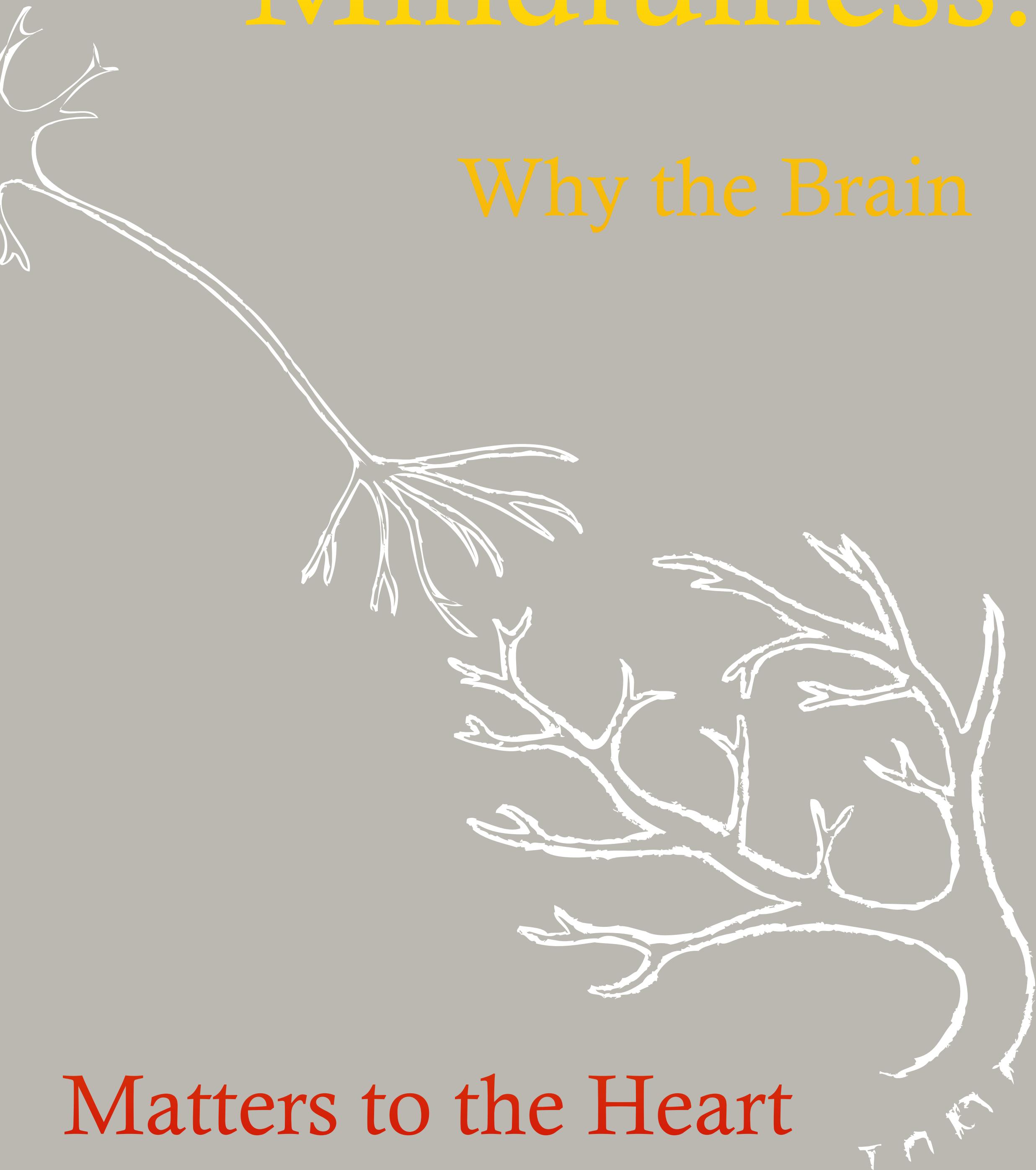
Mindfulness:

Why the Brain



Matters to the Heart

Rinske A. Gotink

Mindfulness: Why the Brain Matters to the Heart

Mindfulness: waarom het brein er voor het hart toe doet

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Chapter 1

General introduction and outline

Dear reader,

Before you lies the result of three years of research. But not only of three years, the findings are inseparably connected to earlier experiences and acquired knowledge of others.
Similarly, all within a person is connected: the outer world is reflected upon internally. It is observed, interpreted, and remembered. Experiences are linked to emotions, earlier experiences, and to experiences of others. All this, originally, so that in case of threat, our fight-flight system can operate more efficiently.
In our Western society, however, threats nowadays are more often social or financial than physical. Mankind has become the dominant species, but at the same time has become so complex that there seems little grip on the exchanges between the outer- and inner world. To what extent can we be conscious of all the steps leading to our reactions? And why worry about those internal processes?
Sometimes, reaction patterns can be conflicting desires. Someone reacting externalizing to stressors can push away those around him or her, where he or she might actually want to be heard and helped. When struggling long enough, such internal conflict can find its way to psychological healthcare. People can be struggling with work, family, their past, chronic illness, feelings of powerlessness, all of which can be expressed as anger, anxiety, or sadness. Often enough, thoughts and behaviour do not occur to the person suffering: these are logical consequences of the situation. In psychology, one looks how childhood, acquired patterns, current coping styles and current problems are interconnected. In the development of psychology, different schools have emerged that offer different causes and solutions of problems, also known as the three generations behavioural therapy. The behavioural school, the cognitive school, and recently, the meta-cognitive or mindfulness school. As often in history, they build on each other in their development and their search. Behavioural training and exposure can help with certain emotional problems, but not all. Thoughts are involved: questioning and challenging those brings us closer to the subconscious steps leading to the issue. After all, making the subconscious conscious gives us the possibility to choose. Where cognitive therapy concerns a verbal treatment and focusses on the content of thoughts, mindfulness returns to the experiential approach, aimed at the attitude towards thoughts.

History of mindfulness

Mindfulness has a millennia old history in which people studied the capacities of concentration and awareness [1,2]. These techniques of meditation, contemplation, and inquiry have been passed on from teacher to teacher, in life-long journeys in search of enlightenment. This was a religious path, chosen by monks spending their lives in monasteries. But slowly these techniques of training awareness, encompassing pains and discomfort in observation without judgment, and being able to see the coming and going of experiences in the here and now, raised interest in the West. Western society, where everything is future-oriented, aims at prosperity and making everything better, faster, higher, stronger. There is no time for standing still, stagnation is even considered decline.

Our focus on the positive and rejection of the negative can create marvelous inventions and scientific advances that can help a great many people in their daily lives. For some individuals, however, improvement is no longer an option and even stagnation would mean relief. Mindfulness teaches that thoughts are not facts, and that what comes, also passes. Especially the de-identification 'I am not my thoughts', offers an extra platform to cope with not-helping thoughts: do you follow their first impulse, or do you choose a different direction? Based on this theory, Jon Kabat-Zinn started integrating the old techniques of observing, non-judging and acceptance in the care of chronic pain patients who had not improved with traditional medical care [3]. He adapted the Buddhist teachings on mindfulness by removing the religious framework, and developed the structured eight-week course Mindfulness-Based Stress Reduction (MBSR) [4]. With an intensive schedule, participants are trained in noticing what happens internally: from awareness of bodily sensations, to changes in emotional state, to eventually being able to observe one's own thought processes. Five main skills are taught: observing (noticing, or attending to thoughts, feelings, perceptions, or sensations); describing or labelling observations with words (for instance 'an itch', 'anger', or 'memory'); non-reactivity to inner experiences ('I see the anger but I do not have to go with it'); non-judging of experiences ('it is okay that there is anger'), and acting with awareness [5]. Especially describing, non-reacting, and non-judgment were found to contribute significantly to and independently mediate the relationship between mindfulness and well-being [6]. Offering this program to his patients resulted in significantly less pain, mood disturbance and other somatic symptoms in patients that were otherwise considered beyond help [4, 7, 8]. Mindfulness did not take the pain away, it provided no cure. But it did seem to give patients a way to self-regulate their reaction to the pain and be more aware of moments in between the suffering. Could it be that by accepting pain as a coming and going experience, their quality of life improved? How would that link between attitude and physical sensation work? The results of Kabat-Zinn's studies evoked a chain of applications of secular mindfulness in healthcare. In recurrent depression, Mindfulness-Based Cognitive Therapy (MBCT) seemed to enable patients to break the negative spiral of thoughts often leading to relapse [9, 10]. Subsequently, mindfulness was incorporated in the supportive care of burn-out, cancer, and addiction patients, and it was introduced in schools [11-14]. MBSR and MBCT were registered as evidence based by the US government in 2012 [15].
But what do we know of all these applications' effectiveness, is it just a hype or could it be that this third generation of therapy really offers a new step in treating and preventing psychological problems? And what about physical problems?

Aim and outline of the thesis

The aim of this thesis is to gain knowledge of the effects of offering the mindfulness based protocol in chronic patients, the neuronal working mechanisms underlying these effects, and future fields of application.

By performing systematic reviews and meta-analyses we summarized the evidence of mindfulness-based interventions in health care. Within a large population based study we evaluated the correlation between meditating, psychological functioning, and brain structure. Additionally, we aimed to assess the long term effectiveness of an online mindfulness training on exercise capacity in cardiovascular patients in a large randomized trial. Combining these explorations, our aim was to provide insight in the connection between psychological functioning and physiological parameters, by linking psychological effects to changes in the brain and in cardiovascular health. Finally, two pilot studies were performed. One on walking in nature as a pragmatic method to sustain the effects of an eight-week mindfulness training, using detailed Experience Sampling Method to examine the relationship between mindfulness and mood from moment to moment. The second pilot study assessed the safety and applicability of an adapted mindfulness protocol in Borderline Personality Disorder patients. The possibility of double blinding in psychotherapeutic intervention studies is discussed to further improve this field of research.

Part I of this thesis will give an extensive overview of current scientific literature on MBCT and MBSR RCTs in health care (**Chapter 2**). In which chronic patient categories are these techniques being applied and in which is the benefit such that these interventions can be indicated as supportive treatment?

Part II of this thesis aims to evaluate the effect of MBCT and MBSR on neuroimaging results, to discover the neuronal pathway behind the changes found in Chapter 2. **Chapter 3** summarizes current scientific literature on the effect of MBSR, MBCT, and aspects of the trainings on brain activity and structure, focusing on structures known from traditional meditation. **Chapter 4** reports the use of meditation and yoga in a well-defined suburb of the city of Rotterdam, The Netherlands. Although less specific than the standardized MBSR protocol, we aimed to assess the association between these practices, experienced stress, and amygdala and hippocampal volume, both cross-sectional and longitudinal.

Part III aims to evaluate the effectiveness of mindfulness in cardiovascular patients, to further add knowledge on the link between psychological training and physiological outcome measures. In **Chapter 5** we systematically review the literature and pool results on the effectiveness of different meditation styles in patients with cardiac disease and their effect on several clinically relevant physiological and psychological outcome parameters. **Chapter 6** summarizes the literature on yoga on these outcomes in cardiovascular disease. **Chapter 7** and **Chapter 8** aim to evaluate the execution and assessment of a 12-week online mindfulness training in a randomized controlled trial in patients with structural heart disease conducted at the cardiology outpatient clinic of the Erasmus Medical Center, Rotterdam, The Netherlands. Although longer than the standard 8-week MBSR protocol, this online training was less intensive and had no teacher contact hours. The goal was to test a pragmatic self-help training that was easy accessible and low cost, and that could be beneficial when added to standard care. Main outcome was exercise capacity assessed with a six-minute walking test, to see whether learning to cope differently with stress improved physical functioning in a population at higher risk of physical consequences in case of stress. **Chapter 7** describes the effects directly post-intervention, and in **Chapter 8** we discuss the long-term effects one year after inclusion.

Part IV aims to explore future directions of mindfulness research. **Chapter 9** is a pilot study focused on how to sustain the beneficial effects of MBSR and MBCT, and it takes a closer look at the relationship between mindfulness and mood. **Chapter 10** is another pilot study, exploring the feasibility and effectiveness of an adjusted MBCT protocol for Borderline Personality Disorder. **Chapter 11** discusses the possibility of conducting double blind trials in psychotherapeutic interventions, in order to improve research on this type of interventions.

Finally, in **Part V** we will reflect on, and discuss, the most important findings of this thesis. In which chronic patients is MBCT or MBSR recommended to add to current standard treatment? How does training in mindfulness affect physiological parameters related to the brain and the heart? Which forms can this training take to be more applicable for other patient groups? Concluding remarks and future perspectives are provided for clinical practice and research.

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Part I

Mindfulness in different patient populations

Chapter 2

Standardized mindfulness-based interventions in healthcare: an overview of systematic reviews and meta-analyses of RCTs.

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PlosOne (2015).

Abstract

Background: Mindfulness-based therapies are being used in a wide range of common chronic conditions in both treatment and prevention despite lack of consensus about their effectiveness in different patient categories.

Objective: To systematically review the evidence of effectiveness MBSR and MBCT in different patient categories.

Methods: A systematic review and meta-analysis of systematic reviews of RCTs, using the standardized MBSR or MBCT programs. We used PRISMA guidelines to assess the quality of the included reviews and performed a random effects meta-analysis with main outcome measure Cohen's d. All types of participants were considered.

Results: The search produced 187 reviews: 23 were included, covering 115 unique RCTs and 8,683 unique individuals with various conditions. Compared to wait list control and compared to treatment as usual, MBSR and MBCT significantly improved depressive symptoms (d=0.37; 95%CI 0.28 to 0.45, based on 5 reviews, N=2814), anxiety (d=0.49; 95%CI 0.37 to 0.61, based on 4 reviews, N=2525), stress (d=0.51; 95%CI 0.36 to 0.67, based on 2 reviews, N=1570), quality of life (d=0.39; 95%CI 0.08 to 0.70, based on 2 reviews, N=511) and physical functioning (d=0.27; 95%CI 0.12 to 0.42, based on 3 reviews, N=1015). Limitations include heterogeneity within patient categories, risk of publication bias and limited long-term follow-up in several studies.

Conclusion: The evidence supports the use of MBSR and MBCT to alleviate symptoms, both mental and physical, in the adjunct treatment of cancer, cardiovascular disease, chronic pain, depression, anxiety disorders and in prevention in healthy adults and children.

Introduction

Chronic illness is the largest cause of morbidity and mortality worldwide, causing 63% of all deaths[1]. Often there is no cure for these illnesses and patients face a high burden due to symptoms or side-effects of treatment. Consequently, stress, depression and anxiety are very common among these patients. Equally important as finding cures are efforts to provide chronic care and teach patients coping mechanisms to improve their quality of life. One adjunct therapy in chronic care that has gained popularity in the last 40 years is a secular variant of mindfulness.

Traditionally, mindfulness has been described as “a state of presence of mind which concerns a clear awareness of one's inner and outer experiences, including thoughts, sensations, emotions, actions or surroundings as they exist at any given moment” [2,3]. Unfortunately, such classical descriptions of mindfulness do not easily lend themselves to scientific investigation. Core components are usually described as follows: ‘full attention to internal and external experiences as they occur in the present moment’ and ‘an attitude characterized by non-judgment of, and openness to, this current experience’ [4-6]. Recently, Goyal et al. published a review of mindfulness interventions compared to active control and found significant improvements in depression and anxiety[7]. However, they included quite a heterogeneous group of meditation styles. Although the history of mindfulness as a way of life goes back 2500 years 1, a standardised version of mindfulness interventions for Western health care was only recently developed. In 1979, Jon Kabat-Zinn integrated mindfulness in his treatment of chronic pain patients and showed how changing the way patients relate to their pain can change their experience of pain 4. His program, known as Mindfulness Based Stress Reduction (MBSR), spread quickly to other hospitals and other health problems. Teasdale, Williams and Segal converted MBSR to Mindfulness Based Cognitive Therapy (MBCT) for the treatment of depression. Since their initial promising results (50% relapse prevention in patients with 3 or more episodes of depression), studies repeatedly confirmed the benefit of MBCT in depression [8]. Subsequently, both MBSR and MBCT were well-defined and introduced in the care of various chronic conditions; MBSR, focusing more on the physical level of stress, found its way into supportive care for cancer, chronic pain, heart disease and fibromyalgia, whereas MBCT pays more attention to cognitive aspects and is used in the treatment of depression, anxiety, burn-out and eating disorders. Since mindfulness as a life style intervention is unlikely to have dangerous side-effects and can reduce stress, a risk factor for both mental and physical disorders, it is also being used in prevention (e.g. in education, parenting, the work place, pregnancy, and in prisons) [9,10]. Despite the expanding application of MBSR and MBCT, the evidence for their use and the appropriate indications are debated. The aim of this study is to provide a systematic overview of the effectiveness of MBSR and MBCT in different patient populations in order to identify the patient categories in which these interventions are indicated.

Methods

Inclusion and exclusion criteria

We performed a systematic overview (based on Cochrane guidelines[11]) of systematic reviews of randomized controlled trials (RCTs) of the secular mindfulness techniques as Kabat-Zinn and Teasdale, Williams and Segal designed them (MBSR and MBCT, respectively). Although MBCT focuses more on cognitive skills, both MBSR and MBCT are delivered in an 8-week group course designed to cultivate the same non-judgmental, moment-to-moment awareness and involve the same meditative exercises and expectations for home practice, and were therefore judged to be equivalent in approach.

To be included the studies had to have the following characteristics: 1) be a systematic review of 2) randomized controlled trials with 3) MBCT and/or MBSR as the intervention 4) performed for treatment or prevention and 5) reporting any health outcome measure. Other types of mindfulness or meditation based techniques, such as Transcendental Meditation and Attention Control Training, were excluded. Also, articles that combined other types of interventions with MBSR or MBCT without calculating the effects separately for mindfulness were excluded. When reviews reported RCTs as well as other designs, they were only included if they reported the RCT results separately from the non-RCT studies. We also performed a separate search to check for RCTs published after the most recent systematic review. Unpublished dissertations and conference papers were excluded. As the aim of this study was to define indication areas, we did not restrict the search by patient population, publication date or number of RCTs reviewed.

Search strategy

Six electronic databases were searched: PubMed, Embase, PsycInfo, Cochrane Reviews, Medline OvidSP and Web-of-Science. The databases were searched for English language publications using the following terms: “mindfulness” or “meditation” or “mindfulness-based stress reduction” or “MBSR” or “mindfulness-based cognitive therapy” or “MBCT”, in combination with “RCT” or “randomized” or “clinical trial'' and “review” or “systematic” or “meta-analysis” (see for exact search strategy S1 Table).

Study selection process

Reviews were independently selected by title and abstract by the first two authors. Any citation considered potentially relevant by at least one reviewer was retrieved in full text form in order to determine whether it met the selection criteria stated previously. Disagreements about the relevance of particular reviews were resolved by discussion with a third reviewer with methodological expertise. A log of rejected reviews along with reasons for their rejections is available in the supplementary material (S2 Table).

Data extraction and quality assessment

The systematic reviews were evaluated independently by the first two authors for both content and quality. They extracted data based on the PRISMA guidelines for systematic reviews[12]. If information was missing or data were incomplete, the authors of the review were contacted or the RCTs concerned were retrieved in order to give an overview as thorough as possible. To assess the quality of the systematic reviews, a checklist was created using the validated PRISMA guidelines[12] (for items see Table 1).

Table 1. Quality assessment items based on the PRISMA criteria for systematic reviews.

Item	Question	Item on original checklist
1	Was the objective of the review explicitly described with reference to the participants, interventions, comparisons, and outcomes (PICO)?	PRISMA item 4
2	Were study eligibility criteria (inclusion/ exclusion criteria) and study selection process reported?	PRISMA item 6 + 9
3	Was a comprehensive literature search performed?	PRISMA item 7
4	Was the search strategy reported for at least one database?	PRISMA item 8
5	Was a list of studies (included and excluded) provided?	
6	Was study selection and data extraction done by at least two independent authors?	PRISMA item 10
7	Was the risk of bias of individual studies assessed and presented?	PRISMA item 12 + 19
8	Were also unpublished studies included (risk of publication bias)?	PRISMA items 15 + 22
9	If applicable, was the method for combining results appropriate?	PRISMA item 14 + 16
10	Were the strengths and limitations of the review addressed?	PRISMA item 25
11	Is the conclusion supported by the data, taking into account the quality of the studies?	PRISMA item 26
12	Were the findings interpreted independently of the funding source?	PRISMA item 27

Main outcome measures and measures of effect size

Since we evaluated the effects of MBCT and MBSR in health care in general, we extracted both mental and physical outcome measures. We report the summarised RCT results of the reviews in different patient categories in order to address which indications are appropriate. No primary or secondary outcome measures in specific fields were pre-defined and all reported effect measures were considered.

Data synthesis

Intergroup comparison effects (improvement intervention vs control group) are reported unless mentioned otherwise. If the intergroup results were insignificant, we also looked at intragroup differences in order to see if the intervention had at least a pre-post effect (which is already incorporated in significant intergroup effects). The control group includes: wait list control (WL), treatment as usual (TAU) or active treatment (AT). Results reported as a standardized mean difference (smd, including Cohen's d and Hedges' g) were combined using software specially designed for meta-analysis (RevMan version 5.3, 2014) [13]. The results are pooled by outcome (anxiety, depression, stress, quality of life and physical functioning), to indicate in which populations these symptoms are amenable to mindfulness. Data synthesis was performed with random effects analysis. Reviews that reported effect measures other than smd were excluded from the data synthesis due to incomparability (heterogeneity in effect measure). Since we included reviews instead of individual trials, there is a risk of multiple included RCTs. We therefore a priori set the maximum of double counting in the meta-analyses at 10% per patient category and excluded reviews that reported more duplicate data. Furthermore, in order to be totally transparent, in the supplementary material a table is provided to show exactly which RCTs were included more than once per meta-analysis (S3 Table).

Results

Study Selection

A total of 299 potentially eligible articles were identified, retrieved, and screened for potential inclusion (see for the flowchart the online supplementary material S1 Figure). 112 reviews were duplicate records. From the remaining 187 articles, 146 were excluded based on the abstract: 34 were not systematic reviews, 33 were not reviews of RCTs and 79 did not have MBCT or MBSR as intervention. Five results were conference abstracts and not yet published. The full text of the remaining 36 articles was reviewed. Eight articles were excluded because the RCT results were not reported separately and five were excluded due to too much overlap in RCTs with other reviews. All excluded articles and the reason for their rejection are listed in supplementary S2 Table. 23 reviews met our inclusion criteria and were reviewed by the first and second author. The search for RCTs published after the most recent included review gave 9 results, which are reported on at the end of the result section, together with 7 RCTs included in systematic reviews that were excluded from our review.

Data extraction and quality assessment

Characteristics of the study, patient population, intervention, control condition, and outcome measures of the 23 included reviews are shown in Table 2.

2

Table 2. Study characteristics.

Author (year)	Design	Population (# participants)	Intervention (# RCT's)	Control intervention	Outcome measure
Ledesma (2009)	Syst &Meta	Cancer (381)	MBSR (4)	2 TAU,	Mental health, physical health
Piet (2012)	Syst & Meta	Cancer (955)	Both (9)	6 WL, 3 TAU	Depression, anxiety
Cramer (2012)	Syst & Meta	Cancer (327)	MBSR (3)	TAU, 2 AT	Quality of life, mental health
Ott (2006)	Syst	Cancer (326)	MBSR (3)	WL, 2 AT	Mental health, sleep, nutrition
Smith (2005)	Syst	Cancer (268)	MBSR (3)	WL, TAU, AT	Mental health, sleep
Shennan (2011)	Syst	Cancer (215)	Both (3)	WL, 2 TAU	Anxiety, mood, mental health
Veehof (2011)	Syst & Meta	Chronic Pain (409)	MBSR (7)	3 WL, TAU, 3 AT	Mood, mental health
Cramer (2012)	Syst	Chronic Pain (117)	MBSR (3)	2 WL, AT	Pain intensity, disability, safety
Kozasa (2012)	Syst	Chronic Pain (208)	MBSR (2)	WL, TAU	Depression, quality of life
Abbott (2014)	Syst & Meta	Cardiovascular (557)	Both (9)	6 WL, TAU, 2 AT	Depression, anxiety, stress, hypertension
Bohlmeijer (2009)	Syst & Meta	Chronic somatic dis. (667)	MBSR (7)	WL	Mood, anxiety, mental health
Lakhan (2013)	Syst & Meta	Chronic somatic dis. (883)	Both (10)	6 WL, 4 AT	Symptom severity
Chiesa (2011)	Syst & Meta	Depression (781)	MBCT (14)	12 TAU, 2 AT	Depression (relapse), quality of life
Coelho	Syst	Depression	MBCT	TAU	Mood

(2007)		(265)	(3)		
Piet (2011)	Syst & Meta	Depression (593)	MBCT (6)	4 TAU, 2 AT	Depression relapse
Chen (2012)	Syst & Meta	Anxiety (1244)	Both (13)	8 WL, 5 AT	Anxiety
Klainin (2012)	Syst & Meta	Mental disorders (964)	Both (13)	10 TAU, 3 AT	Mood, anxiety, mental health
Galante (2012)	Syst & Meta	Mental disorders (859)	MBCT (11)	10 TAU, AT	Depression (relapse), anxiety
Davis (2012)	Syst	Mental disorders (90)	Both (2)	WL, AT	Clinical functioning, mindfulness
Strauss (2014)	Syst & Meta	Mental disorders (550)	Both (11)	WL, 4 TAU, 6 AT	Anxiety, symptom severity
De Vibe (2012)	Syst & Meta	Mixed population (1942)	MBSR (31)	21 WL, 3 TAU, 7 AT	Mental health, physical health, quality of life, social functioning
Regehr (2012)	Syst & Meta	Healthy adults (247)	MBSR (5)	Unknown	Mood, anxiety, stress
Burke (2009)	Syst	Children (330)	Both (2)	TAU, activities	Social skills, attention, temperament, stress

Syst=Systematic Review; Meta=Meta-analysis; MBSR=Mindfulness Based Stress Reduction; MBCT=Mindfulness Based Cognitive Therapy;
TAU=treatment as usual; WL=waiting list; AT=Active Treatment

Synthesis of results

The results of the reviewed RCT's are summarized below, categorized by patient population (see also Table 4). 115 unique RCTs were included, with a combined total of 8683 participants. 3830 individuals had various somatic conditions; 4276 patients had various psychological problems and the remaining 577 subjects were recruited from the general population. Effect sizes used were Cohen's d, Hedges g, Standard Mean Difference, Weighted Mean Difference (wmd), T-value, Odds Ratio, Hazard Ratio and Risk Ratio. Of note, most systematic reviews demonstrated a significant effect size.

The results of the quality assessment are shown in Table 3. The inter-rater correlation was moderate (k=0.48), and was influenced by structurally lower scoring of item 4 (search strategy reported) and item 9 (appropriate methods for combining results) by one reviewer due to different interpretation. The quality scores shown are those agreed upon after discussion. Nearly all reviews performed well on items related to the description of the objective, the literature search, and the study selection process (items 1-4). The list of included and excluded RCTs was not always complete (item 5). Although some reviews employed independent data extractors, many did not, and several were unclear about this item (item 6). Approximately half of the reviews assessed and presented the risk of bias of individual RCTs and the risk of publication bias (items 7 and 8). A meta-analysis of the individual RCTs was often not performed (item 9). In general, strengths and limitations were discussed, conclusions were supported by the data, and findings were interpreted independently of the funding source (items 10-12).

Table 3. Quality assessment of included reviews.

Items	1	2	3	4	5	6	7	8	9	10	11	12
Ledesma	+	+	+	+	?	+	-	-	+	+	?	?
Piet (2012)	+	+	+	+	?	+	+	+	+	+	+	?
Cramer	+	+	+	+	?	+	+	?	N/A	+	+	+
Ott	?	?	?	+	?	?	-	+	N/A	?	?	?
Smith	+	+	+	+	?	+	-	+	N/A	?	+	?
Shennan	+	+	+	+	?	?	-	+	N/A	+	+	+
Veehof	+	+	+	+	?	?	+	+	+	+	+	?
Cramer	+	+	+	+	?	+	+	-	+	+	+	+
Kozasa	-	+	-	?	?	?	?	-	N/A	-	+	+
Abbott	+	+	+	+	-	+	+	?	+	+	+	+
Bohlmeijer	+	+	+	-	?	?	?	-	+	+	?	?
Lakhan	?	+	+	?	+	?	-	?	+	+	+	+
Chiesa	+	+	+	+	+	+	+	-	+	+	+	?
Coehlo	?	+	+	+	?	+	+	+	?	+	+	-
Piet (2011)	+	+	+	+	?	-	+	-	+	+	+	+
Chen	+	+	+	+	?	+	?	-	+	+	+	+
Klainin-Yobas	+	+	+	+	?	?	+	+	+	?	+	+
Galante	+	+	+	+	?	+	+	-	+	+	?	+
Davis	?	+	+	+	?	?	-	-	?	+	?	?
Strauss	+	+	+	+	-	?	+	+	+	+	+	+
De Vibe	+	+	+	-	+	+	+	+	+	+	+	+
Regehr	+	+	+	-	?	?	-	-	+	+	+	+
Burke	+	+	+	+	?	-	-	-	N/A	+	+	?

+ = yes; ? = unclear; - = no; N/A = not applicable

Table 4. Results. Effect sizes reported as in reviews in different outcome measurements for the intergroup comparisons. Values are significant except when in parentheses.

Author (year)	Effect measure	Depression	Depression Relapse	Anxiety	Stress	Quality of Life	Pain	Mindfulness	Other
Cancer									
Ledesma (2009)	Cohen's d								Mental health 0.37 (Physical health 0.17)
Piet (2012)	Hedges g	0.44		0.37				0.39	
Cramer (2012)	Smd	0.37		0.51					
Ott (2006)	T (paired sample test)	5.52		6.19	3.63				(Sleep); (nutrition)
Smith (2004)	Narrative	(Improved)							(Sleep)
Shennan (2011)	Narrative	Improved		Improved	Improved	(Improved)		Improved	
Chronic Pain									
Veehof (2011)	Smd	0.26		(0.55)		(0.25)	0.25		Physical health 0.43
Cramer (2012)	Narrative					WL, (AT)	WL, (AT)	(Improved)	(Self-efficacy)
Kozasa (2012)	Narrative	Improved				Improved			

Cardiovascular disease							
Abbott (2014)	Smd	0.35		0.50	0.38		Hypertension 0.78
Chronic Somatic Diseases							
Bohlmeijer (2009)	Hedges g	0.26		0.47	0.32		
Lakhan (2013)	Hedges g						Symptom severity MBSR 0.45; MBCT 0.64
Depression							
Chiesa (2011)	Wmd, OR	(11.24)	0.36 OR	13.8 bipolar, (2.34 soc ph)			
Coelho (2007)	HR		0.40 - 0.47				
Piet (2011)	RR	0.66					
Anxiety							
Chen (2012)	Smd			0.51			
Mental Disorders							
Klainin-Yobas (2012)	Cohen's d	0.39	Improved	(CBT)			
Galante (2012)	Wmd, RR, smd	2.46 HAMD; 10.39 BDI	0.61 (RR)	0.42 (smd)			
Davis (2012)	Narrative	Improved		Improved	(AT)	Improved	Clinical

2

Strauss (2014)	Hedges g						functioning Symptom severity (0.75 MBSR), 0.39 MBCT
Mixed Population							
De Vibe (2012)	Hedges g	0.54	0.53	0.56	0.57	0.70	Mental health 0.53 Physical health 0.31
Healthy adults							
Regehr (2012)	Smd		0.73				
Children							
Burke (2009)	Cohen's d		Improved	Improved			Attention 0.39–0.60 Mental health 0.28–0.92

Smd=standard mean difference; OR=Odds Ratio; Wmd=weighted mean difference; HR=Hazard Ratio; RR=Risk Ratio. Interpretation: Co hen's d, Hedges'g and smd: effect size 0-0.19=no effect; 0.2-0.49=small effect; 0.5-0.79=medium effect; 0.8 and above = large effect. ()=not significant. WL=compared to Wait list control; AT=compared to active treatment contro

Also, 8 reviews were included in the meta-analysis based on reported intergroup smd's of MBCT/MBSR and the pooled effect per outcome. Reviews that did not conduct a meta-analysis reporting in smd were excluded from our meta-analysis due to heterogeneity of effect size, but were only reviewed. The forest plots (Figure 1) demonstrate significant differences in favour of MBCT/MBSR. Three reviews that reported smd's on our outcome measures were omitted from the meta-analyses which ensured that the number of double counted RCTs remained under 10% [14-16]. The meta-analysis on reviews with outcome depression had 3% double counting (1 out of 34 RCTs), anxiety 8.6% (3 out of 35 RCTs), both stress and quality of life had 0% double counting and physical functioning had 6% (1 out of 17 RCTs). An overview of the RCTs in each meta-analysis outcome and a more elaborate description of the results can be found in the online supplementary material.

Mindfulness and Cancer

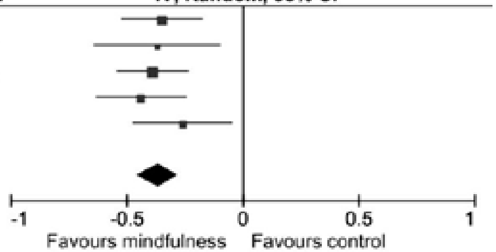
The search identified six systematic reviews covering 16 unique RCTs performed in 1668 unique cancer patients. 12 RCTs spread over two reviews were included in the meta-analysis, with one RCT duplication (8%). Most reviews found significant intergroup improvements in mental health but no significant results in physical health16. Significant improvements were demonstrated repeatedly in depressive symptoms, anxiety, stress, and quality of life [14,17-20]. Sleep quality did not change significantly; neither did body mass or fat consumption. A dose-response relationship was found between the number of minutes spent on meditating and improvement in total mood disturbance, and between the number of sessions attended and stress reduction [18,20]. An association between the KIMS-subscale Observing [21] (a measure of mindfulness) and a decrease in anxiety, isolation and over-identification was also found.

Mindfulness and Chronic Pain

For chronic pain patients we found three systematic reviews including 13 unique RCTs in 722 unique patients. One review containing 9 RCTs was included in the meta-analysis. Significant intergroup improvements were found in depressive symptoms, pain burden, and physical health, but neither in anxiety nor overall quality of life [22]. Pain intensity and pain disability decreased significantly and pain acceptance increased compared to wait list control but not when compared to a health education program. Self-efficacy showed no significant improvements. Quality of life favoured MBSR compared to the health education program but did not reach statistical significance when compared to wait list control [23]. MBSR also improved quality of life and depressive symptoms significantly in fibromyalgia patients [24].

Study or Subgroup	Population	SMD	SE	Mindfulness Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abbott 2014	Cardiovascular	-0.35	0.09	193	192	24.0%	-0.35 [-0.53, -0.17]
Cramer 2012	Cancer	-0.37	0.14	91	99	9.9%	-0.37 [-0.64, -0.10]
Klainin-Yobas 2012	Mental disorders	-0.39	0.08	475	489	30.4%	-0.39 [-0.55, -0.23]
Piet (2012)	Cancer	-0.44	0.1	477	478	19.5%	-0.44 [-0.64, -0.24]
Veehof 2011	Chronic Pain	-0.26	0.11	156	164	16.1%	-0.26 [-0.48, -0.04]
Total (95% CI)				**1392**	**1422**	**100.0%**	**-0.37 [-0.45, -0.28]**

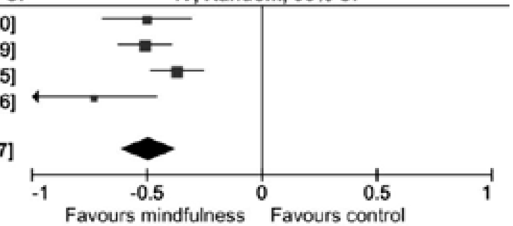
Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 4 (P = 0.81); I² = 0%
Test for overall effect: Z = 8.32 (P < 0.00001)



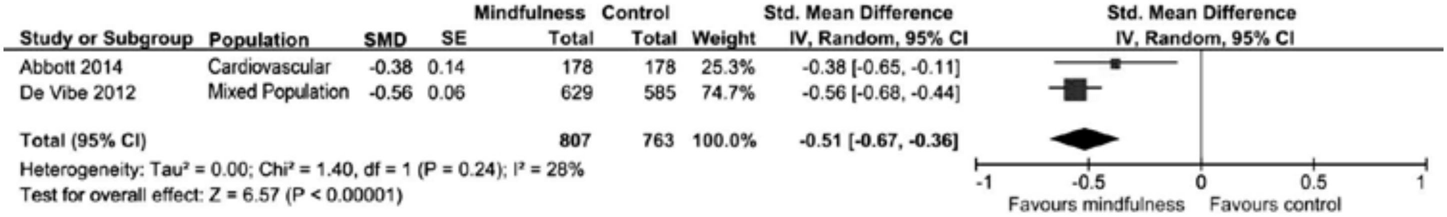
a) Depression

Study or Subgroup	Population	SMD	SE	Mindfulness Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abbott 2014	Cardiovascular	-0.5	0.1	149	144	21.0%	-0.50 [-0.70, -0.30]
Chen 2012	Anxiety	-0.51	0.06	435	424	32.6%	-0.51 [-0.63, -0.39]
Piet (2012)	Cancer	-0.37	0.06	479	480	32.6%	-0.37 [-0.49, -0.25]
Regehr 2012	Healthy	-0.73	0.14	222	192	13.7%	-0.73 [-1.00, -0.46]
Total (95% CI)				**1285**	**1240**	**100.0%**	**-0.49 [-0.61, -0.37]**

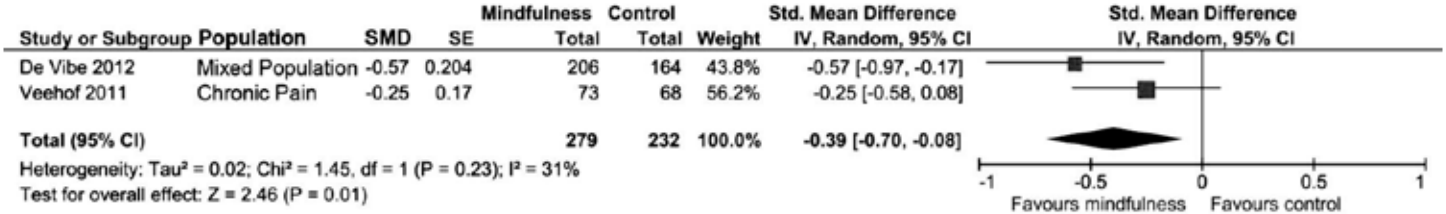
Heterogeneity: Tau² = 0.01; Chi² = 6.76, df = 3 (P = 0.08); I² = 56%
Test for overall effect: Z = 8.00 (P < 0.00001)



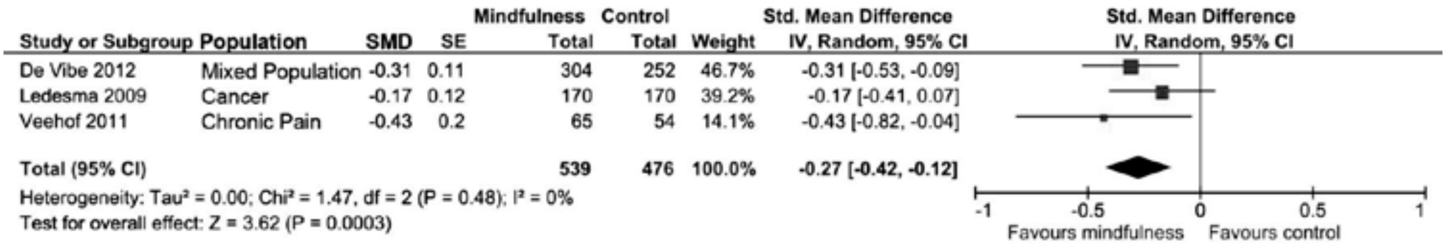
b) Anxiety



c) Stress



d) Quality of life



e) Physical Functioning

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Figure 1. Forest plots showing the effectiveness of mindfulness interventions compared with wait list control or treatment as usual on the outcomes a) Depression, b) Anxiety, c) Stress, d) Quality of life and e) Physical functioning in different populations. The size of the marker per review indicates the size of the study population. The breadth of the line indicates the 95%CI. All values lower than 0 indicate a significant difference in favour of MBSR/MBCT. Values between 0 and -0.2 indicate negligible effect; between -0.2 and -0.5 small effect; between -0.5 and -0.8 medium effect and lower than -0.8 a large effect.

Mindfulness and cardiovascular disease

One review looked at the effects of MBSR and MBCT on psychological and physical outcomes in 577 cardiovascular patients in 9 RCTs [25]. Depression, anxiety and stress showed significant medium effects (smd 0.35 to 0.50), and hypertension improved with a significant smd of 0.78.

Mindfulness and various chronic somatic diseases

Two reviews included 16 unique RCTs on MBSR and MBCT for various chronic somatic diseases (cancer, chronic pain, CVD, and fibromyalgia). In total 1331 unique patients were assessed. These reviews were excluded from the meta-analysis outcomes due to too much RCT overlap with other reviews in the meta-analysis. MBSR had a significant positive effect on depression symptoms, anxiety and psychological distress [26]. One of the reviews compared MBSR to MBCT for reducing symptom severity and found that MBCT was more effective, however no explanation was given[27].

Mindfulness and Depression

Three systematic reviews of 17 unique RCTs with 1058 currently or recovered depressed patients were retrieved, none of which were included in the meta-analysis. The overall effect on depressive symptoms comparing MBCT with TAU was positive but not significant. However, in participants with 3 relapses or more, MBCT reduced depressive symptoms significantly between groups. Anxiety in bipolar patients was also reduced significantly[28]. The relapse rate decreased significantly in patients who had 3 depression episodes or more with a risk reduction of 43% compared to TAU[29]. Treatment in patients with 2 previous episodes, however, favoured TAU with a risk reduction of 49%. MBCT compared with antidepressants demonstrated a non-significant risk reduction of 20%[30].

Mindfulness and anxiety

A review of 13 RCTs with a total of 1244 patients with different anxiety disorders found a significant beneficial effect on anxiety [31]. Interestingly, RCTs conducted in Western countries showed bigger effects than those conducted in Eastern countries.

Mindfulness and various mental disorders

Four reviews assessed the effect of MBCT and MBSR among people with various mental disorders. 30 unique RCTs among 1974 unique participants were included. Two were included in the meta-analysis without overlap as one reported on depression [32], the other on anxiety[15]. Significant benefits were found in depressive symptoms, depression relapses and anxiety, and a significant increase in metacognitive awareness of negative thoughts and feelings was found. Relapse prevention was still significant at 1 year follow-up [15]. Not all RCTs, however, showed significant changes in relapse occurrence, and cognitive behavioural therapy was found to be superior to MBSR in reducing social anxiety [32]. In bipolar disorder, significant lower depression and anxiety scores were found. In schizophrenia there was significant intragroup improvement in clinical functioning and mindfulness of distressing thoughts and images; intergroup differences, however, did not reach significance [33]. In patients with a current anxiety or depression disorder, MBCT showed more effect than MBSR. Compared with WL and TAU there was a very large effect on symptom severity, however compared with active treatment this effect almost disappeared[34].

Mindfulness in Mixed populations

We included one review with heterogeneous populations, as excluding it would result in missing 18 unique RCTs [35]. Compared to meditation alone, MBSR had a positive effect on perceived stress, rumination and forgiveness. Compared to muscle relaxation in a study population of 31 inmates, however, MBSR caused no substantial differences in anger, egocentricity, stress reactivity or salivary cortisol. Mindfulness combined with light therapy diminished skin clearing rates of psoriasis patients significantly. There was no significant effect in treatment outcomes in a study with drug addicts. In a neuroimaging study of healthy employees a MBSR intervention produced increases in left-sided anterior cortical activation, which is associated with positive affect, and significant increase in influenza antibody titres.

Mindfulness in Healthy populations

Among healthy subjects, 5 RCT's were performed in 247 students[36]. Anxiety decreased significantly compared to students that did not receive MBSR, and although depressive symptoms and stress also seemed to improve, this effect was analysed together with the effect of cognitive behavioural therapy, so the results could not be reported here.

Mindfulness in Children

One review assessed the effects of mindfulness in 330 children studied in two RCTs. Significant intergroup improvements were reported in anxiety, teacher-rated attention, social skills and objective measures of selective (visual) attention, but not in sustained attention. A study with adolescents under current or recent psychiatric outpatient care showed significant intergroup improvements in stress, anxiety, and several psychopathological symptoms. The study also found that more time spent in sitting meditation predicted improved functioning and a decline in depression and anxiety symptoms. A study including non-clinical 4-5 year olds indicated significant improvements in executive functioning on teacher ratings, but not on parent ratings [37].

Individual RCTs

Our search for individual RCTs not included in assessed systematic reviews resulted in 16 studies. Although some conclusions were not congruent with those in the reviews, overall the results supported use of the program. One RCT reports that currently non-depressed patients with one or two relapses benefit more from MBCT than patients with 3 or more relapses [38], whereas an included review [30] claimed the opposite. Note that both groups improved significantly in both studies, but results disagreed on which group improved more. Furthermore, the improvements in 39 Chinese chronic pain patients were not significant compared to active pain management [39] and no physical improvements were found in 86 elderly COPD patients [40].

Apart from these results, the other 13 RCTs demonstrated similar results as reported in the reviews: significant improvements in perceived stress, quality of life, symptom severity, anxiety and depression in patients with cancer [41], HIV [42], depression [43], mental disorders [44], ulcerative colitis [45], fibromyalgia [46], nonspecific chronic pain [47 48], insomnia [49] and Parkinson [50], and in healthy participants [51-53].

Discussion

Summary of main results

This review provides an overview of more trials than ever before and the intervention effect has thus been evaluated across a broad spectrum of target conditions, most of which are common chronic conditions. Study settings in many countries across the globe contributed to the analysis, further serving to increase the generalizability of the evidence. Beneficial effects were mostly seen in mental health outcomes: depression, anxiety, stress and quality of life improved significantly after training in MBSR or MBCT. These effects were seen both in patients with medical conditions and those with psychological disorders, compared with many types of control interventions (WL, TAU or AT). Further evidence for effectiveness was provided by the observed dose-response relationship: an increase in total minutes of practice and class attendance led to a larger reduction of stress and mood complaints in four reviews [18,20,37,54].

Strengths and limitations of the systematic review

As one of the aims was to identify how different patient populations respond to mindfulness, we included a heterogeneous group of populations. However, even when we categorized them by diagnosis, some reviews included very heterogeneous populations themselves. Excluding these would cause us to miss 18 unique RCTs, so we defined a category 'mixed

population' representing heterogeneous patient populations. Although we tried to report their results as clearly as possible, interpretation of this group's effects is difficult.
Also, though MBSR and MBCT were considered equal in approach, the small heterogeneity of interventions could have resulted in some bias towards the null, thereby strengthening the validity of our findings of consistent effects of these interventions. Due to the nature of the intervention, double blinding cannot be implemented in RCTs of mindfulness, leading to a risk of bias. As with all RCTs involving an unblinded treatment, patients' attitudes towards mindfulness alone may lead to an effect: a placebo effect in the active intervention group and disappointment in the control group for not receiving mindfulness ("frustrebo response") [55]. Whereas a placebo effect would overestimate the effect size, the frustrebo response can lead to control patients starting mindfulness on their own, underestimating the effect size. However, it might also be that frustration of not receiving the intervention leads to worse depression or anxiety scores in the control group, resulting in an overestimation of the effect. Because of the need for active participation, it is desirable that mindfulness is actively chosen: as bias is inherent in self-selected samples, the results might be extrapolated only to patients or participants who are interested in and able to participate in the intervention [16]. This, however, applies to most types of psychotherapy: motivation for and trust in the technique are essential. Furthermore, some RCTs were included in multiple reviews, so overlap in the described results exists. However, this was not believed to cause an overestimation of effect as the description of effect itself does not change by the number of RCTs. In the meta-analysis the overlap was 8% at most, reducing the overestimation inevitable in reviewing reviews to a minimum. There is risk of publication bias since we included only published reviews, although several of the included reviews contained both published and non-published RCTs. Also, despite our separate RCT search we may have missed RCTs by excluding reviews that analysed them together with other study designs or interventions (such as yoga). Although most individual RCTs included are in line with the results reported in the reviews, some did report disputing conclusions regarding Chinese patients treated for pain and elderly COPD patients. Another limitation may be that the heterogeneity of studies within the systematic reviews may be masked within the overview, as each systematic review has a single confidence interval that may or may not contain all the point estimates of the studies in that review. This could give a false impression of homogeneity at the meta-meta level.
Several reviews reported that the quality of included RCTs corresponded with the effect sizes [31,32], with lower quality RCTs tending to report a larger effect than high-quality RCTs. Some were pilot studies presenting preliminary results without confirmatory evidence. Despite these limitations, the quality of the reviews was generally quite high and suggests that the conclusions drawn from these pragmatic RCTs provide relevant estimates of effectiveness in clinical practice. The interventions were compared repeatedly to both wait list and treatment as usual subjects. A recent review compared meditation to only active control groups, and although lower, also found a beneficial effect on depression, anxiety,

stress and quality of life. This review was excluded in our study for its heterogeneity of interventions [7].

Clinical implications

In chronic care, both MBCT and MBSR help patients cope with pain, depressive symptoms, anxiety, and stress, which improves their quality of life. In mental health, there are more ambiguous results: some disorders improve, others such as social anxiety and schizophrenia respond better to traditional treatment. In prevention, mindfulness is valuable in reducing stress and other psychopathological symptoms that might otherwise develop into clinical conditions. In education and parenting, teaching children how to cope with stress and upsetting situations in a mindful way can help them deal with those aspects of life in the future. We also have to take into account the meaning of effect sizes in different populations: an effect size of 0.5 in anxiety might mean something different in anxiety patients than in cancer patients. In the first case, depending on the exact anxiety disorder, other treatments might have a larger effect. In cancer patients however, reducing this much anxiety may have a huge impact on quality of life. This discrepancy helps make a distinction as to where to apply mindfulness as adjunct treatment.

There are several benefits of adding mindfulness to usual treatment. First, MBSR and MBCT are easy to implement and they allow patients to take a more active role in their treatment. Second, there is little emotional and physical risk involved. Third, the costs are relatively low as one trainer can lead a rather large group and most exercises can be done at home, without the help of external means [17]. However, they do require commitment in both adherence and time of both the patient and the therapist.

Gaps in evidence

Aim of this review was to assess in which populations MBSR and MBCT are effective, and in which not. Most insignificant effects found were based on pilot studies using outcome measures that are only indirectly affected by mindfulness (e.g. nutrition, HIV, psoriasis, drug addiction), therefore no definitive conclusions can be drawn for these outcome measures.

Since MBSR and MBCT consist of not just meditation, but also psycho-education and yoga-like exercises, it is difficult to pinpoint which aspect contributes most to the observed improvements. According to psychological theory [56], stress is usually caused by an external factor which evokes fear, anger, or other states of discontentment. Stress is also experienced proportionately; the larger the discrepancy between the actual and desired situation, the higher the level of stress. Apart from the initiating event, individuals themselves tend to magnify stress by worrying about the cause and consequences of the event, which often evokes more stress than the event alone. Mindfulness intervenes in this psychological process by creating a different relationship with both the event and the internal response to the event. Chronic as opposed to acute conditions respond particularly well to mindfulness techniques since acceptance and reflection may be more applicable to chronic symptoms than to acute symptoms. In acute settings the undesired situation may still be altered, making acceptance untimely.

Support for this theory of stress reduction by coping with psychological stress factors is found in the demonstrated physiological effects of mindfulness. Blood pressure, heart rate, respiration rate and oxygen consumption have been shown to respond favourably to mindfulness [57,58]. Similar physiological effects are seen in the relaxation response [59,60]. It activates the autonomic nervous system to release endorphins and serotonin, and the parasympathetic response influencing endocrine and immune responses [61].

Future research

Future research will benefit from creative strategies that measure placebo effects and non-specific effects, and distinguish these from actual effects. Nevertheless, the reviews included in our overview are methodologically strong and demonstrate that MBSR and MBCT are effective for certain conditions. Since the available evidence demonstrates that mindfulness exceeds WL control, future research should probably focus on comparison with active treatment. Further research should also look more into the mechanisms whereby these therapies are efficacious. Alongside investigating working mechanisms, studies should also explore the cost-effectiveness of these interventions: as there are few if any side effects and there seem to be benefits for chronic patients, insight in financial consequences is useful for further practical implementation in health care.

Conclusions

Although there is continued skepticism in the medical world towards MBSR and MBCT, the evidence indicates that MBSR and MBCT are associated with improvements in depressive symptoms, anxiety, stress, quality of life, and selected physical outcomes in the adjunct treatment of cancer, cardiovascular disease, chronic pain, chronic somatic diseases, depression, anxiety disorders, other mental disorders and in prevention in healthy adults and children.

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Part II

Mindfulness and neuroimaging

Chapter 3

8-week Mindfulness Based Stress Reduction induces brain changes similar to traditional long-term meditation practice – A systematic review.

Gotink RA, Meijboom R, Vernooij MW, Smits M, Hunink MGM.

Brain and Cognition (2016).

Abstract

Background: The objective of the current study was to systematically review the evidence of the effect of secular mindfulness techniques on function and structure of the brain. Based on areas known from traditional meditation neuroimaging results, we aimed to explore a neuronal explanation of the stress-reducing effects of the 8-week Mindfulness Based Stress Reduction (MBSR) and Mindfulness Based Cognitive Therapy (MBCT) program.
Methods: We assessed the effect of MBSR and MBCT (N = 11, all MBSR), components of the programs (N = 15), and dispositional mindfulness (N = 4) on brain function and/or structure as assessed by (functional) magnetic resonance imaging. 21 fMRI studies and seven MRI studies were included (two studies performed both).
Results: The prefrontal cortex, the cingulate cortex and hippocampus showed increased activity, connectivity and volume in stressed, anxious and healthy participants. Additionally, the amygdala showed decreased functional activity, improved functional connectivity with the prefrontal cortex, and earlier deactivation after exposure to emotional stimuli.
Conclusion: Demonstrable functional and structural changes in the prefrontal cortex, cingulate cortex, insula and hippocampus are similar to changes described in studies on traditional meditation practice. In addition, MBSR led to changes in the amygdala consistent with improved emotion regulation. These findings indicate that MBSR-induced emotional and behavioral changes are related to functional and structural changes in the brain.

Introduction

Mindfulness has a millennia old history and is usually referred to as a mental state characterized by 'full attention to internal and external experiences as they occur in the present moment', and 'an attitude characterized by non-judgment of, and openness to, this current experience'[1-3]. Stripped of all religious aspects, application of Mindfulness Based Stress Reduction (MBSR) [1] as a stress reduction method, and Mindfulness Based Cognitive Therapy to prevent relapse in depression [4], has increased over the past 35 years. In 8 weeks, MBSR and MBCT participants learn to cope with stress by means of cognitive exercises, concentration training and mental exposure, using a standardized evidence based protocol [5]. The MBSR- and MBCT protocol comprises both focused attention, open monitoring, and breathing meditation but without the transcending atmosphere of traditional meditative practice. The goal is not to reach Nirvana or Enlightenment. Instead, by learning to recognize automatic reactions, and letting go of dysfunctional ones in a non-judgmental manner, participants gain a new coping mechanism that studies have shown to improve perceived stress, anxiety, depression, and quality of life in all types of patients [6,7].
Previous research on traditional meditation styles (i.e. Zen, Vipassana, Tibetan etc.) found that individuals who have regularly practiced meditation for several years exhibit significant altered brain structure, when compared to demographically matched controls[8-13]. Recent meta-analyses report eight regions to consistently show structural and functional differences in long-term meditators: the prefrontal cortex (related to enhanced meta-awareness and reappraisal), the sensory cortices and insula (related to body awareness), the hippocampus (related to memory processes), and the cingulate cortex (related to self and emotion regulation)[14-18].
Former neuroimaging literature focused on traditional meditation styles, or a combination of traditional and secular mindfulness. MBSR and MBCT are in some core aspects different from traditional meditation (i.e. duration and goal), and may therefore have different neuronal effects. In this article, we want to explore how the distilled mindfulness techniques in MBSR and MBCT, rather than spirituality of the traditional styles, are related to changes in brain structures and activity. We focus on regions described in studies on long-term meditators, but have not restricted ourselves to these areas. The current systematic review focusses on functional and structural magnetic resonance imaging (MRI) in order to understand the neuronal base of the psychological effects of MBSR and MBCT.

Methods

Inclusion and exclusion criteria

In this systematic review we give an overview of the published effects of the secular mindfulness program MBSR and MBCT, as designed by Kabat-Zinn [1] and Teasdale[4], on the function and structure of the brain. Studies reporting specific aspects of the program such as nonjudgmental awareness or focus on the breath, were also included to see whether these components have an impact on the brain and thus could explain more about the working mechanism of the 8-week program. To be included, the studies had to have the following characteristics: MBSR/MBCT or aspects of the program as intervention, and functional and/or structural MRI as imaging technique. When the intervention concerned a specific aspect of the 8-week protocols or it was a very similar secular derivative, like Mindfulness Based Exposure Therapy, studies were captioned under 'supportive studies'. Dispositional mindfulness was also included in order to take its effect into account in discussing found neuronal differences. There were no inclusion restrictions regarding age range, health status or ethnicity. Our primary outcome was activation, deactivation or functional connectivity, or structural changes (density, concentration or volume). As spatial resolution of Electroencephalography (EEG) is less, we restricted imaging method to (f)MRI. Other types of meditation such as Transcendental Meditation, Vipassana or Zen meditation were excluded, as heterogeneity of method and focus would make comparison to the standardized 8-week program difficult. Unpublished dissertations and conference papers were not taken into consideration.

Search strategy

Five electronic databases were used: PubMed, Embase, PsycInfo, Medline OvidSP and Web-of-Science. The databases were searched for English language studies using the following terms: "mindfulness" or "meditation" or "mindfulness-based stress reduction" or "MBSR", in combination with "MRI" or "magnetic resonance imaging" or "neuroimaging" and "brain".

Study selection process

Two reviewers (RG and RM) independently read the abstracts of the studies to exclude those that were irrelevant. Any citation considered potentially relevant by at least one reviewer was retrieved in full text form. Inclusion was based on inclusion criteria mentioned earlier, studies of all date and design were considered. Discrepancies were evaluated together with a third reviewer (MH) and decisions were made by consensus.

Data extraction and quality assessment

Studies were analyzed independently on both content and on quality by the two reviewers. The data extracted were study design, population characteristics, type of intervention, type of measurement and neuronal changes. If information was missing or data were incomplete, the authors of the study were contacted to provide missing data. To assess the quality of the included RCTs we used the Cochrane Collaboration tool for assessing Risk of Bias [19] and for non-RCTs we used the Newcastle-Ottowa criteria [20]. We searched for explicit mentioning of each criterium, for example 'blinding'; when mentioned as present or not present explicitly, that article would receive a + or a – respectively, when nothing regarding this criterium was mentioned, the article would get a '?'. To assess the degree of consensus we calculated the proportional agreement between the quality scores.

Outcome measures

The outcome measures were changes in (de)activation, functional connectivity and gray matter density/volume. As meta-analyses on the traditional styles identified the prefrontal cortex, the insula, cingulate cortex, and the hippocampus as main areas of change, we reported these as main areas of interest.

Meta-analysis

Due to the heterogeneity in population (healthy participants, anxiety disorder and patients with neurodegenerative disease), task-based versus resting state, and outcome measures (structural voxels, connectivity and activity), the number of comparable studies within the included sample was too small to conduct formal quantitative meta-analysis of the results. An activation Likelihood Estimation meta-analysis was therefore not performed, and conclusions were drawn using a qualitative approach.

Results

Literature Search

A total number of 1156 potentially relevant articles were identified, retrieved, and screened for potential inclusion (Figure 1). 597 studies were excluded as being duplicates and 425 studies were discarded based on their titles. From the remaining 134 articles, 74 were excluded based on the abstract: 67 did not have MBSR, MBCT, or components as intervention, 26 did not use MRI or fMRI as imaging technique, and five were conference abstracts. Overall, 36 articles met our inclusion criteria and were reviewed by the two reviewers independently. In six cases, authors published multiple articles of one actually performed study; these were therefore presented together as one study (see Table 1), resulting in 30 actual studies. 11 neuroimaging studies reported on MBSR effects, 15 studies on aspects of the MBSR program and four on dispositional mindfulness. There were 13 RCTs, nine cohort studies and eight cross-sectional studies. An overview of rejected studies along with reasons for their rejections is available upon request.

Study characteristics

Study characteristics are summarized in Table 1. Seven RCTs and four intervention cohort studies performed functional or structural MRI brain scans of MBSR participants [21-32]. Six

RCTs, four cohort studies, and five cross-sectional studies investigated what effect aspects of the MBSR program have on the brain assessing certain fMRI tasks. Tasks that were performed were Feeling vs. Thinking, Affect Labeling vs. Gender labeling, Affect matching vs Face matching, and Reappraising emotions vs Reacting to emotional stimuli [33-46]. Observing vs suppressing (for instance participants learned to label affects, reappraise emotions or focus on their breath). And finally, one cohort and three cross-sectional studies [47-50] measured the correlation between pre-disposition to mindfulness and brain activity or structure. Predisposition was measured using the Mindful Attention Awareness Scale (MAAS)[2] and the Five Facet Mindfulness Questionnaire (FFMQ)[51]. These are validated questionnaires that assess the following aspects: living in the present moment, observing, non-judgment, awareness, non-reactivity to inner experiences, and acceptance. These qualities can be present in a person without following the MBSR program, for instance due to education, personality or culture. We first report the results of full MBSR training, after which supportive studies investigating aspects of the training are discussed. To keep interpretation of the results of the studies comprehensively, we have placed the comparison condition in Table 1, instead of in the text.

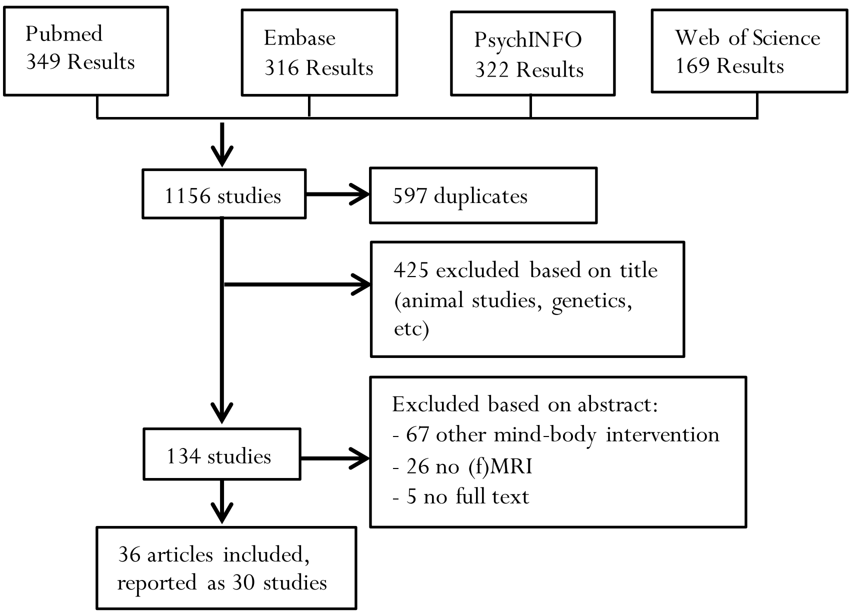

Figure 1. Flowchart of the literature search (Search performed 14-06-2016).

Table 1. Study Characteristics.

Author (year)	Outcome	Design	Participants (N)	Mindfulness condition	Comparator condition	Task (if applicable)
Farb (2007, 2010, 2013)	fMRI	RCT	Healthy (36)	MBSR (20)	WL (16)	Narrative vs experiential focus
Ives-Deliperi (2011)	fMRI	Cohort	Healthy (10)	Post-MBSR	Population norms	Random numbers vs Open monitoring
Goldin (2009, 2010)	fMRI	Cohort	Social anxiety (14)	Post-MBSR	Pre-MBSR	Distraction vs breath focus
Holzel (2013)	fMRI	RCT	Generalized Anxiety Disorder (26)	Post-MBSR	SME (11)	Labeling facial expressions
Kirk (2016)	fcMRI	RCT	Healthy (51)	MBSR (27)	Muscle Relaxation (24)	Economic decisions
Kilpatrick (2011)	fcMRI	RCT	Healthy (32)	MBSR (17)	WL (15)	pay attention to sounds of scanner
Roland (2015)	fcMRI	Cohort	Tinnitus (13)	Post-MBSR	Pre-MBSR	N.A.
Wells (2013)	Both	RCT	Alzheimer (13)	MBSR (8)	TAU (5)	N.A.
Smart (2016)	MRI	RCT	Alzheimer (8)	Post-MBSR (8)	Pre-MBSR	N.A.
Holzel (2010, 2011)	MRI	Cohort	Stressed (26)	Post-MBSR MBSR (16)	Pre-MBSR WL (17)	N.A.
Pickut (2013)	MRI	RCT	Parkinson (27)	MBSR (14)	TAU (13)	N.A.

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Supportive studies						
King (2016)	fMRI	RCT	PTSD (23)	16 week MBET (14)	Group therapy (9)	N.A.
Haase (2016)	fMRI	RCT	Marines (35)	MMFT (19)	Usual fitness training (16)	Processing with restricted breathing
Allen (2012)	fMRI	RCT	Healthy (38)	6 week MT	Group reading	N.A.
Desbordes (2012)	fMRI	RCT	Healthy (36)	8 week MT, CBCT	Health discussion group	Facial expressions
Braden (2016)	fMRI	RCT	Back pain (23)	4 week MBSR (12)	Reading group (11)	Sadness induction
Haase (2015)	fMRI	Cohort	Motocross athletes (7)	Post 6 week MT	Pre 6 week MT	Processing with restricted breathing
Yang (2016)	fcMRI	Cohort	Healthy (13)	Post 40 week MBSR	Pre 40 week MBSR	Rest vs. meditation
Doll (2015, 2016)	fMRI	Cohort	Healthy (26)	Attention to Breath	Passive observing	Aversive pictures
Strawn (2016)	fMRI	Cohort	Children with anxiety (9)	Post 12 week MBCT	Pre 21 week MBCT	Processing task with emotional and neutral distractors
Smoski (2015)	fMRI	Cross-sectional	Depression (37)	Remitted depressed (18)	Healthy (19)	Reappraisal vs. emotional acceptance
Herwig (2010)	fMRI	Cross-sectional	Healthy (27)	'Feel'	'Think', 'Wait'	Think or Wait vs Feel
Creswell (2007), Way	fMRI	Cross-sectional	Healthy students (27)	Affect labeling Affect	Gender labeling Face matching	Gender vs Affect Labeling Face vs Affect

(2010)				matching		
Modinos (2010)	fMRI	Cross-sectional	Healthy students (18)	Reappraising emotions	Reacting to emotions	Reacting vs Reappraising
Murakami (2015)	fMRI	Cross-sectional	Healthy (21)	Observing	Suppressing	Emotional visual stimuli
Zeidan (2015)	Both	RCT	Healthy (75)	4-day MT	Placebo, sham-MT, book listening	Pain inducement
Friedel (2015)	MRI	Cohort	Adolescents (82)	MAAS at age 19	MAAS at age 16	N.A.
Murakami (2012)	MRI	Cross-sectional	Healthy (19)	FFMQ high score	FFMQ low score	N.A.
Taren (2013)	MRI	Cross-sectional	Healthy (145)	MAAS high score	MAAS low score	N.A.
Kong (2016)	MRI	Cross-sectional	Healthy (290)	MAAS high score	MAAS low score	N.A.

(f)(c)MRI: (functional) (connectivity) Magnetic Resonance Imaging, RCT: Randomized Controlled Trial, MBSR: Mindfulness Based Stress Re duction, WL: Waiting List, N.A.: Not applicable, SME: Stress Management Education, TAU: Treatment As Usual, MBET: Mindfulness Based Exposure Training, MMFT: Mindfulness-based Mental Fitness Training, MT: Mindfulness Training, CBCT: Cognitive Behavioral Compassion Training, FFMQ: Five Facet Min dfulness Questionnaire, MAAS: Mindful Awareness Assessment Scale.

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Table 2. Quality analysis of RCTs and non-RCTs.

Author (year)	**Selection bias**		**Perfor manc e bias**	**Dete ction bias**	**Attr ition bias**	**Repor ting bias**
	Sequence generat	**Allocation concealm**				
Farb (2007)	+	?	+	+	NA	+
Holzel (2013)	+	+	+	+	+	+
Kirk (2016)	?	?	+	+	?	-
Kilpatrick (2011)	+	-	-	+	+	?
Wells (2013)	+	?	+	+	+	+
Smart (2016)	-	+	+	+	+	+
Pickut (2013)	+	+	+	+	+	+
King (2016)	?	?	+	+	+	+
Allen (2012)	+	?	+	+	+	+
Braden (2016)	-	?	+	?	?	+
Desbordes (2012)	+	+	+	+	?	+
Zeidan (2015)	+	?	?	+	?	+
Haase (2016)	-	?	+	+	+	+

Non-RCTs	**Selectio n bias**	**Compa rability**	**Outcome Assessment**	**Follow-up**	**Other**
Ives-Deliperi (2011)	+	NA	+	NA	NC
Goldin (2009, 2010)	+	+	+	+	
Roland (2015)	+	NA	+	+	NC
Holzel (2010)	+	NA	+	NA	NC
Yang (2016)	+	NA	?	+	NC
Doll (2015, 2016)	?	NA	+	NA	NC
Strawn (2016)	?	NA	+	+	NC
Smoski (2015)	?	+	+	NA	
Herwig (2010)	?	NA	+	NA	NC
Creswell (2007), Way (2010)	?	NA	+	NA	NC
Modinos (2010)	?	NA	+	NA	NC
Murakami (2015)	?	NA	+	NA	NC
Murakami (2012)	?	NA	+	NA	NC
Taren (2013)	?	NA	+	NA	NC
Kong (2016)	+	NA	+	NA	NC
Haase (2015)	-	NA	+	NA	NC
Friedel (2015)	+	+	+	+	

+ low risk; ? unknown risk/not mentioned; - high risk; N/A not applicable; NC no control group

Quality assessment

The results of the quality assessment are shown in Table 2. The proportion of inter-rater agreement was moderate (75%), the scores shown in the table are consensus scores. Of all studies, 11 studies were unclear about participant selection, although the groups compared were demographically not significantly different. Furthermore, in four of the RCTs randomization and allocation concealment were not obtained, which increases risk of selection bias. The method of measuring baseline characteristics and outcomes was reliable and with the exception of one study there was no risk of reporting bias. There was no indication of attrition bias in the longitudinal studies, as group demographics were still alike after drop-out occurred.

The results are reported per structure that has been described in earlier meta-analyses on traditional meditation. In addition to these regions of interest, the amygdala was reported so many times that we added this region to our outcomes. The areas are also shown in Figure 2.

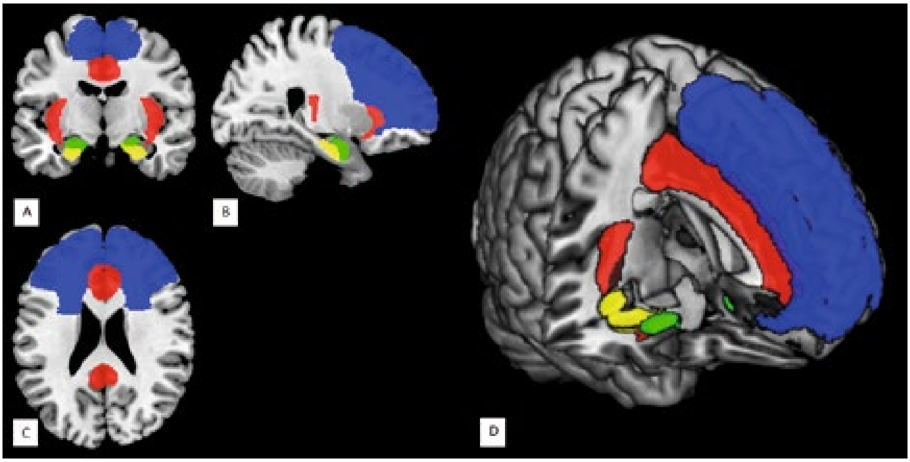

Figure 2. Based on Hammers ROIs[49]. Coronal (A), Sagittal (B), Axial (C), and 3D (D) view of gray matter areas involved in MBSR. Prefrontal cortex (blue), Cingulate cortex and insula (red), hippocampus (yellow) and amygdala (green).

Prefrontal cortex

Overall, prefrontal cortex (PFC) shows increased activity after MBSR [21], particularly dorsolateral and dorsomedial [28,52]. The PFC also shows increased functional connectivity with the salience network [53], the superior temporal gyrus, the visual cortex, the amygdala, the hippocampus and the posterior cingulate cortex [24,25,54]. Specifically, there was negative functional connectivity with the amygdala, where the PFC seemed to down-regulate the amygdala responses [29]. Mindfulness-based tasks were positively associated with activation in areas of ventrolateral, medial, dorsolateral and orbitofrontal PFC [33,40,45,46,55-57]. Also, amount of practice predicted increased medial and dorsolateral PFC activation during mindful emotional processing [44]. One study found that acceptance rather than reappraising sad images, was associated with less PFC activation [34]. No structural changes were reported.

Insula

The insular regions are reported in two MBSR studies, one showing less activity [26], and one showing more activity [29]. Seven studies, however, reported increased activity in relation to mindfulness-based tasks [33,39,46,55-58]. Dispositional mindfulness was positively associated with activation in the left insula and right anterior volume [47,49], and less cortical thinning in the left anterior insula [48]. Amount of practice during MBSR predicted right anterior insula and frontoinsular activation during negative emotional processing [44]. One study showed that compared to muscle relaxation, the MBSR group had greater ability to effectively regulate the anterior insula and thereby promote a more cooperative decision making style [22]. In healthy adults, greater activation in left insula while accepting than while reappraising sad images was associated with greater intensity of negative affect post-acceptance, suggesting that this activation either reflected less effective emotion regulation, or reflected heightened emotional awareness rather than regulation [34].

Cingulate cortex

The cingulate cortex also shows disparate results. In two MBSR studies less activity was reported [26,28], while in four MBSR studies increased functional connectivity with the prefrontal cortex, the left temporal cortex, the parietal cortex and visual cortex were found [24,25,54], as well as increased cingulate volume [59]. Eight supportive studies report increased activation [35,39,40,44,55,56,58], of which one during mindfulness-based tasks [46]. Compared to baseline, traumatized veterans showed increased connectivity between the posterior cingulate and the dorsal anterior cingulate and left dorsolateral PFC, which was correlated to decreased trauma-symptoms [41]. No structural changes were reported.

Hippocampus

The hippocampus shows more activity and more volume in four MBSR studies [32,60,61], including less Parkinson-related atrophy [54]. Three supportive studies underline the increase in activity and volume [33,47,49], but one does not [50].

Amygdala

In two MBSR studies the right amygdala showed less activity compared to controls [28,29], the left amygdala in one study [21]. Only in Parkinson patients more right amygdala volume was found [32], though it was not clear whether volume in Parkinson patients increased or whether volume in controls decreased more. MBSR-induced stress reduction was associated with right amygdala volume decrease [30]. Three supportive studies report less amygdala activity in association with mindfulness tasks: mindfulness training was associated with less right amygdala activity, where compassion training was associated with more right amygdala activity [62]. When comparing ruminating to observing ones feelings, the left amygdala is more active during the 'think'-condition and, notably, deactivated during the 'feel'-condition [55]. Affect labeling showed less bilateral amygdala activity compared to the control task gender labeling [33,45]. Two studies report negative functional connectivity with the prefrontal cortex [29,46]. While suppression showed a positive association with the dorsolateral PFC, observing showed a negative correlation with the medial PFC [57]. When reappraising emotions, the left amygdala was negatively correlated with dorsolateral PFC activation in more mindful individuals [33]. Dispositional mindfulness was positively associated with bilateral amygdala deactivation. The structural supportive studies report a positive association between right amygdala volume and the describing facet of the FFMQ [47], and a negative association with overall mindfulness [50].

Other results

This section reports regions not indicated by traditional meditation neuroimaging studies as affected consistently. More activity or volume in relation to MBSR or mindfulness-based tasks was found in the parietal cortex (somatosensory, precuneus), temporal cortex (middle and superior gyrus), occipital cortex (cuneus, middle gyrus), cerebellum, and basal ganglia (caudate nucleus, thalamus and putamen), though most structures were only reported once. One study reported less activity in temporal lobe and the precuneus compared to population norms [26], and another study reported no changes in the default mode network [24]. Another study reported less volume in the cerebellum [32].

Table 3. Results

Author (year)	Prefrontal cortex	Insula	Cingulate cortex	Hippocampus	Amygdala	Other
Farb (2007, 2010, 2013)	More activity (4928 mm^3)				Less activity (576 mm^3 L)	More activity somatosensory cortex
Ives-Deliperi (2011)	Less activity	Less activity anterior	Less activity anterior			Less activity in temporal lobe, precuneus
Goldin (2009, 2010, 2012)	More activity dorsomedial		Less activity posterior	More activity	Less activity (1180 mm^3 R) Earlier deactivation	More activity inferior and superior parietal lobule, cuneus, precuneus, middle occipital gyrus
Holzel (2013)	More activity, Improved connectivity amygdala	More activity			Less activity (784 mm^3 R)	
Kirk (2016)		increased coupling between septal region and posterior insula				
Kilpatrick (2011)	Increased connectivity salience network		stronger anticorrelation visual cortex			

Roland (2015)	Increased connectivity temporal gyrus (647 mm^3 L), visual cortex (224 mm^3)		Frontal (242 mm^3 L, 354 mm^3 R), left temporal and parietal cortex (540 mm^3)			No changes in default network.
Wells (2013)	Increased connectivity hippocampus		Increased connectivity prefrontal	242 mm^3 less atrophy	No subcortical changes	
Smart (2016)						More total brain volume change
Holzel (2010, 2011)			More volume posterior	More volume (L)	Correlation stress reduction and volume decrease (13 mm^3 R).	More volume temporo-parietal junction, cerebellum
Pickut (2013)				More volume (229 mm^3 R; 54 mm^3 L)	More volume (8 mm^3 R)	More volume caudate nucleus (260), thalamus (57), temporal lobe (30) and left occipital lobe (174); cerebellum in TAU (128)
King (2016)	Increased connectivity with posterior		Increased connectivity anterior with posterior			
Haase		Increased	Increased activation			

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(2016)		activation anterior (R)	anterior			
Allen (2012)	More activity dorsolateral, frontal gyrus	Posterior L anterior R	cingulate gyrus			amount of practice predicted increased frontoinsular activation
Desbordes (2012)					MT: less activity (R) CBCT: more activity (R)	Whole-brain analysis: no significant differences in any of the groups.
Braden (2016)	Increased activity (L)		Increased activity anterior			Correlation anterior cingulate (L) and sad valence ratings r=0.65
Haase (2015)	decreased connectivity with posterior cingulate	Increased activation anterior	Increased activation anterior, decreased connectivity between anterior and posterior			
Yang (2016)	Decreased connectivity anterior cingulate		Decreased connectivity anterior - posterior			Decreased connectivity anterior cingulate with occipital, termporal, cuneus. Increased with cerebellum, parietal.
Doll (2015, 2016)	Increased activation				Less activity	More intrinsic functional connectivity between default mode network and salience network
Strawn		Increased	Increased activation			Increased activation

(2016)		activation	anterior			thalamus and nucleus
Smoski (2015)	Acceptance: less activation dorsolateral than Reappraisal	Acceptance: greater activation than Reapp				Greater activation in L insula to accept than reappr was associated with greater intensity of negative affect post-accept.
Herwig (2010) more activity	Think: anterior, dorsolateral Feel: superior, medial, inferior	Think: L Feel: R	Think: Posterior Feel: middle gyrus		Think: more activity (L) Feel: less activity (L)	Think: parietal, occipital cortex.Feel: temporal, somatosensory cortex, intraparietal sulcus.
Creswell (2007), Way (2010)	More activity medial (63,004 mm^3); ventrolateral (4,910 mm^3); dorsolateral (2,675 mm^3)	More activity (5,380 mm^3 L)		More activity	Less activity ($r = -.60$ LR) (10,752 mm^3 R; 908 mm^3 L)	More activity thalamus
Modinos (2010)	More activity dorsolateral, inferior gyrus		More activity anterior		Negative correlation dorsolateral PFC ($r = -.50$ L)	More activity temporal gyrus, angular gyrus, cerebellum
Murakami (2015)	Increased activation frontal gyrus (L)	Increased activation anterior			Suppress: DLPFC Observe: MPFC	middle temporal gyrus, inferior parietal lobule, putamen
Zeidan (2015)	Greater activation orbitofrontal	Greater activation anterior	Greater activation anterior			Greater activation subgenual

3

Friedel (2015)	No correlation	Less prior cortical thinning				
Murakami (2012)		More volume anterior(R)		More volume (R)	More volume (R)	
Taren (2013)				Less volume (r= -0.2 R)	Less volume (r = -0.2 R)	Caudate (L r = −0.22; R r= −0.19), nucleus accumbens (L r=-0.20)
Kong (2016)	Orbitofrontal 768 mm^3; inferior frontal - 1024 mm^3	920 mm^3		Parahipp gyrus 880 mm^3		

L: left, R: right, TAU: treatment as usual, MT: mindfulness training, CBCT: compassion based cognitive therapy, (DL)/(M)PFC: (dorsolateral)/(medial) prefrontal cortex.

Discussion

In this study we systematically reviewed the evidence of effect of secular mindfulness on function and structure of the brain, hence aiming to understand the neurobiological explanation of this increasingly popular stress reduction training. Long-term meditation has been associated with structural and functional differences in the prefrontal cortex, the sensory cortices and insula, the hippocampus, and the cingulate cortex [14,16-18], associated with emotion regulation and response control [12,13,16,63]. Only one MBCT study was found, therefore the interpretation of results was mainly focused on the neuronal working mechanisms of MBSR. After 8 weeks of MBSR training, participants demonstrated similar changes in the PFC, the hippocampus, insula and the cingulate cortex, associated with attention regulation, self-referential processing, and perspective taking, all stimulated in both long-term meditation and MBSR exercises. Based on the task-based studies, the insula shows increased activation, but the MBSR studies showed no consensus. The insula is associated with perception, motor control, self-awareness, interoception, and interpersonal experience [64], and with linking behavioral outcomes to motivation (which results in learning) [65]. It could be that this area needs longer practice to be affected, or that these functions are too diverse to refer to the insula as a whole, or that the insula is activated regardless of valence of stimuli (positive or negative) when connecting sensory information to emotions [66,67].

In addition to these four prior appointed regions, the amygdala seems to play a larger role in the neuronal working mechanism of MBSR, than it does in traditional meditation. The amygdala is related to the fight-or-flight reaction: it adds emotional value to sensory input [64] and functions as a pre-conscious warning system [68]. If a threat is significant, the amygdala responds within milliseconds and activates the sympathetic nervous system [69], prior to conscious awareness of the stimuli [70]. When the situation allows for cortical processing, the PFC can regulate the amygdala, either increasing or decreasing its activity [71]. MBSR seems to be associated with more efficient PFC inhibition of amygdala responses, improving emotion regulation. Different aspects of the training (reappraising emotions, affect labeling and breath focus exercises) are associated with increased prefrontal activity, hippocampal activity and less amygdala activity, suggesting a neuronal explanation that provides support for the stress-reducing effects of the training found in traditional meditation research. While in line with these results a negative association was found between amygdala volume and overall mindfulness as measured with the MAAS (N=145), a positive association was found between right amygdala volume and the describing facet of the FFMQ (N=19). It is possible that as in this group the other factors (observing, acting with awareness, nonjudging of, and nonreactivity to inner experiences) were not associated with amygdala differences, describing in itself may not be a very stress-reducing activity.

It may be logical that MBSR participants show more effect in the amygdala than long-term meditators, as the room for improvement may be larger. Monks or nuns are not expected to experience a lot of stressful events in their monastery, and if they do, their long experience will enable them to cope mindfully. Western participants, however, are more likely to experience stress in daily life, and their amygdala might therefore have a higher baseline activity. The down-regulation of the amygdala underlines the stress-reducing effect of MBSR with a neuronal map.

There are several limitations that should be taken into account. First, unfortunately no quantitative meta-analysis was possible in this sample of studies, due to the wide variety of outcome measures and participants. The inclusion of studies examining populations that have brain pathology (e.g., Alzheimer's and Parkinson's disease) make interpretation of findings hard enough. Second, the functions of each of the mentioned brain structures are still assumptions, and too much deducting should be discouraged as the significance of found changes is controversial. Also, correlational fMRI studies using self-reported measures should be interpreted with caution as they often overestimate the correlation, and they report means of just the subset of voxels exceeding chosen thresholds [72]. The three correlational fMRI studies in this review did not explain their calculation method sufficiently to assess whether this is a risk, although one study reported $r=-0.88$, which might indicate overestimation [33]. Third, to ascribe these neuronal effects solely to the training is precarious: MBSR is a multifaceted group program and some positive effects may result from components not specific to meditation or mindfulness, such as social interaction within the group, or gentle stretching exercises. A fourth limitation is the design of many of the included studies: small study populations with a large inter-study heterogeneity make comparison difficult, and increase the risk of small study bias. Only three non-RCTs had a control group [34,48,73]. Longer prospective studies will be necessary to determine if MBSR and MBCT training also results in long-term changes in brain activity and structure. Finally, in this field there is a high risk of publication bias.

In summary, the findings suggest that the 8-week MBSR training evokes similar brain responses to traditional long-term meditation styles. The connectivity between prefrontal cortex, hippocampus and amygdala indicates a neuronal working mechanism of how this secular training induces emotional and behavioral changes.

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Chapter 4

Meditation and yoga practice are associated with smaller right amygdala volume: The Rotterdam Study.

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Submitted.

One way to look at meditation is as a kind of intrapsychic technology that's been developed over thousands of years by traditions that know a lot about the mind/body connection. Jon Kabat-Zinn

Abstract

Objective: To determine the association between meditation and yoga practice, experienced stress, and amygdala and hippocampal volume in a large population-based study.

Methods: This study was embedded within the population-based Rotterdam Study (visit 2009-2013) and included 3742 participants for cross-sectional association. Participants filled out a questionnaire assessing meditation and yoga practice, experienced stress and underwent an MRI scan of the brain. Both cross-sectional and longitudinal data were obtained. Amygdala and hippocampal volumes were regions of interest, as these are known structures from studies on meditation. Multivariable linear regression analysis and mixed linear models were performed adjusted for age, sex, educational level, intracranial volume, cardiovascular risk, anxiety, depression and stress.

Results: 15.7% of individuals participated in at least one form of practice. Those who performed meditation and yoga practices reported significantly more stress (mean difference 0.2 on a 1-5 scale, $p<.001$) and more depressive symptoms (mean difference 1.03 on CESD, $p=.015$), while 90.7% reported that doing their practice helped them in coping with stress. This indicates possible confounding by indication. Partaking in meditation and yoga practices was associated with a significantly lower right amygdala volume (β = -31.8 mm^3, $p=.005$), and lower left hippocampus volume (β = -75.3 mm^3, $p=.025$). Repeated measurements showed a significant effect over time on the right amygdala of practicing meditation and yoga (β = -24.4 mm^3, SE 11.3, $p=.031$).

Conclusions: Partaking in meditation and yoga practice is associated with more experienced stress while it also helps cope with stress, and is associated with smaller right amygdala volume.

Introduction

Mind-Body practices are becoming increasingly popular in both supporting medical treatment of chronic patients and prevention of disease in the healthy population [1,2]. Approximately 20% of the US population use mind-body practices, such as meditation and yoga, to gain a more active role in their health. Mindfulness for instance teaches awareness of bodily sensations of stress and of reaction patterns in a non-judgmental manner. Meditation and yoga have been shown to reduce anxiety, depression and stress, and to improve quality of life [3,4]. Unfortunately, there is no clear understanding of how these practices exert their positive effect. A recent meta-analysis showed that cognitive and emotional reactivity are the largest mediators underlying the improvements, together with mindfulness, rumination, self-compassion and psychological flexibility [5]. Previous neuroimaging meta-analyses on traditional meditation styles (i.e. Zen, Vipassana, Tibetan etc.) show that long term meditators consistently exhibit a different gray matter morphometry in several regions: the prefrontal cortex (PFC) (which is related to attentional processes), the sensory cortices and insula (related to body awareness), the hippocampus (related to memory processes), the cingulate cortex (related to self and emotion regulation), and the amygdala (related to the fight-flight response) [6-12]. A review on neuroimaging in yoga practitioners also showed decreased blood flow in the amygdala and increased activity in the prefrontal cortex, suggesting that practitioners do notice the negative stimuli, but are less affected by it [13].
The amygdala seems to be typically involved in stress and anxiety: related to instinct and the fight-flight reaction, it adds emotional value to sensory input [14] and functions as a pre-consciousness warning system [15]. Stress reduction has been associated with less amygdala volume [16], and research has found significant differences in amygdala activity and structure in connection with both training and pre-dispositional mindfulness [17-20]. So it seems that this neural structure could be affected by the stress reducing effects of meditation and yoga. The amygdala is of course part of an extended neural network [21]; earlier studies on the effect of meditation also showed a stronger connectivity between the ventromedial PFC and the amygdala, where the former down-regulated the activity of the latter [18,22] and an increase in activity in the hippocampus [17,23]. However, all these previous studies have been performed either in specific patient populations or in small samples of healthy, young volunteers. No study has yet been conducted in a large population-based setting. Doing so would give greater insight in practitioner characteristics in real-life, and whether these methods are effective in an uncontrolled population setting rather than a controlled clinical setting. Also it could give insight in practice associated mental health, and in underlying neuronal differences between practitioners and non-practitioners.
The current study investigates the effects of meditation and yoga on experienced stress levels, and whether these effects are associated with differences in amygdala volume in a large Dutch population-based sample of middle aged and elderly subjects.

Methods

Study population

The Rotterdam Study is an ongoing population-based cohort in the Netherlands that aims to investigate causes and determinants of diseases in elderly adults [24]. Recruitment began in 1990, and the current study population consisted of 14,926 subjects 45 years and older at baseline. The whole cohort undergoes physical and psychological re-examinations every two to three years. Since 2005, all participants of the Rotterdam Study without contraindications to Magnetic Resonance Imaging (MRI) are invited to undergo a brain MRI examination as part of the Rotterdam Scan Study, which aims to investigate causes and consequences of age-related brain changes [25].

For our study, we included individuals examined at the research center between 2008 and 2013. We included all participants that responded to a meditation and yoga practice questionnaire and had undergone an MRI of the brain (n = 3827). Diagnosis of clinical stroke, dementia and Parkinson were reason for exclusion (n = 34). After removing uninterpretable MRI scans, 3742 participants were included for the cross-sectional analyses. We also analyzed a subgroup that underwent multiple brain scans in the study period to see whether there was a difference in brain structure changes between the groups over time. For this we chose a time span of 5 years in between two scans to maintain comparability, and allocated participants to the practitioner group if they practiced for 5 years or longer (see Figure 1).

The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. Written informed consent was obtained from all participants.

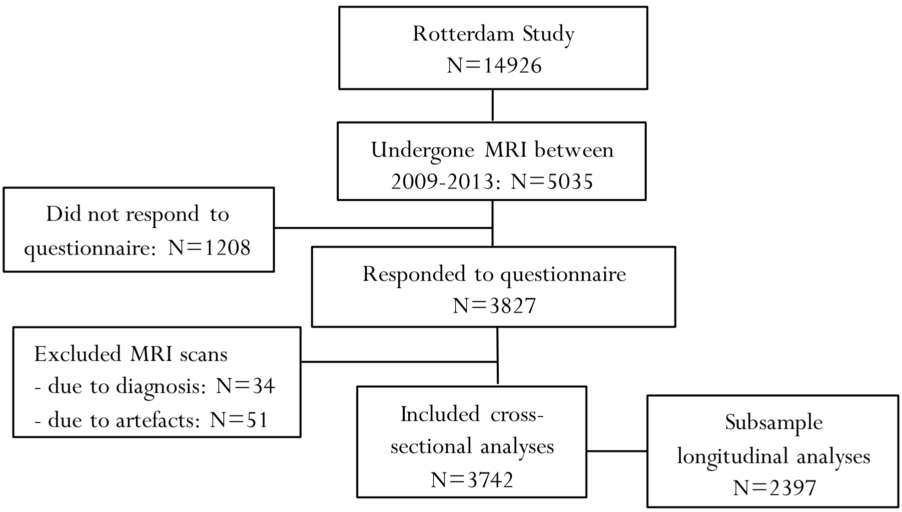

Figure 1. Flow chart of participant selection.

Measurement of meditation and yoga practices

During a one-time home interview, trained interviewers questioned individuals if they performed meditation and yoga practices, which were defined as 'looking for stillness inside oneself', 'meditation' or 'mindfulness' (captured in this article under 'meditation'), 'yoga', 'Tai Chi', 'Qi Gong' or 'similar movement therapy' (captured under 'yoga'), and relaxation or breathing exercises (referred to as 'breathing exercises'). As breathing exercises are such a core aspect of both meditation and yoga, this category is included without being named separately in this article. Additionally, the interview contained a question whether practicing this particular technique helped participants in coping with stress. The questionnaire also included the amount of time per week spent on the practice (0 hours, <1 hour, 1-2 hours, >2 hours), and the amount of years practicing. For the intervention group, a cut-off of at least one hour per week was chosen in order to assess the effect of practice, and at least one year of practice. Participants practicing less than one hour (N=239) were allocated to the control group.

Brain MRI acquisition and post-processing for amygdala volume

Brain MRI data were acquired with a 1.5-Tesla scanner (GE Healthcare, Milwaukee, Wisconsin) using an eight-channel head coil during a 30-minute brain imaging protocol that was previously described in detail [25,26]. Two trained technicians performed all examinations in a standardized way. This protocol included high-resolution axial fluid-attenuated inversion recovery (FLAIR), T1-weighted, and T2-weighted sequences. The T1-weighted image was used for amygdala segmentation and consisted of a 3D spoiled gradient-recalled echo (SPGR) scan, with voxel volume of 0.49 x 0.49 x 0.80 mm^3. Automatic segmentation of subcortical brain structures, including the amygdala left and right, was performed on T1-weighted images using Freesurfer software (version 4.5.0) [27]. This rendered volumetric measures of the amygdala gray matter (in mm3). Exact processing details are described elsewhere [28-30].

Co-variables

In order to assess the effect of meditation and yoga practice on amygdala volume we took demographic variables, total intracranial volume (ICV in mm3, derived from automated brain segmentation), cardiovascular risk factors and psychological functioning into account as variables that can otherwise affect brain structure measurements. Highest education achieved was categorized as "primary education", "lower and intermediate general education or lower vocational education", "intermediate vocational education or higher general education", or "higher vocational education or university", according to the UNESCO guidelines [31]. Cardiovascular risk factors that were taken into account were body-mass index (BMI), systolic and diastolic blood pressure, antihypertensive medication, total serum cholesterol, high density lipoprotein cholesterol, triglycerides, low-density lipoprotein-cholesterol calculated with the Friedewald Formula [32], diabetes mellitus, smoking and use of alcohol in the assessment of the amygdala volume, see for exact measurement methods elsewhere [33].

Smoking status was categorized as never, former, and current smoker. Alcohol use was categorized as never, regular use (>2-3 times per week at least 1 beverage), and occasional use (< 2-4 times per month at least 1 beverage).

Psychological functioning was assessed during home interviews with validated questionnaires and comprises measurements of stress, depression and anxiety. The level of experienced stress was assessed with a 1 item 5-point Likert scale ("how much stress do you experience on a scale from 1 (not at all) to 5 (very much)?"). Stress unfortunately was measured only once, so no longitudinal data was available. To identify current depressive symptoms, we used the Center for Epidemiological Studies Depression (CES-D) scale, a 20-item questionnaire which has been validated in a variety of populations [34]. Anxiety was measured with the seven anxiety items of the Hospital Anxiety and Depression Scale (HADS-A)[35]. These items are scored on a 4-point scale ranging from 0 (absence of the symptom) to 3 (extreme presence), the sum score indicates the anxiety level.

Statistical analysis

ANCOVA analyses were performed to compare characteristics of individuals in the intervention group compared to the control group. Apart from demographics, all other variables were adjusted for age, sex and education level. All imaging outcomes were also adjusted for ICV.

Subsequently, we conducted multivariable linear regression analyses to evaluate the effect of meditation and yoga practice on left and right amygdala volume. As literature indicates that cortical thickness increases with meditation practice [6,36,37], we also performed an analysis on the ratio between amygdala volume and total brain volume. On an exploratory basis we also looked at the prefrontal lobe and the hippocampus, structures that have been reported to be affected by meditation practice. To account for repeated measurements in the longitudinal analyses, linear mixed models were used adjusted for all covariables. 2% of values were missing, none of which concerned outcome variables. Multiple imputation was performed using 10 iterations with all variables as predictors. In the variables assessing how many years participants practiced their activity, missing values due to remembrance issues ("I don't remember how many years I have been practicing") were imputed by the median value of the group to account for right censoring. A p-value less than 0.05 was considered to indicate statistical significance. All data were analyzed with IBM SPSS Statistics version 21.0 [38].

Results

Participant characteristics

Mean age at the time of the MRI scan was 64.1 years (SD 7.7) and 55% were women. A total of 588 individuals (15.7%) reported engaging in any form of practice. Using a cut-off of 1 hour per week, meditation was the most often performed practice (N=159). 98 participants practiced yoga or similar movement therapy, and breathing exercises were done by 75 participants (Table 1). 43 individuals took part in more than one practice, so 289 unique participants were categorized to the intervention group of more than 1 hour per week. Compared to those who did not report partaking in meditation and yoga, individuals who did a form of practice were higher educated, significantly more often female (73%) and younger (61.9 years, SD 6.8) (Table 2). The median duration of practice in the intervention group was 10 years.

Table 1. Types of practice, mean duration and hours spent per week [a].

	Meditation	Yoga	Breathing exercises
N 0-1 hours per week	96	37	106
N 1-2 hours per week	83	69	36
N >2 hours per week	76	29	39
Mean duration, years (SD)	14.9 (15.5)	11.2 (10.6)	13.7 (13.2)
N (%)*	159	98	75

[a] Some participants performed more than one practice (e.g. both meditation and yoga. Unique N=289, unique total N=588). *Cut-off: practice 1 hour or more per week.

Meditation and yoga practices and mental health

Stress and depression were rated significantly higher among practitioners, while 90.7% of practitioners reported that doing their activities helped them cope with stress (5.5% reported it did not and 3.8% didn't know). Anxiety did not differ significantly between practitioners and non-practitioners. Looking at sub-groups, current depressive symptoms were rated significantly higher amongst meditators but not in yoga or breathing exercise practitioners, whereas stress was significantly higher in these groups and not in meditators.

Cross-sectional analyses: Meditation and yoga practices and amygdala volume

Total brain volume was larger in those practicing compared to controls, but not statistically significant (943.1 ml versus 940.4 ml, p-value = 0.32) (see Table 1). The left and right amygdala were smaller in the intervention group: left amygdala 1321.4 mm3 versus 1334.8 mm3 (age-, sex-, education- and ICV-adjusted, p-value = 0.21); and the right amygdala significantly so: 1386.8 mm3 versus 1415.8 mm3 (p = 0.01). The ratio between right amygdala and total brain volume was significantly smaller in practitioners than in non-practitioners (0.147% versus 0.151%, p-value = 0.001). Looking at subgroups, the right amygdala was smallest in the meditation group, whereas the left was smallest amongst the breathing participants. The yoga group had the largest amygdalae, though this difference was not statistically significant. The ratio between right amygdala and total volume was significantly smaller in the meditation and breathing group. The prefrontal lobe was not significantly different between groups and neither was the right hippocampus. The left hippocampus, however, showed to be significantly smaller in the practitioner group (3891.2 mm^3) compared to the control group (3958.1 mm^3), p=0.036.

Table 2. Characteristics of the study population.

	No Meditation and yoga practices (N=3453)	Meditation and yoga practices (N=289)
Mean age, years (SD)	64.3 (7.7)	61.9 (6.8)*
Women	53%	73%*
Highest education, score (SD)	1.7 (0.9)	2.0 (0.9)*
BMI (SD)	27.5 (4.3)	26.6 (4.4)*
SBP mmHg (SD)	139.7 (19.9)	138.3 (20.3)
DBP mmHg (SD)	83.2 (11.3)	82.9 (11.6)
Diabetes mellitus	8.3%	6.4%
HDL Cholesterol, mmol/L (SD)	1.5 (0.4)	1.5 (0.4)
LDL Cholesterol, mmol/L (SD)	3.7 (1.1)	3.8 (1.0)
Smoking score (SD)	0.43 (0.6)	0.45 (0.7)
Alcohol score (SD)	1.45 (0.6)	1.48 (0.8)
Stress (1-5), mean (SD)	2.0 (1.0)	2.2 (1.0)*
Depression, mean (SD)	5.2 (6.8)	6.2 (6.9)*
Anxiety, mean (SD)	15.8 (3.4)	15.4 (3.5)
Total brain, ml (SD)	940.4 (44.3)	943.1 (45.0)
Left frontal lobe, ml (SD)	163.4 (0.2)	163.8(0.6)
Right frontal lobe, ml (SD)	164.0 (0.2)	164.8 (0.6)
Left Amygdala, mm^3 (SD)	1334.8 (170.9)	1321.4 (173.5)
Right Amygdala, mm^3 (SD)	1415.8 (169.4)	1386.8 (172.0)*
Left hippocampus, mm^3 (SD)	3958.1 (511.3)	3891.2 (519.0)*
Right hippocampus, mm^3 (SD)	3959.6 (496.1)	3920.9 (503.5)

Analyses of lifestyle, cardiovascular risk factors and psychological measures were performed adjusted for age, sex and education level. Analyses of brain volumes were also adjusted for ICV. *: Significantly different ($p<0.05$). Groups are based on a cut-off of at least 1 hour per week practice. 1 ml = 1000 mm^3

Linear regression analyses of the left and right amygdala volume with adjustment for demographics, intracranial volume, cardiovascular risk and psychological functioning resulted in the models shown in Table 3. Practicing meditation or yoga compared to not was associated with lower right amygdala volume (β = -31.8 mm3, SE 11.2, p = .005). The left amygdala showed no significant effects (β = -14.5 mm3, SE 11.2, p = .192). The ratio between right amygdala and total brain volume was affected significantly (β = -.38%, SE .116, p = .001). Linear regression also showed that practice was associated with a smaller left hippocampus: β = -75.3 mm3, SE 33.6, p = .025. The right hippocampus and prefrontal lobe were not statistically significant.
Depression score was significantly correlated with right amygdala volume in the control group (r= -0.09, p<0.001), but not in the practitioner group (r= -0.10, p=0.078). Stress was not significantly correlated with right amygdala volume (r= -0.02, p=0.227), but it was with practice (r= 0.09, p<0.001). However, the amount of practice was not correlated with amygdala volume, depression or stress.

Table 3. Cross-sectional analyses. Association between meditation and yoga practice and different brain volumes (N=3742).

				95% Confidence Interval	
	β (mm^3)	SE	p-value	Lower	Upper
Total brain (mm^3)	1352.6	2922.0	.643	-4374.4	7079.6
Left frontal lobe (mm^3)	204.8	708.3	.772	-1183.4	1893.0
Right frontal lobe (mm^3)	686.0	712.0	.335	-709.5	2081.5
Left Amygdala (mm^3)	-14.5	11.1	.192	-36.3	7.3
Right Amygdala (mm^3)*	-31.8	11.2	.005	-53.8	-9.8
Left hippocampus (mm^3)*	-75.3	33.6	.025	-141.1	-9.5
Right hippocampus (mm^3)	-36.8	32.8	.262	-101.0	27.4

Regression analyses adjusted for age, sex, ICV, education, cardiovascular risk factors, depression, anxiety, and stress.
* Significantly different (p<0.05)

Longitudinal analyses

For analyzing structural change over time, 2397 participants were included who had MRI scans taken five years apart. In this sample, only 9% (N=218) practiced meditation or yoga for 5 years or longer. Linear mixed models adjusted for all covariates showed a significant interaction effect over time of practicing meditation and yoga on right amygdala volume (β = -24.4 mm3, SE 11.3, p = .031) (Table 4). The left amygdala did not show a significant effect (β = -11.6 mm3, SE 11.7, p = .32), nor did right and left hippocampus (β = -36.5 mm3, SE 37.4, p = .33 and β = -5.7 mm3, SE 40.5, p = .89 respectively). Depression scores showed an increase over 5 years with similar effects in practitioners and controls (0.6

and 1.0 on the CESD respectively, $p=.73$). Furthermore, elucidating the causal relationship between higher depression scores and smaller amygdala volume, there was no effect of right amygdala volume on CESD score ($\beta = -0.001$, SE 0.001, $p = .21$).

Table 4. Longitudinal analyses of the effect of meditation and yoga practice on volume over 5 years follow-up (N=2397).

Parameter	β (mm^3)	SE	p-value	95% Confidence Interval	
				Lower	Upper
Left amygdala	-11.8	11.7	.312	-34.7	11.1
Right amygdala*	-24.4	11.3	.031	-46.5	-2.3
Left hippocampus	-59.4	87.1	.495	-230.6	111.7
Right hippocampus	116.5	84.6	.169	-49.7	282.7

Linear Mixed models adjusted for age, gender, education, ICV, cardiovascular risk factors, depression, anxiety, and stress.
* Significantly different ($p<0.05$)

Discussion

In this large population-based study we demonstrated that individuals involved in meditation and yoga practice experienced higher stress levels, whereas brain imaging shows smaller right amygdala and left hippocampal volume compared to those not practicing. These results are in line with previous correlational research amongst healthy participants [19]. Practicing meditation and yoga had a significant effect over time on right amygdala volume, but not on left hippocampal volume.

Elucidating the causal pathways of meditation and yoga practice, stress and amygdala volume in this context is complex. Smaller amygdala volumes could indicate a vulnerability to stress/depression, though the results of our longitudinal analyses imply otherwise. Early life stressors seem to have an increasing effect in later life on amygdala volume, and a decreasing effect on hippocampal volume [39]. Also, depression has been associated with a larger right amygdala volume [16,40], where in the present study we observed that the meditation and yoga group had a smaller right amygdala. Stress reduction has been associated with less amygdala volume [16], and research has found significant differences in amygdala activity and structure in connection with mindfulness training [17,22,23,41,42].

The higher levels of stress and depressive symptoms in practitioners could also indicate the possibility of confounding by indication which can obscure the effect of meditation and yoga practice on psychological functioning [43]. Meditation and yoga practices are known for their stress-reducing intent, making it plausible that people experiencing stress make use of these strategies. Also there was a significant positive correlation between both stress and depression, and practice. This could mean that meditation and yoga lead to more stress and depression, or that more stress and depression lead to more practice. It could also mean that meditation and yoga practitioners may become more aware of their stress whereas at the same time they learn to cope better with stressful events, as 90% of practitioners reported that their practice helps them cope with stress. In cross-sectional research, this complex relationship between stress and meditation and yoga practice completely obscures the exact pathway meditation and yoga practice follows to a smaller amygdala. The longitudinal data showed an increase in depression over time but no difference between the groups, so the difference in the cross-sectional data seem to refer to confounding by indication.

Volumetric effects were only found in the right amygdala, not in the left. This is in line with previous smaller studies and is explained by the fact that the right amygdala, as opposed to the left amygdala, is associated with negative emotions and immediate action taking, whereas the left is associated with positive emotions and memory [44-46].

A number of limitations of this study deserve attention. Although performed in a very large population-based sample, this is still a selection of participants that are generally healthy and motivated to join research. The prevalence of meditation and yoga practice is slightly lower in this study population (15.7%) than in other studies (18.9%), where the latter population was notably younger [1]. It could be that people with a smaller right amygdala are naturally drawn to meditation and yoga practices. There is also risk of information bias since the questionnaire assessed amount of practice retrospectively. Also, stress was measured with a one-item Likert-scale instead of a validated questionnaire, which can increase the risk of information bias due to inaccuracy. Furthermore, this study contains mainly elderly individuals, who may not be as actively involved in meditation and yoga practices as younger people might, and who also might show a different structural response than younger participants due to decreased brain plasticity. Finally, this study took a broad approach to the intervention of interest: Practice involved meditation, yoga and breathing exercises, which in turn can comprise different styles.

Despite these limitations, the results do give direction for future research on the stress reducing effects of lifestyle interventions. Meditation and yoga practice are associated with structural differences in right amygdala volume and the vast majority of practitioners report that it helps them cope with stress. This suggests that meditation and yoga practices might be a feasible and accessible lifestyle intervention for people suffering from stress and stress-related diseases. Such practices could be helpful in prevention of stress-related diseases, by recognizing early stages of stress and changing the neural response to stressful stimuli.

Conclusion

Partaking in meditation and yoga practice is associated with more experienced stress while it also helps cope with stress, and is associated with smaller right amygdala volume.

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Part III

Mindfulness in cardiovascular disease

Chapter 5

Mind–body practices for patients with cardiac disease: a systematic review and meta-analysis.

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Abstract

Background: Due to new treatment modalities in the last decades, a decline in cardiovascular deaths has been observed. There is an emerging field of secondary prevention and behavioural programmes with increased interest in the use of mind–body practices. Until now, these have not been established in cardiovascular disease treatment programmes. Design: We performed a systematic review and meta-analysis of the available evidence on the effectiveness of mind–body practices for patients with diagnosed cardiac disease.

Methods: We included randomized controlled trials (RCTs), published in English, reporting mind–body practices for patients with diagnosed cardiac disease. EMBASE, MEDLINE, Pubmed, Web of Science, The Cochrane Central Register of Controlled Trials and PsycINFO were searched up to July 2013. Two reviewers independently identified studies for inclusion and extracted data on study characteristics, outcomes (Quality of Life, anxiety, depression, physical parameters and exercise tolerance) and quality assessment. Standardized effect sizes (Cohen's d) were calculated comparing the outcomes between the intervention and control group and random effects meta-analysis was conducted.

Results: We identified 11 unique RCTs with an overall low quality. The studies evaluated mindfulness-based stress reduction, transcendental meditation, progressive muscle relaxation and stress management. Pooled analyses revealed effect sizes of 0.45 (95%CI 0.20–0.72) for physical quality of life, 0.68 (95%CI 0.10–1.26) for mental quality of life, 0.61 (95%CI 0.23–0.99) for depression, 0.52 (95%CI 0.26–0.78) for anxiety, 0.48 (95%CI 0.27–0.69) for systolic blood pressure and 0.36 (95%CI 0.15–0.57) for diastolic blood pressure.

Conclusions: Mind–body practices have encouraging results for patients with cardiac disease. Our review demonstrates the need for high-quality studies in this field.

Introduction

Advances in medical treatment have resulted in a decline in mortality from cardiovascular disease (CVD).[1] CVD is, however, still the leading cause of death globally.[2] Furthermore, the decline in CVD mortality has led to an increase in prevalent CVD, requiring treatment and secondary prevention of more and more patients with documented disease.
Traditionally, secondary prevention has focused on well-established and modifiable risk factors, such as smoking, hypertension, diabetes, dyslipidaemia and physical inactivity. An emerging field is that of psychosocial risk factors (anxiety, depression and stress) in the aetiology and prevention of CVD.[3–5] Clinical trials studying modification of psychosocial risk factors in CVD have focused on the use of behavioural and psychological interventions in the setting of cardiac rehabilitation. Multiple studies show promising results of stress management on psychological outcomes and mind–body practices have become popular for stress reduction.[6] Commonly used in Eastern cultures for centuries, mind–body practices have more recently been making their way into Western lifestyle and clinical practice with currently almost 20% of the population routinely doing some form of mind–body practice.[7,8] Furthermore, evidence is accumulating that mind–body practices can be used as safe adjuncts to existing medical treatment and are effective in several conditions, such as insomnia, chronic pain, depression, post-traumatic stress, irritable bowel syndrome (IBS), hypertension and cardiovascular disease (CVD).[9–13]
Mind–body practices predate modern biomedicine but there is accumulating evidence on the connection between the mind and body.[14] The encouraging results on improved psychological well-being and measurable changes in physical parameters suggest that mind–body practices can be of added value in patients with CVD. The aim of this review was to evaluate the effectiveness of meditation-based mind–body practices on quality of life, anxiety, depression, physical parameters and exercise tolerance in patients with diagnosed cardiac disease.

Methods

Search strategy
Together with a professional librarian we conducted electronic searches through Embase, Medline, Pubmed, Web of Science (WoS), The Cochrane Central Register of Controlled Trials (CENTRAL) and PsycINFO of the literature published up to 31 July 2013. We reviewed mind–body practices with the focus on meditation and relaxation in patients with diagnosed cardiac disease[15] that could be taught without external biofeedback techniques. Practices considered included: (transcendental) meditation, mindfulness meditation, autogenic training and relaxation methods. The diagnosed cardiac diseases included were: heart failure, ischaemic heart disease, hypertensive heart disease, inflammatory heart disease, valvular heart disease, congenital heart disease and cardiomyopathy. The search included

keywords corresponding to the mind–body techniques and cardiac diseases. To optimize the search strategy, we used synonyms including 'text words' and MeSH (Medical Subject Headings) (Appendix A, see online Supplementary Material). We screened for other potentially relevant randomized controlled trials by searching through the references and citation lists from identified papers meeting our inclusion criteria.

Study selection

Two reviewers (JY and CB) independently selected all potential studies, which were identified through the results of our search strategy. Disagreements were resolved by consensus. We included relevant studies if they met the following criteria: (1) written in English; (2) study design was a randomized controlled trial (RCT); (3) study population with diagnosed cardiac disease; (4) the mind–body practice was compared to standard care, pharmacological intervention, psychological intervention or no treatment at all; (5) at least one of the following clinically relevant outcomes was assessed – any form of Quality of life (QoL) measurement as described by Ski et al.[16] and Wenger et al.[17] including subjective health status and health-related QoL, mental health scales on anxiety or depression, physical parameters (blood pressure and heart rate) or exercise tolerance (measured by 6-minute walk test or cardiopulmonary exercise testing). We selected studies reporting both objective and physiological outcomes because in cardiac disease especially, physiological parameters are good indicators of overall physical well-being. Several studies show the hypothesis and rational of mind–body interaction. We know that hypertension is one of the major risk factors of cardiovascular morbidity and mortality.[18] The prevalence of hypertension is projected to increase to about 60% in 2025.[19] Conventional medical treatment may be associated with various adverse effects,[20] especially in cases of multiple drug use and treatment-resistant hypertension, which has led to investigations of the supporting role of non-pharmacological interventions. We chose to limit our search to English written studies based on two reports, which showed no systematic bias with the use of a language restriction.[21,22] We excluded studies if they met one of the following criteria: (1) the article was a review or meta-analysis; (2) data were from abstracts or letters; (3) studies that evaluated psychological or psychosocial interventions focusing on interactions between people; (4) studies in which the mind–body practice was not the main area of interest; (5) studies that evaluated stress management with a major cognitive component; (6) studies evaluating practices using an external biofeedback technique; and (7) studies that evaluated practices performed during the peri-operative phase.

Data extraction

Data from studies were extracted independently by two authors (JY and RG) using a data extraction form in accordance with the Cochrane handbook of systematic reviews.[23] The following information was obtained using this form: author, journal, year of publication, country, setting, funding, number of patients, cardiac diagnosis, mean age, gender, comorbidity, use of medication, type of mind–body practices, details of the practices, comparators, follow-up duration, outcome definition, unit of measurement, pre- and post-outcome measurements on exercise tolerance, QoL, anxiety, depression, blood pressure and heart rate. If more than one practice or control arm was present, we included only the mind–body practices versus the control group. Disagreements were resolved by consensus. If data were unclear or unavailable, the authors were contacted by email. In case of multiple publications from one source, we only included data from different papers if different outcomes were reported. Resting heart rate and blood pressure results were used and not values measured during the relaxation practice.

Quality assessment

Two reviewers (JY and RG) independently scored the methodological quality of each study by using the Cochrane Collaboration 'risk of bias' tool[23] in which the following domains are considered: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other sources of bias. The judgment is categorized as follows: A. 'Low risk' of bias. B. 'High risk' of bias. C. 'Unclear risk' of bias. Additionally, the heterogeneity between studies was reported and the PRISMA statement for reporting systematic reviews and meta-analysis was used for reporting of results.[24] Disagreements were resolved by consensus. Small sample size can lead to bias but no formal agreement exists on how large the sample size of a study should be to limit the risk of bias. Consensus between JY and RG led to the cut-off point of 30 participants per study to score the study at high risk of 'other bias' due to their small sample size.

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Data synthesis and analysis

To analyse the maximum treatment effect we used data of post-treatment values on the pre-defined outcome measurements. If multiple follow-up data were available, we used the outcome assessment at the end of the intervention period in order to determine the maximum treatment effect. If multiple follow-up data were unavailable we used the data as reported. We calculated the Cohen's d effect size, comparing the intervention and control groups, of the means and confidence intervals according to the equations as shown in Appendix B (see online Supplementary Material). Data for each outcome were summarized in forest plots, and random effects models were used to calculate summary estimates with 95%CI. Funnel plots were constructed to check for the presence of publication bias. Of the eight domains of the Short-Form Health Survey-36, we present the summary measures of the Physical and Mental Component Score (PCS and MCS respectively). QoL measures were grouped according to their subscale (i.e. physical, mental/emotional or other). If more than one QoL measure was reported (i.e. The Short-Form Health Survey 36 (SF-36) and the Minnesota Living With Heart Failure Questionnaire (MLWHFQ)), the SF-36 was used over the other measures in the random effects meta-analysis.

Results

Study selection

Our literature search resulted in 1487 studies, 1485 from the original search and two from reference lists (Figure 1). Of these, 551 studies were excluded because they were duplicates and 902 studies were excluded when title and abstract were reviewed. Of the 34 studies selected for full text review, 21 were excluded for not meeting the predefined inclusion criteria (Figure 1).

Finally, 13 RCTs, consisting of 11 unique studies, met our inclusion criteria and were included in this review. They were published between 1996 and 2012 and were carried out in six different countries (UK, USA, China, Brazil, India and Portugal).

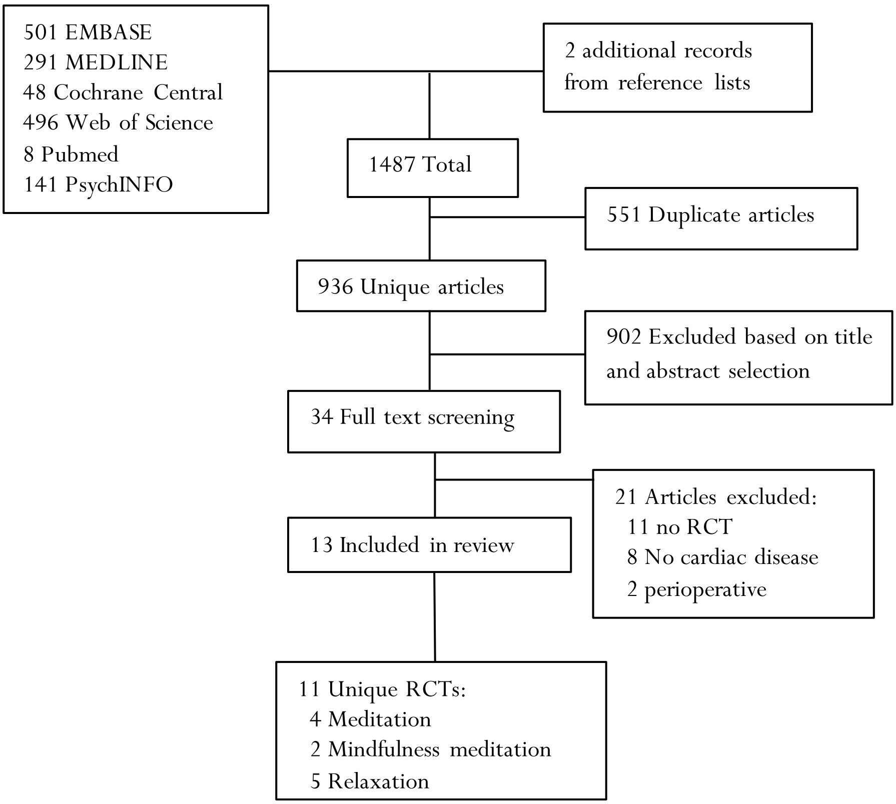

Figure 1. Flow diagram of identified studies.

General characteristics

The characteristics of interventions and patients are presented in Table 1. The studies included 793 unique patients (46% female) with a mean age of 66 (11 years). The studies ranged in sample size from 18 to 201 patients. There were two cases of duplicate reports on the same patient population.[25,26] One study did not fully report its baseline characteristics.[27]

Table 1. Study characteristics of included randomized controlled trials.

Author (year)	Study location	Cardiac diagnosis	Age (SD)	% Female	N
Trzcieniecka-Green (1996)	UK	AMI/CABG	60 (10)	13	100
Wilk (2002)	USA	CABG/MI/ Angioplasty	63 (NR)	14	14
Tacon (2003)	USA	Cardiac[a]	61 (9)	100	18
Robert-McComb (2004)	USA	Cardiac[a]	61 (8)	100	18[b]
Curiati (2005)	Brazil	HF	75 (7)	74	19
Chang (2005)	USA	HF	70 (14)	0	63
Paul-Labrador (2006)	USA	CAD	67 (14)	18	103
Jayadevappa (2007)	USA	HF	64 (11)	61	23
Yu (2007)	China	HF	76 (8)	51	121
Yu (2009)	China	HF	76 (8)	51	121[b]
Neves (2009)	Portugal	CAD	60 (15)	85	81
Schneider (2012)	USA	CAD	59 (15)	43	201
Nehra (2012)	India	CHD	NA	NA	50
All			66 (11)	51	743[b]

AMI acute myocardial infarction; CABG coronary bypass artery grafting; CVD cardiovascular disease; CAD coronary artery disease; HF heart failure; CHD coronary heart disease; NA not available. [a] Patients diagnosed with angina pectoris, valvular disease, hypertension or CAD. [b] 743 unique patients.

Patients

Most studies included patients with heart failure (N=5),[26,28–31] or coronary artery disease (N= 4).[27,32–34] One study only recruited heart failure patients after optimal medical treatment and at least two months of carvedilol therapy.[29] Two studies included patients following AMI, angioplasty or CABG, when considered in a stable condition (2–3 months post-surgery or percutaneous intervention).[35,36] Two studies included various diagnoses including angina, hypertension, valve disorders and coronary artery disease.[25,37]

Interventions

The included studies compared the effects of different mind–body practices with various control interventions. The mind–body practices studied were: mindfulness based stress reduction,[25,27,37] transcendental meditation,[30,33,34] meditation (which consisted of three components: breathing, mental repetition of a word and a guided image),[29] progressive muscle relaxation training,[26,31,36] relaxation response (which consisted of eight different components: breathing awareness; mental repetition of a word, sound, phrase or prayer; mindfulness meditation; guided body scan; progressive muscle relaxation; guided countdown; autogenic and guided imagery),[28] relaxation,[32] and stress management (based on autogenic training).[35] Further details and the content of the interventions are shown in Table 2. Two studies evaluated a mind–body practice in addition to regular cardiac rehabilitation compared to cardiac rehabilitation alone.[32,36] The duration of the interventions ranged from 4 to 26 weeks. One study did not provide the duration of the intervention.[34] All but one study[32] gave daily home exercises by audiotape or instructions. In one study the trial was conducted in two parts due to a hiatus in funding.[34]

Control intervention

The control interventions used were: waiting list,[25,35,37] usual care (in which the patients were expected to solely attend the two moments of study outcome assessment and were not invited to group sessions),[27,28] attention control (extra attention by phone calls to balance the effect of the extra attention that patients received in the PMRT training).[13,26,31] Some studies made comparisons with an active intervention, such as health education[30,33,34] or cardiac rehabilitation.[32,36] One study had weekly talks on stress management.[29] The study by Chang et al.[28] used two control groups (education and usual care) of which we present only the usual care.

Table 2. Details of interventions in included studies.

Intervention						
Author	Year	Name	Details	Home assignments	Duration (weeks)	Control goup
Trzcieniecka-Green	1996	Stress management	Weekly sessions	Audiotape on relaxation, twice daily	10	Waiting list
Wilk	2002	Progressive muscle relaxation (+Cardiac rehabilitation)	50 minute weekly sessions	Audiotape on PMR	4	Cardiac rehabilitation
Tacon	2003	Mindfulness based stress reduction	Two-hour weekly sessions	Audiotape, daily	8	Waiting list
Robert-Mccomb	2004	Mindfulness based stress reduction	Two-hour weekly sessions	Audiotape, daily	8	Waiting list
Curiati	2005	Meditation	Two classes 1hour introduction	Audiotape	12	Weekly talks
Chang	2005	Relaxation response	Weekly 90 min group sessions	Audiotape	15	Usual care
Paul-Labrador	2006	Transcendental meditation	Introduction week, one month of biweekly meetings, weekly thereafter	Daily home assignments	16	Health education
Jayadevappa	2007	Transcendental meditation	Seven days introduction, 3 months biweekly meetings, 3 months monthly meetings	Twice daily, 20 minutes of TM	26	Health education
Yu	2007	Progressive muscle relaxation (grade 2)	One-hour weekly sessions, biweekly phone calls, skill skill revision at 4 weeks	Audiotape	14	Attention control (phone calls)
Yu	2009	Progressive muscle relaxation	One-hour weekly sessions, biweekly phone calls, skill skill revision at 4 weeks	Audiotape	14	Attention control (grade 2) (phone calls)
Neves	2009	Relaxation (+ Cardiac rehabilitation)	3 one-hour weekly sessions after cardiac rehabilitation session	None	10	Cardiac rehabilitation
Schneider	2012	Transcendental meditation	Introduction week, 1 month weekly meetings, 2 months biweekly meetings, monthly meetings thereafter	Twice daily, 20 minutes of TM	n/a	Health education
Nehra	2012	Mindfulness based stress reduction	Eight weekly individual 150 minutes sessions and one 7 hour weekend session and extended MBCT	Yes	10–17	Usual care

PMR, progressive muscle relaxation; TM, transcendental meditation; MBCT, mindfulness-based cognitive therapy.

Risk of bias

The risk of bias of included studies is shown in Table 3. Due to the nature of the intervention, none of the studies was able to blind the participants and personnel teaching the intervention. Blinding of the outcome assessor is possible and was included in Table 3. Furthermore, the presence of small groups often made the risk of other bias inevitable.

Random sequence generation Five studies reported the randomization procedure used.[26–28,30,31,33] The other studies did not provide enough information to judge which randomization procedure was used and were classified as 'Unclear risk'.
Allocation concealment Only three studies reported allocation concealment.[30,33,34] Most studies failed to state clearly how randomization had been achieved and were judged as 'Unclear risk'.
Blinding of participants, personnel and outcome assessment The outcome assessor was blinded in five studies.[26,30,31,33,34] In one study the outcome assessor was also the instructor of the intervention making blinding to the outcome impossible.[36] In the other studies the assessment procedure of the outcome was unclear.
Addressing incomplete outcome data Almost all studies reported missing data whereas three studies did not.[26,31,35] Eight studies reported adequate information about how many participants had withdrawn after having consented to participate.
Selective reporting Most studies reported outcomes that were predefined in the methods section and were thus judged as low risk of selective reporting bias. In three studies the risk of selective reporting was considered high since some of the outcomes mentioned in the methods section were not reported.[25,27,37] Furthermore, one study failed to provide enough statistical data (i.e. standard deviations were missing).[36]
Other bias We considered other sources of bias to be present if the study included a small sample size ($n < 30$), was reported to be underpowered, or minimal or no group comparison at baseline was reported. Almost all studies had a small sample size. Only four studies included 100 or more patients.[26,31,33,35]

Heterogeneity across studies Overall, based on the clinical diversity of the included patients in the studies (Table 1), the methodological diversity in study design and risk of bias (Table 3) and the statistical heterogeneity of outcomes reported, we conclude there is significant heterogeneity across studies.

Publication bias. Funnel plots of the subjective and physiological outcomes were constructed and are shown in Appendix C (see online Supplementary Material). Overall, the funnel plots show no clear evidence of publication bias.

Table 3. Risk of bias in included studies.

Author (year)	Random sequence generation	Allocation concealment	Blinding of patient and personnel	Incompl outcome data adressed	Selective reporting	Other bias
Trzcieniecka-Green (1996)	?	?	-	?	-	?
Wilk (2002)	?	?	-	-	?	-
Tacon (2003)	?	?	-	?	+	-
Robert-McComb (2004)	?	?	-	?	+	-
Curiati (2005)	?	?	-	?	+	-
Chang (2005)	+	?	-	?	+	-
Paul-Labrador (2006)	+	+	-	+	+	?
Jayadevappa (2007)	+	+	-	+	+	-
Yu (2007)	+	?	-	+	-	+
Yu (2009)	+	?	-	+	-	+
Neves (2009)	?	?	-	?	+	?
Schneider (2012)	?	+	-	+	?	-
Nehra (2012)	+	?	-	?	+	-

Subjective outcomes

Quality of Life. Six RCTs reported quality of life outcomes assessed with five different questionnaires. Results measurements used are presented in Table 4. Pooled effect sizes of the physical QoL measures revealed an overall medium statistically significant effect size of d=0.45 (95% CI 0.18–0.72) and an overall medium statistically significant effect size of d=0.68 (95%CI 0.10–1.26) for mental scores (Figure 2). The other subscales showed a small non-significant effect of d=0.25 (95%CI -0.10–0.61). The results were mainly influenced by the large study of Yu et al.[26]

Depression. Depression was assessed with only two instruments: the Center for Epidemiologic Studies Depression Scale (CESD) and the Hospital Anxiety and Depression scale (HADS). Depression was reported in six studies. The study by Schneider et al.[34] consisted of repeated measurements over a period of 5.4 years. The depression outcomes revealed an overall medium statistically significant effect size of d=0.61 (95% CI 0.23–0.99) (Figure 3). Results were heterogeneous with small effects of d=0.14 in the study by Schneider et al.[34] and large effects of d=1.25 in the study of Yu et al.[31] (Figure 3).

Anxiety. Anxiety was reported in five studies. An overall medium statistically significant effect of 0.52 (95% CI 0.26–0.78) was found (Figure 3). Again, results were heterogeneous with small effect sizes ranging from d=0.31 in the study of Paul-Labrador et al.[33] to large effects of d=1.34 in the study of Tacon et al.[37] (Figure 3).

Table 4. Type of outcome in included studies (methods).

Author (year)	Outcome	Type of scale	Moment of assessment (weeks)
Trzcieniecka-Green (1996)	QoL, anxiety, depression	GWB, HADS	0, 10, 26
Wilk (2002)	Anxiety, DPB, SBP, HR	STAI	0, 4
Tacon (2003)	Anxiety	STAI	0, 8
Robert-McComb (2004)	QoL	SF-36	0, 8
Curiati (2005)	QoL, exercise tolerance, DPB, SBP, HR	MLWHFQ, VO2max	0, 14
Chang (2005)	QoL, exercise tolerance	MLWHFQ, VO2max	0, 14-19
Paul-Labrador (2006)	Anxiety, depression, DBP, SBP	STAI, CESD	0, 16
Jayadevappa (2007)	QoL, depression, exercise tolerance	SF-36, MLWHFQ, QWB, CESD, 6MWT	0, 12, 26
Yu (2007)	Anxiety, depression	HADS	0, 8, 14
Yu (2009)	QoL	WHOQOL-BREF	0, 8, 14
Neves (2009)	DBP, SBP, HR		0, 12
Schneider (2012)	Depression, DBP, SBP, HR	CESD	0, 12, 26
Nehra (2012)	Anxiety, depression	HADS	0, 10-17

QoL quality of life; GWB general well-being; HADS Hospital Anxiety and Depression Scale; DBP diastolic blood pressute; SBP systolic blood pressure; HR heart rate; STAI State-Trait Anxiety Inventory; SF-36 36-item Short Form Health Survey; MLWHFQ Minnesota Living with heart failure questionnaire; HRV heart rate variability; CESD center for epidemiologic studies depression scale; QWB quality of well-being; 6MWT six-minute walk test; WHOQOL-BREF world health organization quality of life-BREF.

Physiological outcomes

Resting blood pressure. Blood pressure was reported in five RCTs. Due to missing SDs no effect size with 95% CI could be calculated for Wilk et al.[36] Effect sizes for SBP ranged from small effects of d=0.42 in the study of Schneider et al.[34] to a large effect of d=1.10 in the study of Curiati et al.[29] (Figure 4). The meta-analysis resulted in an overall medium statistically significant effect of d=0.48 (95% CI 0.27–0.69). Effect sizes for DBP showed a similar heterogeneous pattern with results of d ranging from 0.25 in the study by Schneider et al.[34] to 0.80 in the study by Curiati et al.[29] Results showed an overall lower, but statistically significant, effect than the SBP results (0.36, 95% CI 0.15–0.57) (Figure 4).
Resting heart rate. Four RCTs reported on resting heart rates (Figure 4). Wilk et al.[36] reported that a significant difference was found but no effect size with 95% CI could be calculated due to missing SDs. An overall small effect of d=0.15 (95%CI -0.08– 0.39) was found. All studies showed small effects of d ranging from 0.13 to 0.20 (Figure 4).
Exercise tolerance. Only three studies reported exercise tolerance as outcome (Table 5).[28–30] No effect size could be calculated for Wilk et al.[36] due to missing SDs. A medium effect of d=0.51 was seen for VO2 max testing and a large effect of d=1.04 was seen on the six minute walk test in the study of Jayadevappa et al.[30] (Table 5).

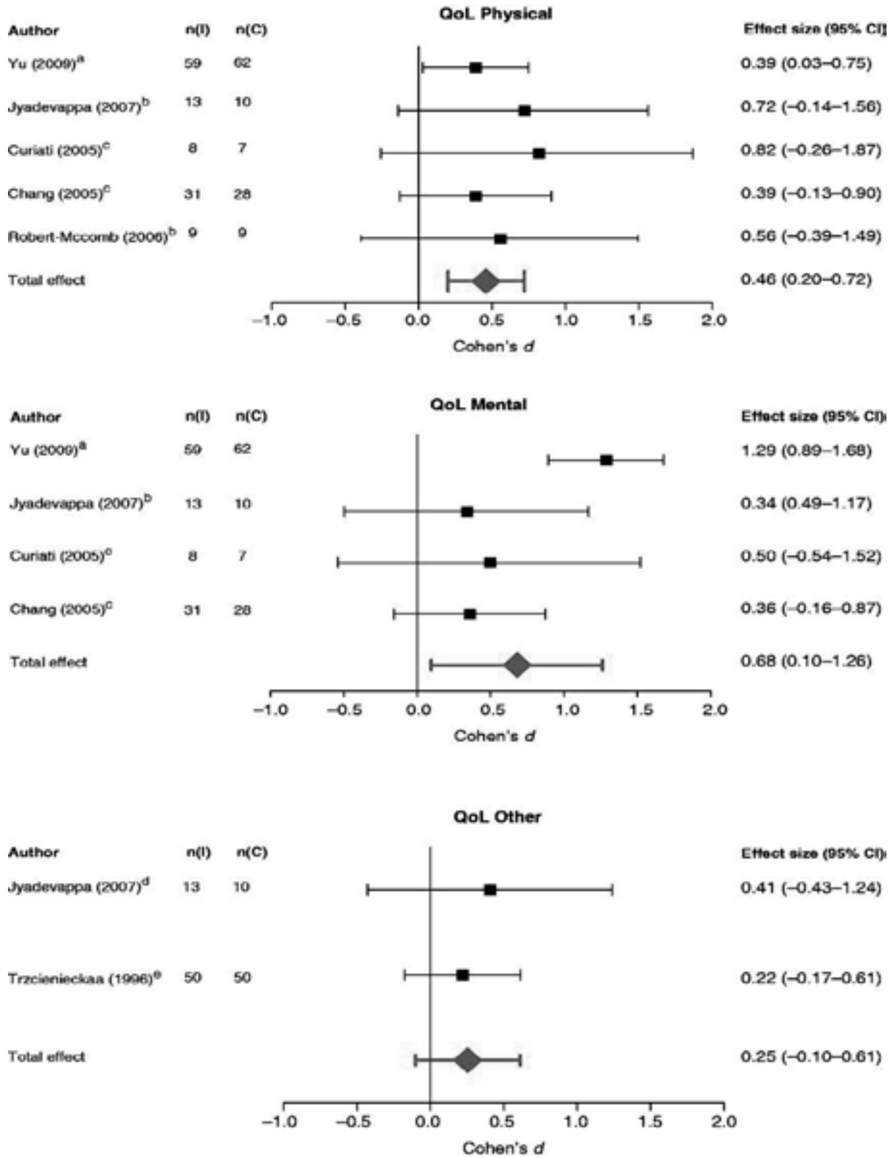

Figure 2. Forest plot of QoL results.
CI, confidence interval; n(I), number of patients in intervention group; n(C), number of patients in control group. aWHOQOL-BREF-HK, World health Organization Quality of Life Hong Kong version. bSF-36, Short-Form Health Survey 36. cMLWHQ, Minnesota Living With Heart Failure Questionnaire. dQWB, Quality of Well-Being. eGWB, General Well-Being.

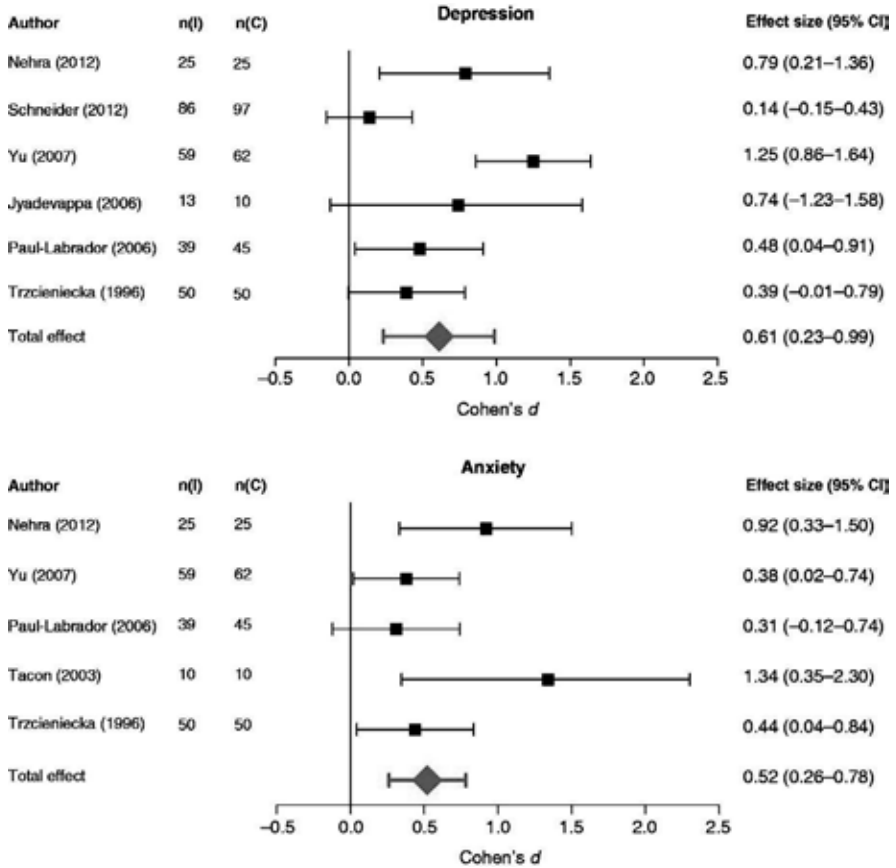

Figure 3. Forest plots of depression and anxiety.
n(I), number of patients in intervention group; n(C), number of patients in control group; CI, confidence interval.

Table 5. Results of studies that reported exercise tolerance.

Author (year)	Intervention (N)	Control (N)	Effect size (95%CI)[b] Exercise tolerance	Exercise test
Curiati (2005)	8 (5)[a]	7 (5)[a]	0.51 (-0.75-1.77)	VO2max
Chang (2005)	31	28	N/A	VO2max
Jayadevappa (2007)	13	10	1.04 (0.15-1.91)	6MWT

CI confidence interval; N/A not applicable; 6MWT six minute walk test
[a]Five patients did VO2max testing. [b] effect size is Cohen's d

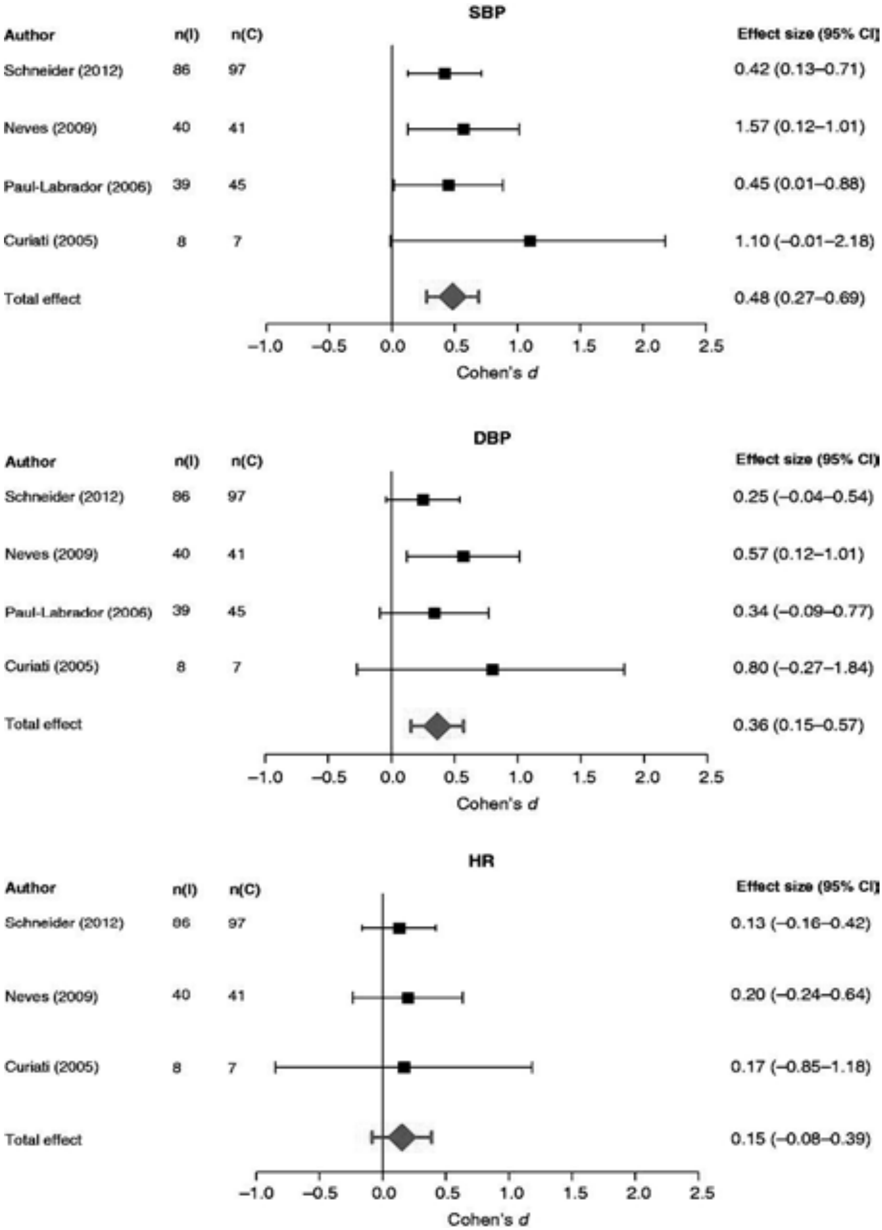

Figure 4. Forest plots of physiological parameters.

SBP, systolic blood pressure; n(I), number of patients in intervention group; n(C), number of patients in control group; CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate.

Discussion

The eleven unique studies in this review had an overall low quality and used a variety of outcome measurements. There was some evidence for the effectiveness of mind–body practices for patients with diagnosed cardiac disease. Promising but heterogeneous results were seen on overall effect sizes of mental and physical QoL, anxiety, depression and blood pressure.

There are several reasons why patients engage in mind–body practices. Firstly, these therapies are easy to learn and they allow patients to take a more active role in their treatment. Secondly, most exercises can be done at home without the help of external means. Thirdly, low emotional and physical risk is involved. Finally, the costs are relatively low [38–40]. Although mind–body practices require commitment in both adherence and time, they are becoming more and more popular.[7, 8] Studies on the effectiveness of mind–body practices in CVD have shown some promising results. They improved psychosocial risk factors, reduced blood pressure and even showed survival benefits.[41–44] It is hypothesized that patients with CVD are more likely to seek additional treatment since psychological stress, whether cause or consequence, often accompanies their clinical condition.[45,46] Stress can cause an imbalance between the mind and body, and several studies suggest stress is related to CVD at several stages of the disease from the development of arteriosclerosis to acute cardiac events to chronic disease.[5,47] Furthermore, other studies have shown associations between psychosocial variables and vascular function, inflammation and increased blood clotting.[48–50] Thus, although the precise pathophysiological mechanism still needs to be unraveled, it is clear that a relationship exists between stress and CVD. Many biological pathways have been studied that could explain the working mechanism of mind–body practices. Several studies show positive physiological effects in blood pressure, heart rate, respiration rate and oxygen consumption with mind–body practices.[10,51] Three studies showed that the autonomic nervous system releases endorphin and serotonin, which leads to counteraction of norephinephrine and activates the parasympathetic response.[10,12,51] In a small study on the effect of yoga and meditation on endothelial function, favourable changes were observed in endothelial-dependent vasodilatation in CAD patients.[44] A mechanism illustrating how mind–body practice can have influence on health is provided by research on the interaction between the central nervous system (CNS) and the endocrine, immune and peripheral autonomic nervous systems.[52] There is also evidence for a positive effect on the immune system and endothelial functioning.[51,53,54] All together, these studies show the profound effects of stress reduction and meditation techniques on the body, suggesting that the mind may be able to influence the working of the heart.

Until now, a core component in the treatment of CAD patients is cardiac rehabilitation with the components exercise training, healthy nutrition and smoking cessation.[55] Lifestyle modification programmes have been shown to be of added value in treating patients with CAD.[56] These interventions have proven to be favourable for physical and psychosocial risk

factors and also showed a survival advantage.[57–59] Additional stress management has been shown to have additional value in cardiac rehabilitation programmes.[60,61] Even though the American Heart Association (AHA) has recognized the importance of psychosocial interventions as a core component in cardiac rehabilitation programmes,[62] these interventions have only been integrated in a limited number of settings. Furthermore, only 25–31% of eligible patients participate in these comprehensive programmes.[63]
Some limitations of this systematic review must be addressed. Firstly, we limited our search strategy to English studies exclusively, with no consideration of studies conducted in the East – for example written in Chinese – from which mind–body practices originate. Secondly, we focused primarily on meditation-based mind–body practices that could be undertaken by patients at home without external tools. Therefore, no conclusions can be drawn on the effect of other mind–body practices in CVD. The connection between the mind and heart is a complex phenomenon and the use of meditation-based mind–body practices is still limited in clinical practice. Clearly, the role of mind–body practices in the advanced treatment of cardiac patients still needs to be defined. Behavioural cardiology is an emerging field that is bringing about awareness of the mind–heart connection and the management of psychosocial risk factors.[57]
However, current evidence on the efficacy and effectiveness of most mind–body practices has not been established due to a lack of well-performed randomized clinical trials. Mind–body research has several drawbacks that can hamper the internal validity and generalizability of published studies. A paper by Caspi et al.[64] showed several important features to consider in meditation research such as monitoring, assessment procedures, integration of qualitative methods and a pragmatic design. Most of the studies included in this review failed to provide detailed information on the randomization procedure and a study protocol was often not available. Furthermore, most studies lacked power and were too small to draw firm conclusions from. Until now, there is no clear understanding of the study design in mind–body research and future methodological studies should provide guidance.

Conclusions

In our review we showed that mind–body practices have encouraging results for patients with cardiac disease on selected QoL outcomes, anxiety, depression and blood pressure. Due to an overall low quality of studies, no firm conclusions can be drawn. Future clinical trials should focus on using a rigorous study design in order to minimize methodological flaws and enhance their validity and generalizability.

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Chapter 6

The effectiveness of yoga in modifying risk factors for cardiovascular disease and metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials.

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European Journal of Preventive Cardiology (2014).

Abstract

Background: Yoga, a popular mind-body practice, may produce changes in cardiovascular disease (CVD) and metabolic syndrome risk factors.
Design: This was a systematic review and random-effects meta-analysis of randomized controlled trials (RCTs).
Methods: Electronic searches of MEDLINE, EMBASE, CINAHL, PsycINFO, and The Cochrane Central Register of Controlled Trials were performed for systematic reviews and RCTs through December 2013. Studies were included if they were English, peer-reviewed, focused on asana-based yoga in adults, and reported relevant outcomes. Two reviewers independently selected articles and assessed quality using Cochrane's Risk of Bias tool.
Results: Out of 1404 records, 37 RCTs were included in the systematic review and 32 in the meta-analysis. Compared to non-exercise controls, yoga showed significant improvement for body mass index (0.77 kg/m^2 (95% confidence interval 1.09 to 0.44)), systolic blood pressure (5.21 mmHg (8.01 to 2.42)), low-density lipoprotein cholesterol (12.14 mg/dl (21.80 to 2.48)), and high-density lipoprotein cholesterol (3.20 mg/dl (1.86 to 4.54)). Significant changes were seen in body weight (2.32 kg (4.33 to 0.37)), diastolic blood pressure (4.98 mmHg (7.17 to 2.80)), total cholesterol (18.48 mg/dl (29.16 to 7.80)), triglycerides (25.89 mg/dl (36.19 to 15.60), and heart rate (5.27 beats/min (9.55 to 1.00)), but not fasting blood glucose (5.91 mg/dl (16.32 to 4.50)) nor glycosylated hemoglobin (0.06% Hb (0.24 to 0.11)). No significant difference was found between yoga and exercise. One study found an impact on smoking abstinence.
Conclusions: There is promising evidence of yoga on improving cardio-metabolic health. Findings are limited by small trial sample sizes, heterogeneity, and moderate quality of RCTs.

Introduction

Background

Cardiovascular disease (CVD) and metabolic syndrome are major public health problems in the USA and worldwide.[1,2] Metabolic syndrome is defined as having at least three metabolic risk factors – increased blood pressure, high blood sugar level, excess body fat, and abnormal cholesterol levels – and greatly increases the chance of future cardiovascular problems.[3] Lifetime risk of CVD is substantial as estimated through risk functions like those from the Framingham Heart Study,[4] underlining the need for prevention and control of risk factors.

CVD and metabolic syndrome share many of the same modifiable risk factors. Several guidelines name physical inactivity, the fourth leading risk factor of global mortality,[5] as an important modifiable risk factor for CVD and metabolic syndrome.[6–8] They state that regular and adequate levels of physical activity in adults can reduce the risk of hypertension, coronary heart disease, stroke, diabetes, and can help maintain a healthy weight. Yoga, an ancient practice from India that incorporates physical, mental, and spiritual elements, may be an effective form of physical activity.

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Yoga therapy

In recent years, clinical literature has reported cardiovascular health benefits from mind-body therapies.[9–11] Yoga, one type of mind-body therapy, has been increasing in popularity in the USA and in many parts of the world. Yoga, meaning ‘‘union’’ in Sanskrit, incorporates physical, mental, and spiritual elements. In the West, Hatha yoga, one style of yoga, has been most commonly practiced. Hatha yoga consists of a series of physical exercises that focus on stretching and stimulating the spine and muscles in coordination with breath control, thought to stabilize the hypothalamic-pituitary-adrenal axis and sympathoadrenal activity.[12–14] According to the 2007 National Health Interview Survey, about 20% of the US population used some form of mind-body practice.[15] Another study estimates that about 15 million adults in America report having practiced yoga at least once in their life,[16] seeking wellness or treatment for specific health conditions.

Rationale

A 2005 Cochrane study reviewed the evidence of yoga for secondary prevention of coronary heart disease on mortality, cardiovascular events, hospital admissions, and quality of life and found no randomized controlled trials (RCTs) meeting its inclusion criteria.[17] Another review done in 2005 examined CVD clinical endpoints and insulin resistance with observational studies, uncontrolled trials, and nonrandomized controlled trials and found improvements in insulin resistance syndrome with yoga.[13] Other reviews have shown yoga to be beneficial in treatment of coronary heart disease, post-myocardial infarction rehabilitation, and hypertension.[11,13,18–22] Since this time, several new RCTs have been published. We sought to comprehensively review recent RCT evidence of the effectiveness of yoga on these risk factors and provide a pooled quantitative measure.

Objectives

Our objectives were (a) to identify and systematically evaluate the evidence on the effectiveness of yoga for modifying risk factors for CVD and metabolic syndrome in adult populations using published systematic reviews, (b) to update the evidence by conducting a systematic review of recent RCTs and (c) to estimate a summary measure of effectiveness by conducting a meta-analysis of the evidence of yoga's effectiveness versus no-exercise and exercise controls.

Methods

Data sources and search terms

The protocol for this review has been published on the PROSPERO website (http://www.crd.york.ac.uk/PROSPERO) with the registration number CRD42013006375. An amendment was added to the protocol including an exercise control group and published in an online revision note. Articles in this review were identified by accessing the following biomedical electronic databases with the assistance of a medical librarian: MEDLINE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, EMBASE, and PsycINFO. Using existing published systematic reviews (SRs) as a starting point for gathering evidence, SRs and/or meta-analyses were searched through December 2013. To collect any recent data that may have been missed, we supplemented the search by searching for RCTs published in the last three years through December 2013. Citations were also retrieved by manually searching reference lists of relevant articles. The databases were searched using the keywords ''yoga'' and ''systematic review'' for published SRs and ''yoga'' and ''randomized controlled trials'' for recent RCTs (see online Supplementary Table S1 for search strategies).

Study selection and inclusion process

Records were pooled from the various databases. Titles and abstracts of SRs that appeared to meet the inclusion criteria were retrieved for further evaluation. Systematic reviews were defined as articles that included an explicit and repeatable literature search method and had explicit and repeatable inclusion and exclusion criteria for studies. RCTs included in the SRs were then retrieved. The process was repeated for the supplementary search of RCTs. For inclusion in our SR, the studies had to be published in English in a peer-reviewed journal, be conducted in adults (18+ years) who were either healthy, at risk, or with a history of CVD or metabolic syndrome and no other major comorbidities, test an asana- (or posture-) based intervention, and report relevant outcomes. We focused only on SRs that included at least one randomized controlled trial with yoga therapy as a trial arm. No restrictions were placed on style of yoga practiced, frequency, or duration. Articles were excluded if we were unable to isolate the effect of yoga (i.e. yoga was part of a multimodal intervention whose non-yoga components were given to the active intervention group but not to the control group), outcomes reported only psychosocial risk factors or psychological outcomes like stress and anxiety, and the population treated focused on other conditions or comorbidities (e.g. women with breast cancer, populations with renal disease). Two investigators (PC and RG) independently selected studies for inclusion; disagreements were resolved by discussion.

Outcomes

The outcomes of interest were changes in the levels of modifiable risk factors for CVD and metabolic syndrome. Particularly, we were interested in measures of body composition, blood pressure, lipid panel, glycemic control, heart rate, and smoking status. Primary outcomes include body mass index (BMI), systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Other outcomes – body weight, diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), heart rate, and smoking status – were considered secondary outcomes. Outcomes were kept in their natural units.

Data extraction and quality assessment

From each eligible study we extracted the characteristics, of the participants, intervention description (type, length of session, frequency), control group description, duration of follow-up, number of patients randomized at baseline and number at follow-up, and effect measures (pre- and post-mean and standard deviations in intervention and control arms, mean change scores and standard deviations if reported). Data from the longest follow-up was extracted. Data extraction was performed by one investigator (PC) and checked for accuracy and completeness by a second reviewer (RG). Any discrepancies were resolved by discussion. RCTs were appraised using the Cochrane Collaboration's Risk of Bias (ROB) tool, a commonly used tool to assess risk of bias.[23] Trial quality was evaluated by using categories of high, low, or unclear risk in regards to randomization method, allocation concealment, blinding of study personnel and outcomes assessment, attrition, and reporting methods. Two reviewers (PC and RG) independently evaluated RCT quality and resolved any discrepancies by discussion.

Statistical analysis

Change scores, mean differences (MDs) between treatment arms, and sample sizes reported were on an intention-to-treat basis. MDs were calculated by subtracting the change score in the control group from the change score in the yoga group. Where MDs and standard deviations were not reported, standard deviations were calculated using a conservative correlation coefficient of 0.5 for within-patient correlation from baseline to follow-up. MDs between groups and 95% confidence intervals (CIs) were calculated for each outcome. The magnitude of heterogeneity was evaluated using the I^2 statistic testing the null hypothesis that all studies are evaluating the same effect.[24] I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high heterogeneity, respectively. Because meta-analysis pools studies that are clinically and methodologically diverse, data on MDs from trials were statistically pooled using a random effects model.[25] We also categorized patients into four subgroups based on patient conditions –healthy, with CVD risk factors, with diabetes or metabolic syndrome, and diagnosed with coronary artery disease (CAD) – to depict heterogeneity in the populations included and their response to treatment. Healthy patients are those free of clinical manifestations of any medical or psychiatric illness including clinically significant CVD and diabetes mellitus. Those with CVD risk factors included patients with hypertension, high cholesterol levels, obesity, and current smokers. Diabetes and metabolic syndrome were diagnosed through medical examination or history, and CAD was confirmed through angiography. Controls were separated into aerobic exercise (physical training, aerobic exercise, cycling, running, brisk walking) and non-aerobic exercise groups. Yoga was compared to these two control groups separately to obtain an estimate of its effectiveness versus active controls and versus non-active controls (details published in protocol amendment). Reference Manager (RevMan) Version 5.2 software from the Cochrane Collaboration was used for data analysis.[26]

Publication bias

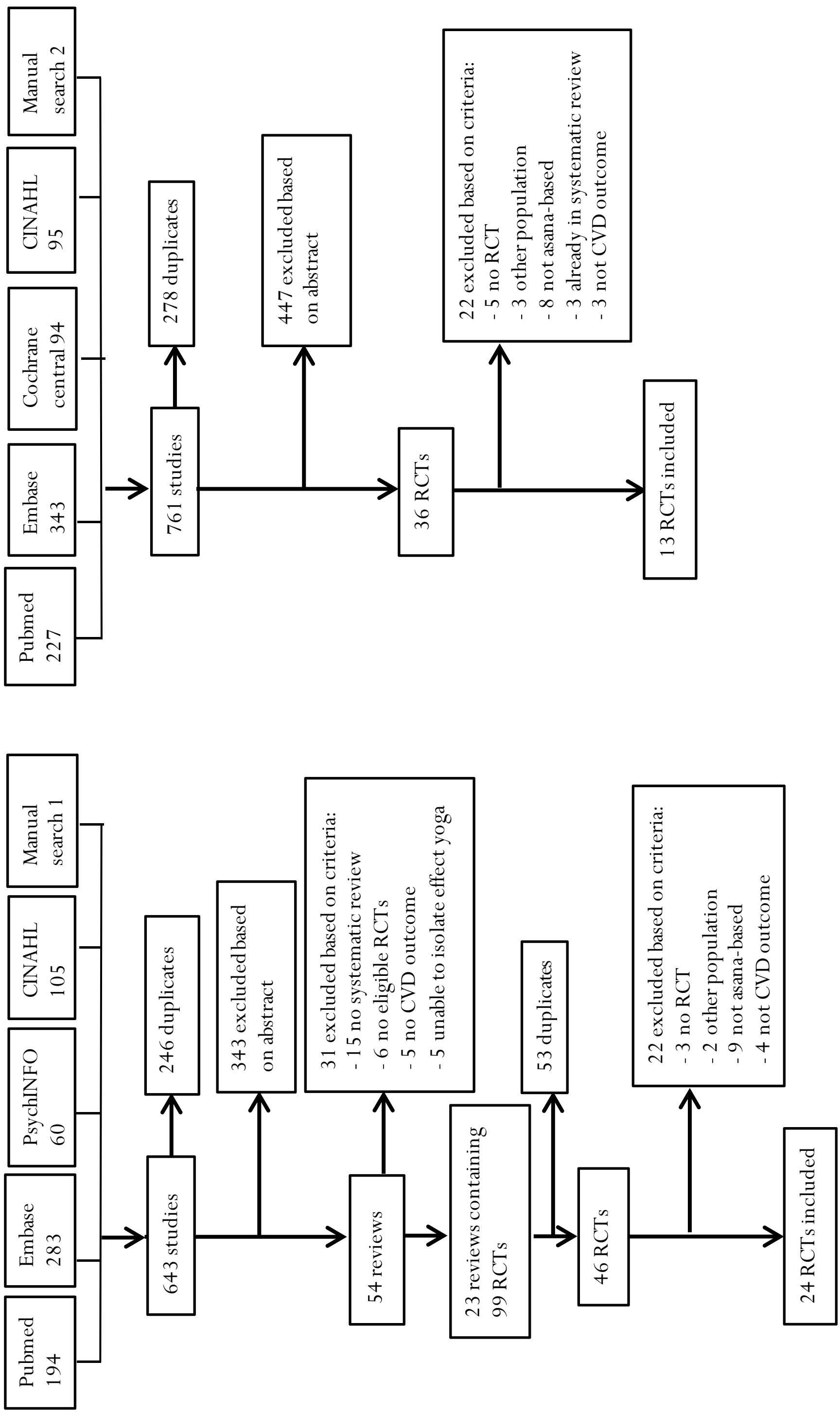
Publication bias was assessed for each of the primary outcomes by visual inspection of funnel plots generated using RevMan software. The MDs were plotted on the x-axis and the standard errors, a measure of study size, on the y-axis. In the absence of bias, the scatterplot should be approximately symmetrical; the more asymmetry, the more bias is present.

Results

Literature search

We identified 643 studies from the SR search and 761 studies from the RCT search for a total of 1404 records (Figure 1). After removal of duplicates, a total of 880 titles and abstracts were screened. A total of 37 RCTs (24 RCTs from 18 SRs and 13 additional RCTs) met our criteria for inclusion in the review. Although 37 studies met criteria, five studies did not report exact numbers for our primary or secondary outcomes and could not be included in the meta-analysis,[27–31] leaving 32 studies for statistical analysis.

Figure 1. Systematic review search



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Study quality

Study quality and description of methodology varied amongst the included studies (see Table 1). Thirteen studies [32–43] provided details on the specific randomization method that was used in the RCT and four [31,35,37,38] described treatment assignment. Due to the nature of the intervention, all studies had high risk of bias for blinding of participants; however, three studies reported blinding of the personnel, indicating that technicians were blinded to treatment assignment of individuals.[34,44,45] Almost all studies except one[34] had unclear risk for blinding of outcome assessment. However, there was generally low risk of bias for incomplete reporting of outcomes and selective reporting of outcomes. A summary of study quality can be seen in online Supplementary Figure S1.

Study characteristics

Characteristics of the included studies are listed in Table 1. The included studies comprised a total of 2768 participants, with about an equal mix of men (47%) and women (53%). RCTs included adult participants of all ages with an average age of 50 years. Of these participants, 1287 (47%) were assigned to receive the yoga intervention and 1461 (53%) assigned to the control arm. Altogether 1094 (85%) of yoga participants completed the study while 1301 (89%) of control participants made it to follow-up. Duration of studies varied, with follow-up times ranging from 3 weeks to 52 weeks, with a median of 12 weeks. Dividing into subgroups, 38% (14/37) of studies were conducted in healthy populations, 22% (8/32) of studies in populations with CVD risk factors, 27% (10/32) in populations with diabetes or metabolic syndrome, and 13% (5/32) in populations with CAD. Control arms included usual care or conventional medical therapy (23%), a form of relaxation (6%), education (11%), diet alone (4%), waiting list or no intervention (32%), cognitive-based therapy (2%), and exercise (21%). Five two-arm RCTs,[41–43,46,47] three three-arm RCTs,[27,40,45] and one four-arm RCT[48] used exercise as one of the comparator strategies. Exercise controls consisted of physical training, cycling, running, brisk walking, or resistance training [43]. One exercise trial[27] was excluded from the meta-analysis due to incomplete reporting of effect measures.

Table 1. Included randomized controlled trial study characteristics by population

Author (year) systematic review	N randomis yoga/cont followup yoga/cont	Treatment group	Mean age (SD) Age range	% female	Intervent. Time per session	Control	Freq./ Duration	Outcome measure	Study quality[b]
HEALTHY ADULTS									
Blumenthal et al. (1989)[60, 61]	101 (34/33/34) 97 (34/31/32)	Community dwelling elderly with no CAD	Yoga 67.8 (5.9), control 66.5 (4.3) (1), 66.8 (4.3) (2) Range: 60-83	50	Yoga and flexibility 60 min	1) Aerobic exercise 60 min 2) Waiting list	2x/wk 16 weeks	BW, SBP, DBP, TC, LDL-C, HDL-C	2/3/1
Cusumano et al.(1993)[13]	90 (45/45) 90 (45/45)	Japanese under-graduates	Range: 18-20	100	Hatha yoga 80 min	Progressive muscle relaxation	1x/wk 3 weeks	HR	2/3/1
Bowman et al. (1997)[13, 61, 22]	40 (20/20) 26 (12/14)	Healthy sedentary elderly	68 Range: 62-81	38	Hatha yoga 90 min	Aerobic training 40 min	2x/wk 6 weeks	SBP, HR	0/3/3
Stachenfeld e al. (1998)[60, 62]	17 (8/9) 15 (8/7)	Healthy older women	Yoga: 73 (3), control 71 (2) Range: >65	100	Yoga exercises 60 min	Aerobic training 40-50 min	3-4x/wk 12 weeks	BW, SBP, DBP, HR	1/3/2
Ray et al. (2001a)[11]	40 (20/20) 28 (17/11)	Healthy men from	Yoga 21.9 (1.5), control 22.7 (2.0)	0	Hatha yoga 60 min	Physical army training 60 min	6x/wk 24 weeks	BW, HR	2/2/2

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		Indian army	Range: 19-23						
Ray et al. (2001b) [13]	54 (28/26) 54 (28/26)	Healthy adults	Yoga 23.4 (4.0), control 22.2 (5.1) Range: 20-25	19	Hatha yoga 60 min	No intervention	3x/wk 20 weeks	SBP, HR	2/3/1
Fields et al. (2002)[28]	15 (6/3/6) 15 (6/3/6)	Healthy seniors	Yoga 74 (6), control 76 (10) (1), control 77 (7) (2) Range: >65	NR	Mahrishi Vedic Medicine 60 min	1) Modern medicine ; 2) Usual care	7x/wk 52 weeks	SBP, DBP, TC, LDL-C, HDL-C TG, FBG, HbA1c	4/1/1
Harinath et al. (2004)[63, 13]	30 (15/15) 30 (15/15)	Healthy army soldiers	29.6 (4.9) Range: 25-35	0	Hatha yoga 60 min	Routine physical army training	7x/wk 12 weeks	SBP, DBP, HR	3/2/1
Chen et al. (2008)[60, 61]	204 (67/65/72) 176 (57/53/66)	Seniors in a community activity center	69 (6.3) Range: 60-75	73	1) Silver yoga 70 min 2) Silver yoga (without meditation) 55 min	Waiting list	3x/wk 24 weeks	BW, BMI, SBP	1/3/2
Vogler et al. (2011)	40 (20/20) 38 (19/19)	Physically inactive	Yoga 76, control 72 Range: 56-94	NR	Iyengar yoga 90 min Home	Usual daily routine	2x/wk 3x/wk (home	SBP, DBP	2/3/1

		older adults			practice 15-20 min		practice) 8 weeks		
Kanojia et al. (2013)	50 (25/25) 50 (25/25)	Young healthy females	Yoga 18.6 (1.1), control 18.1 (0.8) Range: 18-20	100	Yoga 40 min	No intervention	6x/wk	BW, SBP, DBP, HR	2/3/1
Kim et al. (2012)	47 (27/20) 34 (16/18)	Normal premeno-pausal women	Yoga 45.7 (5.2), control 43.2 (4.5) Range: 35-50	100	Ashtanga yoga 60 min	Normal daily lifestyles	2x/wk 32 weeks	SBP, DBP, HR	1/4/1
Wolever et al. (2012)	239 (90/96/53) 205 (76/82/47)	Employees of a national insurance carrier	Yoga 41.6 (10.1), control 44.3 (9.4) (1), 42.7 (9.7) (2)	77	Viniyoga stress reduction program 60 min	1) Mindfulness at Work program 2) List of resources	1x/wk 12 weeks	SBP, DBP	2/3/1
Tracy et al. (2013)	32 (21/11) 21 (10/11)	Young healthy adults	Yoga 29 (6), control 26 (7) Range: 21-39	52	Bikram yoga 90 min	Normal lifestyle	3x/wk 8 weeks	SBP, HR	0/3/3
ADULTS WITH CVD RISK FACTORS									
van Montfrans et al. (1990)[19]	42 (23/19) 35 (18/17)	Adults with mild uncomplicated hypertension	Yoga 40, control 43 Range: 24-60	49	Hatha yoga + progressive muscle relaxation + stress management 60 min	Passive relaxation	1x/wk; 2x/wk (home practice) 52 weeks	BW, SBP, DBP, TC	2/3/1
Mahajan	93 (52/41)	participa	Range: 56-59	0	4d yoga	Conventional	4 days +	BW, TC,	1/4/1

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et al. (1999)[13, 11, 62, 60]	93 (52/41)	nts with CAD risk factors			camp + diet; yoga practice + lifestyle advice 60 min	therapy + lifestyle advice	7x/wk 14 weeks	LDL-C, HDL-C, TG	
Murugesan et al. (2000)[13, 11, 68, 14, 60, 19, 69]	33 (11/11/11) 33 (11/11/11)	Hypertensive patients	Range: 35-65	NR	Yoga 60 min	1) Daily medical treatment with antihypertensives 2) No intervention	7x/wk 11 weeks	BW, SBP, DBP	2/3/1
McCaffrey et al. (2005)[19, 70, 69]	61 (32/29) 54 (27/27)	Adults with diagnosed hypertension	Yoga 56.7, control 56.2	65	Yoga practice with instructional booklet and tape 63 min	General education about hypertension	3x/wk 8 weeks	BMI, SBP, DBP, HR	2/2/2
Cohen et al. (2011)[69, 19]	78 (46/32) 57 (26/31)	Adults with untreated pre-/ Stage 1 hypertension	Yoga 48.2±1.6, control 48.3±2.4 Range: 22-69	50	Iyengar yoga 70min	Enhanced usual care with dietary education	2x/wk first 6 weeks; 1x/wk next 6 weeks 12 weeks	BW, SBP, DBP, HR	1/3/2
Subramanian et al.	100 (25/25/25/	Young adults	Yoga 23, control 23.3	33	Yoga 30-45 min	1) No intervention,	5x/wk 8 weeks	SBP, DBP	2/3/1

(2011)[19]	25); 94 (25/25/23/ 21)	with (pre-) hypert	(1), 23.7 (2), 23.7 (3)			2) physical exercise 50-60min, 3) Salt intake reduction			
Bock et al. (2012)[72]	55 (32/23) 55 (32/23)	Middle age female smokers that intended to quit smoking	45.6±8.3	100	Vinyasa yoga + CBT	Wellness sessions for health education + CBT	2x/wk 8 weeks	7-day point-prevalenc e smoking abstinenc e	3/2/1
Lee et al. (2012)	16 (8/8) 16 (8/8)	Obese postmen opausal women	Yoga 54.5±2.8, control 54.3±2.9	100	Yoga 60 min	No exercise	3x/wk 16 weeks	BW, BMI, TC, LDL-C, HDL-C, TG, FBG	2/3/1
ADULTS WITH DIABETES OR METABOLIC SYNDROME									
Monro et al. (1992)[13, 74, 14, 75]	21 (11/10) 21 (11/10)	Patients with non -insulin-depende nt DM	Yoga 53, control 57	NR	Yoga + normal medication and diet 90 min	Usual care (continuation of medication, diet)	2-4x/wk 12 weeks	FBG, HbA1c	1/3/2
Kerr et al. (2002)[14, 75]	37 (17/20) 33 (17/16)	Patients with type 1 and 2 DM	Yoga 60.3±7.8, control 61.4±10.7	NR	Hatha yoga + education + continued insulin 90 min	Education + simple exercises + continued insulin	2x/wk 16 weeks	BW, BMI, TC, LDL-C, HDL-C, TG,	1/2/3

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								HbA1c	
Cohen et al. (2008)[57, 76, 19]	26 (14/12) 24 (12/12)	Underactive, overweight adults with metabolic syndrome not taking medic	Yoga 52±9, control 52±8 Range: 30-65	85	Yoga 90 min + 3 hr intro	Waiting list	2x/wk for 5 wks, then 1x/wk for 5 weeks; 3x/week (home practice) 10 weeks	BW, BMI, SBP, DBP, TC, LDL-C, HDL-C, TG, FBG	3/2/1
Gordon et al. (2008)[60, 22, 76]	231 (77/77/77) 231 (77/77/77)	Elderly patients with type 2 DM	Yoga 64, control 63.9 (1), 63.6 (2)	81	Hatha yoga + continued diet and medication 120 min	1) Conventional physical aerobic exercise (180 min) + continued diet and medication 2) Nothing	1x/wk; 3-4x/wk (home practice) 24 weeks	TC, LDL-C, HDL-C, TG, FBG	3/3/0
Saptharishi et al. (2009)[19]	120 (30/30/30/30); 102 (21/29/27/25)	Young adults not taking anti-hypertensive	Yoga: 22.5±1.36, control 22.5±1.4 (1), 22.4±1.3 (2), 22.5±1.47 (3)	33	Yoga 30-45 min	1) No intervention 2) Brisk walking 50-60 min 3) Salt intake reduction	5x/wk 8 weeks	SBP, DBP	3/2/1

		medic							
Skoro-Kondza et al. (2009)[48]	59 (29/30) 59 (29/30)	Patients with type 2 DM not taking insulin	60±10	61	Yoga + advice 90 min	Waiting list + advice	2x/wk 12 weeks	HbA1c	2/2/2
Yang et al. (2011)[74, 60]	25 (13/12) 23 (12/11)	Patients with metabolic syndrome not taking medic	51.7±4.9 Range:45-65	91	Vinyasa style yoga 60 min	General health education materials every 2 weeks	2x/wk 12 weeks	BW, SBP, DBP, TC, LDL-C, FBG HDL-C, TG,	2/3/1
Vaishali et al. (2012)	60 (30/30) 57 (27/30)	Elderly subjects with type 2 DM	Yoga 65.8±3.2, control 64.4±3.8 Range: >60	37	Yoga + education + medication as in control 45-60 min	Education + conventional hypoglycemic medications	6x/wk 12 weeks	TC, LDL-C, HDL-C, TG, FBG, HbA1c	4/1/1
Hegde et al. (2013)	29 (14/15) 29 (14/15)	Prediabetic subjects	Yoga 46.5±13.0, control 44.7±9.6 Range: 30-75	52	Yoga 75-90 min	Waiting list	7x/wk 12 weeks (one wknd break)	BMI, SBP, DBP, FBG, HbA1c	3/2/1
Shantakumari et al. (2013)	100 (50/50) 100 (50/50)	Patients with type 2	Yoga 45.5±8, control 44.5±11	48	Yoga + drugs as in control	Oral hypoglycemic drugs	7x/wk 12 weeks	BW, BMI, TC, LDL-C,	2/3/1

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		DM and dyslipidemia			60 min			HDL-C, TG	
ADULTS WITH DIAGNOSED CORONARY ARTERY DISEASE (CAD)									
Manchanda et al. (2000)[13, 11, 62, 60]	42 (21/21) 42 (21/21)	Male patients with CAD and chronic stable angina	Yoga 51±9, control 52±10 Range: 32-72	0	Yoga + medication for angina as in control 90 min	Conventional medical therapy + medication for angina	7x/wk 4 days training	BW, TC, LDL-C, HDL-C, TG	3/3/0
Jatuporn et al. (2003)[13]	44 (22/22) 44 (22/22)	Adults with CAD without prior therap interven	Yoga 61.5 ±4.7, control 56.8±7.6	20	yoga, support, dietary advice, relaxation 60 min	Conventional treatment with lipid-lowering drugs	3x/wk 16 weeks	BMI, TC, LDL-C, HDL-C, TG	2/3/1
Ades et al. (2005)[43]	51 (25/26) 42 (21/21)	Community-dwelling women with established CAD	Yoga: 71.5±4.8, control 72.9±6.1 Range: >65	100	Light yoga + continued medication as in control 30-40 min	Resistance exercise training + continued medication	3x/wk 24 weeks	BW, BMI	3/2/1
Pal et al. (2011)[35]	160 (85/85) 154 (80/74)	Patients diagnosed with	Yoga 58.9 (9.4), control 58.6 (10.5)	16	Yoga + medication 35-40 min	Medication only	5x/wk 24 weeks	BMI, SBP, DBP,	4/1/1

		CAD						TC, LDL-C, HR HDL-C, TG,	
Pal et al. (2013)[36]	258 (129/129) 208 (105/103)	Patients diagnosed with CAD	Yoga 59.1 (9.9), control 56.4 (10.9)	20	Yoga + medication 35-40 min	Medication only	5x/wk 72 weeks	BMI, SBP, DBP, HR	2/3/1

[a] Findings only described in text, numbers not reported

[b] Based on the Cochrane Collaboration's risk of bias tool, numbers correspond to number rated low risk, unclear risk, and high risk on 6 domains

Unless otherwise noted, the yoga group also received usual care in addition to the listed interventions.

Abbreviations: NR=not reported, SD=standard deviation, CAD=coronary artery disease, DM=diabetes mellitus, CBT=cognitive behavioral therapy, AHA=American Heart Association, SBP=systolic blood pressure, DBP=diastolic blood pressure, BW=body weight, BMI=body mass index, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides, FBG=fasting blood glucose, HbA1c=glycosylated hemoglobin

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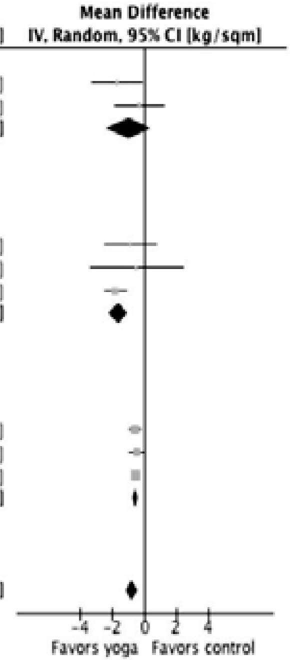
Risk factor outcomes

Yoga versus non-exercise controls. Yoga showed significant improvement of risk factors versus non-exercise controls for each of the primary outcomes: BMI (0.77 kg/m2 (1.09 to 0.44)), SBP (5.21 mmHg (8.01 to 2.42)), LDL–C (12.14 mg/dl (21.80 to 2.48)), and HDL-C (3.20 mg/dl (1.86 to 4.54)) (Figure 2). For the secondary outcomes, significant improvement was seen in all risk factors except FBG (5.91 mg/dl (16.32 to 4.50)) and HbA1c (0.06% Hb (0.43 to 0.31)) (online Supplementary Figure S2). Improvements reported in secondary outcomes include reductions of body weight (2.35 kg (4.33 to 0.37)), DBP (4.98 mmHg (7.17 to 2.80)), TC (18.48 (29.16 to 7.80), TG (25.89 mg/dl (36.19 to 15.60)), and heart rate (5.27 beats/min (9.55 to 1.00)) (online Supplementary Figure S2). Only one trial was found which evaluated the impact of yoga on smoking status.[32] When twice-weekly Vinyasa-style yoga was given in addition to cognitive behavioral therapy (CBT) for smoking cessation, smokers in the intervention group had higher odds of seven-day and 24-hour abstinence compared to a control group receiving CBT and education at the end of the eight-week study period (seven-day quit odds ratio (OR) 4.56 (95% CI 1.12 to 18.57), 24-hour quit OR 4.19 (1.16 to 15.11). These results did not last, however, when abstinence was measured at six-month follow-up (seven-day quit OR 1.54 (0.34 to 6.92), 24-hour quit OR 1.87 (0.43 to 8.16)). When yoga is used in addition to medication, significant improvement was found in body weight,[49] BMI,[35,36] blood pressure,[20,50] lipid levels,[35,38,49,51] FBG,[38,52] HbA1c,[38,52] and heart rate[36] in patients with type 2 diabetes or CAD. As a substitute for medical therapy, results are less definitive. Two RCTs found yoga more effective than drug therapy in controlling blood pressure[53] and body weight.[53,54] In a three-arm trial in which yoga was directly compared to a group that received antihypertensive treatment and a group receiving no treatment in patients at high risk for CVD, yoga reduced SBP almost three times more than the antihypertensive therapy (MD 29.17 mmHg (37.75, 20.59) and 9.60 mmHg (18.78, 0.42), respectively).[53] When yoga is included in addition to continued medication in CAD patients, an additional benefit, although smaller, is still observed.[35,36] Among CAD patients, yoga is less effective as a substitute for medication such as statins and lipid-lowering drugs in lowering LDL-C;[55] however, as an adjunct treatment to medication, yoga provides an additional statistically significant benefit.[35,49]

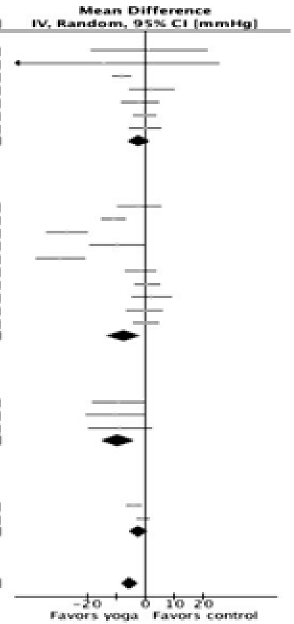
Study or Subgroup	Yoga Mean [kg/sqm]	Yoga SD [kg/sqm]	Yoga Total	Control Mean [kg/sqm]	Control SD [kg/sqm]	Control Total	Weight	Mean Difference IV, Random, 95% CI [kg/sqm]
1.1.1 CVD risk factors								
Lee et al. 2012	-0.89	1.54	8	0.82	1.66	8	3.8%	-1.71 [-3.28, -0.14]
McCaffrey et al. 2005	-0.24	2.79	32	0.05	3.25	29	4.0%	-0.29 [-1.82, 1.24]
Subtotal (95% CI)			**40**			**37**	**7.9%**	**-0.99 [-2.38, 0.40]**
Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 1.62$, df = 1 (P = 0.20); $I^2 = 38\%$								
Test for overall effect: Z = 1.39 (P = 0.16)								
1.1.2 Diabetes or metabolic syndrome								
Cohen et al. 2008	-0.1	0.9	14	0.8	2.7	12	3.7%	-0.90 [-2.50, 0.70]
Hegde et al. 2013	-0.4	3.6	14	0.1	4.35	15	1.2%	-0.50 [-3.40, 2.40]
Shantakumari et al. 2013	-1.53	1.47	50	0.3	2.02	50	13.3%	-1.83 [-2.52, -1.14]
Subtotal (95% CI)			**78**			**77**	**18.3%**	**-1.63 [-2.25, -1.01]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.71$, df = 2 (P = 0.43); $I^2 = 0\%$								
Test for overall effect: Z = 5.14 (P < 0.00001)								
1.1.3 CAD								
Jatuporn et al. 2003	-0.8	0.6	22	-0.2	0.5	22	25.0%	-0.60 [-0.93, -0.27]
Pal et al. 2011	-1.45	1.74	85	-0.96	1.16	85	20.6%	-0.49 [-0.93, -0.05]
Pal et al. 2013	-0.52	0.89	129	0.03	1.07	129	28.2%	-0.55 [-0.79, -0.31]
Subtotal (95% CI)			**236**			**236**	**73.8%**	**-0.56 [-0.73, -0.38]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.16$, df = 2 (P = 0.92); $I^2 = 0\%$								
Test for overall effect: Z = 6.14 (P < 0.00001)								
Total (95% CI)			**354**			**350**	**100.0%**	**-0.77 [-1.09, -0.44]**
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 14.47$, df = 7 (P = 0.04); $I^2 = 52\%$								
Test for overall effect: Z = 4.60 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 10.87$, df = 2 (P = 0.004), $I^2 = 81.6\%$								



a) Body mass index (kg/m^2)

6

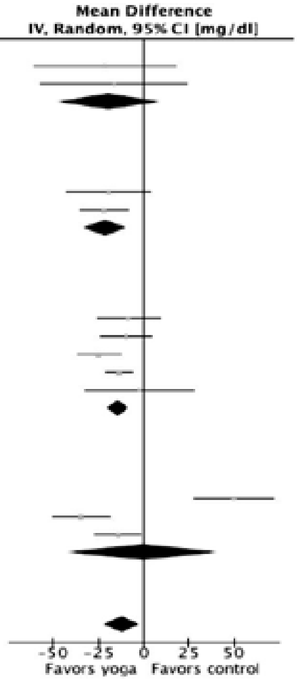
Study or Subgroup	Yoga Mean [mmHg]	Yoga SD [mmHg]	Yoga Total	Control Mean [mmHg]	Control SD [mmHg]	Control Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
2.1.1 Healthy								
Fields et al. 2002 (1)	-6.3	9.2	6	-7.7	23	6	1.5%	1.40 [-18.42, 21.22]
Fields et al. 2002 (2)	-6.3	9.2	6	7.7	34	3	0.5%	-14.00 [-53.17, 25.17]
Kanojia et al. 2013	-5.2	4.75	25	2.88	6.7	25	6.0%	-8.08 [-11.30, -4.86]
Kim et al. 2012	-0.4	16.57	27	-2.6	9.8	20	4.4%	2.20 [-5.38, 9.78]
Ray et al. 2001b	-5.64	10.77	28	-3.74	12.8	26	4.9%	-1.90 [-8.23, 4.43]
Wolever et al. 2012 (3)	-0.8	13.37	90	-0.67	14.06	96	5.7%	-0.13 [-4.07, 3.81]
Wolever et al. 2012 (4)	-0.8	13.37	90	-0.87	16.83	53	5.3%	0.07 [-5.24, 5.38]
Subtotal (95% CI)			**272**			**229**	**28.2%**	**-2.07 [-5.95, 1.82]**
Heterogeneity: Tau² = 13.54; Chi² = 15.21, df = 6 (P = 0.02); I² = 61%								
Test for overall effect: Z = 1.04 (P = 0.30)								
2.1.2 CVD risk factors								
Cohen et al. 2011	-6	18.35	46	-4	14.93	32	4.5%	-2.00 [-9.41, 5.41]
Lee et al. 2012	-8.25	4.89	8	2.62	3.45	8	5.7%	-10.87 [-15.02, -6.72]
McCaffrey et al. 2005	-24.85	11.89	32	1.89	15.76	29	4.6%	-26.74 [-33.80, -19.68]
Murugesan et al. 2000 (5)	-33.36	9.71	11	-23.76	12.12	11	3.8%	-9.60 [-18.78, -0.42]
Murugesan et al. 2000 (6)	-33.36	9.71	11	-4.19	10.8	11	4.0%	-29.17 [-37.75, -20.59]
Saptharishi et al. 2009 (7)	-1.6	9.61	30	-0.1	10.61	30	5.3%	-1.50 [-6.62, 3.62]
Saptharishi et al. 2009 (8)	-1.6	9.61	30	-2.3	7.5	30	5.6%	0.70 [-3.66, 5.06]
Subramanian et al. 2011 (9)	-0.4	12.02	25	-2.6	12.76	25	4.7%	2.20 [-4.67, 9.07]
Subramanian et al. 2011 (10)	-0.4	12.02	25	-0.3	10.11	25	4.9%	-0.10 [-6.26, 6.06]
van Montfrans et al. 1990	-2.2	7.7	23	-2.5	6.8	19	5.6%	0.30 [-4.09, 4.69]
Subtotal (95% CI)			**241**			**220**	**48.7%**	**-7.36 [-13.39, -1.33]**
Heterogeneity: Tau² = 83.85; Chi² = 96.61, df = 9 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 2.39 (P = 0.02)								
2.1.3 Diabetes or metabolic syndrome								
Cohen et al. 2008	-3.6	13.9	14	5.6	9.3	12	3.9%	-9.20 [-18.18, -0.22]
Hegde et al. 2013	-6.4	16.07	14	3.8	11.96	15	3.4%	-10.20 [-20.57, 0.17]
Yang et al. 2011	-5.17	12.4	13	3.6	15	12	3.3%	-8.77 [-19.61, 2.07]
Subtotal (95% CI)			**41**			**39**	**10.6%**	**-9.39 [-15.14, -3.63]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 2 (P = 0.98); I² = 0%								
Test for overall effect: Z = 3.20 (P = 0.001)								
2.1.4 CAD								
Pal et al. 2011	-11.02	9.46	85	-7.05	6.29	85	6.2%	-3.97 [-6.39, -1.55]
Pal et al. 2013	-5.41	11.4	129	-4.71	1.54	129	6.3%	-0.70 [-2.69, 1.29]
Subtotal (95% CI)			**214**			**214**	**12.5%**	**-2.26 [-5.46, 0.94]**
Heterogeneity: Tau² = 4.07; Chi² = 4.20, df = 1 (P = 0.04); I² = 76%								
Test for overall effect: Z = 1.38 (P = 0.17)								
Total (95% CI)			**768**			**702**	**100.0%**	**-5.21 [-8.01, -2.42]**
Heterogeneity: Tau² = 31.32; Chi² = 127.86, df = 21 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 3.66 (P = 0.0003)								
Test for subgroup differences: Chi² = 6.61, df = 3 (P = 0.09), I² = 54.6%								



(1) for high risk subjects versus usual care
(2) for high risk subjects versus modern medicine (exercise, diet, education)
(3) versus Mindfulness at Work program
(4) versus educational resources
(5) versus medical treatment
(6) versus no intervention
(7) versus no intervention
(8) versus salt reduction diet
(9) versus salt reduction diet
(10) versus no intervention

b) Systolic blood pressure (mmHg)

Study or Subgroup	Yoga Mean [mg/dl]	Yoga SD [mg/dl]	Yoga Total	Control Mean [mg/dl]	Control SD [mg/dl]	Control Total	Weight	Mean Difference IV, Random, 95% CI [mg/dl]
3.2.1 Healthy								
Fields et al. 2002 (1)	-10.3	38	6	11.3	22	3	4.1%	-21.60 [-60.90, 17.70]
Fields et al. 2002 (2)	-10.3	38	6	6.2	34	6	3.9%	-16.50 [-57.30, 24.30]
Subtotal (95% CI)			**12**			**9**	**8.0%**	**-19.15 [-47.45, 9.16]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%								
Test for overall effect: Z = 1.33 (P = 0.18)								
3.2.2 CVD risk factors								
Lee et al. 2012	-8.63	23.84	8	10.88	23.5	8	7.3%	-19.51 [-42.71, 3.69]
Mahajan et al. 1999	-22.32	34.04	52	-0.45	32.02	41	10.1%	-21.87 [-35.35, -8.39]
Subtotal (95% CI)			**60**			**49**	**17.4%**	**-21.27 [-32.93, -9.62]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%								
Test for overall effect: Z = 3.58 (P = 0.0003)								
3.2.3 Diabetes or metabolic syndrome								
Cohen et al. 2008	-1.4	21	14	6.9	23.2	12	9.0%	-8.30 [-25.43, 8.83]
Gordon et al. 2008 (3)	-3.09	47.51	77	6.57	40.72	77	10.0%	-9.66 [-23.64, 4.32]
Shantakumari et al. 2013	-24.23	31.79	50	0.49	27.42	50	10.7%	-24.72 [-36.36, -13.08]
Vaishali et al. 2012	-21.04	11.95	30	-7.44	16.8	30	11.8%	-13.60 [-20.98, -6.22]
Yang et al. 2011	-12.41	34.57	13	-10.1	41.47	12	5.7%	-2.31 [-32.37, 27.75]
Subtotal (95% CI)			**184**			**181**	**47.2%**	**-14.42 [-20.47, -8.36]**
Heterogeneity: Tau² = 6.91; Chi² = 4.62, df = 4 (P = 0.33); I² = 13%								
Test for overall effect: Z = 4.66 (P < 0.00001)								
3.2.4 CAD								
Jatuporn et al. 2003	24.7	36.3	22	-25.3	37.79	22	7.7%	50.00 [28.10, 71.90]
Manchanda et al. 2000	-38	33	21	-3.3	16.83	21	9.4%	-34.70 [-50.54, -18.86]
Pal et al. 2011	-15.1	45.23	85	-1.09	39.64	85	10.3%	-14.01 [-26.80, -1.22]
Subtotal (95% CI)			**128**			**128**	**27.4%**	**-0.36 [-41.98, 41.26]**
Heterogeneity: Tau² = 1276.19; Chi² = 38.56, df = 2 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 0.02 (P = 0.99)								
Total (95% CI)			**384**			**367**	**100.0%**	**-12.14 [-21.80, -2.48]**
Heterogeneity: Tau² = 192.48; Chi² = 45.66, df = 11 (P < 0.00001); I² = 76%								
Test for overall effect: Z = 2.46 (P = 0.01)								
Test for subgroup differences: Chi² = 1.63, df = 3 (P = 0.65), I² = 0%								



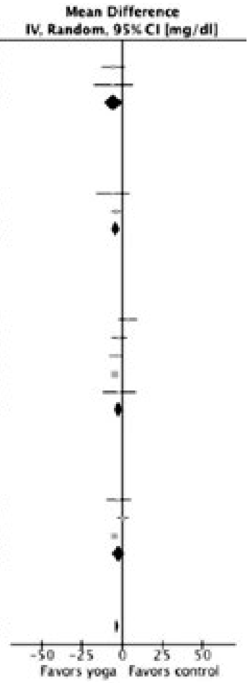
(1) for high risk subjects versus modern medicine (exercise, diet, education)
(2) for high risk subjects versus usual care
(3) versus no intervention

c) Low-density lipoprotein cholesterol (mg/dL)

6

Study or Subgroup	Yoga Mean [mg/dl]	Yoga SD [mg/dl]	Yoga Total	Control Mean [mg/dl]	Control SD [mg/dl]	Control Total	Weight	Mean Difference IV, Random, 95% CI [mg/dl]
3.3.1 Healthy								
Fields et al. 2002 (1)	-2.2	7.5	6	3.3	3.2	3	3.2%	-5.50 [-12.51, 1.51]
Fields et al. 2002 (2)	-2.2	7.5	6	3.5	13	6	1.2%	-5.70 [-17.71, 6.31]
Subtotal (95% CI)			**12**			**9**	**4.4%**	**-5.55 [-11.60, 0.50]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0\%$								
Test for overall effect: Z = 1.80 (P = 0.07)								
3.3.2 CVD risk factors								
Lee et al. 2012	-3.5	10.7	8	2.38	9.78	8	1.7%	-5.88 [-15.93, 4.17]
Mahajan et al. 1999	-5.75	6.09	52	-1.9	5.31	41	14.9%	-3.85 [-6.17, -1.53]
Subtotal (95% CI)			**60**			**49**	**16.6%**	**-3.95 [-6.21, -1.69]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0\%$								
Test for overall effect: Z = 3.43 (P = 0.0006)								
3.3.3 Diabetes or metabolic syndrome								
Cohen et al. 2008	2	9.9	14	-1.7	3.5	12	4.8%	3.70 [-1.85, 9.25]
Gordon et al. 2008 (3)	-1.16	15.55	77	0.77	13.57	77	6.4%	-1.93 [-6.54, 2.68]
Shantakumari et al. 2013	-2.52	8.82	50	1.1	10.72	50	8.4%	-3.62 [-7.47, 0.23]
Vaishali et al. 2012	-5.85	0.99	30	-1.24	1.45	30	25.5%	-4.61 [-5.24, -3.98]
Yang et al. 2011	3.75	11.69	13	5.6	13.88	12	1.6%	-1.85 [-11.95, 8.25]
Subtotal (95% CI)			**184**			**181**	**46.7%**	**-2.45 [-5.24, 0.33]**
Heterogeneity: $Tau^2 = 5.27$; $Chi^2 = 10.11$, df = 4 (P = 0.04); $I^2 = 60\%$								
Test for overall effect: Z = 1.72 (P = 0.08)								
3.3.4 CAD								
Jatuporn et al. 2003	-2	13.76	22	0.58	10.89	22	3.0%	-2.58 [-9.91, 4.75]
Manchanda et al. 2000	-0.5	5.6	21	-0.95	4.41	21	11.2%	0.45 [-2.60, 3.50]
Pal et al. 2011	-6.44	4.92	85	-2	6.88	85	18.1%	-4.44 [-6.24, -2.64]
Subtotal (95% CI)			**128**			**128**	**32.4%**	**-2.27 [-6.05, 1.50]**
Heterogeneity: $Tau^2 = 7.40$; $Chi^2 = 7.36$, df = 2 (P = 0.03); $I^2 = 73\%$								
Test for overall effect: Z = 1.18 (P = 0.24)								
Total (95% CI)			**384**			**367**	**100.0%**	**-3.20 [-4.54, -1.86]**
Heterogeneity: $Tau^2 = 1.73$; $Chi^2 = 20.20$, df = 11 (P = 0.04); $I^2 = 46\%$								
Test for overall effect: Z = 4.69 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 1.49$, df = 3 (P = 0.68), $I^2 = 0\%$								

(1) for high risk subjects versus modern medicine (exercise, diet, education)
(2) for high risk subjects versus usual care
(3) versus no intervention



d) High-density lipoprotein cholesterol (mg/dL) Note: signs are reversed so axis stay consistent with other forest plots even though an increase in HDL-C levels reflects clinical improvement.

Figure 2. Forest plots of body mass index (a), systolic blood pressure (b), low-density lipoprotein (c), and high-density lipoprotein cholesterol (d) results. Negative mean differences between groups favor the yoga intervention, positive mean differences favor control.

Yoga versus exercise. Five out of nine trials comparing yoga to exercise were conducted in healthy populations[27,41,42,46,47,56] and the remaining were conducted in young patient populations with hypertension,[40,48] an elderly female population with CAD,[43] and a population with type 2 diabetes mellitus.[45] Among the outcomes that were reported by more than one study, there was no significant difference in the effectiveness of yoga versus aerobic exercise in modifying body weight (0.61 kg (2.70, 1.49)),[41,43,47] SBP (0.64 mmHg (6.71, 5.43)),[40,42,46–48] DBP (0.14 mmHg (5.73, 5.44)),[40,42,47,48] and heart rate (1.42 beats/min (6.11, 3.27))[41,42,46,47,56] (Figure 3). In addition, there was also no difference comparing the two strategies for BMI,43 LDL-C,45 HDL-C,45 TC,45 TG,45 or FBG.[45] When all studies were pooled together, all trends remained irrespective of controls. MDs in risk factor reductions changed only slightly (online Supplementary Table S2).

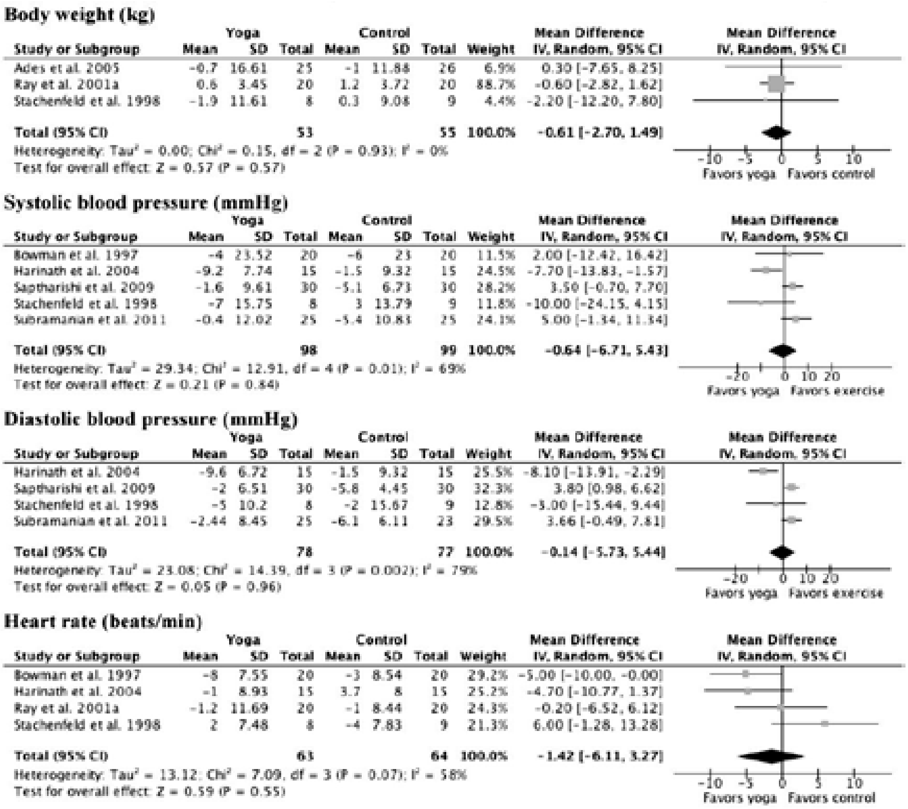


Figure 3. Forest plots of yoga versus physical exercise results for body weight, systolic blood pressure, diastolic blood pressure, and heart rate.

Publication bias

Funnel plots assessing publication bias of the primary outcomes are shown in online Supplementary Figure S3. As the funnel plots are mostly symmetrical, we do not find evidence of strong publication bias.

Discussion

The review shows that the practice of yoga may be beneficial to managing and improving risk factors associated with CVD and metabolic syndrome. This finding, however, should be cautiously interpreted as the RCTs included were of limited sample size, heterogeneous, and had unclear or high risk of bias on several domains. When trials were pooled, all but two of the outcomes examined in this review showed improvement after a yoga intervention when compared to non-exercise controls. Compared to traditional aerobic exercise controls, there was no significant difference in how exercise or yoga changed risk factors, suggesting similar effectiveness of the two forms of physical activity and possibly similar underlying mechanisms. The mechanism behind the therapeutic effect of yoga for CVD is still unclear; studies have suggested that yoga may modulate autonomic function and beneficially alter markers of sympathetic and parasympathetic activity.[12–14] Through practicing yoga, the effects of stress can be reduced, leading to positive impacts on neuroendocrine status, metabolic and cardio-vagal function, and related inflammatory responses.[12–14] The similarity in effectiveness on risk factors between the two forms of exercise suggest that there could be comparable working mechanisms, with some possible physiological aerobic benefits occurring with yoga practice, and some stress-reducing, relaxation effect occurring with aerobic exercise. This review helps strengthen the evidence base for yoga as a potentially effective therapy for cardiovascular and metabolic health. Our results support earlier reviews on the positive benefits of yoga on primary and secondary prevention of CVD and metabolic syndrome.[11,13,18–20,22,50,57] Two systematic reviews that were recently published find that there is some evidence for yoga having favorable effects on CVD risk factors.[58,59] One review, conducted by the Cochrane Collaboration, included 11 trials with its more restrictive inclusion criteria and found significant improvement in DBP, TG, and HDL.[59] The second review, with broad inclusion criteria and a wider list of outcomes, included 44 trials and found that yoga improves SBP, DBP, heart rate, respiratory rate, waist circumference, waist/hip ratio, TC, HDL, very low density lipoprotein, HbA1c, and insulin resistance.[58] All studies find that published RCTs on yoga are small, of short duration, and heterogeneous, precluding any strong conclusions on the effectiveness of yoga. Yoga may provide the same benefits in risk factor reduction as traditional physical activity such as cycling or brisk walking, supporting a previous narrative review.[22] This finding is significant as individuals who cannot or prefer not to perform traditional aerobic exercise might still achieve similar benefits in CVD risk reduction. Evidence supports yoga's accessibility and acceptability to patients with lower physical tolerance like those with pre-existing cardiac conditions, the elderly, or those with musculoskeletal or joint pain.[28] Lastly, in addition to

CVD risk factor improvements, other benefits may result from practicing yoga. For example, yoga may provide health-related quality of life improvements such as reductions in stress and anxiety and better coping mechanisms distinct from other forms of exercise. Yoga may also be practiced in a variety of settings with no special equipment needed, potentially increasing the frequency and ease of practice. These benefits may produce greater willingness to engage in a form of physical activity and better adherence and sustainability, ultimately facilitating greater long-term individual- and population-level CVD and metabolic risk reductions.

Limitations

There are potential limitations of this review. First, we included only English language articles and articles published in peer-reviewed journals. Second, several outcomes are related to cardiovascular and metabolic health; we focused on the major risk factors and surrogate markers for these conditions, as they are predictive of CVD risk[4] and concrete outcomes such as cardiac death and myocardial infarction were not reported in the RCTs. As with all RCTs, findings are applicable to the patient population in which the study was conducted and wide generalizations should be avoided. There was a great deal of heterogeneity across included studies. Because part of the appeal and feasibility of yoga is the customizability of the practice to individual practitioners, a wide variety of yoga interventions, frequencies and lengths of practice and follow-up were included. To deal with some of this variation, we used random effects in the meta-analysis and divided patient populations into subgroups. Although I^2 values did drop within subgroups compared to overall, heterogeneity was still present. As more studies are undertaken and published, further division by yoga tradition, duration of follow-up, and other factors can be performed. Lastly, study quality and assessment could be improved. Many studies had small sample sizes and did not fully report all methods and outcomes, leading to high or unclear ratings in the risk of bias on several domains. On a related note, although the Cochrane Risk of Bias tool is widely used and applicable, the definitions and structure of the rating system can lead to inaccurate estimation of study quality. For example, blinding of participants is not possible in RCTs, automatically leading to a high bias rating in the ‘performance bias’ domain, which assesses blinding of participants and personnel. Study quality could thus be underestimated in many cases. Nevertheless, more complete reporting of methodology and outcomes by authors can help enhance the usefulness and rigor of the trials.

Future research directions

Despite the growing evidence on the health implications of yoga, the physiological mechanisms behind the observed clinical effects of yoga on cardiovascular risk remains unclear. Inquiries into the minimum effective dose of yoga and the dose-response relationship can help elucidate yoga’s potential as a medical therapy. Research is also still lacking on the costs and economic implications; more research can be done comparing the relative costs and benefits of yoga versus traditional methods like exercise or medication. Yoga has the potential to be a cost-effective treatment and prevention strategy given its low cost, lack of expensive equipment or technology, potential greater adherence, health-related quality of life improvements, and possible accessibility to larger segments of the population.

Conclusion

Our review finds emerging evidence to support a role for yoga in improving common modifiable risk factors of CVD and metabolic syndrome. Whereas previous reviews have looked at a single or a few risk factors, our review updates the existing literature and encompasses numerous CVD and metabolic risk factors that can be used to calculate overall CVD risk. We believe that these findings have important implications for the acceptance of yoga as an effective therapeutic intervention. Given the growing popularity of yoga in the US and around the world, there is a need for larger randomized controlled studies that meet explicit, high quality methodological standards to ascertain the effects of yoga. This review demonstrates the potential of yoga to have an impact on concrete, physiological outcomes that represent some of the greatest health burdens today.

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Chapter 7

Web-Based Mindfulness Intervention in Heart Disease: A Randomized Controlled Trial.

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Abstract

Background. Evidence is accumulating that mindfulness training has favorable effects on psychological outcomes, but studies on physiological outcomes are limited. Patients with heart disease have a high incidence of physiological and psychological problems and may benefit from mindfulness training. Our aim was to determine the beneficial physiological and psychological effects of online mindfulness training in patients with heart disease.
Methods. The study was a pragmatic randomized controlled single-blind trial. Between June 2012 and April 2014 we randomized 324 patients (mean age 43.2 years, 53.7% male) with heart disease in a 2:1 ratio (n=215 versus n=109) to a 12-week online mindfulness training in addition to usual care (UC) compared to UC alone. The primary outcome was exercise capacity measured with the 6 minute walk test (6MWT). Secondary outcomes were other physiological parameters (heart rate, blood pressure, respiratory rate, and NT-proBNP), subjective health status (SF-36), perceived stress (PSS), psychological well-being (HADS), social support (PSSS12) and a composite endpoint (all-cause mortality, heart failure, symptomatic arrhythmia, cardiac surgery, and percutaneous cardiac intervention). Linear mixed models were used to evaluate differences between groups on the repeated outcome measures.
Results. Compared to UC, mindfulness showed a borderline significant improved 6MWT (effect size, meters: 13.2, 95%CI: -0.02; 26.4, p=0.050). There was also a significant lower heart rate in favor of the mindfulness group (effect size, beats per minute: -2.8, 95%CI: -5.4;-0.2, p=0.033). No significant differences were seen on other outcomes.
Conclusions. Mindfulness training showed positive effects on the physiological parameters exercise capacity and heart rate and it might therefore be a useful adjunct to current clinical therapy in patients with heart disease.

Introduction

In recent decades, cardiovascular disease (CVD) has become the foremost cause of health burden worldwide.[1] Especially the group of adults with congenital heart disease has increased over the last decades. While cardiovascular disease cause significant stress,[2] chronic stressors such as anxiety and depression are themselves independent risk factors for cardiovascular morbidity and mortality.[3,4] Chronic stress can negatively affect not only quality of life, but also physiological parameters such as respiration rate, heart rate, blood pressure, inflammatory markers and brain activity.[5]

As heart rate is associated with long-term survival, patients are recommended to try reducing heart rate in the management and prevention of CVD.[6] Often medication, such as betablockers, is prescribed for this goal. Stress reduction in itself may also have a beneficial effect on heart rate and physical fitness. While the best approach to stress management is unclear, increased attention is now being paid to lifestyle interventions such as mindfulness therapy.[7,8] Mindfulness is described as the capacity to live with open and non-judgmental awareness towards all experiences within the present moment.[9,10] Several core features, such as meditation, yoga, and cognitive assignments, can increase the ability to accept negative experience or emotions.[11] Mindfulness therapy has been found to positively affect psychological outcomes in patients with chronic pain, obesity, hypertension, depression, anxiety and cardiovascular disease.[12-16]

We hypothesized that, besides these psychological effects, mindfulness therapy may influence heart rate, breathing patterns and blood pressure through a favorable effect on the autonomic nervous system and therefore may positively affect exercise capacity and thus long-term outcome[17]. In a randomized controlled trial (RCT), we therefore investigated the effectiveness of online mindfulness training on exercise capacity in patients with heart disease.

Methods

Study design

The current study is a single blinded, pragmatic RCT performed at the outpatient cardiology clinic of the Erasmus MC, Rotterdam, The Netherlands. Ethical approval was obtained from the Medical Ethics Committee (METC) of the Erasmus Medical Center and the study complied with the Declaration of Helsinki (see supporting information). The study was registered at the Dutch trial register, 3453, http://www.trialregister.nl. Patients received written information about the study at home, 2-4 weeks prior to their scheduled visit to the cardiologist at the outpatient clinic. Full disclosure was given about the nature of the intervention. The current study reports the results of 3 month follow-up, which ended in July 2014, whereas the 12-month follow-up is still ongoing.

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Participants

Adult patients, between 18 and 65 years of age, with diagnosed heart disease (ischemic, valvular, congenital heart disease, or cardiomyopathy) were eligible for inclusion between June 2012 and April 2014. Patients were excluded based on the following criteria: (1) planned operation or percutaneous intervention within the upcoming year; (2) inability or unwillingness to give informed consent; (3) inability to understand Dutch, inability to read or write Dutch; (4) no internet access, email, or cell phone; (5) patients who did not fill out the baseline questionnaires or did not show up for the scheduled baseline tests. All participants provided written informed consent.

Intervention

The active intervention was mindfulness training which consisted of a 12-week structured standardized online program. The training was offered in addition to usual care (UC) as provided by the treating cardiologist. All patients received a book about mindfulness by a renowned author to support the 12-week training [18]. The training was designed to be self-directed and to be easily accessible and engaging to a wide audience by keeping practice sessions and lessons short. The program teaches different meditations, self-reflection, and yoga. Furthermore, it includes practical assignments and suggestions for mindfulness in day-to-day life. The use of breath as a reminder for present moment awareness is emphasized in all meditations. The program was divided into four components (see supporting information). During the course participants also received biweekly reminders by e-mail and standardized text messages. Adherence to the intervention was monitored by whether the questions of the online program were completed. For privacy reasons, the content of the answers remained undisclosed. Both the program and the book were provided free of charge to participating patients.

Control

The control group received UC by their treating cardiologist. Treatment and frequency differs between patients, but general components are regular outpatient visits, lifestyle advice regarding nutrition, smoking, exercise, stress reduction, medication and other procedures if indicated. We chose for a pragmatic study design without a placebo online training in order to measure effectiveness rather than efficacy. This choice is justified by the likelihood of a partial placebo effect that is part-and-parcel of the training as it would be implemented in future practice.

Randomization

After a patient's eligibility was established by one of the study investigators, written informed consent was obtained and baseline measurements were performed. Subsequently, patients were randomized according to a 2:1 ratio via dedicated computer software (ALEA®) with a block size of 12 to receive the online Mindfulness training or UC.[19] The investigator entered the patients into the computer software, but did not receive the result of the allocation. The result of the randomization procedure was sent to an independent employee (medical secretary) of the outpatient clinic, who was not involved in establishing eligibility, outcome assessment, or data analyses. Subsequently, this employee contacted the participant with the result and provided instructions on how to access the web-based training.

Blinding

Due to the nature of the intervention, blinding of patients was not feasible. The intervention started as soon as patients logged on to the mindfulness training website. The outcome assessors (investigators) were unaware of patients' treatment allocation. Therefore, the design of this study can be considered as a single-blinded randomized controlled trial in which the investigators remained blinded throughout the duration of the study. Additionally, patients were instructed not to say anything about their treatment allocation, neither to study investigators nor to their cardiologist.

Outcome measures

Outcomes were measured in all patients pre- (T0) and post-intervention (12 weeks, T1). We were interested in evaluating the physical effects of mindfulness and thus chose as primary outcome measure the 6MWT, which is an overall measure of exercise tolerance, has reproducible results, and has shown to be an independent predictor of long term outcome.[20-22] The 6MWT was performed in a 20-meter-long corridor at the outpatient clinic.[23] The corridor had well-indicated 'start' and 'finish' marks with colored pawns.

Secondary outcome measures were:
Physical parameters: weight, blood pressure, respiratory rate and heart rate. BMI was calculated by weight in kilograms divided by height in meters squared. Blood pressure was measured using an automated non-invasive monitor (Mindray Datascope Duo) after the participant had rested for 5 minutes in the sitting position. This monitor also reports the heart rate. Respiratory rate was measured in rest within a set amount of 30 seconds.
Blood sampling laboratory tests: N-terminal pro-brain natriuretic peptide (NT-proBNP, Elecsys system, Roche Diagnostics, Basel, Switzerland: normal values ≤ 14pmol/L) and creatinin were measured from peripheral venous blood samples.
Subjective health status: The Short-Form Health survey 36 (SF-36) was used to evaluate subjective health status. For each of the 8 subdomains a transformed score is generated, ranging from 0 to 100,[24] with a higher score indicating better health.[25] The subdomains were used to construct the mental component summary (MCS) measure, which consists of the subdomains vitality, social functioning, role-emotional functioning and mental health, and the physical component summary (PCS) measure, which consists of the subdomains physical functioning, role physical functioning, bodily pain and general health.[26]

A Visual Analogue Scale (VAS) was used to assess subjective perceived QoL ("Indicate on the line above where you would situate yourself in terms of your overall quality of life'', ranging from 0 to 100, with a higher score indicating better QoL.[27]
Psychological well-being: To assess symptoms of anxiety and depression, the Hospital Anxiety and Depression scale was used. The questionnaire contains 14 items on depression and anxiety with a higher score on the 3 point Likert scale indicating a greater level of emotional distress.[28]
Stress: The Dutch version of the Perceived Stress Scale (PSS) was used to evaluate perceived stress. The scale consists of fourteen 5-point Likert scales, with a higher score indicating a higher level of stress (0=never, 4=very often). A total perceived stress score is made by summing all individual ite.[29]
Social support: To evaluate perceived social support, the Dutch version of the Perceived Social Support Scale 12 Blumenthal (PSSS12) was used. The PSSS12 has 12 items with a 7-point Likert scale addressing the degree of perceived social support with a higher score indicating a greater feeling of support (1=very strongly disagree, 7= very strongly agree).[30] For the purpose of this study we used the total score.
Adverse events: Adverse events were defined as all-cause mortality, heart failure, symptomatic arrhythmia, cardiac surgery, and percutaneous cardiac intervention. Arrhythmias were defined as symptomatic if antiarrhythmic medication was prescribed, cardioversion or ablation had been applied, or a pacemaker or intracardiac defibrillator (ICD) was implanted. Heart failure was defined as an event when either medication or hospitalization was necessary.

Other study parameters

In order to document baseline risk levels, traditional cardiovascular risk factors and demographics were determined: age, sex, length, weight, smoking, type of heart disease, and employment status. Additionally participation in other mindfulness-based exercises and the use of other complementary care was monitored with a questionnaire (type, frequency, and intensity).

Quality control and audit

The digitalization of the paper case record forms (CRFs) in the database was independently performed by 2 persons (JY and MW). After digitalization, an error rate of <0.5% was observed between JY and MW. An independent audit was performed and the study was found to comply with Good Clinical Practice and Scientific Integrity standards.

Sample size justification

To demonstrate an improvement of 5% in the intervention group vs 1% in the control group on the 6MWT, this study required 99 patients in the control group and 198 in the active intervention group (SD10%, alpha=0.05, power=0.90, ratio experimental to controls= 2).

Even if only 50% of patients in the experimental group adhered to the training, this would give us a power of 0.80 in the as-treated analysis. To account for non-adherence and loss to follow-up our aim was to randomize at least 300 patients. This number of patients is sufficient to demonstrate a smaller difference (5% in the intervention group vs 2% in the control group) in a repeated measurements analysis with a power of 75% (2 follow-up measurements, correlation between follow up measurements=0.70, correlation between baseline & follow-up=0.50).

Statistical analysis

Descriptive analyses were performed to describe the baseline characteristics of demographic and clinical variables stratified by treatment group. Changes in outcomes at 12 weeks compared with baseline (intragroup effect) and differences between treatment groups (difference in delta's, intergroup effect) on physiological and psychological outcomes were calculated. To simultaneously account for the correlation between the multiple measurements of each patient and dropout, a repeated measurements analysis was performed using a multivariate linear regression mixed model to determine intergroup effects. In the mean structure of the mixed model we included the time effect, the intervention effect and their interaction, while a fully unstructured variance-covariance matrix was assumed for the error terms. Due to randomization only p-values for the interaction effect are reported.

An intention-to-treat (ITT) analysis was performed to address whether offering a mindfulness training was effective compared to UC. An as-treated (AT) analysis was performed to address whether the mindfulness training was beneficial if actually performed. In the AT analysis, patients were considered adherent if they completed 50% or more of the exercises. Patients allocated to the UC group who sought mindfulness training on their own were excluded from the AT analysis. For both ITT and AT, Cohen's D was calculated to enable comparison of effect sizes. This calculation was performed based on the results of the mixed model. A p-value less than 0.05 was considered to be indicative of statistical significance. All data were analyzed with IBM SPSS Statistics version 21.0 (IBM Corp., Somers, NY).

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Results

Patient recruitment and characteristics

A flowchart of the patients' recruitment is shown in Figure 1. Patients' baseline characteristics (Table 1) demonstrated no significant differences between the intervention and control group which confirmed a successful randomization, also on important characteristics such as: age (p=0.98) and, gender (p=0.28). In total, 5 patients did not complete any assignment of the mindfulness training whereas 115 patients completed at least 50% of the assignments (as-treated analysis) with a mean 53% (SD 34%).

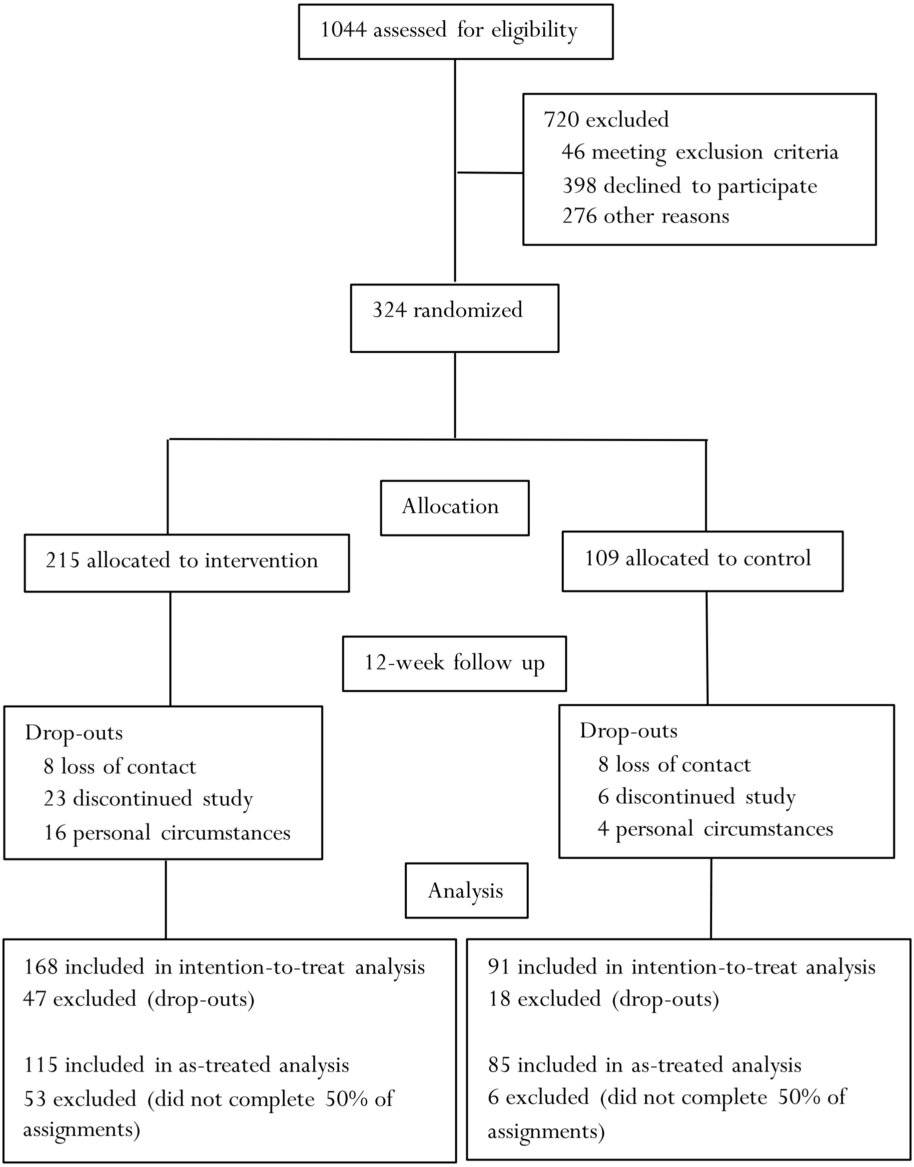

Figure 1. Flowchart of mindfulness training and control group

Table 1. Baseline characteristics of study participants

	Mindfulness Group N=215	**Control Group N=109**
Demographics		
Age (years), mean (SD)	43.2 (14.1)	43.2 (13.7)
Female (%)	44.2	50.5
Employed (%)	68.7	67.9
Physiological parameters		
Heart rate (beats/min), mean (SD)	68 (12)	69 (11)
Systolic blood pressure (mm Hg), mean (SD)	128 (16)	125 (15)
Diastolic blood pressure (mm Hg), mean (SD)	78 (11)	80 (10)
Resting respiratory rate (breaths/min), median (IQR)	15 (2)	15 (3)
Body mass index (kg/m²), mean (SD)	25.9 (4.6)	25.7 (4.7)
Obesity* (%)	16.7	15.6
Psychological parameters		
PCS, mean (SD)	46.6 (9.6)	45.3 (10.3)
MCS, mean (SD)	50.2 (10.6)	50.8 (9.6)
HADS Anxiety, mean (SD)	8.2 (3.6)	9.0 (3.4)
HADS Depression, mean (SD)	3.8 (2.9)	3.8 (2.9)
VAS, mean (SD)	75.0 (13.2)	72.7 (13.2)
PSS, mean (SD)	22.4 (7.8)	22.0 (7.5)
PSSS12, mean (SD)	69.5 (11.6)	71.5 (12.3)
Exercise tolerance		
6 minute walk test distance (meters), mean (SD)	537.5 (77.0)	539.3 (67.3)
Laboratory works		
NT-proBNP, median (IQR), pmol/L	16.7 (28.5)	18.3 (33.9)
Creatinine, median (IQR), µmol/L	79.0 (21.0)	77.0 (21.0)
Cardiac history, type of heart disease, (%)		
Congenital heart disease	41.9	42.2
Cardiomyopathy	39.5	29.4
Valvular heart disease	18.6	28.4
Other comorbidity, (%)		
Diabetes Mellitus**	3.2	3.7
Number of interventions in life***, mean (SD)	1.4 (1.4)	1.4 (1.2)
Time since first intervention (years), mean (SD)	19.1 (14.0)	15.9 (11.7)
ICD (%)	5.9	4.3
PM (%)	9.3	5.2
Current medication (%)	70.2	72.5
Beta-blocker	43.2	36.7
Statin	18.6	13.8
Aspirin	16.3	14.7
Ace-inhibitor	23.3	22.0
Angiotensin II antagonist	8.8	11.9

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Calcium channel blocker	9.8	6.4
Nitroglycerin	2.3	0.0
Cardiac glycoside	2.3	2.8
Diuretic	16.8	19.3
Anticoagulant	24.6	33.9
Antidepressant	5.1	2.8
Tranquilizer	1.9	1.8
Other	43.3	57.8
Intoxication, (%)		
Current smoking	14.4	18.3
Current alcohol use	62.1	55.0
Current drugs use	3.3	2.8
Prior use of complementary therapies****, (%)	14.4	12.8

* Obesity was defined when the BMI was ≥30 kg/m2
** Diabetes was defined when a patient reported use of anti-diabetes medication
*** Include both surgical and percutaneous interventions
**** Contains yoga, meditation, mindfulness, tai chi, Qigong and acupuncture
SD, standard deviation; PCS, physical component summary measure; MCS, mental component summary measure; VAS, visual analogue scale; HADS, hospital anxiety and depression scale; PSS, perceived stress score; PSSS12, perceived social support; NT-proBNP, N-terminal pro-Brain Natriuretic Peptide; IQR, interquartile range; ICD, implantable cardioverter-defibrillator; PM, pacemaker.

Safety/side effects

No major side effects were reported during the follow-up period. In 7 patients (5 mindfulness (2.3%), 2 control (1.8%)) at baseline and 13 patients (8 mindfulness (4.8%), 5 control (5.5%)) at follow-up, fatigue, dizziness, shortness of breath, or pain due to pre-existing conditions were described while performing the 6MWT.

Outcome analysis

At 12 weeks, the mindfulness group showed a notable improvement on their mean 6MWT, which was borderline significantly different compared with UC ($p = 0.050$) (Table 2). The intergroup comparison showed that heart rate was significantly lower in the mindfulness group ($p = 0.033$) (Table 2). Mean systolic and mean diastolic blood pressure decreased in the mindfulness and UC group, but no significant differences were found in the intergroup comparison (Table 2).

Table 2. Changes in outcomes at 12 weeks compared with baseline (intragroup effect) and differences between treatment groups (difference in delta's, intergroup effect) on physiological and psychological outcomes. Intention-to-treat analyses.

Physiological outcomes	Treatment group	Δ 12-week vs baseline (intragroup)[a] (mean, SD)	Effect estimate (intergroup)[b] (95%CI)	p-value
6MWT, meters	Mindfulness	10.42 (49.0)	13.2 (-0.02 to 26.4)	0.050
	Control	-4.0 (55.6)		
Heart rate, beats/minute	Mindfulness	-2 (10.9)	-2.8 (-5.4 to -0.2)	0.033
	Control	0.5 (9.0)		
SBP, mmHg	Mindfulness	4.2 (15.4)	-2.2 (-6.1 to1.7)	0.268
	Control	-1.9 (15.5)		
DBP, mmHg	Mindfulness	-1.9 (8.9)	1.6 (-0.8 to 4.0)	0.186
	Control	-3.4 (10.1)		
Respiratory rate, breath/minute	Mindfulness	-0.5 (3.6)	-0.02 (-0.04 to 0.01)	0.189
	Control	-0.1 (4.0)		
NT-proBNP, pmol/L	Mindfulness	0.3 (9.7)	-0.04 (-0.1 to 0.04)	0.333
	Control	0.0 (11.1)		
SF-36 PCS	Mindfulness	0.5 (6.3)	-0.4 (-2.0 to 1.3)	0.668
	Control	0.7 (6.7)		
SF-36 MCS	Mindfulness	0.2 (7.4)	0.7 (-1.4 to 2.8)	0.489
	Control	1.2 (8.8)		
VAS	Mindfulness	0.4 (10.4)	-0.4 (-3.0 to 2.1)	0.745
	Control	0.7 (9.3)		
HADS anxiety	Mindfulness	-0.5 (3.2)	0.6 (-0.2 to 1.4)	0.145
	Control	-0.9 (3.0)		
HADS depression	Mindfulness	-0.5 (2.9)	-0.4 (-1.1 to 0.2)	0.203
	Control	0.0 (2.3)		
PSS	Mindfulness	-2.4 (6.3)	-1.0 (-2.7 to 0.6)	0.226
	Control	-0.9 (6.8)		
PSSS12	Mindfulness	0.6 (7.4)	0.4 (-1.6 to 2.4)	0.685
	Control	0.1 (8.0)		

SD standard deviation; SE standard error; 6MWT six minute walk test; SBP systolic blood pressure; DBP diastolic blood pressure; NT-proBNP N-terminal pro-brain natriuretic peptide; SF-36 short form health survey; PCS physical scale; MCS mental scale; VAS visual analogue scale; HADS hospital anxiety depression scale; PSS perceived stress score; PSSS12 percieved social support
[a] delta value was calculated for those who attended the 12-week follow-up
[b] linear mixed model analyses for repeated measurements for differences between treatment groups (time x intervention effect).

Analyses showed no significant differences between the groups on the PCS and MCS of the SF-36 (Table 2). At 12 weeks, anxiety levels were lower than baseline scores in both the mindfulness and the UC group, but no significant differences were found in the intergroup comparison (Table 2). Depressive symptoms decreased at 12 weeks, but did not significantly differ between the groups. Neither perceived stress scores nor perceived social support were statistically significant different in the intergroup comparison (Table 2). No significant differences were found on adverse events.

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The results of the physiological outcomes are summarized in Figure 2, the results of the psychological outcomes are summarized in Figure 3.

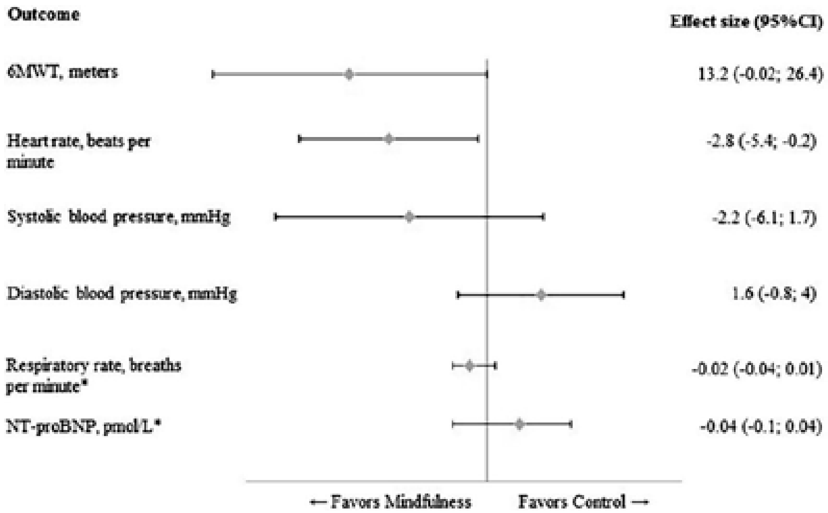

Figure 2. Forest plot of physiological outcomes. All values on the left of the Y-axis indicate a difference in favour of the mindfulness group. 6MWT, six-minute walk test; IC, confidence interval, NT-proBNP, N-terminal pro-brain natriuretic peptide; * Log-transformed scores.

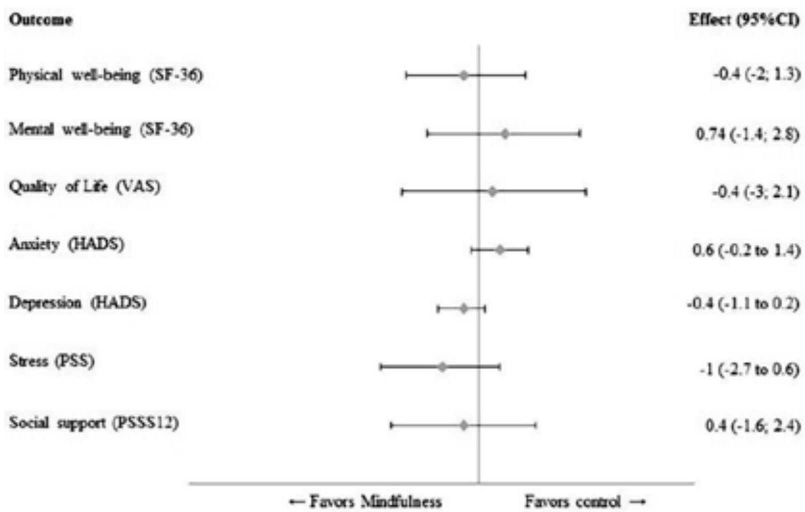

Figure 3. Forest plot of psychological outcomes.
All values on the left of the Y-axis indicate a difference in favour of the mindfulness group.

The results of AT-analyses were comparable with the ITT analyses (Table 3).

Table 3. Changes in outcomes at 12 weeks compared with baseline (intragroup effect) and differences between treatment groups (intergroup effect) on physiological and psychological outcomes, as-treated analyses.

Physiological outcomes	Treatment group	Δ 12-week vs baseline (intragroup)[a] (mean, SD)	Effect estimate (intergroup)[b] (95%CI)	p-value
6MWT, meters	Mindfulness	9.4 (35.9)	10.6 (-1.7 to 23.0)	0.091
	Control	-1.9 (51.7)		
Heart rate,	Mindfulness	-3.1 (11.7)	-3.4 (-6.3 to 0.4)	0.027
beats/minute	Control	0.5 (9.2)		
SBP, mmHg	Mindfulness	5.2 (14.5)	-3.8 (-8.0 to 0.3)	0.072
	Control	-1.5 (15.5)		
DBP, mmHg	Mindfulness	-2.3 (8.9)	0.8 (-1.8 to 3.5)	0.524
	Control	-3.4 (10.1)		
Respiratory rate,	Mindfulness	-0.7 (3.5)	-0.7 (-1.8 to 0.3)	0.173
breath/minute	Control	-0.1 (4.1)		
NT-proBNP,	Mindfulness	1.0 (28.7)	-0.04 (-0.2 to 0.1)	0.540
pmol/L	Control	4.7 (21.7)		
SF-36 PCS	Mindfulness	0.7 (6.4)	0.1 (-1.7 to 2.0)	0.893
	Control	0.4 (6.8)		
SF-36 MCS	Mindfulness	-0.1 (7.5)	1.2 (-1.1 to 3.5)	0.302
	Control	1.5 (8.9)		
VAS	Mindfulness	0.4 (10.4)	-0.2 (-3.0 to 2.6)	0.878
	Control	0.7 (9.3)		
HADS anxiety	Mindfulness	-0.5 (3.2)	0.5 (-0.4 to 1.4)	0.267
	Control	-0.9 (3.0)		
HADS depression	Mindfulness	-0.5 (2.9)	-0.4 (-1.2 to 0.3)	0.267
	Control	0.0 (2.3)		
PSS	Mindfulness	-2.4 (6.3)	-1.1 (-3.0 to 0.8)	0.244
	Control	-0.9 (6.8)		
PSSS12	Mindfulness	0.6 (7.4)	0.5 (-1.7 to 2.6)	0.670
	Control	0.1 (8.0)		

SD standard deviation; SE standard error; 6MWT six minute walk test; SBP systolic blood pressure; DBP diastolic blood pressure; NT-proBNP N-terminal pro-brain natriuretic peptide; SF-36 short form health survey; PCS physical scale; MCS mental scale; VAS visual analogue scale; HADS hospital anxiety depression scale; PSS perceived stress score; PSSS12 percieved social support

[a] delta value was calculated for those who attended the 12-week follow-up

[b] linear mixed model analyses for repeated measurements for differences between treatment groups (time x intervention effect).

Cohen's D

In order to compare different outcome measures, Cohen's D effect sizes were calculated. In the intention-to-treat analyses (Figure 4 and 5), heart rate and depression showed, small, but significant improvement (D=0.20, 95%CI 0.04 to 0.36 and d=0.17, 95%CI 0.01 to 0.33 respectively). In the As-Treated analysis, exercise capacity, heart rate, systolic blood pressure and stress improved significantly, with small effect sizes ranging from D=0.19 to D=0.21 (Figure 6 and 7).

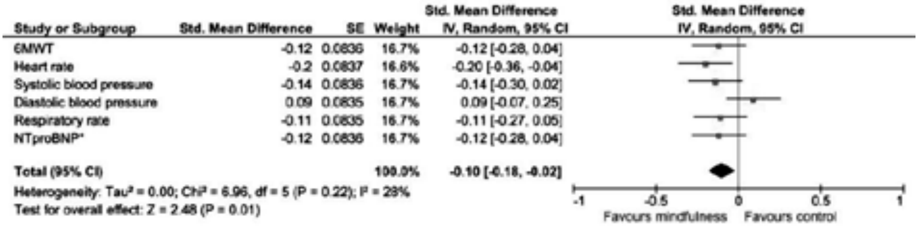

Figure 4. Forest plot showing the Intention-to-Treat Cohen's D results of the effectiveness of the mindfulness intervention compared to usual care on the physiological outcomes. The width of the line indicates the 95%CI. All values lower than 0 indicate a significant difference in favour of the mindfulness group.

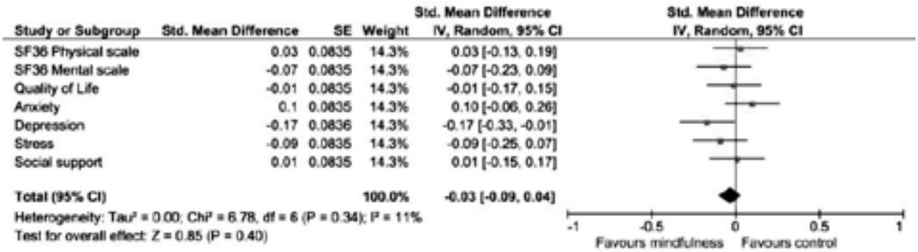

Figure 5. Forest plot showing the Intention-to-Treat Cohen's D results of the effectiveness of the mindfulness intervention compared to usual care on the psychological outcomes. The width of the line indicates the 95%CI. All values lower than 0 indicate a significant difference in favour of the mindfulness group.

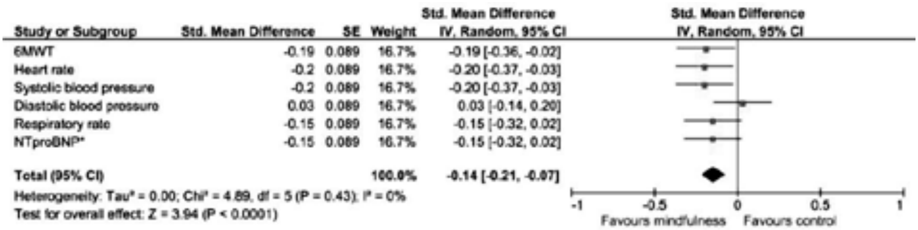

Figure 6. Forest plot showing the As-Treated Cohen's D results of the effectiveness of the mindfulness intervention compared to usual care on the physiological outcomes. The width of the line indicates the 95%CI. All values lower than 0 indicate a significant difference in favour of the mindfulness group.

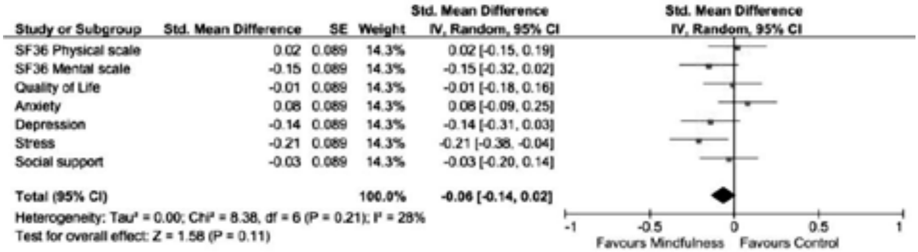

Figure 7. Forest plot showing the As-Treated Cohen's D results of the effectiveness of the mindfulness intervention compared to usual care on the psychological outcomes. The width of the line indicates the 95%CI. All values lower than 0 indicate a significant difference in favour of the mindfulness group.

Discussion

To our knowledge, this is the first randomized trial to evaluate the effectiveness of mindfulness training in patients with heart disease. By taking physiological parameters as its main outcome parameter, it is also an innovative study. On the primary endpoint – exercise capacity – we found a borderline significant but clinically small effect in favor of mindfulness. Heart rate also decreased significantly more with mindfulness training. Remarkably, no significant improvements were found on subjective outcome measures, although anxiety and depressive symptoms did decrease.

Limited exercise capacity is an important predictor for outcome for cardiac disease, and several studies have reported an association with survival.[17,31-33] Since a decrease in physical performance is also an important predictor of adverse outcomes in patients with congenital heart disease, improving physical performance may be an important target of treatment. In recent years, cardiac rehabilitation programs, many of them conducted in patients with post-myocardial infarction, have had good results on total and cardiovascular mortality.[34,35] Our results indicate that mindfulness training could be part of future treatment modalities intended to improve physical performance in heart disease patients. It remains to be shown whether this will also affect long-term outcome. Several epidemiological studies in patients with hypertension, acute coronary syndromes[36], stable coronary heart disease[37] and heart failure[38] have shown that resting heart rate is a risk factor for cardiovascular and all-cause mortality. These epidemiological results suggest that the beneficial effect of mindfulness on heart rate demonstrated in our study is clinically meaningful.

To date, very few studies have evaluated mindfulness training in patients with cardiac disease. A pilot study that offered a brief mindfulness-based stress-reduction program to patients with, or at risk of, coronary artery disease[16] showed significant but moderate reductions on two psychological outcomes, depression (Cohen's d=0.54) and perceived

stress (d=0.68). Unlike in our study, the participants were not randomized and the intervention was fairly short (4-weeks). Two reports of the same study population showed that mindfulness-based stress-reduction mainly improved anxiety, emotional control and coping, rather than resting-stress hormones or physical functioning.[39,40] Recently, a brief group-MBSR intervention in patients undergoing a percutaneous coronary intervention showed favorable effects on quality of life.[41] Additionally, anxiety, depression, and stress appeared to be influenced positively but only in the younger age group (<60 years).[41] Lastly, an individual MBSR training in patients with coronary heart disease showed significant reductions in anxiety, depression, perceived stress and the physiological parameters BP and BMI.[42] However, this study had limited power and was only performed in males. In contrast to previous reports, in our study psychological outcomes did not significantly improve by mindfulness training. Whereas in previous studies patients were often selected on the basis of reduced psychological well-being, in our study they were not. In fact, baseline psychological scores were similar to scores in the general population [43-47] implying that improvement was hardly possible (a ceiling effect). Also, our training was online without any personal contact, which probably resulted in smaller effects. There is increased interest in the effect of acceptance and commitment therapy, which has similarities with mindfulness training, focusing on the relationship between persons' own thoughts and feelings that could potentially have a positive effect on several modifiable CVD risk factors.[48]
Similar to the ceiling effect for psychological outcomes, we observed a floor effect for blood pressure, as our patients had regular blood pressure monitoring and (extra) medication was given when necessary. Previous studies, some of which showed potential benefits on blood pressure, investigated populations whose blood pressures at baseline were higher than average.[7,49]

Accumulating evidence suggests that mind and body do indeed show an interaction and that physiological changes are underlain by several neuro-humoral mechanisms. For example, in an extensive study of a framework in mind-body medicine, Benson and colleagues focused on the relaxation response as a core component in autonomic function and physical changes.[50,51] It has been shown that, through emotions and thoughts, the autonomic nervous system is key in the brain-heart connection.[52] By working through the autonomic nervous system, mind-body practices can also benefit endothelial, neuroendocrine and immune function.[53-55] However, the mechanism between the mind and body is not merely unidirectional: several levels of the neuro-axis have been found to contribute to the "top-down and bottom-up mechanisms" in mind-body practices.[56]

To date, web-based mindfulness training studies have been limited to small studies on stress reduction. A study by Gluck et al.[57] reported a trend towards lower levels of stress. Two other studies on online mindfulness training showed not only that it was feasible to conduct online mindfulness training, but also that it was effective in reducing stress.[58,59] It is important to emphasize that their study populations consisted of mainly females recruited from the healthy general population, and in one, no randomization was performed.

Limitations of the current study must be addressed. Our own study used neither a placebo nor a waiting list for the control group. We considered the placebo effect of the online training to be inherent to the active intervention: we evaluated the training and the control as they would be implemented in real-world practice and measured effectiveness rather than efficacy. We acknowledge that by doing so our study is pragmatic rather than explanatory. Our inclusion of the placebo effect as part of the mindfulness intervention compared with UC without placebo in the control group is further justified by the fact that no competing therapy exists. Every placebo online training similar to the intervention we could think of would likely have an unwanted beneficial effect in the control group.
Another limitation is that only 80.6% (n=261) of the patients returned for follow-up. Reasons for trial discontinuation were not reported due to recommendations from the local ethics committee. A possible explanation for the follow-up rate is the fact that the intervention was not offered in a group-based setting. The impact of online training may be lower than that of personal or group training. While this would mean that the results of mindfulness therapy may therefore be even stronger in other settings, the easy accessibility of online training may have allowed better generalizability of the results, as patients could do the training in their own environment and fit it into a busy schedule. Although we monitored participants' training activity, detailed adherence was difficult to assess and control for. Furthermore, ethical considerations prevented us from blinding patients to the nature of the intervention during the informed consent procedure and patients' expectation of the interventions was not addressed. The control group was therefore aware that the online mindfulness training was available and that they were not receiving it. This could have led to selective follow-up but we found no significant difference between the groups at follow-up with regard to demographic and clinical variables. A placebo lifestyle intervention in the control group could underestimate the effectiveness of the active intervention compared to what can be expected in real-world practice. Thus, rather than comparing to a unrealistic placebo intervention, we considered the placebo effect as part-and-parcel of the procedure. In addition, we did not assess maintenance of blinding, but the inability to blind patients could have potentially led to unblinding of the investigators (outcome assessors), even though extensive precautions were made to limit this bias.

Conclusions

Online mindfulness training is feasible in patients with heart disease and shows a small positive effect on exercise capacity and heart rate. The current study found no significant effect on psychological outcomes.

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Chapter 8

12 -month Follow-up of Online Modified Mindfulness Based Stress Reduction Training in Heart Disease: a Randomized Controlled Trial.

Gotink RA, Younge JO, Wery MF, Utens EMWJ, Michels M, Rizopoulos D, Van Rossum EFC, Roos-Hesselink JW, Hunink MGM.

Submitted.

Abstract

Objective: There is increasing evidence that mindfulness can reduce stress, and thereby affect other psychological and physiological outcomes as well. In patients with heart disease, we evaluated the effect of an online modified mindfulness based stress reduction training at 12-month follow-up.
Methods: 324 patients (mean age 43.2 years, 53.7% male) were randomized in a 2:1 ratio to additional 3-month online mindfulness training or to usual care (UC) alone. The primary outcome was exercise capacity measured with the 6 minute walk test (6MWT). Secondary outcomes were blood pressure, heart rate, respiratory rate, NT-proBNP, cortisol levels (scalp hair sample), mental and physical functioning (SF-36), anxiety and depression (HADS), perceived stress (PSS), and social support (PSSS12). Differences between groups on the repeated outcome measures were analyzed with linear mixed models.
Results: At 12-months follow-up, participants showed a beneficial but not significant effect on exercise capacity (6MWT: 17.9 meters, p=0.055) compared to UC. Cohen's D showed small but significant improvement on the 6MWT (d=0.22, 95%CI 0.05 to 0.39), systolic blood pressure (d=0.19, 95%CI 0.03 to 0.36), mental functioning (d=0.22, 95%CI 0.05 to 0.38) and depressive symptomatology (d=0.18, 95%CI 0.02 to 0.35). All other outcome measures did not change statistically significant. In the as-treated analysis, systolic blood pressure decreased significantly with 5.5 mmHg (p=0.045; d=0.23 (95%CI 0.05-0.41)).
Conclusion: Online mindfulness training shows favorable albeit small long-term effects on exercise capacity, systolic blood pressure, mental functioning, and depressive symptomatology in patients with heart disease and might therefore be a beneficial addition to current clinical care.

Introduction

In recent decades, Mindfulness-Based Stress Reduction (MBSR) has grown to be a well-known adjunct intervention in Western healthcare with reproducible significant psychological improvements in multiple patient populations regarding depressive symptomatology, anxiety, stress, and quality of life [1]. Mindfulness is described as 'the capacity to observe with open and non-judgmental awareness towards all experiences within the present moment' [2]. Techniques taught as part of the eight-week MBSR training, mainly meditation, yoga and cognitive reappraisal, teach participants to be more present in the here and now and to be more aware of bodily sensations and internal psychological processes, which can increase the ability to recognize stress symptoms at an early stage. Stress from the mindfulness perspective refers to the tension that arises when we have negative experiences that we do not want [3]: MBSR teaches acceptance of negative emotions or thoughts as passing experiences and thereby reducing the stress associated with them [4]. People with chronic conditions are prone to having negative thoughts and feelings they do not want (depression and anxiety comorbidity is high [5,6]) and MBSR has been found to positively affect psychological outcomes in patients with chronic pain, obesity, hypertension, depression, anxiety and cardiovascular disease [7-11]. Over one million people in the Netherlands suffer from cardiovascular disease, and each year 100.000 get diagnosed. Healthcare costs are eight billion euro; 9.2% of total healthcare costs [12]. Cardiovascular disease is affected by stress: high perceived stress is associated with a risk ratio of 1.27 for incident coronary heart disease [13], presence of psychosocial stressors is associated with increased risk of acute myocardial infarction [14] and it negatively affects heart rate, blood pressure and inflammatory factors [15]. Low and variable heart rate and low blood pressure are associated with long-term survival and according to the ESC Guidelines cardiovascular patients are recommended to reduce stress in order to favorably affect these risk factors [16]. Often preventive medical therapy is prescribed, but this may have side-effects and be costly. In previous studies on cardiovascular patients, MBSR was found to improve heart rate, breathing patterns and blood pressure [17,18]. These factors have been related to exercise capacity: lower blood pressure and heart rate are directly related to exercise capacity [19-21] and a walking distance of <300 meters on the six minute walking test is a prognostic marker of subsequent cardiac death in patients with mild to moderate congestive heart failure [22]. The aim of this study was to investigate the long-term effects of an online mindfulness training on exercise capacity in patients with heart disease in a randomized controlled trial. In 3-month post-intervention follow-up, participants had a higher mean distance on the 6-minute walk test, however this was small and not statistically significant (13.4 metres, $p=0.050$) [23]. The rationale of this study is that in reducing stress, mindfulness therapy might influence heart rate, breathing patterns and blood pressure. These physiological effects may in turn improve exercise capacity and thus long-term outcome in cardiovascular patients [24].

Methods

Study design

The current study reports the results of the 12-month follow-up of a single blinded, pragmatic RCT performed at the outpatient cardiology clinic of the Erasmus MC, Rotterdam, the Netherlands. Detailed description of design and methodology, and 3-month results have been reported elsewhere [23]. Ethical approval was obtained from the Medical Ethics Committee of the Erasmus Medical Center and the study complies with the Declaration of Helsinki. The study was registered with the Dutch trial registry, NTR3453, http://www.trialregister.nl.

Participants

Adult patients, between 18 and 65 years of age, with existing diagnosed heart disease (ischemic, valvular, congenital heart disease, or cardiomyopathy) were approached between June 2012 and April 2014 during their scheduled yearly visit at the outpatient clinic. Patients were excluded when there was: (1) a planned operation or percutaneous intervention within the upcoming year; (2) inability to understand, read, or write Dutch; (3) no internet access, email, or cell phone. After written informed consent was obtained and baseline measurements were performed, patients were randomized according to a 2:1 ratio to the intervention or control group via dedicated computer software (ALEA®) with a block size of 12 [25]. The result of the randomization was sent to an employee not involved in outcome assessment, who contacted the participants about their allocation, to ensure outcome assessors were blinded.

Intervention

The mindfulness training consisted of a 12-week structured online program (see Appendix Table 1), which was offered in addition to usual care (UC) as provided by the treating cardiologist. Participants also received a book about mindfulness by a renowned author to support the 12-week training [26]. The intervention started as soon as patients logged in on the mindfulness training website, to which they gained access the day of the inclusion. Online delivery of the training was chosen for pragmatic reasons: the training was designed to be self-directed, easily accessible and engaging to a wide audience by keeping practice sessions and lessons short, usually ten to fifteen minutes per exercise. The program teaches different meditations, self-reflection, and yoga exercises. Furthermore, it includes practical assignments and suggestions for mindfulness in daily life. The use of the breath as a reminder for present moment awareness is emphasized in all meditations. During the course participants also received biweekly reminders by e-mail and standardized text messages. After the 12-week online intervention, these reminders continued until the 12 month follow-up. Adherence was monitored by whether the questions of the online program were completed, without disclosing the content of the answers. The control group received UC by their treating cardiologist. We considered any partial placebo effect an integral part of the active intervention as it would be when implemented in day-to-day practice.

Outcome measures

Please see for details the publication on short-term outcomes [23]. Outcomes were measured in all patients at baseline, post-intervention (3 months), and 9 months after the intervention was completed (12 months). Blinding of patients was not possible due to the nature of the intervention, but the outcome assessors were unaware of patients' treatment allocation, and patients were instructed not to disclose their treatment allocation to the study investigators nor to their cardiologist.

To measure exercise capacity, the 6 Minute Walking Test (6MWT) was chosen as primary outcome measure, performed in a quiet corridor of the outpatient clinic [27]. Patients were instructed to walk the greatest distance they could in 6 minutes. Secondary outcome measures were physical parameters (blood pressure, respiratory rate, and heart rate), blood sampling laboratory test (N-terminal pro-brain natriuretic peptide (NT-proBNP) measured from peripheral venous blood samples), and hair cortisol as a biomarker of stress using ELISA as previously described[28]. Details on lab procedures can be found in Younge et al. [21].

To assess psychological functioning, we measured quality of life (using the Short-Form Health survey 36 [29] and a Visual Analogue Scale ranging from 0 to 100 [30]), anxiety and depression (Hospital Anxiety and Depression scale [31]), perceived stress (Perceived Stress Scale [32]) and social support (Perceived Social Support Scale (PSSS12)[33]). The use of other complementary care was monitored with a questionnaire (type, frequency, and intensity).

Quality control and statistical analyses

An independent audit was performed and the study was found to comply with Good Clinical Practice and Scientific Integrity standards. To demonstrate an improvement of 5% in the intervention group vs 1% in the control group on the 6MWT, this study required at least 99 patients in the control group and 198 in the intervention group (SD10%, alpha=0.05, power=0.90, ratio experimental to controls=2). A detailed sample size calculation can be found in Younge, 2015 [23].

Changes in outcomes at 12 months were compared with baseline and between treatment groups. An intention-to-treat (ITT) analysis was performed to address whether offering a mindfulness training was effective compared to UC. An as-treated (AT) analysis was performed to address whether the mindfulness training was beneficial if actually performed. In the AT analysis, patients were considered adherent if they completed 50% or more of the exercises. Patients allocated to the UC group who sought mindfulness training on their own initiative were excluded from the AT analysis.

Linear mixed models were used to determine intergroup effects and to simultaneously account for the correlation between the repeated measurements of each patient and for dropouts. Time effect and its interaction with treatment were included as a categorical variable, while the covariance matrix was assumed unstructured. The F-test was used to test treatment effect. In order to compare effect sizes, Cohen's d was calculated based on the linear mixed model results. Finally, we performed log linear regression analyses to see which participants were most likely to adhere to the training, and if adherent, what characteristics predicted the most benefit from the training. $P<0.05$ was considered to be indicative of statistical significance. All data were analyzed with SPSS version 21.0 [34].

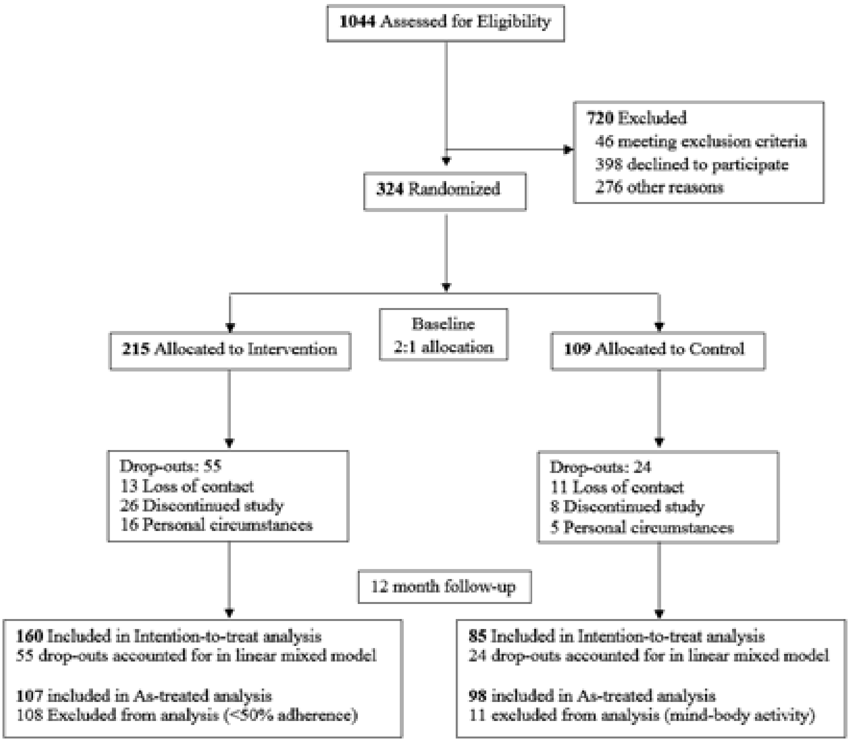

Figure 1. Flowchart of mindfulness intervention group and control group

Results

Patient characteristics

Figure 1 displays the flowchart of the patients' recruitment and follow-up. A total of 324 patients were included and successfully randomized over the two treatment arms. Of the initial study population, 245 participants returned for long-term follow-up (75.6%), and 224 participants were present at all three measurement moments.
Table 1 shows participants' baseline characteristics. No significant differences were found between the groups at follow-up with regard to demographic and clinical variables, and this percentage of follow-up still gives us sufficient power and the assumptions of our statistical tests were met. No major side effects were reported during the follow-up period.

Table 1. Baseline characteristics of study participants

	Mindfulness Group N=215	**Control Group N=109**
Demographics		
Age (years), mean (SD)	43.2 (14.1)	43.2 (13.7)
Female (%)	44.2	50.5
Employed (%)	68.7	67.9
Body mass index (kg/m²), mean (SD)	25.9 (4.6)	25.7 (4.7)
Cardiac history		
Type of heart disease, (%)		
· Congenital heart disease	41.9	42.2
· Cardiomyopathy	39.5	29.4
· Valvular heart disease	18.6	28.4
Number of interventions* mean (SD)	1.4 (1.4)	*1.4 (1.2)*
Time since first intervention (years) mean (SD)	19.1 (14.0)	*15.9 (11.7)*
Implantable cardioverter-defibrillator (%)	5.9	*4.3*
Pacemaker (%)	9.3	*5.2*
Intoxication, (%)		
· Current smoking	14.4	18.3
· Current alcohol use	62.1	55.0
· Current drugs use	3.3	2.8
Prior use of complementary therapies** (%)	14.4	12.8

* Includes both surgical and percutaneous interventions
** Includes yoga, meditation, mindfulness, Tai Chi, Qigong and acupuncture

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Outcome analysis

In the ITT analyses, the mindfulness group showed an improvement of 17.9 meters on their mean 6MWT at 12 months compared to UC, which was not statistically significant (p=0.055) (Table 2). Heart rate, systolic and diastolic blood pressure, and hair cortisol level decreased over time, but not significantly different from UC. NT-proBNP did not change significantly. Analyses on psychological outcomes showed no significant differences between the groups Anxiety, depression and stress levels decreased stronger in the mindfulness group than in UC, but not statistically significantly. In the AT analyses, 205 participants (63.3%) were adherent to their allocated group: in the intervention group 49.8% (N=107) completed at least 50% of the training, and in the control group 89.9% (N=98) performed no mind-body practice. Systolic blood pressure decreased significantly with 5.5 mmHg (p = 0.045) compared to UC. The other outcomes were similar to the ITT analysis.

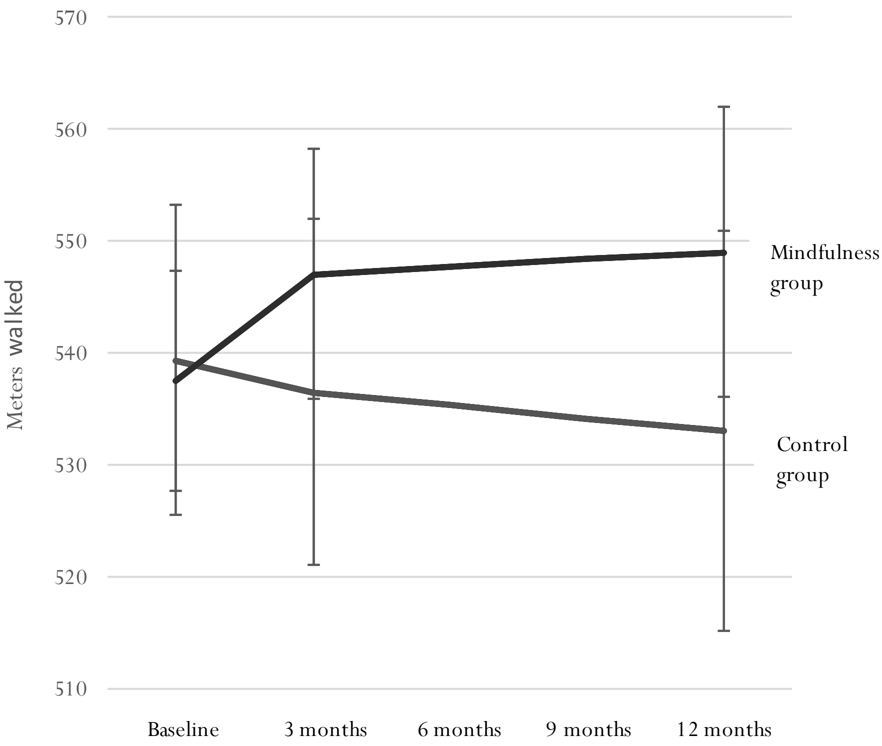

Figure 4. Plot showing Linear Mixed Models results: the mean distance walked in meters by the Intervention group (red) and the Control group (blue) at each of the three measurement moments.

Table 2. Outcomes at baseline and 12 months, and Linear Mixed Models-based estimated difference (β) of intervention group compared to control over time.

Intention-to-treat analysis

Outcome	Treatment group	Baseline (mean, SD) N=324	12 months (mean, SD) N=245	Difference (β)	95% Confidence Interval	p-value
6MWT, meters	Mindfulness	537.5 (77.0)	549.0 (81.6)	+17.9	-0.4 to 36.2	0.055
	UC	539.3 (67.3)	532.9 (82.8)			
Heart rate, beats/min	Mindfulness	68 (12)	67 (12)	-0.2	-3.2 to 2.8	0.897
	UC	69 (11)	68 (12)			
SBP, mmHg	Mindfulness	127.5 (16)	123.8 (17)	-3.8	-8.2 to 0.5	0.085
	UC	125.4 (15)	125.4 (17)			
DBP, mmHg	Mindfulness	78.0 (11)	77.0 (10)	+1.5	-1.0 to 4.1	0.240
	UC	79.7 (10)	77.1 (10)			
NT-proBNP, pmol/L °	Mindfulness	2.9 (1.2)	2.9 (1.3)	+0.01	-0.2 to 0.2	0.902
	UC	3.0 (1.2)	3.0 (1.2)			
Cortisol (Hair pg/mg)	Mindfulness	35.8 (145.4)	32.0 (34.2)	+6.5	-18.9 to 31.8	0.614
	UC	40.2 (199.6)	30.0 (45.2)			
Physical QoL (SF-36)	Mindfulness	46.7 (9.6)	46.3 (9.2)	-1.6	-3.4 to 0.3	0.091
	UC	45.3 (10.3)	46.4 (9.4)			
Mental QoL (SF-36)	Mindfulness	50.1 (10.6)	51.6 (10.5)	+2.2	-0.5 to 4.8	0.108
	UC	50.8 (9.6)	50.1 (10.5)			
Quality of life (VAS)	Mindfulness	75.0 (13.2)	75.5 (12.0)	-1.8	-4.9 to 1.4	0.265

	UC	72.5 (13.2)	74.8 (12.2)			
Anxiety (HADS)	Mindfulness	8.2 (3.6)	7.5 (3.6)	+0.7	-0.2 to 1.5	0.156
	UC	9.0 (3.4)	7.6 (3.6)			
Depression (HADS)	Mindfulness	3.8 (2.9)	3.3 (2.7)	-0.5	-1.2 to 0.2	0.143
	UC	3.8 (2.9)	3.8 (2.7)			
Stress (PSS)	Mindfulness	22.4 (7.8)	20.2 (8.1)	-1.4	-3.4 to 0.7	0.189
	UC	22.0 (7.5)	21.1 (8.2)			
Social support (PSSS12)	Mindfulness	69.5 (11.6)	70.7 (12.4)	+1.7	-1.3 to 4.6	0.262
	UC	71.2 (12.3)	70.7 (12.5)			

As-treated analysis

Outcome	**Treatment group**	**Baseline (mean, SD) N=205**	**12 months (mean, SD) N=205**	**Difference (β)**	**95% Confidence Interval**	**p-value**
6MWT, meters	Mindfulness	532.6 (96.9)	541.5 (139.6)	+16.5	-6.2 to 39.3	0.153
	UC	538.2 (101.3)	530.6 (148.5)			
Heart rate, beats/min	Mindfulness	68.4 (16.6)	67.8 (18.4)	+1.0	-2.6 to 4.6	0.582
	UC	68.9 (17.3)	67.3 (19.7)			
SBP, mmHg	Mindfulness	129.7(22.8)	124.4 (27.3)	-5.5*	-10.9 to -0.1	0.045
	UC	125.8(23.8)	126.1 (29.2)			
DBP, mmHg	Mindfulness	79.4 (15.4)	77.8 (16.3)	+0.6	-2.5 to 3.7	0.687
	UC	79.9 (16.1)	77.6 (17.4)			
NT-proBNP, pmol/L °	Mindfulness	3.0 (1.4)	3.1 (1.4)	+0.07	-0.2 to 0.3	0.527

	UC	2.9 (1.4)	3.0 (1.4)			
Cortisol (Hair pg/mg)	Mindfulness	41.8 (165.0)	31.4 (41.7)	+1.6	-31.2 to 34.4	0.924
	UC	41.9 (194.8)	29.9 (45.1)			
Physical QoL (SF-36)	Mindfulness	45.7 (13.6)	45.2 (15.0)	-1.9	-4.1 to 0.2	0.081
	UC	45.4 (14.2)	46.9 (15.9)			
Mental QoL (SF-36)	Mindfulness	49.8 (13.5)	50.8 (17.0)	+2.3	-0.6 to 5.3	0.119
	UC	51.7 (14.1)	50.0 (18.2)			
Quality of life (VAS)	Mindfulness	74.5 (18.4)	74.6 (18.8)	-1.9	-5.5 to 1.6	0.288
	UC	73.4 (19.3)	75.4 (20.1)			
Anxiety (HADS)	Mindfulness	8.3 (4.8)	7.6 (5.4)	+0.6	-0.4 to 1.5	0.248
	UC	9.0 (5.0)	7.8 (5.8)			
Depression (HADS)	Mindfulness	3.8 (4.0)	3.2 (4.4)	-0.7	-1.5 to 0.1	0.100
	UC	3.6 (4.2)	3.7 (4.7)			
Stress (PSS)	Mindfulness	22.4 (10.5)	20.5 (12.4)	-1.3	-3.6 to 1.0	0.275
	UC	21.8 (11.0)	21.2 (13.3)			
Social support (PSSS12)	Mindfulness	69.2 (16.7)	70.0 (19.9)	+1.2	-2.5 to 4.9	0.522
	UC	71.9 (17.4)	71.6 (21.5)			

SD, standard deviation; SE, standard error; 6MWT, six-minute walk test; UC, usual care; SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; SF-36, Short Form Health survey; QoL, Quality of Life; VAS, visual analogue scale; HADS, hospital anxiety and depression scale; PSS, perceived stress score; PSSS12, perceived social support scale
° log-transformed, * Significant at $p<0.05$

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Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
6MWT	-0.22	0.086	7.7%	-0.22 [-0.39, -0.05]
Heart rate	-0.04	0.085	7.8%	-0.04 [-0.21, 0.13]
Systolic blood pressure	-0.19	0.085	7.8%	-0.19 [-0.36, -0.02]
Diastolic blood pressure	0.09	0.085	7.8%	0.09 [-0.08, 0.26]
NTproBNP*	0.01	0.085	7.8%	0.01 [-0.16, 0.18]
Cortisol	0.03	0.106	6.5%	0.03 [-0.18, 0.24]
SF36 Physical scale	0.14	0.085	7.8%	0.14 [-0.03, 0.31]
SF36 Mental scale	-0.22	0.085	7.8%	-0.22 [-0.39, -0.05]
Quality of Life	0.12	0.085	7.8%	0.12 [-0.05, 0.29]
Anxiety	0.13	0.085	7.8%	0.13 [-0.04, 0.30]
Depression	-0.18	0.085	7.8%	-0.18 [-0.35, -0.01]
Stress	-0.16	0.085	7.8%	-0.16 [-0.33, 0.01]
Social support	-0.12	0.085	7.8%	-0.12 [-0.29, 0.05]
Total (95% CI)			**100.0%**	**-0.05 [-0.13, 0.03]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 32.59$, df = 12 (P = 0.001); $I^2 = 63\%$
Test for overall effect: Z = 1.21 (P = 0.23)

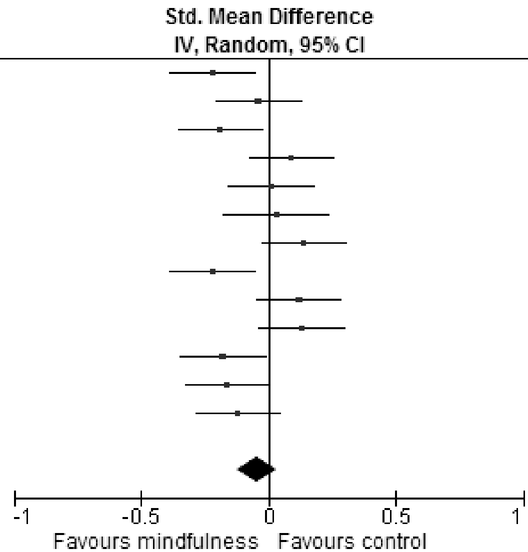

Figure 2. Forest plot showing Cohen's D of online mindfulness compared to treatment as usual in the Intention-To-Treat analysis. All values lower than 0 indicate a significant difference in favor of mindfulness. The breadth of the line indicates the 95%CI. Values between 0 and -0.2 indicate negligible effect; between -0.2 and -0.5 small effect; between -0.5 and -0.8 medium effect and lower than -0.8 a large effect.

*: log transformed values

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
6MWT	-0.17	0.089	7.8%	-0.17 [-0.34, 0.00]
Heart rate	0.02	0.089	7.8%	0.02 [-0.15, 0.19]
Systolic blood pressure	-0.23	0.09	7.7%	-0.23 [-0.41, -0.05]
Diastolic blood pressure	0.03	0.089	7.8%	0.03 [-0.14, 0.20]
NTproBNP*	0.14	0.089	7.8%	0.14 [-0.03, 0.31]
Cortisol	-0.06	0.102	7.0%	-0.06 [-0.26, 0.14]
SF36 Physical scale	0.2	0.089	7.8%	0.20 [0.03, 0.37]
SF36 Mental scale	-0.18	0.089	7.8%	-0.18 [-0.35, -0.01]
Quality of Life	0.14	0.089	7.8%	0.14 [-0.03, 0.31]
Anxiety	0.12	0.089	7.8%	0.12 [-0.05, 0.29]
Depression	-0.25	0.089	7.8%	-0.25 [-0.42, -0.08]
Stress	-0.16	0.089	7.8%	-0.16 [-0.33, 0.01]
Social support	-0.08	0.089	7.8%	-0.08 [-0.25, 0.09]
Total (95% CI)			**100.0%**	**-0.04 [-0.12, 0.05]**

Heterogeneity: Tau² = 0.02; Chi² = 36.42, df = 12 (P = 0.0003); I² = 67%
Test for overall effect: Z = 0.84 (P = 0.40)

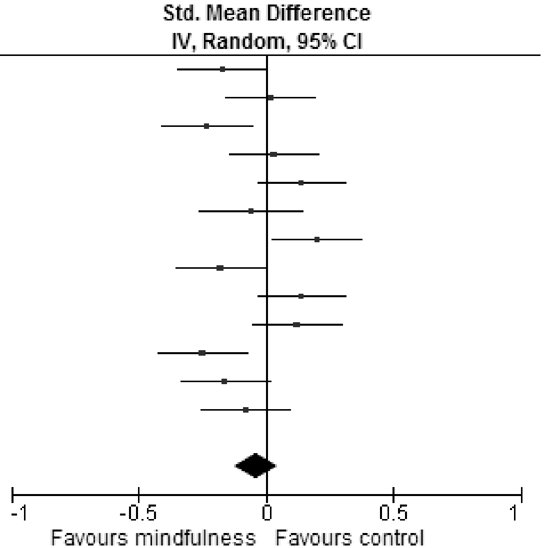

Figure 3. Forest plot showing Cohen's D of online mindfulness compared to treatment as usual in the As-Treated analysis. All values lower than 0 indicate a significant difference in favor of mindfulness. The breadth of the line indicates the 95%CI. Values between 0 and -0.2 indicate negligible effect; between -0.2 and -0.5 small effect; between -0.5 and -0.8 medium effect and lower than -0.8 a large effect.

*: log transformed values

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Standardized Effect Size

Cohen's D calculation of outcome measures resulted in small but significant differences on the 6MWT (d=0.22, 95%CI 0.05 to 0.39), systolic blood pressure (d=0.19, 95%CI 0.03 to 0.36), mental functioning (d=0.22, 95%CI 0.05 to 0.38) and depression (d=0.18, 95%CI 0.02 to 0.35) compared to UC. All other outcomes showed no significant differences (Figure 2). Similar though smaller effects were found in the as-treated analyses (Figure 3).

Effect of compliance

Regression modelling of adherence showed that women (β=0.86, p=0.045), and with a higher diastolic blood pressure (β=0.04 mmHg, p=0.031) are more often compliant (Table 3). However, when compliant to the online training, men (β=-23.1, p=0.015) with a lower BMI (β=-2.1 kg/m, p=0.048) improve more on the 6MWT (Table 4). Also having higher stress levels (PSS β=2.6, p=0.007) and experiencing little mental hindrances (MCS β=1.7, p=0.011) are associated with a better effect of the training on the 6MWT.

Table 3. Regression model of training adherence (N=215)

	β	**SE**	**Standard. B**	**p-value**
Intercept	-5.34	1.6		0.001
Gender	0.86	0.43	0.13	0.045
Age	0.03	0.02	0.16	0.084
Diastolic Blood Pressure	0.04	0.02	0.15	0.031

Effect of variables on LN(adherence%/1-adherence%), range -5 to 5.

Table 4. Regression model of improvement on 6MWT when adherent (N=107).

	β	**SE**	**Standard. B**	**p-value**
Intercept	-71.0	48.9		0.151
Gender	-23.1	9.3	-0.28	0.015
BMI	-2.1	1.0	-0.23	0.048
Perceived stress	2.6	0.9	2.77	0.007
Mental QoL	1.7	0.6	0.46	0.011

Effect of variables on Delta6MWT.

Discussion

To our knowledge, this is the first randomized trial to evaluate the long-term effectiveness of an online mindfulness training on physical fitness in patients with heart disease. Our rationale was that by improving stress-related cardiovascular risk factors, mindfulness could improve physical functioning in these patients. On the primary endpoint we found that the original improvement of 13.4 meters (p=0.050) measured directly after the online training was extended to 17.9 meters (p=0.055) in favor of the mindfulness group (Figure 4). Although this implies potential long-term improvement on participants' exercise capacity, the demonstrated effect was small. In patients with chronic lung disease, clinically meaningful differences on the 6MWT of 35-54 meters have been reported [35, 36].

As our sample size was sufficient and the randomization procedure succeeded, our lack of convincing results could be because in our aim to construct a pragmatic and easy-accessible training, the working components of the MBSR protocol were cut too short. The online training was low in intensity and our hypothesis concerned an indirect effect of a psychological intervention on physical fitness. Regarding the level of statistical significance, a slight increase in intensity could improve results. A full MBSR RCT in 30 male coronary heart patients found significant improvements in anxiety, depression and systolic blood pressure [37], although their baseline levels were higher than ours. In our study, psychological improvements were not found, which could be because these patients' baseline psychological scores were similar to scores in the general population [38-42]. The possible improvement on stress, anxiety and depression symptoms was thereby diminished by a ceiling effect. Similarly, our participants' blood pressure was monitored regularly by the outpatient clinic and medication was given if necessary, resulting in fairly normal baseline values and little room for improvement. Other studies showing effects on either psychological symptoms or on blood pressure, investigated populations whose values at baseline were higher than average [17, 43]. Three other studies on web-based mindfulness training showed that it is feasible to conduct online mindfulness training, and also that it was effective in reducing stress [44 45, 46]. Due to limited power for sub-group analyses, we have to be careful drawing firm conclusions, but results indicate that although older women with a higher diastolic blood pressure are generally more compliant to this type of intervention, they appear to benefit less. Possibly this could be taken into account as well in intensifying the future online program.

Using Cohen's D, four outcomes came out statistically significant, where the initial mixed model results did not, due to the different distributions that these analyses use: mixed models is based on a T-distribution, whereas Cohen's D uses a Z-distribution. Using different calculation methods for Cohen's D [47-50] resulted in similar findings. This shows how choice of statistical method can make a difference in conclusions, especially when p-values are close to the significance level. While 17.9 meters with a d=0.22 is a small effect, it still gives an indication of potential long-term health benefit for patients with heart disease by using mindfulness.

There are several limitations to take into account. Our control group received neither a placebo nor a waiting list period. A placebo effect of the online training was in our view part of the active intervention as it would be when implemented in real-world practice. By doing so this study is pragmatic rather than explanatory implying that we evaluated effectiveness rather than efficacy. Second, the training was expected to have less effect than MBSR due to its lower intensity, but it also lacked other aspects: there was no social interaction nor any form of feedback. As there was no social control, it was completely left to participants whether they practiced or not. This can lead to less motivation and lower adherence than a training with teacher and other group members. The current online training may therefore have been too 'light' and too far withdrawn from the original MBSR. While this would mean that MBSR may have stronger effects, the accessibility of online training possibly allows better generalizability of the results, as patients can do the training in their own environment and fit it into their schedule. A middle way would therefore be ideal: an easily accessible online training, but with more content and feedback from a trainer. Third, although we monitored participants' online activity, it was difficult to assess detailed adherence. Additionally, the control group was aware that they were not receiving the online mindfulness training. Finally, we did not measure mindfulness skills, so we cannot confirm that changes are correlated with improvement of mindfulness skills. Although the only difference between the randomized groups was the online training, it would add confirmation if future studies also include this outcome.

Conclusions

Online mindfulness training shows promising long-term effects on exercise capacity in patients with heart disease, but further research is necessary.

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Appendix Table 1. Content of the standardized 8-week MBSR protocol compared to the online training 'Mindfulness for a healthier heart'.

Week	MBSR	Online training
1	**Automatic pilot**	**Do you really feel alive**
	- Introduction to mindfulness - Raisin exercise - 40 minutes Bodyscan - Working of the breath - Automatic pilot	- Introduction film Edel Maex - Likert-scale 'really living' - Exercise focused attention, watch your computer - 15 minutes Bodyscan - Observing pictures - What deserves more attention in your life?
Home-work	- Daily 40 min Bodyscan - Daily mindful eating - 3x a day aware breathing - Daily journal keeping - Puzzle	- Weekly 15 min Bodyscan
2	**Supporting factors**	**Hear what people say, avoid the automatic pilot**
	- 40 min Bodyscan - 8 supporting factors - Plan your practices - Pain, disease and attention - Thoughts, feelings and bodily sensations	- Adjust questioning and listening behavior - Short film on living separated from your surroundings - List of daily activities performed on automatic pilot
Home-work	- Daily 40 min Bodyscan - Daily 10 min. Sitting meditation - Daily routine-activity - Calendar of pleasant events - 3x per day 3-minutes breathing space	- Execute 3 automatic activities with mindfulness
3	**Bodily experiences**	**Learn to meditate**
	- 25 min sitting meditation - 45 min Yoga - Boundaries of the body - Movement with health issues	- Short film Edel Maex - 15 min sitting meditation - Planning sitting meditation - Remember what deserves more attention?
Home-work	- Daily Bodyscan or Yoga (40 min) - Daily 15 min attention training - Calendar of unpleasant events - Noticing the automatic pilot	- Daily 15 min sitting meditation
4	**Stress**	**Dealing with stress**
	- 40 min sitting meditation - 25 min Yoga - Stress reaction and symptoms - Reaction on unpleasant events - Resistance or avoidance	- Short film stress reaction - 3-minute breathing space - Description of current day

Home-work	- Stress aware responding - 3-minute breathing space - Daily Bodyscan or Yoga (40 min) - Daily 20 min sitting meditation - Calendar of stressful events - 3x per day 3-minute breathing space	
5	**Habits and change**	**Learn to stop aware**
Home-work	- 40 min sitting meditation - Habits and patterns - Our self-healing abilities - Change begins with awareness - 10 min walking meditation - Daily sitting meditation or Yoga (40 min) - 3x per day 3-minute breathing space - Calendar of stressful conversations - Daily activity with awareness	- Inventory stopping with current activity - Short film with quotes - Short film about death - 3x per day 20 minutes stopping current activity; with awareness
6	**Thoughts and senses**	**You are not your thoughts**
Home-work	- 40 min sitting meditation - Approach without judgment - Experience the senses - 20 min walking meditation - Daily 40 min sitting meditation, Yoga or Bodyscan - Integrating mindfulness in conversations - Noticing sensory experiences - Noticing the automatic pilot	- Thoughts are not facts, you are not your thoughts - Difficult memories - Being compassionate
7	**Feelings**	**The art of living consciously**
Home-work	- 40 min sitting meditation - Present in the place you are - The 4 quadrants - The continuüm of anger - Daily meditation without CD - Noticing sensory experiences - Evaluation of the training	- Intention to give more love to … - Attention to seasons/environment
8	**And now onwards…**	**Mindfulness for the rest of your life**

	- 40 min sitting meditation
	- Planning meditation after training
	- Living with attention
	- Formulating goals:
	  o 3 short term
	  o 3 long term
		- Likert-scale feeling of being really alive
		- Evaluation of what you have learned
		- Short film of laughing people

8

Follow-up online training 'Mindfulness for a healthier heart'

Phase 2	**Week 9**	**Staying Mindful**
Four weeks continuing training		6-minute meditation practice Planning mindfulness
	Week 10	**Rewrite your personal book of laws**
		What rules do you impose on yourself? Which rules do you really have to adhere to? What do you allow yourself to do?
	Week 11	**Mindful eating**
		Short film about eating in between daily chores Assignment eating breakfast, lunch and dinner mindfully Note your experiences
	Week 12	**Yoga for your heart**
		Yoga 30 minutes (film) Likert-scale experiences Planning Yoga into your schedule
Phase 3	**Week 14**	**Rediscover your body**
Reminders every two weeks		Go back to week 1 3 websites with more meditation information
	Week 16	**Really listening**
		Go back to week 2
	Week 18	**Stopping consciously**
		Go back to week 5, 4 websites with group training information
	Week 20	**Learning to meditate again**
		Go back to week 3, 8 book titles about mindfulness
	Week 22	**Planning Meditation**
		Go back to week 3, 3 CD tips with guided meditations
	Week 24	**Feeling alive**
		5 likert scales
Phase 4	**Week 28**	**How do you deal with stress now?**
Monthly reminders		Reflection on stressful situations and reactions, what would be a mindful reaction?
	Week 32	**Dealing with difficult thoughts**
		Reminder: when ruminating, consider facts
	Week 37	**Remember what you wanted to give more love?**
		3 things you can do with love
	Week 42	**A beautiful quote**
		Reflection on Kabat-Zinn's quote 'human beings vs human doings'
	Week 46	**Extra attention**
		Choose an activity to do more aware this week
	Week 51	**The feeling that you are alive**
		5 Likert scales Apps to continue practice

Part IV

Future directions of mindfulness

Chapter 9

Mindfulness and mood stimulate each other in an upward spiral: a mindful walking intervention using Experience Sampling.

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Abstract

The aim of this study was to explore the feasibility and effectiveness of mindful walking in nature as a possible means to maintain mindfulness skills after a Mindfulness Based Cognitive Therapy (MBCT) or Mindfulness Based Stress Reduction (MBSR) course. Mindful walking alongside the river Rhine took place for 1, 3, 6 or 10 days, with a control period of a similar number of days, one week before the mindful walking period. In 29 mindfulness participants, Experience Sampling Method (ESM) was performed during the control and mindful walking period. Smartphones offered items on positive and negative affect and state mindfulness at random times during the day. Furthermore, self-report questionnaires were administered before and after the control and mindful walking period, assessing depression, anxiety, stress, brooding, and mindfulness skills. ESM data showed that walking resulted in a significant improvement of both mindfulness and positive affect, and that state mindfulness and positive affect prospectively enhanced each other in an upward spiral. The opposite pattern was observed with state mindfulness and negative affect, where increased state mindfulness predicted less negative affect. Exploratory questionnaire data indicated corresponding results, though not-significant due to the small sample size. This is the first time that ESM was used to assess interactions between state mindfulness and momentary affect during a mindfulness intervention of several consecutive days, showing an upward spiral effect. Mindful walking in nature may be an effective way to maintain mindfulness practice and further improve psychological functioning.

Introduction

The psychological effects of the eight weeks Mindfulness Based Stress Reduction (MBSR) and Mindfulness Based Cognitive Therapy (MBCT) are getting increased attention in scientific research, with mindfulness techniques being recommended as valuable strategies to relate to negative thoughts and emotions. Mindfulness training aims to make participants more aware of their automatic reactions on a behavioral, emotional and cognitive level, by encouraging them to engage in daily meditation practices. Non-judgmental observing of emotions or thoughts present in the here and now enables participant to react in a calm and 'wise' manner in stressful situations [1]. Mindfulness has been shown to lead to improvements in depression, anxiety, stress and quality of life in a variety of clinical populations as well as healthy participants [2].

Although studies directly examining the necessity of ongoing practice are lacking, mindfulness participants are recommended to maintain mindfulness practice in order to maximize and sustain benefits. As many find it difficult to do this on their own, many mindfulness centers offer reunion meetings or silent days. Attendees have reported to experience these as a booster reminding them of their mindfulness practices and as a sanctuary where these practices are further nurtured [3]. So, it might be valuable to offer other easily accessible means to former participants of MBCT or MBSR courses to help maintaining their mindfulness practice.

One possibility that is available to many people is mindful walking. During the MBCT and MBSR training, participants are asked to pay attention to their senses (i.e. sight, hearing, smelling, tasting, bodily sensations), emotions, thoughts, and automatic behavioral patterns. They are encouraged to experiment with letting go of automatic behaviors (i.e. high demands, hurrying) and with approaching difficult emotions or situations (i.e. annoyance, sadness). During the training, participants get introduced to mindful walking, which has been described as 'meditation in motion'. Mindful walking uses the everyday activity of walking as a mindfulness practice to become more aware of bodily sensations. The physical sensation of walking enables people to feel more 'grounded' in the present moment [4]. When people's minds are occupied or stressed, paying attention to their physical movements can be an easy way to become more mindful.

Walking does not require expensive gear or tools, and it can usually be integrated into a person's schedule without too many difficulties. Mindfulness and walking share similar experiences. Both require paying attention to bodily sensations and other sensory input like sights, sounds or smells. In addition to the intrinsic link between mindfulness and walking, physical exercise in itself has a positive influence on psychological functioning and can reduce depressive symptoms [5-7]. A recent meta-analysis in the UK shows that outdoor walking can lead to lower blood pressure, resting heart rate, body fat, body mass index, total cholesterol and depression, and increased VO2max and physical functioning [8]. Other studies on environment and mental health have shown the benefits of walking in nature [9-12]. In

summary, mindful walking in nature could contribute to keeping up both mindfulness practice as well as a healthy lifestyle, thereby reducing stress-related symptoms and diseases. Little is known about how exactly mindful walking may affect mindfulness and psychological functioning. One method to measure relationships between mental states in a detailed way is Experience Sampling Method (ESM). ESM enables repeated in-the-moment assessments of experiential states to measure detailed fluctuations in participants [13,14], thereby minimizing retrospective bias and enhancing reliability and ecological validity [13]. Earlier ESM studies found that mindfulness stimulates upward spirals of positive affect and positive cognition [15], and that induced mindfulness enhanced valence and calmness, where induced rumination reduced these states [16]. Furthermore, Snippe (2015) investigated daily affect changes during an MBSR training, and reported that changes in mindfulness preceded changes in affect [17]. The current study is the first to investigate the relationship between state mindfulness and momentary affect with ESM during a multi-day mindful walking intervention.
This pilot study aims to explore the feasibility and effectiveness of mindful walking as a way to maintain mindfulness skills in people who previously participated in either an MBCT or MBSR course. Using ESM data, we tested whether mindful walking has beneficial effects on momentary positive and negative affect, allowance of thoughts and emotions, and state mindfulness and compared to a control period. With time-lagged analyses, we also investigated temporal relations between state mindfulness (at time t-1) and momentary positive and negative affect (at time t), and vice versa. Finally, we tested whether walking more days leads to added benefits, compared to the first day of walking. On an exploratory base, we used questionnaires to see whether ESM results corresponded with changes in self-reported depression, anxiety, stress, brooding, and mindfulness skills.

Methods

Participants

All adult participants who had previously completed either an MBSR or an MBCT course at the Radboudumc Centre for Mindfulness in Nijmegen, the Netherlands, were eligible to participate in the study. There were no restrictions in terms of age, current psychopathology or duration since completion of the mindfulness course. Of the 49 people attending the organized information meeting, 32 chose to participate in the study. Three participants were excluded from analyses due to acquired brain damage associated with cognitive impairments, which raised uncertainty about whether they could properly complete the assessments. The remaining 29 participants were on average 54.3 years old (SD 9.0) and 69% were female (see Table 1). Six persons had participated in an MBSR course (general population) and 23 in an MBCT course (mainly patients with recurrent depressive disorder). Participation in these courses took place 2.7 years (SD 1.5) before the study. Many of the participants regularly attended reunion meetings at the Radboudumc Centre for Mindfulness. Ten people (34.5%) participated in the one-day walking retreat, 14 (48.3%) in the three days walking retreat and five (17.2%) walked for six or more days.

Table 1. Characteristics of study participants.

Participants (N=29)	**1 day N=10 (34%)**	**3 days N=14 (48%)**	**6 or more days N=5 (17%)**
Age (SD)	55.1 (7.5)	52.5 (9.1)	57.9 (12.5)
Female	9 (90%)	10 (71%)	1 (20%)
Education			
Lower education	3 (30%)	4 (29%)	1 (20%)
Higher education	7 (70%)	10 (71%)	4 (80%)
Living situation			
Alone	2 (20%)	6 (43%)	2 (40%)
Partner	2 (20%)	3 (21%)	2 (40%)
Partner and children	6 (60%)	5 (36%)	1 (20%)
History of depression	5 (50%)	14 (100%)	4 (80%)

Procedure

By means of the center's website, a Facebook group, and on reunion days at the center, adult participants of previous training groups were invited to an informal meeting at which they were informed about both the mindful walking period itself and the associated self-report measures and experience sampling. After the meeting, people gave their definitive consent to participate. For participants of the one and three days walking periods, all costs were reimbursed. Participants of the six or more days walking periods received €50 per day as a compensation for their accommodation costs. Participants were provided with smartphones to complete the experience sampling for ten quasi-random times a day both during the mindful walking period and control period (five times a day for those walking six or more days). In addition, participants were asked to complete self-report questionnaires before and after both the mindful walking period, and the control period of similar duration exactly one week before. As participants were no (longer) patients of the Radboud University Medical Center and the intervention and assessments were not considered to represent any risk to the participants, the medical ethics committee of the hospital waived the need to apply for formal ethical permission (CMO registration no. 2014/250).

The walking route took place alongside the river Rhine, from where it enters the Netherlands to where it joins the North Sea, reaching a total length of 240 km. The route was mostly unpaved, and participants were instructed to keep the river on their right and to overcome obstacles they might come across, such as fences and detours, in their own way. They received a map with a rough description of the route and available accommodation addresses.

People were offered three different possibilities to participate in the mindful walking: either as a one-day walking retreat in a group, accompanied by a mindfulness teacher; or a three-day walking retreat in a group, accompanied by two mindfulness teachers; or a solitary walking retreat of six days or more, with the possibility of daily contact with a mindfulness teacher by telephone, text or email. Participants were instructed to walk the route silently except for times conversation was necessary for practical purposes (i.e. arrival at accommodation). They were reminded to pay attention to their senses (i.e. sight, hearing, smelling, tasting, bodily sensations), emotions, thoughts and automatic behavioral patterns. They were encouraged to experiment with letting go of automatic behaviors (i.e. high demands, hurrying) and with approaching difficult emotions or situations (i.e. annoyance, sadness). They were also encouraged to choose wisely between walking alongside the river, the grass bank or the surfaced road on the dyke. For the one-day walking retreat, there was a 15-minute sitting meditation at the start of the day, at lunchtime, and at the end of the day. For the three-day walking retreat, participants were offered standing yoga exercises for 30 minutes before breakfast, a sitting meditation of 30 minutes followed by a plenary enquiry in the evening and the possibility of individual interviews with one of the mindfulness teachers. The participants walking for six or more days walked on their own and hence only received the general walking meditation instructions. They were, however, encouraged to spend at least half an hour every day to write about their experiences and process in a personal diary. They also had the possibility of individual interviews at the end of the day to discuss their process with a mindfulness teacher.

The control period was of similar duration as the mindful walking period the participant had opted for and took place exactly one week before the intervention period, i.e. when the mindful walking period was from Friday to Sunday, the control period was from Friday to Sunday as well. The participants received no particular instructions about what to do during the control period.

Measures

The assessments consisted of both electronic brief questions using the Experience Sampling Method (ESM) at quasi-random times during the control and intervention periods, and self-report questionnaires before and after the control and mindful walking periods.

To closely monitor the course of participants' experiential state, we collected ESM data using smartphones that quasi-randomly gave a signal several times a day between 9 AM and 4 PM to cover the period of mindful walking, with a maximum time in between of 90 minutes. For the one and three-day walking periods samples were taken 10 times a day, for the six and more day retreats five times a day. After each signal, participants answered 18 Likert scale items each ranging from 0 (not at all) to 7 (very much). All items are listed in Table 2. The first nine items comprised different moods 18 with five items measuring positive affect (content, cheerful, relaxed, energetic, and calm) and four negative affect (sad, irritated, insecure, tense). The selection of affect items was based on previous experience sampling studies in this area of research [19,20]. Cronbach's alpha of the positive affect items was .92 and of negative affect items .89. The items on affect were followed by four items measuring suppressing or allowing negative thoughts and emotions. These items were combined into one outcome 'allowing', indicating the ability to allow negative thoughts and emotions, and not suppress them. Cronbach's alpha of these four items was .79. Finally, participants answered the items with the highest factor loadings on four of the five subscales of the Five Facet Mindfulness Questionnaire (FFMQ) [21], namely Observing, Acting with awareness, Non-judgment and Non-reacting. An item on self-compassion was added instead of an item for Describing, which has not been found influential in previous research [22]. The Cronbach's alpha of these five items was .80.

All items not filled in within 15 minutes after the signal were excluded from analysis, as reports completed after this interval are considered less reliable and less ecologically valid [23]. Experience sampling data (control or intervention period) with fewer than 33% valid reports were also excluded from the analysis.

The Dutch version of the Depression Anxiety Stress (DASS-21) questionnaire was used to measure depression, anxiety and stress. The three subscales each consist of seven items scored on a Likert scale ranging from 0 (never) to 3 (very often). The DASS-21 has good validity and reliability in a non-clinical sample [24], Cronbach's alpha in this sample was 0.90. The brooding subscale of the 22-item Ruminative Response Scale (RRS) [25] was used to assess rumination. This scale consists of five items scored on a Likert scale ranging from 0 (never) to 3 (very often). Cronbach's alpha of this subscale was 0.84.

As the pre and post assessments were so close together, particularly during the one-day walking retreat, we selected a measure assessing mindfulness as a state rather than a trait, i.e. the subscales Decentering and Curiosity of the Toronto Mindfulness Scale [26]. These two subscales are significantly and positively correlated with absorption and awareness of one's surroundings. Curiosity is also significantly correlated with awareness of internal states (thoughts and feelings). The 13 items are scored on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much so). Their Cronbach's alpha was 0.81.

Table 2. ESM items and Cronbach's alpha.

Outcome	Item	Cronbach's alpha
Positive affect	Right now, how cheerful are you? Right now, how content are you? Right now, how energetic are you? Right now, how calm are you? Right now, how relaxed are you?	.92
Negative affect	Right now, how sad are you? Right now, how insecure are you? Right now, how irritated are you? Right now, how tense are you?	.89
Allowing	My thoughts will not leave me alone I try to ignore my thoughts My feelings carry me away I try to suppress my feelings	.79
Mindfulness	I pay attention to sensations, such as the wind in my hair or sun on my face I perceive my feelings and emotions without having to react to them. When I have distressing thoughts or images, I just notice them and let them go. I find it difficult to stay focused on what's happening in the present. I am friendly and kind to myself	.80

All Likert scale items ranged from 1 (not at all) to 7 (very much). Cronbach's alpha's are based on between subject analyses.

Data Analysis

All analyses were performed in SPSS 22.0 27. The approach used for the ESM data was the following: ESM data have a hierarchical structure. Thus, multiple observations (level 1) are clustered within participants (level 2). Mixed effect multilevel analyses with random (i.e., participant-specific) intercepts were used in order to take the variability associated with each level of nesting into account 28. On top of the random intercept, all time-lagged analyses used auto-correlated covariance structures with a random slope.

In the questionnaire data, 6.9% of values were missing, and these were imputed based on multiple imputation regression with 10 iterations. ANCOVA analyses describe the levels of dependent variables depression, anxiety, stress, brooding, mindfulness decentering, and mindfulness curiosity at each time point adjusted for gender, clinical indication, and number of days walked. This way the effect of the intervention could be observed more accurately, as gender, clinical indication and number of days walked may influence the outcome. In order to compare the different outcome measures, Cohen's d for within subject measurements 29 was calculated by comparing the mean delta of the pre-measurement with the mean delta of the post-measurements (based on the ANCOVA results). In other words: Cohen's d indicates whether the change during the walking period was larger than during the control period.

Results

In addition to the three cognitively impaired participants, data from two more participants were excluded from the ESM analysis because the proportion of valid assessments was less than 33%. The baseline assessment of one participant was excluded from the analyses due to procedural problems during data collection; the data of the intervention period were still used.

The results of the regression analyses are presented in Table 3. Compared to the control period, the mindful walking periods resulted in a significant increase of positive affect (β=0.91, $p<0.001$) and state mindfulness (β=0.98, $p<0.001$), and a reduction of negative affect (β=-0.71, $p<0.001$). Allowing thoughts and emotions showed only a trend of effect (β=0.43, p=0.067). Positive affect and mindfulness were highly correlated (r=0.75, $p<0.001$), and there was a negative correlation between negative affect and mindfulness (r= -0.66, $p<0.001$). State mindfulness in the previous moment appeared to predict positive affect in the next, even after controlling for affect at the previous moment (β=0.18, $p<0.001$). Similarly, positive affect at the previous moment appeared to predict mindfulness in the next, even after controlling for mindfulness at the previous moment (β=0.21, $p<0.001$). Negative affect showed an opposite relationship: after controlling for the previous level, state mindfulness predicted a reduction of negative affect in the next moment (β=-0.14, $p<0.001$) and negative affect predicted a reduction of mindfulness in the next moment (β=-0.19, $p<0.001$).

Mindfulness on the previous day did not predict positive affect on the next day, even after controlling for positive affect on the previous day (β=.23, p=.192), nor did mindfulness on the previous day predict a reduction of negative affect on the next day (β=-0.11, p=0.411). Positive affect on the previous day did however significantly predict the level of mindfulness on the next day when controlling for the level of mindfulness on the day before (=-0.36, p=0.027), and negative affect on the previous day predicted a reduction of mindfulness the next day (β=0.41, p=.002). Both state mindfulness and positive affect appeared to significantly improve with the number of days walked (β=0.14, $p<0.001$ and β=0.12, p=0.011, respectively), but negative affect did not (β=-0.04, p=0.286).

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Table 3. Effect estimates of hypotheses tested in ESM data analysis.

Hypothesis	Outcome	Parameter	β	SE	p-value	95% CI Lower	95% CI Upper
Effect of the intervention	Positive affect	Intercept	4.27	0.15	<.001	3.97	4.57
		Intervention	0.91	0.21	<.001	0.48	1.33
	Negative affect	Intercept	2.56	0.13	<.001	2.29	2.82
		Intervention	-0.71	0.19	<.001	-1.08	-0.34
	Mindfulness	Intercept	4.24	0.15	<.001	3.94	4.54
		Intervention	0.98	0.21	<.001	0.56	1.40
	Allowing	Intercept	5.06	0.16	<.001	4.73	5.39
		Intervention	0.43	0.23	.067	-0.03	0.90
Time-lagged analyses: effect of previous moment on following moment[4]	Positive affect	Intercept	1.39	0.12	<.001	1.15	1.63
		Previous mindfulness	0.18	0.03	<.001	0.12	0.25
		Previous positive affect	0.53	0.03	<.001	0.47	0.60
		Interaction terms[1]			NS		
	Negative affect	Intercept	1.62	0.23	<.001	1.17	2.07
		Intervention	0.10	0.31	NS	-0.52	0.71
		Previous mindfulness	-0.14	0.04	<.001	-0.21	-0.07
		Previous negative affect	0.59	0.04	<.001	0.52	0.67
		Interaction terms[2,3]	-0.16	0.05	.002	-0.27	-0.06
	Mindfulness	Intercept	1.75	0.13	<.001	1.49	2.02
		Previous mindfulness	0.43	0.03	<.001	0.36	0.49
		Previous positive affect	0.21	0.03	<.001	0.14	0.27
		Interaction terms[1]			NS		
	Mindfulness	Intercept	2.91	0.21	<.001	2.50	3.31
		Previous mindfulness	0.48	0.03	<.001	0.42	0.54

		Previous negative affect	-0.19	0.03	<.001	-0.25	-0.12
		Interaction terms[2]			NS		
Time-lagged analyses: effect of previous on following day	Positive affect	Intercept	2.18	0.64	.001	0.90	3.47
		Mindfulness previous day	0.23	0.17	.192	-0.12	0.58
		Positive affect previous day	0.36	0.19	.060	-0.02	0.74
	Negative affect	Intercept	1.74	0.91	.063	-0.10	3.58
		Mindfulness previous day	-0.11	0.13	.411	-0.38	0.16
		Negative affect previous day	0.38	0.15	.012	0.09	0.68
	Mindfulness	Intercept	3.50	0.53	.005	1.91	5.09
		Mindfulness previous day	0.66	0.17	.002	0.29	1.03
		Positive affect previous day	-0.36	0.12	.027	-0.65	-0.06
	Mindfulness	Intercept	0.86	1.10	.435	-1.30	3.02
		Mindfulness previous day	0.67	0.15	<.001	0.31	1.03
		Negative affect previous day	0.41	0.13	.002	0.15	0.67
Effect of extra days walking	Positive affect	Intercept	4.89	0.19	<.001	4.51	5.27
		Day	0.12	0.04	.011	0.03	0.20
	Negative affect	Intercept	2.04	0.16	<.001	1.72	2.37
		Day	-0.04	0.04	.286	-0.12	0.04
	Mindfulness	Intercept	4.92	0.16	<.001	4.58	5.27
		Day	0.14	0.00	<.001	0.14	0.14

95% CI: 95% confidence interval; SE: standard error; NS: not statistically significant

[1] Interaction terms positive affect: previous mindfulness x intervention, previous positive affect x intervention

[2] Interaction terms negative affect: previous mindfulness x intervention, previous negative affect x intervention

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[3] Interaction term intervention x previous negative affect was significant, therefore split file on condition was performed:

Split file	Parameter	β	SE	P-value	Lower 95%CI	Upper 95%CI
Intervention group	Intercept	1.99	0.26	<.001	1.49	2.50
	Negative affect previous moment	0.41	0.04	<.001	0.32	0.49
	Mindfulness previous moment	-0.17	0.04	<.001	-0.25	-0.10
Control group	Intercept	1.88	0.25	<.001	1.39	2.38
	Negative affect previous moment	0.48	0.04	<.001	0.39	0.56
	Mindfulness previous moment	-0.14	0.04	.001	-0.22	-0.06

Outcome: Negative affect

[4] Interaction with group condition was non-significant, therefore data were collapsed across the control and intervention period.

Because the questionnaire data are underpowered, we present Cohen's d to give an indication of the effect size, rather than focusing on statistical significance. During the control period (between measurement 1 and 2), there were no consistent or large changes from pre to post (Table 4). Depression, anxiety, stress, brooding, and mindfulness all improved moderately (Cohen's d ranged from 0.27 for depression to 0.53 for brooding) from pre to post during the intervention period (between measurement 3 and 4), but not statistically significant compared to the control period.

Table 4. Questionnaire data: ANCOVA repeated measures analysis, Delta within control period and intervention period, and Standardized Effect size (Cohen's d)

	Time	Mean (95%CI)	Δ	Cohen's d (95% CI)
Depression	1	6.7 (5.3-8.2)	-0.6	0.27 (-0.26 to 0.79)
	2	6.1 (4.6-7.5)		
	3	5.7 (4.2-7.1)	-1.8	
	4	3.9 (2.5-5.4)		
Anxiety	1	5.1 (4.2-6.1)	0.0	0.45 (-0.08 to 0.98)
	2	5.1 (4.1-6.0)		
	3	4.6 (3.6-5.5)	-1.7	
	4	2.9 (2.0-3.8)		
Stress	1	9.9 (8.6-11.2)	-0.5	0.49 (-0.05 to 1.02)
	2	9.4 (8.1-10.7)		
	3	9.3 (8.0-10.6)	-3.0	
	4	6.3 (5.0-7.6)		
Brooding	1	6.4 (5.3-7.5)	+0.3	0.53 (-0.006 to 1.06)
	2	6.7 (5.6-7.8)		
	3	6.3 (5.3-7.4)	-1.7	
	4	4.6 (3.4-5.6)		
Mindfulness Decentering	1	12.6 (11.2-14.0)	-0.5	0.53 (-0.005 to 1.06)
	2	12.1 (10.7-13.6)		
	3	13.2 (11.8-14.6)	+2.2	
	4	15.4 (14.0-16.8)		
Mindfulness Curiosity	1	14.8 (13.2-16.4)	-0.1	0.20 (-0.32 to 0.73)
	2	14.7 (13.1-16.4)		
	3	16.0 (14.3-17.6)	+0.9	
	4	16.9 (15.2-18.5)		

N=29. Time 1 (pre) and 2 (post) represent the control period. The intervention took place between Time 3 (pre) and Time 4 (post). Analyses are adjusted for sex, number of days walked, and MBSR/MBCT.
95% CI: 95% Confidence Interval. A positive Cohen's d indicates a stronger improvement on the outcome measure during the intervention than during the control period.

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Discussion

This pilot study explored the feasibility and effectiveness of mindful walking as a way of maintaining practice after having participating in an MBCT or MBSR course, using standard questionnaires as well as experience sampling. The ESM data shows that mindful walking resulted in significant improvements of both mood and mindfulness skills. Moreover, the ESM data provided more detailed insight in how the moment-to-moment changes in mood and mindfulness affect each other during the mindful walking period: an earlier randomized controlled trial showed that MBCT increases positive affect as well as individual's susceptibility to rewarding situations in daily life [30]. The current data corroborate and extend this finding by showing that state mindfulness and positive affect, measured during a mindfulness intervention which covered a period of consecutive days, appear to stimulate each other. Increased state mindfulness predicted a more positive affect in the next moment and less negative affect, which in turn predicted a higher state mindfulness, thereby creating an upward spiral from one moment to the next. The moment-to-moment ESM data have enough power to monitor this relationship. The less well powered day-to-day data show a different trend, in the sense that positive affect seemed to predict less mindfulness and negative affect more. It could be that over such a period, having a good day slackens mindfulness practice on the next, where having more negative feelings increases practice the next day.

Our findings are in accordance with previous research showing that changes in mindfulness precede changes in affect [17]. Garland and colleagues compared interactions between positive affect and cognitions before and after MBCT and found that MBCT appeared to enhance upward spirals between positive affect and cognition [15]. While Garland and Snippe investigated the influence of mindfulness training on mood, we investigated the moment-to moment temporal relationships between mindfulness and mood. Our method of analysis adheres to state of the art principles in multilevel time-series modeling, which has also been used in previous high-impact publications [17,20,31]. Regarding the (underpowered) self-report questionnaires, the results were in line with the ESM outcomes: mindful walking can reduce depression, anxiety, stress and brooding, and increase mindfulness skills, although these changes did not reach statistical significance, compared to a control period of similar length.

Although the current study offers promising results, there are several limitations that have to be taken into account. First, this is a small sample of self-referred participants. Chances are that there is a selection bias of people who benefitted from the mindfulness training or believe in the effect of walking in nature, and thus were more motivated to participate in this study. As the study population was limited to people who previously participated in MBCT of MBSR, it is not sure what the effectiveness of the mindful walking would have been in people who do not have that experience. Our choice of restricting the study population to graduates of the mindfulness courses was influenced by the fact that we anticipated that being in silence for prolonged periods of time would not be easy for people who are naïve to meditation. We also anticipated it would not have been easy for them to pay non-judgmental attention to bodily sensations, emotions and thoughts, to become aware of automatic patterns and start experimenting with alternative ways of dealing with situations without any further guidance. However, as the mean time since completion of the MBCT or MBSR course was several years for most participants, it remains unsure whether the effectiveness of the mindful walking was due to consolidating prior practice or rather due to being offered something new. Many of the participants, though, had been maintaining their mindfulness skills by attending the reunion meetings of the Radboudumc Centre for Mindfulness.

With regard to the small sample size, the questionnaire results have been more affected than the ESM data due to the number of repeated measurements per person. In addition, although pragmatic, using subscales of validated questionnaires may reduce validity and reliability of our questionnaire measurements [32]. Also, while most participants previously participated in an MBCT group for their recurrent depression, no formal psychiatric assessment has been done before inclusion of participants, so apart from demographic information unfortunately no further information about current psychopathology is available.

Although the study included a control period, it did not include a control group. Consequently, it remains unclear if similar effects would be evident with any other activity in a group or in nature. Furthermore, the intervention varied in length and in presence of a group leader. As the intervention consisted of a combination of mindfulness practice and physical exercise, it also remains unclear to what extent either of these is helpful. Possibly, monitoring of physical exercise in addition to mood and mindfulness skills in a next study might enable us to further disentangle this process. Finally, the study did not include a follow-up period, preventing conclusions about the consolidation of the treatment effects.

The results of this study should be regarded as preliminary. Replication in a properly powered randomized controlled trial, including a control group and a follow-up period, is necessary. The ESM data however, give us a glimpse of a possible working mechanism between mindfulness and enhanced well-being, through upward spiral effects between state mindfulness and improved mood from one moment to the next.

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Chapter 10

Mindfulness based emotion regulation training for borderline personality disorder.

Design of the program and results of a pilot study in an inpatient treatment.

Veerkamp M, Gotink RA, Schoorl M.

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Abstract

Mindfulness is an important skill for patients with Borderline Personality Disorder (BPD). Mindfulness Based Emotion Regulation Training (MB-ERT) specifically addresses the development of mindfulness and self-compassion in this population, characterized by emotion regulation problems. This exploratory study investigates the applicability and clinical relevance of MB-ERT as an autonomous module.

Ten BPD patients in inpatient psychotherapeutic treatment in Centrum Persoonlijkheidsstoornissen Jelgersma in Oegstgeest, the Netherlands, received MB-ERT between February and June 2013. Mindfulness skills, rumination and borderline symptoms were measured and the training was evaluated by participants.

Despite the limitations of this study, the results indicate a safe applicability of MB-ERT in BPD patients and significant improvements in mindfulness skills, rumination and borderline symptoms.

Introduction

BPD and emotion regulation

Borderline Personality Disorder (BPD) is characterized by impulsiveness, deficient emotion regulation and a pattern of instability in self-image and interpersonal relationships [1]. The easy emotional disruption forms the foundation for the BPD characteristic patterns in cognitive and behavioral instability [2-4]. The behavior of BPD patients includes suicide attempts, auto mutilation, substance abuse, physical aggression, eating disorders and other forms of destructive behavior for both the patient and the environment [1,5]. BPD patients have a strong tendency to avoid unpleasant thoughts, emotions or bodily sensations. Situations that can evoke these experiences are also avoided [6,7]. (Self) destructive behavior can be regarded as an inadequate method to temporarily avoid the (emotional) suffering.
The Trimbos Institute estimates that in the Netherlands around 100.000 patients live with BPD: less than 1% of the population [8]. Compared to other patients with psychological disorders, BPD patients rely heavily on mental health care [9,10]. The direct and indirect costs of BPD patients for the Dutch society are calculated to be two billion euro per year. Although almost 25% of this amount is spent on health care, the largest part is caused by the inability to work and job absence [11]. Furthermore, there is high axis-1 comorbidity in BPD[12, 13]. Treatment modules for depression, anxiety and trauma related disorders, eating disorders and addiction could therefore also have value in the treatment of BPD.

DBT and mindfulness

Dialectical Behavioral Therapy (DBT) is the most investigated treatment for BPD [12, 14]. The Multidisciplinary Guideline for Personality Disorders [15] states that "DBT is an effective treatment for the reduction of acute hospitalization and symptoms (...) and for improving social functioning in patients with Borderline Personality Disorder." According to DBT bio-social theory, the ongoing emotional disruption is caused by mutual influence of innate vulnerability and invalidation from the environment. This disruption is further increased by the self-invalidation following the combination of these two factors [14]. DBT teaches four clusters of skills, aimed at five areas in which BPD patients experience disruption. These areas are: emotions, interpersonal relations, self-image, cognitions and behavior. The four skill clusters are mindfulness, interpersonal effectiveness, emotion regulation and stress tolerance [14].
Mindfulness in DBT is defined as the ability to focus all attention on that what arises in this moment, without judgment. The goal of mindfulness in DBT is becoming one with or engrossed in an experience or a task, which is called 'participation' [14, 16]. Who participates, will act intuitively. In mindfulness, Linehan distinguishes three 'what'-skills: observing, describing and participating; and three 'how'-skills: without judgment, one task at a time, and acting effectively. She experimented with offering formal sitting meditation to BPD patients, in which they had to focus their attention on their breath for half an hour. This was no success: participants reported a large increase in tension and limited behavioral control [17].

Linehan concluded that patients benefit more from short and practical exercises aimed at participation. Another important concept in DBT is validation: the therapist actively expresses to the patient that her thoughts, feelings and behavior are understandable and meaningful in the context of her current situation [16]. Mindfulness and validation are grouped under acceptance-increasing strategies. They are combined with cognitive behavioral therapy's change-increasing strategies and together they form the dialectical approach of DBT. During treatment patients gain necessary, sometimes life-saving, control over their impulses and over the following (self)destructive behavior. It is also important that patients learn to validate their own behavior and emotions, and to do what is possible to change their invalidating environment into a validating one.

The three skill clusters of DBT mentioned earlier are based on mindfulness skills. Especially the emotion regulation skills and the stress tolerance skills build on mindfulness. To be able to regulate emotions, the patient will have to be aware of her experience in the 'here and now'. Standing still, observing and describing without judgment of what is happening in this moment are important, but often painful challenges. Opening up to inner experiences like thoughts, emotions and bodily sensations are a form of exposure and can reduce anxiety and avoiding behavior on the long term. Linehan describes three goals of training in emotion regulation skills: understanding experienced emotions, reducing emotional vulnerability – for instance by taking good care of yourself and increasing positive emotions-, and reducing emotional suffering by focusing attention on the emotion present in this moment. This shows a lot of similarities to Mindfulness Based Cognitive Therapy (MBCT).

Until now very little research has been done on the effectiveness of mindfulness as a single element of DBT. Regular ambulatory treatment usually takes a year and is costly in that. The search for an effective and efficient treatment of BPD asks for detailed research on the working elements of DBT. Mindfulness could be an important factor in the treatment.

MBCT and self-compassion.

Mindfulness Based Cognitive Therapy is based on Mindfulness Based Stress Reduction (MBSR), developed in 1982 by Jon Kabat-Zinn [18]. MBCT comprises attention training combined with cognitive behavioral therapy elements, such as recognizing dysfunctional conceptions and attitudes, and changing them. In developing MBCT, Segal, Williams, and Teasdale concluded that 'decentering' is an important element in the training: patients learn to take an attentive, benevolent attitude towards every inner experience. They learn about the passing nature of their thoughts, emotions and bodily sensations, and develop a different relationship with their experiences ('you are not your thoughts, you have them'). Participants learn to discover and to break automatic reaction patterns[19]. In MBCT, patients diagnosed with recurrent depression are offered experience focused exercises and psycho-education during eight weekly sessions of approximately two hours. Homework exercises in between the weekly sessions are an essential part of the training. Multiple meta-analyses show the effectiveness of MBCT in patients with three or more recurrent depressive episodes [20-22]. Many of the MBCT interventions can be found in Linehan's validating strategies [14], and there are many adapted mindfulness-based programs and interventions described for Axis-1 disorders, like compulsive disorder [23], eating disorder [24], and autism spectrum disorder [25]. In recent years, therapists acquainted with mindfulness show a growing interest in self-compassion [26-28]. Compassion is 'the ability to feel involved in pain or suffering in both ourselves as in others. It is accompanied by the desire to alleviate this suffering and the willingness to take responsibility in that [29]. Developing self-compassion can be salutary for BPD patients, as they are inclined to invalidate themselves. Furthermore, self-compassion seems effective in reducing experiential avoidance [30].

MB-ERT

Research shows that after DBT treatment, mindfulness skills together with the ability to endure crises are most applied by BPD patients [31], up to 44% of all DBT skills [32]. In a pilot study, 40 borderline patients received mindfulness training in addition to standard treatment. Compared to 19 control patients, the intervention group showed increased attention and impulse control [33]. The number of minutes participants practiced showed a positive relationship with self-reported emotion regulation and clinical (depressive) symptoms. An adjusted MBCT treatment in BPD patients showed decreased experiential avoidance, anxiety, and somatoform dissociation [34].

However, MBCT was not always fitting for BPD patients: exercises were experienced as overflowing, and the idea rose to develop a mindfulness training for this specific patient group. Mindfulness Based Emotion Regulation Training (MB-ERT) is based on the MBCT protocol, the mindfulness and emotion regulation skills of DBT and contains self-compassion exercises. The training comprises 13 weekly sessions of 75 minutes and is preferably given by two therapists (Table 1). Similarly to MBSR and MBCT, in MB-ERT the body forms the starting point. Patients learn to focus attention on bodily sensations in general, or in specific places like the breath. They are invited to stop experiential avoidance by using small steps and short exercises. Just like in MBCT, they learn to distinguish experiences as cognitions, feelings and bodily sensations, the so-called 'triangle of attention'.

Table 1. MB-ERT training

Week	Theme	Subjects
1	The automatic pilot	Biosocial theory
		The 'why' of the training
		Connection to emotion regulation
2	Awareness without judgment	Importance of awareness without judgment*
		Awareness practices*
		Triangle of attention*
		Fundamental attitude*
3	The body – here and now	Body as point of departure*
		Attention and aversion
		The 'here and now'-stone
		Walking with awareness (audio)*
4	From the outside to inside	Bodyscan (audio)*
		Awareness of the breath (audio)*
5	Compassion towards yourself and others	The importance of (self)compassion
		Self-compassion in between (audio)
		Developing kindness for yourself (audio)
6	Perceiving and labeling positive emotions	Positive emotion*
		Logbook pleasant events*
		Nice little moment
7	Perceiving and labeling negative emotions	Negative emotion*
		Labeling emotions (audio)*
		Breathing space (audio)*
		Logbook unpleasant events*
8	Staying with	Pain x resistance = suffering*
		Intense emotions x resistance = submerging emotions
		Fighting, fleeing and drowning*
		Mountain meditation (audio)*
		Sitting with difficulties (audio)*
9	Making conscious choices	Action plan to create space for wise decisions*
		Softening, soothing, and allowing (audio)
10	Thoughts are not facts	Automatic thoughts*
		Content of thoughts*
		Thoughts are not facts (audio)*
11	Dealing with destructive thoughts	Destructive thoughts x resistance = increased tendency for destructive behavior
		Action plan in case of destructive thoughts
12	Awareness in contact	Action plan meeting*
		Passive, assertive and aggressive behavior*
13	Taking care of yourself	Energy givers – energy takers*
		Eight helping factors*
		Five ways for self-compassion
		Getting into action*
		Relaxing (audio)*

* Corresponding to MBCT and MBSR protocol

Contrary to MBSR and MBCT, in MB-ERT the development of self-compassion has an explicit place. Second, in MB-ERT focusing attention on positive experiences is emphasized by acknowledging 'a beautiful little moment' every week.
In the Centre Personality disorders Jelgersma (CPJ) in Oegstgeest, the Netherlands, there were two treatment programs available for BPD patients: Mentalisation Based Therapy (MBT) and DBT. Short-term clinical DBT was offered to severe BPD patients, in whom suicidality and auto-mutilation were profound. To explore whether mindfulness can improve emotion regulation, this department decided to start offering MB-ERT on experimental basis. Patients received mindfulness additional to the mindfulness in DBT. During 13 weeks, MB-ERT was offered for 75 minutes by one therapist, in groups of 5-9 patients. From January 2012, the program was improved along the way by experiences and critical feedback of 32 patients. In September 2013 the protocol was published in a book: 'Stilstaan in de storm, mindfulness bij heftige emoties' [35]. Audio exercises can be downloaded from the publisher's website.

The pilot study

The goal of this pilot study was to explore the applicability and effectiveness of the MB-ERT protocol as an independent module. From February to June 2013 MB-ERT was offered on the clinical MBT department. Contrary to DBT, on this department mindfulness is not a taught skill.

Outcome measures

Mindfulness

The Kentucky Inventory of Mindfulness Skills-Extended (KIMS-E) [37] contains 46 items measuring five aspects of mindfulness: observing, describing, acting consciously, accepting without judgment and not reacting to inner experiences. These five subscales can be combined in a total score. The 46 items are 5-point Likert scales ('never to seldomly true' to 'very often or always true'). The KIMS-E contains the original KIMS [37], and the seven items of the Five Factor Mindfulness Questionnaire (FFMQ) subscale 'not reacting on inner experiences' [38]. Validity and reliability of the original KIMS are good [37], the internal consistency of the Dutch KIMS-E is between 0.78-0.88 [39].

Brooding

The Penn State Worry Questionnaire (PSWQ) measures brooding and has strong internal consistency and good test-retest reliability [40]. The questionnaire contains items on the amount, intensity and disability to control brooding. The PSWQ consists of 16 items, of which 11 items are phrased positive and five items negative. The items are 5-point Likert scales, ranging from 'Not at all typical of me' (1) to 'Very typical of me' (5).

Borderline Personality Symptoms

The Borderline Personality Disorder Severity Index (BPDSI-IV) is a questionnaire containing 47 items using 5-point Likert scales ('not at all' to 'very much so')[41]. The BPDSI-IV measures BPD symptoms based on the DSM IV [42] in the preceding month, and has a very good internal consistency and validity [41,46].

Patient Evaluation

An evaluation form with open questions was composed, based on the MBCT/MBSR evaluation form. The form contained items on the appreciation of the training, possible difficulties participants experienced, the effect of the training, the expectations of participants, the execution of home exercises, the rating of the workbook and audio exercises, and feedback on the therapist's approach.

Procedure

Two weeks before the start of the additional mindfulness training, patients were informed verbally and in writing, and had the opportunity to ask questions. The staff was informed in a work meeting. There was no financial compensation for participation. The questionnaires were taken anonymously, and distributed and collected by the team psychologist before and within two weeks after the training.

Analysis

Baseline and follow-up measurements of the KIMS-E, PSWQ and BPDSI-IV were analyzed using a paired samples T-test. Furthermore, we analyzed per patient whether chances in outcome were clinically significant and reliably, using the Jacobson en Truax (1991) formula [45]. An effect is clinically signifianc when a patient's score shifts from one belonging to a clinical population, to one belonging to a non-clinical population after the intervention. The cut-off is based on the means of functional and dysfunctional populations. For the KIMS-E cut-off we used the results of 215 students [37] and 101 patients with Post Traumatic Stress Disorder[39]. Of the subscale Not reacting to inner experiences there was no mean score available, so no cut-off could be calculated here [36] (Table 2). For the PSWQ we used the mean score of a 'normal' population [43] and of 22 patients with Generalized Anxiety Disorder [44]. On the BPDSI-IV a score of 100 or higher indicates BPD, and a score of 67 is the cut-off for recovery [41].

Using the Reliable Change Index (RCI) [8,45] we calculated whether the difference between pre- and post-measurement is reliable [37,40,43,46].

Results

Patient Characteristics

Within the study period, fifteen patients were treated on the MBT department, divided in two groups of seven and eight patients. The maximum treatment duration on this department is nine months. MB-ERT was offered weekly in these two groups by one therapist. Although five patients refused to fill in the questionnaires, they participated in the training (5.4 meetings). These five were women with a mean age of 24.8 years (range 19 – 38 years). Four were diagnosed with BPD, one with Paranoid Personality Disorder. All of them had one or more Axis-1 disorders (mean 1.6), were not married and unemployed. The ten patients participating both measurements (eight women and two men, see Table 2), were present at least eight of the 13 sessions (mean 10.1). Their mean age was 35.5 years (range: 19 – 51 years).

One participant was diagnosed with Personality disorder Not Otherwise Specified; the other nine had BPD as main diagnosis (seven had two or more personality disorders). All ten participants were diagnosed with one or more Axis-1 disorders (mean 1.6). All had Axis-IV issues: especially problems in the primary surroundings and problems with work. All were unemployed and were on welfare based on illness or not being able to work. Six had no partner (one was divorced); four were living with their partner.

Table 2. Patient demografics

	Participants (N=10)
Female	80%
Age (year, SD)	35.5 (11.6)
Number of sessions attended	10.1 (1.9)
BPD diagnosed	90%
Axis-1 disorder	1.6 (range 1-3)
Unemployed	100%
Single	60%

Questionnaires

Table 3 shows the mean scores on both measurements. Before MB-ERT all mindfulness subscale scores were similar to those of a clinical population. The mean PSWQ score (brooding) was between scores of a normal population [43] and those of a clinical population with anxiety disorders [44]. The mean BPDSI-IV score of 116 was above the score indicating BPD [41].

Table 3. Questionnaire scores

	Cut-off score	Baseline (SD)	Follow-up (SD)	Statistical significance	Clinical significance
Mindfulness					
Observing	37.4	32.3 (6.4)	38.8 (6.9)	$p < .001$	-
Describing	25.9	21.5 (6.2)	27.3 (7.3)	$p = .003$	N=4
Acting with awareness	27.3	28.8 (6.3)	29.4 (7.2)	$p < .001$	-
Acceptating	27.5	22.1 (9.7)	25.5 (9.5)	$p = .06$	N=1
Not-responding		16.2 (4.4)	20.3 (3.7)	$p = .01$	-
Total score	136.5	120.8 (23.2)	141.3 (27.7)	$p < .001$	N=2
Brooding	53.7	59.7 (9.7)	54.5 (12.0)	$p = .005$	N=2
Borderline Symptoms	67	116 (26.2)	93.8 (26.7)	$p = .015$	-

After the training

On a group level mindfulness skills increased significantly (range 8-35). Whether this is clinically significant cannot be calculated, as the baseline score is already above the cut-off. In two patients the increase was clinically significant, and in three patients the change on the KIMS-E Total was reliable according to the RCI. Subscale Observing showed a significant mean increase. In one patient the change was reliable, but not clinically significant as the value was above the cut-off (37.4). Subscale Describing also showed a significant mean increase. In four patients this increase was both reliable and clinically significant. Scores on subscale Conscious acting increased significantly too, though none of the changes were clinically significant nor reliable. On the subscale Accepting the mean increase was not statistically significant ($p = 0.6$), but in one patient the increase was both reliable and clinically significant. The mean score on subscale Non-reacting increased significantly, but clinical significance and reliability could not be assessed due to missing test data.

The mean brooding score decreased significantly (PSWQ -5.5; range 2-12). Baseline scores of three patients were below the cut-off; in all three the decrease was reliable and in two patients the decrease was clinically significant.

On a group level Borderline symptoms decreased significantly (BPDSI-IV -22.2, range 6-68). None of the patients showed a clinically significant decrease of BPD (below the cut-off of 67). In two patients the decrease was reliable according to the RCI.

All participants reported on the evaluation form that they noticed an improved ability to regulate their emotions. Five participants expressed the wish that MB-ERT would become a standard addition to MBT treatment. Participants appreciated the protocol and its applicability, the workbook, and the audio-exercises. The biggest change 9 out of 10 participants noticed was that they applied attention more aware in their daily lives. Three participants mentioned difficulty with the amount of theory and the speed of the training. We should note that half of the participants did not practice at home. The therapist was prized for her clarity and patience, but was also experienced as too directive. Two participants did not rate the training, the other eight gave the training an 8.5 out of ten.

Some statements of participants:
'I have learned to pause for reflection and I am more aware of small positive moments'
'I succeed more often in stopping myself. I notice that I get caught up less often in a negative spiral'
'The training is very much written on Borderline (PD), so that the theory is recognizable and the exercises endure. Finally I succeed in bringing myself to a stop regularly and accessing my emotions. This provides space for choosing with awareness how to react, instead of using my negative automatic pilot.'

Discussion

In recent decades, evidence has grown on the effectiveness of mindfulness in treatment of psychological disorders. In looking for applicability in BPD, the first therapy that comes to mind is DBT, a mindfulness-based therapy in itself. In this protocol, however, mindfulness is intertwined with other skills, which makes studying the effect of mindfulness itself becomes difficult. It could even be the most effective element in DBT. The aim of this pilot study was to gain clinical experience with MB-ERT as an independent module and assessing the applicability in a clinical setting for BPD patients.
It seems that the MB-ERT protocol can be applied safely in this setting: no patients have deteriorated. The number of non-completers (33%; five out of fifteen) is comparable to other BPD studies, with drop-outs ranging from 15% [47] to 51% [34, 41, 46].

On a group level we found the expected changes. Mindfulness skills increased, and brooding and BPD symptomatology decreased. The qualitative evaluations were positive. On individual level the changes were clinically significant and/or reliable only in a (small) minority of participants. Assessing reliability with the Reliable Change Index takes the standard error of the delta between two measurements into account. The test corrects for coincidental results, which can be larger in individuals than in groups. Downside of this method is that due to this correction, only very big changes can be labeled 'reliable', often bigger than occurs in patients (especially patients with severe and long-term problems like BPD). In the assessment of clinical significance, the cut-off value is based on a value in between scores of the 'normal' population and those of a dysfunctional population. In a number of participants, the baseline measurement showed scores already below or above (dependent of the questionnaire) the cut-off score. In these patients, clinical significance was already unachievable. Furthermore, wellknown criticism on this technique states that for some populations (autism, schizophrenia), recovery is not possible [48]. One could imagine that this might also apply in (therapy resistant) BPD patients.

Previous attempts of Soler e.a. (2012) and Sachse e.a. (2010) to offer mindfulness training to BPD patients showed that patients who did not improve in mindfulness skills after MBCT, had underwent much more therapy than fellow participants that did improve. This indicates that therapy resistance could interfere with the possible benefit of the treatment. They also found a dose-effect relation between the number of attended sessions and the decrease of experiential avoidance, anxiety and dissociation [34]. This is in line with a relationship between improved emotion regulation skills and a decrease of depressive symptoms, and the number of minutes participants practiced formal mindfulness skills [33]. This might indicate that more sessions, like in MB-ERT, are needed to induce change in this chronic population.

Without a control group we cannot determine whether the changes are attributable to MB-ERT. Randomization is not easy in this population, as commitment is a condition for this training. N=1 studies with repeated measurements, so-called case series, can be executed in clinical practice and could be a valuable alternative for single-group studies, and maybe even randomized studies [49]. Another limitation is that next to the MB-ERT training, participants received regular MBT therapy. This also obscures to which elements of the treatment improvements can be attributed. The high scores at baseline and the fact that they participated in a clinical psychotherapeutic treatment (often after earlier ambulatory or part-time treatment was insufficient), indicates the severity of pathology. Furthermore, the conclusions of this pilot study are limited by the small number of participants.

The goal of the pilot study was to explore the applicability and effectiveness of the MB-ERT protocol. The results are positive: patients and therapists regard MB-ERT as a valuable addition to current options. As this study is limited by design, it is important that future studies use more elaborate methods to sustain current preliminary findings.

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Chapter 11

Double blinding in psychotherapeutic intervention trials.

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Submitted.

Abstract

In psychotherapy research, double blind trials are deemed nearly impossible, as participants play such an active role in the intervention. In this article, we discuss the possibility of implementing double blind trials in psychotherapy research. We discuss essential components of psychotherapy, several methods used in literature, and the implications of their results. The Zelen design seems a feasible solution to meet the methodological issue of double blinding in psychotherapeutic intervention trials, as participants are unaware of the other treatment arm, would still have free choice in participation to the study, and would not be harmed by the randomization procedure. We therefore propose this model to be considered more often as an alternative in future psychotherapeutic research.

Introduction

In methodology, there are different study designs for different purposes, and each design has certain guidelines of how trustworthy its outcome can be interpreted as being correct, and when risk of bias may be present. Most of the time, a double-blind experiment is regarded to have a higher standard of scientific rigor than a single-blind or non-blind experiment. Double blinding in trials refers to the unawareness of group allocation of participants in both outcome assessors, intervention administrators, and participants themselves. If succeeded, during the trial none of these parties know which intervention is being received by which participant. This is most relevant when it is possible that conscious or unconscious interference on the part of researchers, participants, or both, can affect the outcome (i.e. information bias). In psychotherapy research, however, double blind trials are deemed nearly impossible, as participants play such an active role in the intervention.

For years, surgical research also claimed that double blind studies were impossible[1]. It was considered unethical to give a control group a sham incision without the prospect of a therapeutic benefit (which violates the principle of "do no harm"). Furthermore, surgeons expressed concerns that delaying a certain surgical procedure until after well-defined trials could harm patients. These arguments could also apply to psychotherapy research: keeping patients from treatment or offering them fake treatment could be considered unethical. However, ethically one can also question this rejection of procedure. How many patients underwent unnecessary surgical procedures and suffered adverse effects that might have been avoided had proper clinical trials been done beforehand? The general public can be protected from a treatment protocol that is ineffective, unanticipated adverse effects can be discovered before large numbers of patients are exposed, and post hoc analyses provide new insights for designing protocols that might have a better chance of success. In this argumentation the greater good of the population's health outweighs participants' needs. Recently, by giving participants in the placebo control group a sham operation, keeping the administrating surgeons outside of the investigating group and keeping the outcome assessors blind, this claim of impossibility proved untrue. A meta-analysis on placebo controlled trials of surgical procedures concluded they are a powerful, feasible way of showing efficacy with small risk of adverse effects. Furthermore, in half of 53 studies results provided evidence against continued use of the investigated surgical procedures [2]. Inclusion rates of placebo-controlled surgery studies show one in twelve participants consent, with oral explanation by the surgeon (69%) and contribution to research (90%) being the most important reasons to participate [3].

However, the main difficulty double blinding faces in psychotherapy trials is not fear of harm, but the active role patients play in the intervention. In this article, we discuss the possibility of implementing double blind trials in psychotherapy research. First, it is important to understand what is meant by psychotherapy. According to Orlinsky, psychotherapy contains the following aspects: a formal aspect (the therapeutic contract), technical aspect (the therapeutic interventions), interpersonal aspect (the therapeutic relationship), intrapersonal aspect (client's characteristics), clinical aspect (impact of sessions) and temporal aspect (sequence of events during treatment) [4]. Psychotherapy is defined as: "the informed and intentional application of clinical methods and interpersonal stances derived from established psychological principles for the purpose of assisting people to modify their behaviours, cognitions, emotions, and/or other personal characteristics in directions that the participants deem desirable."[5, 6]. Second, it is important to separate the question whether blinding is possible from the question how we can measure whether psychotherapy is effective: one is the means to the other. The first is a technical problem, which if solved can serve clinical research with implications for practice. Once blinding is achieved, one can experiment more accurately with comparing therapies, components of therapy, therapists and patients.

Terminology

Placebo

Literally meaning 'I will please' in Latin, a placebo effect influences the outcome of interest, and thereby obscures the pure effect of the intervention investigated. For instance, compared to baseline performance, participants taking a pill every day may improve over time even when the pill itself does nothing. This effect is then embedded in the overall measurement of real medication, enlarging the outcome attributed to the substance itself. To measure purely the effect of the intervention itself, investigators therefore often use a placebo intervention in the control group. A placebo intervention has been defined as 'a substitute for a treatment or intervention, which has no known activity that would be expected to affect the outcome' [7, 8]. Blinding of participants applies specifically to the perception of the participant. When offering a placebo to keep participants blinded, it therefore has to have the exact same characteristics as the intervention in order to raise the same expectations, except for not having the working component of interest. The easiest example can be found in medication trials. The placebo pill should have the same colour, shape, taste, weight, intake instructions, and packaging, so that there is no information from which the participant can deduct his or her allocation, and the effect of solely taking a pill on a daily basis has been neutralized.

When comparing psychotherapy to pharmacological treatment however, patients randomized to psychotherapy know to which condition they have been allocated[9, 10]. This may result in expectations affecting both treatment arms, inflating or deflating the effect sizes of psychotherapy[11]. In studies with wait lists or care-as-usual control conditions, information bias can be introduced. As an illustration of this problem, a recent meta-analysis on randomized trials comparing psychotherapy to pharmacotherapy found that single-blind studies (studies using no pill placebo) showed significant effect on depression in favour of pharmacotherapy over psychotherapy (Hedges g=0.13, 0.03 to 0.23), where double-blind studies (where pill placebo was implemented) did not show significant differences between groups (g=0.07, -0.07 to 0.21) [12].

Blinding

Where blinding of outcome assessors creates a problem less often, blinding of intervention administrators is in some cases more difficult. Handing out a blinded box of pills is a different procedure than, for instance, performing surgery or psychotherapy. As opposed to using an external vessel like medication, these professionals themselves are a vital part of the treatment: they have to know what they do with whom. Surgeons can be blinded to who is lying on their table, to a certain extent, and during some operations but not all. Likewise, it has long been convention that blinding in psychotherapeutic interventions is not possible [13, 14]. After all, psychotherapy does not use pills that can be fabricated to look alike, but depends on communication, contact, interaction between patient and therapist. Where pills have characteristics that can be copied in detail, communication is very fluent and variable. The intervention administrator in psychotherapy has to have knowledge of what he is doing and why, and blinding him can cause serious damage to the therapeutic relationship, and thus to the patient. Furthermore, genuineness is an important factor in the therapeutic relationship [15, 16]: when a therapist does not believe in the treatment he is giving, the patient will often somehow notice. The patient, however, has a smaller role in choosing therapeutic interventions, and could therefore technically be blinded to which therapy he is receiving. As long as outcome assessor and patient are unaware of treatment allocation, double blinding may be considered achieved.

In this article we propose a method to blind participants in psychotherapeutic intervention studies. To clarify our method, we will use the example of randomizing patients with recurrent depression to either Cognitive Behavioural Therapy (CBT), or Mindfulness Based Cognitive Therapy (MBCT).

Method 1: Pre-randomization

One way of keeping participants unaware of allocation (intervention or control), is if they do not know what the other group is receiving. A Zelen design [17] could provide that unawareness: after first randomising participants to a treatment arm and then asking them whether they would want to participate in a study on this particular intervention, patients would not be given information about the other treatment (Figure 1). Therefore, it is harder for them to distinguish whether they are receiving the intervention of interest or the control intervention. Second, a frustrebo response is eliminated: patients consenting because they wish to receive mindfulness but end up disappointed in the other treatment arm (and thereby interfering with treatment effect) will not occur. Another way of keeping the treatment options obscured is not naming the exact intervention, but calling it an investigation on 'two psychotherapy treatments for recurrent depression', treatment A and treatment B.

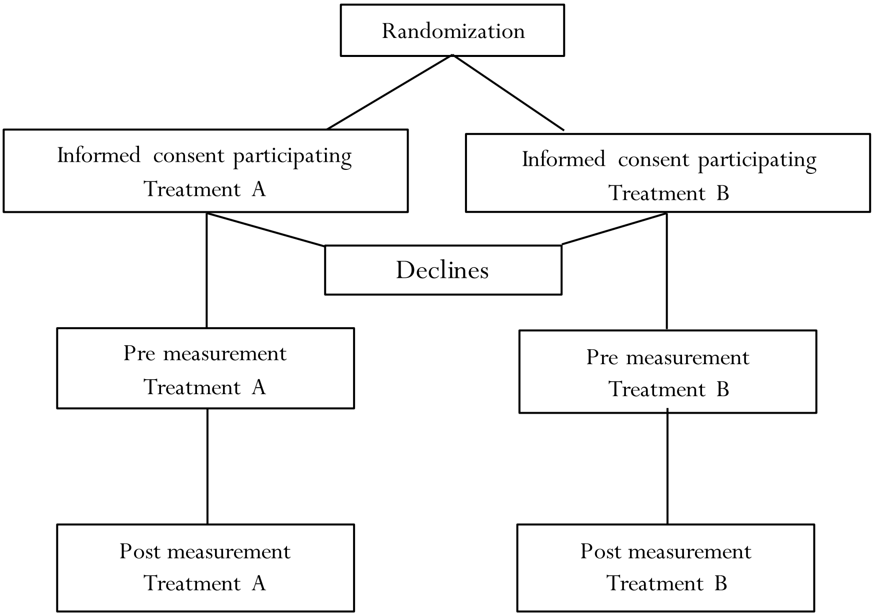

Figure 1. Zelen design.

When comparing an additional intervention with care as usual, the participants randomized to the control group would be asked whether they would consent to observational research and partake at several measurement moments. This could also lower the threshold of partaking in research.

Some ethical concerns on the Zelen design have been raised: by first randomizing and then asking permission of the patient, the investigator crosses privacy rules protecting the patient. On the other hand, the patient will notice nothing of the randomization process, and can still decide freely to join or decline partaking in the study. The only thing different from a standard randomization procedure is that he will not know about the other intervention group. Second, not specifying the treatment but obscuring the name is withholding important information from the study participant. However, expected side-effects, duration, frequency of contact and possibly the goal of the treatment can still be mentioned.

Method 2: Language

When not using a Zelen design and participants are aware of the other treatment arm, all treatment arms should offer a similar intervention: if CBT is to be compared to antidepressants, the CBT group should receive placebo pills, and the medication group some kind of weekly meetings. The placebo group session should only offer the structure and

social interaction, without the actual exercises given by the group therapist. As mentioned above, blinding applies to the senses concerned, and the primary sense in psychotherapy is social perception. This is such a delicate sense that our means to fake and withhold information in such a way that both treatment arms keep their credibility seem inadequate. Using language to conceal the comparison between an intervention and a wait list control group in a randomized setting is therefore nearly impossible.
When comparing two psychotherapeutic interventions, one way to conceal allocation is to resolve the different vocabularies of different psychological protocols but offer the actual exercises unaltered. Rather than calling it a meditation exercise, which most likely would lead the participants to the conclusion they participate in a mindfulness treatment arm, one could refer to the exercise as 'internal exposure practice' or 'concentration training'. Using similar terminology in the CBT group, a lay participant would probably not be able to distinguish what name 'treatment A' carries outside of the study setting. Therefore, the effect can be attributed to the content of the exercises themselves rather than a person's attitude towards a certain treatment allocation.
One could also try to keep all common factors the same (group size, contact hours, therapist attention) and vary the techniques implemented. Treatment A would be a group therapy conducting only the challenging thoughts intervention of CBT, Treatment B would perform just the observing of thoughts (open monitoring) of MBCT. To examine full therapy protocols, one would need many treatment arms, and as the differences between interventions are small, a very large population.

Method 3: Computer based therapy

Another option is to rule out the psychotherapist as intervention administrator, and to offer the intervention techniques by computer or audio tape. Although in this way the effect of solely the exercises can be tested without the social, empathic aspect of therapy, the same difficulties apply in blinding of the patient. If the participant is to be unaware of treatment allocation, language has to be equalised. Furthermore, these exercises would fit less well to personal needs of the patient, as a therapist might vary in pace, timing or emphasis depending on the patient's needs. A recent systematic review of computerized CBT for anxiety and depression identified 16 studies on e-health programmes (including 11 RCTs), showing some evidence that computer based cognitive therapy is as effective as therapist-led cognitive behaviour for the treatment of depression/anxiety and phobia/panic [18]. Another meta-analysis showed a medium effect size of Hedges $g = 0.63$ (two trials, $N=58$) in favour of face-to-face therapies (no confidence intervals given) [19]. When comparing computer treatments with wait-list or treatment as usual, they found an effect size of $g=0.34$ (no confidence intervals given) in favour of computerised treatments in three studies ($N=155$).

Effects vs side effects

Like in any other field of medicine, uniqueness of psychiatric patients plays a vital role in choice of treatment. Personality, background, childhood, social environment and personal wishes make a fitting choice of content and course of psychotherapy essential. Therefore, no treatment will work for all patients.

Studies often make use of instruction manuals, and monitor whether or not the therapist follows that protocol. However, use of treatment manuals suggests that each manual contains strategies that are unique and essential to the treatment, while in practice all of these therapies consist of multiple interventions. Studies often do not show which treatment exercises are important and which ones are not, or even more importantly, which ones may even be counterproductive. This effectiveness of exercises is highly dependent on personal features: some will appeal to one and not with another. Also, delivery of techniques is often more important than the techniques themselves. Techniques can be performed skilfully, or in an abrasive, authoritarian, or uninterested way. Research suggests that the skill of the therapist can be more important for good results than individual exercises [20].

If we expect exercises to be effective, one must assume that side-effects can also occur. Psychological research is often assumed 'safe' and low-risk for participants, but there certainly are risks involved, sometimes only noticeable on the long term [21]. Psychologically vulnerable people can be much affected by the attitude of the therapist, certain exposure exercises, or the feeling of failure for instance when the therapy takes longer than expected. Sometimes one particular remark can give a patient a great insight, but just as well sometimes one remark is enough to cause tremendous stress without the therapist intending to do so.

Discussion

Blinding patients from a psychotherapeutic intervention is more difficult than from pills, but not necessarily impossible. This article offers three options by which participants can remain unaware of their allocation: the Zelen design, language synchronization, and computer based therapy. If combined, double blinding can almost certainly be obtained. If due to ethical reasoning the Zelen design is undesirable, applying the two therapy administration adjustment strategies could still obtain a certain level of participant blinding. Adjusting vocabulary can be a lot of work, and our example is just an example as group dynamics can change the direct application of certain techniques. This framework therefore has to be adjusted depending on which psychotherapeutic protocol is being investigated in which population. Furthermore, computer based therapy could lack in flexibility and empathy where a human psychotherapist would not. Therefore, the Zelen design seems to be the most suitable option to keep participants blind to their allocation in psychotherapeutic intervention trials. Participants would still have free choice in participation to the study, and would not be harmed by the randomization procedure. It would, however, lose its advantages if patients were in contact with each other [22]. Previous studies using the Zelen design report that it may be preferable in drug addiction trials for reducing drop-out [23] and can increase internal validity [24]. A review on 58 Zelen trials [25] reports that the most common reason for this method was to avoid the introduction of bias and that few had explicitly used the design to enhance participant recruitment. Most trials (n=41) did experience some crossover from one group to the other although this was usually within acceptable limits. The use of blinding serves the research question 'does this therapy really work, or do expectations, placebo effect, attention, therapeutic relationship, and a certain structure explain the effect?' One has to realize, though, expectations will always be present in human patients. Furthermore, in our view, attention, the therapeutic relationship and structure are a vital part of psychotherapy, as we address persons rather than enzymes or cells. These aspects of the intervention serve the delivery of techniques and exercises in such a way that should certain exercises prove helpful on their own, these components should still be part of the intervention.

Also, one can argue that a (partial) placebo effect is not a bad thing. If a patient improves because he feels supported and seen by the therapist, they can then build a strategy by which the patient can provide himself with that support. One could go even further and say that perhaps in psychotherapy there is no such thing as a placebo effect: all variables in the therapeutic relationship are psychological and all are active, having some direct or specific effects on the patient [26].
There is also the difference between effectiveness versus efficacy. Effectiveness refers to the extent to which an intervention achieves its intended effect in the usual clinical setting, whereas efficacy refers to the extent to which an intervention has the ability to bring about its intended effect under ideal circumstances, such as in a randomized clinical trial [27]. Therefore, as participants are unaware of the other treatment arm, implementing a Zelen design could result in outcomes closer to reality, showing effectiveness of the intervention rather than efficacy.

Conclusion

The Zelen design seems a feasible solution to meet the methodological issue of double blinding in psychotherapeutic intervention trials.

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Part V

Epilogue

Chapter 12

Summary and general discussion

Summary and general discussion

In this thesis, our aim was to gain insight in whether offering mindfulness training to patients with different chronic diseases can reduce psychological distress and improve quality of life. Additionally, we tried to elucidate which brain structures are involved in the MBSR training, to improve our knowledge on a neuronal working mechanism of this eight-week protocol. Next to the link between mindfulness and the brain, was the effect of mindfulness training in heart patients. Lastly, a perspective on future applications of mindfulness is offered, and how we could improve research on psychotherapeutic interventions. In this chapter we report and discuss the main findings of our studies, and we close with concluding remarks and suggestions for future research on the link between mind and body.

Main findings

Overview of Mindfulness in different patient populations

As so many trials have been conducted since 1982 [1], and in turn so many systematic reviews have been performed to summarize the trials, in **Chapter 2** we systematically reviewed systematic reviews of RCTs assessing MBSR and MBCT, summarizing the effects per patient category. This overview of MBSR and MBCT shows that both patients with medical conditions and those with psychological disorders benefit from these training protocols. Patients with cancer, chronic pain, cardiovascular disease, mental disorders, and healthy participants show significant improvements in depression, anxiety, stress and quality of life. This says little about the 'how' these outcomes improve, but the observed results can help trigger awareness in physicians to take mindfulness into account in weighing supportive treatment options. In prevention, mindfulness can be valuable in teaching a coping style that prevents long-term stress and other psychopathological symptoms that might otherwise develop into clinical conditions. Since MBSR and MBCT consist of not just meditation, but also psycho-education and yoga exercises, it is difficult to pinpoint which aspect contributes most to the observed improvements. In our meta-analysis, chronic as opposed to acute conditions seemed to respond better to the training as acceptance and reflection may be more applicable to chronic symptoms than to acute symptoms. In acute settings, the focus often still lies on changing the undesired situation, making acceptance untimely. Publication bias is always a risk in reviewing current literature, as we have not assessed this we have no estimation of how many studies we miss. The 115 unique RCTs included, however, show that MBSR and MBCT have value in offering a new way of coping with daily struggles.

Mindfulness and neuroimaging

In **chapter 3** we wanted to know more about the neuronal changes that accompany using this coping method, so that we might begin to understand how these trainings affect psychological functioning. We reviewed studies that looked at functional and structural differences in the brain after MBSR, MBCT, and aspects of the protocols. We hypothesized that the distilled techniques of MBSR and MBCT would have similar effects on brain structures known from neuroimaging studies on traditional meditation. Earlier meta-analyses on traditional meditation identified increased activation in the prefrontal cortex, the insula, cingulate cortex and hippocampus [2-5]. Although MBSR and MBCT are only eight weeks and cannot be expected to have the same structural effect as years of meditation, activation and connectivity change could give an indication of structural effects on the long term. The 30 neuroimaging studies on MBSR and aspects of the protocol reported similar effects on prefrontal cortex, insula, cingulate cortex and hippocampus. At the same time, the amygdala seemed to have a larger effect in MBSR participants. It showed less activity, increased connectivity with the prefrontal cortex and earlier deactivation after emotional stimuli. The amygdala is known for its central role in the fight-flight response [6], and might therefore be affected by learning to cope differently with stress using mindfulness. It seems that the prefrontal cortex, the hippocampus and the amygdala form a network that reflects the acquired emotion regulation by MBSR on a neuronal map. The prefrontal cortex is more able to down-regulate the amygdala response, taking previous experiences (hippocampus) into account in conscious decision making. This is in line with neuroimaging results of other emotion-regulation strategies, as Tang and collegues argue[7], alongside with higher awareness of present-moment experiences. One of the explanations of the fact that the amygdala shows more effect in MBSR participants than in long-term meditators could be that there might be more room for improvement. Monks might not experience many stressful events in their monastery, and if they do, their long experience may enable them to cope mindfully better. It seems likely that Western participants, however, experience more stress in daily life, whether this is in proportion to the actual threat or not. Their amygdala probably shows a higher baseline activity than long-term meditators [8]. The down-regulation of the amygdala and the increased activation of prefrontal cortex and hippocampus underline the stress-reducing effect by using MBSR. However, a strong limitation of this review is the variety in methodology included: of the MBSR studies five were RCTs, but they used different imaging techniques. More RCTs are needed to confirm our hypothesis.

Chapter 4 takes the observations made in the systematic review to a subcohort of the Rotterdam Study, a large population-based cohort in the Ommoord region of Rotterdam. A total of 3,742 participants were interviewed on whether they practiced any form of meditation, yoga, or other methods 'to find stillness in themselves'. Furthermore, they underwent an MRI brain scan. Our hypothesis was that participants practicing meditation or yoga for more than one hour per week, report less stress and show different amygdala and hippocampal volumes than non-practitioners. A number of 588 participants (15.7%) reported practicing meditation and/or yoga, similar to other studies (18.9%)[9]. After adjustment for covariables that could also explain structural differences, we found that the practitioners actually reported more stress and depressive symptoms, but had a smaller right amygdala and left hippocampus volumes than the control group. This was remarkable, as more stress and depressive symptoms are associated with larger amygdala volume. At the same time, 90% of practitioners did report that their method helped them cope with stress. This might be placebo effect (knowing they do something relieves stress but the practice itself has no effect), or it could indicate confounding by indication. As people experience more stress, it is more likely that they seek methods that are known to reduce stress. That way, meditation and yoga practice could be perceived as a biomarker of stress.

Acknowledging the limitations of cross-sectional research, we looked at a subsample that underwent a scan five years earlier as well. In total 2,397 participants were included, of whom 9.8% practiced meditation and/or yoga for five years or longer. Over time, practitioners showed a stronger decrease of right amygdala volume than the control group, whereas the left hippocampus did not show significant differences in volume reduction. The latter is in line with the MBSR-studies, where hippocampal volume even increased. The initial smaller hippocampus could have been due to atrophy. Depression showed no difference in increase between the two groups, further underlining the possibility of confounding by indication. Although practitioners report more experienced stress, their brains show no compatible increased stress-structure. In other words, their higher stress scores might also be explained by them being more aware of their stress levels rather than their having higher stress levels per se.

Even though we used longitudinal data, there are still limitations to take into account. First, although depression and anxiety were measured with validated questionnaires, stress was assessed with a one-item rating scale, and at only one time point, which can increase the risk of information bias due to inaccuracy or variability. To fully understand the relationship between the amygdala and stress over time, more information is needed on for instance experience sampling of stress or cortisol values. Second, there might be selection bias as this is an elderly population which is generally healthy and motivated to join research, but who may not be as actively involved in meditation and yoga practices as younger people. They might also show a different structural response than younger participants due to decreased brain plasticity. In addition, there is also a risk of information bias since the amount of practice was assessed retrospectively.

Finally, this study took a broad approach to the intervention of interest. Practice involved meditation, yoga and breathing exercises, which in turn can comprise different styles and is broader than MBSR and MBCT. This makes accurate research harder and the recommendations following the results less valid.

Although none of these brain structures can be seen separately from another and the brain only functions as a whole, the connectivity between prefrontal cortex, hippocampus and amygdala could elucidate a working mechanism underlying the psychological changes measured earlier.

Mindfulness in cardiovascular disease

In **Chapter 5** we reviewed the current evidence of the effect of meditation in cardiovascular patients. In this systematic review and meta-analysis, we included not only MBSR, but also other meditation-based interventions like Zen, Vipassana and relaxation, with studies from various countries. Our meta-analysis showed that systolic and diastolic blood pressure improved, as did depressive symptoms, anxiety and quality of life. However, the standardized effect size was often moderate and studies were generally low in quality with a small sample size. Furthermore, in the pooled analyses all these different interventions (some of which were not meditation) were combined, inducing bias. Meditation practice shows encouraging results in patients with cardiac disease, but firmer research is necessary. Not all meditation practices are the same, just like not all cardiac patients can be compared. More knowledge of the working mechanism could help to decide which meditation technique to apply in which patient.

Chapter 6 is a systematic review and meta-analysis on yoga in cardiovascular patients. Results showed that in patients with heart disease yoga improved body mass index, systolic and diastolic blood pressure, cholesterol, triglycerides, and heart rate. There is promising evidence of yoga on improving cardio-metabolic health, although findings are limited by small trial sample sizes, heterogeneity, and moderate quality of RCTs.
Both meditation and yoga being part of the MBSR protocol, the findings of these two chapters support the effectiveness of MBSR in these patients. The included studies however, often had small sample sizes, so we designed a large RCT of high methodological quality to measure the effect of mindfulness in cardiovascular patients.

In **Chapter 7** we aimed to investigate the effectiveness of a 12-week online mindfulness training in a randomized controlled trial in patients with diagnosed structural heart disease, at the time under surveillance at the outpatient clinic of the Erasmus Medical Center, Rotterdam, the Netherlands. 324 patients with structural heart disease were included. The hypothesis was that by reducing stress, mindfulness can reduce cardiovascular risk in lowering blood pressure and improving heart rate and respiratory rate. These improvements in cardiovascular patients have been found in our meta-analyses on meditation and yoga, and in a meta-analysis on MBSR included in our meta-review as well [10]. As these outcomes are related to exercise capacity, we wanted to see whether mindfulness could affect exercise capacity as measured by a six-minute walking test. We chose an online delivery of the training which was adapted to patient specific symptoms but less intensive than the standard MBSR program in order to be a realistic possible additive to standard treatment. After 12 weeks, the intervention group had better exercise tolerance and a lower heart rate, although this was borderline significant.

To see how the participants developed after the online mindfulness training, **Chapter 8** reports the one-year follow-up results of this RCT. Our primary outcome, exercise tolerance, further improved compared to the control group. Where the intervention group walked 13.4 meters further than the control group right after the intervention, at 12 months they walked 17.9 meters further. However, the difference between groups was still borderline significant. All other physiological and psychological outcome measures did not improve significantly. Post-intervention 261 patients (80.5%) returned for follow-up measurement, where at 12 months 245 patients (75.6%) came back for follow-up measurements. Although we monitored participants' training activity, we only have a rough estimation of adherence. The expected non-adherence of 50% found in the intervention group was anticipated adequately in the 2:1 randomization structure.

To be able to compare the effect size of different outcome measures, we calculated the Cohen's D standardized mean difference, which is based on a different distribution than the Linear Mixed Model uses. Using this method, the improvement on the 6MWT was significant, as were systolic blood pressure and depression symptoms. This again shows how choice of statistical method affects the interpretation of results. Whichever way the balance falls, one can question whether the improvement of walking 17.9 meters further is clinically meaningful: in severe COPD patients a clinical improvement was determined at 35 meters [11]. However, these patients might have more room for improvement as they walked 360 meters at baseline, where our patients walked 540 meters and healthy participants walk 655 meters [12]. Additionally, we studied which characteristics of participants were indicative of treatment outcome: although women were generally more adherent, stressed men with a lower BMI and less psychological struggling seemed to benefit most from the program regarding the 6MWT. This could indicate that physicians can keep this adjunct treatment option in mind when seeing men, or that it might be beneficial to adjust the training to be more effective for women as well. For this a qualitative interview on the experiences of participants could be conducted in order to improve the content and delivery of the training.

Our results do not correspond with those of the RCTs included in our reviews: stress, anxiety and quality of life did not improve. This could be partially explained by a ceiling effect, as the psychological baseline scores of the included patients were similar to population norms. The other part of lack of effect could be sought in the intervention itself. The low intensity of exercises of our 12-week program was part of the pragmatic and easy-accessible approach, but it could have cut out the effective components of the original protocol. Intensifying the program could lead to more profound improvements as seen in MBSR. Intrinsic motivation is key to the effect size in these kinds of interventions, as active participation is required [13]. The high percentage of non-adherence could be improved by giving some type of online feedback by a trainer. When participants can ask questions or express frustrations they are more likely to commit than when the information is one-way.

Online training is less intense than face-to-face contact, which may influence participation and compliance, and is therefore expected to have a smaller effect. Furthermore, when getting frustrated during an online training, it is easy for a participant to drop out. Drop-out rates in online programs are often twice as high compared to group trainings with weekly meetings [14-16]. In a group training the trainer could take the frustration of the participant as an object of mindfulness and as a metaphor for other frustrations in life. This opportunity is missed in our online training and could prove a beneficial addition in future application. Also in decreasing the intensity of the MBSR protocol, we altered an evidence-based format into an unfamiliar intervention. As we did not measure mindfulness, we do not know whether the changes found are related to an increased ability to be mindful. Furthermore, we were not able to blind patients to the nature of the intervention during the informed consent procedure. The control group therefore knew that the online mindfulness training was available and that they were not receiving it. This could have led to selective follow-up, although we found no significant difference between the groups at follow-up with regard to demographic and clinical variables. Nevertheless, these changes in physical functioning give an indication of the possibilities of an online adjunct intervention to support cardiovascular patients.

Future applications of mindfulness training

To continue in the exercise realm, in **Chapter 9** we studied whether walking in nature can sustain the long term effects of mindfulness training. By using Experience Sampling, we were able to study the moment-by-moment changes in mood, mindfulness and coping behavior. This revealed a positive relationship between mindfulness and positive mood, which stimulate each other in an upward spiral. Though this pilot study has methodological limitations which could have affected the questionnaire data, the ESM data are less affected by the small sample size and the lack of a control group [17]. Using this method for the first time during evoked mindfulness state, we could get a glimpse of the subtle psychological changes during mindful walking in nature. Although not significantly in this small, non-clinical population, mindfulness did increase and stress, depression, anxiety, and brooding all decreased. Whether the changes were mostly affected by mindfulness or by being outdoor remains unclear, but walking in nature and mindfulness can mutually affect each other and form an easy accessible method for people to maintain their mindfulness practice.

Chapter 10 describes a pilot study performed among Borderline Personality disorder patients. As earlier research showed that the meditation exercises in the regular protocol are too long and evoke too many fierce emotions in this population, this pilot implemented shorter meditations and focused on emotion regulation. Within Dialectical Behavior Treatment, mindfulness represents more of a distraction method away from the emotion ('keep your attention on the task at hand' Linehan 1993[18]) than a de-identification and letting go. Compassion is also an important concept taught in MB-ERT, as this population is very sensitive to (self) judgment [18]. The pilot study showed that this adapted 13-week protocol is feasible in borderline patients, and that it could be effective in reducing symptoms, both statistically and clinically relevant. It is however limited due to lack of a control group, a small sample size and the fact that all participants also received MBT. A methodologically stronger study is under development to test these preliminary results.

Chapter 11 is a methodological study that takes a broader scope to psychotherapeutic research. As it is nearly impossible to blind patients to a psychotherapeutic intervention, strategies are discussed that could enable research that resolves the problem of participants' expectations towards the allocated treatment arm. As these type of interventions address different senses than for instance medication studies, blinding requires a more extensive strategy than merely copying a pill. Also, it is discussed whether these expectations are really a problem, as these will always be present in the clinical situation and psychotherapeutic interventions can adapt to them, even work with them, unlike medication.

Clinical implications

With our studies we have shown that there is evidence for the beneficial effects of MBSR and MBCT in supportive care of chronic conditions. Psychological functioning improves, which can be related to alterations in brain activity, connectivity, and structure. Online delivery showed borderline significant effects on exercise capacity which insinuates intensifying our training could attain real benefits. The studies show that the core techniques of MBSR can be adjusted to many different patient categories. Mindful awareness of bodily sensations, of negative thoughts, or of disruptive emotions like in Borderline personality disorder, all lead to patient-specific improvements when adjusted to patient-specific symptoms. We have touched on multiple methods to indicate the effect of mindfulness: from meta-analysis techniques using the Cohen's D standardized effect size, to regression analysis estimates on the relation between psychological and physical outcomes, to detailed experience sampling method, to calculating clinical significance over statistical significance. All these approaches form a rich diversity in which we tried to elucidate the effects of MBSR and derivatives of the protocol from multiple perspectives. Not only physical versus psychological, not only brain, heart and mind, but also statistically versus clinically relevant. Because in the end all statistics, all methodology and all hypothesizing are aimed to better understand and possibly improve the outer world. The real world, where there are people, not participants. Lives, not scores on a questionnaire or reading instrument. The true art of research is to build the bridge between science and practice, so the numbers and p-values have actual meaning.

It seems the techniques and experiences encompassed in the eight-week mindfulness training can help patients cope with daily life struggles, and that the experiential and cognitive teachings have an effect on physical parameters. Brain activation, connectivity, and thereby structures are affected by learning new response patterns. In heart patients, a mild dose of the training almost affected physical fitness. The connection between a mental training and physical outcomes shows that there is much more to learn about ways to improve patients' health, and thereby how to organize healthcare.

By teaching individuals to recognize automatic patterns and early signs of stress, it increases the ability to self-reflect and to make conscious decisions. Mindfulness teaches de-identification ('I have sad thoughts, but as I can observe them, I am not the thoughts'). Accepting thoughts as passing entities instead of identifying with or suppressing them also relieves a tension between you and your experience. It is okay that this feeling is here, it will come, pass, come again and pass again. Compassion is also an important instrument as we tend to judge ourselves for our flaws, which can obstruct acceptance of the situation and in some cases makes this worse.
As these aspects are not easy to master, participants are recommended to apply patience with themselves, and not strive for perfection. As different derivatives of the initial MBSR program quickly arose to fit different patient populations, like we did in the online training and MB-ERT, Carmody & Baer (2009) studied how long the program should be in order to still be effective[20]. They report that although the eight-week program was designed to be long enough for participants to grasp the principles of self-regulation through mindfulness and develop skill and autonomy in their own practice, adaptations of MBSR that include less class time than the traditional format may be worthwhile for populations for whom reduction of psychological distress is an important goal (such as the shorter exercises in MB-ERT for Borderline Personality Disorder patients) and for whom a lesser time commitment may be an important determinant of their ability to participate. MBSR, however, still has the most empirical support for its efficacy, and may be the format of choice for many applications. One study showed that more knowledge of the intervention in 140 medical students was strongly associated with an increased willingness to administer or recommend it [21]. As the protocol seems to have beneficial applications in the additional care of many patient categories, it is important to increase knowledge about this program in medical professionals and integrate psychological and physical health care more.

Future research

As addressed in Chapter 11, studies on psychotherapeutic interventions such as MBSR and MBCT can lead to more bias than in intervention studies where blinding of participants is easier. Psychological research therefore seems to have a set-back. Furthermore, group-based therapy trials should be wary of assuming independent observations: participants may influence each other and thus create dependencies between observations [22]. One or two very depressed or unmotivated participants could aggravate outcomes of the rest of the group, and, one or two very motivated participants could facilitate progress in their entire group. Williams & Russel (2008) recommend that in designing group-based therapy trials (MBCT training in particular) intragroup correlation should be taken into account, as should its variance inflation and, thus, the necessary sample size [23]. Furthermore, Bergomi (2013) raised several issues regarding self-report measures of mindfulness [24]. Limitations include ambiguous interpretations of some items of these scales, a lack of consensus on which aspects of mindfulness should be included in a scale, and the kind of relationships existing between them. Given the increasing application of mindfulness in research and in health-related fields, the assessment of mindfulness could use a more solid theoretical and methodological basis. The development of one golden standard that carries the consensus of the developers of the existing questionnaires would greatly help mindfulness research.

Future research could focus on the exact link between the mind and the body, so often seen as separate entities. Where does the upward spiral between mindfulness and positive affect touch the amygdala? Where does less depression touch on walking further? In my opinion, there is no cut-off where mind ceases and body begins. We are one, a whole. We have the awareness capacity to observe both mental and bodily sensations, identifying with only one of them neglects a vital part of your being.

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Nederlandse Samenvatting

Samenvatting en Algemene Discussie

Ons doel in deze thesis was om te onderzoeken of het aanbieden van Mindfulness Based Stress Reduction (MBSR) en Mindfulness Based Cognitive Therapy (MBCT) bij chronische patiënten psychologisch lijden kan verminderen. Vervolgens probeerden we erachter te komen welke breinstructuren betrokken zijn bij hetgeen geleerd wordt in MBSR, om onze kennis van het neuronale werkingsmechanisme van dit achtweken protocol te vergroten. Volgend op de verbinding tussen mindfulness en het brein onderzochten we het effect van mindfulness training bij hartpatiënten. We sluiten af met een toekomstperspectief op toepassingen van mindfulness, en hoe we onderzoek naar psychotherapeutische interventies zouden kunnen verbeteren. In dit hoofdstuk bespreken we de hoofdbevindingen van de studies en besluiten we met concluderende opmerkingen en suggesties voor toekomstig onderzoek betreffende de verbinding tussen psyche en lichaam.

Belangrijkste bevindingen

Overzicht van Mindfulness in verschillende patiëntpopulaties

Aangezien zoveel studies zijn uitgevoerd sinds 1982 [1], en daaropvolgend zoveel systematische reviews zijn uitgevoerd om de studies samen te vatten, hebben wij in **Hoofdstuk 2** een systematische review van systematische reviews van gerandomiseerde gecontroleerde interventiestudies van MBSR en MBCT uitgevoerd, om per patiëntencategorie de resultaten samen te kunnen vatten. Dit overzicht laat zien dat zowel patiënten met medische aandoeningen als degenen met psychologische stoornissen baat hebben van deze trainingen. Patiënten met kanker, chronische pijn, hart-en-vaatziekten, psychische stoornissen en gezonde deelnemers rapporteerden significante verbeteringen wat betreft symptomen van depressie, angst, stress en kwaliteit van leven. Het zegt nog weinig over hoe deze uitkomstmaten verbeteren, maar de geobserveerde resultaten kunnen artsen aansporen mindfulness te overwegen als ondersteunende behandeloptie. In de preventieve zorg kan mindfulness waardevol zijn door een coping methode aan te leren die op de lange termijn stress en andere psychopathologische symptomen kan voorkomen die anders zouden kunnen ontwikkelen tot stoornissen. Omdat MBSR en MBCT niet alleen uit meditatie bestaat maar ook psycho-educatie en yoga-oefeningen bevat, is het moeilijk om aan te wijzen welk aspect het meeste bijdraagt aan de geobserveerde verbeteringen. In onze meta-analyse leken mensen met chronische condities beter te reageren op de training dan mensen met acute aandoeningen, waarbij acceptatie en reflectie mogelijk te vroeg gevraagd zijn. In acute situaties ligt de focus immers nog vaak op het veranderen van de ongewenste toestand. Publicatiebias is altijd een risico bij het reviewen van bestaande literatuur; aangezien we dit niet hebben gemeten hebben we geen schatting van hoeveel studies we missen. De 115 unieke RCTs laten echter zien dat MBSR en MBCT waardevol zijn door een nieuwe manier van coping met dagelijkse problemen aan te leren.

Mindfulness en neuroimaging

In **Hoofdstuk 3** wilden we meer weten over de neuronale veranderingen die met het leren gebruiken van deze coping methode gepaard gaan, zodat we mogelijk beginnen te begrijpen hoe deze training het psychologisch functioneren beïnvloedt. We bestudeerden studies die het effect van MBSR, MBCT en componenten van de training op hersenactiviteit en -structuur. Onze hypothese was dat de gedestilleerde technieken van MBSR en MBCT vergelijkbare hersengebieden zouden aanspreken als gebieden die bekend zijn uit traditionele meditatie onderzoeken. Eerdere meta-analyses lieten namelijk verhoogde activatie van de prefrontale cortex, de insula, cingulate cortex en de hippocampus zien [2-5]. Hoewel MBSR en MBCT maar acht weken beslaan en daarom niet verwacht kan worden dat het dezelfde structurele verandering kan bewerkstelligen als jarenlange beoefening van meditatie, zouden verandering in activatie en connectiviteit van gebieden een indicatie kunnen geven van structurele veranderingen op de lange termijn. De 30 gevonden neuro-imaging studies rapporteerden vergelijkbare effecten van MBSR op de prefrontale cortex, insula, cingulate cortex en hippocampus. Tegelijkertijd leek de amygdala juist een groter effect te vertonen in MBSR deelnemers: minder activiteit, verbeterde connectiviteit met de prefrontale cortex en eerdere de-activatie na blootstelling aan emotionele stimuli.

De amygdala is bekend van zijn rol in de fight-flight respons [6], en zou daarom beïnvloed kunnen worden door anders te leren omgaan met stress. Het lijkt dat de prefrontale cortex, de hippocampus en de amygdala een netwerk vormen dat de verworven emotieregulatie door MBSR in kaart brengt. De prefrontale cortex is beter in staat de amygdalarespons te temperen, door eerdere ervaringen (hippocampus) mee te nemen in het maken van bewuste beslissingen. Dit is in lijn met hersenscanresultaten van andere emotieregulatie strategieën, zoals Tang en collega's aanvoeren[7], samen met een vergroot bewustzijn van ervaringen in het hier en nu. Dat de amygdala meer effect laat zien in MBSR-deelnemers dan in jarenlange beoefenaars van traditionele meditatiestijlen, zou verklaard kunnen worden door een grotere ruimte voor verbetering. Hiervoor zou gekeken moeten worden naar het stressniveau van monniken versus Westerse mensen, en hun baseline amygdala activiteit. Monniken ervaren wellicht minder stressvolle gebeurtenissen in een klooster, en als ze dan toch plaatsvinden kunnen ze er door hun lange ervaring mogelijk gemakkelijker mindful mee omgaan. Het is waarschijnlijk dat Westerse deelnemers meer dagelijkse stress ervaren, of dit nu proportioneel is of niet. Het zou daardoor kunnen dat hun amygdala hogere baseline activiteit vertoont dan lange termijn beoefenaars [8]. De afremming van de amygdala en de toegenomen activiteit van de prefrontale cortex en hippocampus onderstrepen het stress-reducerende effect van MBSR. Een grote beperking van deze review is echter de variatie in methodologie gebruikt door de geïncludeerde studies: van de studies naar MBSR waren er vijf RCTs, maar deze gebruikten verschillende hersenscantechnieken. Er zijn meer RCTs nodig om onze hypothese te bevestigen.

Hoofdstuk 4 toetst de gevonden resultaten van hoofdstuk 3 in een sub-cohort van de Rotterdam Study, een groot bevolkingscohort in de regio Ommoord, Rotterdam. 3742 deelnemers werden geïnterviewd over hun beoefening van meditatie, yoga, of andere methoden 'om stilte in henzelf te vinden'. Ook ondergingen ze een MRI hersenscan. Onze hypothese was dat deelnemers die meer dan een uur meditatie of yoga beoefenden minder stress zouden rapporteren en andere amygdala en hippocampus volumes zouden laten zien dan niet-beoefenaars. 588 deelnemers (15.7%) gaven aan meditatie en/of yoga te beoefenen, vergelijkbaar met ander bevolkingsonderzoek (18.9%) [9]. Rekening houdend met andere factoren die ook verschillen in hersenstructuur zouden kunnen verklaren, vonden we dat beoefenaars meer stress en depressieve symptomen rapporteren dan de controlegroep, maar een kleinere rechteramygdala en linker hippocampus hadden. Dit was opvallend, aangezien meer stress en depressieve symptomen juist geassocieerd zijn met een groter amygdalavolume. Dit zou placebo-effect kunnen zijn (weten dat ze iets doen vermindert stress, niet de beoefening zelf), of het wijst op confounding by indication. Omdat mensen meer stress ervaren, is het waarschijnlijker dat ze op zoek gaan naar methoden waarvan bekend is dat ze stress verminderen. Op deze manier zou meditatie en yoga beoefening gezien kunnen worden als een zogenaamde 'marker' van stress.

Gezien de beperkingen van cross-sectioneel onderzoek hebben we ook gekeken naar een subgroep die vijf jaar daarvoor ook een MRI scan had. 2397 deelnemers werden geïncludeerd, waarvan 9.8% minstens vijf jaar meditatie of yoga beoefende. Gedurende die periode lieten beoefenaars een sterkere afname van rechter amygdalavolume zien dan de controlegroep, waar de linker hippocampus echter geen significante verschillen in volumeafname liet zien. Dit laatste is weer in lijn met MBSR-studies, waarbij de hippocampus zelfs toenam in volume. De initieel gevonden kleinere hippocampus zou dus ook atrofie kunnen zijn. De mate van toename van depressie verschilde niet tussen de twee groepen, hetgeen confounding by indication onderschrijft. Hoewel beoefenaars dus meer ervaren stress rapporteren, tonen hun hersenscans geen overeenkomstige toename van stress-structuur. Met andere woorden, hun hogere stress-scores zouden ook verklaard kunnen worden doordat ze zich beter bewust zijn van hun stressniveau.

Hoewel we longitudinale data hebben gebruikt, zijn er nog steeds beperkingen die aangestipt moeten worden. Ten eerste, hoewel angst en depressie met gevalideerde vragenlijsten werden gemeten, werd stressniveau met een enkele schaal vastgesteld op een enkel meetmoment. Dit kan het risico op informatiebias vergroten door onnauwkeurigheid of variabiliteit. Om de relatie tussen de amygdala en de ontwikkeling van stress beter te begrijpen is meer informatie over nodig, bijvoorbeeld door experience sampling of door cortisolwaarden mee te nemen. Ten tweede bestaat er risico op selectiebias, aangezien de studiepopulatie uit oudere mensen bestaat die over het algemeen gezond zijn en gemotiveerd zijn om deel te nemen aan onderzoek, maar wie tegelijkertijd misschien niet zo actief zijn op

het gebied van yoga en meditatie als jongeren. Ook zouden ze een andere neuronale reactie kunnen vertonen dan jongere deelnemers, door verminderde hersenplasticiteit. Bovendien is er risico op informatiebias doordat de mate van oefenen retrospectief gevraagd werd. Tenslotte nam deze studie een ruime benadering van de interventie: meditatie, yoga en ademhalingsoefeningen zijn verschillende activiteiten, die bovendien intern nog kunnen variëren door verschillende stijlen en dus breder zijn dan MBSR of MBCT. Dit maakt het onderzoek minder nauwkeurig en het advies wat eruit volgt minder valide.
Hoewel geen van deze hersenstructuren als afgezonderd van elkaar kan worden gezien en het brein als geheel functioneert, zou de verbinding tussen prefrontale cortex, hippocampus en amygdala een werkingsmechanisme kunnen illustreren dat onder de reeds aangetoonde psychologische verbeteringen ligt.

Mindfulness in hart- en vaatziekten

In **Hoofdstuk 5** hebben we de huidige literatuur over het effect van meditatie in cardiovasculaire patiënten bestudeerd. In deze systematische review en meta-analyse hebben we niet alleen MBSR, maar ook andere meditatie-interventies zoals Zen, Vipassana en ontspanningsoefeningen geïncludeerd. Onze meta-analyse liet zien dat systolische en diastolische bloeddruk verbeterden, alsook depressieve symptomen, angst en kwaliteit van leven. Wanneer gestandaardiseerd was dit effect echter vaak klein, en de studies waren van magere kwaliteit. In de gepoolde analyses waren deze verschillende interventies (waarvan sommigen ook geen meditatie bevatten) bovendien gecombineerd, wat bias introduceert.
Het beoefenen van meditatie laat veelbelovende resultaten zijn bij cardiovasculaire patiënten, maar zorgvuldiger onderzoek is nodig. Niet alle meditatievormen zijn hetzelfde, net zoals niet alle cardiovasculaire patiënten hetzelfde zijn. Meer kennis van het werkingsmechanisme kan helpen bij de beslissing welke meditatietechniek het beste toegepast kan worden door welke patiënt.

Hoofdstuk 6 is een systematische review en meta-analyse van yoga bij cardiovasculaire patiënten. De resultaten tonen dat yoga bij deze patiënten BMI, systolische en diastolische bloeddruk, cholesterol, triglyceriden, en de hartslagfrequentie verbetert. Er is dus veelbelovend bewijs dat yoga cardio-metabolische gezondheid kan bevorderen, hoewel de resultaten beperkt zijn door kleine onderzoeksgroepen, heterogeniteit en matige RCT kwaliteit.

Meditatie en yoga vormen belangrijke onderdelen van het MBSR protocol, en de bevindingen van deze twee hoofdstukken wijzen op de effectiviteit van MBSR bij deze patiënten. De studies waarop dit gebaseerd is bevatten echter vaak kleine onderzoekspopulaties, dus daarom hebben we een grote RCT van hoge methodologische kwaliteit opgezet om het effect van mindfulness in cardiovasculaire patiënten te meten.

In **Hoofdstuk 7** onderzochten we de effectiviteit van een 12-weken online mindfulness training in een gerandomiseerde gecontroleerde studie bij patiënten met gediagnostiseerde structurele hartafwijkingen, op dat moment onder ambulante zorg van het Erasmus MC. 324 patiënten werden geïncludeerd. De hypothese was dat mindfulness door het verminderen van stress het cardiovasculaire risico kan verlagen door bloeddruk, hartslagfrequentie en ademhalingsfrequentie te verbeteren. Deze verbeteringen zijn eerder gevonden in onze reviews over meditatie en yoga, en in een meta-analyse die in Hoofdstuk 1 is geïncludeerd [10]. Omdat deze uitkomstmaten effect hebben op fysieke conditie, hebben we als primaire uitkomstmaat een zes-minuten looptest afgenomen. Een online training was gekozen vanuit praktisch oogpunt: zo konden de deelnemers de oefeningen thuis uitvoeren en gemakkelijk inpassen in hun agenda. De training was aangepast naar patiëntspecifieke symptomem, maar minder intensief dan de MBSR training. Zo zou de training als realistische mogelijke toevoeging aan de huidige standaardbehandeling overwogen kunnen worden. Na 12 weken liet de interventiegroep een betere fysieke conditie en een lagere hartslag zien, hoewel dit op het randje niet significant was.

Om te zien hoe de deelnemers presteerden op de lange termijn, rapporteert **Hoofdstuk 8** de 12-maanden follow-up van deze studie. De fysieke conditie van de interventiegroep bleek nog verder te verbeteren ten opzichte van de controlegroep: waar de interventiegroep direct na de online training 13.4 meter verder liep dan de controlegroep, liep deze groep op 12 maanden 17.9 meter verder. Het verschil tussen de groepen was echter nog steeds net niet statistisch significant. Alle andere fysiologische en psychologische uitkomstmaten verbeterden ook niet significant. Na de interventie kwamen 261 patiënten terug (80.5%) terug voor de follow-up meting, en op 12 maanden 245 patiënten (75.6%). Hoewel trainingsactiviteit werd bijgehouden, hebben we alleen een ruwe schatting van mate van adherentie. Op de verwachte non-adherentie van 50% die werd gevonden was daarom adequaat geanticipeerd door 2:1 te randomiseren.

Om de effecten op verschillende uitkomstmaten met elkaar te kunnen vergelijken, hebben we de Cohen's D 'standardized mean difference' berekend, welke gebruik maakt van een andere verdeling dan de Linear Mixed Model methode. Volgens deze berekenmethode was de verbetering op de 6MWT wel significant, alsmede systolische bloeddruk en depressie symptomen. Dit toont opnieuw aan dat keuze van statistische methode de interpretatie van resultaten kan beïnvloeden, zeker als de resultaten zich op het randje van significantie bevinden. Welke kant de balans ook uitslaat, je kunt je afvragen hoe relevant een afstand van 17.9 meters is: in ernstig COPD patiënten is een klinisch relevante verbetering van 35 meter vastgesteld [11]. Deze patiënten hebben echter mogelijk meer ruimte voor verbetering, aangezien ze 360 meter op baseline liepen, waar onze patiënten 540 meter liepen, en gezonde deelnemers zelfs 655 meter [12]. We hebben ook bestudeerd of er deelnemers waren die meer baat hadden van de training dan anderen: hoewel vrouwen gemiddeld meer adherent waren, hadden licht gestreste mannen met een lagere BMI meer effect op de 6MWT. Dit zou kunnen betekenen dat artsen online mindfulness in het achterhoofd kunnen houden als aanvullende leefstijlinterventie bij deze groep mannen; of dat de training aangepast zou kunnen worden zodat deze beter aansluit bij vrouwen. Hiervoor zou kwalitatief onderzoek naar de ervaringen van deelnemers uitgevoerd kunnen worden om de inhoud en methode van de training te optimaliseren.

Onze resultaten komen niet overeen met die van de RCTs in onze reviews: stress, angst en kwaliteit van leven verbeterden niet. Dit kan gedeeltelijk verklaard worden door een zogenaamd plafond-effect: het psychologisch functioneren op de meting vóór de studie was niet anders dan populatiegemiddelden, waardoor hier ook weinig verbeterruimte aanwezig was. Het andere gedeelte kan in de interventie zelf gezocht worden: hoewel de lage intensiteit van het 12-weken programma onderdeel was van een pragmatische en toegankelijke benadering, kan het zijn dat we de werkzame elementen van het originele protocol te ver hebben ingekort. Het intensiveren van de online training zou kunnen leiden tot duidelijkere effecten zoals gezien bij MBSR. Intrinsieke motivatie is essentieel voor de mate van effect bij dit type interventies, daar actieve eigen bijdrage vereist is [13]. Het hoge percentage non-adherence zou verbeterd kunnen worden door een vorm van feedback door een trainer toe te voegen. Wanneer deelnemers vragen kunnen stellen of frustraties kunnen uiten, blijven ze wellicht langer gemotiveerd dan wanneer de informatieoverdracht eenrichtingsverkeer is. Online training is minder intensief dan face-to-face groepstraining, hetgeen mate van participatie kan beïnvloeden en een kleiner effect zou kunnen teweegbrengen. Wanneer tijdens een online training frustratie opkomt, is het immers gemakkelijker om te stoppen. Uitval bij online programma's is vaak tweemaal zo hoog als bij groepstrainingen met wekelijkse bijeenkomsten [14-16]. Bij een groepstraining kan de trainer de frustratie van een deelnemer nemen als object van mindfulness en als een metafoor voor andere frustraties in het leven. Deze kans wordt gemist in onze online training en zou een goede toevoeging kunnen zijn. Met het verlagen van de intensiteit van het oorspronkelijke MBSR protocol hebben we een evidence-based methode veranderd in een onbekende interventie. Omdat we mindfulness niet gemeten hebben weten we bovendien niet of de veranderingen die we gevonden hebben, samenhangen met een verbeterde vaardigheid om mindful te zijn. Daarnaast konden we de deelnemers niet blinderen voor de interventie tijdens informed consent procedure. De controlegroep wist daardoor dat de online mindfulness training beschikbaar was en dat zij die niet ontvingen. Dit zou geleid kunnen hebben tot een selectieve follow-up, hoewel we geen significante verschillen tussen de groepen op de nameting hebben gevonden wat betreft demografische en klinische uitkomstmaten. Al met al wijzen de gevonden resultaten erop dat een online mindfulness training de standaardbehandeling van cardiovasculaire patiënten zou kunnen ondersteunen.

Toekomstige toepassingen van mindfulness training

We blijven nog even bij het onderwerp lichaamsbeweging, want in **Hoofdstuk 9** bestudeerden we of wandelen in de natuur de lange termijn effecten van mindfulness training kan onderhouden. Door gebruik te maken van Experience Sampling konden we van moment tot moment veranderingen in stemming, mindfulness en coping gedrag nauwgezet bestuderen. Dit onthulde een positieve relatie tussen mindfulness en positieve stemming, waarbij deze elkaar stimuleren in een opwaartse spiraal. Hoewel deze pilotstudie verschillende methodologische beperkingen had die de data van de vragenlijsten kan beïnvloeden, heeft de ESM data minder last van de kleine studiepopulatie en het ontbreken van een controlegroep [17]. Dit is de eerste keer dat deze methode is gebruikt tijdens een staat van mindfulness (in plaats van voor en na MBSR), en hierdoor konden we een glimp opvangen van de subtiele psychologische veranderingen tijdens mindful wandelen in de natuur. Hoewel het in deze kleine, niet klinische populatie niet statistisch significant was, namen over de tijd mindfulnessvaardigheden toe en namen stress, depressie, angst, en piekeren af. Het blijft onduidelijk of deze verschillen toe te wijden zijn aan mindfulness of aan het buiten wandelen, maar het lijkt alsof wandelen in de natuur en mindfulness elkaar kunnen beïnvloeden en een gemakkelijk toegankelijke methode voor mensen vormen om hun mindfulnessoefening te onderhouden.

Hoofdstuk 10 beschrijft een pilot studie bij Borderline persoonlijkheidsstoornis patiënten. Omdat eerdere studies aantoonden dat de meditatieoefeningen in het standaardprotocol te lang zijn voor deze patiënten en teveel heftige emoties oproepen, maakte deze pilot gebruik van kortere oefeningen en werd er gefocust op emotieregulatie. Binnen Dialectische gedragstherapie staat mindfulness voor een focus weg van de emotie ('houd je aandacht bij de taak omhanden', Linehan 1993 [18]) en minder rondom de-identificatie en het loslaten van de emotie. Compassie is ook een belangrijk concept van MB-ERT, omdat deze populatie erg gevoelig is voor (zelf)veroordeling [19]. De pilot studie liet zien dat dit aangepaste 13-weken protocol uitvoerbaar is bij borderline patiënten, en dat het zowel klinisch als statistisch gezien symptomatologie kan verbeteren. De studie wordt echter beperkt door het ontbreken van een controlegroep, het hebben van een kleine onderzoekspopulatie en het feit dat alle deelnemers ook MBT ontvingen. Een methodologisch sterkere studie wordt momenteel voorbereid om deze voorlopige resultaten verder te onderzoeken.

Hoofdstuk 11 is een methodologisch artikel dat een breder perspectief neemt op onderzoek naar psychotherapie. Omdat het vrijwel onmogelijk is patiënten te blinderen voor een psychotherapeutische interventie, stelt dit artikel methoden voor om onderzoekers in staat te stellen met de invloed van verwachtingen van deelnemers om te gaan. Omdat psychotherapeutische interventies andere zintuigen aanspreken dan bijvoorbeeld medicatiestudies, vraagt het blinderen van deelnemers een uitgebreidere strategie dan het kopiëren van een pil. Het pre-randomisatie ontwerp van Zelen lijkt een waardevol alternatief op de traditionele gerandomiseerde studies. Er wordt ook ingegaan op de vraag of deze verwachtingen van deelnemers daadwerkelijk een probleem zijn, daar ze altijd aanwezig zullen zijn in de klinische werkelijkheid. Bovendien kunnen psychotherapeutische interventies daar soepel op aangepast worden, en er zelfs mee werken, in tegenstelling tot medicatie.

Implicaties voor de praktijk

Met onze studies hebben we laten zien dat er bewijs is voor de gunstige effecten van MBSR en MBCT in de ondersteunende zorg van chronische aandoeningen. Het psychologische functioneren verbetert, hetgeen verbonden kan worden aan veranderingen in hersenactiviteit, verbindingen en structuur. Onze online training resulteerde in een randsignificant effect op fysieke conditie, wat impliceert dat het intensiveren van de training (door meer oefeningen, langere oefeningen, of het invoegen van persoonlijk contact) deze patiënten echt kan helpen. De studies die gedaan zijn, laten zien dat de kerneigenschappen van MBSR naar verschillende patiëntencategorieën aangepast kunnen worden. Mindful bewustzijn van lichamelijke sensaties, van negatieve gedachten, of van heftige emoties zoals in Borderline persoonlijkheidsstoornis, leiden tot patiënt-specifieke vooruitgang wanneer aangepast naar patiënt-specifieke symptomen.

We hebben van verschillende methoden gebruik gemaakt om het effect van mindfulness in kaart te brengen: van vragenlijst tot MRI-scan, van meta-analyse technieken met de Cohen's D gestandaardiseerde effectmaat, tot regressieanalyse van de relatie tussen psychologische en fysieke uitkomstmaten, tot de gedetailleerde Experience Sampling methode, tot het berekenen van klinische significantie ten opzichte van statistische significantie. Al deze benaderingen vormen een diversiteit van perspectieven waarin we de effecten van MBSR en afleidingen daarvan probeerden te belichten. Niet alleen lichamelijk versus psychologisch, niet alleen brein, hart en geest, maar ook statistisch versus klinisch relevant. Want uiteindelijk zijn alle statistieken, alle methodologie en alle hypotheses bedoeld om de buitenwereld beter te begrijpen en mogelijk te verbeteren. De echte wereld, waar mensen zijn, niet deelnemers. Levens, niet scores op een vragenlijst of instrument. De kunst van onderzoek is een brug tussen wetenschap en praktijk te bouwen, zodat de getallen en p-waarden betekenis krijgen.

Het lijkt erop dat de technieken en ervaringen binnen de acht-weken mindfulness training patiënten kunnen helpen leren omgaan met dagelijkse problemen, en dat de experiëntiele en cognitieve technieken een effect hebben op fysieke parameters. Hersenactiviteit, connectiviteit, en daarmee hersenstructuren worden beïnvloed door het leren van nieuwe reactiepatronen. Bij hartpatiënten heeft een lage dosis van online mindfulness bijna fysieke conditie verbeterd. Deze verbinding tussen een mentale training en lichamelijke uitkomstmaten laat zien dat er nog veel te leren valt over hoe we de gezondheid van patienten kunnen verbeteren, en daarmee ook hoe we de gezondheidszorg kunnen organiseren.

Door mensen te leren hun automatische reactiepatronen en vroege signalen van stress te herkennen, kan mindfulness het vermogen tot zelfreflectie en het bewust keuzes maken vergroten. Mindfulness leert de-identificatie (‘ik heb droevige gedachten, maar aangezien ik ze kan observeren, ben ik ze niet’). Het accepteren van gedachten als voorbijgaande ervaringen, in plaats van je ermee te identificeren of ze te onderdrukken, lost ook een spanning op tussen jou en je ervaring. Onderdrukking werkt alleen op de korte termijn, waar het toelaten van ervaringen om er te zijn en ze te erkennen ontspanning kan bieden. Het is oké dat dit gevoel er is, het zal opkomen, voorbijgaan, weer opkomen en weer voorbijgaan. Compassie is ook een belangrijk element aangezien we de neiging hebben onszelf te veroordelen voor onze beperkingen, wat deze in sommige gevallen zelfs erger maakt.

Aangezien deze aspecten niet gemakkelijk aan te leren zijn, wordt deelnemers aangeraden geduldig te zijn en niet perfectie na te streven. Na de ontwikkeling van MBSR zijn in korte tijd verschillende afgeleide programma’s ontwikkeld voor andere patiëntenpopulaties, zoals wij ook de online training en MB-ERT hebben gebaseerd op de originele MBSR. Carmody & Baer (2009) hebben bestudeerd hoe lang de training moet zijn om nog steeds effectief te zijn [20]. Ze rapporteren dat hoewel het 8-weken programma ontworpen is om deelnemers voldoende tijd te geven de principes van zelfregulatie door mindfulness te begrijpen en door eigen oefening vaardigheid en autonomie te ontwikkelen, aanpassingen van MBSR die minder groepstijd bevatten dan het traditionele format waardevol kunnen zijn voor populaties waarvoor het reduceren van psychologische stress een belangrijk doel is (zoals de kortere oefeningen in MB-ERT voor Borderline Persoonlijkheidsstoornis patiënten) en waarvoor minder tijdsbesteding een belangrijke factor is voor de mogelijkheid om deel te nemen. MBSR heeft echter nog steeds de meest empirische ondersteuning voor effectiviteit, en zou in vele gevallen de voorkeur hebben. Een andere studie liet zien dat mate van kennis van de mindfulness training sterk geassocieerd was met de bereidheid MBSR toe te passen of aan te raden [21]. Aangezien de training gunstige effecten lijkt te hebben wanneer toegevoegd aan de standaardzorg bij veel patiëntencategorieën, is het belangrijk om de kennis over dit programma bij medische professionals te vergroten en psychologische en lichamelijke zorg meer te integreren.

Toekomstig Onderzoek

Zoals gezien in Hoofdstuk 11 kan in studies naar psychotherapeutische interventies zoals MBSR en MBCT meer ruis optreden dan in studies waar de blindering van deelnemers gemakkelijker is. Psychologisch onderzoek lijkt daardoor een achterstand te hebben. Bovendien zouden studies met groepstherapie behoedzaam moeten omgaan met de aanname onafhankelijke metingen te doen: deelnemers kunnen elkaar beïnvloeden [21]. Enkele zeer depressieve of ongemotiveerde deelnemers kunnen de uitkomsten van de rest van de groep naar beneden trekken, en enkele zeer gemotiveerde kunnen het groepsproces juist versnellen. Williams & Russel (2008) raden aan dat in het ontwerpen van groepstherapie studies (met name de MBCT-training) rekening wordt gehouden met intragroep correlaties, evenals variantie inflatie en dus de nodige groepsgrootte [23]. Verder heeft Bergomi (2013) aandacht gevraagd voor de zelfrapportage van mindfulness als meetmethode [24]. Er zijn verschillende vragenlijsten, maar er is geen consensus over welke elementen van mindfulness bij welke schaal zouden moeten horen, en meerdere vragen kunnen op verschillende manieren worden geïnterpreteerd. Gezien het groeiende gebruik van mindfulness in onderzoek en in gezondheidgerelateerde velden is een steviger theoretisch onderbouwde en methodologische basis gewenst voor het meten van mindfulness. De ontwikkeling van één vragenlijst die de consensus van de makers van de andere draagt zou het onderzoek naar mindfulness zeer helpen.

Onderzoek in de toekomst zou zich kunnen richten op de exacte verbinding tussen lichaam en geest, zo vaak bezien als afgescheiden entiteiten. Hoe beïnvloedt de opwaartse spiraal tussen mindfulness en positief affect de amygdala? Waar raakt minder depressie op verder lopen? Naar mijn mening is er geen grens waar de geest eindigt en het lichaam begint. We zijn een geheel. We hebben het bewustzijn om zowel mentale als lichamelijke sensaties te kunnen observeren; het identificeren met slechts een ervan verzaakt een essentieel deel van ons wezen.

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List of publications

1. **Gotink RA**, Chu P, Busschbach JJ, Benson H, Fricchione F, Hunink MGM. Standardized mindfulness-based interventions in healthcare: an overview of systematic reviews and meta-analyses of RCTs. *PlosOne* (2015)
2. **Gotink RA**, Meijboom R, Vernooij MW, Smits M, Hunink MGM. 8-week Mindfulness Based Stress Reduction induces brain changes similar to traditional long-term meditation practice – A systematic review. *Brain and Cognition* (2016)
3. **Gotink RA**, Vernooij MW, Ikram MA, Niessen WJ, Krestin GP, Hofman A, Tiemeier H, Hunink MGM. Meditation and yoga practice are associated with smaller right amygdala volume: The Rotterdam Study. *Submitted*
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8. Younge JO, Wester V, Rossum EFC, **Gotink RA**, Wery MF, Utens EMWJ, Hunink MGM, Roos-Hesselink JW. Cortisol levels in scalp hair of patients with structural heart disease. *International Journal of Cardiology* (2015)
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11. **Gotink RA**, Hofman A, Speckens AEM, Hunink MGM. Double blinding in psychotherapeutic intervention trials. *Submitted*

PhD Portfolio

Name PhD student:	Rinske Annebeth Gotink
Erasmus MC Departments:	Epidemiology, Radiology, and Psychiatry (section Medical Psychology and Psychotherapy)
PhD period:	January 2013 to January 2016
Promotoren:	Prof. Dr. M.G.M. Hunink Prof. Dr. A.E.M. Speckens

PhD Training

	Year	ECTs
Research skills		
Master of Science in Clinical Epidemiology Netherlands Institute for Health Sciences, Rotterdam	2013-2015	76.7
In-depth courses		
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	2015	1.5
Psychiatric Epidemiology	2013	
Quality of Life Measurement	2014	
Preventing Failed Interventions in Behavioral Research	2014	
Symposia – congresses		
Radboud Universiteit Landelijk Symposium Mindfulness	2014	0.3
E-health Symposium Erasmus MC	2014	0.3
Invitational Symposium on Mindfulness Research Radboud	2015	0.3
Creating Connections III	2015	0.3
Teaching		
1st year medical students 'How to read a scientific paper'	2013-2014	0.6
4th year medical students 'Clinical Trials'	2014	0.4
Teaching assistant 'Advanced Topics in Decision Making in Medicine'	2015	0.6
Supervising three master students' theses	2013-2015	3
Total ECTs		**84**

Master of Clinical Epidemiology

Course	ECTs
Study Design (CC01)	4.3
Principles of Research in Medicine (ESP01)	0.7
Courses for the Quantitative Researcher (SC17)	1.4
English Language (SC01)	1.4
The Practice of Epidemiologic Analysis (ESP65)	0.7
Clinical Epidemiology (CE02)	5.7
Clinical Trials (ESP14)	0.7
Health Economics (ESP25)	0.7
Methods of Clinical Research (ESP10)	0.7
Markers and Prognostic Research (ESP62)	0.7
Methodologic Topics in Epidemiologic Research (EP02)	1.4
Diagnostic Research (EWP05)	0.9
Clinical Decision Analysis (ESP04)	0.7
Intermediated Clinical Decision Making	1.0
Advanced Topics in Decision-making in Medicine (EWP02)	1.9
Biostatistical Methods I: Basic Principles (CC02)	5.7
Biostatistical Methods II: Classical Regression Models (EP03)	4.3
Logistic Regression (ESP66)	1.4
Topics in Meta-analysis (ESP15)	0.7
Repeated Measurements in Clinical Studies (CE08)	1.4
Advanced Topics in Clinical Trials (EWP10)	1.9
Psychiatric Epidemiology (EP12)	1.1
Quality of Life Measurement (HS11)	0.9
Preventing Failed Interventions in Behavioral Research (MP05)	1.4
Thesis 'Standardized mindfulness-based interventions in healthcare: an overview of systematic reviews and meta-analyses of RCTs'	35.0
Total	**76.7**

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About the author

Rinske Annebeth Gotink was born on May 23, 1989 in Arnhem, The Netherlands. In 2007 she graduated from secondary school (Stedelijk Gymnasium Arnhem) and enrolled in Health Sciences at Maastricht University. Choosing the clinical psychology direction, she graduated as Master of Mental Health in 2011. After working for one year as a psychologist, she started her PhD-thesis in 2013 at the departments of epidemiology, radiology, and psychiatry (section medical psychology) of the Erasmus MC in Rotterdam, under the supervision of Prof.dr. MGM Hunink and Prof.dr. AEM Speckens. In her research she focused on the evidence and working mechanisms of secular mindfulness-based interventions. During her PhD she also obtained her Master of Clinical Epidemiology at the Netherlands Institute of Health Sciences (NIHES, Rotterdam, The Netherlands).

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