main findings of this thesis are summarized, potential mechanisms are discussed in light of theoretical models, and implications for clinical practice and directions for future research are discussed.

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Chapter 2

The association between dispositional mindfulness and emotional distress in adults with diabetes: could mindfulness serve as a buffer? Results from Diabetes MILES - The Netherlands.

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ABSTRACT

Objective People with diabetes have a higher risk of anxiety and depression than the general population. Therefore, identification of factors that can decrease emotional distress is of interest. The aim of the present study was to examine 1) the association between dispositional mindfulness and emotional distress; and 2) whether mindfulness might moderate the association between potential adverse conditions (stressful life events and comorbidity) and emotional distress.

Methods Analyses were conducted using cross-sectional data from Diabetes MILES - The Netherlands. The sample consisted of 666 participants with diabetes (type 1 or type 2) who completed measures of dispositional mindfulness (Five Facet Mindfulness Questionnaire – Short Form; FFMQ-SF), depressive symptoms (Patient Health Questionnaire; PHQ-9), and anxiety symptoms (General Anxiety Disorder assessment; GAD-7).

Results Hierarchical multiple regression analyses showed significant associations between mindfulness facets (acting with awareness, non-judging, and non-reacting) and symptoms of anxiety and depression (β =-0.20 to -0.33, all $p < 0.001$). In addition, in general, these mindfulness facets appeared to have a moderating effect on the association between stressful life events, but not comorbidity, and depression and anxiety (all $p < 0.01$), the association being weaker when mindfulness was high.

Conclusions Mindfulness is negatively related to both depression and anxiety symptoms in people with diabetes and shows promise as a potentially protective characteristic against the influence of stressful events on emotional well-being. Intervention and longitudinal studies are needed to examine the value of learning mindfulness for people with diabetes.

INTRODUCTION

People living with diabetes face several challenges, e.g., managing medications and coping with prospect of long-term complications, such as retinopathy, neuropathy, kidney damage, and cardiovascular disease.[1] To avoid or delay these complications, most people with diabetes have to manage their blood glucose concentrations 24 hours/day, by using oral medication and/or insulin therapy. Unsuccessful attempts to optimize blood glucose levels can result in very unpleasant hyperglycemic or hypoglycemic episodes, especially in people using insulin. Moreover, having long-term diabetes complications and the self-care involved to prevent them is often burdensome. Unsurprisingly, people with diabetes are at increased risk for impaired emotional well-being compared to the general population.[2, 3] Indeed, 20-40% percent of people with diabetes experience feelings of anxiety, depression, diabetes-specific or general distress;[2, 4, 5] and the presence of multiple comorbidities places people at greater risk of impaired emotional well-being.[6-9] In addition to these health-related and diabetes-specific challenges, general life stressors, such as losing a job or loved one, are also associated with impaired emotional well-being.[7] Often, it is the perceived uncontrollability of these events and conditions (diabetes-specific or not) that makes them adverse. However, people differ in the extent to which they are resilient in the midst of such adversities.[10] It is of clinical interest to find out which factors, such as individual characteristics or coping skills, are responsible for these inter-individual differences. They could function as a so-called "buffer" against the negative effects of stressful situations/adversities on emotional well-being, especially when these factors or skills can be deployed or learned.

One factor that may play such a buffering role is dispositional mindfulness. In the past decade, there has been growing attention to the concept of mindfulness in the literature. Mindfulness is defined as paying attention to the present moment, in an open and non-judgmental way.[10] This attention and mode of awareness gives people a way of dealing with uncontrollable negative situations, negative feelings, and stressful thoughts.[10] In addition, it prevents the onset or exacerbation of automatic behavior patterns responsible for reduced emotional well-being, such as worrying and rumination,[11, 12] and it facilitates relaxation.[13] Mindfulness can be seen as both a trait, a basic human characteristic that varies both between and within persons, and as a skill, that can be learned through meditation practice.[14] It is suggested that the concept consists of various measurable aspects: a) non-reactivity to inner experience (*non-reacting*); b) observing sensations, perceptions, thoughts, and feelings *(observing*); c) *acting with awareness*; d) describing verbally one's inner experience *(describing)*; and e) non-judging of experience (*non-judging*).[15] In previous research, as a trait, mindfulness has been associated with lower levels of emotional

distress, in people with or without a chronic disease,[14-17] though the relationship between the *observing* facet and well-being is less clear.[15, 16, 18] In addition, mindfulness-based interventions have been found to be effective in improving people's well-being,[19, 20] mediated by an increase in the participants' level of mindfulness.[21-24] To the best of our knowledge, the relationship between trait mindfulness and emotional well-being in people with diabetes has not been examined yet. Two randomized controlled trials did show that a mindfulness-based intervention reduced symptoms of anxiety and depression, but it is unclear whether these effects were mediated by an increase in mindfulness.[25, 26]

Evidence is emerging to suggest a potential buffering role of dispositional (trait) mindfulness. For example, one study in the general population that tested the moderating role of mindfulness showed that associations of perceived stress with depressive symptoms and perceived health were less strong for people with higher levels of trait mindfulness.[16] Two other studies showed that mindfulness moderated the relation between neuroticism and current depressive symptoms: neuroticism was only or more strongly associated with depression in those with low to medium levels of trait mindfulness.[18, 27] In addition, mindfulness moderated the association between unavoidable distressing experiences and mental health (psychological symptoms and negative affect) in another study by Bergomi et al..[28] Moreover, in a stressful laboratory task, trait mindfulness seemed to modulate the onset of negative affect and also cortisol responses to the stressor.[29] In people with a somatic condition, only one study has been conducted. This study of people with rheumatoid arthritis showed that the negative association between disability and psychological well-being across a 12-month period diminished for those with higher levels of baseline mindfulness.[17] Although the results of these studies all point in the same direction, more research is needed to extend the findings to other populations and contexts, such as adverse events and situations in people with diabetes.

The first objective of the present study was to test the hypothesis that people with diabetes who report a higher level of dispositional mindfulness (non-judging, acting with awareness, non-reacting, and describing) also report lower levels of emotional distress. The second and main objective was to examine the hypothesis that mindfulness facets act as moderators in the possible associations of comorbidity and stressful life events with emotional distress. That is, in people with a higher level of dispositional mindfulness (non-judging, acting with awareness, non-reacting, or describing), the associations of stressful life events and comorbidity with anxiety and depression are diminished.

METHODS

This research is part of Diabetes MILES (Management and Impact for Long-term Empowerment and Success) – The Netherlands, a national, online survey of people with diabetes. The rationale and methods of this large-scale study have been published elsewhere.[30]

Participants and procedure

Participants were Dutch adults with diabetes. There were multiple methods of recruitment,[30] one of which was via an advertisement in the magazine of the Dutch Diabetes Association (Diabetesvereniging Nederland). The survey was accessible online from September 6th to October 31st 2011. All respondents were invited to complete the core questionnaire, after which they were randomized to complete one of five complementary modules. One of these modules focused on mindfulness, which is the focus of the current analysis. This "mindfulness module" was completed by 666 people with type 1 or type 2 diabetes.

Measures

Mindfulness

Mindfulness was measured by means of the Five Facet Mindfulness Questionnaire short form (FFMQ-SF).[31] This questionnaire assesses five components of mindfulness: observing 4 items), describing (5 items), acting with awareness (5 items), non-judging (5 items), and non-reactivity(5 items).[15] Respondents are asked to rate the extent to which each statement is true for them on a five point Likert scale ranging from 1 (never or very rarely true) to 5 (very often or always true).[31] The FFMQ-SF has been shown to be reliable and valid, with Cronbach's α of the subscales ranging from 0.75 to 0.87.[31] In the present sample, Cronbach's α was 0.75 for observing; 0.79 for describing; 0.82 for acting with awareness; 0.73 for non-judging; and 0.71 for non-reacting.

General emotional distress

Emotional distress was measured by means of two questionnaires: the Patient Health Questionnaire (PHQ-9) to measure depressive symptoms [32] and the Generalized Anxiety Disorder assessment (GAD-7) to measure symptoms of anxiety.[33]

The PHQ-9 evaluates the presence of the nine core criteria for major depressive disorder (according to the Diagnostic and Statistical Manual of Mental Disorders IV-TR [34]).[32] Items are answered using a four-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). The total score of this scale ranges from 0 to 27, with higher scores representing

higher levels of depressive symptoms.[32] The PHQ-9 has proven validity and reliability.[32, 35] In the present sample, the Cronbach's α was 0.87.

The GAD-7 consists of the seven core symptoms of generalized anxiety disorder (DSM-IV [34]).[33] Respondents indicate how often (during the last two weeks) they have been bothered by each symptom, using a four-point Likert scale (0 = not at all, 3 = nearly every day). The total score ranges from 0 to 21, with higher scores representing higher levels of anxiety symptoms.[33] The GAD-7 has been shown to be valid and reliable.[33, 36] In the current sample, the GAD-7 had a Cronbach's α of 0.89.

Stressful life events and the presence of comorbidity

Stressful life events were measured by means of a single self-report item: "Have you experienced a stressful life event (or events) in the past year?" (yes/no). In addition, respondents indicated (yes/no) whether they had certain pre-specified comorbid conditions (including diabetes complications): myocardial infarction; stroke; peripheral arterial disease; chronic heart failure; diabetic nephropathy; diabetic retinopathy; diabetic neuropathy; diabetic foot problems; cancer; asthma or COPD; stomach, liver, or intestinal disease; skin disease; thyroid disorder; rheumatoid arthritis; osteoporosis; migraine; epilepsy; restless legs syndrome; multiple sclerosis; and Parkinson disease. Based on the literature, which states that especially the existence of two or more comorbid conditions influences emotional distress,[7-9] comorbidity was categorized into three groups: no comorbid condition/complication; one comorbid condition/complication; two or more comorbid conditions/complications.

Demographic and clinical variables

Information included sex, age, marital status, education, current employment, diabetes type, diabetes duration, current treatment regimen, and Body Mass Index. These were all based on self-report. In addition, respondents were asked to provide their most recent HbA_{1c} or tick the box "I don't know".

Statistical Analyses

Data were analyzed using SPSS version 19 (IBM SPSS Statistics, Somers, New York). Correlations between variables were measured with Pearson product-moment correlations. Hierarchical multiple linear regression analyses were used to study the association between the independent and dependent variables. The dependent variables anxiety and depression were examined separately. In step 1, demographic and clinical variables (except comorbidity) were included as potential correlates of emotional distress. In step 2, comorbidity (including diabetes complications) and stressful events were entered into

this model. Finally, in step 3, the mindfulness facets were included (to test hypothesis 1). For the variables comorbidity and education (both comprising of three categories), we made two dummy variables (with no comorbidity and low education as reference groups). In addition, we made two dummy variables for a combination variable of diabetes type and insulin-therapy (type 1; type 2 and insulin use; type 2 and no insulin use). To test whether the mindfulness facets moderated the association between comorbidity and stressful life events with anxiety and depression (hypothesis 2), interactions between comorbidity and mindfulness facets and between stressful life events and mindfulness facets (product terms) were entered into a model (in separate analyses), while controlling for demographic and clinical variables as well as the main effects of all correlates. In order to deal with multicollinearity in the moderator analyses, the mindfulness facets (being the only continuous variables of interest) were centered around the mean.[37] In case of a moderator effect by mindfulness, for interpretation of the results, the mindfulness subscales were categorized into a low (<-1 standard deviation (SD)), medium (from -1 SD to 1 SD), or high (>1 SD) level of mindfulness group [37] for which separate regression analyses were run. This allowed examination of the associations between comorbidity or stressful events and emotional distress per mindfulness facet group. Given the higher risk of a type I error due to multiple testing, the alpha level for significance was set at 0.005 for all analyses (Bonferroni correction of the alpha of 0.05 divided by 10 (i.e., 5 mindfulness facets by 2 adversity factors)).

RESULTS

In the present study, the number of missing data was negligible (i.e., for mindfulness n = 4; for anxiety and depression n = 0). An exception was HbA_{1c}, because 181 participants indicated that they did not know their most recent HbA_{1c}.

Descriptive analyses

Demographic and clinical characteristics are presented in Table 1. The sample consisted of 666 persons with diabetes (45% type 1; 55% type 2). The mean age was 55 years (SD = 14) and the number of men and women was almost equal (53% men). In general, respondents were highly educated (43% had high-level vocational education or university) and were living with a partner (82%). The average duration of diabetes was 17 years (SD = 13), and for most people, insulin-therapy was part of the diabetes treatment (total 72%; 49% of people with type 2 diabetes). Fifty-three percent of the participants had one or more comorbid conditions (including diabetes complications) and, on average, they had a Body Mass Index (BMI) of 27.8 (SD = 6.2). The mean depression and anxiety scores were 4.4

(SD = 4.8) and 2.9 (SD = 3.5) respectively, indicating that the current sample, on average, reported a minimal level of emotional distress.

Table 1. Characteristics of the sample

		Total (n = 666)
Demographics		
Age[a], M (SD)		55 (14)
Men, n (%)		314 (53)
High educational level[b], n (%)		289 (43)
Having a partner, n (%)		543 (82)
Clinical characteristics		
Type 1 diabetes, n (%)		299 (45)
Type 2 diabetes, using insulin, n (%)		180 (27)
Type 2 diabetes, not using insulin, n (%)		187 (28)
HbA_{1c} (mmol/mol)[d], M (SD)		56.1 (12.0)
Duration of diabetes[a], M (SD)		16.5 (13.1)
Comorbidity[e], M (SD)		1.1 (1.6)
	None, n (%)	314 (47)
	One, n (%)	176 (26)
	Two or more, n (%)	176 (26)
Body Mass Index, M (SD)		27.8 (6.2)
Emotional distress		
Depressive symptoms (PHQ9), M (SD)		4.4 (4.8)
Anxiety symptoms (GAD7), M (SD)		2,9 (3.5)
Mindfulness (FFMQ-SF)		
Total score, M (SD)		84.1 (11.8)
	Observing, M (SD)	13.6 (3.6)
	Describing, M (SD)	18.3 (3.9)
	Actaware, M (SD)	19.3 (3.8)
	Non-judging, M (SD)	17.7 (4.0)
	Non-reacting, M (SD)	15.3 (3.9)
Stressful life event(s) in past year, n (%)		290 (44)

[a] in years; [b] high-level vocational education and university; [c] Most recent HbA_{1c}; [d] Comorbid conditions including diabetes complications. PHQ-9 – Patient Health Questionnaire; GAD-7 – Generalized Anxiety Disorder scale; FFMQ-SF – Five Facet Mindfulness Questionnaire – Short Form.

Demographic, clinical, and adversity variables as correlates of emotional distress

First, it was tested whether stressful life events/comorbid diseases were associated with levels of anxiety and depression, as these associations are a prerequisite for the potential moderating effect of mindfulness. In the hierarchical multiple regression analyses, demographic and clinical variables (entered in step 1) explained 10% and 6% of the variance in depression and anxiety, respectively. After entry of comorbidity and stressful life events (step 2), the total variance explained by the model was 20% for depression ($F(12,631) = 13.45$, $p < 0.001$) and 15% for anxiety ($F(12,631) = 9.41$, $p < 0.001$). After controlling for demographic and clinical variables, comorbidity and stressful life events explained an additional 11% of the variance in depression ($\Delta R^2 = 0.11$, $\Delta F(3,631) = 27.75$, $p < 0.001$) and 9% of the variance in anxiety ($\Delta R^2 = 0.09$, $\Delta F(3,631) = 22.82$, $p < 0.001$). For depression, stressful life events appeared to be a significant correlate ($\beta = 0.27$, $p < 0.001$), in addition to multi-comorbidity (≥2 comorbidities in contrast to ≤1 comorbidity) ($\beta = 0.13$, $p = 0.003$), whereas comorbidity (yes or no) was not a significant correlate ($\beta = 0.06$, $p = 0.21$). Other (marginally) significant variables were: age ($\beta = -0.26$, $p < 0.001$) and BMI ($\beta = 0.11$, $p = 0.006$). For anxiety, stressful life events was a significant predictor ($\beta = 0.27$, $p < 0.001$), in contrast to comorbidity ($\beta = -0.00$, $p = 0.98$), while having multi-comorbidity showed a trend towards significance ($\beta = 0.12$, $p = 0.01$). Of all the other variables, only age showed a significant positive association with anxiety ($\beta = -0.25$, $p < 0.001$).

Table 2. Correlations between mindfulness facets and emotional distress

	Depression[a]	Anxiety[b]
Observing	-0.13**	-0.08*
Describing	-0.34***	-0.30***
Actaware	-0.52***	-0.51***
Non-judging	-0.40***	-0.45***
Non-reacting	-0.24***	-0.19***

*p < 0.05, **p < 0.01, ***p < 0.001. [a] Measured with PHQ-9; [b] measured with GAD-7; Mindfulness facets from FFMQ-SF.

Mindfulness facets as correlates of emotional distress

Table 2 presents the correlations between the mindfulness subscales and anxiety/depression. All correlations were negative and medium-sized ($r = -0.19$ to -0.52, all $p < 0.001$), except for the observing facet that showed small negative correlations with depression and anxiety ($r = -0.13$, $p < 0.01$ and $r = -0.08$, $p < 0.05$ respectively). After entry of the mindfulness facets into the regression model described above (step 3), the explained variance

Table 3. Hierarchical multiple linear regression and moderator analyses on adversities and mindfulness facets in relation to emotional distress

	Total regression model[a]					
	Depression[b]			Anxiety[c]		
	β	t	*p*	β	t	*p*
Demographic and clinical variables (step 1)						
Female gender	02	.56	.57	-.01	-.27	.79
Age	-.13	-3.20	**.001**	-.14	-3.11	**.002**
Single	.06	1.80	.07	-.01	-.15	.89
Highly educated[d]	.01	.32	.75	.03	.88	.38
Body Mass Index	.12	3.47	**.001**	.02	.58	.57
Diabetes duration	-.04	-1.00	.32	-.04	-1.06	.29
Diabetes type 2	.01	.25	.80	.01	.19	.85
Insulin therapy	.03	.77	.44	.00	.02	.98
Adversities (step 2)						
Comorbidity (yes/no)[e]	.04	1.06	.29	-.01	-.26	.80
Multi-comorbidity (≥2)[e]	.11	2.95	**.003**	.09	2.24	.03
Stressful life event	.19	6.31	**<.001**	.19	6.08	**<.001**
Mindfulness[f] (step 3)						
Observing	-.00	-.13	.90	.01	.19	.85
Describing	-.04	-1.16	.25	-.02	-.52	.61
Act aware[g]	-.33	-8.87	**<.001**	-.30	-7.87	**<.001**
Non-judging	-.20	-5.69	**<.001**	-.27	-7.34	**<.001**
Non-reacting	-.22	-5.80	**<.001**	-.20	-4.95	**<.001**
Moderator analyses[h] (separate analyses)	**Δ R^{2i}**	**β**	***p***	**Δ R^{2i}**	**β**	***p***
Stressful event x observing	0.3%	-.07	.13	0.2%	-.07	.18
Stressful event x describing	0.4%	-.09	.05	0.3%	-.08	.11
Stressful event x act aware	1.0%	-.14	**.002**	3.0%	-.25	**<.001**
Stressful event x non-judging	1.4%	-.16	**<.001**	3.1%	-.24	**<.001**
Stressful event x non-reacting	1.2%	-.14	**.001**	1.0%	-.13	.007
Multi-comorbidity x observing	0.8%	-.10	.01	0.8%	-.11	.01
Multi-comorbidity x describing	0.0%	.00	.92	0.3%	.06	.14
Multi-comorbidity x act aware	0.4%	-.08	.05	0.3%	-.07	.08
Multi-comorbidity x non-judging	0.3%	-.06	.11	1.0%	-.12	**.003**
Multi-comorbidity x non-reacting	0.2%	-.05	.23	0.1%	-.04	.31

[a] Results when all variables were entered into the model; [b] measured with PHQ-9; [c] measured with GAD-7; [d] high-level vocational education or university; [e] comorbid conditions including diabetes complications; [f] measured with FFMQ-SF; [g] act aware = acting with awareness; [h] controlled for demographic and clinical variables and the main effects of the variables in the interaction term; [i] change in explained variance by including interaction term into the model. Bold *p*-values indicate statistical significance.

for depression was 47% ($F(17,626) = 31.96$, $p < 0.001$) and for anxiety 42% ($F(17,626) = 26.24$, $p < 0.001$). Thus, after controlling for demographics, clinical variables, comorbidity, and stressful life events, the mindfulness facets explained an additional 26% of the variance in depression ($\Delta R^2 = 0.26$, $\Delta F(5,626) = 61.04$, $p < 0.001$) and 26% of the variance in anxiety ($\Delta R^2 = 0.26$, $\Delta F(5,626) = 56.69$, $p < 0.001$).

In step 3 of the model, for depression, three mindfulness facets were significant correlates of depression: acting with awareness ($\beta = -0.33$, $p < 0.001$), non-judging ($\beta = -0.20$, $p < 0.001$), and non-reacting ($\beta = -0.22$, $p < 0.001$) (Table 3). Observing and describing yielded no significant association with depression. Only in an analysis in which the mindfulness facets were included in step 3 of the model separately (instead of all together), describing was a significant correlate also ($\beta = -0.30$, $p < 0.001$). Furthermore, stressful life events ($\beta = 0.19$, $p < 0.001$) and multi-comorbidity ($\beta = 0.11$, $p = 0.003$) remained significant correlates, in addition to age ($\beta = -0.13$, $p = 0.001$) and BMI ($\beta = 0.12$, $p = 0.001$). Results were similar for anxiety (Table 3). Acting with awareness, non-judging, and non-reacting were significantly associated with anxiety ($\beta = -0.30, -0.27, -0.20$ respectively, all $p < 0.001$). In addition, stressful life events ($\beta = 0.19$, $p < 0.001$) and age ($\beta = -0.14$, $p = 0.002$) remained significantly associated with levels of anxiety.

Moderator effect of mindfulness

To examine the moderating effect of mindfulness on the association of multi-comorbidity and stressful life events with anxiety and depressive symptoms, the interactions between these adversities and the separate mindfulness facets were studied in multiple regression analyses, while controlling for demographic and clinical variables as well as the main effects of stressful life events, having multi-comorbidity, and the particular mindfulness facet.

Three mindfulness facets particularly showed significant moderating effects in the relationship between stressful life events and depressive symptoms, as was shown by the significant interaction terms (Table 3): acting with awareness $\Delta R^2 = 0.010$, $\beta = -0.14$, $p = 0.002$; non-judging $\Delta R^2 = 0.014$, $\beta = -0.16$, $p < 0.001$; non-reacting $\Delta R^2 = 0.012$, $\beta = -0.14$, $p = 0.001$. None of the mindfulness facets moderated the association of multi-comorbidity and depressive symptoms.

For anxiety, both acting with awareness and non-judging significantly moderated the association with stressful life events ($\Delta R^2 = 0.030, 0.031$, β's $= -0.25, -0.24$ respectively, both $p < 0.001$), while non-reacting showed a trend for a moderator effect ($\Delta R^2 = 0.010$,

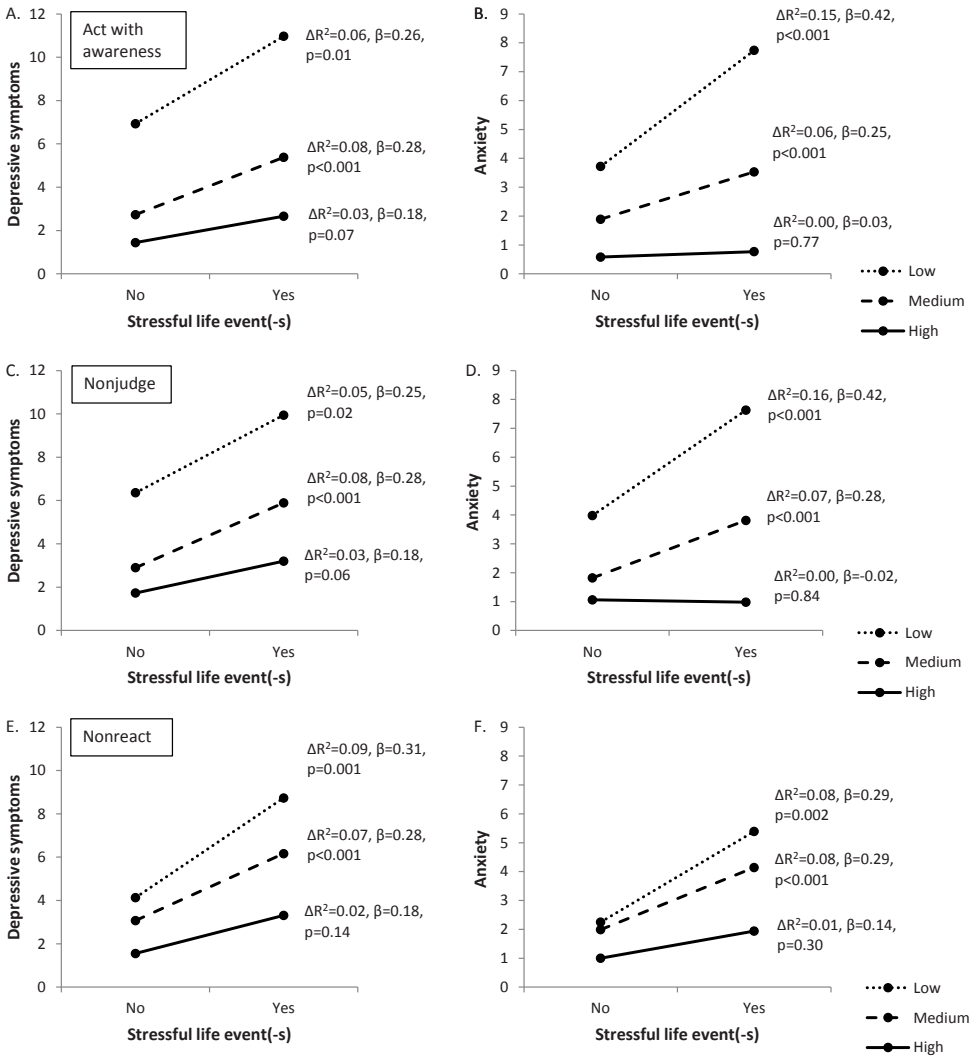

Figure 1. Relationship between stressful life events and emotional distress for different mindfulness facets. A: Depression, moderation by acting with awareness; B: Anxiety, moderation by acting with awareness; C: Depression, moderation by non-judging; D: Anxiety, moderation by non-judging; E: Depression, moderation by non-reacting; F: Anxiety, moderation by non-reacting. Low = group with low level of particular mindfulness facet (<-1 SD); Medium = group with medium level of particular mindfulness facet (-1 SD – 1 SD); High = group with high level of particular mindfulness facet (>1 SD). Depression from Patient Health Questionnaire (PHQ-9); Anxiety from Generalized Anxiety Disorder scale (GAD-7). ΔR^2 = change in explained variance after inclusion of stressful life event(s) as potential predictor; β = standardized coefficient of stressful life event(s).

β =-0.13, p = 0.007) (Table 3). Regarding the association between multi-comorbidity and anxiety, only non-judging showed a moderating effect (ΔR^2 = 0.010, β =-0.12, p = 0.003).

In general, for people scoring high (>1 SD) on the particular mindfulness facet, the association between stressful life events and anxiety and depression was not significant, while for people scoring medium (-1 to 1 SD) or low (<-1 SD), the association was significant (Figure 1).

DISCUSSION

The aims of the present study were (1) to examine the relation between facets of dispositional mindfulness and emotional distress in adults with diabetes and (2) to test whether dispositional mindfulness could statistically diminish (moderate) any association between stressful life events or comorbidity and emotional distress. As expected, the mindfulness facets (except for *observing*) showed a clear negative association with feelings of anxiety and depression. All together, the mindfulness facets explained an additional 26% of the variance in both anxiety and depression, after controlling for demographic and clinical variables (including comorbidity) and stressful life events. In particular, lower scores on *acting with awareness*, *non-judging*, and *non-reacting* were significantly associated with higher scores on anxiety and depression, while *observing* and *describing* yielded no significant associations. These findings are consistent with previous research in other populations. For example, Baer et al. (2006) also found the facets *acting with awareness*, *non-judging*, and *non-reacting* to be most important in predicting psychological symptoms in a sample of undergraduates, accounting for additional explained variance above the other facets, while *describing* did not. *Observing* did not show a negative correlation with psychological symptoms in their study.[15] In addition, Bränström et al. (2011) found, in a general population sample, *non-judging*, *acting with awareness*, and *non-reacting* to be significantly associated with anxiety, and the latter two facets also with depression. In their study, *describing* was only related to positive affect, while *observing* yielded no significant association with well-being.[16]

Regarding the presumed associations between the measured adversities and emotional distress, stressful life events and multi-comorbidity were significantly associated with levels of depression and anxiety, though multi-comorbidity to a lesser extent than stressful life events. Concerning the potential buffer effect, the three previous significant mindfulness facets (*acting with awareness, non-judging,* and *non-reacting*) appeared to have a moderating effect on the association between stressful life events and emotional

distress. In the current sample of people with diabetes, in participants who scored high on these mindfulness facets, stressful life events were not associated with feelings of anxiety and depression. Thus, in these people, these mindfulness facets might have been a protective characteristic against the adverse effect of stressful events. *Observing* and *describing* showed no moderator effects. These findings correspond with previous research in other populations that examined a potential buffering role of mindfulness. In a comparable study in a community sample, total level of mindfulness moderated the association between unavoidable distressing events and psychopathological symptoms and negative affect.[28] In addition, the previously mentioned study by Bränström et al. showed that the associations between perceived stress and depression were diminished for those with higher levels of mindfulness, especially regarding the mindfulness facets *acting with awareness*, *non-judging*, and *non-reacting*.[16] Besides these studies on moderator effects of mindfulness in the association between stress(-ful events) and outcome, some research focused on moderator effects in the relationship between a dispositional vulnerability to experience negative emotions (neuroticism) and depressive symptoms. These studies also found total level of mindfulness to have a moderating role.[18, 27]

Consistent with previous research,[7] having two or more comorbid conditions was associated with more depressive symptoms and to a lesser extent with higher levels of anxiety. In contrast to our expectations, in general, dispositional mindfulness did not diminish this association, indicating that the relationship between multi-comorbidity and emotional distress was of equal magnitude for those with high levels of mindfulness as for those with low levels. An exception was *non-judging* in relation to the association between multi-comorbidity and anxiety, reflecting that for people who scored high on the dispositional non-judging facet of mindfulness, having multiple comorbid diseases was not associated with anxiety. Nonetheless, perhaps for dealing with a chronic stressor, such as comorbid medical diseases, high trait mindfulness is not enough and actual mindfulness meditation practice may be necessary. This hypothesis is supported by research on the effect of mindfulness interventions, showing improvements in depression in people with chronic pain [38] and severe medical illnesses, such as cancer.[39]

This is the first study that showed a moderating role of dispositional mindfulness for the association between adversities and emotional distress in people with diabetes. Since emotional distress in people with diabetes is related to worse quality of life and glycemic control,[40, 41] factors associated with emotional distress are worthy of investigation. Hence, the suggestion that dispositional mindfulness is a potential protective factor for maintaining emotional well-being for people with diabetes might be of relevance in clinical practice. Mindfulness is a human characteristic that can be cultivated through training

and practice. The cultivation of mindfulness is the central component of mindfulness-based interventions. In clinical care, referring people with diabetes at risk for depression (i.e., people high on neuroticism or who have experienced stressful life events) to a mindfulness-based intervention might be worthwhile. Indeed, two recent randomized controlled trials showed the effectiveness of a mindfulness intervention in the reduction of feelings of depression, general stress, and anxiety in people with diabetes.[25, 26]

The current study has several limitations, many of which are discussed elsewhere.[30] First, the cross-sectional nature of the data does not allow statements about causality. Hence, instead or besides the hypothetical buffer effect by mindfulness, it might be that people who experience minimal emotional distress, even despite stressful life events, naturally have less difficulty being mindful. As a result of lower emotional distress, they may ruminate less, making it easier to be more attentive and less judgmental. These alternatives need not be mutually exclusive. Nevertheless, available evidence supports a direction of causality from mindfulness to lower emotional distress, since research has shown that mindfulness-based interventions have a positive influence on anxiety and depressive symptoms [19] and that these effects are (partly) mediated by an increase in levels of mindfulness.[21-24] In addition, one recent study that measured weekly change in mindfulness during a mindfulness intervention showed that an increase in mindfulness preceded the reduction of perceived stress.[42] Nonetheless, prospective data from cohort studies and randomized controlled trials are necessary to more rigorously test the buffering potentials of mindfulness. Second, all measures were based on self-report and so potentially subject to reporting bias. This includes comorbidity, as there is an increased risk of reporting a false-positive disease status in people with emotional problems.[43] In addition, the assessment of mindfulness by means of self-report is currently subject to debate,[44] yet, to date, it remains the most used and viable approach for measuring mindfulness.[45] In addition, research has shown that the FFMQ has adequate psychometric properties (i.e., good reliability and predictive validity).[15] Moreover, for a more in-depth analysis of mindfulness, in a recent review the FFMQ has been suggested as the recommended scale.[45] Third, we did not control for levels of HbA_{1c}, as there were many missing values for this particular variable. Nevertheless, sensitivity analyses in which HbA_{1c} was included yielded similar results (not reported), indicating that this factor did not introduce a meaningful bias. Fourth, the current sample of people with diabetes is not representative for the general Dutch diabetes population (e.g., in the present sample, a relatively large group of people with diabetes type 2 take insulin), as the way of recruitment probably resulted in a selection bias of those who are actively engaged in their diabetes care or for whom diabetes is explicitly present in their daily lives.[30]

In conclusion, in the current study, dispositional mindfulness was associated with lower levels of depression and anxiety in people with diabetes, in particular the mindfulness facets acting with awareness, non-judging, and non-reacting. In addition, results of this study suggest that these latter mentioned mindfulness characteristics may have the potential to buffer against the adverse influence of stressful life events on depressive and anxious feelings. Hence, mindfulness-based interventions might be valuable to apply in the clinical care of people with diabetes who experience stressful life events. However, first longitudinal and intervention studies are required to more rigorously examine the protective potential of mindfulness facets in this population.

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Chapter 3

Testing the effectiveness of a mindfulness-based intervention to reduce emotional distress in outpatients with diabetes (DiaMind): design of a randomized controlled trial

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ABSTRACT

Background Approximately 20-40% of outpatients with diabetes experience elevated levels of emotional distress, varying from disease-specific distress to general symptoms of anxiety and depression. The patient's emotional well-being is related to other unfavorable outcomes, like reduced quality of life, sub-optimal self-care, impaired glycemic control, higher risk of complications, and increased mortality rates. The purpose of this study is to test the effectiveness of a new diabetes-specific, mindfulness-based psychological intervention. First, with regard to reducing emotional distress; second, with respect to improving quality of life, dispositional mindfulness, and self-esteem of patients with diabetes; third, with regard to self-care and clinical outcomes; finally, a potential effect modification by clinical and personality characteristics will be explored.

Methods/Design The Diabetes and Mindfulness study (DiaMind) is a randomized controlled trial. Patients with diabetes with low levels of emotional well-being will be recruited from outpatient diabetes clinics. Eligible patients will be randomized to an intervention group or a wait-list control group. The intervention group will receive the mindfulness program immediately, while the control group will receive the program eight months later. The primary outcome is emotional distress (anxiety, stress, depressive symptoms), for which data will be collected at baseline, four weeks, post intervention, and after six months follow-up. In addition, self-report data will be collected on quality of life, dispositional mindfulness, self-esteem, self-care, and personality, while complications and glycemic control will be assessed from medical files and blood pressure will be measured. Group differences will be analyzed with repeated measures analysis of covariance.

Discussion It is hypothesized that emotional well-being, quality of life, dispositional mindfulness, self-esteem, self-care, and blood pressure will improve significantly more in the mindfulness group compared to the control group. Results of this study can contribute to a better care for patients with diabetes with lowered levels of emotional well-being. It is expected that the first results will become available in 2012.

BACKGROUND

It has been estimated that worldwide, approximately 285.000.000 persons have diabetes mellitus (DM) and this number is expected to rise to 439.000.000 by 2030.[1] This sharp increase in prevalence is partly due to the ageing of the population and the increase in the number of people having overweight and who are physical inactive.[2] DM is a chronic disease characterized by high levels of blood glucose resulting from a deficit in the secretion of the hormone insulin (absolute insulin deficiency: Type 1 DM), or insufficient insulin action (insulin resistance) and/or a failure of the beta-cells to produce enough insulin, i.e. beta-cell dysfunction (Type 2 DM).[3] Type 2 DM is the most frequent form, prevalent in approximately 90% of the cases.[4] For all patients with diabetes, appropriate glycemic control by means of adequate self-management is required in order to prevent or delay the development of diabetes complications: macrovascular complications (e.g. coronary artery disease) and microvascular complications (i.e. nephropathy, retinopathy, and neuropathy). This self-management consists for example of a healthy diet, physical exercise, frequent assessment of the blood glucose levels, and (in many cases) the use of medication to control the blood glucose (an oral hypoglycemic agent and/or insulin).[3]

A considerable proportion of the patients with diabetes (20-40%) experience emotional problems, which vary from disease-specific worries (such as fear of hypo's or worries about complications) to more general symptoms of distress, anxiety and depression.[5-7] These problems are not only unpleasant for the persons experiencing them, but studies show also that co-morbid emotional distress in patients with DM is associated with reduced quality of life,[8] poor self-care behaviors,[9] more negative appraisals of insulin therapy,[10] reduced glycemic control [9] and subsequent adverse cardiovascular outcomes, and even mortality.[8, 11]

Despite the fact that emotional distress is so common in patients with diabetes, the attention for emotional problems in both practice and research is still limited. In practice, the recognition rates of emotional problems by clinicians are low and so are treatment rates.[12] Similarly, in the field of diabetes research, studies that test psychological interventions to improve the emotional well-being in patients are scarce. In addition, those studies that have been conducted often have important limitations, such as lack of controlled designs and small sample sizes.[13] However, it is true that the attention for emotional problems in DM patients is increasing since the last decade. In practice, screening for emotional problems is recommended in the latest versions of the standards of care of the International Diabetes Federation [14] and the American Diabetes Association.[15] In addition, in research, there are more and more studies examining the effectiveness of psychological interven-

tions on clinical depression. Anxiety symptoms and diabetes-specific emotional distress have received, however, much less attention in diabetes research.

The results of well-designed studies that have been conducted to test psychological interventions in diabetes patients with emotional problems show that cognitive behavioral therapy is an effective treatment for major depression in diabetes patients [16] and a potentially effective treatment in reducing symptoms of anxiety, perceived stress, and diabetes-specific emotional distress.[17, 18] Another promising psychological intervention that may help to reduce symptoms of depression, anxiety, and diabetes-specific emotional distress is based on the cultivation of mindfulness. Mindfulness can be defined as the self-regulation of one's attention focusing on direct experience, while adopting a curious, open, and accepting attitude towards these experiences, especially one's psychological processes, such as thoughts and feelings.[19] Mindfulness-based interventions can be considered promising as positive effects of mindfulness programs on emotional well-being and quality of life have been reported in diverse patients groups, like chronic pain patients and patients with cancer.[20-22] In addition, research has shown that the program is beneficial for patients with recurrent depression. In these patients, the intervention appeared to be superior to traditional cognitive behavioral therapy in the prevention of relapse of depression.[23] While in a recent meta-analysis, mindfulness-based interventions have been found to have medium to large effects regarding the reduction of symptoms of anxiety and depression,[24] only two studies have focused on the effects of a mindfulness program on patients with diabetes. These studies showed that the interventions resulted in improved emotional well-being (Cohen's d = 0.86 for depressive symptoms and 0.43 for anxiety),[25] improved self-care behaviors (Cohen's d = 0.68)[26] and decreased HbA_{1c} values (Cohen's d = 0.46)[25] (Cohen's d = 0.35)[26]. However, only one of the two studies was a randomized controlled trial, but this study did not include emotional well-being as an outcome measure.[26] Therefore, there is a clear need for randomized controlled studies in this area, examining the potential benefits of mindfulness interventions on emotional well-being in patients with DM.

In addition to the potential contribution of mindfulness to emotional well-being, mindfulness may also have a beneficial influence on self-management in DM patients. First, because mindfulness interventions enhance emotional well-being, and a better mood is associated with better self-care behavior, mindfulness is expected to enhance self-care behavior as well. Second, mindfulness improves one's ability to behave oneself constructively in harmony with his/her values, even during the experience of difficult thoughts and emotions.[27] Finally, because considerable focus is placed on bodily sensations during

mindfulness interventions, mindfulness leads people to become more in touch with their body and its signals and needs,[28] which is expected to lead to better self-care.

A positive effect of a mindfulness intervention may also be expected on blood pressure. It is known that episodic or chronic emotional distress can increase blood pressure.[29] This is unfavorable for patients with diabetes, as the prevalence of high blood pressure in people with diabetes is approximately twice as high compared to the general population [30] and both diabetes and high blood pressure are important risk factors for cardiovascular disease.[30] To date, only two studies have examined the influence of mindfulness on blood pressure, finding a reduction in mean arterial pressure in DM patients [25] and a reduction in resting systolic blood pressure in normotensive students.[31]

If the mindfulness intervention appears to be effective in reducing emotional distress in DM patients, it is useful to know which patients will most likely benefit from the intervention. However, research into differences in effectiveness of the intervention between groups of patients with different characteristics (e.g. differences in personality and demographic and medical characteristics) is scarce.

Objectives and hypotheses

Because of the paucity of studies on the effectiveness of psychological interventions for emotional problems in DM patients, especially regarding mindfulness based interventions, the purpose of this study is to test the effectiveness of a mindfulness-based psychological intervention. The primary outcome is emotional distress (symptoms of depression, anxiety, diabetes-specific stress, and general perceived stress). Secondary outcomes are quality of life, (diabetes-specific) mindfulness, and self-esteem, and our tertiary outcomes are self-management, glycemic control, and blood pressure. Finally, we will examine which patient characteristics (like the extent of complications and personality) predict which patients most likely benefit from the intervention.

With regard to our first outcome measure, we hypothesize that after an eight-week mindfulness-based training DM patients will experience significant greater reductions in emotional distress (diabetes-specific stress, anxiety, and depressive symptoms) compared to a wait-list control group. Concerning our secondary outcome measures, we hypothesize that the intervention will lead to greater improvements in psychological quality of life, dispositional (diabetes-specific) mindfulness, and self-esteem compared to a wait-list control group. In addition, we expect, consistent with two other studies,[32, 33] that changes in dispositional mindfulness will mediate the hypothesized effects of the intervention on above mentioned outcomes. Regarding our tertiary, more clinical, outcome measures, we

hypothesize that the intervention will lead to better diabetes self-care, lower HbA_{1c}, and lower BP in people with elevated BP. Finally, we are interested in personality and clinical factors that could possibly act as effect modifiers. We do not have clear expectations about the direction of the possible influence of these characteristics, being complications (yes/no), diabetes type (DM1 versus DM2), co-morbidity (yes/no), and personality.

METHODS/DESIGN

Study design

The Diabetes and Mindfulness (DiaMind) study will be conducted as a randomized controlled trial (RCT). Dutch speaking patients with DM with low levels of emotional well-being recruited from outpatient diabetes clinics will be randomly allocated to the intervention group or the wait-list (usual care) control group. The intervention group will receive the mindfulness program immediately, while the control group will receive the program eight months later (six months after the training of the intervention group).

Eligibility

We will include adult men and women (aged 18 - 80 years) who were diagnosed with diabetes (type 1 or 2) and have poor emotional well-being as evidenced by a score of < 13 on the WHO-5 well-being Index.[34] Patients will be excluded when they have a recent history of severe psychopathology (i.e., psychosis, risk of suicide attempts); or alcohol/drugs abuse; have a severe physical co-morbidity (i.e., severe forms of cancer or heart failure); when they have insufficient reading and comprehension skills of the Dutch language; when they are already in an (extensive) psychological treatment which started within a period of 6 weeks before the start of the training; and when they already have meditation experience (with Vipassana, Zen, or Dzogchen).

Recruitment and screening process and enrolment

The recruitment of patients will take place in outpatient diabetes clinics. At present, internists of the outpatient clinic of the Maxima Medical Center (Veldhoven and Eindhoven), the Catharina Hospital (Eindhoven) and the TweeSteden Hospital (Tilburg) have agreed to participate. Depending on the preferences of the diabetes teams in the participating hospitals, the screening will be conducted by the internists, diabetes nurses or by a researcher of our team. The screening tool will be the WHO-5 well-being Index.[34] This short (5-item) screening instrument, which assesses emotional well-being, is validated in the general population, but also in different patient samples, including patients with type 1 diabetes [35] and is recommended for use by the International Diabetes Federation

(IDF).[14] If patients have a low score on this scale (< 13) they will receive an information letter about the training and study. One week later these patients will be telephoned and asked whether they are interested to participate in the project. Eligible patients who are interested to participate will be invited for a short interview. This interview will take place in the hospital or, if logistically difficult for the patient, at their home. During this interview the in- and exclusion criteria will be checked once again, and expectations of the patient about the training will be checked and if necessary adjusted. Eligible patients will receive a written informed consent form during the interview that has to be signed and returned before the start of the training. Furthermore, at the end of the interview the blood pressure of the patients will be measured. If blood pressure is elevated (≥140/90 mmHg) the patient will be attached to an ambulatory blood pressure device which will measure blood pressure the following 24 hours. One day later the device will be brought back to the hospital by the patient or be picked up at the patient's home by a researcher.

Randomization

After the inclusion of every 16 to 20 patients the participants will be randomized into two groups: the intervention group and the control group. The randomization will be done as follows. After the interview and upon receipt of a signed informed consent form, the patient will be assigned to a participant number. Subsequently the participant will receive the baseline questionnaire by mail or email. When the first author receives the baseline assessment, she passes on the corresponding participant number to the second author who has no further involvement in the practical recruitment, enrolment, and assessment of the patients. The second author will refer to the computer generated (through PASW Statistics 17) random list (uneditable and concealed for others) prepared by a statistician with no involvement in the trial. The second author will inform the first author about the allocation by email and will archive the allocations in a secured document on his computer. The first author will document the allocation in the general inclusion database, which will be checked by the second author. The first author will inform the patients both by telephone and letter about their allocation. The above described procedure will eliminate experimenter bias in group assignment. The computer program the statistician will use utilizes a random number generator and will be programmed to insure equal numbers of subjects in each arm of the study within a block of 4 participants.

Masking

The nature of this psychological intervention does not allow "masking" or blinding of patients, and trainers. However, the statistician who will be involved in data analyses will be blinded for treatment allocation. All the questionnaires and homework forms will only be marked with a participant number, which is unknown to the trainer and researcher.

Intervention

Training

The protocolised mindfulness training is based on the Mindfulness-Based Stress Reduction and Mindfulness-Based Cognitive Therapy programs as described in Kabat-Zinn [28] and Segal et al.,[36] consisting of eight weekly two-hour sessions. A few modifications have been made to the original protocol and the workbook in order to make the intervention suitable for patients with diabetes. For example, the trainers explain the potential associations between emotional problems and diabetes management and diabetes outcomes (e.g., the associations between emotional stress and eating behaviors will be discussed). Instead of the silent day that is part of the original program, a two-hour booster session has been added three months after the end of the intervention. At each session the participants will receive homework assignments that take about 30 minutes 5 days per week. All the sessions will be supervised by certified psychologists who have at least four years practical experience with mindfulness, and also completed a mindfulness instructors training of eight days in The Netherlands. The standard format of the sessions is as follows: the session starts with an exercise, which is followed by a discussion about the exercise and the homework exercises of the preceding week. Subsequently, a discussion about the theme of the session takes place, followed by the administration and discussion of one or two other mindfulness exercises. Finally, the homework assignments of the following week are discussed. All sessions end with a short meditation and/or a relevant poem or story.

Session 1

The first session of the course will consist of: 1) an invitation to all participants to introduce themselves sequentially, 2) a brief overview of the coming eight weeks, 3) a discussion about the relationship between diabetes, diabetes management, diabetes outcomes and emotional distress. After this, participants will be invited to slowly and mindfully eat a raisin with all their senses (the raisin exercise), which will be followed by a discussion about the fact that many people live their lives in a unmindful way, often do not pay much attention to what they are doing. Subsequently, the participants will be led through a body scan exercise of thirty-five minutes, during which the participants are encouraged to focus on the physical sensations in different body parts and to bring their attention back to that focus when they get distracted from it by thoughts or other momentary phenomena. At the end of the first session the participants will receive a CD containing several exercises and will be asked to practice the bodyscan on five occasions in the following week. In addition, they will be advised to perform one daily activity (e.g. to wash the dishes, to brush their teeth) in a mindful way and to eat one meal per day mindfully.

Session 2

At the beginning of the second session the participants will be guided again through the body scan, after which they will be invited to express and share their experiences with the mindfulness exercises and the homework of the preceding week. Subsequently there will be a discussion about coping with obstacles to doing the exercises (e.g., irritation, wandering mind) and attitudes that support the cultivation of mindfulness (e.g., not judging, letting go). After that, participants will be led through an exercise 'thoughts and feelings', which explains a basic component of cognitive behavioral therapy: our emotions are not caused by events but by our perception of events. Subsequently, the participants will practice 'sitting meditation', with breathing as the primary object of attention. Home practice for the following week will include awareness of pleasant events, a new routine daily activity, the bodyscan, and brief sitting meditation.

Session 3

The third session will start with a short 'Seeing and/or hearing exercise', in which participants are instructed to exercise non-judgmental seeing or hearing for a couple of minutes. This exercise will be followed by a sitting meditation with focus on breathing and bodily sensations. After the homework discussion, there will be a talk by the trainer about attention to breathing, followed by the practice and discussion of the '3-minute breathing space'. This meditation has three phases: attention to the experiences in the moment, attention to the breathing, attention to the body. Subsequently, an exercise in mindful body movements will be introduced and discussed. Exercises to be practiced during the following week will include sitting meditation, bodyscan or body movement exercises, 3-minute breathing space, new mindful daily activity, and awareness of unpleasant events.

Session 4

The fourth sessions will start with a sitting meditation with attention to the breathing, the body, sounds, and thoughts (so called 'sitting meditation with four focuses'). Subsequently, there will be a discussion about the stress response and common reactions of individuals to difficult situations, and alternative attitudes and reactions will be discussed. Then a Dutch documentary about MBSR (entitled 'Aandachttraining') will be shown to the participants. At the end of the session an exercise in mindful walking will be introduced and practiced. The homework assignments for this fourth session will consist of practicing sitting meditation, the bodyscan or mindful body movements, 3-minute breathing space (also during unpleasant events), to fill in the questionnaire 'automatic thoughts' (optional), and to read an inspiring book about mindfulness (optional).

Session 5

At the beginning of the fifth session the participants will be guided through the sitting meditation with four focuses (see Session 4). A poem will be read and the psychologist will discuss the theme of the fifth session: 'Acknowledging and accepting the reality of the present situation as it is.' Subsequently, the second series of mindful body movements will be introduced. The recommended home work will consist of sitting meditation, 3-minute breathing space, 3-minute breathing space during unpleasant events, and a new daily activity performed mindfully.

Session 6

The sixth session will begin with the 3-minute breathing space. The homework assignments will be discussed mindfully in pairs. An exercise called 'mood, thoughts, and different view points' will be discussed plenary, as well as the theme of the sixth session: 'The content of our thoughts is (often) not factual'. Subsequently, the participants will be guided through four linked up meditation exercises, with a total duration of one hour. For the following week participants will be encouraged to choose a combination of meditations that fits their needs and personal preferences. In addition, the home practice includes the 3-minute breathing space (also during unpleasant events), a new mindful daily activity, and having a mindful conversation while paying attention to one's automatic patterns (optional).

Session 7

The seventh sessions will start with the meditation exercise with four focuses and open awareness (to whatever enters consciousness from moment to moment). The theme of the session, 'What is the best way to care for oneself', will be discussed, followed by an exercise during which participants explore daily activities that are pleasant versus unpleasant and learn to plan sufficient pleasant activities. The 3-minute breathing space is performed, followed by a loving-kindness meditation during which one practices kindness towards oneself and others. The home practice includes a meditation combination of one's choice, 3-minute breathing space (also during unpleasant events), a new daily activity performed mindfully, and filling in a form including warning signals for emotional distress.

Session 8

The session will begin with a body-scan. The theme of the last session will be discussed: 'Using what you have learned'. Subsequently the psychologist will guide the participants through a 3-minute breathing space and will read a story called 'Five chapters', which is about the steps one can take to overcome our pitfalls in the practice of mindfulness.

Finally, the whole training will be evaluated with the participants. For example the following questions will be asked: did the training meet their expectations, do participants have a sense of 'personal growth', do they feel that they have expanded their coping skills and do they want to continue practicing mindfulness. In addition, resources for continued practice will be given (e.g. titles of books and addresses of local meditation centers).

Evaluation

After completing the training the patients will be invited for a short interview, in which the patient's perceptions regarding the quality of the intervention will be evaluated and the procedure with the ambulant blood pressure measurement will be repeated.

Table 1. Measurements and time points

Concept	**Questionnaire**	**Measurement time points**								
		T1	**T2**	**T3**	**T4**	**T5**	T6	T7	T8	T9
Perceived stress	PSS (14)*	**x**	**x**	**x**		**x**	x	x		x
Anxiety and depressive symptoms	HADS (14)	**x**	**x**	**x**		**x**	x	x		x
Mood	POMS (32)	**x**	**x**	**x**		**x**	x	x		x
Diabetes related problems	PAID (20)	**x**	**x**	**x**		**x**	x	x		x
Quality of life	SF12 (12)+3 items WHOQOL	**x**		**x**		**x**		x		x
Self-care behavior	ADSCI (11)	**x**		**x**		**x**		x		x
Extraversion	EPQ-E (12)	**x**								
Type D Personality	DS14 (14)	**x**		**x**		**x**		x		x
Mindfulness	FFMQ(31)	**x**		**x**		**x**		x		x
Diabetes related mindfulness	AADQ (11)	**x**		**x**		**x**		x		x
Self-esteem	RSES (10)	**x**		**x**		**x**		x		x
Patient's background (demographics, clinical, psychological)	- (21)	**x**								
Clinical measurements		**Measurement**								
Glycemic control (from hospital database)	HbA_{1c}	**x**			**x**	**x**			x	x
Blood pressure	Amb.24h BP	**x**		**x**						

T1 – baseline; T2 – after 4 weeks of intervention; T3 – after 8 weeks (post intervention); T4 – after 12 weeks (4 weeks post intervention); T5 – after 8 months (6 months post intervention = start training for control group). T6 thru T9 only for control group: repetition of T2 thru T5. PSS – Perceived Stress Scale; HADS – Hospital Anxiety and Depression Scale; POMS – Profile of Mood States; PAID – Problem Areas in Diabetes Survey; SF-12 – Short Form Health Survey; 3 items WHOQOL-bref[9]; ADSCI – Amsterdam Diabetes Self Care Inventory; EPQ-E - Eysenck Personality Questionnaire subscale Extraversion; DS14 – Type D personality scale; FFMQ - Five Factor Mindfulness Questionnaire; AADQ – Acceptation and Action Diabetes Questionnaire; RSES - Rosenberg Self-esteem Scale. HbA_{1c} = hemoglobin A_{1c} (the amount of glycated hemoglobin in blood). Amb. 24 h BP = Ambulatory 24 hour Blood Pressure monitoring.

* = number of items in questionnaire. Total number of items = 205.

Data collection

Table 1 shows the assessment instruments and data collection time points. Assessments will take place before the start of the intervention, at 4 weeks, at 8 weeks (= post intervention), at 12 weeks and at 34 weeks (6 months post intervention). The control group will receive another four measures, namely at 38 weeks (4 weeks after start of control group intervention), at 42 weeks (post control group intervention), at 46 weeks, and at 62 weeks (6 months post control group intervention). Process variables (e.g., attendance, adherence, and drop-out) will be collected continuously. The patients who have access to the internet and email will receive the questionnaire via the internet. If this is not the case, they will receive a paper version of the questionnaire along with a stamped addressed envelope.

Outcome parameters

1. Primary outcome measures

Stress, anxiety and depressive symptoms

We will include the Hospital Anxiety and Depression Scale (HADS) to measure symptoms of anxiety (HADS-A: e.g., "Worrying thoughts go through my mind") and depression (HADS-D: e.g., "I feel as I am slowed down") in DM patients.[37] The self-report scale consists of 14 items, answered on a 4-point Likert scale, with the HADS-A and HADS-D both comprising 7 items (*0-3*). The score range for the anxiety and the depressive symptoms subscales is 0 to 21. The HADS has been validated in the general population and in somatic and psychiatric patients.[38, 39] It has been shown to be a valid and reliable instrument with Cronbach's α ranging from 0.67 to 0.93 for the two subscales.[37-39]

The Dutch version of the Perceived Stress Scale (PSS) will be included to measure general perceived stress (the degree to which situations in one's life are appraised as stressful) (e.g. "In the last month, how often have you felt nervous and stressed?"). It has been shown to be a reliable measure with Cronbach's α ranging from 0.84 to 0.86.[40] The present version consists of 10 items which are answered on a five-point Likert scale, ranging from 'never' to 'very often' *(0-4).*[41]

The short Dutch version of the Profile of Mood States (POMS) [42] will be used to assess transient, fluctuating mood states. The scale consists of 32 adjectives about positive and negative mood states which have to be rated on a five-point Likert scale *(0 = not at all, 4 = very much)* based on how well each item describes one's mood during the last couple of weeks. For the interpretation of the results the items are divided into five subscales:

Tension-anxiety (6 items); Depression-dejection (8 items); Anger-hostility (7 items); Vigor-activity (5 items); and Fatigue-inertia (6 items). The scale has sufficient consistency reliability and construct validity, with Cronbach's α's of the five subscales varying between 0.82 and 0.91.[42, 43]

Diabetes specific emotional problems

We will include the Dutch version of the self-report questionnaire Problem Areas in Diabetes Survey (PAID), which consists of 20 statements about common negative feelings related to living with diabetes (e.g., "Feeling depressed when you think about living with diabetes", "feeling discouraged with your diabetes regimen").[44] The items are rated on a six-point Likert scale *(1 = not a problem, 6 = a serious problem)*. PAID scores are transformed to a 0-100 scale, to facilitate interpretation.[45] A higher score indicates more emotional distress, with a cut-off score of 40 indicating seriously elevated emotional distress.[46] Factor analysis revealed that the factor structure can be represented by a one factor model (PAID total: emotional adjustment) and a four factor model (subscales: emotional problems, treatment problems, food problems, and lack of social support).[45] We will examine the results with both models. The survey has proven to be a reliable measure, with a Cronbach's α of 0.95 for the one factor model. For the four factor model the Cronbach's α's are in range of 0.93 (emotional problems), 0.74–0.76 (treatment problems), 0.70–0.74 (food problems), and 0.69–0.72 (lack of social support).[45] In addition, research in Dutch and American patients found support for convergent and discriminative validity of the PAID.[45, 47]

2. Secondary outcome measures

Quality of life

We will include the Dutch version of the Short-Form Health Survey (SF-12) to measure health related quality of life. The self-report scale consists of 12 items that are grouped into two component summary scores: a physical (PCS) and a mental component score (MCS). Both component scores are measured on a scale from 0 to 100, with a high score indicating good health related quality of life. The SF12 has proven to be a valid and reliable measurement.[48]

In addition, we will use three items of the WHOQOL-BREF [49] to measure satisfaction with oneself and life in general: "How much do you enjoy life?"; "To what extent do you feel your life to be meaningful?"; "How satisfied are you with yourself?". The questions will be analyzed separately at item level if Cronbach's α will show to be below 0.65.

Mindfulness

To measure mindfulness we will include the Dutch version of the Five Facet Mindfulness Questionnaire (FFMQ). FFMQ is based on a factor analytic study of five independently developed mindfulness measurement scales.[50] The factors we will use are: *Observing*, which refers to noticing or attending to internal and external experiences, such as thoughts, sensations, emotions, sounds, sights, and smells; *Acting with awareness*, which includes attending to one's activities in the present moment; *Non-judging of inner experience*, which refers to taking a non-evaluative attitude toward thoughts and feelings; and *Non-reactivity to inner experience*, which includes allowing thoughts and feelings to come and go, without getting caught up in or carried away by them.[51] The factor *Describing* will be omitted, because describing one's emotions and feelings is not a primary focus of MBSR/MBCT and we do not want to burden our patients unnecessarily. Each factor consists of 7 or 8 items, which will be answered on a five-point Likert scale (*1 = never or very rarely true, 5 = very often or always true*). The four facets demonstrated adequate to good internal consistency (alphas ranging from 0.75 to 0.87).[50]

Changes in diabetes-specific mindfulness and acceptance processes will be assessed by the Acceptance and Action Diabetes Questionnaire (AADQ).[26] This self-report questionnaire consists of 11-items that are answered on a 7-point Likert scale. It measures acceptance of diabetes-related feelings and thoughts and the extent to which they interfere with valued action (e.g., "I avoid thinking about what diabetes can do to me").[26] For this measure, a Cronbach's α of 0.94 has been reported.[26]

Self-esteem

Self-esteem will be measured by the Dutch version of the Rosenberg Self-Esteem Scale (RSES), wherein self-esteem is defined as a person's overall evaluation of his or her worthiness as a human being.[52] The questionnaire consists of 10 items answered on a four-point Likert scale, ranging from 'I totally disagree' to 'I totally agree'. A sample item is "I take a positive attitude toward myself". A higher score reflects a higher global self-esteem. The Cronbach's alpha was .86, indicating a high internal consistency.[52]

3. Tertiary outcome measures

Self-care behavior

Self-care behavior (or self-management) will be assessed with the Amsterdam Diabetes Self Care Inventory (ADSCI). The questionnaire has 11 items, which will be examined separately. Each item is divided into three or four subquestions. Higher scores indicate higher levels of self-care. The questionnaire is developed by colleagues of the VU University

Medical Center in Amsterdam and used in previous trials.[53, 54] The psychometric properties of the ADSCI have not yet been published.

Glycemic control

To measure glycemic control we will consult the three-monthly standard measurements of HbA_{1c} of the hospital, which are documented in the hospital's patient database. The percentage HbA_{1c} is a function of the glucose concentration to which the red blood cells are exposed and gives an indication of the average blood glucose concentration of the preceding six to eight weeks.[3]

Blood pressure

The patients' blood pressure will be measured by an ambulant device, called the Mobil-O-Graph, which is based on the oscillometric method and which has been shown to provide reliable and valid assessments.[55] The patients, who have an elevated blood pressure (≥ 140 mmHg systolic or 90 mmHg diastolic of the mean values of 3 measurements) during the interview, will wear the meter 24 hours following the interview. The ambulatory measurements will occur two times per hour. To keep the burden for the patients as low as possible, we decided to measure the blood pressure only during the daytime. The device will be attached to the patient by the researcher who does the interviews (JvS).

4. Additional outcome measures

Personality

To measure personality dimensions we will use the subscale Extraversion (EPQ-E) of the shortened revised Eysenck Personality Questionnaire (EPQ-RSS) and the DS-14 to measure Type D personality. Persons with a Type D personality tend to experience high levels of emotional distress, but do generally not express these emotions. For the EPQ-E, the subscale Extraversion reflects sociability, assertiveness, and the tendency to experience positive emotions. The subscale consists of 12 dichotomous (yes/no) items.[56] The Committee on Test Affairs Netherlands rates the EPQ to be a reliable measure.[57]

The 14-item Type D scale (DS14) measures both negative affectivity (NA) (e.g. "I often feel unhappy"; 7 items) and social inhibition (SI) (e.g. "I am a closed kind of person"; 7 items).[58] Items are answered on a five-point Likert scale ranging from 'false' to 'true' *(0-4)*, with the score range for the NA and SI subscales being 0 to 28.[58] We will use the standardized cut-off ≥ 10 on both subscales to identify Type D caseness.[58, 59] The DS14 has been shown to be a valid and reliable instrument, with Cronbach's α of 0.88 and 0.86 and a 3-month test-retest reliability of r = 0.72 and 0.82 for the NA and SI subscales,

respectively.[58] Furthermore, a recent study showed that Type D personality is a stable construct over an 18-month period and is not confounded by disease severity and measures of anxiety and depression.[60, 61] Results from a study by Denollet et al. [62] suggest that particularly the interaction between NA and SI is predictive of adverse health outcomes, more than the single traits. [62]

Demographic and clinical variables

Demographic variables will be collected by means of a questionnaire, which will be completed by the patients during the baseline assessment. Data will be collected regarding the participant's age, marital status, education, and job status. In addition, the baseline questionnaire will be used to gather information on history of emotional problems and use of psychotropic medication, level of meditation experience, sleep quantity and quality, participant's perceived importance of adequate blood glucose regulation, and amount of participant's effort to manage their blood glucose. Furthermore, the baseline questionnaire will be used to assess clinical data, such as length and weight of participants, last HbA_{1c}, number of severe hypoglycemic episodes and/or hospitalizations because of a diabetic coma during the past year, existing diabetes complications, co-morbidities, and smoking and drinking behavior. The clinical variables (which are available) will also be retrieved from the hospitals' patient information database.

5. Additional process measures

During the intervention process data will be collected, like drop-out, patients' attendance of the sessions, patients' adherence to the home work assignments, and trainers' adherence to the protocol. The adherence to the protocol will be determined each session by the trainers by means of the completion of a checklist including all components of each session. The components are divided into important and less important, facilitating decision making when time constraints are present.

Statistical analyses

Sample size and power calculation

The total number of patients that have to be included and complete the study is 160, with 80 patients in each arm, taking into account a medium effect size, a power of 0.80, an alpha of 0.05, patient attrition, and subgroup analyses involving two equally sized groups (e.g. yes vs. no complications). It is expected to reach this number of participants during the course of the study.

Planned analyses

Repeated measures analysis of variance ((M)ANCOVA) will be used to test the hypotheses concerning the differences between groups on the dependent variables over time. In these tests age, sex, and co-morbidity will be included as covariates, in addition to those other potentially confounding variables that will show an at least marginally significant ($p < .10$) difference between groups. The analyses concerning the subgroup effects will be conducted on the sample as a whole, whereby possible moderating variables, like complications and personality will be included in the analyses as between-subjects factors. All analyses will be based on the intention-to-treat approach.

Ethical principles

The study protocol has been approved by the medical ethical committee of the St. Elisabeth Hospital in Tilburg, The Netherlands (P0948).

DISCUSSION

The present article provides an outline of the background and design of the Diabetes and Mindfulness (DiaMind) study. This study's objective is to test an intervention based on mindfulness training supplemented with elements from cognitive therapy that aims to improve emotional well-being of distressed patients with diabetes. For this purpose, an intervention group will be compared with a wait-list control group with treatment as usual.

Research on psychological interventions that aim to reduce emotional problems in DM patients is important, as emotional problems are associated with a higher risk of impaired quality of life,[8] less optimal self-care,[9] incident complications, and mortality.[8, 11] However, to date there are few methodologically well-designed studies on the effectiveness of psychological interventions for people with diabetes and emotional complaints. In addition, the majority of these studies have focused on improving self-management instead of emotional well-being. Moreover, the few randomized studies that have examined the effectiveness of interventions in reducing emotional problems in people with diabetes often focused on depression. For this reason, this study is clearly of added value in the research field of diabetes and emotional problems, as we have taken a broader perspective and focused on emotional distress (depression, anxiety, and general distress).

The study design has a number of important strengths. First, the present study has more power to generate knowledge on the effectiveness of a mindfulness-based intervention

for DM patients with emotional problems than former studies examining mindfulness in DM patients. As mentioned before, only two studies have been done on this subject, of which one lacked a control group and one did not include emotional well-being as an outcome.[25, 26] Second, an additional strength of this study is the inclusion of both psychological and clinical measures, while most randomized controlled trials examining mindfulness interventions include psychological measures only. Finally, another strong aspect of this study is the examination of factors that potentially moderate the effectiveness of the mindfulness intervention, including clinical (e.g. complications) and psychological (e.g. personality) variables. Results may facilitate more effective allocation of patients to treatments.

The recruitment has already started in the Catharina Hospital in Eindhoven in spring 2010 and in the Maxima Medical Center in autumn 2010. At present, 969 individuals have been screened for emotional problems. Of those, 811 did not qualify: 658 had a score above 12 on the WHO-5 screening instrument, and 153 were ineligible (no mastery of the Dutch language, psychiatric disorder, or severe physical condition). Of the eligible patients, 120 declined participation (no perceived need or motivation for the training or an incompatible working schedule). At present, 42 patients are interested to participate, of whom 16 have been enrolled so far. The recruitment of a sufficient number of patients will be a challenge. For instance, the mindfulness intervention requires participants to commit to attending eight two-hour group sessions and to practice exercises at home for five days per week. For people who have busy lives this sometimes is a challenge to comply with, which may make them decline participation or drop out of the study.

Concerning the benefits of the present study, the results will provide valuable information regarding the effectiveness of the mindfulness intervention for DM patients in improving emotional well-being. We will also gain insight in the pros and cons of a possible implementation of the intervention in usual medical care of DM patients. By doing this, we aim to find ways that can contribute to increased emotional well-being and quality of life in patients with diabetes mellitus.

In conclusion, considering the prospected increase of the prevalence of diabetes, the levels of emotional distress in this patient group, and the incompleteness of the current literature on effective psychological interventions for the distressed patients, well-designed trials on psychological interventions are a welcome addition in the diabetes research. In the present randomized controlled trial the effectiveness of a psychological intervention will be examined in which the cultivation of mindfulness (the direction of attention to one's experiences in the present moment in an open and accepting manner) plays

a central role. This intervention may be an effective alternative to traditional cognitive behavioral therapy in improving emotional well-being in DM patients. The first results of the study will become available in 2012.

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Chapter 4

The effects of a mindfulness-based intervention on emotional distress, quality of life, and HbA_{1c} in outpatients with diabetes (DiaMind): a randomized controlled trial

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ABSTRACT

Objective Emotional distress is common in outpatients with diabetes, affecting approximately 20-40% of the patients. The aim of this study was to determine the effectiveness of group therapy with Mindfulness-Based Cognitive Therapy (MBCT), relative to usual care, for patients with diabetes with regard to reducing emotional distress and improving health-related quality of life and glycemic control.

Research design and methods In the present randomized controlled trial, 139 outpatients with diabetes (type 1 or type 2) and low levels of emotional well-being were randomized to MBCT (n = 70) or a waiting list group (n = 69). Primary outcomes were perceived stress (Perceived Stress Scale), anxiety and depressive symptoms (Hospital Anxiety and Depression Scale), mood (Profiles of Mood States), and diabetes-specific distress (Problem Areas in Diabetes). Secondary outcomes were health-related quality of life (12-Item Short-Form Health Survey), and glycemic control (HbA_{1c}). Assessments were conducted at baseline and at 4 and 8 weeks of follow-up.

Results Compared with control, MBCT was more effective in reducing stress ($P < 0.001$, Cohen's $d = 0.70$), depressive symptoms ($P = 0.006$, $d = 0.59$), and anxiety ($P = 0.019$, $d = 0.44$). In addition, MBCT was more effective in improving quality of life (mental: $P = 0.003$, $d = 0.55$; physical: $P = 0.032$, $d = 0.40$). We found no significant effect on HbA_{1c} or diabetes-specific distress, although patients with elevated diabetes distress in the MBCT group tended to show a decrease in diabetes distress ($P = 0.07$, $d = 0.70$) compared with the control group.

Conclusions Compared with usual care, MBCT resulted in a reduction of emotional distress and an increase in health-related quality of life in diabetic patients who had lower levels of emotional well-being.

INTRODUCTION

Emotional distress, which can consist of symptoms of depression, anxiety and diabetes-specific distress affects around 20 to 40% of outpatients with type 1 or type 2 diabetes,[1-3] making it a common comorbid health problem in these patients. Emotional distress results in lower quality of life[4] and more negative appraisals of insulin therapy.[5] In addition, depression is associated with suboptimal self-care behaviors,[6] suboptimal glycemic control,[7] adverse cardiovascular outcomes, and higher mortality rates.[8, 9] Although the emotional problems in diabetic patients have received increasing attention in the last decade, they are still often not recognized in clinical practice and remain untreated.[10]

Previous research has shown that antidepressant medication and cognitive behavioral therapy are effective treatments for major depression in diabetic patients.[11, 12] However, the use of antidepressant medication is often accompanied by serious side effects, and a substantial percentage of the patients (approx. 30-50%) still do not respond to treatment or relapse.[13] Hence, we need to conduct new studies, testing new treatments for emotional distress in diabetes. Because the number of diabetic patients is rapidly increasing, we need to develop interventions that are not only effective but also affordable. Web-based therapies and group therapies are good candidates.

One easily accessible group intervention that proved successful reducing emotional distress and improving quality of life in nonpatients and in diverse patient groups[14-16] is Mindfulness-Based Cognitive Therapy (MBCT).[17] MBCT is an 8-week protocolized group therapy program that combines meditation exercises with elements of cognitive therapy. The central component of this intervention is the cultivation of mindfulness. This can be defined as the self-regulation of one's attention focusing on direct experience, while adopting a curious, open, and accepting attitude toward these experiences, especially one's psychological processes, such as thoughts and feelings.[18] A recent meta-analysis has shown medium to large effect sizes for mindfulness-based interventions in reducing symptoms of anxiety and depression.[19]

Two other studies examined the effect of a mindfulness-based intervention on emotional distress in people with diabetes.[20, 21] In one uncontrolled study, the mindfulness group showed a significant decrease in depressive symptoms at post intervention and in HbA_{1c} at the 1-month follow-up.[20] The other study found no significant effects directly after the intervention, but significant improvements in depressive symptoms (Cohen's d = 0.71) and mental health-related quality of life (Cohen's d = 0.54) were reported at the 1-year follow-up.[21] The results of these studies are in line with the notion that mindfulness-based

interventions could adequate in reducing emotional problems in people with diabetes. However, the presence of emotional distress was not an inclusion criterion in either study, and only the latter study was a randomized controlled trial.[21] In addition, studies testing the effectiveness of a mindfulness-based intervention in outpatients with type 1 diabetes are still lacking.

Therefore, the purpose of the current study was to test the effectiveness of MBCT for people with type 1 or type 2 diabetes and co morbid emotional distress. The primary outcome was the effect on emotional distress, including symptoms of depression, anxiety, diabetes-specific distress, and general perceived stress. Secondary outcomes were health-related quality of life and glycemic control. From the results of two systematic reviews,[19, 22] we hypothesized that after MBCT, diabetic patients would experience significant greater reductions in emotional distress compared with a waiting list control group. We also hypothesized that MBCT would lead to better health-related quality of life and lower HbA_{1c}.

RESEARCH DESIGN AND METHODS

The Diabetes and Mindfulness (DiaMind) study is a randomized controlled trial. The study protocol has been approved by the medical ethics committee of the St. Elisabeth Hospital in Tilburg, the Netherlands (P0948), and the study is performed according to the 2000 revised version of the Helsinki Declaration. An extensive overview of the methods of the DiaMind study has recently been published elsewhere.[23]

Participants

Dutch-speaking adult patients with diabetes (type 1 or type 2) with low levels of emotional well-being (as evidenced by a score of < 13 on the World Health Organization-5 Well-Being Index[24]) were recruited from outpatient diabetes clinics between May 2010 and November 2011. Exclusion criteria are reported in the DiaMind study protocol.[23] Eligible patients (n = 139) were randomly allocated to the MBCT group (n = 70) or the waiting list (usual care) control group (TAU; n = 69). The TAU group received the program six months after the intervention of the MBCT group. The first MBCT group started in September 2010 and the last TAU group in October 2012. All participants provided written informed consent.

Intervention

The protocolized mindfulness intervention was based on the Mindfulness-Based Stress Reduction (MBSR) and MBCT programs as described by Kabat-Zinn[25] and Segal et al.[17],

consisting of eight weekly 2-hour sessions in groups of 4 to 10 participants. Because the program is closest to the protocol as described by Segal et al.[17] we decided to call it MBCT. The central component of the program was the development of mindfulness, which was done by practicing several meditation exercises. A specific theme was also discussed in each session (e.g., "how to cope with thoughts"). At the end of the sessions, the participants received homework assignments that took about 30 min, 5 days/week. Instead of one whole-day session, which is part of the original program, a 2-hour booster session was added 3 months after the end of the intervention as a means to boost mindfulness practice. All sessions were supervised by certified psychologists who had at least 4 years of personal experience with mindfulness practice and also completed at least one certified mindfulness instructors training of 8 days in The Netherlands.

Randomization

After completion of the baseline assessment, participants were randomized according to a 1:1 ratio within blocks of 4 to receive MBCT or TAU. A random list was prepared by an independent statistician using PASW Statistics 17 software with a random number generator.

Outcome measures

The primary outcome assessment for MBCT and TAU took place at pre- (T1), mid- (at 4 weeks: T2), and post-intervention (at 8 weeks: T3). The secondary outcome, health-related quality of life, was only assessed at T1 and T3. HbA_{1c} values were looked up pre- and post-intervention, but within a wider period of time (see below).

Demographic and clinical variables

Demographic and clinical variables, such as existing diabetes complications and co-morbid conditions, were collected by means of a questionnaire, which the participants completed during the baseline assessment. HbA_{1c} was retrieved from the hospitals' computerized patient records. The policy in the outpatient diabetes clinics is to measure HbA_{1c} every 3 months. Because HbA_{1c} reflects the state of the preceding ~ 2 to 3 months, the value for the pre-intervention assessment was obtained between 24 weeks before and 1 week after the start of the intervention, and this period for the post-intervention measures was between 6 and 24 weeks after the intervention.

Emotional distress

We defined emotional distress as symptoms of anxiety, depression and/or (diabetes-specific) distress and operationalized the concept by means of four questionnaires. We included the Dutch version of the Perceived Stress Scale (PSS) to measure general

perceived stress, defined as the degree to which situations in one's life are appraised as stressful (e.g., "lately, how often have you felt nervous and stressed?"). The items of the present 10-item version of the PSS are answered on a 5-point Likert scale, ranging from "never" (0) to "very often" (4).[26] The Cronbach's α was 0.81 in this sample.

The Hospital Anxiety and Depression Scale (HADS) was included to measure symptoms of anxiety (e.g., "Worrying thoughts go through my mind") and depression (e.g., "I feel as I am slowed down").[27] Both subscales comprise of seven items that are answered on a 4-point Likert scale of 0 to 3. The score range for the anxiety and the depressive symptoms subscales is 0 to 21. The Cronbach's α in this sample was 0.75 for the anxiety and 0.81 for the depression subscale.

In addition, we used the short Dutch version of the Profile of Mood States (POMS)[28] to assess transient, fluctuating mood states. In this scale, 32 adjectives about positive and negative mood states are rated on a 5-point Likert scale (0 "not at all", 4 "very much") according to how well each item describes one's mood during the last couple of weeks. We selected the most relevant subscales: Tension-anxiety (six items); Depression-dejection (eight items); and Fatigue-inertia (six items). These subscales in the present sample had a Cronbach's α of 0.77-0.93. There is an overlap between the HADS and POMS. We decided to include both scales in the study because they have complementary qualities: whereas the HADS is a more used and well-known instrument in medical settings, the POMS has three additional subscales and appears to be more sensitive for change.[29]

The Dutch version of the Problem Areas in Diabetes (PAID) survey was included to measure diabetes-specific distress. This scale consists of 20 statements about common negative feelings related to living with diabetes (e.g., "Feeling depressed when you think about living with diabetes", "feeling discouraged with your diabetes regimen").[30] The items are rated on a 6-point Likert scale (1 "not a problem"; 6 "a serious problem"). To facilitate interpretation, the PAID scores were transformed to a 0-100 scale.[31] A higher score indicates more distress, with a cutoff score of 40 indicating seriously elevated diabetes distress.[32] The Cronbach's α in this sample was 0.91.

Health-related quality of life

The Dutch version of the 12-item Short-Form Health Survey (SF-12) was included to assess health-related quality of life. The 12 items of this self-report scale are grouped into two component summary scores: a physical (PCS) and a mental component score (MCS). Both component scores are measured on a scale from 0 to 100, with a high score indicating good health-related quality of life. The Dutch SF-12 has established reliability and validity.[33]

Data Analyses

The χ^2 test, or the Fisher's Exact test, as appropriate, were used to examine differences on discrete variables. Possible differences on continuous variables were examined with the Student's *t*-test for independent samples. Mixed-Models analyses (SPSS 18 software) were used to test the differences between groups on the dependent variables (time x group interaction effect). We used mixed-models analysis instead of repeated-measures ANOVA to make more efficient use of our data with likely occasional missing values. In sensitivity analyses, linear regression analyses on change scores were conducted after multiple imputation was used to address missing data. In instances when the groups differed on pre-treatment variables, these variables would be included as covariates. Age, sex, and co-morbidity were regarded as important variables to be included as covariates at all occasions.[23] All analyses were based on the intention-to-treat approach.

To determine clinically significant change, we followed the definition of Jacobson et al.[34] The first step was to identify participants who had moved outside the range of the "dysfunctional population" at post-intervention assessment (the "recovered" participants) by using a cutoff score of ≥8 on both subscales of the HADS.[35] The second step was to identify individuals who showed a significant improvement at post-intervention. Therefore, for each individual, we calculated the Reliable Change Index (RCI = x2-x1/Sdiff.) on the HADS.[34] The participants who both "recovered" and showed a "significant improvement" were considered as being "clinically significantly improved".

RESULTS

Recruitment and attrition

Figure 1 displays the participants' flow chart. Of 5,710 diabetic patients were assessed for eligibility, 1,299 (23%) were directly invited by the researcher, diabetes nurse, or secretary in the outpatient diabetes clinic during a regular appointment, and 4,411 (77%) were invited by an invitational letter. Of the latter group, the response rate was 43% (n = 1,898). Of the remaining 3,197 patients, 2,126 (67%) did not meet inclusion criteria (e.g., they had good to optimal emotional well-being), 638 (20%) declined to participate, and 294 (9%) were excluded because of other reasons, including insufficient information on the patient or inability to contact the patient. The two main reasons for decline were no interest or no need for an intervention, and practical problems, such as being too busy to follow the intervention or not being able to attend the meetings.

In the MBCT group, 2 patients (3%) dropped out before the start of the intervention, 13 (19%) before the fourth session, and 5 (7%) between the fourth and the eighth session. Of

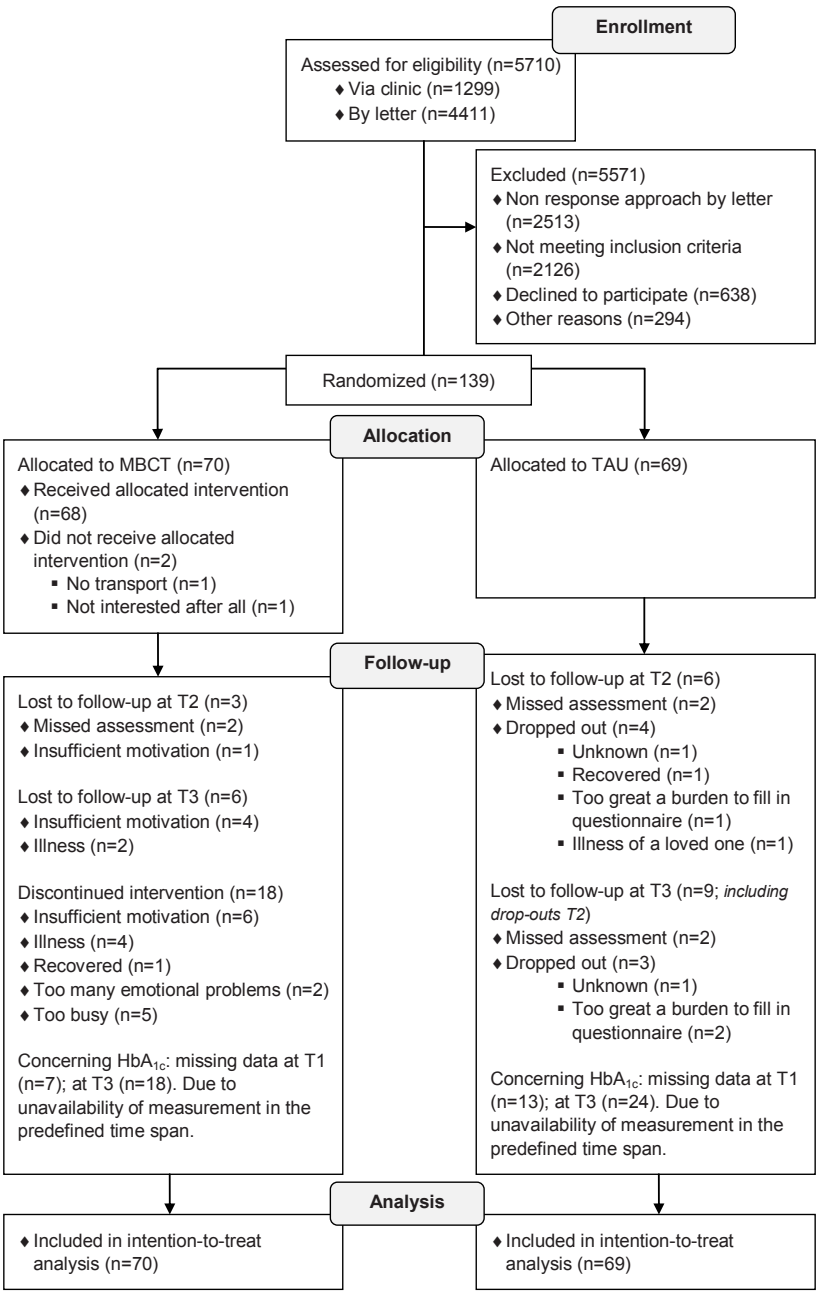

Figure 1. Flow diagram of patient enrolment, allocation, and attrition. MBCT – Mindfulness-Based Cognitive Therapy intervention group; TAU – Waiting list (usual care) control group. Pre – baseline assessment; Mid – assessment after 4 weeks; Post – post intervention assessment.

the remaining 50 participants, 41 (82%; 59% of total MBCT group) attended at least six of the eight sessions. The overall average attendance was 5.5 (SD = 2.5) sessions. Seven patients (10%) in the TAU group dropped out of the study. Ten dropouts in the MBCT group continued to fill in the questionnaires. Eventually, we missed data of 9 participants (MBCT: n = 3; TAU: n = 6) at T2, and 16 participants (MBCT: n = 7; TAU: n = 9; Fig. 1) at T3. Participants who prematurely stopped with the intervention were less likely to have a partner (55% vs. 80%, *P* = 0.034) and to have prior experience with meditation (5% vs. 31%, *P* = 0.022). The MBCT and TAU participants who did not complete the T3 assessment were younger (*P* = 0.028) and had a higher score on the POMS fatigue subscale at baseline (*P* = 0.007). They were also less likely to have a partner (53% vs. 77%, *P* = 0.042) and more likely to use psychotropic medication (47% vs. 18%, *P* = 0.010) and to smoke (40% vs. 14%, *P* = 0.010). The HbA_{1c} data were missing for 20 participants at T1 (MBCT: n = 7; TAU: n = 13) and for 42 participants at T3 (MBCT: n = 18; TAU: n = 24). There were no significant differences regarding our outcomes between participants of which the HbA_{1c} measurement was or was not available.

Characteristics of study participants

The baseline characteristics of the sample, stratified by group (MBCT or TAU), are presented in Table 1. At baseline, there were no statistically significant differences between the two groups on demographic and clinical variables.

Table 1. Demographic and clinical characteristics of MBCT and TAU group

	MBCT (n = 70)	TAU (n = 69)	*P**
Age, *years* (SD)	56 (13)	57 (13)	0.62
Male, *n* (%)	33 (47)	37 (54)	0.45
High education†, *n* (%)	31 (44)	28 (41)	0.66
Working, *n* (%)	28 (40)	19 (28)	0.12
Living with a partner, *n* (%)	51 (73)	53 (77)	0.59
Children living at home, *n* (%)	23 (33)	19 (28)	0.50
Diabetes type 2, *n* (%)	52 (74)	45 (65)	0.41
HbA_{1c}, *mmol/mol* (SD)	59.0 (13)	59.2 (13)	0.92
HbA_{1c}, *%* (SD)	7.5 (1)	7.6 (1)	0.92
Complications, *n* (%)	32 (46)	33 (48)	0.87
Co-morbidity, *n* (%)	54 (77)	47 (68)	0.23
Past psychological treatment, *n* (%)	39 (56)	44 (64)	0.33
Use of psychotropic medication, *n* (%)	18 (26)	12 (17)	0.23
Meditation experience, *n* (%)	16 (23)	11 (16)	0.30

*Chi-square for nominal variables and t-test for continuous variables. †High education: high-level professional education and university. MBCT –Mindfulness-Based Cognitive Therapy group; TAU – Waiting list (usual care) control group.

Effect on primary outcome emotional distress

The mean scores of MBCT and TAU on the emotional distress measures are presented in Table 2. Mixed-models analyses showed that the individuals in the MBCT group had a significantly larger decrease in levels of perceived stress over time compared with TAU ($P < 0.001$). The effect size of the difference from pre- to post-intervention between the two conditions was medium to large (Cohen's $d = 0.70$). Post hoc between-subjects analyses indicated that the groups differed at post-intervention ($P < 0.001$) but not at T2 ($P = 0.204$).

The analyses also showed a significant effect of MBCT on depressive symptoms (HADS) compared with TAU ($P = 0.006$) with a medium effect size (Cohen's $d = 0.59$; Fig. 2a). This difference between groups was already significant at T2 ($P = 0.011$), as post hoc analyses revealed, but increased at post-intervention ($P < 0.001$). The results on the depression subscale of the POMS were comparable, but with a larger effect size (Cohen's $d = 0.71$; Table 2).

Concerning symptoms of anxiety (HADS), there was a significant improvement in the MBCT group compared with TAU ($P = 0.019$). The effect size was small to medium (Cohen's d =

Table 2. Mean (SD) scores and results of Mixed Models Analyses for primary outcomes

Measure		Pre	Mid	Post	Time effect		Time x treatment effect			*95%CI*[†]
		M (SD)	M (SD)	M (SD)	F	*P*	F	*P*	*d*[*]	
Stress[‡]	MBCT	19.5 (6.0)	17.3 (6.9)	14.2 (6.9)	17.40	<0.001	9.37	<0.001	0.70	0.63-0.77
	TAU	20.5 (5.9)	19.1 (6.4)	19.6 (6.7)	2.14	0.13				
Anxiety[§]	MBCT	8.4 (3.3)	7.5 (4.1)	6.3 (3.5)	13.26	<0.001	4.09	0.02	0.44	0.42-0.46
	TAU	9.2 (3.6)	9.0 (3.7)	8.7 (4.1)	0.98	0.38				
Anxiety[‖]	MBCT	20.3 (4.5)	19.0 (5.2)	17.3 (4.1)	24.04	<0.001	9.86	<0.001	0.82	0.80-0.85
	TAU	20.1 (4.4)	20.0 (4.6)	19.7 (5.1)	0.64	0.53				
Depression[§]	MBCT	7.9 (3.8)	6.4 (4.3)	5.4 (4.1)	14.96	<0.001	5.37	<0.01	0.59	0.56-0.61
	TAU	8.9 (3.9)	8.5 (4.2)	8.5 (4.7)	0.61	0.55				
Depression[‖]	MBCT	25.3 (5.8)	23.5 (6.4)	21.6 (4.5)	25.25	<0.001	8.38	<0.001	0.71	0.68-0.75
	TAU	26.6 (6.3)	26.0 (6.1)	26.2 (7.0)	0.41	0.67				
Diabetes distress[¶]	MBCT	34.3 (17.8)	28.1 (16.4)	27.8 (20.6)	6.42	<0.01	0.71	0.49	0.21	0.11-0.32
	TAU	36.1 (18.9)	31.8 (18.9)	33.3 (22.0)	2.76	0.07				
Fatigue[‖]	MBCT	22.9 (5.5)	20.3 (5.9)	19.5 (5.1)	14.14	<0.001	4.55	0.01	0.58	0.54-0.62
	TAU	23.4 (6.4)	23.0 (6.8)	22.5 (6.9)	1.07	0.35				

[*]The effect size (Cohen's d) was calculated on pre to post intervention change scores. [†]95%CI - The 95% Confidence Interval of the effect size. MBCT – Mindfulness-Based Cognitive Therapy group; TAU – Waiting list (usual care) control group; [‡]from PSS – Perceived Stress Scale; [§]from HADS – Hospital Anxiety and Depression Scale; [‖]from POMS – Profiles of Mood States; [¶]from PAID – Problem Areas in Diabetes survey.

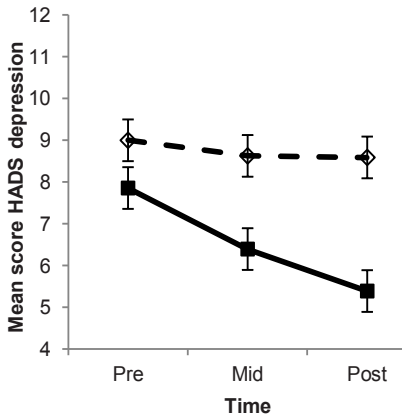

Figure 2a. Effect of MBCT on depressive symptoms Data are presented as means and standard errors. Solid line: MBCT – Mindfulness-Based Cognitive Therapy intervention group; Dashed line: TAU – Waiting list (usual care) control group. Pre – baseline assessment; Mid – assessment after 4 weeks; Post – post intervention assessment; HADS – Hospital Anxiety and Depression Scale. Results Mixed Models Analyses: $p < 0.01$, Cohen's $d = 0.52$.

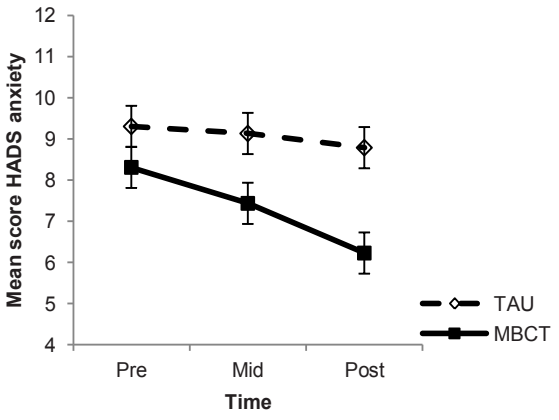

Figure 2b. Effect of MBCT on anxiety symptoms Data are presented as means and standard errors. Solid line: MBCT – Mindfulness-Based Cognitive Therapy intervention group; Dashed line: TAU – Waiting list (usual care) control group. Pre – baseline assessment; Mid – assessment after 4 weeks; Post – post intervention assessment; HADS – Hospital Anxiety and Depression Scale. Results Mixed Models Analyses: $p = 0.02$, Cohen's $d = 0.44$.

0.44) (Fig. 2b). Post hoc analyses showed a trend for significance at T2 ($P = 0.064$) and a significant difference at post-intervention ($P = 0.001$). The results on the anxiety subscale of the POMS were comparable, but the effect size was larger (Cohen's $d = 0.82$; Table 2). Similar results were also obtained for the POMS subscale of fatigue (Table 2).

In contrast, there was no significant difference between MBCT and TAU on diabetes-specific distress ($P = 0.488$, Cohen's $d = 0.21$). Post hoc analyses revealed that there was a significant decrease in diabetes-specific distress over time in the MBCT group ($P = 0.003$), whereas the TAU group showed a trend for significant decrease over time ($P = 0.072$). Because the participants were selected on general emotional distress, a considerable percentage (52%) did not have elevated diabetes distress at baseline. Therefore, we conducted an ad hoc subgroup analysis in participants with elevated diabetes distress levels (PAID ≥ 40). This analysis revealed a trend for a significant mean (SD) reduction in the MBCT [35 (20)] compared with the TAU group [49 (17); $P = 0.066$], with a moderate to large effect size (Cohen's $d = 0.70$).

Clinical significance

At baseline, 81 participants (MBCT: n = 40; TAU: n = 41) had a score above the anxiety cut-off at baseline and 71 (MBCT: n = 33; TAU: n = 38) had a score above the depression cutoff. In the MBCT group, 37% of these participants showed a clinically significant improvement on symptoms of anxiety compared with 5% in the TAU group ($P = 0.001$, $\varphi = 0.39$) and 27% on symptoms of depression versus 8% in the TAU group ($P = 0.064$, $\varphi = 0.26$).

Effect on secondary outcomes health-related quality of life and HbA_{1c}

Mixed-models analyses showed that the MBCT group had a significantly more strongly improved mental quality of life ($P = 0.003$; Cohen's $d = 0.55$) as well as physical quality of life ($P = 0.032$; Cohen's $d = 0.40$) compared with the TAU group (Table 3).

Mixed-model analyses showed no significant difference in HbA_{1c} change in MBCT compared with TAU ($P = 0.346$; Cohen's $d = 0.14$; Table 3). Post hoc analyses revealed that there was no significant difference in HbA_{1c} over time in the MBCT group ($P = 0.366$), whereas the TAU group showed a trend for a significant increase in HbA_{1c} over time ($P = 0.064$).

Table 3. Mean (SD) scores and results of Mixed Models Analyses for secondary outcomes

Measure		Pre M (SD)	Post M (SD)	Time effect		Time x treatment effect			*95%CI*†
				F	*P*	F	*P*	*d**	
Quality of life‡									
Mental	MBCT	33.9 (11.0)	42.9 (10.7)	37.7	<0.001	9.48	<0.01	0.55	0.49-0.61
	TAU	32.5 (11.6)	35.7 (12.5)	7.85	0.01				
Physical	MBCT	41.5 (9.9)	43.5 (10.5)	5.04	0.03	4.71	0.03	0.40	0.33-0.47
	TAU	38.9 (11.4)	38.5 (11.7)	0.42	0.52				
HbA_{1c}									
mmol/mol %	MBCT	58.6 (12.6) 7,5 (1,2)	59.6 (12.1) 7,6 (1,1)	0.83	0.37	0.90	0.35	0.14	0.06-0.23
mmol/mol %	TAU	59.3 (12.9) 7,6 (1,2)	61.8 (16.4) 7,8 (1,5)	3.64	0.06				

*The effect size (Cohen's d) was calculated on pre to post intervention change scores. †95%CI - The 95% Confidence Interval of the effect size. ‡From SF-12 – Health Continuum Short Form; Mental – Mental Component Summary; Physical – Physical Component Summary.

Sensitivity analyses

Sensitivity analyses based on multiple imputation data showed highly similar results; for example, all significant results reported above were also significant except for physical

quality of life, which became marginally significant $P = 0.057$). In addition, sensitivity analyses in which diabetes type and diabetes type-by-time interaction were included as covariates revealed highly similar results. The diabetes type-by-time interaction was not significant in any analysis (all $P > 0.05$), showing that results were similar for both types.

DISCUSSION

The present report describes the results of the DiaMind study. This study's main objective was to test the effectiveness of MBCT in improving the emotional well-being of distressed diabetic patients. The findings were largely in line with our a priori hypotheses regarding the effect of the intervention on emotional well-being and quality of life. Patients receiving MBCT showed significantly larger decreases in perceived stress, symptoms of depression and anxiety, and had significantly better improvements in health-related quality of life compared with those in the TAU group. The effect sizes were medium to large. To the best of our knowledge, this is the first randomized trial to find immediate effects of a mindfulness-based intervention on emotional well-being and quality of life in outpatients with type 1 and type 2 diabetes.

The participants in the MBCT group were approximately seven times more likely to show a clinically significant improvement at post-intervention in symptoms of anxiety and three times more likely to show this improvement in symptoms of depression compared with the participants in the TAU group. Altough the effect sizes were medium, the difference for depressive symptoms was almost significant. This can probably be considered as a power problem, because only approximately half of the participants scored above the HADS cutoff score of anxiety and depressive symptoms at baseline.

Interestingly, although the MBCT group also showed a significant reduction in diabetes-specific distress over time, we did not find a significant difference between MBCT and TAU at post-intervention for this outcome. General emotional distress was an inclusion criterion, yet only a fraction of the participants (48%) experienced elevated diabetes distress (PAID ≥ 40). Hence, the non-significant finding could be caused by a floor effect. When we tested the effect of the intervention in the subgroup with elevated diabetes distress at baseline, the results revealed that MBCT reduced the diabetes distress with a moderate to large effect size compared with TAU. However, this finding was not statistically significant, probably due to a lack of statistical power, given the smaller size of this subsample.

No significant difference was obtained between the groups regarding change in HbA_{1c}. Although the MBCT group showed no significant change in levels of HbA_{1c} from pre- to post-intervention, the control group showed marginally significant increased values at post-intervention. The non-significant difference between the MBCT and TAU groups is in line with the discrepancy in findings regarding the effect of psychological interventions on HbA_{1c} in patients with diabetes, with one meta-analysis finding an effect[36] and one systematic review[37] and another meta-analysis finding no effect.[38] One possible explanation for the absence of a decrease in the current study is that poor glycemic control was not an inclusion criterion, and so the mean (SD) HbA_{1c} at baseline [59 mmol/mol (13) or 7,6% (1.2)] was slightly above target level. This fairly good baseline glycemic control contrasts with previous studies in the latter meta-analysis. Future research in a group with poor glycemic control should examine this possibility.

As mentioned before, only two other studies have tested the effectiveness of mindfulness therapy for patients with diabetes. Hartmann et al.,[21] did not find significant reductions in depressive and stress symptoms or an increase in health-related quality of life compared with usual care directly after the intervention, whereas improvements for some of these outcomes were found at the 1-year follow-up. The main explanation for the difference in findings compared with the DiaMind study may be because the presence of emotional distress was an inclusion criterion in the current study. Rosenzweig et al.[20] did show a reduction in depressive symptoms and general psychological stress, but not in anxiety symptoms, in diabetic patients immediately after the intervention. However, they did not use a randomized controlled design, had a small sample size, and again, the presence of emotional distress was not an inclusion criterion.

The DiaMind study had a number of limitations. First, selection bias may have affected our results, because only a small portion of the patients we assessed for eligibility decided to participate in the trial. Therefore, generalizability of the findings is limited to diabetic patients who are open to participate in a psychological intervention. This effect applies for all psychological interventions but perhaps even more strongly for one based on mindfulness, although care was taken to use more neutral terms in communication to patients, such as “attention” or “attention exercises” instead of “mindfulness” or “meditation”. Second, the study had a significant dropout rate in the MBCT group: ~ 26% (n = 18) stopped participating in the program. Although the dropout rate is comparable to some studies,[14, 15] it is relatively high compared with other studies.[39, 40] A possible explanation is that the participants were approached, instead of being the requesting party. Fortunately, efforts to collect the data of all randomized participants, even when treatment was prematurely terminated, were fruitful: 59% (n = 10) of the dropouts of the MBCT group were

willing to continue to fill in the questionnaires. Third, we did not investigate and control for changes in medication for diabetes or mental health. Fourth, we used a non-active control group design, which can lead to differences between the two conditions in attrition and in expectancy effects (placebo vs. nocebo) resulting in a risk of an overestimation of the treatment effect. However, we decided to use this design, because 1) we wanted to test the effectiveness of MBCT for patients with diabetes relative to usual care instead of comparing it with another psychological intervention, and 2) in this sample of patients with emotional problems, we felt it would be unethical to use a placebo intervention. Future studies should incorporate active control groups to examine to what extent our findings are mindfulness specific. Finally, a substantial number of missing data was present for HbA_{1c} due to unavailability of the measurements in the predefined time span in the patient information databases. The policy in the outpatient diabetes clinics is to measure HbA_{1c} every 3 months. However, this is not always feasible in practice; therefore, we had lower statistical power to measure significant differences between the two conditions.

In conclusion, the DiaMind study demonstrated that MBCT could be used to treat comorbid emotional problems in patients with type 1 or type 2 diabetes. The emotional well-being and quality of life of these patients increased compared with the control group, whereas no significant effect was found for diabetes-specific distress and HbA_{1c}, possibly due to a floor effect. MBCT may be offered as part of standard care to diabetic patients with emotional problems. However, the implementation of a group MBCT intervention may be more feasible if mixed chronic disease patient groups are formed. Although this should be tested in future research, such an approach is expected to be as effective as the present one focusing on patients with diabetes because 1) mindfulness-based interventions are broadly applicable, and 2) previous studies have found these interventions are effective in other chronic disease patient groups.[41] In addition, given the prospected increase in people with diabetes and the increasing health care costs, it will be worthwhile to examine the effectiveness of internet-based mindfulness therapy also.

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Chapter 5

The effect of Mindfulness-Based Cognitive Therapy on blood pressure in people with diabetes: explorative findings from the DiaMind randomized controlled trial.

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Submitted for publication

ABSTRACT

Aims This study aimed to explore the impact of Mindfulness-Based Cognitive Therapy (MBCT) on blood pressure in outpatients with diabetes and emotional distress.

Methods This explorative research was part of a larger study in which 139 adults with diabetes were randomized into an MBCT-group or a waiting list control group (TAU). Participants with an elevated blood pressure during an intake interview, received an ambulatory blood pressure measurement at baseline and post intervention (MBCT: n = 25; TAU: n = 17). Mixed models analysis was used to examine the difference between the two conditions over time. All analyses were based on intention-to-treat.

Results There was a small, but statistically non-significant effect of MBCT versus TAU on systolic blood pressure (P = 0.650, Cohen's *d* = 0.24), and diastolic blood pressure (P = 0.552, Cohen's *d* = 0.21), showing decreased blood pressure after MBCT.

Conclusions The present study found a small, statistically non-significant effect of MBCT on daily life blood pressure in people with diabetes who had an elevated blood pressure during an intake interview. The small sample size resulted in a limited power to show a small effect. Future larger studies are needed in order to be able to answer the question whether MBCT has public health relevant blood pressure lowering effect in people with diabetes.

INTRODUCTION

Hypertension is a common co morbid condition in people with diabetes mellitus and, just as diabetes, an important risk factor for cardiovascular disease and microvascular complications. Hence, keeping the blood pressure (BP) at an adequate level (< 130/80mmHg) is an important element of diabetes care.[1] High levels of emotional distress also are common in outpatients with diabetes, affecting approximately 30 percent of the patients.[2-4] It is known that episodic or chronic emotional distress can increase BP.[5]

A psychological intervention that could have a positive effect on both emotional distress and high blood pressure would be valuable for people with diabetes. Mindfulness-Based Cognitive Therapy (MBCT) is a psychological intervention that has been applied successfully within diverse (chronic) patient samples, including people with diabetes, as a means of reducing stress, disease symptoms, and emotional problems.[6-9]

The aim of the present explorative study was to examine the impact of MBCT on ambulatory BP in people with diabetes and emotional distress. We hypothesized that MBCT participation would lead to a reduction in systolic and diastolic BP in daily life of people with diabetes.

METHODS

The Diabetes and Mindfulness (DiaMind) study methods have been extensively discussed elsewhere,[10] as well as the results on emotional distress (primary outcome) and health status.[9] The present study is part of this randomized controlled trial, in which 139 Dutch speaking adult individuals with diabetes (type 1 or 2) and emotional complaints were randomized into an MBCT group (n = 70) or a waiting list usual care control group (TAU: n = 69), who received the program eight months later. In the present study we examined a subgroup of participants with an elevated BP, defined as ≥140mmHg systolic BP (SBP) or 90mmHg diastolic BP (DBP) of the mean values of 3 measurements performed at the end of the intake interview (MBCT: n = 25; TAU: n = 17). All participants provided written informed consent. The study protocol was approved by the medical ethics committee of the St. Elisabeth Hospital in Tilburg, The Netherlands (P0948).

Intervention

The protocolised mindfulness intervention was based on the Mindfulness-Based Cognitive Therapy (MBCT) program as described in Segal et al.,[11] consisting of eight weekly two-hour

sessions. The central component of the program was the development of mindfulness (an open and accepting/non-judgmental awareness of the present moment[12]), which was done by practicing several meditation exercises. All the sessions were supervised by certified psychologists with personal experience with mindfulness practice.

Outcome measures

The outcome assessment for MBCT and TAU took place at pre (T1) and post intervention (T2). The BP was measured by an ambulatory device, the Mobil-O-Graph, which is based on the oscillometric method and which has been shown to provide reliable and valid assessments.[13] The participants wore the device 24 hours following (i) the intake interview and (ii) following an evaluation interview after the intervention of the MBCT group (around eight weeks later). The ambulatory measurements occurred two times per hour during daytime. The participants were asked to keep a diary to answer questions after each measurement, about a) their position during the measurement, b) their level of physical activity, c) how they felt (between 1 'very relaxed' to 5 'very tense') during 10 minutes before the measurement, and d) whether they had drunk coffee the last hour.

Power analysis

Considering the number of included participants, this study would have 80% power to show an effect size of Cohen's $d = 0.4$, implying a mean BP difference of ≥8 mmHg (with a SD = 20) between the two conditions over time (G Power 3.0.10).

Data analysis

SPSS (version 18) Mixed Models multilevel analyses were used to test whether MBCT had an impact on BP compared to TAU. The fixed part of the analysis included a regression formula with the effect of time (T1 vs. T2), condition (MBCT vs. TAU), and time by condition interaction. The random part consisted of modeling the covariance pattern structure of our data, with the intercept on level 3 (individual) and level 2 (time) plus the first-order mixed autoregressive-moving average process (ARMA) model for level 1 (BP measurement). We chose the ARMA model because this covariance pattern structure best fitted our data (tested with log-likelihood ratio test and the smallest Schwarz's Bayesian Criterion (BIC)).[14] We were primarily interested in the fixed effects part. In order to minimize bias by physical activity, only BP data were analyzed of measurements performed while sitting with no or minimal physical activity within 10 minutes prior to the measurement. In addition, anti-hypertensive medication was included as a factor and Body Mass Index (BMI) as a covariate, because these are known to influence BP and may bias the results. In case of a baseline difference between the two groups on the diary variables we collected (tension and coffee consumption) and a significant influence of these variables on SBP or

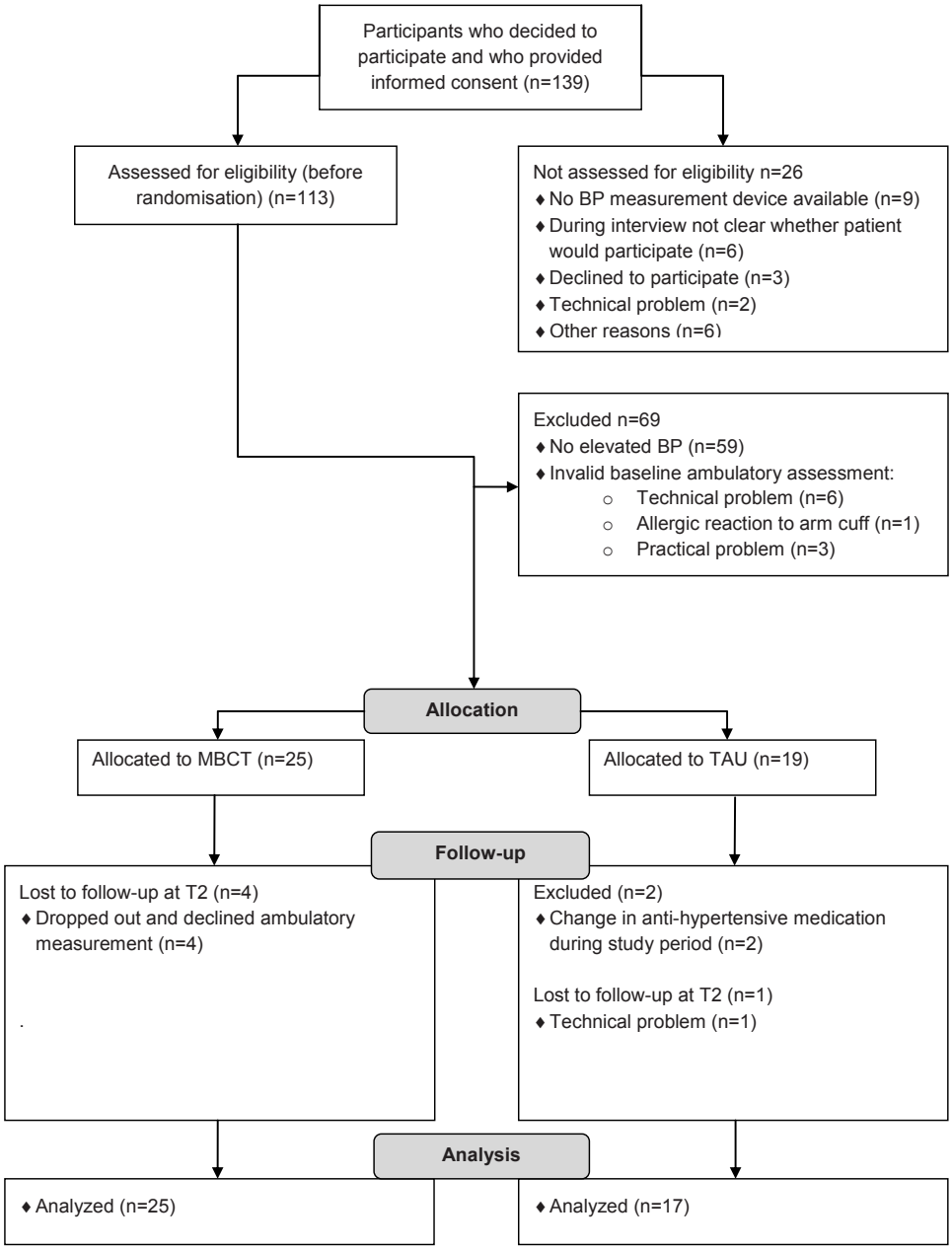

Figure 1. Flow diagram of patient enrolment, allocation, and attrition MBCT – Mindfulness-Based Cognitive Therapy intervention group; TAU – Waiting list (usual care) control group. T2 - post intervention assessment.

DBP, these variables would be included as a covariate also. All analyses were based on the intention-to-treat approach. A small exception on this approach is that two participants were excluded after T1, because of a change of anti-hypertensive medication during the study period. In addition, Cohen's *d* effect sizes were calculated ($(M_1-M_2)/\sigma_{pooled}$), with a Cohen's *d* between 0.2-0.5 indicating a small effect, between 0.5-0.8 a moderate effect, and >0.8 a large effect.[15]

RESULTS

Of the 139 individuals who participated in the DiaMind study, 81% (n = 112) had a BP measurement during the interview. Twenty-seven participants received no measurement (Fig. 1). Forty-seven percent (n = 53) of those who did receive a baseline BP measurement showed an elevated BP (≥140/90mmHg). Of these participants, 91% (n = 48) received

Table 1. Demographic and clinical characteristics of MBCT and TAU group

	MBCT (n = 25)	TAU (n = 17)	P*
N (%)	25 (60)	17 (40)	-
Age, years (SD)	58 (12)	62 (7)	0.20
Male, n (%)	11 (44)	10 (59)	0.53
High education†, n (%)	11 (44)	7 (41)	1.00
Working, n (%)	9 (36)	3 (18)	0.35
Living with a partner, n (%)	22 (88)	13 (77)	0.57
Children living at home, n (%)	12 (48)	4 (24)	0.20
Diabetes type 2, n (%)	13 (72)	20 (77)	0.48
HbA_{1c}, mmol/mol (SD)	64 (10)	59 (9)	0.15
HbA_{1c}, % (SD)	8.0 (1)	7.5 (1)	0.15
Systolic blood pressure, mmHg (SD)	137 (11)	141 (19)	0.43
Diastolic blood pressure, mmHg (SD)	82 (11)	84 (10)	0.53
Complications, n (%)	14 (58)	9 (53)	0.98
Co-morbidity, n (%)	18 (72)	13 (77)	1.00
Body Mass Index, kg/m^2 (SD)	29 (6)	31 (6)	0.18
±30 minutes physical exercise per day	20 (80)	8 (47)	0.06
Use of anti-hypertensive medication, n (%)	15 (60)	10 (60)	1.00
Use of psychotropic medication, n (%)	5 (20)	3 (18)	1.00
Past psychological treatment, n (%)	10 (40)	12 (71)	0.10
Meditation experience, n (%)	9 (38)	4 (24)	0.54

*Chi-square for nominal variables and t-test for continuous variables. †High education: high-level professional education and university. MBCT – Mindfulness-Based Cognitive Therapy group; TAU – Waiting list (usual care) control group.

the ambulatory BP equipment. Four participants were not included because of invalid baseline measurements. Eventually, we had data of 25 participants in the MBCT and of 17 in the TAU group. Of five participants we had no post intervention measurement.

The baseline characteristics of the sample, stratified by group (MBCT or TAU), are presented in Table 1. There were no significant differences between the two groups on baseline and clinical variables. Mixed Models analyses showed that there was no significant difference between the MBCT and the TAU group over time regarding ambulatory SBP ($F(1,40) = 0.21$, $P = 0.650$, Cohen's $d = 0.24$: CI95% = 0.10-0.37), nor regarding DBP ($F(1,37) = 0.36$, $P = 0.552$, Cohen's $d = 0.21$: CI95% = 0.08-0.33) (Fig. 2). The covariate BMI had a significant influence on SBP ($F(1,43) = 13.49$, $P = 0.001$). Anti-hypertensive medication had no significant influence on BP in this sample.

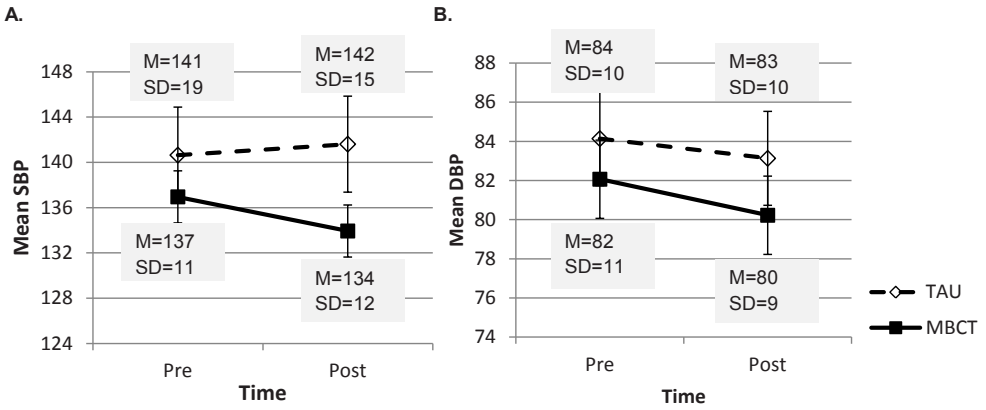

Figure 2a. Effect of MBCT on SBP Data are presented as means and standard errors. Solid line: MBCT – Mindfulness-Based Cognitive Therapy intervention group; Dashed line: TAU – Waiting list (usual care) control group. Pre – baseline assessment; Post – post intervention assessment; SBP – Systolic blood pressure.

Figure 2b. Effect of MBCT on DBP Data are presented as means and standard errors. Solid line: MBCT – Mindfulness-Based Cognitive Therapy intervention group; Dashed line: TAU – Waiting list (usual care) control group. Pre – baseline assessment; Post – post intervention assessment; DBP – Diastolic blood pressure.

DISCUSSION

One of the objectives of the DiaMind randomized controlled trial was to examine the influence of MBCT on elevated blood pressure in people with diabetes, which was the goal of the present paper. In contrast to our hypothesis, the intervention showed a small but

non-significant effect on SBP or DBP. There are a few possible explanations for this finding. First, the current study had one main limitation, namely the small sample size and was therefore underpowered to show a small effect. Mainly this was the result of the fact that only 55% of the participants showed a mean SBP at baseline in the hypertensive range for ambulatory measurements (≥135 mmHg[19]). Second, the daily life setting in ambulatory BP measurements introduces a relatively large amount of situational variability, which is included in the error term in analyses, reducing the power to find effects.

The effect sizes of other studies on the effect of mindfulness-based programs on BP range from small to large.[7, 16-18] However, most of these studies are potentially biased, due to inadequate BP measurement, the absence of a suitable control group, or a non-randomized design. An important strength of the current study was the use of ambulatory BP measurements, which is a more adequate measure of the 'real' BP during daily life.

In conclusion, the present study found a small, but non-significant effect of MBCT on SBP and DBP. Small effects may be relevant from the perspective of public health, if occurring frequently, which may be the case as mindfulness-based interventions are popular and frequently applied. Future larger studies are needed to be able to confirm whether MBCT has a small BP lowering effect, which is relevant from a public health perspective.

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Chapter 6

Mindfulness-Based Cognitive Therapy for people with diabetes and emotional problems: long-term follow-up findings from the DiaMind randomized controlled trial

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ABSTRACT

Objective The DiaMind trial showed beneficial immediate effects of mindfulness-based cognitive therapy (MBCT) on emotional distress, but not on diabetes distress and HbA_{1c}. The aim of the present report was to examine if the effects would be sustained after six months follow-up.

Methods In the DiaMind trial, 139 outpatients with (type 1 or type 2) diabetes and a lowered level of emotional well-being were randomized into MBCT (n = 70) or a waiting list with treatment as usual (TAU: n = 69). Primary outcomes were perceived stress, anxiety and depressive symptoms, and diabetes distress. Secondary outcome was glycemic control (HbA_{1c}).

Results Compared to TAU, MBCT showed sustained reductions at follow-up in perceived stress ($p < 0.001$, $d = 1.07$), depressive symptoms ($p = 0.004$, $d = 0.68$), and anxiety ($p < 0.001$, $d = 1.06$). No significant between-group effect was found on diabetes distress and HbA_{1c}.

Conclusion This study showed sustained benefits of MBCT six months after the intervention on emotional distress in people with diabetes and a lowered level of emotional well-being.

INTRODUCTION

The prevalence of emotional distress in people with diabetes is relatively high (i.e., diabetes-specific emotional distress approximately 18%[1], anxiety symptoms approximately 40%[2] and depressive symptoms 20-40%)[1, 3] and is associated with negative outcomes, such as lower quality of life, suboptimal self-care behaviors and glycemic control, risk of adverse cardiovascular outcomes, and higher mortality rates.[4-8] A new promising psychological intervention in people with diabetes with emotional problems is the Mindfulness-Based Cognitive Therapy (MBCT) program. It has been used in various chronically ill populations, effectively decreasing feelings of distress, anxiety, and depression.[9] A previous report from the current study showed that MBCT, immediately at post intervention, was associated with a significant reduction in perceived stress, anxiety and depressive symptoms in people with diabetes and a lowered level of emotional well-being.[10] However, it is yet unclear if the beneficial effects are sustained over a longer period of time.

One randomized trial in cancer patients did not find sustained effects of MBCT on perceived stress, anxiety or depressive symptoms after six months follow-up,[11] while other studies in different patient groups did show maintained improvements in psychological distress after six or twelve months.[12-14] In people with type 2 diabetes, only one previous study reported longer-term outcomes. That study showed an effect on levels of depression one year after the intervention,[15] although no sustained effects were found on levels of stress. The present study attempts to extend these findings by also including people with type 1 diabetes and to examine the effect on symptoms of anxiety and diabetes-specific distress.

METHOD

The Diabetes and Mindfulness (DiaMind) study design, a randomized controlled trial (approved by the medical ethics committee of the St. Elisabeth Hospital in Tilburg) has been discussed in detail elsewhere.[16] Adults with diabetes (type 1 or type 2) with low levels of emotional well-being (as evidenced by a score of < 13 on the WHO-5 well-being Index) were recruited from outpatient diabetes clinics. Eligible patients who agreed to participate (n = 139) were randomized to a waiting list, treatment-as-usual, (TAU: n = 69) or to an MBCT group (n = 70), consisting of eight weekly two-hour group sessions.[17] Three months after the end of the intervention a two-hour booster session had been added. The assessment of the outcomes took place at pre (T1) and post intervention (T2), and after 6 months post intervention (T3). Demographic and clinical variables (e.g., existence of diabetes complications and co-morbid conditions) were assessed at baseline using questionnaires, except

for HbA_{1c} values (the amount of glycated hemoglobin in blood) which were evaluated by chart review. Emotional distress was defined as symptoms of anxiety, depression and/or (diabetes-specific) stress.[18] The 10-item Perceived Stress Scale (PSS) (5-point Likert scale)[19] and the Hospital Anxiety (7-items) and Depression (7-items) Scale (HADS) (4-point Likert scale),[20] and the Profile of Moods States (POMS) (5-point Likert scale)[21] were used, as well as the 20-items Problem Areas in Diabetes Survey (PAID) to assess diabetes specific stress (6-point Likert scale).[22] For secondary outcomes the following questionnaires were used: Short-Form Health Survey (SF-12),[23] Five Facet Mindfulness Questionnaire (FFMQ)(except for the subscale describing),[24] Acceptance and Action Diabetes Questionnaire (AADQ),[25] and the Rosenberg Self-Esteem Scale (RSES).[26] Because our primary outcome of interest was emotional distress, the status of the variables 'diabetes distress' and 'health status' was changed from respectively secondary and primary as registered originally (Netherlands Trial Registry 2145) to respectively primary and secondary.[16] In addition, we also decided to (i) include people with type 1 diabetes to be able to examine the broader applicability of the intervention, and (ii) not measure heart rate variability to prevent loss of participants due to complex daily measurements.[16]

Data Analyses

SPSS linear regression analyses on change scores (T3-T1) were used to test the differences between groups on the dependent variables. All analyses were based on the intention-to-treat approach. Multiple imputation (20 imputations using the Predictive Mean Matching procedure) was used to address missing data. Given the analysis of six primary outcome measures and subsequent higher risk of a type I error, the alpha level for significance was set at 0.008 for the main analyses (Bonferroni correction of alpha of 0.05 divided by 6). Sensitivity analyses included mixed models analyses using all three time points without

Table 1 Demographic and clinical characteristics of MBCT and TAU group

	MBCT (n = 70)	TAU (n = 69)	p^*
Mean age, years (SD)	56 (13)	57 (13)	.62
Male, n (%)	33 (47)	37 (54)	.45
High education†, n (%)	31 (44)	28 (41)	.66
Working, n (%)	28 (40)	19 (28)	.12
Living with a partner, n (%)	51 (73)	53 (77)	.59
Diabetes type 2, n (%)	52 (74)	45 (65)	.41

*Chi-square for nominal variables and t-test for continuous variables. †High education: high-level vocational education and university. MBCT – Mindfulness-Based Cognitive Therapy group; TAU – Waiting list (usual care) control group.

imputed missing values. Cohen's *d* effect sizes were calculated on the mean change scores between T1 and T3 of the two conditions, with the following formula $(M_{MBCT}-M_{TAU})/\sigma_{pooled}$. A Cohen's *d* between 0.2-0.5 indicates a small effect, between 0.5-0.8 a moderate effect, and larger than 0.8 a large effect.[27]

RESULTS

There were no significant differences between the MBCT and TAU group on baseline variables (Table 1, see also prior article[10]). Figure 1 shows the flow of participants during the study. Participants of both conditions who did not fill in the T3 measurement, were younger (p = 0.013), had a lower BMI (p = 0.006), and a higher score on the HADS-A (p = 0.013*)* at baseline. In the MBCT group, 59% of the participants attended at least 6 of the 8 sessions (overall mean attendance was 5.5 ±2.5 sessions) and 30% attended the booster session three months after the end of the intervention.

Linear regression analysis showed a significant effect of MBCT on perceived stress from baseline to six months follow-up compared to TAU (p < 0.001). The effect size of the difference from T1 to T3 between the two groups was moderate to large (Cohen's d = 0.76)(Table 2). In addition, in the MBCT group a significantly larger reduction in depressive symptoms (HADS) from baseline to six months was found (p = 0.004), with a medium effect size (Cohen's d = 0.51)(Table 2). Also, the MBCT group showed a larger decrease on symptoms of anxiety over time (p < 0.001). The effect size was large (Cohen's d = 0.83)(Table 2). The results on the depression and anxiety subscale of the POMS were comparable (Cohen's d = 0.41 and 0.92 respectively for pre- to follow-up difference between groups). There was no significant difference between MBCT and TAU on diabetes distress change scores (p = 0.034, Cohen's d = 0.41) from T1 to T3 (Table 2). In addition, linear regression analysis showed no significant difference between MBCT and TAU in HbA_{1c} change scores from T1 to T3 (p = 0.82; Cohen's d = 0.06). Sensitivity analyses based on mixed models using all time points yielded similar results (e.g., all significant results mentioned above were also significant with similar effect sizes).

DISCUSSION

The present paper shows that the reduction in perceived stress, anxiety and depressive symptoms in the MBCT group was sustained six months after the intervention (all medium to large effect sizes). In correspondence with the results that were found immediately

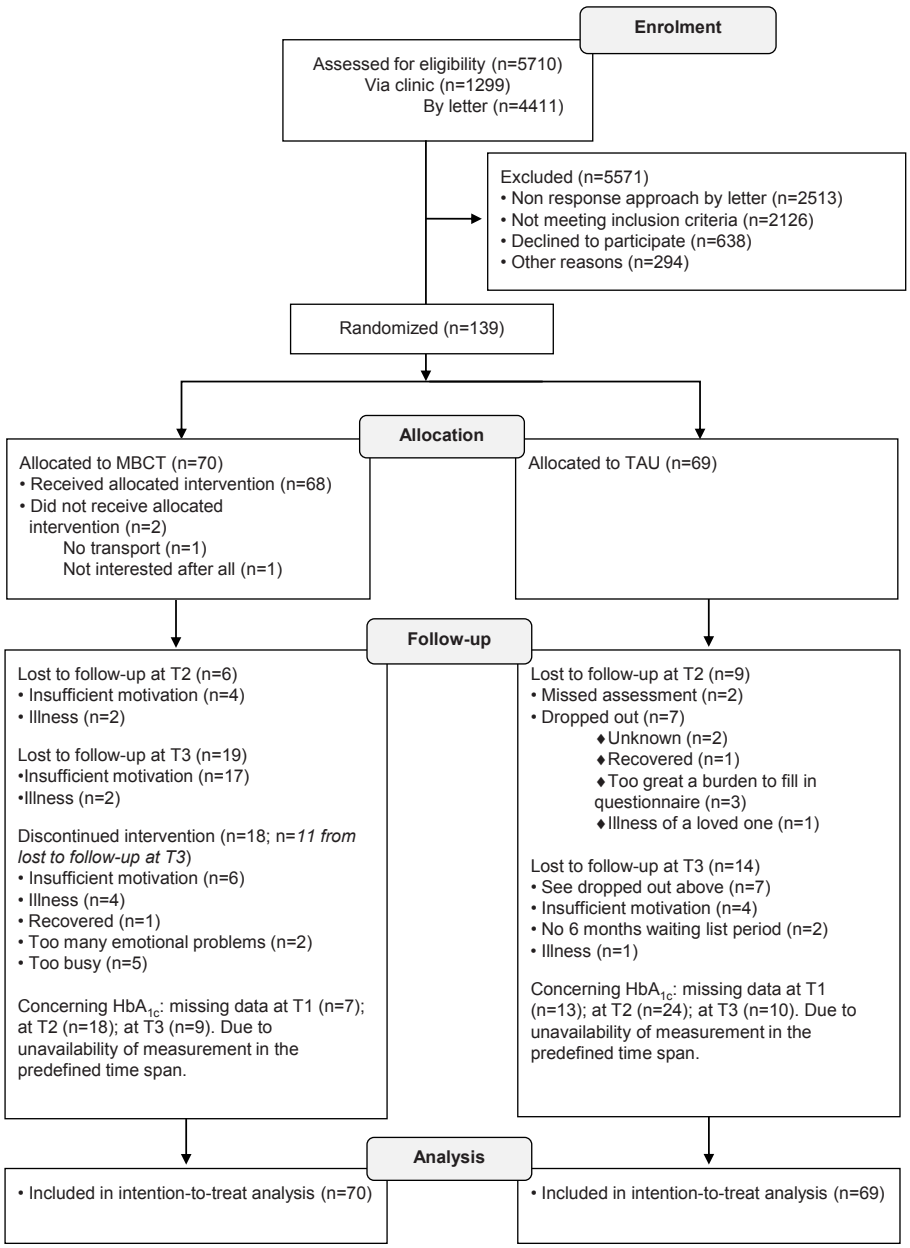

Figure 1 Flow diagram of patient enrolment, allocation, and attrition MBCT – Mindfulness-Based Cognitive Therapy intervention group; TAU – Waiting list (usual care) control group. T1 – baseline assessment; T2 – post intervention assessment; T3 – six months follow-up assessment. The *lost to follow-up* numbers of T2 and T3 each show the total number lost to follow-up at the consecutive time points.

Table 2 Mean (SD) scores and results of linear regression analyses

Measure		Pre	Post	6-m FU	Time x treatment effect		
		M (SD)	M (SD)	M (SD)	*t*	*p*	*d*[a]
Stress[b]	MBCT	19.5 (6.0)	14.4 (7.1)	13.4 (6.7)	-3.93	<.001	0.76
	TAU	20.4 (5.9)	19.0 (6.7)	18.9 (7.0)			
Anxiety[c]	MBCT	8.6 (3.3)	6.7 (3.6)	5.4 (3.1)	-4.24	<.001	0.83
	TAU	9.4 (3.6)	8.8 (4.1)	8.8 (3.9)			
Anxiety[d]	MBCT	20.5 (4.5)	17.4 (4.1)	16.4 (3.4)	-4.43	<.001	0.92
	TAU	20.2 (4.4)	19.8 (5.1)	19.4 (5.0)			
Depression[c]	MBCT	8.2 (3.8)	5.6 (4.0)	5.2 (3.6)	-2.89	.004	0.51
	TAU	9.2 (3.9)	8.6 (4.7)	8.2 (4.5)			
Depression[d]	MBCT	25.3 (5.8)	21.4 (4.5)	21.8 (4.7)	-2.41	.016	0.48
	TAU	26.7 (6.3)	26.2 (7.0)	25.7 (7.3)			
Diabetes distress[e]	MBCT	35.5 (17.8)	28.7 (21.0)	25.0 (19.7)	-2.12	.034	0.41
	TAU	36.6 (18.9)	33.5 (22.0)	32.8 (20.1)			
HbA_{1c}							
mmol/mol	MBCT	59.0 (12.6)	59.3 (12.1)	59.2 (11.7)	-0.23	.816	0.06
%		7.5 (1.2)	7.5 (1.1)	7.6 (1.1)			
mmol/mol	TAU	59.2 (13.0)	61.7 (16.4)	60.6 (16.2)			
%		7.6 (1.2)	7.9 (1.5)	7.7 (1.5)			
Mental health status[f]	MBCT	32.8 (11.0)	41.1 (10.7)	42.5 (10.3)	4.24	<.001	0.77
	TAU	31.7 (11.6)	35.0 (12.5)	33.9 (11.7)			
Physical health status[f]	MBCT	39.4 (9.9)	40.7 (10.5)	40.4 (10.8)	2.12	.034	0.40
	TAU	37.4 (11.4)	36.6 (11.7)	35.6 (13.0)			
Mindfulness[g]	MBCT	96.2 (13.8)	104.6 (17.0)	108.2 (15.7)	3.46	.001	0.64
	TAU	94.3 (12.4)	96.6 (14.1)	98.1 (13.5)			
Diabetes acceptance[h]	MBCT	58.4 (8.6)	60.3 (8.3)	60.6 (8.5)	1.62	.105	0.32
	TAU	58.2 (7.2)	58.7 (7.5)	58.2 (7.1)			
Self-esteem[i]	MBCT	18.6 (5.4)	21.4 (5.3)	20.9 (5.7)	0.53	.597	0.11
	TAU	15.9 (5.4)	17.4 (5.4)	17.7 (6.0)			

[a]The effect size (Cohen's d) was calculated on pre to six months follow-up intervention change scores. MBCT – Mindfulness-Based Cognitive Therapy group; TAU – Waiting list (usual care) control group; [b]from PSS – Perceived Stress Scale; [c]from HADS – Hospital Anxiety and Depression Scale; [d]from POMS – Profile of Mood States; [e]PAID – Problem Areas in Diabetes survey; [f]from SF12 – Short Form Health Status; [g]from FFMQ - Five Facet Mindfulness Questionnaire (N.B.: total score without describing subscale); [h]from AADQ – Acceptance and Action Diabetes Questionnaire; [i]from RSES - Rosenberg Self-Esteem Scale.

at post intervention,[10] there was no effect of MBCT on diabetes distress and glycemic control after follow-up. Since only a fraction of the participants in the present sample (48%) experienced elevated diabetes distress (PAID ≥ 40) and the mean baseline HbA_{1c} value of the two groups appeared to be already fairly good (59 mmol/mol, SD = 13; *in general, the treatment goal is ≤53, while in more complex diabetes it is ≤64*[28]),[10] the non-

significant findings could be caused by floor effects. Future research on the effect of MBCT on diabetes distress and HbA_{1c} should focus on people with poor glycemic control and elevated diabetes distress at baseline.

The follow-up results of the present study are encouraging. The MBCT group maintained their gains over a period of six months with no to minimal further intervention (only 30% of the MBCT participants attended the booster session three months after the intervention), which corresponds with most of the few studies that have examined longer-term effectiveness of mindfulness-based intervention in medical patients.[12, 13, 15] In addition, the results are similar to the results of the few studies on long-term effectiveness of cognitive (behavioral) therapy on depressive symptoms,[29] but more research is needed.

This study had several limitations. First, we had no data on (the quality/quantity of) home mindfulness practice after the intervention. Therefore, we could not distinguish the effect in the group who continued mindfulness practice after the intervention and the group who did not. Second, there was a considerable drop-out rate in the MBCT group. Around a quarter of the participants (n = 18) stopped with the program, which however is in line with previous studies in somatic patient groups.[11, 30] Third, we had no a priori plan for statistical adjustment considering the multiple primary outcomes, and finally, the use of a waiting list control group may have overestimated effect sizes due to the inclusion of non-specific treatment effects in the relative improvement of the MBCT group.

In conclusion, the current study showed sustained effectiveness of MBCT in reducing emotional distress for participants with diabetes and a lowered level of emotional well-being. Because emotional distress is related to poor diabetic outcome, MBCT might be an important additional strategy in adequately treating people with diabetes.

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Chapter 7

Does personality and dispositional mindfulness influence the effectiveness of Mindfulness-Based Cognitive Therapy in people with diabetes? Findings from the DiaMind trial.

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Submitted for publication

ABSTRACT

Research has shown the effectiveness of mindfulness-based interventions for a variety of problems in different samples, but not every individual experiences the same level of benefit. The current study examined which factors (demographic, personality, and baseline mindfulness) moderated the effectiveness of Mindfulness-Based Cognitive Therapy (MBCT) in a sample of outpatients with diabetes and lowered emotional well-being (n = 67). Mixed models moderator analyses showed that negative affectivity appeared to be a significant moderator of the effect of MBCT on levels of anxiety (p = 0.002, Cohen's d = 0.88-1.27) and depressive symptoms (p < 0.001, Cohen's d = 0.55-1.27), reflecting that MBCT was more effective in reducing symptoms in individuals with a high level of negative affectivity than individuals with a low level of negative affectivity. For depressive symptoms, this effect was independent of baseline symptom level. There were no moderator effects of demographic factors, social inhibition, and baseline mindfulness. A direct comparison with traditional cognitive behavioral therapy is needed to determine if level of negative affectivity may help clinical decision-making as to which therapy may be most suitable for which patient.

INTRODUCTION

The number of randomized studies that have tested the efficacy and effectiveness of mindfulness-based interventions is increasing rapidly (with 109 randomized controlled trials in February 2013[1]). The central component of these mindfulness interventions, such as Mindfulness-Based Stress Reduction (MBSR)[2] and Mindfulness-Based Cognitive Therapy (MBCT),[3] is the cultivation of "mindfulness". Mindfulness is defined as the direction of one's attention to internal (i.e., thoughts and feelings) and external (i.e., sensory) experiences in the present moment with a non-judgmental, open, and curious attitude.[4] Mindfulness can be both viewed as a personal characteristic, a quality of consciousness, and also as a trainable skill.

A comprehensive meta-analysis that had included trials that were conducted in various patient samples indicated that mindfulness training is effective in reducing psychological complaints, such as anxiety and depressive symptoms, with moderate to large effect-sizes.[5] However, such general effect sizes are based on average treatment effects over all studied participants without any information regarding the variability of such effects across individuals.[6] To answer the clinically relevant question for whom a mindfulness intervention is beneficial and for whom it is less or not beneficial, it is important to identify potential moderators of treatment effect. Moderators of treatment effect are by definition baseline variables, such as demographic factors (i.e., sex, age, or education) or personality characteristics (i.e., extraversion).[6] Identified moderators of effect could help health care professionals to provide patient-tailored advises in such a way that efficiency of health care provision may be enhanced. Given the limited societal financial health care resources, this would not only benefit the patient, but also the society as a whole.

The literature on moderators of effect of mindfulness interventions is limited. A recent meta-analysis identified therapists' experience (in years) with mindfulness as a moderator of treatment.[1] In addition, results of a randomized controlled trial showed that the level of pretreatment trait mindfulness was a significant moderator of MBSR intervention effects, with participants with higher levels showing more benefit regarding mindfulness, subjective well-being and perceived stress up to one year after the intervention.[7] Another recent study explored moderators for MBSR versus traditional Cognitive Behavioral Treatment (CBT) in participants with an anxiety disorder. This study revealed that MBSR outperformed CBT regarding change in diagnostic severity of the anxiety disorder for participants with moderate to severe depressive symptoms and participants with average anxiety sensitivity, while CBT outperformed MBSR for participants with no to mild depressive symptoms.[8]

The current study is part of the Diabetes en Mindfulness (DiaMind) project, which is a randomized controlled trial in which people with diabetes with a lowered emotional well-being received a mindfulness intervention and were compared with a waiting list control group.[9] Previously, this study revealed the effectiveness of MBCT in reducing emotional distress.[10] In the present article, this research will be extended by examining three kinds of potential moderators of treatment effect, namely demographic factors, personality, and level of mindfulness.

Concerning demographic characteristics, one prior study indicated that a mindfulness intervention was less effective in reducing symptoms of anxiety and depression in cardiac patients who were older than 60 years.[11] Yet, based on literature on other psychological interventions which yield no clear evidence for an impact of age,[12, 13] different MBCT benefit for young versus older individuals is not expected. To the best of our knowledge, no other published study examined moderating influences of demographic characteristics on the effectiveness of a mindfulness intervention. Because it has been argued that every randomized trial should examine sex, race, ethnicity, and age as potential moderators of treatment,[6] they were included in the present study.

In addition, no study has been published that examined the influence of personality characteristics on MBCT effectiveness, while it is reasonable to assume that personality could account for individual differences in mindfulness intervention effects. In this context, two dimensions of personality could be of particular interest, namely negative affectivity and social inhibition. Negative affectivity (NA) is a general propensity to experience emotional distress, which is a personality dimension closely related to neuroticism and influences a wide range of mental and somatic health parameters.[14] Research on moderators of treatment in traditional CBT suggests that high neuroticism scores are associated with worse outcome.[12, 15, 16] Hence, it may be hypothesized that this also applies to MBCT. Social inhibition (SI) refers to the tendency to experience difficulties in expressing oneself in social interaction (i.e., individuals high on SI are more likely to feel inhibited, tense, and insecure when with others)[17] and is strongly related to introversion, another basic personality trait.[18] In previous research on CBT, extraversion has sometimes been found to be associated with better outcome.[16] This effect may be even more pronounced regarding social inhibition. It is reasonable to assume that socially inhibited people experience difficulties sharing their experiences with the other group members, which is an important part of MBCT. Therefore, it may be hypothesized that they benefit less from MBCT compared to socially uninhibited participants.

Regarding a potential moderating influence of the level of pre mindfulness on MBCT effectiveness, the study of Shapiro et al. (2011) is the only study that has examined this. They

hypothesized that higher baseline mindfulness was associated with larger effects because more mindful people may find the mindfulness practice easier or more comfortable, or may persist longer at them.[7] In light of their results, we expect to find similar findings.

Summarizing, the central question of the current study is: which characteristics predict gaining benefit from MBCT? Three sorts of participant characteristics were examined: 1) demographic factors (age, sex, and education), 2) personality variables (negative affectivity and social inhibition), and 3) baseline mindfulness skills. While no clear expectations were formulated regarding demographic characteristics, it is hypothesized that participants low in negative affectivity and social inhibition and high in baseline mindfulness will show the largest benefits of MBCT for people with diabetes regarding symptoms of anxiety and depression.

METHODS

The methods of the Diabetes and Mindfulness (DiaMind) study are extensively described elsewhere.[9] The study protocol of this randomized controlled trial has been approved by the medical ethics committee of the St. Elisabeth Hospital in Tilburg.

Participants and intervention

Adults with (type 1 or type 2) diabetes with low levels of emotional well-being (as evidenced by as score of < 13 on the WHO-5 well-being Index) were recruited from four outpatient diabetes clinics, between May 2010 and November 2011.[9] There were 139 eligible people who agreed to participate. They provided written informed consent and were randomized to an MBCT group (n = 70), who received the MBCT intervention immediately, or a waiting list, treatment as usual, control group (TAU: n = 69), who received the intervention eight months later (six months after the end of the intervention of the MBCT group).

The MBCT intervention consisted of eight weekly two-hour sessions and was based on the original program of Segal et al. (2002). There were 4 to 10 participants in each group. The main element of the intervention was the cultivation of mindfulness, which was done by the practice of diverse meditation techniques. The sessions were supervised by certified psychologists, who had completed a mindfulness instructors training and had personal experience with mindfulness practice.

Outcome measures

The assessment of the outcomes took place at pre intervention (T1), four weeks after the start of the intervention (T2), post intervention (T3), and after 6 months post intervention (T4).

Demographic and clinical variables

Demographic and clinical variables (e.g., existence of diabetes complications and co-morbid conditions) were part of the baseline questionnaire.

Emotional distress

The subscales 'tension-anxiety' and 'depression-dejection' of the short Profile of Mood States (POMS) were used to assess emotional distress. The subscales comprise of 6 and 8 adjectives, respectively, of which participants had to indicate (on a 5-point Likerts scale) how well each adjective described their mood during the last couple of weeks (0 = not at all, 4 = very much). In the present sample, the Cronbach's α of the subscales ranged from 0.77 to 0.93. In the DiaMind study, there was also data available on the Hospital Anxiety and Depression Scale (HADS), which overlap with the POMS. We decided to use the POMS as an outcome measure, since the POMS appeared to be more sensitive for change in our previous analyses.[10] However, the HADS was used in sensitivity analyses (i) instead of POMS (yielding similar results); (ii) in case of a moderating effect of NA, to control for state anxiety or depression.

Personality

The 14-item Type D scale (DS14) was used to measure negative affectivity (NA) (e.g. "I often feel unhappy"; 7 items) and social inhibition (SI) (e.g. "I am a closed kind of person"; 7 items).[19] NA is the tendency to experience high levels of emotional distress and correlates 0.64-0.68 with neuroticism.[18] SI is the tendency to feel inhibited and uncomfortable in social interactions and this correlates 0.52-0.65 with extraversion.[18] Items are answered on a 5-point Likert scale ranging from 'false' to 'true' *(0-4)*, with the score range for the NA and SI subscales being 0 to 28.[19] The DS14 has been shown to be a valid and reliable instrument, with Cronbach's α of 0.88 and 0.86 for the NA and SI subscales, respectively.[19] Furthermore, a study showed that Type D personality (the combination of high NA and high SI) is a stable construct over an 18-month period and is not confounded by disease severity and measures of anxiety and depression.[20, 21]

Mindfulness

The Dutch version of the Five Facet Mindfulness Questionnaire (FFMQ) was used to measure mindfulness components.[22] In the DiaMind study, four of the five subscales of the questionnaire were included: 1) *Observing*, which refers to noticing or attending to internal and external experiences, such as thoughts, sensations, emotions, sounds, sights, and smells; 2) *Acting with awareness*, which includes attending to one's activities in the present moment; 3) *Non-judging of inner experience (non-judging)*, which refers to taking a non-evaluative attitude toward thoughts and feelings; and 4) *Non-reactivity to inner*

experience (non-reactivity), which includes allowing thoughts and feelings to come and go, without getting caught up in or carried away by them.[23] *Describing* was not included in the present study because it is not considered as a mindfulness facet, but rather as a potential consequence of mindfulness by several authors (e.g., Grossman[24]). Each factor consists of 7 or 8 items, which are answered on a five-point Likert scale (*1 = never or very rarely true, 5 = very often or always true*). The four facets demonstrated adequate to good internal consistency (alphas ranging from 0.75 to 0.87) and validity.[22]

Data Analyses

In order to achieve the highest level of statistical power possible, all people who eventually followed the intervention were included in the analyses. Therefore, for the participants of the control group, the assessments before, during, and following their own intervention were used instead of the assessments during their waiting list period. All the participants who actually started with the intervention were divided into two groups: 'the completers', defined as the participants who did not quit the intervention and attended at least six of the eight sessions; and 'the low adherence participants', defined as the participants who dropped out or attended less than six sessions. These groups were compared on all baseline variables, including the potential moderators.

SPSS Mixed Models analyses (version 19) were used to examine the possible moderation effects. The potential moderator variables were included in the model in a two-way interaction (time x potential moderator) while controlling for the main effects of these variables. Three separate models were used, with 1) the demographic variables, 2) the personality variables, and 3) the mindfulness components. All continuous variables were centered around the mean. Main analyses were based on the data of the completers. Two approaches were used. First, non-corrected models were analyzed. Second, a hierarchical approach was used, in which in case of a significant moderating influence of a more basic variable, this variable was included in the next model to control for its influence (corrected models; order: demographic → personality → mindfulness). For the interpretation of significant results, besides analyses using moderators as continuous variables, four subgroups were formed based on the quartile scores of the moderator variable and subsequent effect sizes were calculated for each subgroup. Cohen's *d* effect sizes were calculated on the change scores of the dependent variable between T1 and T4, with the following formula $(M_{T1}-M_{T4})/\sigma_{pooled}$. In case of a moderating effect of NA, sensitivity analyses were conducted with state (HADS) anxiety/depression (main effects and interaction with time) as additional covariates.

RESULTS

Flow of participants

In the MBCT group, 2 participants (3%) did not start with the intervention and 18 participants (26%) did not complete the intervention. Forty-one participants (60% of the participants who started) attended at least 6 of the 8 sessions. In the TAU group, 36 (52%) participants eventually started with the intervention. Ten of these participants (28%) did not complete the intervention; the other 26 participants (72%) attended at least 6 of the 8 sessions. Therefore, the total completer sample consisted of 67 and the low adherence

Table 1. Demographic and clinical characteristics of completers and low adherers

	Completers (n = 67)	Low adherers (n = 37)	*P*[a]
General characteristics			
Mean age, years (SD)	56 (12.3)	56 (13.1)	0.85
Male, n (%)	30 (45)	20 (54)	0.48
High education[b], n (%)	34 (51)	12 (32)	0.11
Having a job, n (%)	23 (34)	13 (35)	1.00
Living with a partner, n (%)	53 (79)	26 (70)	0.44
Children living at home, n (%)	21 (31)	14 (38)	0.65
Diabetes type 2, n (%)	47 (71)	25 (68)	0.87
HbA_{1c}, mmol/mol (SD)	61.1 (11.3)	56.0 (15.5)	0.08
Complications, n (%)	31 (46)	19 (53)	0.67
Co-morbidity, n (%)	50 (75)	29 (78)	0.85
Past psychological treatment, n (%)	39 (58)	24 (65)	0.65
Use of psychotropic medication, n (%)	10 (15)	13 (35)	0.03
Meditation experience, n (%)	17 (26)	6 (16)	0.39
Psychological characteristics			
Anxiety[c] (SD)	20.0 (4.4)	21.6 (5.1)	0.10
Depressive symptoms[c] (SD)	25.5 (6.0)	26.8 (6.8)	0.32
Personality characteristics			
Negative affectivity[d] (SD)	14.4 (6.2)	15.5 (5.7)	0.36
Social inhibition[d] (SD)	10.7 (6.8)	12.8 (6.9)	0.13
Mindfulness components[e]			
Observe (SD)	23.9 (6.0)	22.3 (6.4)	0.18
Acting with awareness (SD)	24.5 (6.6)	24.3 (6.5)	0.91
Non-judging (SD)	27.6 (6.9)	27.1 (6.6)	0.71
Non-reactivity (SD)	20.5 (3.7)	19.3 (4.1)	0.13

[a]Chi-square for nominal variables and t-test for continuous variables; [b] high education: high-level professional education and university; [c] from Profile of Mood States; [d] from 14-item Type D Scale; [e] from Five Facet Mindfulness Questionnaire.

group of 37 participants. At T1, we missed data of one participant, at T2 of two participants, at T3 of one participant, and at T4 of thirteen participants (MBCT: n = 7; TAU: n = 6).

Participant characteristics and low adherence

Table 1 presents the characteristics of the sample, stratified by 'the completers group' versus 'the low adherence group'. At baseline, the two groups did not differ regarding most variables, including symptoms of anxiety and depression and personality and mindfulness factors. However, completers were less likely to use psychotropic medication (15% vs. 35% respectively; χ^2 (1, n = 104) = 4.54, p = 0.03). There were no baseline differences between the participants of the MBCT group and the participants of the initial total control group, including those who did not attend MBCT in the end or were low-adherers. In addition, participants of the control group who eventually did not participate in MBCT did not differ on baseline variables from those who did start MBCT after their control period.

The mean scores of the completers on the mindfulness facets were comparable with mean scores of a Dutch sample of undergraduate students, except for *observing* that was somewhat lower in the present sample (±0.5 standard deviation - SD).[25] In addition, their mean score on NA was higher (±1.5 SD) and on SI slightly higher (±0.5 SD) compared with mean scores of a sample of primary care patients with type 2 diabetes.[26]

Table 2. Correlations between baseline personality, mindfulness and anxiety and depressive symptoms

	1	2	3	4	5	6	7	8
Negative affectivity[a] (1)	1							
Social inhibition[a] (2)	.01	1						
Observe[b] (3)	-.12	-.03	1					
Act with awareness[b] (4)	-.34**	-.20	.19	1				
Non-judging[b] (5)	-.48***	-.03	-.08	.25*	1			
Non-reactivity[b] (6)	-.40**	.14	.29*	.28*	.19	1		
Anxiety[c] (7)	.62***	-.002	.01	-.22	-.37**	-.35**	1	
Depressive symptoms[c] (8)	.66***	-.11	-.12	-.23	-.37**	-.28*	.66***	1

*p <.05, **p <.01, ***p <.001. [a] From The 14-item type D Scale; [b] from Five Facet Mindfulness Questionnaire; [c] from Profile of Mood States.

Correlations

Correlations of the baseline personality variables, mindfulness, and anxiety and depression are presented in Table 2. NA showed moderate negative correlations with the mindfulness

subscales act with awareness, non-judging, and non-reactivity (all $r^2 > 0.10$, $p < 0.01$) and high correlations with anxiety and depressive symptoms (both $r^2 > 0.38$, $p < 0.01$), while SI did not correlate significantly with any of these variables. In addition, levels of anxiety and depression correlated moderately with non-judging and non-reactivity (both $r^2 > 0.08$, $p < 0.05$).

Demographic variables as moderators

Mixed model analyses were conducted to test whether age, sex, and education had a moderating role. These analyses yielded no significant two-way interactions (Time x potential moderator) on anxiety or depressive symptoms (all $p > 0.05$). Time showed a significant main effect ($F(3,63) = 15.63$, $p < 0.001$), affirming the previously reported decrease of symptoms over time.[10] This indicates that the effect of MBCT on anxiety and depressive symptoms was similar for participants of different ages, for men and women, and for people with a low and high education (analyses based on education with three categories instead of two yielded similar results). Because a significant difference was found between the completers and low-adherers regarding education, the analysis was rerun including both completers and low-adherers. Results did not change, however.

Personality variables as moderators

Next, a significant Time*NA interaction appeared for symptoms of anxiety ($F(3,65) = 5.65$, $p = 0.002$) and depression ($F(3,63) = 8.00$, $p < 0.001$). In the analysis including quartiles of NA instead of continuous scores, the effect sizes (Cohen's d) for the four groups (from

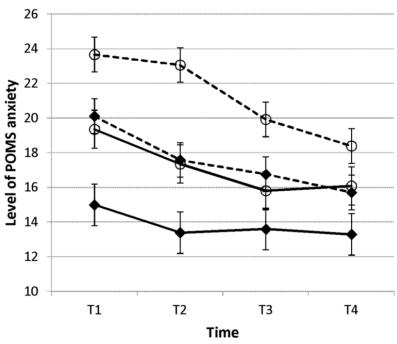

Figure 1. Moderation effect of negative affectivity (NA; in quartiles) on anxiety over time. Data are presented as mean scores and standard errors. POMS = Profile of Mood States; T1 = baseline; T2 = during intervention; T3 = post intervention; T4 = 6 months follow-up.

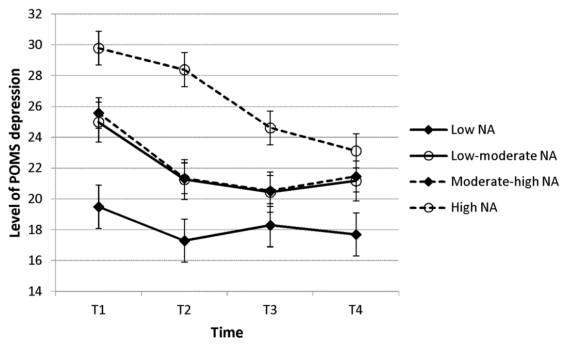

Figure 2. Moderation effect of negative affectivity (NA; in quartiles) on depressive symptoms over time. Data are presented as mean scores and standard errors. POMS = Profile of Mood States; T1 = baseline; T2 = during intervention; T3 = post intervention; T4 = 6 months follow-up.

lowest to highest quartile) were: 0.88, 1.06, 1.27 and 1.17 (Fig. 1). Thus, MBCT was less effective in reducing symptoms in individuals scoring in the lowest quartile of the NA scale, but still showing a large effect in this quartile. However, when the interaction Time*HADS anxiety was added as a covariate the effect was no longer significant ($p = 0.16$).

For the effect on depressive symptoms, the effect sizes of the groups based on quartiles of NA were: 0.55, 0.93, 0.91, and 1.27, respectively (Fig. 2). This again indicates that MBCT was less effective in reducing symptoms for individuals with a low score on NA, here the effect in the lowest quartile group being medium-sized. This finding appeared to be robust ($p < 0.001$) in analysis in which the interaction term Time*HADS depression was included.

The effect of the two-way interaction Time*SI was not significant (anxiety: $F(3,66) = 0.56$, $p = 0.64$; depression: $F(3,63) = 0.61$, $p = 0.61$), indicating that the level of social inhibition did not moderate the effectiveness of MBCT. Similar results were obtained when introversion/extraversion was entered into the analysis instead of social inhibition, as measured with the Eysenck Personality Questionnaire.[27]

Mindfulness variables as moderators

In analyses not adjusted for NA, baseline *non-judging* appeared to be a significant moderator in relation to levels of both anxiety ($F(3,61) = 2.75$, $p = 0.05$) and depressive symptoms ($F(3,59) = 3.64$, $p = 0.018$). In the analysis including quartiles of non-judging the Cohen's d effect sizes (from lowest to highest quartile) were for anxiety: 1.40, 1.47, 0.49, and 0.70; and for depressive symptoms: 1.61, 1.32, 0.44, and 0.45. However, in corrected analyses, in which the significant personality moderator NA was included, this moderating effect was no longer significant for anxiety ($p = 0.57$) and depressive symptoms ($p = 0.28$), while NA still showed a significant interaction with Time ($p = 0.04$; $p = 0.05$, for anxiety and depression respectively).

In addition, concerning anxiety, there was a trend for a significant two-way interaction between Time and *non-reactivity* ($F(3,60) = 2.38$, $p = 0.08$). The effect sizes of the quartiles (from lowest to highest quartile) were 0.64, 1.30, 1.00, and 0.94. This trend was robust in corrected analyses in which Time*NA was included into the model ($p = 0.07$).

DISCUSSION

In an effort to find out which individual baseline characteristics predict benefit from MBCT, the present study examined moderators of treatment outcome (anxiety and depressive

symptoms) in people with diabetes and emotional complaints, who attended MBCT sessions in the context of the DiaMind randomized controlled trial. Three sorts of possible moderators were examined: demographic, personality, and mindfulness variables.

The main finding was that, regarding the personality characteristics, negative affectivity (NA) appeared to be a significant moderator, with people with high NA benefitting more from MBCT than people with low NA. This finding is inconsistent with some findings regarding effects of CBT for people with (subtreshold) depression, in which people low on neuroticism benefitted more.[12, 15, 16] Perhaps an explanation for this can be found in a difference between CBT and MBCT. A study by Bagby et al.[28] showed that people with higher scores on neuroticism were more likely to respond to pharmacotherapy than to CBT. They argued that the high level of emotional dysregulation of these people may hinder their capacity to adopt cognitive strategies required for CBT. This notion is in line with the finding, from a prior study that examined moderators in MBSR and CBT, that MBSR outperformed CBT regarding change in anxiety severity for participants with moderate to severe depressive symptoms. In people with high NA who have difficulties changing their automatic thought patterns, MBCT might work better compared to traditional CBT by the focus on acceptance of reality as it is (including their passing negative thoughts and emotions) and the accompanying relaxation effect,[29, 30] without the need to alter the content of thoughts.

Aside from this, an additional possible explanation for the moderating effect of NA might be that because persons scoring high on NA on average have higher baseline values of anxiety and depression (as confirmed by the high correlations in the present data), they also had more room for improvement. For levels of anxiety this hypothesis seems to be the case, as was shown by the non-significant result when we corrected for baseline levels of anxiety. However, the moderating influence of NA on depression was robust when corrected for baseline depressive symptoms. This suggests that in this case it may be the trait itself rather than just high levels of state depression that predisposed persons with high NA to benefit more from MBCT compared to persons with low NA. Nevertheless, even the lowest quartile of NA showed medium to large effect sizes of reductions of anxiety and depression, indicating that high NA is not a necessary condition for MBCT benefit.

Also in contrast with our hypothesis, social inhibition showed no moderating influence on MBCT treatment outcome, which suggests that having difficulty to share experiences with other group members does not seem to interfere with MBCT benefit. This is at odds with some results from the CBT literature, although results are not consistent and based on depressed persons only.[12, 31] Nevertheless, social inhibition or extraversion may be less

important in mindfulness-based interventions compared to group CBT, because in MBCT the core component (meditation practice) is an individual activity which yields its effects just by doing it,[32] in contrast to CBT, in which participants have to bring in their own experiences in order to learn how they can change their perception in the given situation.[33]

Concerning the level of pre-intervention mindfulness, *non-judgment of inner experiences* moderated the effectiveness of MBCT in reducing anxiety and depressive symptoms, with people who were more judgmental towards their inner experiences benefiting more than people who were less judgmental. However, this finding was not robust when corrected for the moderator NA. NA correlated strongly negatively with non-judging, suggesting a substantial overlap. The results seem to reflect that it is the more basic personality trait of NA rather than the more specific non-judging dimension of mindfulness that may influence efficacy of treatment. *Non-reactivity to inner experiences* approached significance as a moderator and can therefore only be interpreted with caution. People who were very reactive towards inner experiences benefitted less than people who were less reactive. This finding was not affected when corrected for the moderating influence of NA. Perhaps this reflects the mere effect that those who tend to be caught strongly in their cognitive processes just have a relatively larger difficulty letting go of or accept their internal processes, which translates to a lower benefit. Future research should examine this possibility more in depth. *Observe* and *acting with awareness* appeared not to moderate effects of MBCT at all. Overall, the results suggest no clear moderating effects of mindfulness in this sample. This contrasts with findings of Shapiro et al.[7] who found that people with a higher level of pre-intervention mindfulness showed more improvement in subjective well-being and perceived stress than people with a lower mindfulness level. However, their study was based on only 15 participants, strongly enhancing the possibility of Type I error. In addition, those authors assessed mindfulness using the Mindfulness Attention Awareness Scale (MAAS),[34] which measures only one aspect of mindfulness, most strongly corresponding with the *acting with awareness* subscale of the FFMQ (5 of the 8 items of this subscale originate from the MAAS[22]). This facet yielded no moderating effects in the present, larger study in a specific sample of people with diabetes. Thus, the role of pre-intervention mindfulness facets as moderators deserves future investigation.

The demographic factors, sex, age, and education yielded no moderating influence on MBCT effectiveness. This indicated that, in the present sample, the effect of MBCT on anxiety and depressive symptoms was similar for men and women, for people of different ages, and for high and low educated people. The finding regarding education was unchanged when the analysis was performed (i) including also the drop-outs and low-adherers, who appeared to be less educated than completers; (ii) including education

as a variable with three categories instead of two. Because of the paucity of research on demographic moderators in the mindfulness literature, we can hardly relate our results to previous mindfulness studies. To the best of our knowledge, only one recent study explicitly examined the influence of demographic characteristics. In a sample of cardiac patients undergoing percutaneous coronary intervention, a brief mindfulness-based intervention seemed to be effective in reducing symptoms of anxiety and depression only in patients not older than 60 years.[11] However, in that study, a shortened (4 sessions) version of MBSR was applied. Perhaps the full-length MBSR or MBCT is needed to show effects in older individuals. Education did not predict effectiveness,[11] just as in our study.

To put the results into context, it is important to gain insight into predictors of attrition also. However, the only difference between completers of the intervention and the low adherence group was that completers were less likely to use psychotropic medication. Notably, the two groups did not differ on the psychological measures.

A strength of the current study is that it is one of the first studies that examined moderators of MBCT outcome, and the first to examine a potentially moderating effect by basic personality factors. However, this study had also several limitations. First, the sample in this study included people with diabetes and co morbid emotional problems. Since this is a specific sample, it is not possible to generalize the results to the general population. On the other hand, we do not see a clear reason to expect a different effect of moderators in this sample compared to the general population (as most participants of mindfulness-based interventions have emotional problems and many have a somatic disease as well). Second, it cannot be ruled out that the effects are not specific to MBCT. In the analyses, to enhance power we did not make use of data of the randomized control group during their waiting list period and used their active intervention period instead. Theoretically, a similar moderator effect might also exist in the control group during waiting list, perhaps due to differential spontaneous recovery effects. However, this seems unlikely, as the control group did not show effects on symptoms of anxiety and depression [10] and the present results contrast some of the results found in CBT, as discussed above.

In conclusion, in the present sample, the personality trait negative affectivity was a moderator for the effectiveness of MBCT in reducing symptoms of anxiety and depression, with people with high negative affectivity benefitting the most. Future randomized controlled trials should attempt to replicate this finding. Moreover, MBCT seems to be effective for a broad range of person characteristics. It was as effective in men as in women, old and young, and low and highly educated people. In addition, to benefit from MBCT, it was not important if a person was socially inhibited or not. Even regarding negative affectivity, the

subgroup benefitting the least still showed a symptom reduction of medium effect size. The result regarding NA was in the opposite direction to some previous results regarding efficacy of CBT, which should be examined more closely in future studies. If the differential effect of NA in MBCT versus CBT is established, this might help clinical decision making in the future.

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Chapter 8

General discussion

In the present thesis, the relationship between mindfulness and psychological/physiological functioning was examined in people with diabetes. The main aim was to evaluate the effectiveness of Mindfulness-Based Cognitive Therapy (MBCT) in reducing emotional distress in people with diabetes with a lowered level of emotional well-being (the Diabetes and Mindfulness - DiaMind - study). In this general discussion, first, a summary of the content of the present thesis is provided. In addition, the deployment of MBCT in people with diabetes, potential mechanisms, and a number of clinical considerations are described. Further, overall methodological considerations of the DiaMind study are discussed. Finally, remaining questions for future research are considered.

SUMMARY

Diabetes mellitus is a chronic metabolic disease that forms a major health problem worldwide.[1] This chronic condition is often accompanied by levels of depression, anxiety, and general or diabetes-specific distress.[2-4] In turn, these emotional problems are associated with reduced quality of life, poor self-care behaviors, suboptimal glycemic control and an increase in the risk of developing diabetes complications and higher mortality rates.[5-9] Consequently, in people with diabetes, it is worthwhile to examine (i) factors associated with emotional well-being; and (ii) psychological interventions addressing emotional problems. In this respect, one interesting/potentially relevant factor is mindfulness and one promising psychological intervention is based on the cultivation of mindfulness. Mindfulness is defined as the giving of nonjudgmental attention to all experiences in the present moment [10] and has been previously associated with more optimal emotional well-being.[11-14] Mindfulness-Based Cognitive Therapy (MBCT)[15] seems especially promising, because (together with a closely related program: Mindfulness-Based Stress Reduction[10]) several studies concluded that this intervention is effective in improving emotional well-being in people with other chronic medical diseases, such as cancer and chronic pain.[16] Given that emotional distress was found to be associated with suboptimal glycemic control [7] and high blood pressure,[17] which are both important risk factors and clinical indicators in people with diabetes, it was hypothesized that MBCT may also lead to an improvement in their physical functioning as well. This was the background of this thesis, described in **chapter 1**.

As mentioned above, dispositional mindfulness (i.e., mindfulness as a personality trait) has previously been associated with more optimal emotional well-being. In addition, several studies have shown that dispositional mindfulness might have the potential to buffer against the negative effects of stress, neuroticism or specific adversities (e.g., disability

resulting from rheumatic arthritis) on emotional well-being.[13, 14, 18-20] However, it is unclear whether these associations can be extrapolated to people with diabetes with their general and specific adversities. Therefore, in **chapter 2**, these research questions were examined in a large online survey among people with diabetes: Diabetes MILES (Management and Impact for Long-term Empowerment and Success) – The Netherlands.[21] Since comorbidity and stressful life events have been found to significantly affect emotional well-being in people with diabetes,[22] these were examined as potential adversities. Dispositional mindfulness (in particular the mindfulness facets *acting with awareness*, *non-judging*, and *non-reacting*) appeared to be a significant correlate of both anxiety and depression in people with diabetes. In addition, dispositional mindfulness (particularly *acting with awareness*, *non-judging*, and *non-reacting*) appeared to moderate the association between stressful life events and levels of anxiety and/or depression. Specifically, it was found that in people who scored high on these mindfulness facets, stressful life events were not associated with feelings of anxiety and depression. Although these findings were obtained in a cross-sectional study, this may suggest that, in this particular sample, mindfulness may have been a protective characteristic against the adverse effect of stressful events. Prospective studies are needed to further test this hypothesis in other samples. Conversely, dispositional mindfulness generally did not diminish the association between comorbidity and emotional distress, indicating that the relation between comorbidity and anxiety and depression was of equal magnitude for those with high levels as for those with low levels of mindfulness. Chapter 2 concludes with the notion that the findings regarding stressful life events, if replicated in prospective designs, suggest that mindfulness-based interventions may be valuable to apply in the clinical care for people with diabetes. This brings us to the central aim of the current thesis.

The main aim of the present thesis was to evaluate the effectiveness of MBCT for people with diabetes with elevated levels of emotional distress by means of a randomized controlled trial – the Diabetes and Mindfulness (DiaMind) study. **Chapter 3** provided a comprehensive overview of the design of the DiaMind study. Dutch adult outpatients with diabetes (type 1 or type 2) with low levels of emotional well-being (as evidenced by a score of < 13 on the WHO well-being scale) were randomized into the MBCT group (who received the intervention immediately) or the treatment-as-usual waiting list control (TAU) group (who received the program six months after the end of the intervention of the MBCT group). The primary outcome was emotional distress, which was defined as symptoms of depression, anxiety, perceived stress, or diabetes-specific emotional distress. Secondary outcomes included health status, glycemic control, and blood pressure. Assessments were conducted at baseline, at four weeks, at eight weeks, and at six months follow-up.

In **chapter 4**, the short-term follow-up outcomes of the DiaMind study were described. In the trial, eventually 139 people with diabetes were randomized to the MBCT (n = 70) or the TAU group (n = 69). In this sample, MBCT led to reductions in symptoms of depression, anxiety, and perceived stress and an improvement in mental and physical health status, with medium effect sizes (Cohen's *d* = 0.40 - 0.70). However, no significant effect was found on diabetes-specific emotional distress, although participants with elevated diabetes-specific distress in the MBCT group tended to show a decrease in diabetes-specific distress compared to the control group (Cohen's *d* = 0.70). In addition, MBCT was not effective in improving HbA_{1c} (assessed between six weeks and six months after the intervention), possibly due to a floor effect. It was concluded that MBCT can be used as a psychological intervention to treat people with type 1 or type 2 diabetes with co-morbid emotional problems.

The effect of MBCT on blood pressure was examined in **chapter 5**. Blood pressure was measured in a subgroup of participants from the DiaMind study with an elevated blood pressure (≥140mmHg systolic blood pressure (SBP) or 90mmHg diastolic blood pressure) during the study's intake interview. Thus, 42 participants (MBCT = 25; TAU = 17) received an ambulatory device that measured their blood pressure during their daily activities, both pre- and post-intervention. The findings showed that, in this sample, MBCT did not lead to significant reductions in systolic and diastolic blood pressure, although small effect sizes were found (Cohen's *d* = 0.24 and 0.21 respectively). One possible reason for the non-significant findings was the fact that the sample size was small and therefore underpowered to show a small effect. In addition, the complex character of daily life with its many factors influencing a parameter such as blood pressure, resulting in an unfavorable signal-to-noise ratio, may be another possible explanation for the small and non-significant effects.

In **chapter 6**, the long-term follow-up results of the DiaMind study were presented. The reduction in perceived stress, anxiety, and depressive symptoms in the MBCT group were sustained six months after the intervention. All the effect sizes were medium to large, and at least as large as the effect sizes based on the pre to post change scores. Consistent with the results in the first six months after the intervention, there were no effects of MBCT on diabetes-specific distress and glycemic control (the latter measured between six months and one year after the intervention).

A final objective of the DiaMind study was to examine which person characteristics could predict benefit from MBCT. In **chapter 7**, it was shown that, in the DiaMind sample, the personality trait negative affectivity appeared to be a moderator for the effectiveness of

MBCT in reducing symptoms of anxiety and depression, with people with high negative affectivity benefitting the most. For depression this effect was still significant when baseline depressive symptoms were controlled, suggesting that it may be the trait itself rather than just high levels of state depression that predisposes persons with high negative affectivity to benefit more from MBCT compared to persons with low negative affectivity. Further, it was concluded that MBCT appeared to be effective for a broad range of person characteristics. As such, it was evenly effective for men and women, old and young, and low and highly educated people. In addition, to benefit from MBCT, it was not important if a person was socially inhibited or not. Even regarding negative affectivity, the subgroup benefitting the least still showed a symptom reduction of medium effect size.

MINDFULNESS-BASED COGNITIVE THERAPY FOR PEOPLE WITH DIABETES

The Diabetes and Mindfulness (DiaMind) randomized controlled trial is the first study that specifically examined the effect of MBCT on emotional distress, health status, and physical functioning in people with diabetes with a reduced emotional well-being. To date, only three other Mindfulness-Based Intervention (MBI) studies for people with diabetes have been published. One of these studies focused on a workshop of Acceptance and Commitment Therapy (ACT)[23] and the other two studies examined the effectiveness of MBSR.[24, 25] While research on MBIs in people with diabetes thus is still limited, we will here summarize all findings and try to formulate some preliminary conclusions about the effectiveness of MBIs in this population on (i) emotional distress, (ii) health status, (iii) glycemic control, and (iv) blood pressure.

A comment in advance; more scientific weight is given to the findings of the DiaMind study and the study by Hartmann et al. (2012) (the Heidelberger Diabetes and Stress-Study or HEIDIS-study[25]) compared to the two other studies, because these studies were randomized controlled designs with relatively large sample sizes (n = 139 and 110 respectively). The findings of Rosenzweig et al. (2007) are of less scientific importance, as their study had an uncontrolled design and was based on eleven participants only.[24] The study of Gregg et al. (2007) is discussed in less detail because this study examined a one-day workshop of ACT instead of an eight-week MBSR/MBCT intervention.[23]

Emotional distress

Emotional distress was the primary outcome in the DiaMind study and secondary outcome in the two studies on MBSR,[24, 25] whereas Gregg et al. (2007) did not include emotional distress as an outcome at all.[23] The DiaMind study and Rosenzweig et al. (2007) found an

effect of the MBI on depressive symptoms directly after the intervention with moderate to large effect sizes (Cohen's *d* = 0.59 and 0.86 respectively), which was sustained for six months and one month respectively.[24] The HEIDIS-study only found an effect on depressive symptoms at one-year follow-up, although also with a moderate to large effect size (Cohen's *d* = 0.71).[25] The DiaMind trial was the only study that showed an effect of an MBI on symptoms of anxiety and perceived stress (Cohen's *d* = 0.44 and 0.70 respectively). While Rosenzweig et al. (2007) did find a reduction in anxiety and general psychological distress after MBSR (37% and 35% respectively), these reductions did not reach statistical significance in their small sample.[24] In addition, in the HEIDIS-study, no effect of MBSR on stress was observed (while anxiety was not included as an outcome measure).[25] From these results it can be concluded that MBSR or MBCT are effective in reducing symptoms of depression in people with diabetes up to a period of one year, even in a sample with no elevated levels of depression.[25] In such a sample, the effect of the MBI is probably rather reflecting prevention of progression than an actual reduction in symptoms of depression.[25] Concerning symptoms of anxiety and general perceived stress, the DiaMind study provides evidence for the effectiveness of MBCT in reducing these symptoms in people with diabetes and a lowered level of emotional well-being.

Health status

Health status was a secondary outcome in both the DiaMind trial and the HEIDIS-study.[25] Concerning mental health status, the DiaMind study showed an effect already directly after the intervention and both studies found an increase at follow-up (six months and one-year respectively). In addition, the DiaMind study found an improvement in physical health status, whereas the HEIDIS-study did not find such an effect, despite the fact that the mean baseline score of the DiaMind sample was slightly higher (M = 42, SD = 10) compared to the HEIDIS sample (M = 38, SD = 10) (intervention groups).[25] In conclusion, MBSR and MBCT appear to improve mental health status, yet the effect of MBIs on physical health status is less clear.

Glycemic control

From a diabetes clinical care perspective, a possible benefit of psychological interventions on important diabetes physical indices, such as glycemic control, is important. The study by Rosenzweig et al. (2007) found that MBSR was associated with improved glycemic regulation in people with type 2 diabetes at one month post intervention with a large effect-size (Cohen's *d* = 0.88).[24] In addition, the study by Gregg et al. (2007) showed that a greater number of participants who attended the ACT workshop improved in diabetic control status compared to participants who attended the education workshop alone. However, when the difference between HbA_{1c} values were compared, the results showed

only a trend for an effect of the ACT workshop.[23] In contrast to the above promising findings, the DiaMind study did not find an effect of MBCT on HbA_{1c} in the period from one month through one year after the intervention. This result was in correspondence with the HEIDIS-study that showed neither an effect of MBSR on HbA_{1c} directly post intervention, nor at one year follow-up.[25] The mean baseline HbA_{1c} values of the DiaMind trial, HEIDIS-study, and the study of Rozenzweig et al. (2007) were all around 7,5%,[24, 25] whereas the value in the study of Gregg et al. (2007) was 8.2%.[23] In conclusion, evidence is lacking for an effect of MBIs on HbA_{1c} in samples that have a relatively well-controlled glycemic control. Future research should examine if MBIs have the potential to improve HbA_{1c} in samples with a poor glycemic control.

Blood pressure

Blood pressure was an outcome in three of the four MBI studies. In the DiaMind and HEIDIS-study, systolic and diastolic blood pressure was measured with a 24-hour ambulatory device.[25] In the study by Rosenzweig et al (2007) the mean arterial pressure was assessed, but no information was provided about the time period of the measurement.[24] The latter study found a reduction in mean arterial pressure at one month post intervention, with a moderate effect size (Cohen's d = 0.48). In the HEIDIS-study no effects of MBSR on blood pressure were found directly post intervention, but after one-year follow-up the authors did find an effect on diastolic blood pressure (Cohen's d = 0.78), while still no reduction in systolic blood pressure was observed.[25] In the DiaMind study, MBCT did not significantly reduce systolic and diastolic blood pressure at post-intervention in a subsample (n = 42) with an elevated blood pressure during the study's intake interview. Nonetheless, despite the null finding in the DiaMind study, when taking into account MBI studies performed in other patient groups,[26-28] we think that MBIs have the potential to have a modest influence on blood pressure in people with elevated blood pressure. However, future larger studies are needed to confirm this notion.

Potential mechanisms

In the introductory chapter of this thesis, a mechanism was discussed by which mindfulness training could lead to lower levels of emotional distress according to Buddhist theory. In Western scientific literature, related but different concepts and models are described in an attempt to explain the relation between mindfulness and emotional well-being.[29-33] On basis of these mechanisms-of-mindfulness models, in this section, three direct effects of mindfulness are discussed through which mindfulness might lead to a reduction in emotional distress: (i) decentering, (ii), relaxation, and (iii) exposure. In addition, a number of subordinate effects of mindfulness will be described, which potentially are also of interest for emotional well-being.

First, nonjudgmental attention is thought to lead to **decentering** (also named reperceiving, defusion, meta-cognitive insight, or distancing). Decentering refers to the ability to step back from one's internal experiences and observe them instead of being immersed by them.[30] This enables persons to see their internal experiences (especially one's thoughts and emotions) as just passing events in the mind (not requiring a response), rather than as (important) reflections of the self or reality.[10, 33] By decentering, in addition to thoughts and feelings, all processes in one's mind (e.g., attachment, aversion, and behavioral tendencies) can be seen with more clarity and objectivity, resulting in a change in one's relationship with these internal processes and events.[15, 30] Thoughts and feelings that once seemed important are put into perspective: thoughts are just thoughts, and feelings are just feelings.[10] In addition, by present moment attention and decentering, one can see at an earlier stage one's automatic behavioral patterns (e.g., perseverative thinking) that lead to emotional distress,[34, 35] as well as one's state of mind (i.e., distressed).[15] An early notice of these tendencies and emotions facilitates adaptive coping (e.g., if one notices that one is distressed, one could decide to bring his focus to his breathing and/or go for a walk).[15] In addition, all the above described processes prevent the development of negative thinking spirals (perseverative thinking; in Buddhism called mental proliferation) and the related exacerbation of emotions.[15] In cognitive therapy, decentering has been described as an important element of change also. [36, 37]

Second, although often overlooked in mindfulness mechanisms models, **relaxation** is a probable direct effect of the mindful state.[29, 31] While relaxation is not a purpose of mindfulness meditation,[15] a state of physiological relaxation often occurs during mindfulness practice and while being mindful in daily life.[10] In a mindful mode, there is an acceptance of the present situation as it is without the need to alter it. This accepting non-doing and non-reactivity naturally leads to relaxation and is in contrast with a more automatic mode trying to change things which most people find themselves in most of the time.[15] That automatic mode is often characterized by a striving to get rid of the situation (i.e., negative thoughts and feelings) or to behold it (i.e., positive feelings).[15, 31, 32] In addition, while in a relaxed state, one is less inclined to be (pre)occupied by perseverative thinking. Relaxation in itself has been negatively associated with emotional distress before.[38, 39]

Third, nonjudgmental attention for phenomena arising in the present moment, whatever there is, is a direct **exposure** to thoughts and feelings.[30-32] By this exposure, participants learn to face, tolerate and accept unpleasant and/or difficult feelings.[15] It may lead to less emotional distress by habituation and the experience that emotions, thoughts, or physical sensations are not as overwhelming or scary as they were thought to be.[15, 30, 40] In addition, this putatively counteracts avoidance behaviors that are frequently associated

with emotional problems.[41] Indeed, an important part of evidence-based psychological treatments for emotional disorders is often directed at exposure.[15, 40]

Other interrelated subordinate effects of mindfulness in relation to emotional well-being that have been described in mindfulness literature are: **flexible self-regulation** (by disidentification from mental events, one becomes less ruled by automatic behavioral patterns, which results in more behavioral freedom);[30, 31] **values clarification** (disidentification helps to reconsider automatically formed values into values that are truly important in one's life);[30, 31] and **compassion** (nonjudgmental attention and insight into one's own and others' psychological processes result in compassion for oneself and other living beings).[31] In addition, following all these effects, mindfulness is eventually thought to result in **valued action** (behavior that is congruent with one's personal values).[31] In addition to emotional well-being, the above described effects could all be valuable outcomes in relation to diabetes self-care behaviors as well. Therefore, it would be worthwhile to examine these processes in future research on MBIs in people with diabetes.

Clinical considerations: findings from the DiaMind trial

Acceptability of MBCT for people with diabetes

Around one out of five persons who met the inclusion criteria (18%) decided to participate in the MBCT program and accompanying DiaMind study. It is unclear whether this percentage would be higher when no scientific study was involved. Nonetheless, MBCT was generally well accepted by participants in this sample of outpatients with diabetes; by both men and women, people of different ages, different educational background, and with type 1 or type 2 diabetes.

Seventy-three percent of the people who started with MBCT eventually completed the program. Reasons for quitting the intervention included insufficient motivation, serious mental or physical problems, and a lack of time. Hence, although generally well accepted, the intervention did not suit every individual. Participants who prematurely stopped with the intervention were less likely to have a partner and to have prior experience with meditation (chapter 4). In people who completed the intervention, there were no person characteristics that could predict MBCT benefit in a clinically important way (chapter 7).

When evaluating the training with the participants after the end of the MBCT, people were mostly positive about all aspects of the intervention (i.e., experienced benefits, length and duration of the intervention, the psychologist who led the group, group format, etc.). When participants were asked which benefits they experienced from having followed the

training, spontaneous reactions varied from “not much” (only a few participants) to “I have regained meaning in life”. The primary recurring benefits that people described were that they felt more relaxed, had more attention in their daily life, and that they could better cope with stressful situations and ruminating thoughts. In addition, the majority of the participants indicated that they were motivated to maintain practicing after the eight week training. However, one remark that was made regularly in these conversations was the burden of the homework practice. Around half of the participants indicated that the homework mindfulness exercises were too time consuming and that they had difficulty to fit the exercises into their daily routines. This was especially the case for people with a full-time job and/or growing children. The mindfulness intervention requires participants to commit to practice exercises at home at least half an hour per day. Understandably, for people who have busy lives this often is a challenge to comply with. Therefore, for this subgroup, we suggest to examine if shortening the homework mindfulness exercises to about 15-20 minutes per day results in similar benefits as the traditional longer practices. This may be expected because a recent meta-analysis indicated that the effect of MBIs was not moderated by the duration of homework practice.[42]

Implementation of MBCT in clinical care

By several diabetes organizations it has been advocated to screen for depressive symptoms during a regular appointment with the diabetes nurse in the diabetes outpatient clinic.[43, 44] Based on this recommendation, diabetes nurses have now begun to implement this screening procedure. However, there has been a debate about what to do next when people show to have depressive symptoms, especially considering the finding that screening alone does not improve psychological outcome.[45] Although the accessibility differs per hospital, in the Netherlands, diabetes outpatients can be referred to the department of medical psychology, which mostly results in a number of individual consults with the medical psychologist. Group interventions for people with diabetes exist, but generally are mainly educational and directed at improvement of self-management alone (e.g., diet intervention for people with diabetes). However, as group interventions are more cost-effective than individual consults, it might be valuable if generic group interventions could be offered focusing on emotional problems. One such intervention could be MBCT. Hence, it could be suggested to offer MBCT as part of standard care to people with diabetes with a positive screening who indicate that they are in need of psychological help. However, on basis of our experiences during the recruitment phase of the DiaMind trial, we do not expect an implementation of MBCT for people with diabetes alone to be feasible, because: (i) eventually a quite low percentage of eligible people might be interested to participate in such a program (18% in the DiaMind trial); and related to this, (ii) the influx of people into a group intervention of eight to ten persons may go too slow. However,

the implementation of a group MBCT intervention may be more feasible if mixed chronic disease patient groups are formed. Such an approach is expected to be as effective as the present one focusing on people with diabetes only, because (i) MBIs are broadly applicable and (ii) previous studies have found these interventions to be effective in other chronic patient groups as well.[16] It would be worthwhile if future research should test the effectiveness, practical feasibility, and acceptability of this hospital-wide approach.

METHODOLOGICAL CONSIDERATIONS

In interpreting the findings of the described studies, several strengths and limitations should be acknowledged. While specific methodological considerations are already described in the discussions of the particular chapters, in the following section, a number of general methodological considerations of the present thesis, which have not been discussed (extensively) in the chapters, are discussed.

DiaMind study

Study design

A strength of the Diabetes and Mindfulness study was the randomized controlled design, as this design is considered to be the most rigorous way of evaluating a cause-effect relation between treatment and outcome.[46] A potential limitation of the design was, however, the use of a non-active (waiting list) control group, as this prevents controlling for potential placebo effects (e.g., positive expectations) or nonspecific effects (e.g., attention of trainer or group members), resulting in a risk of an overestimation of the treatment effect. Conversely, (i) this comparison group does control for the natural passing of time and potential spontaneous remission of complaints;[47] (ii) the DiaMind study aimed to test the effectiveness of MBCT relative to usual care instead of comparing it with another psychological intervention; (iii) in the present sample of people with emotional problems, we felt it would be unethical to use a placebo intervention.

Study sample

As a group, people with type 1 diabetes differ considerably from people with type 2 diabetes, due to substantial differences in terms of the etiology of and risk factors for developing the disease. In the present thesis, people with type 1 diabetes as well as people with type 2 diabetes were included. Despite the differences, we have not examined these groups separately, except for the examination of the potential moderating effect by type of diabetes. We did not expect a different effect in people with type 1 or

type 2 diabetes as Mindfulness-Based Cognitive Therapy is considered to be a general psychological intervention that is broadly applicable. This expectation was confirmed by the moderator sensitivity analyses in chapter 4, which yielded no significant differences in the effectiveness of MBCT for people with type 1 or type 2 diabetes. However, to provide a more definite answer to this question, a replication in a larger group of people with type 1 diabetes is needed.

Measuring mindfulness by self-report

In two sub studies of the present thesis, described in chapter 2 and 7, mindfulness was measured with the Five Facet Mindfulness Questionnaire (FFMQ) (the short form in chapter 2). Regarding the different mindfulness aspects measured in this questionnaire, it is suggested that while they provide guidance for research, they merely reflect mindful behaviors, whereas the original definitions emphasize qualities of awareness.[29] This is a conceptual problem that needs to be solved in the future. In addition, an important limitation was that the FFMQ is based on self-report and so potentially suffers from reporting bias. This is currently subject of debate.[48, 49] Two important raised critical issues are the existence of (i) potential significant differences among respondents in semantic understanding of mindfulness questionnaire items, an understanding that might be dependent on the level of personal mindfulness practice; and (ii) possible important incongruity between how mindful respondents believe themselves to be, in contrast to, how mindful they actually are.[48] In spite of the mentioned limitations, self-report measures of mindfulness remain virtually the only approach for assessing mindfulness. In addition, recently it has been suggested that for a more in-depth analysis of mindfulness, the FFMQ is recommended to be used.[50] This is mainly due to its good psychometric properties (i.e., good reliability and predictive validity).[12] However, alternative ways to measure mindfulness have been suggested, such as (a) qualitative assessments (e.g., based on interviews); (b) assessment by others (e.g., by significant others or mindfulness experts); and (c) neurophysiologic and neuropsychological measurements (e.g., assessment of possible changes in the brain after MBIs or differences in performance on experimental tasks).[50] Future studies should attempt to develop and incorporate alternative measures of mindfulness in addition to the self-report questionnaires.

Term clarification

Emotional distress versus emotional well-being

In this thesis, the terms “emotional well-being” and “emotional distress” are both used to refer to respectively the *absence* and the *presence* of symptoms of anxiety, depression, general or diabetes-specific distress. However, actually these variables are considered as

two related, but different concepts.[51] Emotional well-being is a broader construct that consists of the extent in which negative affect - including emotional distress - is absent, but also encompasses the level of positive affect (e.g., happiness and vigor) and the level of satisfaction with one's life.[51] While research on the effects of MBIs on these latter aspects of emotional well-being is valuable as well, we have focused on emotional distress.

Health status versus health-related quality of life

In the chapters 3 and 4 of the present thesis, the term health-related quality of life is used, while health status might be a better description of the concept measured. Health-related quality of life and health status are related terms and no consensus exists regarding the extent of their distinctiveness and overlap.[52, 53] However, the following distinction is often advocated: While health status refers to ones physical, mental, and social functioning, quality of life additionally incorporates one's *personal evaluation* of functioning.[52, 54] For example, it is possible that one experiences difficulties with climbing a stair, but do not evaluate this as affecting one's quality of life. In the introductory chapter and the general discussion, we ensured to use the term of health status instead of health-related quality of life.

FUTURE DIRECTIONS

Several recommendations for future research have already been made in the previous paragraphs. In this section, further recommendations are discussed, including directions for MBIs for people with diabetes and for mindfulness research in general. An overview of all provided recommendations can be found in Box 1. Finally, remaining research opportunities of the DiaMind data are described.

Mindfulness-Based Interventions for people with diabetes

Diabetes self-management

Diabetes self-management is an essential part of the treatment of diabetes, and therefore, has been a focus of treatment in many psychosocial interventions.[55] Although enhancing self-care is not a purpose of MBCT, the program might have a beneficial impact on self-care. A rationale for this consists of the following notions. First, as MBIs could reduce emotional distress, and as emotional distress is associated with worse self-care behavior, MBCT might enhance self-care behavior as well. Second, MBIs are considered to improve one's ability to behave oneself constructively in harmony with his/her values, even during the experience of difficult thoughts and emotions,[56] which could facilitate self-care. Finally,

because considerable focus is placed on bodily sensations during MBIs, mindfulness might lead people to become more in touch with their body and its signals and needs,[10] which may result in better self-care as well. Considering these notions, it would be worthwhile to examine this potential effect of MBCT (or MBSR) in future research. To date the study by Gregg et al. (2007) is the only study that examined the effect of a mindfulness-based workshop on self-management in people with diabetes.[23] This study showed that the one-day ACT workshop in combination with diabetes education improved self-management more than an educational workshop alone.[23] Actually, the investigation of an effect of MBCT on diabetes self-care was one of the secondary aims of the DiaMind study (chapter 3). Unfortunately, in the end, this objective could not be reliably and validly tested with the included self-care questionnaire, because its psychometric properties were not established in time.

Internet-based mindfulness interventions

Given the prospected increase in people with diabetes and the increasing health care costs, it will be worthwhile to examine the effectiveness of internet-based psychological therapies also. To date, research on diabetes-specific web-based psychological interventions is still limited, but shows potential. For instance, a study that evaluated an internet-based cognitive behavioral therapy demonstrated significant effects on depressive symptoms and diabetes-related distress in people with type 1 and type 2 diabetes.[57] Currently, web-based mindfulness interventions are still scarce too, but several initiatives are emerging

Box 1 | Recommendations for future research

Mindfulness-based interventions for people with diabetes

- ❖ Examine the effect on self-care
- ❖ Investigate the effect on HbA_{1c} in people with poor glycemic control
- ❖ Examine the effect on blood pressure in a large sample of people with high blood pressure
- ❖ Examine the effectiveness of internet-based mindfulness therapy

Mindfulness and mindfulness-based interventions in general

- ❖ Develop and test more objective measures of mindfulness
- ❖ Continue investigation of mechanisms of mindfulness: mediation analyses, ESM, neurophysiologic and neuropsychological research
- ❖ Continue exploration of potential moderators of MBCT effect
- ❖ Extend the research on the effect on positive mental health outcomes (e.g., positive affect, resilience, vigour, life satisfaction)

and first results are promising.[58-60] For example, a randomized controlled trial in people with irritable bowel syndrome showed significant reductions in anxiety and depressive symptoms after web-based MBCT with moderate effect sizes (Cohen's *d* = 0.64 and 0.43 respectively).[60]

Research on mechanisms of mindfulness

"Perhaps the greatest challenge for those tilling the field of mindfulness research will be to develop empirically grounded, theoretical models examining the directional links between those conditions that support the unfolding and expression of mindfulness (e.g., attitudes like acceptance), mindfulness itself, processes explaining its effects (e.g., insight), and relevant outcomes of mindful states, traits, and interventions."[32]

Although in the section about potential mechanisms of mindfulness, a number of possible effects were described by which mindfulness may positively influence emotional well-being, the testing of these and other proposed mechanisms is still in its infancy. Research on mechanisms of mindfulness is important (i) for a deeper understanding of this human mode of consciousness;[32] and (ii) for the possibility to enhance effectiveness and efficiency of MBIs. Hence, future research should continue to further develop explaining mindfulness models and test these models by means of formal mediation analyses, as research using these analyses is currently limited;[31, 61, 62] and by more neurophysiologic and neuropsychological studies, as these can more objectively measure changes correlated with mindfulness practice.[32] In addition, approaches in which mindfulness facets and outcomes are more frequently assessed are useful in research on mechanisms, as these methods can establish trajectories of change in mindfulness and psychological outcomes and can reveal whether an increase in mindfulness actually precedes changes in these outcomes.[63, 64] For example, a study in which mindfulness and perceived stress were weekly measured, showed that changes in mindfulness preceded changes in perceived stress.[64] An approach that consists of daily assessments is the Experience Sampling Method (ESM). In this method, respondents are asked to rate their current experiences at several quasi-random moments during the day. Next to the above mentioned potential of frequent assessments, this method also allows for an increase in ecological validity and a reduction in memory bias.[65] In addition, it would be an adequate method to gain more insight into a potential change in coping with specific problem situations after MBI.[66]

Remaining research opportunities DiaMind study data

To date, not all the data that has been collected in the DiaMind study, is processed and/or examined yet. This includes data on (i) the quantity of home mindfulness practice; (ii) adherence to the treatment protocol by the psychologists who led the interventions; (iii)

change in mindfulness over time; (iv) positive psychological outcomes, such as optimism, vigour, and life satisfaction. In addition, qualitative data on the evaluation of the intervention by participants were collected but not yet processed. Analysis of this data potentially could answer important additional research questions about, for example, mechanisms by which MBCT was effective in this sample. Hopefully, we will be able to investigate these remaining data in the future.

CONCLUDING REMARKS

The present thesis reflected upon the role of mindfulness in people with diabetes: (i) the association between dispositional mindfulness and emotional distress, and (ii) the effects of cultivating this mode of awareness by Mindfulness-Based Cognitive Therapy (MBCT). The results suggested that mindfulness potentially might function as a protective disposition in the relation between adversities and feelings of anxiety and depression. More importantly, results demonstrated the effectiveness and acceptability of MBCT in people with diabetes in reducing emotional distress and improving health status up to six months after the intervention. Future large randomized controlled trials should more closely examine the effects of MBCT on self-care behaviors, on glycemic control in poor controlled diabetes, and on blood pressure in people with hypertension. In addition, future research on mindfulness in general should continue to examine moderators of treatment effect and mechanisms by which mindfulness exerts its benefits. Finally, the development and incorporation of measures of mindfulness other than self-report are needed.

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Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Introductie

Diabetes mellitus is een chronische stofwisselingsziekte die wereldwijd een groot gezondheidsprobleem vormt. Naar schatting zijn er wereldwijd 366 miljoen mensen met diabetes en dit aantal zal de komende jaren flink toenemen. Redenen hiervoor zijn onder andere de vergrijzing en een toename van het aantal inactieve mensen met overgewicht. Diabetes wordt gekenmerkt door verhoogde bloedglucosewaarden, die veroorzaakt worden door een tekort aan of een onvoldoende werking van het hormoon insuline. Er bestaan verschillende typen diabetes, waarbij de twee belangrijkste type 1 en type 2 diabetes zijn. Type 2 diabetes komt veruit het meeste voor (90-95% van de gevallen). Voor alle mensen met diabetes is het belangrijk om de bloedglucosewaarden te reguleren door middel van adequate zelfzorg. Die zelfzorg kan bestaan uit het hebben van een gezonde leefstijl, het regelmatig controleren van de bloedglucosewaarden en het gebruik van medicatie (bloedglucoseverlagende tabletten en/of insuline). Een goede regulatie van de bloedglucosewaarden kan het ontstaan of het verslechteren van diabetesgerelateerde complicaties (zoals hart- en vaatziekten en nier-, oog- en zenuwproblemen) voorkomen.

Bij diabetes komen vaak emotionele klachten voor, zoals somberheid, angst en algemene of diabetes-gerelateerde stress. Deze emotionele problemen zijn geassocieerd met een verminderde kwaliteit van leven, verminderde zelfzorg, minder optimale glykemische controle, een groter risico op diabetesgerelateerde complicaties en een verhoogd risico op mortaliteit. Daarom is het waardevol om (i) factoren te onderzoeken die geassocieerd zijn met het emotioneel welbevinden van mensen met diabetes; en (ii) psychologische interventies te onderzoeken om deze emotionele problemen te behandelen.

Een interessant en potentieel relevant concept is mindfulness. Mindfulness wordt gedefinieerd als het geven van niet-oordelende aandacht aan alle ervaringen in het huidige moment. Hoewel mensen verschillen in de mate waarin zij van nature op deze manier aandachtig zijn (ook wel dispositionele mindfulness genoemd), kan dit getraind worden door het beoefenen van mindfulness meditatie. Bij deze vorm van meditatie oefen je met het richten van je aandacht (bijv. op de ademhaling) en wanneer je merkt dat je bent afgeleid, merk je op waardoor en breng je je aandacht weer op een niet-oordelende manier terug naar het aandachtsobject. Een veelbelovende psychologische interventie is een op mindfulness gebaseerde cognitieve therapie (in het Engels Mindfulness-Based Cognitive Therapy; afgekort MBCT), een acht weken durende groepsinterventie waarin het aanleren van mindfulness de centrale component is. Dispositionele mindfulness is in eerder onderzoek geassocieerd met een beter emotioneel welbevinden. Daarnaast

hebben verscheidene studies geconcludeerd dat MBCT effectief is in het verbeteren van het emotioneel welbevinden van mensen met diverse chronische lichamelijke ziekten, zoals kanker en chronische pijn. MBCT bij mensen met diabetes zou mogelijk naast een verbetering van het emotioneel welbevinden, ook tot een verbetering in het lichamelijk functioneren kunnen leiden, aangezien emotionele klachten geassocieerd zijn met een verminderde glykemische controle en met een hoge bloeddruk (beiden belangrijke risicofactoren voor het ontwikkelen van diabetes complicaties).

Het onderzoek

In **hoofdstuk 2** werd gekeken naar de relatie tussen dispositionele mindfulness en angst en somberheid bij mensen met diabetes. Daarnaast werd gekeken of de associatie tussen comorbiditeit en stressvolle levensgebeurtenissen, en angst en somberheid anders was voor mensen met een hoge mate van dispositionele mindfulness dan voor mensen met een lage mate van dispositionele mindfulness. Om dit te onderzoeken werd gebruik gemaakt van de data van een groot online vragenlijstonderzoek onder mensen met diabetes: Diabetes MILES (Management and Impact for Long-term Empowerment and Success) – Nederland. De resultaten wezen uit dat mensen met een hogere mate van dispositionele mindfulness minder angst en somberheid rapporteerden dan mensen met een lagere mate van dispositionele mindfulness. De relatie tussen comorbiditeit en angst en somberheid bleek even groot voor mensen met hoge niveaus als voor mensen met lage niveaus van dispositionele mindfulness. Het bleek echter dat bij mensen die hoog scoorden op dispositionele mindfulness stressvolle levensgebeurtenissen niet geassocieerd waren met angst en somberheid, terwijl deze associatie wel aanwezig was bij mensen die lager scoorden op mindfulness. Hoewel deze bevindingen gebaseerd zijn op cross-sectionele data, zou dit erop kunnen wijzen dat in deze steekproef mindfulness een beschermende eigenschap was voor de negatieve effecten van stressvolle gebeurtenissen op het welbevinden. Deze bevindingen suggereren dat het aanleren van mindfulness mogelijk een waardevolle bijdrage zou kunnen leveren aan de zorg voor mensen met diabetes. Dit brengt ons bij de centrale doelstelling van dit proefschrift.

De centrale doelstelling van dit proefschrift was het evalueren van de effectiviteit van MBCT voor mensen met diabetes en een verminderd emotioneel welbevinden door middel van een gerandomiseerd gecontroleerd onderzoek – de Diabetes en Mindfulness (DiaMind) studie. **Hoofdstuk 3** geeft een uitgebreid overzicht van de methoden van de DiaMind studie. Volwassen Nederlandse mensen met diabetes (type 1 of type 2) met een verminderd emotioneel welbevinden (score van <13 op de welbevinden schaal van de World Health Organization) werden gerandomiseerd in de MBCT groep (de groep die de interventie direct ontving) of de wachtlijst groep (TAU groep: die de interventie zes maan-

den na afloop van de interventie van de MBCT groep ontving). De primaire uitkomstmaat was de mate van emotionele klachten, gedefinieerd als symptomen van somberheid, angst, algemene of diabetesspecifieke stressklachten. Secundaire uitkomstmaten waren gezondheidsstatus, glykemische controle en bloeddruk. De metingen in beide groepen vonden plaats voor aanvang van de interventie van de MBCT groep (baseline), vier weken na de start van de interventie, direct na de interventie en zes maanden na de interventie van de MBCT groep. De TAU groep kreeg daarnaast nog dezelfde metingen tijdens en na hun eigen interventie.

Hoofdstuk 4 beschrijft de korte termijn resultaten van de DiaMind studie. Aan het onderzoek deden uiteindelijk 139 mensen met diabetes mee (70 in de MBCT groep en 69 in de TAU groep). In deze steekproef leidde MBCT tot een significante vermindering in symptomen van somberheid, angst en algemene stress, en tot een verbetering in mentale en fysieke gezondheidsstatus. De effectgroottes waren gemiddeld (Cohen's *d* = 0,40 - 0,70). Er was geen significant verschil tussen de twee groepen op diabetesspecifieke stressklachten. Deelnemers met een verhoogd niveau van diabetesspecifieke stress in de MBCT groep lieten echter wel een trend tot vermindering van deze klachten zien in vergelijking tot de TAU groep (Cohen's *d* = 0,70). MBCT bleek niet effectief in het verbeteren van de glykemische controle (metingen tussen 6 weken en 6 maanden na de interventie). Mogelijk komt dit door een vloereffect, omdat de gemiddelde glykemische controle van de deelnemers al redelijk goed was aan het begin van de studie.

Het effect van MBCT op de bloeddruk is het onderwerp van **hoofdstuk 5**. Bloeddruk werd gemeten in een subgroep van deelnemers van de DiaMind studie, die een verhoogde bloeddruk (≥140 mmHg systolische bloeddruk en/of ≥90 mmHg diastolische bloeddruk) hadden tijdens de intake voor de studie. Uiteindelijk werden bij 42 deelnemers (MBCT = 25; TAU = 17) ambulante bloeddrukmetingen verricht tijdens hun dagelijks activiteiten, zowel voor als na de interventie. De bevindingen van het onderzoek laten een verlaging van de systolische en diastolische bloeddruk zien (Cohen's *d* = 0,24 en 0,21) na MBCT, maar het verschil met de TAU groep was niet significant. Een mogelijke verklaring voor de niet-significante bevindingen is de relatief kleine steekproef. Daardoor was er sprake van onvoldoende statistische power om een klein effect te kunnen demonstreren. Een andere mogelijke verklaring voor de kleine en niet-significante effecten is een ongunstige signaal-ruis ratio van de ambulante bloeddrukmeting, veroorzaakt door het complexe karakter van het dagelijkse leven met zijn vele variabelen.

In **hoofdstuk 6** worden de langere termijn resultaten van de DiaMind studie gepresenteerd. De verminderingen in algemene stress, angst en somberheid in de MBCT groep

bleven tot zes maanden na de interventie behouden. Alle effectgroottes waren gemiddeld tot groot (Cohen's *d* = 0,48 - 0,92) en minstens even groot als de eerder beschreven effectgroottes die direct na de interventie werden gevonden. In overeenstemming met de resultaten in de eerste zes maanden na de interventie, waren er geen effecten van MBCT op diabetesspecifieke stress en glykemische controle (het laatste gebaseerd op metingen tussen zes maanden en één jaar na de interventie).

De DiaMind studie had ook tot doel te onderzoeken of bepaalde persoonskenmerken de effectiviteit van MBCT zouden kunnen voorspellen (**hoofdstuk 7**). In de DiaMind steekproef bleek het persoonlijkheidskenmerk negatieve affectiviteit een moderator te zijn voor de effectiviteit van MBCT in het verminderen van angst en somberheid. Mensen met een hoge mate van negatieve affectiviteit bleken het meeste baat te hebben bij de interventie. Voor somberheid bleef dit effect significant wanneer er werd gecontroleerd voor de mate van somberheidsklachten op baseline. Dit resultaat doet vermoeden dat het eerder het persoonlijkheidskenmerk zelf was dan enkel de hoge niveaus van somberheidsklachten dat ervoor zorgde dat mensen met een hoge mate van negatieve affectiviteit het meeste baat hadden bij MBCT. Verder bleek MBCT effectief te zijn voor mensen met een breed scala van persoonskenmerken. De interventie was even effectief voor mannen als voor vrouwen, voor oudere als voor jongere mensen, en zowel voor laag- als voor hooggeschoolde mensen. Ook de mate van sociale geremdheid had geen invloed op de effectiviteit. Zelfs wat betreft negatieve affectiviteit was het zo dat de subgroep die relatief het minste baat had bij MBCT nog steeds een duidelijke vermindering in somberheid liet zien, namelijk van een gemiddelde effectgrootte.

Conclusie

Dit proefschrift beschrijft onderzoek naar mindfulness bij mensen met diabetes. De Diabetes en Mindfulness (DiaMind) gerandomiseerde gecontroleerde studie is het eerste onderzoek naar de effectiviteit van MBCT op emotionele klachten, gezondheidsstatus en fysiek functioneren bij mensen met diabetes en een verminderd emotioneel welbevinden. MBCT was effectief in het verminderen van symptomen van somberheid, angst en algemene stress en het verbeteren van de gezondheidsstatus van mensen met verschillende demografische en persoonskenmerken. Daarnaast komt naar voren dat deze effecten in ieder geval tot een periode van zes maanden na de interventie behouden blijven. Er zijn geen aanwijzingen gevonden dat MBCT ook leidt tot verbeteringen in de glykemische controle en bloeddruk. De glykemische controle in deze steekproef was echter al redelijk goed en voor het aantonen van een klein effect van MBCT op de bloeddruk bleek de subgroep te klein. Toekomstige grote gerandomiseerde studies bij mensen met diabetes zijn nodig om nader onderzoek te doen naar het effect van MBCT op zelfzorggedrag, op

glykemische controle in mensen met slecht gecontroleerde bloedglucosewaarden en op bloeddruk in mensen met hypertensie.

Dankwoord

DANKWOORD

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