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Computerised cognitive training tools and online nutritional group counselling for people suffering from mild cognitive impairment: Study protocol of a completely digital, randomised, controlled clinical trial

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ABSTRACT

Introduction

People with mild cognitive impairment (MCI) are at increased risk of decreasing cognitive functioning. Computerised cognitive training (CCT) and nutrition have been shown to improve the cognitive capacities of people with MCI. For each variable, we developed two kinds of interventions specialised for people with MCI (CCT: 'individualised' CCT [iCCT]; nutrition: a whole-food, plant-based diet [WFPB diet]). Additionally, there are two kinds of active control measures (CCT: 'basic' CCT [bCCT]; nutrition: a healthy diet following the current guidelines of the German Nutrition Society). The aim of the present study is to investigate the effects of the two interventions on cognition in people with MCI in a 2x2 randomised controlled clinical trial with German participants.

Methods and analysis

Participants will be community-dwelling individuals with a psychometric diagnosis of MCI based on the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). With N = 200, effects with an effect size of $f \geq 0.24$ (comparable to Cohen's $d \geq 0.48$) can be detected. Screening, baseline, t6, and t12 testing will be conducted via a videoconferencing assessment, telephone, and online survey. Participants will be randomly allocated to one of four groups and will receive a combination of CCT and online nutritional counselling. The CCT can be carried out independently at home on a computer, laptop, or tablet. Nutrition counselling includes 12 online group sessions every fortnight for 1.5 hours. The treatment phase is six months with follow-ups after six and 12 months after baseline.

Ethics and dissemination

All procedures were approved by the Friedrich-Alexander-University Erlangen-Nuremberg Ethics Committee (Ref. 21-318_1-B). Written informed consent will be obtained from all participants. Results will be published in peer-reviewed scientific journals, conference presentations.

Registration details

ISRCTN, ISRCTN10560738, prospectively registered 23 November 2021, https://doi.org/10.1186/ISRCTN10560738

Keywords

Mild cognitive impairment; community-dwelling; computerised cognitive training; plant-based nutrition; randomised controlled trial

ARTICLE SUMMARY

Strengths and limitations of this study

- This study is being conducted completely remotely: videoconferencing assessments with valid telehealth assessments for cognitive function, telephone-based interviews, computerised cognitive test battery, computerised cognitive training, and online nutritional group counselling.
- Randomised controlled trial with two interventions with an active control group for each component and longitudinal character of the study with an intervention period of six months, follow-ups after six and 12 months, and an open phase (planned) in which study participants might be assessed once a year.

- Individualised computerised cognitive training for the intervention group by means of a machine learning system that chooses computerised exercises that match the person's level of difficulty by estimating the person's likelihood of successfully solving the computerised exercises ('individualised' CCT).
- Highly innovative curricular nutrition intervention based on current clinical evidence, tailored for people with MCI
- Methodological limitations might include a restriction to participants who feel comfortable with the use of technology; have internet access and own a computer, laptop, or tablet; and have MCI as their only a psychometric diagnosis without a clinical diagnosis.

INTRODUCTION

In the general population, the prevalence of mild cognitive impairment (MCI) defined by Petersen [1] increases with age, at 6.7% for ages 60 to 64 and up to 25.2% for ages 80 to 84 [2]. People with MCI have a higher risk of progressing to dementia than cognitively normal individuals [1, 3]. For example, Inui et al. [4] found that 72% of patients with amnestic MCI progressed to Alzheimer's disease over five years. Thus, MCI seems to be the optimal period for intervention before a conversion to dementia occurs.

There is currently no high-quality evidence to support pharmacological treatments for MCI [2]. However, there is ample evidence showing that cognitive training is a significant modifiable risk factor for MCI or dementia [5-11]. Only recently, a systematic review and meta-analysis concluded that evidence-based suggestions on AD prevention include cognitive activity [12]. Computerised cognitive training (CCT) is an effective alternative to paper-and-pencil cognitive training with comparable or better effect sizes in cognitively healthy community-dwelling older adults [13]. One important advantage is that the participants get instant feedback. Moreover, CCT can be custom-tailored for each participant while adapting task difficulty to individual performance [14]. A considerable amount of research evaluating the effects of CCT for people with MCI has been done during the last decade [15]. Various systematic reviews and meta-analyses of CCT intervention studies have already demonstrated positive (even though sometimes just moderate) effects on improving the cognitive capacity of people with MCI [15-20], e.g. with Hedges' g = from 0.23 to 0.52 for global cognitive functioning [15, 16, 20].

Nutritional therapy is an essential part of medicine with clinical implications for a large number of disciplines. 70% of all chronic diseases are in some way associated with diet [21]. Cohort studies and randomised controlled trials (RCT) have demonstrated beneficial effects of nutrition on cognitive functioning, especially related to three types of diet: the

Mediterranean Diet (MedDiet), the *Dietary Approaches to Stop Hypertension* (DASH Diet), and the *Mediterranean-DASH Intervention for Neurodegenerative Delay* (MIND Diet) [22-25]. All three abovementioned diets are predominantly whole-food plant-based diets, primarily containing vegetables, whole grains, legumes, fruits, nuts, and seeds, are rich in poly- and monounsaturated fatty acids, and contain hardly any processed foods [26]. Furthermore, the diets are associated with reductions in various inflammatory markers [27-29]. Since MCI seems to be accompanied by inflammatory processes [30], and exclusively plant-based foods contain bioactive substances, such as phytochemicals and fibre, which have anti-inflammatory properties [31], there is an obvious need to further investigate potential neuroprotective effects of plant-based nutrition in the context of clinical MCI studies. Since cardiometabolic diseases are associated with the occurrence of dementia [32], and weight loss is associated with improved attention and memory performance [25], it can be hypothesised that a well-planned anti-inflammatory, neuroprotective, plant-based diet has the potential to alleviate symptoms of MCI and the progression to dementia.

The aim of the proposed study is to examine the effects of CCT and online nutritional group counselling on the cognition of people with MCI in a completely digital randomised controlled trial. We developed CCT and online nutritional group counselling, both specialised for people with MCI: individualised CCT (iCCT) and nutritional group counselling focusing on a whole-food, plant-based (WFPB) diet. Additionally, there are two active control measures: basic CCT (bCCT) and nutritional group counselling focusing on a healthy diet recommended by the German Nutrition Society (Deutsche Gesellschaft für Ernährung, DGE diet). This manuscript describes the study protocol while following the evidence-based reporting guidelines of the SPIRIT Statement [33].

METHODS AND ANALYSES

Aims and hypothesis

Research hypotheses

Primary hypothesis I: Individualised CCT will lead to statistically significantly greater improvements in cognitive capacities during the intervention period of six months compared with basic CCT.

Primary hypothesis II: Online nutritional group counselling focusing on a WFPB diet will lead to statistically significantly greater improvements in cognitive capacities during the intervention period of six months compared with online nutritional group counselling focusing on a healthy diet recommended by the German Nutrition Society.

Secondary hypothesis: Individualised CCT in combination with online nutritional group counselling focusing on a WFPB diet will have a positive interaction effect. The group with iCCT in combination with online nutritional group counselling focusing on a WFPB diet will show more cognitive improvements than all other groups during the intervention period of six months in people with MCI.

Exploratory study question

Are there changes in the course of depression and activities of daily living during the 12-month observation period?

Study design and setting

A prospective 2x2 randomised controlled clinical intervention study is being conducted to test the abovementioned hypotheses. The overall start date of the study was on 01 June 2021. Recruitment will begin on 3 January 2022 and will continue until 30 June 2022. Because the study is being conducted completely remotely, individuals from all over Germany can

participate. At baseline, all study participants will be randomly assigned to one of four intervention arms (combination of iCCT or bCCT and group counselling on WFPB diet or DGE diet). The CCT intervention is double-blind, the online nutritional group counselling is single-blind. Since the principal usefulness of CCT is well-known [15-20], it would be unethical to use a control group without any CCT. After baseline testing (t0), the participants will receive one of the two computerised training applications for their computer, laptop, or tablet. It is recommended that they use the application at least 30 minutes per day three days a week during the six-month intervention phase. Both computerised training applications contain the same computerised cognitive test battery (ccTB) that will be delivered and collected once a month (t0-t12). After the end of the six-month intervention phase, all participants will be free to continue to use the application. The online nutritional group counselling sessions will focus on either a WFPB diet or a DGE diet. Both groups will receive curricular online nutritional group counselling at regular 14-day intervals for 1.5 hours (twelve appointments total per participant over a period of six months, online group setting in a fixed group, max. 20 participants per group). The intervention phase is from t0 to t6. Follow-up is planned after six (t6) and 12 (t12) months. The open phase of the study will begin after t6 in order to test the hypotheses and exploratory study questions until t12. A follow-up study is planned to observe the participants after t12. Table 1 contains the trial registration data.

190 Table 1 – Trial registration data

Data category	Information
1. Primary registry and trial identification number	ISRCTN
2. Date of registration in primary registry	23 November 2021
3. Secondary identifying numbers	-
4. Source(s) of monetary or material support	Karl and Veronica Carstens-Stiftung
5. Primary sponsor	Karl and Veronica Carstens-Stiftung
6. Secondary sponsor(s)	-
7. Contact for public queries	see point 8
8. Contact for scientific queries	Prof. Dr. Elmar Graessel, elmar.graessel@uk-erlangen.de PD Dr. Christian Kessler, M.A., christian.kessler@charite.de
9. Public title	BrainFit-Nutrition: Intervention study for people suffering from mild cognitive impairment using computerised cognitive training tools and a nutrition intervention
10. Scientific title	Computerised cognitive training tools and online nutritional group counselling for people suffering from mild cognitive impairment: Study protocol of a completely digital, randomised, controlled clinical trial
11. Countries of recruitment	Germany
12. Health condition(s) or problem(s) studied	Mild cognitive impairment (MCI)
13. Intervention(s)	Participants will be randomly allocated to one of four groups with two intervention variables (BrainFit and Nutrition): 1. BrainFit: two versions of CCT: individualised (iCCT), which involves targeted exercises for memory span, information processing, visual-spatial cognition, etc.; and basic (bCCT), which involves basic exercises for memory span, information processing, visual-spatial cognition, etc. 2. Nutrition: two types of nutritional interventions: a WFPB diet and a healthy diet recommended by the German Nutrition Society (DGE).

14. Key inclusion and exclusion criteria	Inclusion criteria: 1. MCI 1.1. Montreal Cognitive Assessment score (MoCA) ≤ 24 1.2. Mini-Mental State Examination score (MMSE) ≥ 24 2. The digital applications and examinations require a PC with microphone and camera (Windows/Linux/MacOS), laptop, or an Android tablet and basic skills in their use and access to the internet 3. Age ≥ 60 4. Informed consent given
	Exclusion criteria: 1. Completely blind or deaf 2. No personal computer, laptop, or tablet 3. Normal cognition, MoCA > 24 4. Dementia, Mini-Mental State Examination score < 24 5. Depression, Patient Health Questionnaire 9 score ≥ 12 6. Diagnosis of another disease that causes cognitive impairment: • Psychosis (schizophrenia, mania, bipolar psychosis) • Morbus Parkinson • Multiple sclerosis • Multiple strokes • Alcohol abuse / drug consummation (addiction) • Severe brain disease (tumour, injury, hydrocephalus) • Severe vitamin B deficiencies
15. Study type	Prospective double-blind randomised controlled clinical intervention study
16. Date of first enrolment	Starting on 03 January 2022
17. Target sample size	200
18. Recruitment status	Not yet recruiting
19. Primary outcome(s)	Cognition measured by the Montreal Cognitive Assessment (MoCA) at baseline and after six months Cognition measured by the computerised cognitive test battery (ccTB) integrated in the digital software at baseline and after 6 and 12 months
20. Key secondary outcomes	Cognitive Function measured by the Mini-Mental State Examination (MMSE) at baseline and after 6 and 12 months Depression measured by the Patient Health Questionnaire 9 (PHQ-9) at baseline and after 6 and 12 months Activities of daily living measured by the Bayer Activities of Daily Living Scale (B-ADL) at baseline and after 6 and 12 months

Data will be collected by means of psychometric tests and structured interviews using videoconferencing, telephone, and an online survey. The data will be collected by trained student assistants who have no knowledge of group allocation at any time. Two days before baseline testing (t0), the study participants will receive an email with a link to download the software for their version of the computerised application and instructions on how to download and install the software.

Sample size estimation

A power analysis was computed with 200 participants distributed to the two groups of the 2x2x2 factorial variance-analytic experimental design with one repeated measure (factor 1: two CCTs; factor 2: two types of online training for dietary modification, factor 3: two time points). With 50 participants in each group, alpha = 0.05, beta = 0.20 (corresponding to a power of 80%), a correlation between repeated measures of 0.5, and a nonsphericity correction of 1, we will have the power to detect effects with an effect size of $f \geq 0.24$ (comparable to Cohen's $d \geq 0.48$).

Recruitment strategies

Participants will be recruited from the general population all over Germany. The project's homepage was designed to provide information about the study. Also, an appointment for a screening can be made via the project homepage. We partnered with a health insurance company that is sending emails to their members aged 60 and above with information about the study and a link to the project homepage. About 25 thousand members will receive an email with information about the study in six waves between December 2021 and May 2022.

Eligibility of participants

Individuals who are interested in the study can make an appointment for a screening via the project homepage. During the screening, we will offer an examination of basic cognitive

functioning including a personal conversation about their screening results afterwards. Individuals who fulfil the criteria for inclusion will be informed about the study and asked to take part in the project.

Criteria for inclusion are: (1) MCI, psychometrically operationalised by a score on the Montreal Cognitive Assessment (MoCA) ≤ 24 (cut-off for cognitive impairment) and at the same time a score on the Mini-Mental State Examination (MMSE) ≥ 24 (cut-off for no dementia), (2) possession of a computer (Windows/Linux/MacOS) with microphone and camera, laptop, or Android tablet with access to the internet and basic skills in their use, (3) age ≥ 60, and (4) informed consent. Criteria for exclusion are (1) completely blind or deaf, (2) no personal computer, laptop, or tablet with access to the internet, (3) normal cognition, operationalised by a score on the MoCA > 24, (4) dementia, operationalised by a score on the MMSE < 24, (5) acute depression, operationalised by a score on the 9-Item Patient Health Questionnaire (PHQ-9) ≥ 12, or (6) other psychiatric or neurologically diagnosed diseases (checklist): psychosis (schizophrenia, major depression, mania, bipolar psychosis), Parkinson's disease, multiple sclerosis, several strokes, alcohol abuse/drug abuse (addiction), other serious brain disease (especially brain tumour, brain injury, hydrocephalus), or severe vitamin B deficiency.

The MMSE and the MoCA will be administered in combination to differentiate between normal cognition, MCI, and dementia. The MoCA will be administered first to differentiate between normal cognition and MCI on the basis of the cut-off score of 24 points [34-36]. The MMSE will be administered to differentiate between MCI and dementia on the basis of the cut-off score of 23 points [37]. For these cut-offs, we will look for an optimised ratio of sensitivity and specificity. The criteria for a positive screening for MCI, normal cognition, or dementia are shown in Table 2.

Table 2 – Definition of MCI

	Normal cognition	MCI	Dementia
Step 1: MoCA	30-25	24-0	24-0
Step 2: MMSE*	-	30-24	23-0
Decision	**Exclusion**	**Inclusion**	**Exclusion**

Abbreviations. MCI: Mild cognitive impairment; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination. * The MMSE will be applied only when the MoCA results are in the range of 24 to 0 points.

Randomisation

Our external biostatistics partner is creating computer-generated randomisation lists (Institute of Medical Informatics, Biometry, and Epidemiology, Friedrich-Alexander University Erlangen-Nürnberg, Waldstraße 6, 91054 Erlangen). All individuals meeting the inclusion criteria will be randomised into one of the four groups (combination of the CCT component: iCCT or bCCT and the online nutritional group counselling component: WFPB diet or DGE diet). Randomisation will be stratified by sex, age, MoCA score at screening. Couples will be assigned to the same group. Participants will not know which treatment condition they are in, and the student assistants who assess the outcomes of the study will be blind to participants' allocation at all times.

Interventions

Computerised cognitive training

Both computerised applications (intervention and control) are available for Windows, MacOS, and Linux PC/laptop and Android tablet.

Individualised CCT for people with MCI

The exercises included in this training application have been selected to address the expected level of performance of people with MCI. All exercises are available with different levels of

difficulty. The ten playful exercise tasks involve the basic parameters of information processing as well as short-term memory and require different types of decision-making (see Table 3). The initial difficulty levels of the exercises are determined by a machine-learning system, which uses (a) a (logistic regression) model that is based on data from people with MCI (individualised by considering each participant's data) and (b) the cognitive status of the participant (i.e. the results of the integrated computerised cognitive test battery) to estimate the likelihood of a participant's success at a certain difficulty level for a task. The initial model is based on data collected prior to the study. The application chooses the highest level the participant is likely to solve as the entry level. With the machine learning system, individual (compensation) strategies are nullified, and the ideal level of difficulty for training is generated for each participant. Thus, the iCCT is aimed at improving the beneficial effects of CCT by providing exercises at the difficulty level that fits each participant best.

Basic CCT (active control group)

This training application uses exercise tasks that are oriented towards quizzes and visual tasks (see Table 3). The exercise tasks are playfully designed and require, among other things, simple strategies and long-term memory. Most of the exercises exist with only a single level of difficulty. The entry-level difficulties of the other exercises are determined solely by the participant's prior successful results on this exercise. The exercises of the bCCT are aimed at providing enjoyable computerised leisure activities with a limited number of cognitive tasks for the active control group.

281 Table 3 – Computerised cognitive exercises

CCT application	Group of tasks	Explanation	Key function	Cognitive domain (DSM-5)
individualised CCT	Finding targets (‘Punkte sammeln’)	For a set of pop-up pictures, participants must click on target pictures before they disappear	Sustained attention	Complex attention
	Applying rules (‘Regel anwenden’)	Select the winner or loser of a rock-paper-scissors game (either hand signs or in written form); if the game is presented with hand signs, the participant has to pick the winner; if presented with words, the loser has to be picked; this exercise has a time limit, depending on difficulty	Mental/cognitive flexibility	Executive function
	Layer sorting (‘Ebenen sortieren’)	A target picture of a vase with flowers is presented; the participant has to reproduce the picture out of layers; easiest: background – foreground, up to 5 layers with distractors	Visuoconstructional reasoning	Perceptual-motor
	Jigsaw puzzle (‘Bild zusammensetzen’)	Sorting of image sections	Visuoconstructional reasoning	Perceptual-motor
	Fill in the gaps (‘Felder füllen’)	A grid has to be filled in according to rules; each symbol is used only once in every row, column, and block; layout 4x4 to 9x9 fields	Working memory	Executive functions
	Remember cards (‘Karten merken’)	Remember a row of (up to 5) cards; compare new card with 5th to last card	Working memory	Executive functions
	Find pairs (‘Paare finden’)	Finding pairs of images in a pool; images covered; each turn two cards can be turned over	Visuo-spatial memory	Perceptual-motor

	Spot the difference (‘Unterschied erkennen’)	A set of x identical pictures is presented, after a blank, the set and 1 extra picture are presented; the extra picture has to be selected	Visual perception	Perceptual-motor
	Pattern recognition (‘Schema erkennen’)	A matrix of elements (combination of concentric geometrical figures) is presented; in one row or column, a figure is presented in the same position in all elements; the row/column has to be found; for small difficulties, hints are given	Decision making	Executive functions
	Word conversion (‘Wörter umwandeln’)	Convert a source word to a target word in x steps; in each step, only 1 letter can be exchanged, and each line must contain a word	Word finding	Language
basic CCT	Rotating picture puzzle (‘Drehpuzzle’)	Picture is sectioned; sections are rotated; sections have to be turned in the right direction	Visuoconstructional reasoning	Perceptual-motor
	Picture quiz (‘Bilder quiz’)	Multiple-choice questions about images	Semantic and autobiographical long-term memory	Learning and memory
	Geography quiz (‘Länderspiel’)	Knowledge quiz based on German federal states	Semantic and autobiographical long-term memory	Learning and memory
	Quiz-Show (‘Wissensquiz’)	Quiz-show simulation with knowledge-based multiple-choice questions	Semantic and autobiographical long-term memory	Learning and memory

Abbreviations. CCT: computerised cognitive training.

Online nutritional group counselling

These types of counselling are based on a structured curriculum including interactive methods and teaching materials, such as handouts, cooking instructions with recipes, and feedback and nutrition-related experience exchange rounds (see Table 4). The use of different group work formats and alternating between a small-step introduction to the content and a person's own elaboration, homework, and reflection are aimed at maximizing participants' attention, participation, and adherence. Furthermore, each participant receives a monthly delivery of a packet with selected food items. These deliveries are meant to be a useful complement regarding recommended products and are intended to invite the participants to get to know new and beneficial food items.

Table 4 – Overview of the six-month online nutritional group counselling

Session	Topic
1	Basics 1: Introduction, nutritional basics
2	Basics 2: Deepening knowledge about nutrition
3	Quantitative proportions and daily planning
4	Kitchen theory: Everything about storage, preparation, baking
5	Kitchen practice: Virtual buffet and virtual live show cooking
6	Scientific background - Impact of nutrition - Proteins
7	Carbohydrates, fibre
8	Oils, fats, nuts, seeds, and drinks
9	Special nutrients, secondary plant substances, spices, age-specific nutrition
10	Circadian factors, periodic fasting
11	Mindful eating, stress, and nutrition
12	Conclusion, evaluation, repetition

Counselling focusing on a whole-food plant-based (WFPB) diet

In this group, a WFPB diet with anti-inflammatory, neuroprotective components is systematically taught and recommended as a regular diet. The WFPB diet essentially consists of vegetables, whole grains, legumes, fruits, nuts, and seeds, without restricting energy intake. In addition, the regular consumption of specific foods that have the potential to beneficially influence cognitive functions, based on current clinical evidence, is

encouraged (e.g. green leafy vegetables [38], mushrooms [39], citrus fruits [40], soy products [41], blueberries [42], nuts [43], turmeric [44], green tea [45], and omega-3 fatty acids [46]). Participants are instructed to exclude animal products from their diets because of the pro-inflammatory potential of animal products and to refrain from consuming highly processed foods [47]. Monthly delivery contains a selection of neuroprotective foods (e.g. plant oil with polyunsaturated fatty acids, nuts, whole grains, green tea).

Counselling focusing on a diet recommended by the German Nutrition Society (Deutsche Gesellschaft für Ernährung, DGE diet)

Participants in this group will receive systematic recommendations according to the official guidelines of the DGE for healthy eating [48]. This means they will be encouraged to establish an omnivorous diet based on vegetables, fruits, and whole grains, including moderate intake of animal products, such as fish, poultry, red meat, eggs, and milk products. The DGE group will also be encouraged to prefer fresh, whole-food, non-processed foods and to reduce their consumption of saturated fatty acids, sweetened drinks, or highly processed foods [48, 49]. Eating products coming from animals is also limited within the DGE context with a greater focus on vegetables, fruits, and whole-grain cereals or bread. The delivery boxes will contain a selection of DGE-appropriate basic foods beneficial to health (e.g. whole grain, plant-based oils or nuts/seeds, sugar alternatives, foods that are not very processed, vegetarian alternatives).

Measures

The data are being collected at baseline and follow-up by student assistants (psychology students) who are well-trained to conduct performance tests and interviews via an online survey. The measures that are being used at the different measurement points are shown in Figure 1.

Primary outcome measure

Montreal Cognitive Assessment (MoCA) [50]. The MoCA is a performance test that is used to screen for MCI. It consists of more difficult items than the MMSE and is thus able to better detect MCI [50-53]. The score ranges from 0 to 30 points, with higher scores indicating better cognitive performance. A score ≤ 24 indicates cognitive impairment [34-36]. There are three parallel versions of the MoCA currently available. The MoCA has been found to be an appropriate measure for cognitive screening and has good reliability and validity values [54].

Computerised cognitive test battery (ccTB). **Both versions of the computerised training application contain a set of exercises for measuring different cognitive abilities monthly, beginning at baseline. Eight tests are used to measure various cognitive abilities (see Table 4).**

Table 5 – Computerised cognitive test battery

Test	Description	Adaptation of
Memory span I: Digit span, unsorted (‘Zahlen merken – unsortiert’)	Rows of single digit numbers are presented (each for 1 second); the numbers must be reproduced immediately afterwards	WAIS-IV [55], task Digit Span
Memory span II: Digit span, ascending (‘Zahlen merken – aufsteigend’)	Like Memory span I; numbers must be reproduced in ascending order	WAIS-IV [55], task Digit Span
Processing speed I: Number Comparison (‘Zahlen vergleichen’)	Comparison of two single-digit numbers separated by a horizontal line (participants should react if same number)	Pattern Comparison\Letter Comparison [56]
Processing speed II: Symbol count (‘Symbole zählen’)	Counting a target symbol in a pool as fast as possible	SKT [57], task ‘counting symbols’
Processing speed III: Numerical Stroop task (‘numerischer Stroop-Test’)	Two single-digit numbers are presented in different sizes (congruent/incongruent mixed);	Numerical stroop task [58, 59]

	number with higher value must be clicked as quickly as possible	
Short term memory I: Free recall ('Wortliste – Erinnern')	12 objects have to be named; afterwards shown for 1 minute; some tests later, the objects must be remembered	SKT [57], task 'delayed recall'
Short term memory II: Cued recall ('Wortliste – erkennen')	The objects from Short term memory I must be selected from a selection of 16 objects	SKT [57], task 'recognition recall'
Logical reasoning: Matrices Test ('Matrizentest')	In a (2x2 or 3x3) matrix of symbols, the bottom right symbol is missing; the composition rule has to be understood, and the correct symbol must be selected	Raven's Standard Progressive Matrices [60]

Abbreviations: SKT: Syndrom-Kurz-Test (Engl. Short Cognitive Performance Test); WAIS-IV: Wechsler Adult Intelligence Scale – Fourth Edition.

Secondary outcome measures

Mini-Mental State Examination (MMSE) **[61]. The MMSE is the most frequently employed screening test for dementia [62]. It measures five areas of cognitive functioning: orientation, registration, attention and calculation, recall, and language. The score ranges from 0 to 30 points, with higher scores representing better cognitive performance. Values above 23 points are interpreted as 'not demented', whereas scores between 0 and 23 indicate a dementia syndrome [37]. The reliability and validity of the MMSE has been established in numerous studies, e.g. [37, 63, 64].**

The 9-Item Patient Health Questionnaire (PHQ-9) [65, 66]. The PHQ-9 is a short self-assessment tool often used in primary care settings to screen for depression [67]. Its nine items cover the nine DSM-IV criteria by asking patients about their experiences during the last two weeks and are rated on a four-point scale ranging from 0 ('not at all') to 3 ('nearly every day'). The total sum score suggests varying levels of depression. A cut-off ≥ 12 was found to show a good balance between sensitivity and specificity [68]. The PHQ-9 was found to be a reliable and valid instrument for screening for depression [65].

The Bayer Activities of Daily Living Scale (B-ADL) [69]. The B-ADL assesses difficulties in the performance of everyday activities. It comprises 25 items, which evaluate general ADL competencies and specific tasks important for management in everyday life. The frequency of difficulties the patient experiences in performing everyday activities is rated on a 10-point scale ranging from 1 ('never') to 10 ('always'). A global score is computed by summing across all items and dividing by the number of items rated. The resulting score ranges from 1 to 10 with higher scores corresponding to more severe deficits.

Other variables

Questionnaire on sociodemographic and health-related data. The following data from a standardised questionnaire will be recorded by the student assistants at baseline: sociodemographic data (age, sex, marital status, highest educational level, employment status, monthly income, household size), modifiable risk factors for MCI (status of general mental activities, physical activities, social participation, sleeping habits, average liquid intake, eating habits, alcohol consumption, nicotine consumption, visual/hearing capacity), and health-related data (diseases, medications, body weight, body height, dementia cases in the family).

User Experience Questionnaire (UEQ) [70]. The UEQ measures attractiveness, perspicuity, efficiency, dependability, stimulation, and novelty of software with 26 bipolar items. The questionnaire consists of pairs of contrasting attributes (e.g. 'understandable' vs. 'not understandable') that can be rated on a 7-point Likert scale. The UEQ was found to show a satisfactory level of reliability and construct validity [70].

Additional digital data. Both CCTs track usage data. The usage data include the duration of use, difficulty, success, and other parameters for each training task run.

Online Food Frequency Questionnaire (FFQ) [71]. A modified FFQ of the DEGS1-Survey from the Robert Koch Institute will be assessed as an online survey

(https://www.rki.de/DE/Content/Gesundheitsmonitoring/Studien/Degs/degs_node.html). It consists of questions about dietary behaviour from the past 4 weeks (on average), containing all relevant plant-based and animal-based foods as well as neuroprotective ingredients, to estimate the frequency of the consumption of different food groups.

Weighing protocol. A non-obligatory weighing protocol (3 days: 2 working days/1 weekend day) will be emailed and is to be completed and scanned back or completed online.

Data collection

The data will be collected at baseline (t0) and at follow-up after six (t6) and 12 months (t12) (see Figure 1). Annual follow-up studies will test for conversions to dementia. The trial will be conducted remotely. All data will be generated via videoconferencing, telephone, online survey, or the ccTB that is integrated into the CCTs.

Testing with the MoCA and MMSE will be conducted via videoconferencing with the student assistants. Videoconferencing assessments with the MoCA and MMSE have very high reliability scores compared with face-to-face testing. The intraclass correlation coefficients (ICCs) for the MoCA and the MMSE have been demonstrated in several studies and go up to ICC = 0.99 for the MoCA [72] and up to ICC = 0.92 for the MMSE [73]. In a recent systematic review [74], the MoCA and the MMSE were described as valid telehealth measures for screening cognitive status. Telemedicine is an emerging new field, and there is evidence that it is a valuable tool for assessing neurodegenerative diseases [74-76].

The questionnaire on sociodemographic and health-related data will be sent to the study participants to prepare them for the interview. The FFQ online survey and the non-obligatory weighing protocol will be emailed to participants and are to be completed and scanned back or completed online. The evaluation will be done pseudonymously via nutrition software with a food database (NutriGuide) to support the accuracy of the FFQ survey. During the six-month intervention period, the data collected by the CCT, including

the ccTB data, will be obtained from the participants. After the monthly ccTB assessment, consent to upload the CCT data will be requested. When consent is given, the data will be uploaded to the Erlangen study centre's server. The server configuration prohibits downloads of the data by people who are not study team members. The data will be pseudonymised.

Data quality management and data protection

The student assistants involved in the study have been thoroughly trained for their tasks by the study centre's staff. When the participants have questions concerning the computerised interventions or the online nutrition groups, they can email the study centre. The quality of the data will be guaranteed by strict data monitoring at the study centre for the total study period. Plausibility checks and logical considerations of the relationships between associated variables will be performed. A data protection concept was developed and was reviewed and approved by the data protection officer of the University Hospital Erlangen.

Patient and public involvement

Study participants or the public will not be involved in developing, designing, or conducting the study. To recruit participants from the general population, our recruitment partner, a health insurance company, will send emails to their customers with information about our study. Additional information about the study can be found on the project homepage.

Data Analysis

All relevant data, sociodemographic, health-related, primary, and secondary outcome variables will be reported descriptively. In order to be able to assess the quality of the randomisation, the baseline data from the intervention and control groups will be tested for statistically significant differences. For the multivariate analyses, we will impute missing values using the expectation maximization algorithm. The primary hypothesis will be tested via ANOVA, which makes it possible to detect interaction effects in the chosen 2x2x2

factorial design. To ensure the robustness of the results, we will perform both intention to treat and per protocol analyses. Intention to treat evaluations are carried out with all cases still alive at the end of the intervention or observation period. The significance level is defined as alpha = 0.05. The data analyses will be performed using the IBM SPSS Statistics 28 software.

ETHICS AND DISSEMINATION

Ethical considerations

All procedures were approved by the Friedrich-Alexander-University Erlangen-Nuremberg Ethics Committee (Ref. 21-318_1-B). Participation will be voluntary, and participants will be free to leave the study at any time. All legal matters, such as voluntariness, right of revocation, and General Data Protection Regulation (EU) are considered. People with MCI are independent and fully capable of conducting business and giving consent. Upon agreement, consent to participate (written informed consent) will be obtained from all participants by the student assistants who are members of the study centre. All participants will be informed about the study in a personal videoconference after they are screened for eligibility. A participant information sheet including important information about participation (e.g. randomisation, data protection, data storage) will be given to every participant (sent by post). The opportunity to ask questions will be granted by videoconference, telephone, and email afterwards at any time. Participants will not be offered any financial inducement to participate. The external funder, the Karl and Veronica Carstens-Stiftung, is continuously being informed about the progress of the study. In the case of important protocol modifications, we will inform the Ethics Committee, the funder, and the trial registry platform.

Data handling

Informed consent will be stored in a locked steel cabinet. A customized digital participant management system webMODYS (Web-based modular control and documentation system; Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen, Germany) will be used for the administration of the study and will be the only location for personal data. webMODYS is hosted in the IT infrastructure of the University Hospital Erlangen. Only members of the study team will have access to the lists of participants' names and codes in webMODYS. All data will be stored in only a pseudonymised form digitally in the data collection system REDCap [77, 78] hosted at the University Hospital Erlangen and Charité Berlin. REDCap is a secure, web-based software platform designed to support data capturing for research studies. The IT architecture including the digital study administration and data collection was 'inspired' by the digiDem Bayern Registry [79]. Results of the study for scientific or other publications will be published only in aggregate form (mean values, etc.). No published material will contain patient-identifying information.

Safety considerations

The CCT applications might have an impact on existing excessive computer use. However, both CCT applications that we developed are not based on motivational or emotional components. The CCT applications require cognitive performance, which could instead lead to exhaustion.

Adverse effects are rare and minor in the context of dietary regimens. The following adverse effects might occur: feeling of heat, changes in mouth and/or body odour, constipation, diarrhoea, meteorism, stomach cramps, nausea, or vomiting. The two dietary recommendations are based either on the recommendations of the German Nutrition Society for a wholesome omnivorous diet or on plant-based dietary recommendations [80]. The

plant-based diet is recognised as a safe, sustainable diet for all lifestyles by various nutrition institutes [81-83].

Dissemination plan

The research group intends to publish the data generated from this study in peer-reviewed journals. In addition, results will be communicated at international conferences, national conventions with the funders, and the press.

TRIAL STATUS

Protocol version 1.0, 22 December 2021. The overall start date of the study was 1 June 2020. Recruitment will begin on 3 January 2022 and will continue until 30 June 2022.

LIST OF ABBREVIATIONS

AD: Alzheimer's disease; CCT: computerised cognitive training; ccTB: computerised cognitive test battery; ICC: intraclass correlation coefficients; B-ADL: Bayer Activities of Daily Living Scale; DGE diet: diet recommended by the German Nutrition Society (Deutsche Gesellschaft für Ernährung, DGE); FFQ: Food Frequency Questionnaire; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; PHQ-9: 9-Item Patient Health Questionnaire; RCT: randomised controlled trial; SKT: Syndrom-Kurz-Test (engl. Short Cognitive Performance Test); UEQ: User Experience Questionnaire; WAIS-IV: Wechsler Adult Intelligence Scale – Fourth Edition; WFPB diet: whole-food plant-based diet.

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Figure 1 – Timeline of measurements

*intended for a follow-up study after t12.

Abbreviations. B-ADL: Bayer Activities of Daily Living Scale; bCCT: basic computerised cognitive training; CCT: computerised cognitive training; ccTB: computerised cognitive test battery; DGE diet: diet recommended by the German Nutrition Society (Deutsche Gesellschaft für Ernährung, DGE); FFQ: Food Frequency Questionnaire; iCCT: individualised cognitive training; MCI: mild cognitive impairment; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; PHQ-9: Patient Health Questionnaire; UEQ: User Experience Questionnaire; WFPB diet: whole-food plant-based diet.

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Authors' contributions

PS contributed to the design of the study, is supervising the study, is contributing to the implementation of the study, and drafted the manuscript. SB contributed to the design of the study, is supervising the study, is contributing to the implementation of the study, and drafted the manuscript. MJ designed the CCT applications, is contributing to the implementation of the study, and drafted parts of the manuscript. EH is contributing to the implementation of the study and drafted parts of the manuscript. MDO designed the nutrition intervention and is contributing to the implementation of the study. JS designed the nutrition intervention and is contributing to the implementation of the study. MJe contributed to the design of the study and is supervising the study. JSS is supervising the study and contributing to the implementation of the study. SoB is contributing to the psychometric examinations and supervising the student assistants. CK initiated the study, contributed to the design of the study, and is supervising the study. EG initiated the study, contributed to the design of the study, is supervising the study, and drafted parts of the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests statement

The authors report no conflicts of interest.

Data availability statement

For this study protocol, no datasets have been generated yet.

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Date and version identifier

Issue date: 22.12.2021

Protocol amendment number: Original

Revision chronology:

22.12.2021
Original

			STUDY PERIOD								
	Enrolment	Allocation	Post-Allocation								
	-t1	0	t_0	t_1	t_2	t_3	t_4	t_5	t_6	t_{12}	t_x*
ENROLMENT											
Eligibility screening	x										
Informed consent	x										
Allocation		x									
INTERVENTION											
iCCT			◆	—	—	—	—	—	◆	- - -	◆
bCCT			◆	—	—	—	—	—	◆	- - -	◆
WFPB diet			◆	—	—	—	—	—	◆	- - -	◆
DGE diet			◆	—	—	—	—	—	◆	- - -	◆
ASSESSMENTS											
Baseline Variables											
Inclusion and exclusion criteria	x										
Primary Outcomes											
Cognitive function: MoCA	x		x						x	x	x
ccTB			x	x	x	x	x	x	x	x	
Secondary Outcomes											
Cognitive function: MMSE	x		x						x	x	x
Depression: PHQ-9	x		x						x	x	x
Activities of daily living: B-ADL			x						x	x	x
Other Variables											
Sociodemographic data			x								
Health-related data			x						x		
Modifiable risk factors for MCI			x						x		
Usability: UEQ									x		
Dietary behaviour: FFQ			x						x	x	
Weighing protocol (optional)						x					

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	Table 1 (9-11)
Protocol version	3	Date and version identifier	36
Funding	4	Sources and types of financial, material, and other support	35-36
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 35
	5b	Name and contact information for the trial sponsor	35
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	35
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8-9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10-11; 12-13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-19
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	20-23
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	23-24
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	24

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	26-27
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	24-25
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	24-25
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	24-25
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	26
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	26-27
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable, 35
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	25
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	25

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4, 25
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	26-27
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	35
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	26
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	27
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Computerised cognitive training tools and online nutritional group counselling for people with mild cognitive impairment: Study protocol of a completely digital, randomised, controlled trial

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Computerised cognitive training tools and online nutritional group counselling for people with mild cognitive impairment: Study protocol of a completely digital, randomised, controlled trial

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Computerised cognitive training tools and online nutritional group counselling for people with mild cognitive impairment: Study protocol of a completely digital, randomised, controlled trial

ABSTRACT

Introduction

People with mild cognitive impairment (MCI) are at increased risk of decreasing cognitive functioning. Computerised cognitive training (CCT) and nutrition have been shown to improve the cognitive capacities of people with MCI. For each variable, we developed two kinds of interventions specialised for people with MCI (CCT: 'individualised' CCT [iCCT]; nutrition: a whole-food, plant-based diet [WFPB diet]). Additionally, there are two kinds of active control measures (CCT: 'basic' CCT [bCCT]; nutrition: a healthy diet following the current guidelines of the German Nutrition Society). The aim of the present study is to investigate the effects of the two interventions on cognition in people with MCI in a 2x2 randomised controlled trial with German participants.

Methods and analysis

Participants will be community-dwelling individuals with a psychometric diagnosis of MCI based on the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). With $N = 200$, effects with an effect size of $f \geq 0.24$ (comparable to Cohen's $d \geq 0.48$) can be detected. Screening, baseline, t6, and t12 testing will be conducted via a videoconferencing assessment, telephone, and online survey. Participants will be randomly allocated to one of four groups and will receive a combination of CCT and online nutritional counselling. The CCT can be carried out independently at home on a computer, laptop, or

tablet. Nutrition counselling includes 12 online group sessions every fortnight for 1.5 hours. The treatment phase is six months with follow-ups after six and 12 months after baseline.

Ethics and dissemination

All procedures were approved by the Friedrich-Alexander-Universität Erlangen-Nürnberg Ethics Committee (Ref. 21-318_1-B). Written informed consent will be obtained from all participants. Results will be published in peer-reviewed scientific journals, conference presentations.

Registration details

ISRCTN, ISRCTN10560738, prospectively registered 23 November 2021, https://doi.org/10.1186/ISRCTN10560738

Keywords

Mild cognitive impairment; community-dwelling; computerised cognitive training; plant-based nutrition; randomised controlled trial

ARTICLE SUMMARY

Strengths and limitations of this study

- This study is being conducted completely remotely: videoconferencing assessments with valid telehealth assessments for cognitive function, telephone-based interviews, computerised cognitive test battery, computerised cognitive training, and online nutritional group counselling.
- Randomised controlled trial with two interventions with an active control group for each component and longitudinal character of the study with an intervention period

of six months, follow-ups after six and 12 months, and an open phase (planned) in which study participants might be assessed once a year.

- Individualised computerised cognitive training for the intervention group by means of a machine learning system that chooses computerised exercises that match the person's level of difficulty by estimating the person's likelihood of successfully solving the computerised exercises ('individualised' CCT).
- Highly innovative curricular nutrition intervention based on current clinical evidence, tailored for people with MCI
- Methodological limitations might include a restriction to participants who feel comfortable with the use of technology; have internet access and own a computer, laptop, or tablet; and have MCI as their only psychometric diagnosis without a clinical diagnosis.

INTRODUCTION

In the general population, the prevalence of mild cognitive impairment (MCI) defined by Petersen [1] increases with age, at 6.7% for ages 60 to 64 and up to 25.2% for ages 80 to 84 [2]. People with MCI have a higher risk of progressing to dementia than cognitively normal individuals [1, 3]. For example, Inui et al. [4] found that 72% of patients with amnestic MCI progressed to Alzheimer's disease (AD) over five years. Thus, MCI seems to be the optimal period for intervention before a conversion to dementia occurs.

There is currently no high-quality evidence to support pharmacological treatments for MCI [2]. However, there is ample evidence showing that cognitive training is a significant modifiable risk factor for MCI or dementia [5-11]. Only recently, a systematic review and meta-analysis concluded that evidence-based suggestions on AD prevention include cognitive activity [12]. Computerised cognitive training (CCT) is an effective alternative to paper-and-pencil cognitive training with comparable or better effect sizes in cognitively healthy community-dwelling older adults [13]. One important advantage is that the participants get instant feedback. Moreover, CCT can be custom-tailored for each participant while adapting task difficulty to individual performance [14]. A considerable amount of research evaluating the effects of CCT for people with MCI has been done during the last decade [15]. Various systematic reviews and meta-analyses of CCT intervention studies have already demonstrated positive (even though sometimes just moderate) effects on improving the cognitive capacity of people with MCI [15-20], e.g. with Hedges' g = from 0.23 to 0.52 for global cognitive functioning [15, 16, 20].

Nutritional therapy is an essential part of medicine with clinical implications for a large number of disciplines. Hence, 70% of all chronic diseases are in some way associated with diet [21]. Cohort studies and randomised controlled trials (RCT) have demonstrated

beneficial effects of nutrition on cognitive functioning, especially related to three types of diet: the *Mediterranean Diet* (MedDiet), the *Dietary Approaches to Stop Hypertension* (DASH Diet), and the *Mediterranean-DASH Intervention for Neurodegenerative Delay* (MIND Diet) [22-25]. All three abovementioned diets are predominantly whole-food plant-based diets, primarily containing vegetables, whole grains, legumes, fruits, nuts, and seeds, are rich in poly- and monounsaturated fatty acids, and contain hardly any processed foods [26]. Furthermore, the diets are associated with reductions in various inflammatory markers [27-29]. Since MCI seems to be accompanied by inflammatory processes [30], and exclusively plant-based foods contain bioactive substances, such as phytochemicals and fibre, which have anti-inflammatory properties [31], there is an obvious need to further investigate potential neuroprotective effects of plant-based nutrition in the context of clinical MCI studies. Since cardiometabolic diseases are associated with the occurrence of dementia [32], and weight loss is associated with improved attention and memory performance [25], it can be hypothesised that a well-planned anti-inflammatory, neuroprotective, plant-based diet has the potential to alleviate symptoms of MCI and the progression to dementia.

The aim of the proposed study is to examine the effects of CCT and online nutritional group counselling on the cognition of people with MCI in a completely digital RCT. We developed CCT and online nutritional group counselling, both specialised for people with MCI: individualised CCT (iCCT) targeting information processing speed, memory-span, short term memory and decision making, and nutritional group counselling focusing on a whole-food, plant-based (WFPB) diet. Additionally, there are two active control measures: basic CCT (bCCT) aiming on simple strategies and long-term memory, and nutritional group counselling focusing on a healthy diet recommended by the German Nutrition Society (Deutsche Gesellschaft für Ernährung, DGE diet). This manuscript describes the study protocol while following the evidence-based reporting guidelines of the SPIRIT Statement [33].

METHODS AND ANALYSES

Aims and hypothesis

Research hypotheses

Primary hypothesis I: Individualised CCT will lead to statistically significantly greater improvements in cognitive capacities during the intervention period of six months compared with basic CCT.

Primary hypothesis II: Online nutritional group counselling focusing on a whole-food, plant-based diet (WFPB diet) will lead to statistically significantly greater improvements in cognitive capacities during the intervention period of six months compared with online nutritional group counselling focusing on a healthy diet recommended by the German Nutrition Society.

Secondary hypothesis: Individualised CCT in combination with online nutritional group counselling focusing on a WFPB diet will have a positive interaction effect. The group with iCCT in combination with online nutritional group counselling focusing on a WFPB diet will show more cognitive improvements than all other groups during the intervention period of six months in people with MCI.

Exploratory study question

Are there changes in the course of depression and activities of daily living during the 12-month observation period?

Study design and setting

A prospective 2x2 randomised controlled intervention study is being conducted to test the abovementioned hypotheses. The overall start date of the study was on 1 June 2021.

Recruitment will begin on 3 January 2022 and will continue until 30 September 2022. Because the study is being conducted completely remotely, individuals from all over Germany can participate. At baseline, all study participants will be randomly assigned to one of four intervention arms (combination of iCCT or bCCT and group counselling on WFPB diet or DGE diet). The CCT intervention is double-blind, the online nutritional group counselling is single-blind. Since the principal usefulness of CCT is well-known [15-20], it would be unethical to use a control group without any CCT. After baseline testing (t0), the participants will receive one of the two computerised training applications for their computer, laptop, or tablet. It is recommended that they use the application at least 30 minutes per day three days a week during the six-month intervention phase. Both computerised training applications contain the same computerised cognitive test battery (ccTB) that will be delivered and collected once a month (t0-t12). After the end of the six-month intervention phase, all participants will be free to continue to use the application. The online nutritional group counselling sessions will focus on either a WFPB diet or a DGE diet. Both groups will receive curricular online nutritional group counselling at regular 14-day intervals for 1.5 hours (twelve appointments total per participant over a period of six months, online group setting in a fixed group, max. 20 participants per group). The intervention phase is from t0 to t6. Follow-up is planned after six (t6) and 12 (t12) months. The open phase of the study will begin after t6 in order to test the hypotheses and exploratory study questions until t12. A follow-up study is planned to observe the participants after t12. Table 1 contains the trial registration data.

195 Table 1 – Trial registration data

Data category	Information
1. Primary registry and trial identification number	ISRCTN
2. Date of registration in primary registry	23 November 2021
3. Secondary identifying numbers	-
4. Source(s) of monetary or material support	Karl and Veronica Carstens-Stiftung
5. Primary sponsor	Karl and Veronica Carstens-Stiftung
6. Secondary sponsor(s)	-
7. Contact for public queries	see point 8
8. Contact for scientific queries	Prof. Dr. Elmar Graessel, elmar.graessel@uk-erlangen.de PD Dr. Christian Kessler, M.A., christian.kessler@charite.de
9. Public title	BrainFit-Nutrition: Intervention study for people with mild cognitive impairment using computerised cognitive training tools and a nutrition intervention
10. Scientific title	Computerised cognitive training tools and online nutritional group counselling for people with mild cognitive impairment: Study protocol of a completely digital, randomised, controlled trial
11. Countries of recruitment	Germany
12. Health condition(s) or problem(s) studied	Mild cognitive impairment (MCI)
13. Intervention(s)	Participants will be randomly allocated to one of four groups with two intervention variables (BrainFit and Nutrition): 1. BrainFit: two versions of CCT: individualised (iCCT), which involves targeted exercises for memory span, information processing, visual-spatial cognition, etc.; and basic (bCCT), which involves basic exercises for memory span, information processing, visual-spatial cognition, etc. 2. Nutrition: two types of nutritional interventions: a WFPB diet and a healthy diet recommended by the German Nutrition Society (DGE).

14. Key inclusion and exclusion criteria	Inclusion criteria: 1. MCI 1.1. Montreal Cognitive Assessment score (MoCA) ≤ 24 1.2. Mini-Mental State Examination score (MMSE) ≥ 24 2. The digital applications and examinations require a PC with microphone and camera (Windows/Linux/MacOS), laptop, or an Android tablet and basic skills in their use and access to the internet 3. Age ≥ 60 4. Informed consent given Exclusion criteria: 1. Completely blind or deaf 2. No personal computer, laptop, or tablet 3. Normal cognition, MoCA > 24 4. Dementia, Mini-Mental State Examination score < 24 5. Depression, Patient Health Questionnaire 9 score ≥ 12 6. Diagnosis of another disease that causes cognitive impairment: • Psychosis (schizophrenia, mania, bipolar psychosis) • Morbus Parkinson • Multiple sclerosis • Multiple strokes • Alcohol abuse / drug consummation (addiction) • Severe brain disease (tumour, injury, hydrocephalus) • Severe vitamin B deficiencies
15. Study type	Prospective double-blind randomised controlled clinical intervention study
16. Date of first enrolment	Starting on 03 January 2022
17. Target sample size	200
18. Recruitment status	Not yet recruiting
19. Primary outcome(s)	Cognition measured by the Montreal Cognitive Assessment (MoCA) at baseline and after six months Cognition measured by the computerised cognitive test battery (ccTB) integrated in the digital software at baseline and after 6 and 12 months
20. Key secondary outcomes	Cognitive Function measured by the Mini-Mental State Examination (MMSE) at baseline and after 6 and 12 months Depression measured by the Patient Health Questionnaire 9 (PHQ-9) at baseline and after 6 and 12 months Activities of daily living measured by the Bayer Activities of Daily Living Scale (B-ADL) at baseline and after 6 and 12 months

Data will be collected by means of psychometric tests and structured interviews using videoconferencing, telephone, and an online survey. The data will be collected by trained student assistants who have no knowledge of group allocation at any time. Two days before baseline testing (t0), the study participants will receive an email with a link to download the software for their version of the computerised application and instructions on how to download and install the software.

Sample size estimation

A power analysis was computed with 200 participants distributed to the two groups of the 2x2x2 factorial variance-analytic experimental design with one repeated measure (factor 1: two CCTs; factor 2: two types of online training for dietary modification, factor 3: two time points). With 50 participants in each group, $\alpha = 0.05$, $\beta = 0.20$ (corresponding to a power of 80%), a correlation between repeated measures of 0.5, and a nonsphericity correction of 1, we will have the power to detect effects with an effect size of $f \geq 0.24$ (comparable to Cohen's $d \geq 0.48$).

Recruitment strategies

Participants will be recruited from the general population all over Germany. The project's homepage was designed to provide information about the study. Also, an appointment for a screening can be made via the project homepage. We partnered with a health insurance company that is sending emails to their members aged 60 and above with information about the study and a link to the project homepage. About 25 thousand members will receive an email with information about the study in six waves between December 2021 and May 2022.

Eligibility of participants

Individuals who are interested in the study can make an appointment for a screening via the project homepage. During the screening, we will offer an examination of basic cognitive

functioning including a personal conversation about their screening results afterwards. Individuals who fulfil the criteria for inclusion will be informed about the study and asked to take part in the project.

Criteria for inclusion are: (1) MCI, psychometrically operationalised by a score on the Montreal Cognitive Assessment (MoCA) ≤ 24 (cut-off for cognitive impairment) and at the same time a score on the Mini-Mental State Examination (MMSE) ≥ 24 (cut-off for no dementia), (2) possession of a computer (Windows/Linux/MacOS) with microphone and camera, laptop, or Android tablet with access to the internet and basic skills in their use, (3) age ≥ 60, and (4) informed consent. Criteria for exclusion are (1) completely blind or deaf, (2) no personal computer, laptop, or tablet with access to the internet, (3) normal cognition, operationalised by a score on the MoCA > 24, (4) dementia, operationalised by a score on the MMSE < 24, (5) acute depression, operationalised by a score on the 9-Item Patient Health Questionnaire (PHQ-9) ≥ 12, or (6) other psychiatric or neurologically diagnosed diseases (checklist): psychosis (schizophrenia, major depression, mania, bipolar psychosis), Parkinson's disease, multiple sclerosis, several strokes, alcohol abuse/drug abuse (addiction), other serious brain disease (especially brain tumour, brain injury, hydrocephalus), or severe vitamin B deficiency.

The MMSE and the MoCA will be administered in combination to differentiate between normal cognition, MCI, and dementia. The MoCA will be administered first to differentiate between normal cognition and MCI on the basis of the cut-off score of 24 points [34-36]. The MMSE will be administered to differentiate between MCI and dementia on the basis of the cut-off score of 23 points [37]. For these cut-offs, we will look for an optimised ratio of sensitivity and specificity. The criteria for a positive screening for MCI, normal cognition, or dementia are shown in Table 2.

Table 2 – Definition of MCI

	Normal cognition	MCI	Dementia
Step 1: MoCA	30-25	24-0	24-0
Step 2: MMSE*	-	30-24	23-0
Decision	**Exclusion**	**Inclusion**	**Exclusion**

Abbreviations. MCI: Mild cognitive impairment; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination. * The MMSE will be applied only when the MoCA results are in the range of 24 to 0 points.

Randomisation

Our external biostatistics partner is creating computer-generated randomisation lists (Institute of Medical Informatics, Biometry, and Epidemiology, Friedrich-Alexander Universität Erlangen-Nürnberg, Waldstraße 6, 91054 Erlangen). All individuals meeting the inclusion criteria will be randomised into one of the four groups (combination of the CCT component: iCCT or bCCT and the online nutritional group counselling component: WFPB diet or DGE diet). Randomisation will be stratified by sex, age, MoCA score at screening. Residents of the same household will be assigned to the same group. Participants will not know which treatment condition they are in, and the student assistants who assess the outcomes of the study will be blind to participants' allocation at all times.

Interventions

Computerised cognitive training

Both computerised applications (intervention and control) are available for Windows, MacOS, and Linux PC/laptop and Android tablet.

Individualised CCT for people with MCI

The exercises included in this training application have been selected to address the expected level of performance of people with MCI. All exercises are available with different levels of

difficulty. The ten playful exercise tasks involve the basic parameters of information processing as well as short-term memory and require different types of decision-making (see Table 3). The initial difficulty levels of the exercises are determined by a machine-learning system, which uses (a) a (logistic regression) model that is based on data from people with MCI (individualised by considering each participant's data) and (b) the cognitive status of the participant (i.e. the results of the integrated computerised cognitive test battery) to estimate the likelihood of a participant's success at a certain difficulty level for a task. The initial model is based on data collected prior to the study. The application chooses the highest level the participant is likely to solve as the entry level. With the machine learning system, individual (compensation) strategies are nullified, and the ideal level of difficulty for training is generated for each participant. Thus, the iCCT is aimed at improving the beneficial effects of CCT by providing exercises at the difficulty level that fits each participant best.

Basic CCT (active control group)

This training application uses exercise tasks that are oriented towards quizzes and visual tasks (see Table 3). The exercise tasks are playfully designed and require, among other things, simple strategies and long-term memory. Most of the exercises exist with only a single level of difficulty. The entry-level difficulties of the other exercises are determined solely by the participant's prior successful results on this exercise. The exercises of the bCCT are aimed at providing enjoyable computerised leisure activities with a limited number of cognitive tasks for the active control group.

286 Table 3 – Computerised cognitive exercises

CCT application	Group of tasks	Explanation	Key function	Cognitive domain (DSM-5)
individualised CCT	Finding targets (‘Punkte sammeln’)	For a set of pop-up pictures, participants must click on target pictures before they disappear	Sustained attention	Complex attention
	Applying rules (‘Regel anwenden’)	Select the winner or loser of a rock-paper-scissors game (either hand signs or in written form); if the game is presented with hand signs, the participant has to pick the winner; if presented with words, the loser has to be picked; this exercise has a time limit, depending on difficulty	Mental/cognitive flexibility	Executive function
	Layer sorting (‘Ebenen sortieren’)	A target picture of a vase with flowers is presented; the participant has to reproduce the picture out of layers; easiest: background – foreground, up to 5 layers with distractors	Visuoconstructional reasoning	Perceptual-motor
	Jigsaw puzzle (‘Bild zusammensetzen’)	Sorting of image sections	Visuoconstructional reasoning	Perceptual-motor
	Fill in the gaps (‘Felder füllen’)	A grid has to be filled in according to rules; each symbol is used only once in every row, column, and block; layout 4x4 to 9x9 fields	Working memory	Executive functions
	Remember cards (‘Karten merken’)	Remember a row of (up to 5) cards; compare new card with 5th to last card	Working memory	Executive functions
	Find pairs (‘Paare finden’)	Finding pairs of images in a pool; images covered; each turn two cards can be turned over	Visuo-spatial memory	Perceptual-motor

	Spot the difference (‘Unterschied erkennen’)	A set of x identical pictures is presented, after a blank, the set and 1 extra picture are presented; the extra picture has to be selected	Visual perception	Perceptual-motor
	Pattern recognition (‘Schema erkennen’)	A matrix of elements (combination of concentric geometrical figures) is presented; in one row or column, a figure is presented in the same position in all elements; the row/column has to be found; for small difficulties, hints are given	Decision making	Executive functions
	Word conversion (‘Wörter umwandeln’)	Convert a source word to a target word in x steps; in each step, only 1 letter can be exchanged, and each line must contain a word	Word finding	Language
basic CCT	Rotating picture puzzle (‘Drehpuzzle’)	Picture is sectioned; sections are rotated; sections have to be turned in the right direction	Visuoconstructional reasoning	Perceptual-motor
	Picture quiz (‘Bilder quiz’)	Multiple-choice questions about images	Semantic and autobiographical long-term memory	Learning and memory
	Geography quiz (‘Länderspiel’)	Knowledge quiz based on German federal states	Semantic and autobiographical long-term memory	Learning and memory
	Quiz-Show (‘Wissensquiz’)	Quiz-show simulation with knowledge-based multiple-choice questions	Semantic and autobiographical long-term memory	Learning and memory

287 Abbreviations. CCT: computerised cognitive training.

Online nutritional group counselling

These types of counselling are based on a structured curriculum including interactive methods and teaching materials, such as handouts, cooking instructions with recipes, and feedback and nutrition-related experience exchange rounds (see Table 4). The use of different group work formats and alternating between a small-step introduction to the content and a person's own elaboration, homework, and reflection are aimed at maximizing participants' attention, participation, and adherence. Furthermore, each participant receives a monthly delivery of a packet with selected food items. These deliveries are meant to be a useful complement regarding recommended products and are intended to invite the participants to get to know new and beneficial food items.

Table 4 – Overview of the six-month online nutritional group counselling

Session	Topic
1	Basics 1: Introduction, nutritional basics
2	Basics 2: Deepening knowledge about nutrition
3	Quantitative proportions and daily planning
4	Kitchen theory: Everything about storage, preparation, baking
5	Kitchen practice: Virtual buffet and virtual live show cooking
6	Scientific background - Impact of nutrition - Proteins
7	Carbohydrates, fibre
8	Oils, fats, nuts, seeds, and drinks
9	Special nutrients, secondary plant substances, spices, age-specific nutrition
10	Circadian factors, periodic fasting
11	Mindful eating, stress, and nutrition
12	Conclusion, evaluation, repetition

Counselling focusing on a whole-food plant-based diet

In this group, a WFPB diet with anti-inflammatory, neuroprotective components is systematically taught and recommended as a regular diet. The WFPB diet essentially consists of vegetables, whole grains, legumes, fruits, nuts, and seeds, without restricting energy intake (see Table 5). In addition, the regular consumption of specific foods that have the potential to beneficially influence cognitive functions, based on current clinical evidence,

is encouraged (e.g. green leafy vegetables [38], mushrooms [39], citrus fruits [40], soy products [41], blueberries [42], nuts [43], turmeric [44], green tea [45], and omega-3 fatty acids [46]). Participants are instructed to exclude animal products from their diets because of the pro-inflammatory potential of animal products and to refrain from consuming highly processed foods [47]. Monthly delivery contains a selection of neuroprotective foods (e.g. plant oil with polyunsaturated fatty acids, nuts, whole grains, green tea).

Counselling focusing on a diet recommended by the German Nutrition Society

Participants in this group will receive systematic recommendations according to the official guidelines of the DGE diet for healthy eating [48]. This means they will be encouraged to establish an omnivorous diet based on vegetables, fruits, and whole grains, including moderate intake of animal products, such as fish, poultry, red meat, eggs, and milk products (see Table 5). The DGE group will also be encouraged to prefer fresh, whole-food, non-processed foods and to reduce their consumption of saturated fatty acids, sweetened drinks, or highly processed foods [48, 49]. Eating products coming from animals is also limited within the DGE context with a greater focus on vegetables, fruits, and whole-grain cereals or bread. The delivery boxes will contain a selection of DGE-appropriate basic foods beneficial to health (e.g. whole grain, plant-based oils or nuts/seeds, sugar alternatives, foods that are not very processed, vegetarian alternatives).

Table 5 – Recommendations of the nutrition interventions (per day, if not specified)

Recommendations per day	WFPB	DGE
Vegetables	At least 3 portions (additionally 1 tbs of sea vegetables/algae)	3 portions
Fruits	2 portions	2 portions
Cereals	Whole-grain, 3-4 portions	Whole-grain, 4 portions, incl. potatoes
Nuts and seeds	1-2 portions	Not specified - mentioned as alternative for 1 fruit portion
Legumes	1 portion	Not specified
Plant oil	2-3 tbs (especially flax seed oil with DHA)	1,5 – 2 tbs
Animal fats	Not recommended	1,5 – 2 tbs (1 tbs plant oil plus 15-30g butter or margarine)
Milk products	Not recommended	3 portions
Meat, poultry, fish, eggs	Not recommended	300-600g meat as well as 1-2 servings of fish (fatty, low-fat), 3 eggs per week plus 3 servings of sausage (à 30g)
Milk alternatives	1-3 portions	Not specified
Sweets, fried foods, fast foods	Not recommended	Max. 1 portion
Neuroprotective foods	Daily (e.g. walnuts, flaxseed oil, berries, green leafy vegetables, herbs, etc.)	Not specified

323 Abbreviations. WFPB: whole-food plant-based diet; DHA: docosahexaenoic acid; DGE:

324 Deutsche Gesellschaft für Ernährung (engl. German Nutrition Society)

Measures

The data are being collected at baseline and follow-up by student assistants (psychology students) who are well-trained to conduct performance tests and interviews via an online survey. The measures that are being used at the different measurement points are shown in Figure 1. (*Please enter figure 1 here*)

Primary outcome measures

Montreal Cognitive Assessment (MoCA) [50]. The MoCA is a performance test that is used to screen for MCI. It consists of more difficult items than the MMSE and is thus able to better detect MCI [50-53]. The score ranges from 0 to 30 points, with higher scores indicating better cognitive performance. A score ≤ 24 indicates cognitive impairment [34-36]. There are three parallel versions of the German translation of MoCA for videoconferencing being used. Version 8.1 is conducted at t1 (screening), version 8.2 at t6 and version 8.3 at t12. The MoCA has been found to be an appropriate measure for cognitive screening and has good reliability and validity values [54].

Computerised cognitive test battery (ccTB). Both versions of the computerised training application contain a set of exercises for measuring different cognitive abilities monthly, beginning at baseline. Eight tests are used to measure various cognitive abilities (see Table 6).

Table 6 – Computerised cognitive test battery

Test	Description	Adaptation of
Memory span I: Digit span, unsorted (‘Zahlen merken – unsortiert’)	Rows of single digit numbers are presented (each for 1 second); the numbers must be reproduced immediately afterwards	WAIS-IV [55], task Digit Span
Memory span II: Digit span, ascending (‘Zahlen merken – aufsteigend’)	Like Memory span I; numbers must be reproduced in ascending order	WAIS-IV [55], task Digit Span

Processing speed I: Number Comparison (‘Zahlen vergleichen’)	Comparison of two single-digit numbers separated by a horizontal line (participants should react if same number)	Pattern Comparison\Letter Comparison [56]
Processing speed II: Symbol count (‘Symbole zählen’)	Counting a target symbol in a pool as fast as possible	SKT [57], task ‘counting symbols’
Processing speed III: Numerical Stroop task (‘numerischer Stroop-Test’)	Two single-digit numbers are presented in different sizes (congruent/incongruent mixed); number with higher value must be clicked as quickly as possible	Numerical stroop task [58, 59]
Short term memory I: Free recall (‘Wortliste – Erinnern’)	12 objects have to be named; afterwards shown for 1 minute; some tests later, the objects must be remembered	SKT [57], task ‘delayed recall’
Short term memory II: Cued recall (‘Wortliste – erkennen’)	The objects from Short term memory I must be selected from a selection of 16 objects	SKT [57], task ‘recognition recall’
Logical reasoning: Matrices Test (‘Matrizentest’)	In a (2x2 or 3x3) matrix of symbols, the bottom right symbol is missing; the composition rule has to be understood, and the correct symbol must be selected	Raven’s Standard Progressive Matrices [60]

Abbreviations. SKT: Syndrom-Kurz-Test (engl. Short Cognitive Performance Test); WAIS-IV: Wechsler Adult Intelligence Scale – Fourth Edition.

Secondary outcome measures

Mini-Mental State Examination (MMSE) [61]. The MMSE is the most frequently employed screening test for dementia [62]. It measures five areas of cognitive functioning: orientation, registration, attention and calculation, recall, and language. The score ranges from 0 to 30 points, with higher scores representing better cognitive performance. Values above 23 points are interpreted as ‘not demented’, whereas scores between 0 and 23 indicate a dementia syndrome [37]. The reliability and validity of the MMSE has been established in numerous studies, e.g. [37, 63, 64]. For the current study, the MMSE was adapted to an audio-visual setting based on [65, 66].

The 9-Item Patient Health Questionnaire (PHQ-9) [67, 68]. The PHQ-9 is a short self-assessment tool often used in primary care settings to screen for depression [69]. Its nine items cover the nine DSM-IV criteria by asking patients about their experiences during the last two weeks and are rated on a four-point scale ranging from 0 ('not at all') to 3 ('nearly every day'). The total sum score suggests varying levels of depression. A cut-off ≥ 12 was found to show a good balance between sensitivity and specificity [70]. The PHQ-9 was found to be a reliable and valid instrument for screening for depression [67].

The Bayer Activities of Daily Living Scale (B-ADL) [71]. The B-ADL assesses difficulties in the performance of everyday activities. It comprises 25 items, which evaluate general ADL competencies and specific tasks important for management in everyday life. The frequency of difficulties the patient experiences in performing everyday activities is rated on a 10-point scale ranging from 1 ('never') to 10 ('always'). A global score is computed by summing across all items and dividing by the number of items rated. The resulting score ranges from 1 to 10 with higher scores corresponding to more severe deficits.

Other variables

Questionnaire on sociodemographic and health-related data. Sociodemographic data (age, sex, marital status, highest educational level, employment status, monthly income, household size) from a standardised questionnaire will be recorded by the student assistants at baseline. Modifiable risk factors for MCI (status of general mental activities, physical activities, social participation, sleeping habits, average liquid intake, eating habits, alcohol consumption, nicotine consumption, visual/hearing capacity), and health-related data (diseases, medications, body weight, body height, dementia cases in the family) will be recorded at baseline, t6 and t12.

User Experience Questionnaire (UEQ) [72]. The UEQ measures attractiveness, perspicuity, efficiency, dependability, stimulation, and novelty of software with 26 bipolar items. The

questionnaire consists of pairs of contrasting attributes (e.g. 'understandable' vs. 'not understandable') that can be rated on a 7-point Likert scale. The UEQ was found to show a satisfactory level of reliability and construct validity [72].

Additional digital data. Both CCTs track usage data. The usage data include the duration of use, difficulty, success, and other parameters for each training task run.

Online Food Frequency Questionnaire (FFQ) [73]. A modified FFQ of the DEGS1-Survey from the Robert Koch Institute will be assessed as an online survey at baseline, t6 and t12 (https://www.rki.de/DE/Content/Gesundheitsmonitoring/Studien/Degs/degs_node.html). It consists of questions about dietary behaviour from the past 4 weeks (on average), containing all relevant plant-based and animal-based foods as well as neuroprotective ingredients, to estimate the frequency of the consumption of different food groups.

Weighing protocol. After 3 months of intervention (t3) a non-obligatory weighing protocol (3 days: 2 working days/1 weekend day) will be emailed and is to be completed and scanned back or completed online.

Data collection

The data will be collected at baseline (t0) and at follow-up after six (t6) and 12 months (t12) (see Figure 1). Annual follow-up studies will test for conversions to dementia. The trial will be conducted remotely. All data will be generated via videoconferencing, telephone, online survey, or the ccTB that is integrated into the CCTs.

Testing with the MoCA and MMSE will be conducted via videoconferencing with the student assistants. Videoconferencing assessments with the MoCA and MMSE have very high reliability scores compared with face-to-face testing. The intraclass correlation coefficients (ICCs) for the MoCA and the MMSE have been demonstrated in several studies and go up to ICC = 0.99 for the MoCA [74] and up to ICC = 0.92 for the MMSE [75]. In a recent systematic review [76], the MoCA and the MMSE were described as valid telehealth

measures for screening cognitive status. Telemedicine is an emerging new field, and there is evidence that it is a valuable tool for assessing neurodegenerative diseases [76-78].

The questionnaire on sociodemographic and health-related data will be sent to the study participants to prepare them for the interview. The FFQ online survey and the non-obligatory weighing protocol will be emailed to participants and are to be completed and scanned back or completed online. The evaluation will be done pseudonymously via nutrition software with a food database (NutriGuide) to support the accuracy of the FFQ survey. During the six-month intervention period, the usage data collected by the CCT, including the ccTB data, will be obtained from the participants. After the monthly ccTB assessment, consent to upload the CCT data will be requested. When consent is given, the data will be uploaded to the Erlangen study centre's server. The server configuration prohibits downloads of the data by people who are not study team members. The data will be pseudonymised.

Data quality management and data protection

The student assistants involved in the study have been thoroughly trained for their tasks by the study centre's staff. When the participants have questions concerning the computerised interventions or the online nutrition groups, they can email the study centre. The quality of the data will be guaranteed by strict data monitoring at the study centre for the total study period. Plausibility checks and logical considerations of the relationships between associated variables will be performed. A data protection concept was developed, reviewed and approved by the data protection officer of the Universitätsklinikum Erlangen.

Patient and public involvement

Study participants or the public will not be involved in developing, designing, or conducting the study. To recruit participants from the general population, our recruitment partner, a

health insurance company, will send emails to their customers with information about our study. Additional information about the study can be found on the project homepage.

Data Analysis

All relevant data, sociodemographic, health-related, primary, and secondary outcome variables will be reported descriptively. In order to be able to assess the quality of the randomisation, the baseline data from the intervention and control groups will be tested for statistically significant differences. For the multivariate analyses, we will impute missing values using the expectation maximization algorithm. The primary hypothesis will be tested via ANOVA, which makes it possible to detect interaction effects in the chosen 2x2x2 factorial design. To ensure the robustness of the results, we will perform both intention to treat and per protocol analyses. Intention to treat evaluations are carried out with all cases still alive at the end of the intervention or observation period. The significance level is defined as $\alpha = 0.05$. The data analyses will be performed using the IBM SPSS Statistics 28 software.

ETHICS AND DISSEMINATION

Ethical considerations

All procedures were approved by the Friedrich-Alexander-Universität Erlangen-Nürnberg Ethics Committee (Ref. 21-318_1-B). Participation will be voluntary, and participants will be free to leave the study at any time. All legal matters, such as voluntariness, right of revocation, and General Data Protection Regulation (EU) are considered. People with MCI are independent and fully capable of conducting business and giving consent. Upon agreement, consent to participate (written informed consent) will be obtained from all participants by the student assistants who are members of the study centre. All participants will be informed about the study in a personal videoconference after they are screened for

eligibility. A participant information sheet including important information about participation (e.g. randomisation, data protection, data storage) will be given to every participant (sent by post). The opportunity to ask questions will be granted by videoconference, telephone, and email afterwards at any time. Participants will not be offered any financial inducement to participate. The external funder, the Karl and Veronica Carstens-Stiftung, is continuously being informed about the progress of the study. In the case of important protocol modifications, we will inform the Ethics Committee, the funder, and the trial registry platform.

Data handling

Informed consent will be stored in a locked steel cabinet. A customized digital participant management system webMODYS (Web-based modular control and documentation system; Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen, Germany) will be used for the administration of the study and will be the only location for personal data. webMODYS is hosted in the IT infrastructure of the Universitätsklinikum Erlangen. Only members of the study team will have access to the lists of participants' names and codes in webMODYS. All data will be stored in only a pseudonymised form digitally in the data collection system REDCap [79, 80] hosted at the Universitätsklinikum Erlangen and Charité Berlin. REDCap is a secure, web-based software platform designed to support data capturing for research studies. The IT architecture including the digital study administration and data collection was 'inspired' by the digiDem Bayern Registry [81]. Results of the study for scientific or other publications will be published only in aggregate form (mean values, etc.). No published material will contain patient-identifying information.

Safety considerations

The CCT applications might have an impact on existing excessive computer use. However, both CCT applications that we developed are not based on motivational or emotional components. The CCT applications require cognitive performance, which could instead lead to exhaustion.

Adverse effects are rare and minor in the context of dietary regimens. The following adverse effects might occur: feeling of heat, changes in mouth and/or body odour, constipation, diarrhoea, meteorism, stomach cramps, nausea, or vomiting. The two dietary recommendations are based either on the recommendations of the German Nutrition Society for a wholesome omnivorous diet or on plant-based dietary recommendations [82]. The plant-based diet is recognised as a safe, sustainable diet for all lifestyles by various nutrition institutes [83-85].

Dissemination plan

The research group intends to publish the data generated from this study in peer-reviewed journals. In addition, results will be communicated at international conferences, national conventions with the funders, and the press.

TRIAL STATUS

Protocol version 1.0, 22 December 2021. The overall start date of the study was 1 June 2020. Recruitment will begin on 3 January 2022 and will continue until 30 September 2022.

LIST OF ABBREVIATIONS

AD: Alzheimer's disease; CCT: computerised cognitive training; ccTB: computerised cognitive test battery; ICC: intraclass correlation coefficients; B-ADL: Bayer Activities of Daily Living Scale; DGE diet: diet recommended by the German Nutrition Society

(Deutsche Gesellschaft für Ernährung, DGE); FFQ: Food Frequency Questionnaire; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; PHQ-9: 9-Item Patient Health Questionnaire; RCT: randomised controlled trial; SKT: Syndrom-Kurz-Test (engl. Short Cognitive Performance Test); UEQ: User Experience Questionnaire; WAIS-IV: Wechsler Adult Intelligence Scale – Fourth Edition; WFPB diet: whole-food plant-based diet.

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LIST OF FIGURES

Figure 1 – Timeline of measurements

*intended for a follow-up study after t12.

Abbreviations. B-ADL: Bayer Activities of Daily Living Scale; bCCT: basic computerised cognitive training; CCT: computerised cognitive training; ccTB: computerised cognitive test battery; DGE diet: diet recommended by the German Nutrition Society (Deutsche Gesellschaft für Ernährung, DGE); FFQ: Food Frequency Questionnaire; iCCT: individualised cognitive training; MCI: mild cognitive impairment; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; PHQ-9: Patient Health Questionnaire; UEQ: User Experience Questionnaire; WFPB diet: whole-food plant-based diet.

LIST OF TABLES

Authors' contributions

PS contributed to the design of the study, is supervising the study, is contributing to the implementation of the study, and drafted the manuscript. SB contributed to the design of the study, is supervising the study, is contributing to the implementation of the study, and drafted the manuscript. MJ designed the CCT applications, is contributing to the implementation of the study, and drafted parts of the manuscript. EH is contributing to the implementation of the study and drafted parts of the manuscript. MDO designed the nutrition intervention and is contributing to the implementation of the study. JS designed the nutrition intervention and is contributing to the implementation of the study. MJe contributed to the design of the study and is supervising the study. JSS is supervising the study and contributing to the implementation of the study. SoB is contributing to the psychometric examinations and supervising the student assistants. CK initiated the study, contributed to the design of the study, and is supervising the study. EG initiated the study, contributed to the design of the study, is supervising the study, and drafted parts of the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests statement

The authors report no conflicts of interest.

Data availability statement

For this study protocol, no datasets have been generated yet.

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Issue date: 22.12.2021

Protocol amendment number: Original

Revision chronology:

22.12.2021	
Original	
25.04.2022	
Revision	

			STUDY PERIOD								
	Enrolment	**Allocation**	**Post-Allocation**								
	-t1	**0**	**t_0**	**t_1**	**t_2**	**t_3**	**t_4**	**t_5**	**t_6**	**t_{12}**	**t_x***
ENROLMENT											
Eligibility screening	x										
Informed consent	x										
Allocation		x									
INTERVENTION											
iCCT			◆	—	—	—	—	—	◆	- - -	◆
bCCT			◆	—	—	—	—	—	◆	- - -	◆
WFPB diet			◆	—	—	—	—	—	◆	- - -	◆
DGE diet			◆	—	—	—	—	—	◆	- - -	◆
ASSESSMENTS											
Baseline Variables											
Inclusion and exclusion criteria	x										
Primary Outcomes											
Cognitive function: MoCA	x								x	x	x
ccTB			x	x	x	x	x	x	x	x	
Secondary Outcomes											
Cognitive function: MMSE	x								x	x	x
Depression: PHQ-9	x								x	x	x
Activities of daily living: B-ADL			x						x	x	x
Other Variables											
Sociodemographic data			x								
Health-related data			x						x	x	
Modifiable risk factors for MCI			x						x	x	
Usability: UEQ									x		
Dietary behaviour: FFQ			x						x	x	
Weighing protocol (optional)						x					

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	Table 1 (9-11)
Protocol version	3	Date and version identifier	36
Funding	4	Sources and types of financial, material, and other support	35-36
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 35
	5b	Name and contact information for the trial sponsor	35
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	35
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8-9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10-11; 12-13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-19
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	20-23
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	23-24
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	24

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	26-27
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	24-25
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	24-25
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	24-25
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	26
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	26-27
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable, 35
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	25
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	25

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4, 25
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	26-27
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	35
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	26
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	27
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Correction: *Computerised cognitive training tools and online nutritional group counselling for people with mild cognitive impairment: study protocol of a completely digital, randomised, controlled trial*

Scheerbaum P, Book S, Jank M, *et al*. Computerised cognitive training tools and online nutritional group counselling for people with mild cognitive impairment: study protocol of a completely digital, randomised, controlled trial. *BMJ Open* 2022;12:e060473. doi: 10.1136/bmjopen-2021-060473

The article has been updated since its online publication. The authors wish to clarify that, during the preparation of the main results publication of the study, an unfortunate error was identified in the originally published study protocol.

The error pertains to the classification of primary and secondary outcomes in the publication. In both the ethics application submitted to the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU) Ethics Committee and our original registration with the International Standard Randomised Controlled Trial Number (ISRCTN), we accurately specified only one main outcome: Cognitive performance assessed through the Montreal Cognitive Assessment (MoCA). Regrettably, the computerised cognitive test battery (ccTB) was inaccurately designated as the main outcome in the publication; however, it is, in fact, a secondary outcome employed to measure cognition.

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