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Effects of a Mindfulness-Based Intervention versus Health Self-Management on Subclinical Anxiety in Older Adults with Subjective Cognitive Decline: The SCD-Well Randomized Superiority Trial

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Keywords
Mindfulness · Compassion · Anxiety · Subjective cognitive decline

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Abstract
Introduction: Older adults experiencing subjective cognitive decline (SCD) have a heightened risk of developing dementia and frequently experience subclinical anxiety, which is itself associated with dementia risk. ***Objective:*** To understand whether subclinical anxiety symptoms in SCD can be reduced through behavioral interventions. ***Methods:*** SCD-Well is a randomized controlled trial designed to determine

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whether an 8-week mindfulness-based intervention (caring mindfulness-based approach for seniors; CMBAS) is superior to a structurally matched health self-management program (HSMP) in reducing subclinical anxiety. Participants were recruited from memory clinics at 4 European sites. The primary outcome was change in anxiety symptoms (trait subscale of the State-Trait Anxiety Inventory; trait-STAI) from pre- to postintervention. Secondary outcomes included a change in state anxiety and depression symptoms postintervention and 6 months postrandomization (follow-up). ***Results:*** One hundred forty-seven participants (mean [SD] age: 72.7 [6.9] years; 64.6% women; CMBAS, $n = 73$; HSMP, $n = 74$) were included in the intention-to-treat analysis. There was no difference in trait-STAI between groups postintervention (adjusted change difference: –1.25 points; 95% CI –4.76 to 2.25) or at follow-up (adjusted change difference: –0.43 points; 95% CI –2.92 to 2.07). Trait-STAI decreased postintervention in both groups (CMBAS: –3.43 points; 95% CI –5.27 to –1.59; HSMP: –2.29 points; 95% CI –4.14 to –0.44) and reductions were maintained at follow-up. No between-group differences were observed for change in state anxiety or depression symptoms. ***Conclusions:*** A time-limited mindfulness intervention is not superior to health self-management in reducing subclinical anxiety symptoms in SCD. The sustained reduction observed across both groups suggests that subclinical anxiety symptoms in SCD are modifiable. ***ClinicalTrials.gov identifier:*** NCT03005652.

Introduction

Individuals experiencing subjective cognitive decline (SCD), even without objective impairment, are at an increased risk of developing dementia [1]. As outlined in the SCD-I framework [2], this risk is further elevated in people aged 60+ years who express concern about their memory and who seek professional help [3, 4]. These individuals frequently experience subclinical symptoms of anxiety, and evidence suggests that anxiety itself, even if subclinical, is associated with an increased risk of dementia [5, 6]. SCD and anxiety symptoms may therefore pose a compounded risk of dementia. Yet, while there are established interventions for anxiety disorders in old age, few attempts have been made to specifically address subclinical levels of anxiety in groups at risk for dementia. Introducing an intervention that addresses this issue would not only benefit the mental health of people with SCD but could also potentially reduce the risk of dementia.

In terms of psychological mechanisms, there is an indication that concern about loss of cognitive function contributes to the elevated anxiety seen in individuals with SCD [7], and anxiety in turn increases alertness for cognitive failures [8, 9]. Mindfulness-based interventions (MBI) may be particularly suited to address this dynamic. By teaching individuals to relate to their present moment experience in a nonjudgemental and acceptant manner, MBI could help people with SCD to recognize and disengage from worry processes and respond to cognitive failures with more acceptance, which may thus reduce anxiety. While mindfulness-based research in older adults is still in its infancy [10–12], there is considerable evidence that MBI can reduce anxiety in a number of populations [13, 14]. In order to investigate the specific benefits that such an approach might offer, comparison against an active control is advisable as MBI contain a number of nonspecific elements, such as social interaction, education, and the provision of treatment expectancies.

Strategies to support brain health have recently been recommended for individuals with SCD. These include physical exercise, a healthy diet, and control of preexisting conditions [3]. Therefore, a group-based health self-management program (HSMP) was deemed an appropriate comparison condition, as it might also benefit people with SCD. HSMPs assist individuals to identify problems, make decisions, and take actions to find solutions. The goal is to promote self-efficacy by providing individuals with skills to live an active and healthy life [15]. With regard to concerns about loss of function experienced in SCD, empowering individuals to maintain function may reduce anxiety through mechanisms of action more distal to those assumed for MBI.

The SCD-Well randomized clinical trial sought to examine whether an MBI specially adapted for older adults with SCD, i.e., a caring mindfulness-based approach for seniors (CMBAS), reduces subclinical symptoms of anxiety from pre- to postintervention (primary outcome) compared to a structurally matched HSMP and whether any reduction in symptoms is maintained at the 6-month follow-up (secondary outcome). We also present here results on the main secondary psychiatric outcomes (state anxiety and depression symptoms) and moderator analyses are shown in the online supplementary material (see www.karger.com/doi/10.1159/000515669 for all online suppl. material).

Materials and Methods

Detailed information about the methodology, including sites, eligibility criteria, interventions, and assessments, is provided in the trial protocol [16].

Study Design

SCD-Well is a multi-center, observer-blind, randomized, controlled superiority trial with 2 intervention arms, i.e., CMBAS and HSMP. The trial included 8 weeks of intervention and a follow-up 24 weeks after the intervention (a total of 6 months). The intervention took place in group settings at 4 sites, and randomization was performed with a 1:1 allocation, stratified by site.

SCD-Well is registered on ClinicalTrials.gov (NCT03005652) and adheres to Consolidated Standards of Reporting Trials (CONSORT) of nonpharmacologic treatments guidelines [17] (online suppl. Table 1).

Participants

Participants were recruited by research teams from medical facilities (i.e., memory clinics) at the 4 European sites where the trial assessments and delivery of the interventions took place (London, Cologne, Lyon, and Barcelona). Participants were either referred to a memory clinic by a physician or were self-referrals. For inclusion, participants must have met eligibility requirements detailed in the paper of Marchant et al. [16], which include research criteria for SCD [2] (self-perceived cognitive decline and normal performance on standardized cognitive tests). These criteria require that participants be without a current clinical diagnosis of mild cognitive impairment or dementia, anxiety, depression, or other psychiatric disorder [2].

Procedures

Participants were recruited in 2 waves at each site. Briefly, participants who fulfilled the eligibility criteria and provided written informed consent were invited to the baseline visit (V1) and then randomized to 1 of the 2 intervention conditions. Participants were then invited to a preclass meeting for their allocated intervention, at which point the allocation was revealed to them. A postintervention visit (V2) was conducted after the end of the intervention, and a follow-up visit (V3) was held 6 months after randomization.

Randomization and Masking

After 14–25 participants in a given site had completed V1 (in order to achieve intervention group sizes between 7 and 13 participants), these participants were randomized by a member of the scientific team (but not the psychometrist) on the same day and in their order of inclusion via a centralized procedure implemented in the study electronic case report form. Randomization was performed with a 1:1 allocation, permuted blocks of size 4 and 6, and stratified by site.

All members of the research team, apart from trial managers, were blind to the participants' intervention condition. This included psychometrists administering and scoring the outcome measures. At the beginning of every interaction with psychometrists, participants were instructed not to disclose their intervention condition. Seven instances of unblinding occurred (3 during an assessment session), all as a result of participant disclosure of their assigned intervention condition. When this occurred a different psychometrist, blinded to the participant's intervention assignment, conducted the subsequent assessments.

Interventions

Caring Mindfulness-based Approach for Seniors

CMBAS followed the general format of a mindfulness-based stress reduction program, consisting of a preclass interview, 8 weekly group-based sessions 2 h in duration, and a half day of meditation practice in the 6th week of the program. It was specifically tailored to the needs of older adults, building on modifications suggested by Zellner Keller et al. [18] together with a focus on compassion and loving-kindness meditation. The psychoeducational components were customized for individuals with SCD to help them to more adaptively manage concerns about cognitive functioning and tendencies to worry. Participants were asked to engage in home practice for approximately an hour a day, 6 days a week, which consisted of formal guided meditations and informal practices aimed at helping to generalize mindfulness skills to daily life.

HSMP Comparison Condition

An HSMP was selected to control for nonspecific factors and treatment expectancies, minimize potential drop-out rates, and harmonize the comparator treatment option across countries [19]. The HSMP followed the same format and structure as the CMBAS and was matched in administration, dosage, and duration; including a half day of review with a healthy lunch and a discussion in the 6th week of the program. This group-based program was based on a published manual for guidance on living with chronic conditions [20] that has been previously adapted and validated in an SCD population [21]. Topics included management of sleep, stress, exercise, medicines and memory, communication, healthy eating, and planning for the future. Each week, participants were asked to create and implement "action plans" to promote engagement in activities to improve health and well-being.

Interventional Engagement

Attendance was taken at each intervention session. After the first session, participants completed a questionnaire to assess their perceptions of intervention credibility and expectations of deriving benefit [22]. Responses were used to gage the equivalency of treatment expectations in the 2 intervention conditions.

Facilitators

Each site had 2 clinically trained facilitators. One facilitator, who had undergone formal training to match criteria of the good practice guidelines of the UK network of mindfulness-based teacher trainers (www.ukmindfulnessnetwork.co.uk), delivered the CMBAS intervention. The other facilitator, who had at least 3 years' experience leading group-based clinical programs and/or psychoeducational interventions (e.g., a clinical psychologist or equivalent), led the health self-management intervention. Facilitators received the intervention manual, instructions, and training about their respective intervention prior to the start of the study, completed self-report checklists to monitor the fidelity of treatment delivery after each class [23], and received ongoing supervision to promote standardization of delivery across sites.

Outcomes

All outcomes were collected at V1, V2, and V3. The primary outcome, i.e.,. the mean change in subclinical symptoms of trait anxiety from V1 to V2, was measured using the trait subscale of the State-Trait Anxiety Inventory (trait-STAI; range 20–80) [24]. trait-STAI scores are representative of a person's general level of anxiety, and they have a test-retest reliability of 0.88 [25]. Intervention effects for secondary outcomes were assessed as change from V1 to V2 or from V1 to V3. Key secondary outcomes included trait-STAI change from V1 to V3, present moment anxiety symptoms assessed using the state subscale of the STAI (state-STAI; range 20–80), and depressive symptoms assessed using the Geriatric Depression Scale (GDS; range 0–15) [26]. See the paper by Marchant et al. [16] for a detailed explanation of the change in primary outcome from state- to trait-STAI.

Statistical Analyses

Sample Size

As the trait-STAI has no absolute cut-off levels, the sample size was based on the effect size (i.e., the ratio between the expected interarm differences from the common SD). With a minimum effect size of 0.50 (indicated as a reasonable expectation from a meta-analysis summarizing efficacy of meditation interventions for reducing anxiety symptoms) [13], 64 participants per arm (128 total) were needed to demonstrate a significant difference in the primary endpoint (mean difference in the change of trait-STAI scores in each intervention arm from V1 to V2) in a *t* test with 80% power and a 2-sided type I error of 5%. A greater number of participants was recruited in anticipation that a small proportion of volunteers (<10%) may have missing data on the primary endpoint (e.g., due to loss of follow-up).

Comparative Analyses

A statistical analysis plan was developed and validated by the Trial Steering Committee before database lock and analyses.

All analyses were adjusted for recruitment site and baseline prognostic factors (median-centered age, sex, median-centered Mini Mental State Examination (MMSE), and median-centered baseline scores of outcome). HSMP was used as the reference group in all comparisons so that a negative (positive) mean difference in change between groups could be interpreted as a higher (lower) decrease in outcome score in CMBAS.

The primary outcome (change in trait-STAI from V1 to V2) was compared between groups using an adjusted linear regression model. This analysis was first conducted according to the intent to treat principle with a "missing = failure" strategy for handling missing data on the primary endpoint. A failure was defined as the maximum trait-STAI increase from V1 to V2 observed across sites. One missing baseline data point in the CMBAS group was replaced by the median of the whole population for the primary analysis. The standardized effect size (Cohen's *d*) for within-group change was computed as the mean observed change divided by the baseline observed SD of the outcome in each group. The standardized effect size for between-group difference was computed as the mean adjusted between-group difference divided by the baseline observed pooled SD of the outcome [27]. A reliable change index was calculated from observed values to determine the number of participants who reported clinically significant improvement or deterioration following intervention [28].

Several sensitivity analyses for missing data were performed, and an additional "minimum intervention" subanalysis was done that included only participants who attended at least 4 classes – the a priori determined adequate minimum dose – with primary endpoint data available. The sensitivity analyses conducted included: (1) maximum bias strategy comparing groups with missing data replaced by a failure in 1 group and by a success (maximum decrease in trait-STAI observed in the whole population) in the other, and vice versa; (2) "missing = failure" strategy using a site-specific failure value; and (3) mixed-effects linear regression model with a slope change occurring 49 days after the start of the intervention (i.e., theoretical time of V2) with an interaction term between time and the intervention arm, assuming missing-at-random data.

The potential moderating effect of baseline intrinsic or extrinsic factors on the primary outcome was evaluated by testing an interaction term in the linear regression model between the intervention group and each factor separately. These factors included recruitment site, sex, baseline trait-STAI, neuroticism, proxy measures of intelligence quotient, subjective cognition, and lifestyle. See the online supplementary material for descriptions of considered moderators. Quantitative variables (all factors apart from recruitment site and sex) were divided into quartiles, and quartile 1 and quartile 3 were considered to present the moderating effect.

For comparison of secondary endpoints, we used mixed-effects regression models incorporating all outcome measurements (V1, V2, and V3) and a slope change 49 days after the start of the intervention (i.e., theoretical time of V2). Post hoc analyses tested whether the changes in trait-STAI, state-STAI, and GDS scores were significantly different from zero from V1 to V2 or from V1 to V3 in each group. Analyses were performed using SAS® software (version 9.3 or higher).

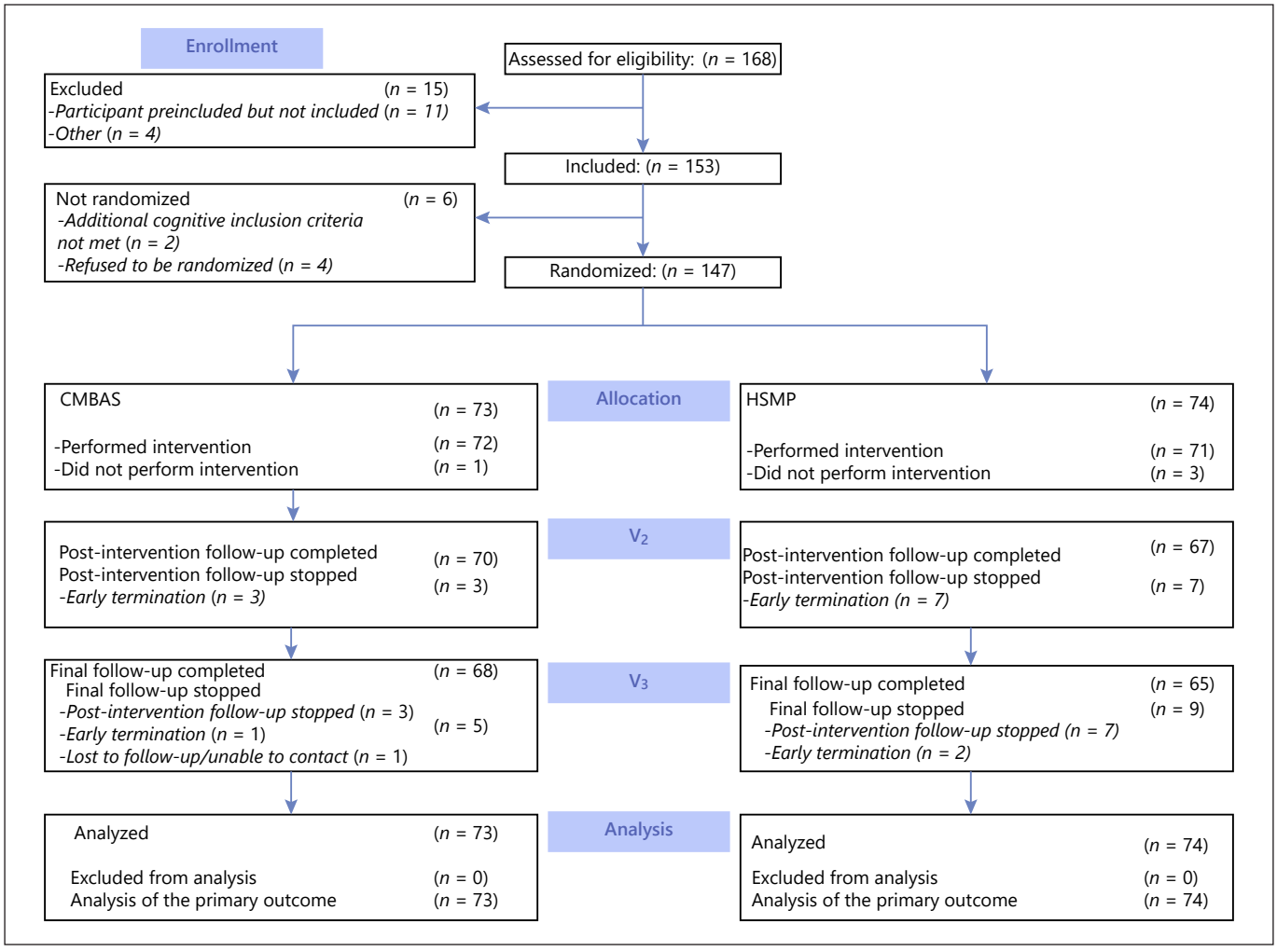
Results

Participant Flow and Baseline Characteristics

Recruitment took place from March 23, 2017, to January 25, 2018. Data collection was completed on September 18, 2018. Figure 1 shows the flow of participants through the study. A total of 147 participants (mean [SD] age 72.7 [6.9] years; 95 females; 65%) were randomized. The CMBAS and HSMP intervention arms did not differ on demographic characteristics (Table 1) or baseline outcome measures (Table 2). The median time between randomization and the start of the intervention was 13 days (CMBAS: 13 days; HSMP: 15 days).

Intervention Fidelity

Checklists completed by facilitators indicated that 87.5% of the sessions in the CMBAS condition were complete, with facilitators missing no more than 1 element in the sessions and all of the missed elements reported being minor in nature (e.g., having missed brief closing practices or shortening of movement practices due to time



Color version available online

Fig. 1. Consort flow diagram of enrolment and randomization to CMBAS and HSMP interventions.

Table 1. Clinical and demographic characteristics of the intention-to-treat sample

	Total sample (*n* = 147)	CMBAS (*n* = 73)	HSMP (*n* = 74)
Sex			
Female	95 (65)	47 (64)	48 (65)
Age, years	72.7±6.9	72.1±7.6	73.3±6.2
Education, years	13.6±3.6	13.9±3.8	13.4±3.4
Ethnicity			
White	142 (97)	69 (94)	73 (99)
Recruitment site			
London, UK	28 (19)	14 (19)	14 (19)
Lyon, France	40 (27)	20 (27)	20 (27)
Cologne, Germany	39 (26)	19 (26)	20 (27)
Barcelona, Spain	40 (27)	20 (27)	20 (27)
Employment			
Retired	123 (85)[a]	58 (82)[b]	65 (88)
MMSE	28.8±1.1	28.7±1.2	28.9±1.0

Data are presented as means ± SD or numbers (%). [a] *n* = 145. [b] *n* = 71.

Table 2. Observed values for all outcomes

	Trait-STAI				State-STAI				GDS			
	CMBAS		HSMP		CMBAS		HSMP		CMBAS		HSMP	
	n	mean (SD)	*n*	mean (SD)	*n*	mean (SD)	*n*	mean (SD)	*n*	mean (SD)	*n*	mean (SD)
V1	72	40.7 (10.5)	74	39.1 (9.4)	73	33.6 (9.8)	74	31.5 (8.4)	73	3.1 (2.5)	74	2.0 (2.0)
V2	68	37.0 (9.8)	66	36.2 (9.1)	68	31.5 (8.8)	66	30.4 (8.3)	68	2.7 (2.9)	66	2.1 (2.2)
V3	68	37.3 (10.4)	65	36.3 (9.8)	68	32.8 (10.2)	65	29.7 (9.1)	68	2.6 (2.8)	64	2.0 (1.9)
Change from V1 to V2	67	−3.3 (7.5)	66	−2.4 (6.7)	68	−2.1 (9.9)	66	−0.9 (8.1)	68	−0.3 (2.0)	66	0.2 (1.9)
Change from V1 to V3	67	−3.0 (8.3)	65	−2.5 (7.9)	68	−0.6 (10.9)	65	−1.4 (8.5)	68	−0.4 (2.0)	64	0.1 (1.0)

Table 3. Results from the primary outcome and secondary outcomes

Primary outcome	Estimated change[a]		Between-group difference in change[a]	*p* value
	CMBAS (*n* = 73)	HSMP (*n* = 74)		
Trait-STAI				
V1 to V2	−1.02 (−3.54 to 1.50)	0.23 (−2.29 to 2.76)	−1.25 (−4.76 to 2.25)	0.48
Secondary outcomes	**Estimated change**		**Between-group difference in change**	***p* value**
	CMBAS (*n* = 73)	HSMP (*n* = 74)		
Trait-STAI				
V1 to V3	−2.92 (−4.67 to −1.17)	−2.49 (−4.27 to −1.17)	−0.43 (−2.92 to 2.07)	0.74
State-STAI				
V1 to V2	−2.47 (−4.74 to −0.21)	−0.88 (−3.16 to 1.40)	−1.60 (−4.81 to 1.62)	0.33
V1 to V3	−0.76 (−2.88 to 1.36)	−1.31 (−3.48 to 0.85)	0.55 (−2.48 to 3.59)	0.72
GDS				
V1 to V2	−0.23 (−0.71 to 0.26)	0.20 (−0.29 to 0.69)	−0.43 (−1.11 to 0.26)	0.22
V1 to V3	−0.34 (−0.80 to 0.12)	0.15 (−0.32 to 0.62)	−0.49 (−1.14 to 0.17)	0.14

Values are presented as means (95% CI). All analyses are adjusted for: recruitment site, median-centered age, sex, median-centered MMSE, and median-centered baseline scores of outcome. [a] For Trait-STAI change between V1 and V2 (primary outcome), estimates and *p* values come from the linear regression model with missing = failure analysis, and for Trait-STAI change between V1 and V3, State-STAI, and GDS (secondary outcomes), estimates come from the mixed effect regression analysis.

constraints). In the HSMP condition, checklists indicated that therapists covered the main steps of the standard session sequence without exception.

Intervention Engagement

No significant differences were observed between the CMBAS and HSMP arms on participant ratings ($n = 143$) of credibility (5.9 [SD 2.2] vs. 5.3 [SD 1.9]) or expectancy (4.5 [SD 1.9] vs. 4.1 [SD 1.8]). One hundred twenty-one (85%) participants attended 4 or more sessions (CMBAS: 82%; HSMP: 87%), the requirement for the minimum intervention analysis. Participants had an average attendance of 6.7 (SD 2.7) out of a maximum of 9 sessions (CMBAS = 6.7 [SD 2.8], HSMP = 6.8 [SD 2.7]). No difference was observed between intervention arms in the number of sessions attended ($p = 0.95$). One hundred

twenty-five (85%) participants completed at least 1 homework practice (CMBAS = 63 [85%]; HSMP = 63 [85%]). Fifty-six percent (75 out of 133) of the participants who returned for V3 reported that they continued practice during the follow-up period, i.e., 59% (40 out of 68) in CMBAS and 54% (35 out of 65) in health self-management ($p = 0.6$). The median time between the start of the group-based intervention and V2 was 65 days (CMBAS: 66 days; HSMP: 62 days), and between the start of the group-based intervention and V3 it was 174 days (CMBAS and HSMP: 174 days).

Primary Outcome

The mean observed change in trait-STAI from V1 to V2 was –3.3 (SD 7.5) points (Cohen's $d = 0.31$) in CMBAS and –2.4 (SD 6.7) points (Cohen's $d = 0.26$) in HSMP (Table 2). There was no significant difference between groups (mean adjusted difference in change: –1.25; 95% CI –4.76 to 2.25, $p = 0.48$; Cohen's $d = 0.13$; Table 3). Sensitivity analyses supported these findings, as did the minimum intervention analysis (–0.39; 95% CI –2.88 to 2.09, $p = 0.75$; online suppl. Table 2). No significant moderating effect was identified for the considered baseline characteristics (online suppl. material).

Secondary Outcomes

The mean adjusted difference in change in trait-STAI from V1 to V3 between intervention arms was not significant (–0.43; 95% CI –2.92 to 2.07, $p = 0.74$; Cohen's $d = 0.04$; Table 3). Neither the mean adjusted difference in change on the state-STAI from V1 to V2 (–1.60; 95% CI –4.81 to 1.62, $p = 0.33$; Cohen's $d = 0.18$) nor that from V1 to V3 (0.55; 95% CI –2.48 to 3.59, $p = 0.72$; Cohen's $d = 0.06$; Table 3) was significant. Regarding the GDS, the mean adjusted differences in change from V1 to V2 (–0.43; 95% CI –1.11 to 0.26, $p = 0.22$; Cohen's $d = 0.19$) and from V1 to V3 (–0.49; 95% CI –1.14 to 0.17, $p = 0.14$; Cohen's $d = 0.22$; Table 3) were also not significant.

Post hoc Analyses

The change in trait-STAI was significantly different from zero in both intervention arms from V1 to V3 (CMBAS: –2.92; 95% CI –4.67 to –1.17, $p = 0.001$; HSMP: –2.49; 95% CI –4.27 to –0.72, $p = 0.006$). This decrease was mainly observed from V1 to V2 (CMBAS: –3.43; 95% CI –5.27 to –1.59, $p = 0.0003$; HSMP: –2.29; 95% CI –4.14 to –0.44, $p = 0.02$) and no change was observed from V2 to V3 (CMBAS: 0.51; 95% CI –0.57 to 1.59, $p = 0.35$; HSMP: –0.20; 95% CI –1.28 to 0.88, $p = 0.71$; Fig. 2). Twenty-one participants (16%) reported a clinically significant improvement in trait-STAI from V1 to V2 (CMBAS: $n = 11$; HSMP: $n = 10$).

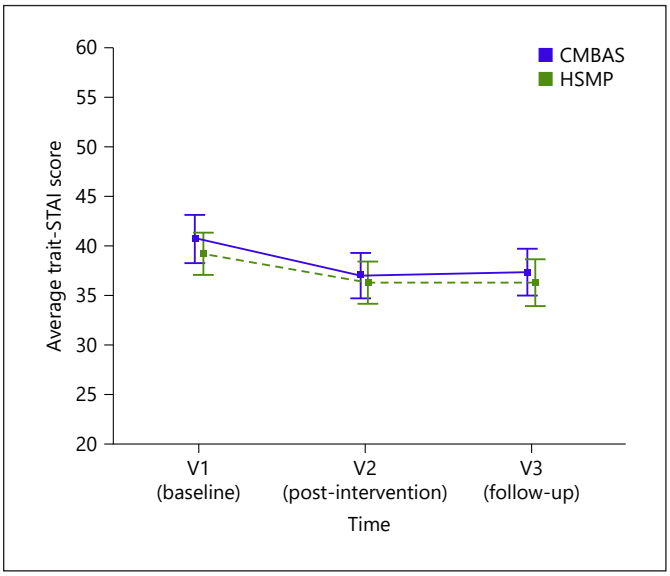


Fig. 2. Evolution of average trait-STAI scores from baseline (V1) to postintervention (V2) and follow-up (V3) for each intervention condition.

Change was not significantly different from zero in either intervention arm from V1 to V3 in state-STAI scores (CMBAS: –0.76; 95% CI –2.88 to 1.36, $p = 0.48$; HSMP: –1.31; 95% CI –3.48 to 0.85, $p = 0.23$) or GDS scores (CMBAS: –0.34; 95% CI –0.8 to 0.12, $p = 0.15$; HSMP: 0.15; 95% CI –0.32 to 0.62, $p = 0.53$). However, the change in state-STAI was significantly different from zero in the CMBAS arm from V1 to V2 (–2.47; 95% CI –4.74 to –0.21, $p = 0.03$). No other changes from V1 to V2 were significantly different from zero.

Deterioration and Adverse Events

Forty-four (33%) of the 133 participants who completed the primary outcome measure at both time points showed an increase (deterioration) in trait-STAI from V1 to V2. There was no difference in deterioration between groups (CMBAS: $n = 22$; 33%; HSMP: $n = 22$; 33%), and only 2 participants (1.5%) reported a clinically significant deterioration. Twenty-five adverse events were recorded in the trial (CMBAS: 18; HSMP: 7), and 5 of them were considered serious adverse events (CMBAS: 4; HSMP: 1; online suppl. Table 3). None in either condition was judged to be related to the study procedures or intervention.

Discussion

In this large, multinational clinical trial of older adults with SCD an 8-week CMBAS intervention was not superior to an HSMP at reducing subclinical anxiety symptoms. Intervention engagement and potential iatrogenic effects were equivalent in both conditions [29], and no study-related adverse events were reported.

Despite the extant literature reporting beneficial effects of MBI on both clinical and subclinical symptoms of anxiety [13, 14], we observed no substantial difference in subclinical anxiety symptom reduction between intervention conditions. This finding further contrasts with that of a previously published trial reporting a differential benefit of an MBI compared with an HSMP on symptoms of anxiety in participants with cognitive complaints [21]. Participants in the previous trial had a current diagnosis of depression and/or anxiety, whereas this was an exclusion for SCD-Well. While participants in our trial did show elevated baseline anxiety symptoms, in line with observational studies of SCD [30], it may be that clinically significant anxiety is needed for a differential effect of MBI to emerge in this population.

In the present study, participants in both intervention groups showed a reduction in trait anxiety at the end of the intervention that was maintained 6 months later. This reduction left participants well within the normal range of anxiety symptoms [31] and suggests that anxiety levels in individuals with SCD are malleable. However, because the trial did not include a passive control, we were unable to directly examine whether changes in anxiety symptoms were specifically due to the interventions. In an effort to answer this question, we extracted the average trait-STAI change from passive control conditions used in 8-week MBI studies across a range of populations that were included in earlier reviews [13, 14] (see online suppl. Table 4 for references). The average reported change from those 6 studies was 0.3 (compared with −3.3 in CMBAS and −2.4 in HSMP reported here), indicating that anxiety was relatively stable over time in a passive condition. When studies were restricted to those with an average participant age of 50 years or older, trait-STAI increased by 2.2 on average over 8 weeks. While only indicative, and not confirmatory, these data support the interpretation that both interventions employed in SCD-Well led to the reduction of anxiety symptoms.

A sustained decrease in state symptoms of anxiety was not observed in either intervention condition. State anxiety describes symptoms experienced in the present moment, while trait anxiety describes symptoms generally experienced over time. The observation of a sustained reduction of trait but not state anxiety indicates that participants experienced an enduring shift in subclinical anxiety levels rather than acute responses to a stressor (e.g., clinical test environment). Despite MBI having been shown to effectively reduce depressive symptoms [14], we found no effect in SCD-Well. As depressive symptoms were already near floor at baseline, there was little room for improvements to be observed. As with trait anxiety symptoms, a positive effect on depressive symptoms might be anticipated in future trials that include older adults with higher or clinically significant levels of depression.

The SCD-Well trial has several strengths. It is the first multicountry intervention study in SCD, which increases the generalizability of the findings. In line with methodological recommendations for randomized controlled trials of psychological interventions [32], we used a manualized intervention with a clinically relevant comparison condition that incorporated the same amount of facilitator contact time as the experimental condition, described the "treatment ingredients" of both interventions [see 16], included a 6-month follow-up assessment, and reported the number of participants who deteriorated (i.e., reported an increase in anxiety symptoms) after treatment. Compared to previous mindfulness trials in SCD [21, 33, 34], our trial had a larger sample size, comprising older adults recruited solely from memory clinics. We followed research recommendations [35] to homogenize our sample by using a standardized definition of SCD [2, 36], by using predefined criteria to exclude MCI [16, 37], and by excluding participants with psychiatric or neurodegenerative disorders.

This study does, however, have limitations. First, there are methodological constraints. Most importantly, no passive control was included so we were unable to ascertain whether the reduction in anxiety symptoms observed in both conditions was specifically due to intervention. Despite the statistically significant reductions in trait-STAI observed in both conditions, clinically significant reductions were limited. Recent meta-analytic evidence suggests that the trait-STAI captures negative affectivity more than anxiety [38], thus offering the possibility that the negative results observed here may be due to measurement insensitivity. We are further unable to explain why no difference was observed between conditions. For example, intervention duration (e.g., most drug trials are significantly longer), the strength of the comparator condition [19], or the limited range of anxiety symptoms due to exclusion of anxiety disorders could all have made the

detection of intervention effects more difficult. Second, the causes of SCD are heterogeneous, and despite making attempts to homogenize the sample, different underlying etiologies of SCD likely remained and could have affected the results. Third, the follow-up was relatively short. Potential long-term effects on anxiety symptoms or dementia incidence could not be assessed. Future analyses from SCD-Well, and its sister trial Age-Well [39], will further characterize the possible specificities of these interventions on cognition, aging, and health.

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Statement of Ethics

This study was approved by Ethics Committees and regulatory agencies of all centers: London, UK (Queen Square Research Ethics Committee: No 17/LO/0056 and Health Research Authority National Health Service, IRAS project ID: 213008); Lyon, France (Comité de Protection des Personnes Sud-Est II Groupement Hospitalier Est: No. 2016-30-1 and Agence Nationale de Sécurité du Médicament et des Produits de Santé: IDRCB 2016-A01298-43); Cologne, Germany (Ethikkommission der Medizinischen Fakultät der Universität zu Köln: No. 17-059); and Barcelona, Spain (Comité Etico de Investigacion Clinica del Hospital Clinic de Barcelona: No. HCB/2017/0062). Written informed consent was secured from all of the participants after the procedures had been fully explained to them and prior to trial participation. The authors assert that all of the procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of Interest Statement

TB has received honoraria for workshops on MBI and is the coauthor of a book on mindfulness-based cognitive therapy. All of the other authors have no conflicts to declare.

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Author Contributions

N.L.M., T.B., M.W., A.L., E.M.A.-U., F.C., G.P., J.G., J.A., E.F., P.K.-S., J.L.M., G.C., F.J., and O.M.K. made substantial contributions to the conception and design of this work. N.L.M., H.D.-K., A.-K.S., N.C.-P., F.D.-C., T.W., Z.W., P.K.-S., J.L.M., F.J., and O.M.K. contributed to data acquisition. N.L.M., T.B., M.W., A.L., E.M.A.-U., F.C., G.P., J.G., G.C., F.J., and O.M.K. contributed to interpretation of the data. N.L.M., R.C., H.D.-K., M.S., J.A., and E.F. contributed to analysis of data. N.L.M., R.C., and E.F. drafted this paper. N.L.M., T.B., R.C., M.W., A.L., E.M.A.-U., F.C., G.P., H.D.-K., A.-K.S., N.C.-P., F.D.-C., T.W., M.S., J.G., J.A., E.F., Z.W., P.K.-S., J.L.M., G.C., F.J., and O.M.K. critically revised this work for important intellectual content and approved the final version.

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