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

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3 34 **Computerised cognitive training tools and online nutritional group counselling for**
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5 35 **people suffering from mild cognitive impairment: Study protocol of a completely digital,**
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7 36 **randomised, controlled clinical trial**
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10 37 **ABSTRACT**
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14 38 **Introduction**

15
16 39 People with mild cognitive impairment (MCI) are at increased risk of decreasing cognitive
17
18 40 functioning. Computerised cognitive training (CCT) and nutrition have been shown to
19
20 41 improve the cognitive capacities of people with MCI. For each variable, we developed two
21
22 42 kinds of interventions specialised for people with MCI (CCT: ‘individualised’ CCT [iCCT];
23
24 43 nutrition: a whole-food, plant-based diet [WFPB diet]). Additionally, there are two kinds of
25
26 44 active control measures (CCT: ‘basic’ CCT [bCCT]; nutrition: a healthy diet following the
27
28 45 current guidelines of the German Nutrition Society). The aim of the present study is to
29
30 46 investigate the effects of the two interventions on cognition in people with MCI in a 2x2
31
32 47 randomised controlled clinical trial with German participants.
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38 48 **Methods and analysis**

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40 49 Participants will be community-dwelling individuals with a psychometric diagnosis of MCI
41
42 50 based on the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination
43
44 51 (MMSE). With N = 200, effects with an effect size of $f \geq 0.24$ (comparable to Cohen’s $d \geq$
45
46 52 0.48) can be detected. Screening, baseline, t6, and t12 testing will be conducted via a
47
48 53 videoconferencing assessment, telephone, and online survey. Participants will be randomly
49
50 54 allocated to one of four groups and will receive a combination of CCT and online nutritional
51
52 55 counselling. The CCT can be carried out independently at home on a computer, laptop, or
53
54 56 tablet. Nutrition counselling includes 12 online group sessions every fortnight for 1.5 hours.
55
56 57 The treatment phase is six months with follow-ups after six and 12 months after baseline.
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58 **Ethics and dissemination**

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

63 **Registration details**

64 ISRCTN, ISRCTN10560738, prospectively registered 23 November 2021,
65 <https://doi.org/10.1186/ISRCTN10560738>

66 **Keywords**

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

70 **ARTICLE SUMMARY**

71 **Strengths and limitations of this study**

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

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3 80 • Individualised computerised cognitive training for the intervention group by means
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5 81 of a machine learning system that chooses computerised exercises that match the
6
7 82 person's level of difficulty by estimating the person's likelihood of successfully
8
9 83 solving the computerised exercises ('individualised' CCT).
10
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12 84 • Highly innovative curricular nutrition intervention based on current clinical evidence,
13
14 85 tailored for people with MCI
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16 86 • Methodological limitations might include a restriction to participants who feel
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18 87 comfortable with the use of technology; have internet access and own a computer,
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20 88 laptop, or tablet; and have MCI as their only a psychometric diagnosis without a
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22 89 clinical diagnosis.
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100 INTRODUCTION

101 In the general population, the prevalence of mild cognitive impairment (MCI) defined by
102 Petersen [1] increases with age, at 6.7% for ages 60 to 64 and up to 25.2% for ages 80 to 84
103 [2]. People with MCI have a higher risk of progressing to dementia than cognitively normal
104 individuals [1, 3]. For example, Inui et al. [4] found that 72% of patients with amnesic MCI
105 progressed to Alzheimer's disease over five years. Thus, MCI seems to be the optimal period
106 for intervention before a conversion to dementia occurs.

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

121 Nutritional therapy is an essential part of medicine with clinical implications for a
122 large number of disciplines. 70% of all chronic diseases are in some way associated with diet
123 [21]. Cohort studies and randomised controlled trials (RCT) have demonstrated beneficial
124 effects of nutrition on cognitive functioning, especially related to three types of diet: the

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3 125 *Mediterranean Diet* (MedDiet), the *Dietary Approaches to Stop Hypertension* (DASH Diet),
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5 126 and the *Mediterranean-DASH Intervention for Neurodegenerative Delay* (MIND Diet) [22-
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7 127 25]. All three abovementioned diets are predominantly whole-food plant-based diets,
8
9 128 primarily containing vegetables, whole grains, legumes, fruits, nuts, and seeds, are rich in
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11 129 poly- and monounsaturated fatty acids, and contain hardly any processed foods [26].
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14 130 Furthermore, the diets are associated with reductions in various inflammatory markers [27-
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16 131 29]. Since MCI seems to be accompanied by inflammatory processes [30], and exclusively
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18 132 plant-based foods contain bioactive substances, such as phytochemicals and fibre, which
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20 133 have anti-inflammatory properties [31], there is an obvious need to further investigate
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22 134 potential neuroprotective effects of plant-based nutrition in the context of clinical MCI
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24 135 studies. Since cardiometabolic diseases are associated with the occurrence of dementia [32],
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26 136 and weight loss is associated with improved attention and memory performance [25], it can
27
28 137 be hypothesised that a well-planned anti-inflammatory, neuroprotective, plant-based diet has
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30 138 the potential to alleviate symptoms of MCI and the progression to dementia.

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34 139 The aim of the proposed study is to examine the effects of CCT and online nutritional
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36 140 group counselling on the cognition of people with MCI in a completely digital randomised
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38 141 controlled trial. We developed CCT and online nutritional group counselling, both
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40 142 specialised for people with MCI: individualised CCT (iCCT) and nutritional group
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42 143 counselling focusing on a whole-food, plant-based (WFPB) diet. Additionally, there are two
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44 144 active control measures: basic CCT (bCCT) and nutritional group counselling focusing on a
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46 145 healthy diet recommended by the German Nutrition Society (Deutsche Gesellschaft für
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48 146 Ernährung, DGE diet). This manuscript describes the study protocol while following the
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50 147 evidence-based reporting guidelines of the SPIRIT Statement [33].
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56 148 **METHODS AND ANALYSES**

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2 149 **Aims and hypothesis**
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5 150 Research hypotheses
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9 151 Primary hypothesis I: Individualised CCT will lead to statistically significantly greater
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11 152 improvements in cognitive capacities during the intervention period of six months compared
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13 153 with basic CCT.
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17 154 Primary hypothesis II: Online nutritional group counselling focusing on a WFPB diet will
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19 155 lead to statistically significantly greater improvements in cognitive capacities during the
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21 156 intervention period of six months compared with online nutritional group counselling
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23 157 focusing on a healthy diet recommended by the German Nutrition Society.
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27 158 Secondary hypothesis: Individualised CCT in combination with online nutritional group
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29 159 counselling focusing on a WFPB diet will have a positive interaction effect. The group with
30
31 160 iCCT in combination with online nutritional group counselling focusing on a WFPB diet will
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33 161 show more cognitive improvements than all other groups during the intervention period of
34
35 162 six months in people with MCI.
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40 163 Exploratory study question
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43 164 Are there changes in the course of depression and activities of daily living during the 12-
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45 165 month observation period?
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49 166 **Study design and setting**
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52 167 A prospective 2x2 randomised controlled clinical intervention study is being conducted to
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54 168 test the abovementioned hypotheses. The overall start date of the study was on 01 June 2021.
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56 169 Recruitment will begin on 3 January 2022 and will continue until 30 June 2022. Because the
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58 170 study is being conducted completely remotely, individuals from all over Germany can
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3 171 participate. At baseline, all study participants will be randomly assigned to one of four
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5 172 intervention arms (combination of iCCT or bCCT and group counselling on WFPB diet or
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7 173 DGE diet). The CCT intervention is double-blind, the online nutritional group counselling is
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9 174 single-blind. Since the principal usefulness of CCT is well-known [15-20], it would be
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11 175 unethical to use a control group without any CCT. After baseline testing (t0), the participants
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13 176 will receive one of the two computerised training applications for their computer, laptop, or
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15 177 tablet. It is recommended that they use the application at least 30 minutes per day three days
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17 178 a week during the six-month intervention phase. Both computerised training applications
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19 179 contain the same computerised cognitive test battery (ccTB) that will be delivered and
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21 180 collected once a month (t0-t12). After the end of the six-month intervention phase, all
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23 181 participants will be free to continue to use the application. The online nutritional group
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25 182 counselling sessions will focus on either a WFPB diet or a DGE diet. Both groups will
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27 183 receive curricular online nutritional group counselling at regular 14-day intervals for 1.5
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29 184 hours (twelve appointments total per participant over a period of six months, online group
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31 185 setting in a fixed group, max. 20 participants per group). The intervention phase is from t0 to
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33 186 t6. Follow-up is planned after six (t6) and 12 (t12) months. The open phase of the study will
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35 187 begin after t6 in order to test the hypotheses and exploratory study questions until t12. A
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37 188 follow-up study is planned to observe the participants after t12. Table 1 contains the trial
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39 189 registration data.
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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	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. MCI <ol style="list-style-type: none"> 1.1. Montreal Cognitive Assessment score (MoCA) \leq 24 1.2. Mini-Mental State Examination score (MMSE) \geq 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 \geq 60 4. Informed consent given <hr/> <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 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 \geq 12 6. Diagnosis of another disease that causes cognitive impairment: <ul style="list-style-type: none"> • Psychosis (schizophrenia, mania, bipolar psychosis) • Morbus Parkinson • Multiple sclerosis • Multiple strokes • Alcohol abuse / drug consumption (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)	<p>Cognition measured by the Montreal Cognitive Assessment (MoCA) at baseline and after six months</p> <p>Cognition measured by the computerised cognitive test battery (ccTB) integrated in the digital software at baseline and after 6 and 12 months</p>
20. Key secondary outcomes	<p>Cognitive Function measured by the Mini-Mental State Examination (MMSE) at baseline and after 6 and 12 months</p> <p>Depression measured by the Patient Health Questionnaire 9 (PHQ-9) at baseline and after 6 and 12 months</p> <p>Activities of daily living measured by the Bayer Activities of Daily Living Scale (B-ADL) at baseline and after 6 and 12 months</p>

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3 191 Data will be collected by means of psychometric tests and structured interviews using
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5 192 videoconferencing, telephone, and an online survey. The data will be collected by trained
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7 193 student assistants who have no knowledge of group allocation at any time. Two days before
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9 194 baseline testing (t0), the study participants will receive an email with a link to download the
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11 195 software for their version of the computerised application and instructions on how to
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14 196 download and install the software.

17 197 **Sample size estimation**

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20 198 A power analysis was computed with 200 participants distributed to the two groups of the
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22 199 2x2x2 factorial variance-analytic experimental design with one repeated measure (factor 1:
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24 200 two CCTs; factor 2: two types of online training for dietary modification, factor 3: two time
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26 201 points). With 50 participants in each group, $\alpha = 0.05$, $\beta = 0.20$ (corresponding to a
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28 202 power of 80%), a correlation between repeated measures of 0.5, and a nonsphericity
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30 203 correction of 1, we will have the power to detect effects with an effect size of $f \geq 0.24$
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32 204 (comparable to Cohen's $d \geq 0.48$).

37 205 **Recruitment strategies**

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39 206 Participants will be recruited from the general population all over Germany. The project's
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41 207 homepage was designed to provide information about the study. Also, an appointment for a
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43 208 screening can be made via the project homepage. We partnered with a health insurance
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45 209 company that is sending emails to their members aged 60 and above with information about
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47 210 the study and a link to the project homepage. About 25 thousand members will receive an
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49 211 email with information about the study in six waves between December 2021 and May 2022.

54 212 **Eligibility of participants**

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57 213 Individuals who are interested in the study can make an appointment for a screening via the
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59 214 project homepage. During the screening, we will offer an examination of basic cognitive
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2 215 functioning including a personal conversation about their screening results afterwards.
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5 216 Individuals who fulfil the criteria for inclusion will be informed about the study and asked to
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7 217 take part in the project.
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9 218 Criteria for inclusion are: (1) MCI, psychometrically operationalised by a score on
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11 219 the Montreal Cognitive Assessment (MoCA) ≤ 24 (cut-off for cognitive impairment) and at
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13 220 the same time a score on the Mini-Mental State Examination (MMSE) ≥ 24 (cut-off for no
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15 221 dementia), (2) possession of a computer (Windows/Linux/macOS) with microphone and
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17 222 camera, laptop, or Android tablet with access to the internet and basic skills in their use, (3)
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19 223 age ≥ 60 , and (4) informed consent. Criteria for exclusion are (1) completely blind or deaf,
20
21 224 (2) no personal computer, laptop, or tablet with access to the internet, (3) normal cognition,
22
23 225 operationalised by a score on the MoCA > 24 , (4) dementia, operationalised by a score on
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25 226 the MMSE < 24 , (5) acute depression, operationalised by a score on the 9-Item Patient
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27 227 Health Questionnaire (PHQ-9) ≥ 12 , or (6) other psychiatric or neurologically diagnosed
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29 228 diseases (checklist): psychosis (schizophrenia, major depression, mania, bipolar psychosis),
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31 229 Parkinson's disease, multiple sclerosis, several strokes, alcohol abuse/drug abuse (addiction),
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33 230 other serious brain disease (especially brain tumour, brain injury, hydrocephalus), or severe
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35 231 vitamin B deficiency.
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41 232 The MMSE and the MoCA will be administered in combination to differentiate
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43 233 between normal cognition, MCI, and dementia. The MoCA will be administered first to
44
45 234 differentiate between normal cognition and MCI on the basis of the cut-off score of 24 points
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47 235 [34-36]. The MMSE will be administered to differentiate between MCI and dementia on the
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49 236 basis of the cut-off score of 23 points [37]. For these cut-offs, we will look for an optimised
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51 237 ratio of sensitivity and specificity. The criteria for a positive screening for MCI, normal
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53 238 cognition, or dementia are shown in Table 2.
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239 **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

240 Abbreviations. MCI: Mild cognitive impairment; MoCA: Montreal Cognitive Assessment;

241 MMSE: Mini-Mental State Examination. * The MMSE will be applied only when the

242 MoCA results are in the range of 24 to 0 points.

243 **Randomisation**

244 Our external biostatistics partner is creating computer-generated randomisation lists

245 (Institute of Medical Informatics, Biometry, and Epidemiology, Friedrich-Alexander

246 University Erlangen-Nürnberg, Waldstraße 6, 91054 Erlangen). All individuals meeting the

247 inclusion criteria will be randomised into one of the four groups (combination of the CCT

248 component: iCCT or bCCT and the online nutritional group counselling component: WFPB

249 diet or DGE diet). Randomisation will be stratified by sex, age, MoCA score at screening.

250 Couples will be assigned to the same group. Participants will not know which treatment

251 condition they are in, and the student assistants who assess the outcomes of the study will be

252 blind to participants' allocation at all times.

253 **Interventions**

254 **Computerised cognitive training**

255 Both computerised applications (intervention and control) are available for Windows,

256 MacOS, and Linux PC/laptop and Android tablet.

257 Individualised CCT for people with MCI

258 The exercises included in this training application have been selected to address the expected

259 level of performance of people with MCI. All exercises are available with different levels of

1
2
3 260 difficulty. The ten playful exercise tasks involve the basic parameters of information
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5 261 processing as well as short-term memory and require different types of decision-making (see
6
7 262 Table 3). The initial difficulty levels of the exercises are determined by a machine-learning
8
9 263 system, which uses (a) a (logistic regression) model that is based on data from people with
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11 264 MCI (individualised by considering each participant's data) and (b) the cognitive status of
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14 265 the participant (i.e. the results of the integrated computerised cognitive test battery) to
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16 266 estimate the likelihood of a participant's success at a certain difficulty level for a task. The
17
18 267 initial model is based on data collected prior to the study. The application chooses the
19
20
21 268 highest level the participant is likely to solve as the entry level. With the machine learning
22
23 269 system, individual (compensation) strategies are nullified, and the ideal level of difficulty for
24
25 270 training is generated for each participant. Thus, the iCCT is aimed at improving the
26
27
28 271 beneficial effects of CCT by providing exercises at the difficulty level that fits each
29
30 272 participant best.

31 32 33 273 Basic CCT (active control group)

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35
36 274 This training application uses exercise tasks that are oriented towards quizzes and visual
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38 275 tasks (see Table 3). The exercise tasks are playfully designed and require, among other
39
40
41 276 things, simple strategies and long-term memory. Most of the exercises exist with only a
42
43 277 single level of difficulty. The entry-level difficulties of the other exercises are determined
44
45 278 solely by the participant's prior successful results on this exercise. The exercises of the
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47
48 279 bCCT are aimed at providing enjoyable computerised leisure activities with a limited
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50 280 number of cognitive tasks for the active control group.
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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

282 Abbreviations. CCT: computerised cognitive training.

283 **Online nutritional group counselling**

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

293 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

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

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

1
2 300 encouraged (e.g. green leafy vegetables [38], mushrooms [39], citrus fruits [40], soy
3
4 301 products [41], blueberries [42], nuts [43], turmeric [44], green tea [45], and omega-3 fatty
5
6 302 acids [46]). Participants are instructed to exclude animal products from their diets because of
7
8 303 the pro-inflammatory potential of animal products and to refrain from consuming highly
9
10 304 processed foods [47]. Monthly delivery contains a selection of neuroprotective foods (e.g.
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12 305 plant oil with polyunsaturated fatty acids, nuts, whole grains, green tea).

13
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16
17 306 Counselling focusing on a diet recommended by the German Nutrition Society (Deutsche
18
19 307 Gesellschaft für Ernährung, DGE diet)

20
21 308 Participants in this group will receive systematic recommendations according to the official
22
23 309 guidelines of the DGE for healthy eating [48]. This means they will be encouraged to
24
25 310 establish an omnivorous diet based on vegetables, fruits, and whole grains, including
26
27 311 moderate intake of animal products, such as fish, poultry, red meat, eggs, and milk products.
28
29 312 The DGE group will also be encouraged to prefer fresh, whole-food, non-processed foods
30
31 313 and to reduce their consumption of saturated fatty acids, sweetened drinks, or highly
32
33 314 processed foods [48, 49]. Eating products coming from animals is also limited within the
34
35 315 DGE context with a greater focus on vegetables, fruits, and whole-grain cereals or bread.
36
37 316 The delivery boxes will contain a selection of DGE-appropriate basic foods beneficial to
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39 317 health (e.g. whole grain, plant-based oils or nuts/seeds, sugar alternatives, foods that are not
40
41 318 very processed, vegetarian alternatives).

42 43 44 45 319 **Measures**

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47
48 320 The data are being collected at baseline and follow-up by student assistants (psychology
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50 321 students) who are well-trained to conduct performance tests and interviews via an online
51
52 322 survey. The measures that are being used at the different measurement points are shown in
53
54 323 Figure 1.

324 Primary outcome measure

325 *Montreal Cognitive Assessment (MoCA)* [50]. The MoCA is a performance test that is used
 326 to screen for MCI. It consists of more difficult items than the MMSE and is thus able to
 327 better detect MCI [50-53]. The score ranges from 0 to 30 points, with higher scores
 328 indicating better cognitive performance. A score ≤ 24 indicates cognitive impairment [34-
 329 36]. There are three parallel versions of the MoCA currently available. The MoCA has been
 330 found to be an appropriate measure for cognitive screening and has good reliability and
 331 validity values [54].

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

336 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]

337 Abbreviations: SKT: Syndrom-Kurz-Test (Engl. Short Cognitive Performance Test); WAIS-

338 IV: Wechsler Adult Intelligence Scale – Fourth Edition.

339 Secondary outcome measures

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

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

1
2 354 *The Bayer Activities of Daily Living Scale (B-ADL)* [69]. The B-ADL assesses difficulties in
3
4
5 355 the performance of everyday activities. It comprises 25 items, which evaluate general ADL
6
7 356 competencies and specific tasks important for management in everyday life. The frequency
8
9 357 of difficulties the patient experiences in performing everyday activities is rated on a 10-point
10
11 358 scale ranging from 1 ('never') to 10 ('always'). A global score is computed by summing
12
13
14 359 across all items and dividing by the number of items rated. The resulting score ranges from 1
15
16 360 to 10 with higher scores corresponding to more severe deficits.

17
18
19 361 Other variables

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21 362 *Questionnaire on sociodemographic and health-related data.* The following data from a
22
23
24 363 standardised questionnaire will be recorded by the student assistants at baseline:
25
26 364 sociodemographic data (age, sex, marital status, highest educational level, employment
27
28 365 status, monthly income, household size), modifiable risk factors for MCI (status of general
29
30 366 mental activities, physical activities, social participation, sleeping habits, average liquid
31
32 367 intake, eating habits, alcohol consumption, nicotine consumption, visual/hearing capacity),
33
34
35 368 and health-related data (diseases, medications, body weight, body height, dementia cases in
36
37
38 369 the family).

39
40 370 *User Experience Questionnaire (UEQ)* [70]. The UEQ measures attractiveness, perspicuity,
41
42 371 efficiency, dependability, stimulation, and novelty of software with 26 bipolar items. The
43
44 372 questionnaire consists of pairs of contrasting attributes (e.g. 'understandable' vs. 'not
45
46 373 understandable') that can be rated on a 7-point Likert scale. The UEQ was found to show a
47
48 374 satisfactory level of reliability and construct validity [70].

49
50 375 *Additional digital data.* Both CCTs track usage data. The usage data include the duration of
51
52 376 use, difficulty, success, and other parameters for each training task run.

53
54 377 *Online Food Frequency Questionnaire (FFQ)* [71]. A modified FFQ of the DEGS1-Survey
55
56 378 from the Robert Koch Institute will be assessed as an online survey
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1
2 379 (https://www.rki.de/DE/Content/Gesundheitsmonitoring/Studien/Degs/degs_node.html). It
3
4
5 380 consists of questions about dietary behaviour from the past 4 weeks (on average), containing
6
7 381 all relevant plant-based and animal-based foods as well as neuroprotective ingredients, to
8
9 382 estimate the frequency of the consumption of different food groups.

10
11 383 *Weighing protocol.* A non-obligatory weighing protocol (3 days: 2 working days/1 weekend
12
13
14 384 day) will be emailed and is to be completed and scanned back or completed online.

17 385 **Data collection**

18
19
20 386 The data will be collected at baseline (t0) and at follow-up after six (t6) and 12 months (t12)
21
22 387 (see Figure 1). Annual follow-up studies will test for conversions to dementia. The trial will
23
24 388 be conducted remotely. All data will be generated via videoconferencing, telephone, online
25
26 389 survey, or the ccTB that is integrated into the CCTs.

27
28
29 390 Testing with the MoCA and MMSE will be conducted via videoconferencing with the
30
31 391 student assistants. Videoconferencing assessments with the MoCA and MMSE have very
32
33 392 high reliability scores compared with face-to-face testing. The intraclass correlation
34
35 393 coefficients (ICCs) for the MoCA and the MMSE have been demonstrated in several studies
36
37 394 and go up to ICC = 0.99 for the MoCA [72] and up to ICC = 0.92 for the MMSE [73]. In a
38
39 395 recent systematic review [74], the MoCA and the MMSE were described as valid telehealth
40
41 396 measures for screening cognitive status. Telemedicine is an emerging new field, and there is
42
43 397 evidence that it is a valuable tool for assessing neurodegenerative diseases [74-76].

44
45
46 398 The questionnaire on sociodemographic and health-related data will be sent to the
47
48 399 study participants to prepare them for the interview. The FFQ online survey and the non-
49
50 400 obligatory weighing protocol will be emailed to participants and are to be completed and
51
52 401 scanned back or completed online. The evaluation will be done pseudonymously via
53
54 402 nutrition software with a food database (NutriGuide) to support the accuracy of the FFQ
55
56 403 survey. During the six-month intervention period, the data collected by the CCT, including
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1
2 404 the ccTB data, will be obtained from the participants. After the monthly ccTB assessment,
3
4 405 consent to upload the CCT data will be requested. When consent is given, the data will be
5
6 406 uploaded to the Erlangen study centre's server. The server configuration prohibits downloads
7
8
9 407 of the data by people who are not study team members. The data will be pseudonymised.
10
11

12 408 **Data quality management and data protection**

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14
15 409 The student assistants involved in the study have been thoroughly trained for their tasks by
16
17 410 the study centre's staff. When the participants have questions concerning the computerised
18
19 411 interventions or the online nutrition groups, they can email the study centre. The quality of
20
21 412 the data will be guaranteed by strict data monitoring at the study centre for the total study
22
23 413 period. Plausibility checks and logical considerations of the relationships between associated
24
25 414 variables will be performed. A data protection concept was developed and was reviewed and
26
27 415 approved by the data protection officer of the University Hospital Erlangen.
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31 416 **Patient and public involvement**

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33
34 417 Study participants or the public will not be involved in developing, designing, or conducting
35
36 418 the study. To recruit participants from the general population, our recruitment partner, a
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38 419 health insurance company, will send emails to their customers with information about our
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40 420 study. Additional information about the study can be found on the project homepage.
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45 421 **Data Analysis**

46
47 422 All relevant data, sociodemographic, health-related, primary, and secondary outcome
48
49 423 variables will be reported descriptively. In order to be able to assess the quality of the
50
51 424 randomisation, the baseline data from the intervention and control groups will be tested for
52
53 425 statistically significant differences. For the multivariate analyses, we will impute missing
54
55 426 values using the expectation maximization algorithm. The primary hypothesis will be tested
56
57 427 via ANOVA, which makes it possible to detect interaction effects in the chosen 2x2x2
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1
2 428 factorial design. To ensure the robustness of the results, we will perform both intention to
3
4 429 treat and per protocol analyses. Intention to treat evaluations are carried out with all cases
5
6
7 430 still alive at the end of the intervention or observation period. The significance level is
8
9 431 defined as $\alpha = 0.05$. The data analyses will be performed using the IBM SPSS Statistics
10
11 432 28 software.

15 433 **ETHICS AND DISSEMINATION**

18 434 **Ethical considerations**

21 435 All procedures were approved by the Friedrich-Alexander-University Erlangen-Nuremberg
22
23 436 Ethics Committee (Ref. 21-318_1-B). Participation will be voluntary, and participants will
24
25 437 be free to leave the study at any time. All legal matters, such as voluntariness, right of
26
27 438 revocation, and General Data Protection Regulation (EU) are considered. People with MCI
28
29 439 are independent and fully capable of conducting business and giving consent. Upon
30
31 440 agreement, consent to participate (written informed consent) will be obtained from all
32
33 441 participants by the student assistants who are members of the study centre. All participants
34
35 442 will be informed about the study in a personal videoconference after they are screened for
36
37 443 eligibility. A participant information sheet including important information about
38
39 444 participation (e.g. randomisation, data protection, data storage) will be given to every
40
41 445 participant (sent by post). The opportunity to ask questions will be granted by
42
43 446 videoconference, telephone, and email afterwards at any time. Participants will not be
44
45 447 offered any financial inducement to participate. The external funder, the Karl and Veronica
46
47 448 Carstens-Stiftung, is continuously being informed about the progress of the study. In the case
48
49 449 of important protocol modifications, we will inform the Ethics Committee, the funder, and
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51 450 the trial registry platform.
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3 451 **Data handling**
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5 452 Informed consent will be stored in a locked steel cabinet. A customized digital participant
6
7 453 management system webMODYS (Web-based modular control and documentation system;
8
9 454 Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen,
10
11 455 Germany) will be used for the administration of the study and will be the only location for
12
13 456 personal data. webMODYS is hosted in the IT infrastructure of the University Hospital
14
15 457 Erlangen. Only members of the study team will have access to the lists of participants’
16
17 458 names and codes in webMODYS. All data will be stored in only a pseudonymised form
18
19 459 digitally in the data collection system REDCap [77, 78] hosted at the University Hospital
20
21 460 Erlangen and Charité Berlin. REDCap is a secure, web-based software platform designed to
22
23 461 support data capturing for research studies. The IT architecture including the digital study
24
25 462 administration and data collection was ‘inspired’ by the digiDem Bayern Registry [79].
26
27 463 Results of the study for scientific or other publications will be published only in aggregate
28
29 464 form (mean values, etc.). No published material will contain patient-identifying information.
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36 465 **Safety considerations**
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38 466 The CCT applications might have an impact on existing excessive computer use. However,
39
40 467 both CCT applications that we developed are not based on motivational or emotional
41
42 468 components. The CCT applications require cognitive performance, which could instead lead
43
44 469 to exhaustion.
45
46

47 470 Adverse effects are rare and minor in the context of dietary regimens. The following
48
49 471 adverse effects might occur: feeling of heat, changes in mouth and/or body odour,
50
51 472 constipation, diarrhoea, meteorism, stomach cramps, nausea, or vomiting. The two dietary
52
53 473 recommendations are based either on the recommendations of the German Nutrition Society
54
55 474 for a wholesome omnivorous diet or on plant-based dietary recommendations [80]. The
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1
2
3 475 plant-based diet is recognised as a safe, sustainable diet for all lifestyles by various nutrition
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5 476 institutes [81-83].
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8 477 **Dissemination plan**

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10 478 The research group intends to publish the data generated from this study in peer-reviewed
11
12 479 journals. In addition, results will be communicated at international conferences, national
13
14 480 conventions with the funders, and the press.
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18 481 **TRIAL STATUS**

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22 482 Protocol version 1.0, 22 December 2021. The overall start date of the study was 1 June 2020.
23
24 483 Recruitment will begin on 3 January 2022 and will continue until 30 June 2022.
25
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28 484 **LIST OF ABBREVIATIONS**

29

30
31 485 AD: Alzheimer's disease; CCT: computerised cognitive training; ccTB: computerised
32
33 486 cognitive test battery; ICC: intraclass correlation coefficients; B-ADL: Bayer Activities of
34
35 487 Daily Living Scale; DGE diet: diet recommended by the German Nutrition Society
36
37 488 (Deutsche Gesellschaft für Ernährung, DGE); FFQ: Food Frequency Questionnaire; MCI:
38
39 489 mild cognitive impairment; MMSE: Mini-Mental State Examination; MoCA: Montreal
40
41 490 Cognitive Assessment; PHQ-9: 9-Item Patient Health Questionnaire; RCT: randomised
42
43 491 controlled trial; SKT: Syndrom-Kurz-Test (engl. Short Cognitive Performance Test); UEQ:
44
45 492 User Experience Questionnaire; WAIS-IV: Wechsler Adult Intelligence Scale – Fourth
46
47 493 Edition; WFPB diet: whole-food plant-based diet.
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3 781 **LIST OF FIGURES**

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6 782 **Figure 1 – Timeline of measurements**

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8 783 *intended for a follow-up study after t12.

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10 784 Abbreviations. B-ADL: Bayer Activities of Daily Living Scale; bCCT: basic computerised
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13 785 cognitive training; CCT: computerised cognitive training; ccTB: computerised cognitive test
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15 786 battery; DGE diet: diet recommended by the German Nutrition Society (Deutsche
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17 787 Gesellschaft für Ernährung, DGE); FFQ: Food Frequency Questionnaire; iCCT:
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19 788 individualised cognitive training; MCI: mild cognitive impairment; MoCA: Montreal
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21 789 Cognitive Assessment; MMSE: Mini-Mental State Examination; PHQ-9: Patient Health
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23 790 Questionnaire; UEQ: User Experience Questionnaire; WFPB diet: whole-food plant-based
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26 791 diet.

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30 792 **LIST OF TABLES**

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34 793 **Table 1 – Trial registration data**

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37 794 **Table 2 – Definition of MCI**

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40 795 **Table 3 – Computerised cognitive exercises**

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43 796 **Table 4 – Overview of the 6-month nutrition interventions**

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46 797 **Table 5 – Computerised cognitive assessment**

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3 803 **Authors' contributions**

4 804 PS contributed to the design of the study, is supervising the study, is contributing to the
5
6
7 805 implementation of the study, and drafted the manuscript. SB contributed to the design of the
8
9 806 study, is supervising the study, is contributing to the implementation of the study, and
10
11 807 drafted the manuscript. MJ designed the CCT applications, is contributing to the
12
13 808 implementation of the study, and drafted parts of the manuscript. EH is contributing to the
14
15 809 implementation of the study and drafted parts of the manuscript. MDO designed the nutrition
16
17 810 intervention and is contributing to the implementation of the study. JS designed the nutrition
18
19 811 intervention and is contributing to the implementation of the study. MJe contributed to the
20
21 812 design of the study and is supervising the study. JSS is supervising the study and
22
23 813 contributing to the implementation of the study. SoB is contributing to the psychometric
24
25 814 examinations and supervising the student assistants. CK initiated the study, contributed to
26
27 815 the design of the study, and is supervising the study. EG initiated the study, contributed to
28
29 816 the design of the study, is supervising the study, and drafted parts of the manuscript. All
30
31 817 authors read and approved the final version of the manuscript.
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43
44 821 interpretation of the data, or in writing the manuscript.
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47

48 822 **Competing interests statement**

49
50 823 The authors report no conflicts of interest.
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54 824 **Data availability statement**

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56 825 For this study protocol, no datasets have been generated yet.
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2
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35 840 Revision chronology:

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39 22.12.2021

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	STUDY PERIOD										
	Enrolment	Allocation	Post-Allocation								
	-t1	0	t0	t1	t2	t3	t4	t5	t6	t12	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											
<i>Cognitive function:</i> MoCA	x		x						x	x	x
ccTB			x	x	x	x	x	x	x	x	
Secondary Outcomes											
<i>Cognitive function:</i> MMSE	x		x						x	x	x
<i>Depression:</i> PHQ-9	x		x						x	x	x
<i>Activities of daily living:</i> B-ADL			x						x	x	x
Other Variables											
Sociodemographic data			x								
Health-related data			x						x		
Modifiable risk factors for MCI			x						x		
<i>Usability:</i> UEQ									x		
<i>Dietary behaviour:</i> FFQ			x						x	x	
Weighing protocol (optional)							x				



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

1 Introduction

2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	6-7
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	6-7
7				
8	Objectives	7	Specific objectives or hypotheses	8
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	8-9
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	
12				

14 Methods: Participants, interventions, and outcomes

15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	8-12
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	10-11; 12-13
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	14-19
23			administered	
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	not applicable
25			change in response to harms, participant request, or improving/worsening disease)	
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	not applicable
27			(eg, drug tablet return, laboratory tests)	
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	not applicable
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	20-23
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation	
32			(eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
33			efficacy and harm outcomes is strongly recommended	
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits	Figure 1
35			for participants. A schematic diagram is highly recommended (see Figure)	
36				
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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
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
5				
6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	Sequence	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
11	generation			
12				
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14				
15				
16	Allocation	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
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
21				
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23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
28				
29				
30				
31	Methods: Data collection, management, and analysis			
32				
33	Data collection	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
34	methods			
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38		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
39				
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1	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
2				
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5	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
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	24-25
9				
10		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
11				
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14	Methods: Monitoring			
15				
16	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
17				
18				
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22		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
23				
24				
25	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
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28	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
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32	Ethics and dissemination			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	25
35				
36				
37	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
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1	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
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
5				
6				
7	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
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9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	35
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13	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
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16	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
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20	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
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
27				
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29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file
32				
33				
34	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
35				
36				

*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](https://creativecommons.org/licenses/by/4.0/)" license.

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

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43 33 Supplemental materials: 0

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3 35 **Computerised cognitive training tools and online nutritional group counselling for**
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5 36 **people with mild cognitive impairment: Study protocol of a completely digital,**
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7 37 **randomised, controlled trial**
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9

10 38 **ABSTRACT**
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14 39 **Introduction**
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16 40 People with mild cognitive impairment (MCI) are at increased risk of decreasing cognitive
17
18 41 functioning. Computerised cognitive training (CCT) and nutrition have been shown to
19
20 42 improve the cognitive capacities of people with MCI. For each variable, we developed two
21
22 43 kinds of interventions specialised for people with MCI (CCT: ‘individualised’ CCT [iCCT];
23
24 44 nutrition: a whole-food, plant-based diet [WFPB diet]). Additionally, there are two kinds of
25
26 45 active control measures (CCT: ‘basic’ CCT [bCCT]; nutrition: a healthy diet following the
27
28 46 current guidelines of the German Nutrition Society). The aim of the present study is to
29
30 47 investigate the effects of the two interventions on cognition in people with MCI in a 2x2
31
32 48 randomised controlled trial with German participants.
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40 50 **Methods and analysis**
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42 51 Participants will be community-dwelling individuals with a psychometric diagnosis of MCI
43
44 52 based on the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination
45
46 53 (MMSE). With $N = 200$, effects with an effect size of $f \geq 0.24$ (comparable to Cohen’s $d \geq$
47
48 54 0.48) can be detected. Screening, baseline, t6, and t12 testing will be conducted via a
49
50 55 videoconferencing assessment, telephone, and online survey. Participants will be randomly
51
52 56 allocated to one of four groups and will receive a combination of CCT and online nutritional
53
54 57 counselling. The CCT can be carried out independently at home on a computer, laptop, or
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2 58 tablet. Nutrition counselling includes 12 online group sessions every fortnight for 1.5 hours.
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4
5 59 The treatment phase is six months with follow-ups after six and 12 months after baseline.
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8 60 **Ethics and dissemination**

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10 61 All procedures were approved by the Friedrich-Alexander-Universität Erlangen-Nürnberg
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12 62 Ethics Committee (Ref. 21-318_1-B). Written informed consent will be obtained from all
13
14 63 participants. Results will be published in peer-reviewed scientific journals, conference
15
16 64 presentations.
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18

19 65 **Registration details**

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21 66 ISRCTN, ISRCTN10560738, prospectively registered 23 November 2021,
22
23 67 <https://doi.org/10.1186/ISRCTN10560738>
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28 68 **Keywords**

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30 69 Mild cognitive impairment; community-dwelling; computerised cognitive training; plant-
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32 70 based nutrition; randomised controlled trial
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37 72 **ARTICLE SUMMARY**

38 73 **Strengths and limitations of this study**

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44 74
- 45 75 • This study is being conducted completely remotely: videoconferencing assessments
46 76 with valid telehealth assessments for cognitive function, telephone-based interviews,
47 77 computerised cognitive test battery, computerised cognitive training, and online
48 78 nutritional group counselling.
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52 79
 - 53 80 • Randomised controlled trial with two interventions with an active control group for
54 81 each component and longitudinal character of the study with an intervention period
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1
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3 80 of six months, follow-ups after six and 12 months, and an open phase (planned) in
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5 81 which study participants might be assessed once a year.
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7 82 • Individualised computerised cognitive training for the intervention group by means
8
9 83 of a machine learning system that chooses computerised exercises that match the
10
11 84 person's level of difficulty by estimating the person's likelihood of successfully
12
13 85 solving the computerised exercises ('individualised' CCT).
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16 86 • Highly innovative curricular nutrition intervention based on current clinical evidence,
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18 87 tailored for people with MCI
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21 88 • Methodological limitations might include a restriction to participants who feel
22
23 89 comfortable with the use of technology; have internet access and own a computer,
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25 90 laptop, or tablet; and have MCI as their only psychometric diagnosis without a
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27 91 clinical diagnosis.
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102 INTRODUCTION

103 In the general population, the prevalence of mild cognitive impairment (MCI) defined by
104 Petersen [1] increases with age, at 6.7% for ages 60 to 64 and up to 25.2% for ages 80 to 84
105 [2]. People with MCI have a higher risk of progressing to dementia than cognitively normal
106 individuals [1, 3]. For example, Inui et al. [4] found that 72% of patients with amnesic MCI
107 progressed to Alzheimer's disease (AD) over five years. Thus, MCI seems to be the optimal
108 period for intervention before a conversion to dementia occurs.

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

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

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3 126 beneficial effects of nutrition on cognitive functioning, especially related to three types of
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5 127 diet: the *Mediterranean Diet* (MedDiet), the *Dietary Approaches to Stop Hypertension*
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7 128 (*DASH Diet*), and the *Mediterranean-DASH Intervention for Neurodegenerative Delay*
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9 129 (*MIND Diet*) [22-25]. All three abovementioned diets are predominantly whole-food plant-
10
11 130 based diets, primarily containing vegetables, whole grains, legumes, fruits, nuts, and seeds,
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14 131 are rich in poly- and monounsaturated fatty acids, and contain hardly any processed foods
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16 132 [26]. Furthermore, the diets are associated with reductions in various inflammatory markers
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18 133 [27-29]. Since MCI seems to be accompanied by inflammatory processes [30], and
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20 134 exclusively plant-based foods contain bioactive substances, such as phytochemicals and
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22 135 fibre, which have anti-inflammatory properties [31], there is an obvious need to further
23
24 136 investigate potential neuroprotective effects of plant-based nutrition in the context of clinical
25
26 137 MCI studies. Since cardiometabolic diseases are associated with the occurrence of dementia
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28 138 [32], and weight loss is associated with improved attention and memory performance [25], it
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30 139 can be hypothesised that a well-planned anti-inflammatory, neuroprotective, plant-based diet
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32 140 has the potential to alleviate symptoms of MCI and the progression to dementia.
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37 141 The aim of the proposed study is to examine the effects of CCT and online nutritional
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39 142 group counselling on the cognition of people with MCI in a completely digital RCT. We
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41 143 developed CCT and online nutritional group counselling, both specialised for people with
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43 144 MCI: individualised CCT (iCCT) targeting information processing speed, memory-span,
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45 145 short term memory and decision making, and nutritional group counselling focusing on a
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47 146 whole-food, plant-based (WFPB) diet. Additionally, there are two active control measures:
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49 147 basic CCT (bCCT) aiming on simple strategies and long-term memory, and nutritional group
50
51 148 counselling focusing on a healthy diet recommended by the German Nutrition Society
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53 149 (*Deutsche Gesellschaft für Ernährung, DGE diet*). This manuscript describes the study
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55 150 protocol while following the evidence-based reporting guidelines of the SPIRIT Statement
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3 152 **METHODS AND ANALYSES**
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6 153 **Aims and hypothesis**
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9 154 Research hypotheses
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12 155 Primary hypothesis I: Individualised CCT will lead to statistically significantly greater
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14 156 improvements in cognitive capacities during the intervention period of six months compared
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17 157 with basic CCT.
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20 158 Primary hypothesis II: Online nutritional group counselling focusing on a whole-food, plant-
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23 159 based diet (WFPB diet) will lead to statistically significantly greater improvements in
24
25 160 cognitive capacities during the intervention period of six months compared with online
26
27 161 nutritional group counselling focusing on a healthy diet recommended by the German
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29 162 Nutrition Society.
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33 163 Secondary hypothesis: Individualised CCT in combination with online nutritional group
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35 164 counselling focusing on a WFPB diet will have a positive interaction effect. The group with
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37 165 iCCT in combination with online nutritional group counselling focusing on a WFPB diet will
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39 166 show more cognitive improvements than all other groups during the intervention period of
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41 167 six months in people with MCI.
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46 168 Exploratory study question
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49 169 Are there changes in the course of depression and activities of daily living during the 12-
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51 170 month observation period?
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55 171 **Study design and setting**
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58 172 A prospective 2x2 randomised controlled intervention study is being conducted to test the
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60 173 abovementioned hypotheses. The overall start date of the study was on 1 June 2021.

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2 174 Recruitment will begin on 3 January 2022 and will continue until 30 September 2022.
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4 175 Because the study is being conducted completely remotely, individuals from all over
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6 176 Germany can participate. At baseline, all study participants will be randomly assigned to one
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8 177 of four intervention arms (combination of iCCT or bCCT and group counselling on WFPB
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10 178 diet or DGE diet). The CCT intervention is double-blind, the online nutritional group
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12 179 counselling is single-blind. Since the principal usefulness of CCT is well-known [15-20], it
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14 180 would be unethical to use a control group without any CCT. After baseline testing (t0), the
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16 181 participants will receive one of the two computerised training applications for their
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18 182 computer, laptop, or tablet. It is recommended that they use the application at least 30
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20 183 minutes per day three days a week during the six-month intervention phase. Both
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22 184 computerised training applications contain the same computerised cognitive test battery
23
24 185 (ccTB) that will be delivered and collected once a month (t0-t12). After the end of the six-
25
26 186 month intervention phase, all participants will be free to continue to use the application. The
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28 187 online nutritional group counselling sessions will focus on either a WFPB diet or a DGE
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30 188 diet. Both groups will receive curricular online nutritional group counselling at regular 14-
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32 189 day intervals for 1.5 hours (twelve appointments total per participant over a period of six
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34 190 months, online group setting in a fixed group, max. 20 participants per group). The
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36 191 intervention phase is from t0 to t6. Follow-up is planned after six (t6) and 12 (t12) months.
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38 192 The open phase of the study will begin after t6 in order to test the hypotheses and
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40 193 exploratory study questions until t12. A follow-up study is planned to observe the
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42 194 participants after t12. Table 1 contains the trial registration data.
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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	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. MCI <ol style="list-style-type: none"> 1.1. Montreal Cognitive Assessment score (MoCA) \leq 24 1.2. Mini-Mental State Examination score (MMSE) \geq 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 \geq 60 4. Informed consent given <hr/> <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 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 \geq 12 6. Diagnosis of another disease that causes cognitive impairment: <ul style="list-style-type: none"> • Psychosis (schizophrenia, mania, bipolar psychosis) • Morbus Parkinson • Multiple sclerosis • Multiple strokes • Alcohol abuse / drug consumption (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)	<p>Cognition measured by the Montreal Cognitive Assessment (MoCA) at baseline and after six months</p> <p>Cognition measured by the computerised cognitive test battery (ccTB) integrated in the digital software at baseline and after 6 and 12 months</p>
20. Key secondary outcomes	<p>Cognitive Function measured by the Mini-Mental State Examination (MMSE) at baseline and after 6 and 12 months</p> <p>Depression measured by the Patient Health Questionnaire 9 (PHQ-9) at baseline and after 6 and 12 months</p> <p>Activities of daily living measured by the Bayer Activities of Daily Living Scale (B-ADL) at baseline and after 6 and 12 months</p>

1
2
3 196 Data will be collected by means of psychometric tests and structured interviews using
4
5 197 videoconferencing, telephone, and an online survey. The data will be collected by trained
6
7 198 student assistants who have no knowledge of group allocation at any time. Two days before
8
9 199 baseline testing (t0), the study participants will receive an email with a link to download the
10
11 200 software for their version of the computerised application and instructions on how to
12
13
14 201 download and install the software.

17 202 **Sample size estimation**

18
19
20 203 A power analysis was computed with 200 participants distributed to the two groups of the
21
22 204 2x2x2 factorial variance-analytic experimental design with one repeated measure (factor 1:
23
24 205 two CCTs; factor 2: two types of online training for dietary modification, factor 3: two time
25
26 206 points). With 50 participants in each group, $\alpha = 0.05$, $\beta = 0.20$ (corresponding to a power of
27
28 207 80%), a correlation between repeated measures of 0.5, and a nonsphericity correction of 1,
29
30 208 we will have the power to detect effects with an effect size of $f \geq 0.24$ (comparable to
31
32 209 Cohen's $d \geq 0.48$).

36 210 **Recruitment strategies**

37
38
39 211 Participants will be recruited from the general population all over Germany. The project's
40
41 212 homepage was designed to provide information about the study. Also, an appointment for a
42
43 213 screening can be made via the project homepage. We partnered with a health insurance
44
45 214 company that is sending emails to their members aged 60 and above with information about
46
47 215 the study and a link to the project homepage. About 25 thousand members will receive an
48
49 216 email with information about the study in six waves between December 2021 and May 2022.

53 217 **Eligibility of participants**

54
55
56 218 Individuals who are interested in the study can make an appointment for a screening via the
57
58 219 project homepage. During the screening, we will offer an examination of basic cognitive
59
60

220 functioning including a personal conversation about their screening results afterwards.

221 Individuals who fulfil the criteria for inclusion will be informed about the study and asked to
222 take part in the project.

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

237 The MMSE and the MoCA will be administered in combination to differentiate
238 between normal cognition, MCI, and dementia. The MoCA will be administered first to
239 differentiate between normal cognition and MCI on the basis of the cut-off score of 24 points
240 [34-36]. The MMSE will be administered to differentiate between MCI and dementia on the
241 basis of the cut-off score of 23 points [37]. For these cut-offs, we will look for an optimised
242 ratio of sensitivity and specificity. The criteria for a positive screening for MCI, normal
243 cognition, or dementia are shown in Table 2.

244 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

245 Abbreviations. MCI: Mild cognitive impairment; MoCA: Montreal Cognitive Assessment;

246 MMSE: Mini-Mental State Examination. * The MMSE will be applied only when the

247 MoCA results are in the range of 24 to 0 points.

248 **Randomisation**

249 Our external biostatistics partner is creating computer-generated randomisation lists

250 (Institute of Medical Informatics, Biometry, and Epidemiology, Friedrich-Alexander

251 Universität Erlangen-Nürnberg, Waldstraße 6, 91054 Erlangen). All individuals meeting the

252 inclusion criteria will be randomised into one of the four groups (combination of the CCT

253 component: iCCT or bCCT and the online nutritional group counselling component: WFPB

254 diet or DGE diet). Randomisation will be stratified by sex, age, MoCA score at screening.

255 Residents of the same household will be assigned to the same group. Participants will not

256 know which treatment condition they are in, and the student assistants who assess the

257 outcomes of the study will be blind to participants' allocation at all times.

258 **Interventions**

259 **Computerised cognitive training**

260 Both computerised applications (intervention and control) are available for Windows,

261 MacOS, and Linux PC/laptop and Android tablet.

262 Individualised CCT for people with MCI

263 The exercises included in this training application have been selected to address the expected

264 level of performance of people with MCI. All exercises are available with different levels of

1
2
3 265 difficulty. The ten playful exercise tasks involve the basic parameters of information
4
5 266 processing as well as short-term memory and require different types of decision-making (see
6
7 267 Table 3). The initial difficulty levels of the exercises are determined by a machine-learning
8
9 268 system, which uses (a) a (logistic regression) model that is based on data from people with
10
11 269 MCI (individualised by considering each participant's data) and (b) the cognitive status of
12
13
14 270 the participant (i.e. the results of the integrated computerised cognitive test battery) to
15
16 271 estimate the likelihood of a participant's success at a certain difficulty level for a task. The
17
18 272 initial model is based on data collected prior to the study. The application chooses the
19
20
21 273 highest level the participant is likely to solve as the entry level. With the machine learning
22
23 274 system, individual (compensation) strategies are nullified, and the ideal level of difficulty for
24
25 275 training is generated for each participant. Thus, the iCCT is aimed at improving the
26
27
28 276 beneficial effects of CCT by providing exercises at the difficulty level that fits each
29
30 277 participant best.

31 32 33 278 Basic CCT (active control group)

34
35
36 279 This training application uses exercise tasks that are oriented towards quizzes and visual
37
38 280 tasks (see Table 3). The exercise tasks are playfully designed and require, among other
39
40
41 281 things, simple strategies and long-term memory. Most of the exercises exist with only a
42
43 282 single level of difficulty. The entry-level difficulties of the other exercises are determined
44
45 283 solely by the participant's prior successful results on this exercise. The exercises of the
46
47
48 284 bCCT are aimed at providing enjoyable computerised leisure activities with a limited
49
50 285 number of cognitive tasks for the active control group.
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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.

288 **Online nutritional group counselling**

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

298 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

299 **Counselling focusing on a whole-food plant-based diet**

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

1
2
3 305 is encouraged (e.g. green leafy vegetables [38], mushrooms [39], citrus fruits [40], soy
4
5 306 products [41], blueberries [42], nuts [43], turmeric [44], green tea [45], and omega-3 fatty
6
7 307 acids [46]). Participants are instructed to exclude animal products from their diets because of
8
9 308 the pro-inflammatory potential of animal products and to refrain from consuming highly
10
11 309 processed foods [47]. Monthly delivery contains a selection of neuroprotective foods (e.g.
12
13
14 310 plant oil with polyunsaturated fatty acids, nuts, whole grains, green tea).

311 **Counselling focusing on a diet recommended by the German Nutrition Society**

312 Participants in this group will receive systematic recommendations according to the official
313 guidelines of the DGE diet for healthy eating [48]. This means they will be encouraged to
314 establish an omnivorous diet based on vegetables, fruits, and whole grains, including
315 moderate intake of animal products, such as fish, poultry, red meat, eggs, and milk products
316 (see Table 5). The DGE group will also be encouraged to prefer fresh, whole-food, non-
317 processed foods and to reduce their consumption of saturated fatty acids, sweetened drinks,
318 or highly processed foods [48, 49]. Eating products coming from animals is also limited
319 within the DGE context with a greater focus on vegetables, fruits, and whole-grain cereals or
320 bread. The delivery boxes will contain a selection of DGE-appropriate basic foods beneficial
321 to health (e.g. whole grain, plant-based oils or nuts/seeds, sugar alternatives, foods that are
322 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)

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2
3
4 325 **Measures**

5
6 326 The data are being collected at baseline and follow-up by student assistants (psychology
7
8 327 students) who are well-trained to conduct performance tests and interviews via an online
9
10 328 survey. The measures that are being used at the different measurement points are shown in
11
12
13 329 Figure 1. *(Please enter figure 1 here)*

14
15
16 330 Primary outcome measures

17
18 331 *Montreal Cognitive Assessment (MoCA)* [50]. The MoCA is a performance test that is used
19
20 332 to screen for MCI. It consists of more difficult items than the MMSE and is thus able to
21
22 333 better detect MCI [50-53]. The score ranges from 0 to 30 points, with higher scores
23
24 334 indicating better cognitive performance. A score ≤ 24 indicates cognitive impairment [34-
25
26 335 36]. There are three parallel versions of the German translation of MoCA for
27
28 336 videoconferencing being used. Version 8.1 is conducted at t1 (screening), version 8.2 at t6
29
30 337 and version 8.3 at t12. The MoCA has been found to be an appropriate measure for cognitive
31
32 338 screening and has good reliability and validity values [54].

33
34 339 *Computerised cognitive test battery (ccTB)*. Both versions of the computerised training
35
36 340 application contain a set of exercises for measuring different cognitive abilities monthly,
37
38 341 beginning at baseline. Eight tests are used to measure various cognitive abilities (see Table 6).
39
40
41
42
43

44 342 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]

343 Abbreviations. SKT: Syndrom-Kurz-Test (engl. Short Cognitive Performance Test); WAIS-

344 IV: Wechsler Adult Intelligence Scale – Fourth Edition.

345 Secondary outcome measures

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

1
2
3 354 *The 9-Item Patient Health Questionnaire (PHQ-9)* [67, 68]. The PHQ-9 is a short self-
4
5 355 assessment tool often used in primary care settings to screen for depression [69]. Its nine items
6
7 356 cover the nine DSM-IV criteria by asking patients about their experiences during the last two
8
9 357 weeks and are rated on a four-point scale ranging from 0 ('not at all') to 3 ('nearly every day').
10
11 358 The total sum score suggests varying levels of depression. A cut-off ≥ 12 was found to show
12
13 359 a good balance between sensitivity and specificity [70]. The PHQ-9 was found to be a reliable
14
15 360 and valid instrument for screening for depression [67].

16
17
18 361 *The Bayer Activities of Daily Living Scale (B-ADL)* [71]. The B-ADL assesses difficulties in
19
20 362 the performance of everyday activities. It comprises 25 items, which evaluate general ADL
21
22 363 competencies and specific tasks important for management in everyday life. The frequency
23
24 364 of difficulties the patient experiences in performing everyday activities is rated on a 10-point
25
26 365 scale ranging from 1 ('never') to 10 ('always'). A global score is computed by summing
27
28 366 across all items and dividing by the number of items rated. The resulting score ranges from 1
29
30 367 to 10 with higher scores corresponding to more severe deficits.

31
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33
34
35 368 Other variables

36
37
38 369 *Questionnaire on sociodemographic and health-related data*. Sociodemographic data (age,
39
40 370 sex, marital status, highest educational level, employment status, monthly income, household
41
42 371 size) from a standardised questionnaire will be recorded by the student assistants at baseline.
43
44 372 Modifiable risk factors for MCI (status of general mental activities, physical activities, social
45
46 373 participation, sleeping habits, average liquid intake, eating habits, alcohol consumption,
47
48 374 nicotine consumption, visual/hearing capacity), and health-related data (diseases,
49
50 375 medications, body weight, body height, dementia cases in the family) will be recorded at
51
52 376 baseline, t6 and t12.

53
54
55
56 377 *User Experience Questionnaire (UEQ)* [72]. The UEQ measures attractiveness, perspicuity,
57
58 378 efficiency, dependability, stimulation, and novelty of software with 26 bipolar items. The
59
60

1
2 379 questionnaire consists of pairs of contrasting attributes (e.g. ‘understandable’ vs. ‘not
3
4 380 understandable’) that can be rated on a 7-point Likert scale. The UEQ was found to show a
5
6 381 satisfactory level of reliability and construct validity [72].
7
8

9 382 *Additional digital data.* Both CCTs track usage data. The usage data include the duration of
10
11 383 use, difficulty, success, and other parameters for each training task run.
12

13 384 *Online Food Frequency Questionnaire (FFQ)* [73]. A modified FFQ of the DEGS1-Survey
14
15 385 from the Robert Koch Institute will be assessed as an online survey at baseline, t6 and t12
16
17 386 (https://www.rki.de/DE/Content/Gesundheitsmonitoring/Studien/Degs/degs_node.html). It
18
19 387 consists of questions about dietary behaviour from the past 4 weeks (on average), containing
20
21 388 all relevant plant-based and animal-based foods as well as neuroprotective ingredients, to
22
23 389 estimate the frequency of the consumption of different food groups.
24
25

26 390 *Weighing protocol.* After 3 months of intervention (t3) a non-obligatory weighing protocol
27
28 391 (3 days: 2 working days/1 weekend day) will be emailed and is to be completed and scanned
29
30 392 back or completed online.
31
32

33 34 35 393 **Data collection**

36
37 394 The data will be collected at baseline (t0) and at follow-up after six (t6) and 12 months (t12)
38
39 395 (see Figure 1). Annual follow-up studies will test for conversions to dementia. The trial will
40
41 396 be conducted remotely. All data will be generated via videoconferencing, telephone, online
42
43 397 survey, or the ccTB that is integrated into the CCTs.
44
45

46
47 398 Testing with the MoCA and MMSE will be conducted via videoconferencing with the
48
49 399 student assistants. Videoconferencing assessments with the MoCA and MMSE have very
50
51 400 high reliability scores compared with face-to-face testing. The intraclass correlation
52
53 401 coefficients (ICCs) for the MoCA and the MMSE have been demonstrated in several studies
54
55 402 and go up to ICC = 0.99 for the MoCA [74] and up to ICC = 0.92 for the MMSE [75]. In a
56
57 403 recent systematic review [76], the MoCA and the MMSE were described as valid telehealth
58
59
60

1
2 404 measures for screening cognitive status. Telemedicine is an emerging new field, and there is
3
4
5 405 evidence that it is a valuable tool for assessing neurodegenerative diseases [76-78].
6

7 406 The questionnaire on sociodemographic and health-related data will be sent to the
8
9 407 study participants to prepare them for the interview. The FFQ online survey and the non-
10
11 408 obligatory weighing protocol will be emailed to participants and are to be completed and
12
13
14 409 scanned back or completed online. The evaluation will be done pseudonymously via
15
16 410 nutrition software with a food database (NutriGuide) to support the accuracy of the FFQ
17
18 411 survey. During the six-month intervention period, the usage data collected by the CCT,
19
20 412 including the ccTB data, will be obtained from the participants. After the monthly ccTB
21
22 413 assessment, consent to upload the CCT data will be requested. When consent is given, the
23
24 414 data will be uploaded to the Erlangen study centre's server. The server configuration
25
26
27 415 prohibits downloads of the data by people who are not study team members. The data will be
28
29
30 416 pseudonymised.
31

32 33 417 **Data quality management and data protection** 34

35
36 418 The student assistants involved in the study have been thoroughly trained for their tasks by
37
38 419 the study centre's staff. When the participants have questions concerning the computerised
39
40 420 interventions or the online nutrition groups, they can email the study centre. The quality of
41
42 421 the data will be guaranteed by strict data monitoring at the study centre for the total study
43
44 422 period. Plausibility checks and logical considerations of the relationships between associated
45
46 423 variables will be performed. A data protection concept was developed, reviewed and
47
48 424 approved by the data protection officer of the Universitätsklinikum Erlangen.
49
50

51 52 53 425 **Patient and public involvement** 54

55
56 426 Study participants or the public will not be involved in developing, designing, or conducting
57
58 427 the study. To recruit participants from the general population, our recruitment partner, a
59
60

1
2 428 health insurance company, will send emails to their customers with information about our
3
4
5 429 study. Additional information about the study can be found on the project homepage.
6
7

8 430 **Data Analysis**

9
10 431 All relevant data, sociodemographic, health-related, primary, and secondary outcome
11
12 432 variables will be reported descriptively. In order to be able to assess the quality of the
13
14 433 randomisation, the baseline data from the intervention and control groups will be tested for
15
16 434 statistically significant differences. For the multivariate analyses, we will impute missing
17
18 435 values using the expectation maximization algorithm. The primary hypothesis will be tested
19
20 436 via ANOVA, which makes it possible to detect interaction effects in the chosen 2x2x2
21
22 437 factorial design. To ensure the robustness of the results, we will perform both intention to
23
24 438 treat and per protocol analyses. Intention to treat evaluations are carried out with all cases
25
26 439 still alive at the end of the intervention or observation period. The significance level is
27
28 440 defined as $\alpha = 0.05$. The data analyses will be performed using the IBM SPSS Statistics 28
29
30 441 software.
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36

37 442 **ETHICS AND DISSEMINATION**

38 39 40 443 **Ethical considerations**

41
42 444 All procedures were approved by the Friedrich-Alexander-Universität Erlangen-Nürnberg
43
44 445 Ethics Committee (Ref. 21-318_1-B). Participation will be voluntary, and participants will
45
46 446 be free to leave the study at any time. All legal matters, such as voluntariness, right of
47
48 447 revocation, and General Data Protection Regulation (EU) are considered. People with MCI
49
50 448 are independent and fully capable of conducting business and giving consent. Upon
51
52 449 agreement, consent to participate (written informed consent) will be obtained from all
53
54 450 participants by the student assistants who are members of the study centre. All participants
55
56 451 will be informed about the study in a personal videoconference after they are screened for
57
58
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60

1
2 452 eligibility. A participant information sheet including important information about
3
4 453 participation (e.g. randomisation, data protection, data storage) will be given to every
5
6
7 454 participant (sent by post). The opportunity to ask questions will be granted by
8
9 455 videoconference, telephone, and email afterwards at any time. Participants will not be
10
11 456 offered any financial inducement to participate. The external funder, the Karl and Veronica
12
13 457 Carstens-Stiftung, is continuously being informed about the progress of the study. In the case
14
15 458 of important protocol modifications, we will inform the Ethics Committee, the funder, and
16
17 459 the trial registry platform.
18
19
20
21

22 460 **Data handling**

23
24 461 Informed consent will be stored in a locked steel cabinet. A customized digital participant
25
26 462 management system webMODYS (Web-based modular control and documentation system;
27
28 463 Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen,
29
30 464 Germany) will be used for the administration of the study and will be the only location for
31
32 465 personal data. webMODYS is hosted in the IT infrastructure of the Universitätsklinikum
33
34 466 Erlangen. Only members of the study team will have access to the lists of participants’
35
36 467 names and codes in webMODYS. All data will be stored in only a pseudonymised form
37
38 468 digitally in the data collection system REDCap [79, 80] hosted at the Universitätsklinikum
39
40 469 Erlangen and Charité Berlin. REDCap is a secure, web-based software platform designed to
41
42 470 support data capturing for research studies. The IT architecture including the digital study
43
44 471 administration and data collection was ‘inspired’ by the digiDem Bayern Registry [81].
45
46 472 Results of the study for scientific or other publications will be published only in aggregate
47
48 473 form (mean values, etc.). No published material will contain patient-identifying information.
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474 **Safety considerations**

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

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

486 **Dissemination plan**

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

490 **TRIAL STATUS**

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

493 **LIST OF ABBREVIATIONS**

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

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2 497 (Deutsche Gesellschaft für Ernährung, DGE); FFQ: Food Frequency Questionnaire; MCI:
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4 498 mild cognitive impairment; MMSE: Mini-Mental State Examination; MoCA: Montreal
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6 499 Cognitive Assessment; PHQ-9: 9-Item Patient Health Questionnaire; RCT: randomised
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8 500 controlled trial; SKT: Syndrom-Kurz-Test (engl. Short Cognitive Performance Test); UEQ:
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10 501 User Experience Questionnaire; WAIS-IV: Wechsler Adult Intelligence Scale – Fourth
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12 502 Edition; WFPB diet: whole-food plant-based diet.
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3 783 **LIST OF FIGURES**
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6 784 **Figure 1 – Timeline of measurements**
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8 785 *intended for a follow-up study after t12.
9

10 786 Abbreviations. B-ADL: Bayer Activities of Daily Living Scale; bCCT: basic computerised
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13 787 cognitive training; CCT: computerised cognitive training; ccTB: computerised cognitive test
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15 788 battery; DGE diet: diet recommended by the German Nutrition Society (Deutsche
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17 789 Gesellschaft für Ernährung, DGE); FFQ: Food Frequency Questionnaire; iCCT:
18
19 790 individualised cognitive training; MCI: mild cognitive impairment; MoCA: Montreal
20
21 791 Cognitive Assessment; MMSE: Mini-Mental State Examination; PHQ-9: Patient Health
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23 792 Questionnaire; UEQ: User Experience Questionnaire; WFPB diet: whole-food plant-based
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26 793 diet.
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30 794 **LIST OF TABLES**
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34 795 **Table 1 – Trial registration data**
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40 797 **Table 3 – Computerised cognitive exercises**
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43 798 **Table 4 – Overview of the six-month online nutritional group counselling**
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50 800 **Table 6 – Computerised cognitive test battery**
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3 805 **Authors' contributions**

4 806 PS contributed to the design of the study, is supervising the study, is contributing to the
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6
7 807 implementation of the study, and drafted the manuscript. SB contributed to the design of the
8
9 808 study, is supervising the study, is contributing to the implementation of the study, and
10
11 809 drafted the manuscript. MJ designed the CCT applications, is contributing to the
12
13 810 implementation of the study, and drafted parts of the manuscript. EH is contributing to the
14
15 811 implementation of the study and drafted parts of the manuscript. MDO designed the nutrition
16
17 812 intervention and is contributing to the implementation of the study. JS designed the nutrition
18
19 813 intervention and is contributing to the implementation of the study. MJe contributed to the
20
21 814 design of the study and is supervising the study. JSS is supervising the study and
22
23 815 contributing to the implementation of the study. SoB is contributing to the psychometric
24
25 816 examinations and supervising the student assistants. CK initiated the study, contributed to
26
27 817 the design of the study, and is supervising the study. EG initiated the study, contributed to
28
29 818 the design of the study, is supervising the study, and drafted parts of the manuscript. All
30
31 819 authors read and approved the final version of the manuscript.
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43
44 823 interpretation of the data, or in writing the manuscript.
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46
47

48 824 **Competing interests statement**

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50
51 825 The authors report no conflicts of interest.
52
53

54 826 **Data availability statement**

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56
57 827 For this study protocol, no datasets have been generated yet.
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59
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1
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35 842 Revision chronology:

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22.12.2021

Original

25.04.2022

Revision

843

	STUDY PERIOD										
	Enrolment	Allocation	Post-Allocation								
	-t1	0	t0	t1	t2	t3	t4	t5	t6	t12	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											
<i>Cognitive function:</i> MoCA	x								x	x	x
ccTB			x	x	x	x	x	x	x	x	
Secondary Outcomes											
<i>Cognitive function:</i> MMSE	x								x	x	x
<i>Depression:</i> PHQ-9	x								x	x	x
<i>Activities of daily living:</i> 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	
<i>Usability:</i> UEQ									x		
<i>Dietary behaviour:</i> FFQ			x						x	x	
Weighing protocol (optional)							x				



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	6-7
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	6-7
7				
8	Objectives	7	Specific objectives or hypotheses	8
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	8-9
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	8-12
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	10-11; 12-13
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	14-19
23			administered	
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	not applicable
25			change in response to harms, participant request, or improving/worsening disease)	
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	not applicable
27			(eg, drug tablet return, laboratory tests)	
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	not applicable
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	20-23
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation	
32			(eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
33			efficacy and harm outcomes is strongly recommended	
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits	Figure 1
35			for participants. A schematic diagram is highly recommended (see Figure)	
36				
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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
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
5				
6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	Sequence	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
11	generation			
12				
13				
14				
15				
16	Allocation	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
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
28				
29				
30				
31	Methods: Data collection, management, and analysis			
32				
33	Data collection	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
34	methods			
35				
36				
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38		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
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1	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
2				
3				
4				
5	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
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	24-25
9				
10		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
11				
12				
13				
14	Methods: Monitoring			
15				
16	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
17				
18				
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20				
21				
22		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
23				
24				
25	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
26				
27				
28	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
29				
30				
31				
32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	25
35				
36				
37	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
38				
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1	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
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
5				
6				
7	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
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	35
11				
12				
13	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
14				
15				
16	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
17				
18				
19				
20	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
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file
32				
33				
34	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
35				
36				

*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](https://creativecommons.org/licenses/by/4.0/)" 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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