PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Computerised cognitive training tools and online nutritional group counselling for people with mild cognitive impairment: Study protocol of a completely digital, randomised, controlled trial
AUTHORS	Scheerbaum, Petra; Book, Stephanie; Jank, Michael; Hanslian, Etienne; Dell´Oro, Melanie; Schneider, Julia; Scheuermann, Julia-Sophia; Bösl, Sophia; Jeitler, Michael; Kessler, Christian; Graessel, Elmar

VERSION 1 – REVIEW

REVIEWER	Bernini, Sara Foundation National Neurological Institute C Mondino Institute for Hospitalization and Care Scientific
REVIEW RETURNED	17-Feb-2022

GENERAL COMMENTS	Authors state that MoCa and MMSE will be conducted via videoconferencing. It would be helpful if they specified whether they used any particular versions of these well-known screening tools traditionally administered in person in pen-and-paper format (i.e., particular versions adapted for remote administration, or computerized versions).

REVIEWER	Wouters, Hans
REVIEW RETURNED	14-Mar-2022

GENERAL COMMENTS	Thank you for inviting me to review this submission. I have quite some thoughts and recommendations to share with the authors. However, in this case this has less to do with doubts and much more to do with my enthusiasm about this study which is so deliberately and carefully designed. The manuscript was truly an exemplary, very clear. My thoughts / recommendations: General: 1. In geriatric medicine (and medicine in general) a new writing style has been advocated. In general it's important to avoid suggestive and (potentially) judgmental writing. Please read the advice by the Journal of the American Geriatrics Society, see: https://agsjournals.onlinelibrary.wiley.com/hub/journal/15325415/forauthors.html • I therefore recommend to change the 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" into "Computerised cognitive training tools and online nutritional group counselling for people with mild cognitive impairment: Study protocol of a completely digital, randomised, controlled clinical trial

	• Throughout the text, I would advice you to prevent potentially judgmental writing 2. Given that the study is mainly conducted online, I suggest you to read about / contact the Trials@Home consortium see e.g.: https://trialsathome.com/. Introduction 3. Well-written. Clear balance of on the one hand sufficient rationale for the intervention (if not clear you could examine everything) while also clarifying the situation of equipoise (otherwise, a control group would be unethical). Thus to me, this RCT, or the RCCT as the authors label their study, is justified. 4. I am a bit struggling with the control groups. If more happens in these control groups than in usual care, the control groups could be actually interventions, albeit weaker than the proposed intervention groups. This in turn may reduce Cohen's d. Please note that this is not to criticise the study. Researcher allegiance in which there happens less in the control groups than in usual care is likely to result in an overestimation of the effect sizes and in such case interventions shown to be effective in RCTs do not live up to their expectations in clinical practice (Leichsenring and Steinert 2017., see: https://jamanetwork.com/journals/jama/article-abstract/2654783). Later on in the Methods and Analyses I read that the comparison between 'individualised CCT' vs. 'standard CCT' was actually chosen for the matter of equipoise as standard CCT was already shown to be effective and thus you cannot withhold it from people (lines 174-175). I would recommend to describe the latter in the Introduction. My sincere compliments for this rationale! And yes, the story of Scylla and Charybdis remains actual to this date. 5. While I like the secondary hypothesis, this could only be true if the diet really sustains the individualised cognitive training beyond the intrinsic potential effects of the training. That remains to be seen. Could you elucidate this with prior evidence which makes this likely to happen? I can also imagine that the effects will be main effects, which would add to each other and which would be an accomplishment in itself or wouldn't it? 6. I appreciate the exploratory study question! We should really look at the broader picture of MCI. Methods and Analyses 7. In the light of pragmatism and generalisation of findings from an artificial setting such as an RCT to clinical practice, I really appreciate the authors' idea to advise people to do the individualised cognitive training a certain amount of time per turn and to do this a number of times per week, but letting them choose themselves in the end (lines 177-178). However, a concern is that this may induce heterogeneity in the fidelity of the intervention, it would be strongly recommended to take this into account. Will you monitor how often and how long people will do the training? From what I read in line 375 this seems to be the case. Something similar can be said about the plant based diet intervention. Will you monitor whether people actually refrained from meat consumption? It seems that you can assess this with the FFQ questionnaire? Nice to read that you will also collect data on weight which could also provide information about the fidelity of the diet intervention. Altogether I would also somehow incorporate the fidelity in the per protocol analyses (vs. intention to treat analyses) which is now restricted to survival (line 429). Alternatively, the fidelity of the intervention could be the independent variable of interest i.e. amount / time of doing cognitive exercises and dieting predicts cognitive function? So more like a dose response relationship? (and a kind of mixture between experimental manipulation and observation?) 8. Eligibility criteria appear correct (either with regard to the aetiology or are defendable from an ethical point of view). 9. Line 250: What is meant with couples? Marital couples?

	10. Line 340 and further: the entire section about the MMSE is in bold letter type (?). Do you want to emphasize something? Overall and in the end, I would like to congratulate you wholeheartedly on designing such a nice study!

REVIEWER	Chandler, Melanie Mayo Clinic, Psychiatry and Psychology
REVIEW RETURNED	23-Mar-2022

GENERAL COMMENTS	The authors are embarking on a study of the impact of individualized cognitive training and whole food, plant based dietary planning over standard CCT and dietary recommendations on the cognition of individuals with MCI. The rationale and methods are generally explained well. I would like to see more detail added to the protocol as follows: -Please provide more explanation of how the WFPB diet differs from the GNS recommendations. -Very little is stated about how adherence to the recommendations (CCT or Dietary) will be measured during the course of the intervention and in the follow-up period. How will the researchers know how much CCT the individual engaged in? Or, how closely they followed the recommended diet? Please describe how this will be done at baseline, during intervention, and in the follow-up period. How will adherence be accounted for in the statistical analyses? -Participants with significant depression based on a PHQ 9 cut off will be excluded. What safety measures are in place for getting any needed emergency care for these individuals and the students handling these sessions with these individuals? While the methods are described clearly for the purposes of a protocol manuscript, I would like to offer two methodology concerns for the authors. If I was later reviewing a manuscript of the results of this study, I would have serious concerns about the operational definition of MCI used in this protocol. Defining MCI based upon a low enough score on the MoCA and high enough score on the MMSE is woefully insufficient. You will misidentify many participants with this method, particularly by excluding many MCI patients who have a MoCA score above 24. While it may be difficult to do a more thorough assessment, you will undoubtedly be asked to justify this selection method when you go to publish results. Lastly, I think the MoCA is limited as a primary cognitive outcome. I would highlight your CCTB as the primary cognitive outcome, as the limited range of scores will likely limit your ability to find change on the MoCA.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1
Comments to the Author:
Authors state that MoCA and MMSE will be conducted via videoconferencing. It would be helpful if they specified whether they used any particular versions of these well-known screening tools traditionally administered in person in pen-and-paper format (i.e., particular versions adapted for remote administration, or computerized versions).
Response:
Thank you for this comment. We specified the information in the study protocol. We wrote: “There are three parallel versions of the German translation of MoCA for videoconferencing being used. Version 8.1 is conducted at -t1 (screening), version 8.2 at t6 and version 8.3 at t12.” (line: 335-328) and “For the current study, the MMSE was adapted to an audio-visual setting based on Munro Cullum et al. (2013) and Timpano et al. (2014)” (line 352-354).

Reviewer #2
Comments to the Author:
Thank you for inviting me to review this submission. I have quite some thoughts and recommendations to share with the authors. However, in this case this has less to do with doubts and much more to do with my enthusiasm about this study which is so deliberately and carefully designed. The manuscript was truly an exemplary, very clear.

My thoughts / recommendations:

General:
1. In geriatric medicine (and medicine in general) a new writing style has been advocated. In general it’s important to avoid suggestive and (potentially) judgmental writing. Please read the advice by the Journal of the American Geriatrics Society, see:
https://agsjournals.onlinelibrary.wiley.com/hub/journal/15325415/forauthors.html

• I therefore recommend to change the 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” into “Computerised cognitive training tools and online nutritional group counselling for people with mild cognitive impairment: Study protocol of a completely digital, randomised, controlled trial

• Throughout the text, I would advice you to prevent potentially judgmental writing

Response: Thank you for this helpful advice. We checked the whole document on judgemental writing carefully.
In addition, we changed the title as you suggested.

2. Given that the study is mainly conducted online, I suggest you to read about / contact the Trials@Home consortium see e.g.: https://trialsathome.com/.

Response: Thank you for your advice. We are aware that, as data collection via teleconference is

increasing, the necessity of a standardised procedure is of utmost importance. We will consider future guidelines of the Trials@Home consortium in subsequent studies.

Introduction

3. Well-written. Clear balance of on the one hand sufficient rationale for the intervention (if not clear you could examine everything) while also clarifying the situation of equipoise (otherwise, a control group would be unethical). Thus to me, this RCT, or the RCCT as the authors label their study, is justified.
Response: We are pleased to read the feedback.

4. I am a bit struggling with the control groups. If more happens in these control groups than in usual care, the control groups could be actually interventions, albeit weaker than the proposed intervention groups. This in turn may reduce Cohen's d. Please note that this is not to criticise the study. Researcher allegiance in which there happens less in the control groups than in usual care is likely to result in an overestimation of the effect sizes and in such case interventions shown to be effective in RCTs do not live up to their expectations in clinical practice (Leichsenring and Steinert 2017., see: https://jamanetwork.com/journals/jama/article-abstract/2654783). Later on in the Methods and Analyses I read that the comparison between 'individualised CCT' vs. 'standard CCT' was actually chosen for the matter of equipoise as standard CCT was already shown to be effective and thus you cannot withhold it from people (lines 174-175). I would recommend to describe the latter in the Introduction. My sincere compliments for this rationale! And yes, the story of Scylla and Charybdis remains actual to this date.
Response: Thank you for your suggestion. We added short descriptions to the introduction. We wrote "individualised CCT (iCCT) targeting information processing speed, memory-span, short term memory and decision making, "(line 144-145) and "basic CCT (bCCT) aiming on simple strategies and long-term memory," (line 147-148)

5. While I like the secondary hypothesis, this could only be true if the diet really sustains the individualised cognitive training beyond the intrinsic potential effects of the training. That remains to be seen. Could you elucidate this with prior evidence which makes this likely to happen? I can also imagine that the effects will be main effects, which would add to each other and which would be an accomplishment in itself or wouldn't it?
Response:
Thank you for your important remarks. The 2x2x2 factorial design was chosen specifically for this reason, please see section "data analysis".
Based on both cohort studies and randomized controlled trials, evidence of dietary patterns on cognitive functions in patients with MCI and dementia is best described for the MedDiet (Mediterranean Diet), the DASH Diet (Dietary Approaches to Stop Hypertension), and the MIND Diet (Mediterranean-DASH Intervention for Neurodegenerative Delay).
A recent analysis of cross-sectional data from the longitudinal study of the German Center for Neurodegenerative Diseases e. V. (DZNE) confirmed the positive effects of a Mediterranean diet as a protective lifestyle factor against cognitive impairment and dementia (Ballarini et al., 2021). Reduced intake of animal proteins and specific amino acids (leucine, histidine) seem to enhance the health benefits of a plant-based diet (Kahleova et al., 2017). The anti-inflammatory effects of phytochemicals, as well as beneficial effects of other plant components, such as dietary fibre and plant proteins, have also been intensively discussed (Poulsen et al., 2020; Tuohy et al., 2012). Since MCI is accompanied by inflammatory processes (Shen et al., 2019) and plant-based foods contain anti-inflammatory bioactive substances (Poulsen et al., 2020), neuroprotective effects of plant-based diets can be assumed.
We have presented the evidence in this regard in the introduction in a sufficient manner.
- Ballarini et al. (2021, May 5). Mediterranean Diet, Alzheimer Disease Biomarkers and Brain Atrophy

in Old Age. Neurology, 96(24), e2920-2932. https://doi.org/10.1212/wnl.0000000000012067
- Kahleova et al. (2017, Aug 9). Cardio-Metabolic Benefits of Plant-Based Diets. Nutrients, 9(8). https://doi.org/10.3390/nu9080848
- Poulsen et al. (2020, Sep). The Effect of Plant Derived Bioactive Compounds on Inflammation: A Systematic Review and Meta-Analysis. Molecular Nutrition and Food Research, 64(18), e2000473. https://doi.org/10.1002/mnfr.202000473
- Tuohy et al. (2012, Sep 12). Up-regulating the human intestinal microbiome using whole plant foods, polyphenols, and/or fiber. Journal of agricultural and food chemistry, 60(36), 8776-8782. https://doi.org/10.1021/jf2053959
- Shen er al. (2019, May). Inflammatory markers in Alzheimer's disease and mild cognitive impairment: a meta-analysis and systematic review of 170 studies. Journal of neurology, neurosurgery, and psychiatry, 90(5), 590-598. https://doi.org/10.1136/jnnp-2018-319148

6. I appreciate the exploratory study question! We should really look at the broader picture of MCI.
Response: Thank you for your valuable opinion.

Methods and Analyses

7. In the light of pragmatism and generalisation of findings from an artificial setting such as an RCT to clinical practice, I really appreciate the authors' idea to advise people to do the individualised cognitive training a certain amount of time per turn and to do this a number of times per week, but letting them choose themselves in the end (lines 177-178). However, a concern is that this may induce heterogeneity in the fidelity of the intervention, it would be strongly recommended to take this into account. Will you monitor how often and how long people will do the training? From what I read in line 375 this seems to be the case.
Response: Thank you for your concerns. As mentioned we are collection the usage data by the CCTs. We clarified the usage data collection in the data collection section (line 382).

Something similar can be said about the plant-based diet intervention. Will you monitor whether people actually refrained from meat consumption? It seems that you can assess this with the FFQ questionnaire? Nice to read that you will also collect data on weight which could also provide information about the fidelity of the diet intervention. Altogether I would also somehow incorporate the fidelity in the per protocol analyses (vs. intention to treat analyses) which is now restricted to survival (line 429).
Alternatively, the fidelity of the intervention could be the independent variable of interest i.e. amount / time of doing cognitive exercises and dieting predicts cognitive function? So more like a dose response relationship? (and a kind of mixture between experimental manipulation and observation?)
Response: We appreciate you concerns. For the data analysis we are going to use per protocol and intention to treat analysis.
Your assumption, that we also monitor meat consumption by means of Food-Frequency-Questionnaires is correct.

8. Eligibility criteria appear correct (either with regard to the aetiology or are defendable from an ethical point of view).
Response: Thank you for the feedback.
9. Line 250: What is meant with couples? Marital couples?
Response: Couples means two people who live together in a household (married or not married). We clarified and wrote: "Residents in the same household" (line 255)

10. Line 340 and further: the entire section about the MMSE is in bold letter type (?). Do you want to emphasize something?

Response: Thank you for the remark. We adapted the letter type in the whole section, the bold letter type has happened by mistake.

Overall and in the end, I would like to congratulate you wholeheartedly on designing such a nice study!
Response: We appreciate your feedback a lot.

Reviewer #3
Comments to the Author:
The authors are embarking on a study of the impact of individualized cognitive training and whole food, plant based dietary planning over standard CCT and dietary recommendations on the cognition of individuals with MCI. The rationale and methods are generally explained well. I would like to see more detail added to the protocol as follows:

- Please provide more explanation of how the WFPB diet differs from the GNS recommendations.
Response: Thank you for this important remark. In order to specify the difference between a WFPB diet and a diet recommended by the GNS we have now added a detailed overview of the recommendations of the nutrition interventions (see table 5)

- Very little is stated about how adherence to the recommendations (CCT or Dietary) will be measured during the course of the intervention and in the follow-up period.
How will the researchers know how much CCT the individual engaged in?
Response: Thank you for your concerns. The CCT records the usage data, as mentioned in “Other variables”/”Additional digital data” (lines 382-383), in the “Data collection”-Section we clarified and added usage data in line 411.

Or, how closely they followed the recommended diet?
Please describe how this will be done at baseline, during intervention, and in the follow-up period.
How will adherence be accounted for in the statistical analyses?
Response: Thank you for your questions. The adherence to the recommended diet will be assessed through FFQs as an online survey at baseline, t6 and t12 as well as a non-obligatory weighing protocol. This will be included as co-variables in the multivariate analyses.

-Participants with significant depression based on a PHQ 9 cut off will be excluded. What safety measures are in place for getting any needed emergency care for these individuals and the students handling these sessions with these individuals?
Response: We appreciate your interest in our regulations to maintain the safety of the participants. The following procedures are established in order to support our student assistants in these crucial situations. Participants with a PHQ 9 score above 12 will receive general information about possible supportive services both verbally and in writing. In case of potential suicidality, student assistants are advised to act as recommended by the guidelines on emergency psychiatry.

While the methods are described clearly for the purposes of a protocol manuscript, I would like to offer two methodology concerns for the authors. If I was later reviewing a manuscript of the results of this study, I would have serious concerns about the operational definition of MCI used in this protocol. Defining MCI based upon a low enough score on the MoCA and high enough score on the MMSE is woefully insufficient. You will misidentify many participants with this method, particularly by excluding many MCI patients who have a MoCA score above 24. While it may be difficult to do a more thorough assessment, you will undoubtedly be asked to justify this selection method when you go to publish results.
Response: Thank you for your remarks. As shown in a meta-analysis by Breton et al. (2019), the

MoCA was as accurate as the extensive diagnostic tool CERAD in detecting MCI. Using the MoCA to screen for MCI is therefore more economical. It has also already been established as a video assessment tool which enables a comparable and standardized execution.
In order to prevent as many false positive or false negative cases, the cut- off of 24 was chosen to ensure an optimal balance between sensitivity and specificity (Ciesielska et al., 2016; O'Caoimh et al., 2016; Thomann et al., 2020)

Breton, A., Casey, D., & Arnaoutoglou, N. A. (2019). Cognitive tests for the detection of mild cognitive impairment (MCI), the prodromal stage of dementia: Meta-analysis of diagnostic accuracy studies. International journal of geriatric psychiatry, 34(2), 233–242. https://doi.org/10.1002/gps.5016

Lastly, I think the MoCA is limited as a primary cognitive outcome. I would highlight your CCTB as the primary cognitive outcome, as the limited range of scores will likely limit your ability to find change on the MoCA.
Response:
Since the MoCA is widely and internationally used, and we can compare our results with other studies, we decided to use MoCA as a primary cognitive outcome.

VERSION 2 – REVIEW

REVIEWER	Chandler, Melanie Mayo Clinic, Psychiatry and Psychology
REVIEW RETURNED	06-May-2022

GENERAL COMMENTS	The authors have addressed my prior concerns for this protocol manuscript.