The effects of a multidomain lifestyle intervention on brain functioning and its relation with immunometabolic markers in ageing

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The primary objective of this study is divided into two steps:Step 1. To investigate the effect of a 26-week (around 6 months) multidomain lifestyle intervention on brain function (working memory, cerebral perfusion) and peripheral immunometabolic...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54045

Source
ToetsingOnline

Brief title
HELI

Condition

- Other condition
- Age related factors

Synonym
brain health, cognitive ageing

Health condition

risicofactoren voor cognitief functioneren (cognitieve veroudering)

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universiteit Nijmegen
Source(s) of monetary or material Support: NWO,DSM Food Specialties,IMEC Netherlands ,Mead Johnson Nutritionals

Intervention

Keyword: brain, gut, intervention, lifestyle

Outcome measures

Primary outcome

Our primary study objectives, with the forthcoming primary study outcomes, are:

Step 1.

a) Brain activity during working memory:

BOLD activity and task-accuracy during N-back fMRI task.

b) Cerebral perfusion levels:

MRI-ASL levels.

c) Peripheral immunometabolic markers:

Inflammation markers (IL-6, TNF-α, hs-CRP; from blood plasma) & gut microbiome

composition (diversity and richness; from faeces).

Step 2.

To investigate intervention-induced immunometabolic-brain links by analysing the relations between the sign-effects of step 1 (see a, b, and c).

Secondary outcome

Our secondary study objectives, with the forthcoming secondary study outcomes, are:

a) To identify baseline predictors for cognitive ageing and intervention efficacy:
Structural MRI (e.g. grey/white matter volume, ventricular enlargement, abdominal adipose T1 assessment, etc.), neurochemical MR assessments (MRS; myo-inositol, QSM; iron accumulation), and participant demographics at baseline (e.g. age, sex, education level, etc.).

b) To investigate the effect of a 26-week multidomain lifestyle intervention on neuropsychological test battery scoring (cognitive functioning):
Z-scoring on cognitive domains predominantly affected by cognitive ageing: executive function, working memory and processing speed.

c) To investigate which specific lifestyle domains bring about effects on specific measures:
Relations between improvement in domain-related questionnaire scores and primary outcome measures.

d) To investigate the effect of a 26-week multidomain lifestyle intervention on

a broad array of other immunometabolic brain markers relevant for cognitive ageing:

Fecal analysis (microbiota quantification of composition; e.g. functional microbiota analysis, analysis for metabolites), plasma analysis (e.g. markers of intestinal integrity, further inflammatory condition assessment, nutritional status, (early) Alzheimer markers, microbiota-derived bioactive compounds), urine analysis (microbiota-derived bioactive compounds), and breath analysis (SIBO; small intestinal bacterial overgrowth).

e) To perform a manipulation check to test whether our multidomain lifestyle intervention-induced changes in brain functioning and perfusion in the hippocampus and dl-PFC (regions of interest) predict improved cognitive performance:

Relations between changes in the hippocampus and dl-PFC (BOLD-responses and perfusion) and changes in the working memory (fMRI task) and cognitive domain performance score (neuropsychological tests) following the intervention.

Study description

Background summary

Population ageing brings significant challenges to our society. With increasing age, the prevalence of incurable neurodegenerative diseases, like Alzheimer*s Disease (AD) - the most common form of dementia - increases likewise. In 2018, 50 million people worldwide were living with dementia and it has been estimated that this number will reach 132 million in 2050. Curative approaches have so far been unsuccessful due to the multiple (irreversible) biological pathways involved and are also hampered by the large individual differences in treatment effects. Therefore, preventing or delaying the onset of dementia has utmost

priority.

Previous lifestyle intervention studies have been conducted that propose effects of lifestyle factors on mechanisms such as cognitive performance, functional brain responses, cerebral blood flow, and peripheral markers (e.g. immune-inflammation, gut microbiome composition). Additionally, it is becoming increasingly clear that peripheral immuno-metabolic markers and the gut microbiome could influence central mechanisms in the brain. However, many of these studies are lifestyle intervention studies focusing on one domain, whilst multiple studies have indicated that multidomain (>=2 domains) interventions show a greater effect on cognitive decline in ageing. It is unclear how multidomain lifestyle interventions influence the brain and the periphery, and additionally, the correlational links between the brain and periphery remain to be further elucidated. We hypothesize that multidomain lifestyle interventions affect multiple peripheral and central mechanisms simultaneously, as well as the interrelated connections between these mechanisms.

To test this hypothesis, we will employ a multidomain lifestyle intervention in older adults with cardiovascular risk: the HELI study. The HELI-study (derived from the Dutch 'Hersenfuncties na Leefstijlinterventie', meaning: 'Brain function after lifestyle intervention') is designed as a multidomain lifestyle intervention that uses five different lifestyle domains (diet, physical activity, sleep, stress/mindfulness, cognitive training) to improve cognitive and immunometabolic outcomes. We will assess its effects on multiple structural and functional MRI-related brain measures as well as peripheral measures in blood (immune-related), faeces and urine (gut microbiome-related), as well as their connections. Additionally, we would like to mechanistically explain individual differences in treatment response by assessing the neurocognitive and immunometabolic (primary) outcome measures.

Study objective

The primary objective of this study is divided into two steps:

Step 1. To investigate the effect of a 26-week (around 6 months) multidomain lifestyle intervention on brain function (working memory, cerebral perfusion) and peripheral immunometabolic markers (IL-6, TNF-α, hs-CRP, composition and richness of the gut microbiome).
Step 2. To investigate intervention-induced immunometabolic-brain links by analysing the relations between the intervention-induced effects of the immunometabolic and brain measures.

Working memory is measured by BOLD activity and task-accuracy during a N-back fMRI task, and cerebral perfusion is measured by MRI-ASL. The immuno-metabolic markers of IL-6, TNF-α en hs-CRP are measured by performing blood plasma analyses, and the gut microbiome composition and richness are analysed by taking faecal samples.

The secondary objectives are (1) to identify baseline predictors for intervention efficacy, (2) to investigate the effect of a 26-week multidomain lifestyle intervention on neuropsychological test battery scoring (cognitive functioning), (3) to investigate which specific lifestyle domains bring about effects on specific outcomes, (4) to investigate the effect of a 26-week multidomain intervention on a broad array of other immunometabolic-brain markers relevant for cognitive ageing, (5) and to perform a manipulation check to test whether our multidomain lifestyle intervention-induced changes in brain functioning and perfusion in the hippocampus and dl-PFC (regions of interest) predict improved cognitive performance.

Study design

HELI is a multicenter, randomised, controlled, multidomain lifestyle intervention study of 26 weeks (around 6 months) with 104 Dutch elderly at risk of cognitive decline (based on established risk factors). Participants are randomised in a 1:1 ratio to either one of two groups of the multidomain lifestyle intervention: high-intensity or low-intensity.

Both lifestyle interventions are accessed online.

Intervention

The HELI multidomain lifestyle intervention contains five domains, namely (1) diet, (2) physical activity, (3) sleep, (4) stress/mindfulness, (5) cognitive training. Every domain will be presented in a comparitive amount during the 26 weeks of the intervention.

Participants are randomised in a 1:1 ratio to either one of two groups of the multidomain lifestyle intervention: high-intensity or low-intensity.
The high-intensity intervention group contains online group meetings and individual progress-meetings. The high-intensity intervention will take on average 3 hours each week for 26 weeks in total. These 3 hours contain the weekly online group meeting of 1.5 hours (where one or more specific domains are explained and where tips can be shared between participants), and 1.5 hours of exercises or training that are completed at home by the participant. The content of the 5 lifestyle domains that are presented in the lifestyle intervention are developed and judged by experts of each respective domain, to oversee and reduce (where needed) the possible risks of the intervention.
The low-intensity intervention group receives online access to general lifestyle-related health information that is published on a monthly basis. Participants in this group will spend an average of 30 minutes each month on this information during 26 weken (around 6 months).

The high-intensity intervention is primarily presented online, although several on-site meetings will take place (especially during the physical activity

domain, to be able to practice physical exercises). The low-intensity intervention will be fully presented online.

Study burden and risks

The high-intensity intervention group contains online group meetings and individual progress-meetings. The high-intensity intervention will take on average 3 hours each week for 26 weeks in total. These 3 hours contain the weekly online group meeting of 1.5 hours (where one or more specific domains are explained and where tips can be shared between participants), and 1.5 hours of exercises or training that are completed at home by the participant. The content of the 5 lifestyle domains that are presented in the lifestyle intervention are developed and judged by experts of each respective domain, to oversee and reduce (where needed) the possible risks of the intervention.
The low-intensity intervention group receives online access to general lifestyle-related health information that is published on a monthly basis. Participants in this group will spend an average of 30 minutes each month on this information during 26 weken (around 6 months).

Apart from the intervention-related activities, both intervention groups will visit both of the study centres in Nijmegen and Wageningen two times (at baseline before intervention start, and at follow-up after the intervention has concluded) for outcome measurements, including neuropsychologic tests, MRI-scan, faecal- and urine sampling, blood-drawing, breath test and questionnaires. Thus, there will be 4 total visits to the study centres (1 time to Nijmegen and Wageningen at baseline, and 1 time to Nijmegen and Wageningen after the intervention). Each visit will take an average of 3 hours.
Participation to this study could be beneficial for the participant, as the participant will receive information to make improvements of lifestyle patterns that could lead to a participant improving their own (brain) health.

Undergoing MRI-scanning can be experienced as tiresome. The blood-drawing can cause mild pain or discomfort, and sometimes it causes a bruise. All these symptoms will dissapear with time.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age between 60-75 years (at pre-screening)
- Fluency in Dutch (speaking, reading and writing)
- Lives near study centres in Nijmegen and Wageningen (maximum of 50km of traveling to either Nijmegen or Wageningen)
- Score >=2 points on the 6 modifiable cardiovascular risk factors listed below:
1. BMI >=25 (1 point)
2. Physical inactivity (below the 2020 WHO guidelines, meaning: <300 min of moderate intensity aerobic physical activity, or <150 min of vigorous intensity aerobic physical activity per week, spread out over several days) (1 point)
3. Hypertension (1 point, 2 points if hypertension is untreated)
4. Hypercholesterolemia (1 point)
5. Diabetes type-II (1 point)
6. Cardiovascular disease (EXCEPT: symptomatic cardiovascular disease such as stroke, angina pectoris, heart failure, myocardial infarction, OR revascularisation surgery in the last 12 months at pre-screening) (1 point)

Exclusion criteria

- Concurrent participation in other intervention trials
- Technologically illiterate (complete incompetence in working with computers, apps, online questionnaires, etc.)

- No internet access from home
- Clinical diagnosis of >=1 of the following:
> Vascular event (CVA);
> Neurological pathology (e.g. MCI, dementia, MS, Parkinson's, epilepsy);
> Current malignant disease(s), with or without treatment;
> Current psychiatric disorder(s) (e.g. depression, psychosis, bipolar episodes);
> Symptomatic cardiovascular disease (e.g. stroke, angina pectoris, heart failure, myocardial infarction);
> Revascularisation surgery in the last 12 months at pre-screening;
> Inflammatory bowel disease (characterised with diarrhoea);
> Visual impairment (e.g. blindness);
> Hearing or communicative impairment.
- Answering "Yes" on >=1 of the Donders Institute MRI safety screening protocol questions (see 8 questions below):
1. Are there metal objects located in your upper body? Exception: tooth-fillings and/or dental crowns.
2. Are there metal splinters in your body, in particular within the eyes? For example: through labour work in the metal industry.
3. Are there jewellery items or piercings that you are unable to take off?
4. Have you had a brain surgery in the past?
5. Are there active implants present? For example: pacemaker, neurostimulator, insulinpump, hearing aid (that is unable to be removed).
6. Are there any medical plasters or patches that you can*t or may not take off? For example: nicotine patch.
7. Do you suffer from epilepsy?
8. Do you suffer from claustrophobia?
- Cognitive impairment as determined by Telephone Interview for Cognitive Status (TICS-M1), performed during pre-screening before inclusion.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-05-2022
Enrollment:	104
Type:	Actual

Ethics review

Approved WMO Date:	02-12-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-02-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-05-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-08-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	Deze studie wordt geregistreerd binnen clinicaltrials.gov voordat de eerste participant is geworven.
CCMO	NL78263.091.21