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Featured Article

The SCD-Well randomized controlled trial: Effects of a mindfulness-based intervention versus health education on mental health in patients with subjective cognitive decline (SCD)

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Abstract

Introduction: Subjectively experienced cognitive decline in older adults is an indicator of increased risk for dementia and is also associated with increased levels of anxiety symptoms. As anxiety is itself emerging as a risk factor for cognitive decline and dementia, the primary question of the present study is whether an 8-week mindfulness-based intervention can significantly reduce anxiety symptoms in patients with subjective cognitive decline (SCD). The secondary questions pertain to whether such changes extend to other domains of psychological, social, and biological functioning (including cognition, self-regulation, lifestyle, well-being and quality of life, sleep, and selected blood-based biomarkers) associated with mental health, older age, and risk for dementia.

Methods: SCD-Well is a multicenter, observer-blinded, randomized, controlled, superiority trial, which is part of the Horizon 2020 European Union-funded "Medit-Ageing" project. SCD-Well compares an 8-week mindfulness- and compassion-based intervention specifically adapted for older

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adults with SCD with a validated 8-week health education program. Participants were recruited from memory clinics in four European sites (Cologne, Germany; London, United Kingdom; Barcelona, Spain; and Lyon, France) and randomized with a 1:1 allocation, stratified by site.

Results: The primary outcome, change in anxiety symptoms, and secondary outcomes reflecting psychological, cognitive, social, and biological functioning are assessed at baseline, postintervention, and 4 months after the end of the intervention.

Discussion: The study will provide evidence on whether a mindfulness-based intervention can effect changes in anxiety and other risk factors for cognitive decline and dementia in older adults with SCD and will inform the establishment of intervention strategies targeted at improving mental health in older adults.

Keywords: Dementia; Meditation; Subjective cognitive decline; Alzheimer's disease; Anxiety; Cognition; Emotion; Mindfulness; Compassion; Psychoeducation; Medit-Ageing; Silver Santé Study

1. Introduction

1.1. Background

Owing to aging populations, incidence of dementia is estimated to triple by 2050, representing the greatest challenge for health care in the 21st century [1]. In addition to affecting the individual living with dementia, there are considerable consequences for wider society given the associated emotional, health, and social care costs. Effective approaches to treating the underlying illnesses that cause dementia are still largely absent, thus emphasizing the need for prevention.

Most neuropathological processes start years before the onset of dementia [2,3]; hence, there is a growing need to target modifiable risk factors in individuals in the earliest stages for intervention when neurodegeneration is still limited [4]. In support of advancing preventative strategies, research shows that approximately a third of dementia cases worldwide might be attributable to potentially modifiable risk factors [5]. Indeed, the risk of dementia increases when adverse factors, including anxiety, depression, stress, and sleep disturbances, are present. Sleep disorders are known to promote dementia-related pathological processes [6], and in older adults, each depressive symptom increases dementia risk by approximately 20% [7]. Importantly, longitudinal studies show that anxiety increases the rate of cognitive decline in individuals at risk of dementia [8], and a recent meta-analysis implicated late-life levels of anxiety symptoms as a predictor of dementia [9]. Increasing evidence supports that subjectively experienced cognitive decline, even when performance on cognitive tests is in the normal range, is also associated with an increased risk for future cognitive decline and dementia [10,11]. A high level of anxiety is a characteristic feature of patients living with subjective cognitive decline (SCD) [12], which may further exacerbate risk for dementia and reduced well-being.

1.2. Mindfulness-based intervention

Although mindfulness-based research in older adults is still in its infancy, there is considerable evidence that these interventions can reduce anxiety in a number of populations, including preliminary studies in older adults [13,14]. Mindfulness-based interventions (MBIs), derived from the generic mindfulness-based stress reduction program developed by Dr. Jon Kabat-Zinn [15], combine intensive training in mindfulness meditation with psychoeducational components and provide individuals with sustainable skills that remain at their disposal beyond the intervention period. MBIs use a secular form of meditation training that emphasizes focused, nonjudgmental awareness of present moment experiences. Participants typically meet for weekly group-based sessions for 8 weeks and engage in home practices between sessions.

In addition to reducing anxiety, promising evidence also shows that MBIs improve cognitive function in areas most sensitive to aging and dementia (such as attention and memory) [16,17]. Further research shows that these interventions can reduce stress, depression, insomnia, feelings of loneliness, and social exclusion [14,18,19], as well as cardiovascular risk factors [20]—all of which are associated with increased risk for dementia [21,22]. Indeed, recent evidence suggests that an MBI altered levels of a blood-based biological marker associated with both stress and dementia in at-risk older adults [23]. Importantly, mindfulness-based training is a scalable, community-based, and low-cost intervention that is broadly available.

1.3. Choice of comparator

Many of the previous studies of MBIs have suffered from a lack of an adequate comparison condition and lack of follow-up to know whether initial benefits are maintained. As MBIs contain a number of nonspecific elements, such as social interaction, light exercise, or the provision of treatment expectancies, the use of active control or comparison interventions is important. Based on the assumption that training in mindfulness is the crucial active component of the intervention and to control for effects due to other aspects of the program, we selected a health education program as the comparison condition. The health education

program is structurally equivalent to the mindfulness-based training in overall course length, class time and home activities, and matched to the training in administration, dosage, and duration. It is a facilitator-led, group-based program, based on a published book [24], and developed and validated in an SCD population by colleagues in the United States [25]. The program was designed to equalize treatment expectancy across conditions, parallel psychoeducational components, and to control for the nonspecific effects of increased social interaction and light physical activity. Moreover, the health education program may have a positive impact on well-being in the SCD population by fostering self-efficacy. Participants with SCD and comorbid clinical anxiety and/or depression in the trial by Wetherell et al. believed this program was a credible intervention and showed nonsignificant improvements in memory, as expected in a comparison condition [25]. However, participants in this condition did not show significant improvement in anxiety symptoms compared with those in the mindfulness-based condition [26].

1.4. Trial objectives and purpose

The SCD-Well trial is part of the "Medit-Ageing" project (public name: Silver Santé Study; www.silversantestudy.eu) funded through the European Union as part of the Horizon 2020 program. SCD-Well will use an MBI that is specifically tailored to the needs of older adults building on modifications suggested by Zellner Keller et al. [27] together with a particular focus on compassion and loving kindness practices. This upgrade takes into account emerging clinical evidence showing a complementary and beneficial role of this style of meditation on anxiety and depression [27–30].

The primary objective of the trial is to test whether an 8-week MBI is superior to an 8-week health education program on reducing anxiety in older adults with SCD in a multicenter randomized controlled trial. We will further examine whether any changes in anxiety symptoms are maintained 4 months after the end of the intervention, and whether the intervention affects a series of outcomes including mental health and cognitive functions, social relations, and biological markers.

2. Methods/design

2.1. Trial design and setting

SCD-Well is a European multicenter, observer-blind, randomized, controlled, superiority trial with two parallel groups: an MBI or a validated health-educational program. The trial includes 8 weeks of intervention and 16 weeks of follow-up (total of 24 weeks) and is designed to compare outcomes from the two intervention groups. The intervention takes place in group settings at four sites, and randomization is performed with a 1:1 allocation, stratified by study site. The study schedule is summarized in Table 1, and detailed descriptions of participant visits are provided in Supplementary Material 1. Briefly, participants are recruited from medical facilities, prescreened, and then invited to a screening visit (V0) where the diagnostic battery is performed (Table 2) and eligibility is assessed. Participants fulfilling eligibility criteria (Table 3) are invited to the baseline visit (V1) and then randomized to one of the two intervention groups. Allocation and assignment of interventions are described in Supplementary Material 1. A postintervention visit (V2) is conducted after the end of the intervention, and a follow-up visit (V3) is held 4 months after the end of the intervention. The primary outcome is change in symptoms of anxiety from V1 to V2. For secondary outcomes, treatment effects are assessed as change from V1 to V2 or V3.

Participants are recruited from medical facilities (e.g., memory clinics) at the four centers where the trial assessments and delivery of the interventions take place (London, UK; Cologne, Germany; Lyon, France; Barcelona, Spain). More detail about the sites is provided in Supplementary Material 1. Participants are patients who are either referred to a memory clinic by a physician or who are self-referrals.

2.2. Data collection

Validated behavioral measures chosen for their sensitivity to aging and early dementia and/or meditation were selected for the trial (see Supplementary Table 1 for details). Briefly, behavioral measures include neuropsychological tests that assess different cognitive functions (e.g., episodic memory, attention, executive function) and questionnaires that include assessments of personality traits; sleep quality; lifetime and current engagement in cognitive, social, and physical activities; Mediterranean diet adherence; health-related behaviors such as self-medication, smoking and alcohol consumption; quality of life and well-being; and mental health indicators such as anxiety and depression and loneliness. Some questionnaires are also given to a participant's close relative or friend (subsequently referred to as the "partner"). Behavioral measures and blood sampling are conducted at V1, V2, and/or V3. Details regarding the collection of blood specimens can be found in Supplementary Material 2.

To standardize the administration and scoring of neuropsychological tests and questionnaires, psychometrists from all sites completed a standardized administration and scoring training that was developed specifically for the study.

2.3. Interventions

The *MBI* uses meditation and yoga practices adapted for older adults [27] and, in line with the standard format of mindfulness-based stress reduction, consists of a pre-class meeting with the facilitator in which the participants are socialized to the treatment, eight weekly group-based sessions of 2 to 2½ hours duration, a half-day of meditation practice after the sixth session of the program (9 sessions

Table 1
Study schedule

Schedule of events	Screening V0	Baseline assessment and randomization V1	Intervention period (8 weeks)	Postintervention assessment V2	4-month follow-up assessment V3
Enrollment					
Eligibility screen	X	X			
Oral and written information	X				
Signed informed consent		X			
Randomization		X			
Assessments					
Baseline characteristics		X			
Primary outcome					
State-Trait Anxiety Inventory (STAI)		X		X	X
Secondary and exploratory outcomes (see Supplementary Table 1 for detailed measures)					
Medical background		X		X	X
Global cognition		X		X	X
Thinking and reasoning				X	
Attention/executive function		X		X	X
Memory		X		X	X
Language		X		X	X
Psychoaffective/emotion		X		X	X
Compassion, support, mindfulness		X		X	X
Sleep		X		X	X
Personality		X			
Lifestyle		X		X	X
Quality of life and well-being		X		X	X
Biological measures		X		X	X
Partner questionnaires		X		X	X
Intervention					
Mindfulness-based intervention			◆———		
Health education program			◆———		
Completion of workbook/questionnaires to monitor intervention adherence and response			◆———		

X indicates that the event occurred during that time in the study schedule. The symbol in question indicates that the intervention period was ongoing for 8 weeks.

in total), and home practices. The intervention combines intensive training in mindfulness and compassion meditation and gentle yoga practices with psychoeducational components targeted at helping individuals to deal more effectively with emotional difficulties and stressors commonly encountered in older age, particularly stressors related to concerns about cognitive functioning and health. The program has a particular emphasis on cultivating wholesome attitudes toward oneself and others. Meditation and yoga practices focus on strengthening attentional capacities and bodily awareness during the first half of the program. Practices in the second half of the program build on these skills to establish more effective ways of responding to difficult experiences. Participants are asked to engage in home practice for approximately an hour per day, 6 days per week. Home practice consists of formal meditation practices guided by meditation recordings and informal practices aimed at helping participants to generalize mindfulness skills to their daily life. Participants receive a workbook that explains the home practices and that is used to record adherence to them.

Table 2
Diagnostic battery

Domains evaluated	Tests
Global cognitive functioning	Cognitive assessment according to site-specific memory clinical standards to diagnose SCD (if needed)
	MMSE [31]
Depression and anxiety	Standardized questions to assess generalized anxiety and major depression (DSM-5 [32]/ICD-10 checklist [33][p10])
SCD criteria	Meets research criteria for SCD [11]
Memory concern	Expressed concern about memory (either by visiting a memory clinic or assessed via a question at screening)

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; MMSE, Mini–Mental State Examination; SCD, subjective cognitive decline.

The *health education control* intervention follows the same format and structure as the MBI and is matched to

Table 3
Eligibility criteria

Inclusion criteria	Exclusion criteria

• Aged ≥60 years.
• Meets research criteria proposed by the SCD-I working group [11].
• Performance within the normal range on standardized cognitive tests already administered at each site as part of standard clinical assessments according to research criteria based on those defined by Jak and Bondi [34,35] for exclusion of MCI as recommended by Molinuevo et al. [36].
  • Participants are excluded if they score below the normative range on two tests within a single cognitive domain (i.e., memory, executive function, language) or if they score below the normative range on one test within each cognitive domain.
  • Results from prespecified tests in memory, executive function, and language from the baseline cognitive assessment are examined as an additional check to ensure comparable cognitive performance across sites using the same measures and criteria.
• Being referred to the memory clinic by a physician or self-referral because of memory concerns.
• Ability to provide informed consent in accordance with International Conference on Harmonization of Good Clinical Practice (GCP/ICH) guidelines and local regulations.
• Stating that they are available for the trial duration (39 weeks).
	• Presence of a major neurological or psychiatric disorder (including anxiety disorders, major depressive disorder, or an addiction to alcohol or drugs) according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision [33] and/or Diagnostic and Statistical Manual of Mental Disorders, fifth edition [32] criteria.
	• Under legal guardianship or incapacitation.
	• History of cerebral disease (vascular, degenerative, physical malformation, tumor, or head trauma with loss of consciousness for more than an hour), which interferes with the aims of the study protocol.
	• Visual or auditory impairment sufficient to interfere with the aims of the study protocol.
	• Presence of a chronic disease or acute unstable illness (respiratory, cardiovascular, digestive, renal, metabolic, hematologic, endocrine, or infectious), which interferes with the aims of the study protocol.
	• Current or recent medication that may interfere with cognitive action (psychotropic, systemic corticosteroid, anti-Parkinson's, or analgesic drugs). The interfering nature of the different treatments is at the discretion of the investigating doctor.
	• Regular or intensive practice of meditation or comparable practices (yoga, Qigong, Alexander technique), that is, more than 1 day per week for more than 6 months consecutively over the last 10 years, intensive practice (internship or retreat > five consecutive days) over the past 10 years, or more than 25 days of retreats (cumulatively) before the last 10 years.

the MBI in administration, dosage, and duration. More specifically, it consists of a pre-class meeting with the facilitator, eight weekly group-based sessions of 2 to 2½ hours duration, a half-day of practice after the sixth session of the program (9 sessions in total), and home practices. The treatment is based on a published manual [24], with every session of the program covering different subjects, including self-management; problem-solving; sleep; stress; exercise; managing medicines and memory; communicating with family, friends, and health care professionals; eating; weight management; and planning for the future. Participants are provided with information about these subjects and engage in group exercises and discussions about them. They are given a workbook and asked to actively engage in activities described in the workbook to improve health and well-being on 6 days each week, matching home assignments in the MBI. The workbook summarizes the most important points of each session, and participants are asked to record engagement in health-related activities on protocol sheets in the workbook.

Each site has two facilitators, each with a psychology/psychotherapy degree and/or significant experience in leading group-based therapies. One facilitator, who has undergone formal training to match criteria of the good practice guidelines of the UK network of mindfulness-based teacher trainers, delivers the MBI. The other facilitator who has at least 3 years' experience leading group-based clinical programs and/or psychoeducational interventions (e.g., a clinical psychologist or equivalent) leads the health education intervention. Both sets of facilitators received the intervention protocol, instruction, and a day-long training about their respective intervention before the start of the study to promote standardization of the intervention delivery across sites. To document manual adherence, facilitators of both interventions complete self-report checklists after each class. Facilitators are supervised in weekly individual sessions by the intervention leads. The two interventions are delivered to groups of approximately 10 participants and take place in a designated room at the memory clinic or investigator-affiliated facility.

After the first session of the intervention, participants of both intervention groups complete a questionnaire to record their expectations for the credibility and efficacy of their intervention [37]. They also report levels of depression over the past week at the beginning of each intervention session. Participants are also encouraged to record any important comments they might have about the practice to provide qualitative information. Adherence (i.e., class attendance) is collected by facilitators. Participants who choose to drop out of the intervention are invited to continue taking part in assessments.

2.4. Outcomes

Given its prevalence in SCD and relation to objective cognitive decline and dementia risk, the primary outcome is the mean change in anxiety from V1 to V2, in each group.

Mean change in anxiety will be measured by the trait version of the State-Trait Anxiety Inventory (STAI) [38]. We had initially intended to use the state version of the STAI as a primary outcome but took the decision to use the trait version for two reasons—(1) the state version assesses transient anxiety symptoms that are more susceptible to situational variation and (2) intermediate reports indicated floor effects of baseline data for the state, but not the trait-STAI, potentially due to entry to treatment in the trial. Trait-STAI scores are more representative of a person's general level of anxiety and less dependent on situational factors, which may not be fully standardized across sites. Previous research has shown that increased trait anxiety is a characteristic of SCD samples [39]. The change in primary outcome measure from state-STAI to trait-STAI was approved by the Trial Steering Committee, before any statistical analyses. Although trait-STAI will be the primary outcome of this trial, the effects of the interventions on state-STAI will be assessed as a secondary outcome. Other secondary outcomes include

- mean change in anxiety (measured by the trait-STAI) from V1 to V3,
- mean change in behavioral measures (see Supplementary Table 1 for specific outcomes) observed (a) from V1 to V2 and (b) from V1 to V3,
- mean change in blood-based markers of stress and dementia risk observed (a) from V1 to V2 and (b) from V1 to V3,
- change in mean numbers of visits to general practitioners/medical doctors and the medication use during and after the intervention, and
- mean changes in measures of emotions/psychoaffective functioning, compassion, support, and mindfulness assessed by partners of participants.

Moderator analyses will establish whether factors including sex, personality characteristics, genetic phenotypes, general thinking and reasoning skills, and life experiences and diet affect the outcomes of the intervention. Study data will also be used for exploratory analyses unrelated to the intervention.

2.5. Statistical considerations

2.5.1. Sample size

As the STAI anxiety score has no absolute cutoff levels, sample size consideration is based on effect size (i.e., the ratio between the expected interarm differences to the common standard deviation). With a minimum effect size of 0.50 (indicated as a reasonable expectation from a meta-analysis summarizing the efficacy of meditative therapies for reducing anxiety) [13], 64 participants per arm need to be included to demonstrate a significant difference in the primary endpoint (mean difference in the change of the trait-STAI score in each trial arm between baseline and the end of the intervention) in a t-test with 80% power and a two-sided type I error of 5%. As the minimum relevant effect size was considered to be the same for the state- and trait-STAI, sample size remained unchanged after the change of the primary endpoint.

2.5.2. Statistical methods

The planned statistical analyses are described in a trial statistical analysis plan and summarized in Supplementary Material 1. Briefly, the primary outcome analyses will be conducted on an intent-to-treat principle, and missing primary endpoint data will be handled with a conservative a "missing = failure" strategy. Additional analyses conducted on both primary and secondary outcomes will include sensitivity analyses, undertreatment and per protocol analyses, and analyses of exposure/dose effects. For exploratory noncomparative analyses, complete case analyses or imputation methods will be considered on a case-by-case basis, depending on the amount of missing data and the specific research question.

2.6. Ethics, safety, and study monitoring

The SCD-Well trial was approved by the necessary ethics committees and regulatory agencies in London, UK (Queen Square Research Ethics Committee and Health Research Authority); Lyon, France (Comité de Protection des Personnes CPP Sud-Est II Groupement Hospitalier and Agence Nationale de Sécurité du Médicament et des Produits de Santé); Cologne, Germany (Ethikkommission der Medizinischen Fakultät der Universität zu Köln); and Barcelona, Spain (Comité Etico de Investigacion Clinica del Hospital Clinic de Barcelona), registered on ClinicalTrials.gov (Identifier: NCT03005652), and adheres to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines for clinical trial protocols [40] (see Supplementary Material 1 for further details and Supplementary Table 2 for SPIRIT checklist).

The sponsor established a Trial Steering Committee according to Good Clinical Practice guidelines with the responsibility to provide oversight on the conduct of the trial, advise on scientific credibility on behalf of the sponsor and the funder, and assess the progress of the protocol. More details on data management, monitoring, dissemination and access, and study governance (blinding, safety, auditing) are contained in the Supplementary Material 1.

3. Discussion

The primary aim of the SCD-Well study is to establish whether an 8-week MBI as compared to 8-week health education training can reduce anxiety levels in older adults with SCD. This will be assessed through the use of a multicenter randomized superiority trial. As anxiety symptoms are not

only prevalent among patients with SCD [12,41] but may also represent a risk factor for dementia [8,21,42], this study aims to provide an initial step toward testing the potential of mindfulness-based training as a new form of intervention to improve well-being and prevent cognitive decline and ultimately delay the onset of dementia. Furthermore, the study is aimed at providing rigorous evidence regarding the immediate and sustained effects of mindfulness training on a range of other psychological and biological factors that are indicators of health, well-being, and cognitive functions.

3.1. Practical issues

The SCD-Well trial is conducted in several countries with the aim of establishing whether an MBI is broadly applicable for older persons with SCD. However, if there are strong cultural differences in the response to the training, this could increase the heterogeneity across sites in the overall expected effect. Analyses of responder characteristics could help to address such biases in future studies. We have excluded participants with anxiety levels reaching clinical significance to limit potential confounding from psychiatric illness, but we have not set a lower limit for anxiety levels as it is well documented that anxiety is a common symptom in people with SCD. This criterion does however create the possibility that we may not detect an effect of the intervention because of participants' low levels of baseline anxiety symptoms.

Although this study benefits from a 4-month follow-up assessment to examine whether any changes due to the intervention are maintained, future studies would profit from still longer-term follow-up assessment(s), which could examine the duration of possible effects and include monitoring of conversion to dementia. Finally, we have included an active comparison condition that will be used to examine whether mindfulness-based training confers a specific advantage over another form of behavioral intervention; however, we did not include a passive control condition due to recruitment and financial constraints. If no difference is found between the mindfulness-based and comparison interventions, it will therefore be difficult to show whether this is because neither or both were effective at reducing anxiety.

3.2. Operational issues

Although great care was taken in the conceptualization and preparation of the SCD-Well trial, there are some operational issues that are inherent in the dependent measures. First, the main endpoint, anxiety, is only assessed through a questionnaire and is thus not blinded to the allocated intervention. Although the employed questionnaire has been extensively validated, our endpoint relies on participants' capacity to give an accurate report of their anxiety levels. To complement potential biases through self-reports in relation to our secondary objectives, participants' partners (for example, spouses, children, neighbors, close friends) are also invited to fill in a set of questionnaires. A second operational issue is encountered by the fact that we only have few objective risk markers for dementia (e.g., apolipoprotein E [*APOE*] ε4 genotype, hypertension) and that neuroimaging-based dementia markers (such as β-amyloid levels, hippocampal volume) are not collected in this study due to feasibility and cost issues. Those measures will, however, be collected in the AGE-Well Study, which is also part of the Medit-Ageing project. Despite minimal collection of biomarkers, we will store whole blood and plasma samples for future analyses as novel blood-based biomarkers are found and refined and will make use of a number of behavioral and psychiatric risk factors that will be measured in SCD-Well (e.g., depressive symptoms, poor sleep).

In summary, the SCD-Well study aims to test whether mindfulness-based training can be regarded as an alternative approach to reduce anxiety and maintain mental health and well-being in older age. If mindfulness-based training can promote healthy aging in people with SCD, it will offer a novel and alternative therapeutic and preventive approach for a population who currently lacks treatment options.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trci.2018.10.010.

RESEARCH IN CONTEXT

1. Systematic review: Older adults with subjective cognitive decline (SCD) report concerns about self-perceived cognitive decline but appear normal on assessment. SCD is associated with increased risk for dementia and also increased anxiety symptoms. Database searches for clinical trials indicate that few nonpharmacologic interventions have been trialed for patients with SCD, and those that have are often unicentric, small, have no active control condition, and/or no longitudinal follow-up.
2. Interpretation: SCD-Well is the first large-scale, multicountry randomized controlled trial with a long-term follow-up in older adults with SCD. It assesses for the first time the effects of an 8-week mindfulness-based intervention compared to a health education program on anxiety symptoms and measures of psychological, cognitive, social, and biological functioning.
3. Future directions: SCD-Well will provide evidence on whether a mindfulness-based intervention can reduce anxiety and other dementia risks. It will inform future trials and strategies to improve mental health and prevent cognitive decline in SCD.

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