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Online mindfulness as a promising method to improve exercise capacity in heart disease: 12-month follow-up of a randomized controlled trial

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Abstract

There is increasing evidence that mindfulness can reduce stress, and thereby affect other psychological and physiological outcomes as well. Earlier, we reported the direct 3-month results of an online modified mindfulness-based stress reduction training in patients with heart disease, and now we evaluate the effect at 12-month follow-up. 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 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. At 12-months follow-up, participants showed a trend significant improvement exercise capacity (6MWT: 17.9 meters, p = 0.055) compared to UC. Cohen’s D showed significant but small improvement on exercise capacity (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 significantly.

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)). 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.

Trial registration: www.trialregister.nl NTR3453
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]. On the contrary, 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].

MBSR has shown to improve heart rate, breathing patterns and blood pressure in cardiovascular patients [17, 18]. 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 rationale of this randomized controlled trial 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 [23]. In 3-month post-intervention follow-up, participants who received an online mindfulness training showed a higher mean distance on the 6-minute walk test, however this was small and borderline statistically significant (13.4 metres, p = 0.050) [24]. This article reports the results of the 12-month follow-up.

Materials and 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. Detailed description of design and methodology, and 3-month results have been reported elsewhere [24]. 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\textsuperscript{R}) with a block size of 12 [25].

Intervention

The mindfulness training consisted of a 12-week structured online program (see Table A in S1 File), 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, yoga exercises, and 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

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 the 3-month article [24].

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 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).

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.

Repeated measurements analyses using a multivariate linear regression mixed model were performed to determine intergroup effects and to simultaneously account for the correlation between the repeated measurements of each patient and for missing values. 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. In order to compare the different outcome measures, 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].

Results and discussion

Patient characteristics

Fig 1 displays the flowchart of the patients’ recruitment and follow-up. Table 1 shows participants’ baseline characteristics. 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. 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.

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. 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 (Table 2), 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.
Standardized effect Size

Cohen’s D calculation of outcome measures resulted in significant improvements 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 (Fig 2). Similar though smaller effects were found in the as-treated analyses (Fig 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 B in S1 File). However when compliant to the online training, men (β = -2.31, p = 0.015) with a lower BMI (β = -2.1 kg/m, p = 0.048) improve more on the 6MWT. 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 C in S1 File).

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
Table 2. Outcomes at baseline and 12 months, and linear mixed models-based estimated difference ($\beta$) 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 ($\beta$) | 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             | 0.180   |
|                          | 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             | 0.255   |
|                          | 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 ($\beta$) | 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)                 |                     |                         |         |

(Continued)
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 (Fig 4). Using Cohen’s D (which is based on a Z-distribution, where mixed models uses a T-distribution), exercise capacity, systolic blood pressure, mental functioning, and depression improved significantly compared to UC. 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. It could be that in our aim to construct a pragmatic and easy-accessible training, the working components of the MBSR protocol were cut too short, as our sample size was sufficient and the randomization procedure succeeded. We anticipated a 50% dropout in our 2:1 randomization ratio, which proved exactly right (49.8% of participants allocated to online mindfulness adhered to the training). Furthermore, the online training was low in intensity and our hypothesis concerned a two-stage effect of a

Table 2. (Continued)

| Outcome                   | Mindfulness | UC          | Standard Mean Difference | 95% CI          | SE  | 95% CI          |
|---------------------------|-------------|-------------|--------------------------|-----------------|-----|-----------------|
| Quality of life (VAS)     | 74.5 (18.4) | 73.4 (19.3) | -1.9                     | -5.5 to 1.6     | 0.288|
| Anxiety (HADS)            | 8.3 (4.8)   | 7.6 (5.4)   | +0.6                     | -0.4 to 1.5     | 0.248|
| Depression (HADS)         | 3.8 (4.0)   | 3.2 (4.4)   | -0.7                     | -1.5 to 0.1     | 0.100|
| Stress (PSS)              | 22.4 (10.5) | 20.5 (12.4) | -1.3                     | -3.6 to 1.0     | 0.275|
| Social support (PSSS12)   | 69.2 (16.7) | 71.9 (17.4) | +1.2                     | -2.5 to 4.9     | 0.522|

Outcomes at baseline and 12 months, and Linear Mixed Models-based estimated difference (β) of intervention group compared to control over time. 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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**Fig 2. Cohen’s D in intention-to-treat analysis.** Plot showing Cohen’s D effect measures of online mindfulness compared to treatment as usual in the Intention-To-Treat analysis. All values lower than 0 indicate a significant difference in favour 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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psychological intervention on physical fitness. Regarding the level of statistical significance, a slight increase in training intensity could strengthen our results, as there is a large difference in dose compared to the full MBSR protocol. Also, our patients’ psychological baseline scores were similar to scores in the general population [35–39] which could explain the abstinence of improvements due to 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, 40]. 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 [41–43]. 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

![Fig 3. Cohen’s D in as-treated analysis. Plot showing Cohen’s D effect measures of online mindfulness compared to treatment as usual in the As-Treated analysis. All values lower than 0 indicate a significant difference in favour 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.](https://doi.org/10.1371/journal.pone.0175923.g003)

![Fig 4. Linear mixed models results. 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.](https://doi.org/10.1371/journal.pone.0175923.g004)
appear to benefit less. This could be taken into account as well in intensifying the future online program.

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. 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.

Supporting information
S1 Document. Study protocol.
(PDF)

S2 Document. Consort checklist.
(DOC)

S1 File. Containing: Table 1. Content of online training compared to standardized 8-week MBSR protocol. Table 2. Regression model of training adherence (N = 215). Table 3. Regression model of improvement on 6MWT when adherent (N = 107).
(DOCX)

Acknowledgments
The online mindfulness training was originally developed and provided by Psychology Magazine and available to clients in the general Dutch population as an 8-week training. For the current study the training was altered in focus and extended to 12 weeks. In particular we would like to thank Peggy van der Lee from Psychology Magazine for her support in the design of the mindfulness training for this study, and secretary Celeste Manley for her fantastic administrative support.

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Conceptualization: JR MH.
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Funding acquisition: JR MH.
Investigation: RG JY MW.

Methodology: RG JY MH.

Project administration: RG JY JR MH.

Resources: RG JY MW MM LR.

Software: DR.

Supervision: JR MH.

Validation: RG JY JR MH.

Writing – original draft: RG JY.

Writing – review & editing: RG JY MW EU MM DR LR JR MH.

References
1. Gotink RA, Chu P, Busschbach JJ, Benson H, Fricchione GL, Hunink MG. Standardised Mindfulness-Based Interventions in Healthcare: An Overview of Systematic Reviews and Meta-Analyses of RCTs. PLoS One 2015; 10(4):e0124344. https://doi.org/10.1371/journal.pone.0124344 PMID: 25881019

2. Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. Gen Hosp Psychiatry 1982; 4(1):33–47. PMID: 7042457

3. Kabat-Zinn J, Hanh TN. Full catastrophe living: Using the wisdom of your body and mind to face stress, pain, and illness: Delta; 2009.

4. Bishop SR, Lau M, Shapiro S, Carlson L, Anderson ND, Carmody J, et al. Mindfulness: A proposed operational definition. Clin Psychol-Sci Pr 2004; 11(3):230–241.

5. Huffman JC, Celano CM, Beach SR, Motivallar SR, Januzzi JL. Depression and Cardiac Disease: Epidemiology, Mechanisms, and Diagnosis. Cardiovascular Psychiatry and Neurology 2013; 2013:14.

6. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. General hospital psychiatry 2007; 29(2):147–155. https://doi.org/10.1016/j.genhosppsych.2006.11.005 PMID: 17336664

7. Hofmann SG, Sawyer AT, Witt AA, Oh D. The Effect of Mindfulness-Based Therapy on Anxiety and Depression: A Meta-Analytic Review. J Consult Clin Psych 2010; 78(2):169–183.

8. Zeidan F, Johnson SK, Gordon NS, Goolkasian P. Effects of Brief and Sham Mindfulness Meditation on Mood and Cardiovascular Variables. J Altem Complerm Med 2010; 16(8):867–873.

9. Baer RA. Mindfulness training as a clinical intervention: A conceptual and empirical review. Clin Psychol-Sci Pr 2003; 10(2); 125–143.

10. Ospina MB, Bond K, Karkhanah M, Tjosvold L, Vandermeer B, Liang Y, et al. Meditation practices for health: state of the research. Evid Rep Technol Assess (Full Rep) 2007(155):1–263.

11. Olivo EL, Dodson-Lavelle B, Wren A, Fang Y, Oz MC. Feasibility and effectiveness of a brief meditation-based stress management intervention for patients diagnosed with or at risk for coronary heart disease: a pilot study. Psychology Health & Medicine 2009; 14(5):513–23.

12. Volkgezondheidentzorg. Kosten van zorg voor hart- en vaatziekten. In: Healthcare Do, ed. Bilthoven: RIVM; 2013.

13. Richardson S, Shaffer JA, Falzon L, Krukowski D, Davidson KW, Edmondson D. Meta-analysis of perceived stress and its association with incident coronary heart disease. Am J Cardiol 2012; 110(12); 1711–6. https://doi.org/10.1016/j.amjcard.2012.08.004 PMID: 22975465

14. Rosengren A, Haksten S, Onupuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364(9438):953–62. https://doi.org/10.1016/S0140-6736(04)17019-0 PMID: 15394186

15. Custodis F, Gertz K, Balikaya M, Prinz V, Mathar I, Stamm C, et al. Heart rate contributes to the vascular effects of chronic mental stress: effects on endothelial function and ischemic brain injury in mice. Stroke 2011; 42(6):1742–9. https://doi.org/10.1161/STROKEAHA.110.598607 PMID: 21527760

16. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Association for Cardiovascular P, Rehabilitation, Guidelines ESCCIP. European Guidelines on cardiovascular disease...
prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012; 33(13):1635–701. https://doi.org/10.1093/eurheartj/ehs092 PMID: 22555213

17. Abbott RA, Whear R, Rodgers LR, Bethel A, Thompson Coon J, Kuyken W, et al. Effectiveness of mindfulness-based stress reduction and mindfulness based cognitive therapy in vascular disease: A systematic review and meta-analysis of randomised controlled trials. J Psychosom Res 2014; 76(5):341–51. https://doi.org/10.1016/j.jspcyres.2014.02.012 PMID: 24745774

18. Goyal M, Singh S, Sibinga EM, Gould NF, Rowland-Seymour A, Sharma R, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern Med 2014; 174(3):357–68. https://doi.org/10.1001/jamainternmed.2013.13018 PMID: 24395196

19. Blair SN, Goodyear NN, Gibbons LW, Cooper KH. Physical fitness and incidence of hypertension in healthy normotensive men and women. Jama 1984; 252(4):487–490. PMID: 6737638

20. De Meersman RE. Heart rate variability and aerobic fitness. American heart journal 1993; 125(3):726–731. PMID: 8438702

21. Strath SJ, Swartz AM, Bassett DR Jr, O’Brien WL, King GA, Ainsworth BE. Evaluation of heart rate as a method for assessing moderate intensity physical activity. Medicine and Science in Sports and Exercise 2000; 32(9 Suppl):S465–70. PMID: 10993416

22. Arslan S, Erol MK, Gundogdu F, Sevimli S, Aksakal E, Senocak H, et al. Prognostic Value of 6-Minute Walk Test in Stable Outpatients with Heart Failure. Texas Heart Institute Journal 2007; 34(2):166–169. PMID: 1762362

23. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, L. et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 2005; 112(6):828–35. https://doi.org/10.1161/CIRCULATIONAHA.104.529800 PMID: 16061735

24. Younge J, Wery M, Gotink R, Utens E, Michels M, Rizopoulos D, et al. Web-Based Mindfulness Intervention in Heart Disease: A Randomized Controlled Trial. PLoS One 2015; 10(12).

25. Trans European Network for Clinical Trials Services. ALEA version 2.2. https://nl.tena.lea.net/.

26. Maex E. Mindfulness ‘in de maaltijd van je leven’: Lannoo; 2006.

27. Laboratories ATSCoPSiCPF. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111–7. https://doi.org/10.1164/ajrccm.166.1.at1102 PMID: 12091180

28. Younge JO, Wester VL, van Rossum EF, Gotink RA, Wery MF, Utens EM, et al. Cortisol levels in scalp hair of patients with structural heart disease. Int J Cardiol 2015; 184:71–8. https://doi.org/10.1016/j.ijcard.2015.02.005 PMID: 25705007

29. McHomey CA, Ware JE Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993; 31(3):247–63. PMID: 8450681

30. Moons P, Van Deyk K, De Bleser L, Marquet K, Raes E, De Geest S, et al. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. Eur J Cardiovasc Prev Rehabil 2006; 13(3):407–13. PMID: 16926671

31. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67 (6):361–70. PMID: 6890629

32. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983; 24(4):385–96. PMID: 666417

33. Pedersen SS, Spinder H, Erdman RA, Denollet J. Poor perceived social support in implantable cardioverter defibrillator (ICD) patients and their partners: cross-validation of the multidimensional scale of perceived social support. Psychosomatics 2009; 50(5):461–7. https://doi.org/10.1176/appi.ps.50.5.461 PMID: 19855031

34. IBM Corp. SPSS Statistics for Windows Version 21.0. In. Armonk, NY; 2012.

35. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998; 51(11):1055–68. PMID: 9817123

36. Cohen S W G. Perceived stress in a probability sample of the United States. In: Oskamp IS S S, ed. The social psychology of health: Claremont Symposium on applied social psychology. Newbury Park, CA: Sage; 1988.

37. Crawford JR, Henry JD, Crombie C, Taylor EP. Normative data for the HADS from a large non-clinical sample. Br J Clin Psychol 2001; 40(4):429–34. PMID: 11760618

38. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ 1998; 316(7133):736–41. PMID: 9529408
39. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The Multidimensional Scale of Perceived Social Support. J Pers Assess 1988; 52(1):30–41.

40. Younge JO, Gotink RA, Baena CP, Roos-Hesselink JW, Hunink MM. Mind-body practices for patients with cardiac disease: a systematic review and meta-analysis. Eur J Prev Cardiol 2014.

41. Gluck TM, Maercker A. A randomized controlled pilot study of a brief web-based mindfulness training. BMC Psychiatry 2011; 11:175. https://doi.org/10.1186/1471-244X-11-175 PMID: 22067058

42. Krusche A, Cyhlarova E, King S, Williams JM. Mindfulness online: a preliminary evaluation of the feasibility of a web-based mindfulness course and the impact on stress. BMJ Open 2012; 2(3).

43. Morledge TJ, Alexandre D, Fox E, Fu AZ, Higashi MK, Kruzikas DT, et al. Feasibility of an online mindfulness program for stress management—a randomized, controlled trial. Ann Behav Med 2013; 46 (2):137–48. https://doi.org/10.1007/s12160-013-9490-x PMID: 23632913