RESEARCH PROTOCOL

MIND-PRO‘

‘mHealth INtervention for Dementia PRevention through lifestyle Optimisation’

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A randomized controlled hybrid effectiveness-implementation trial of a mHealth intervention targeting individual risk factors for dementia in persons over 50 years with low SES and/or migrant background.

Research protocol 'mHealth intervention for dementia prevention through lifestyle optimisation'

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Subsidising party	ZonMw
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PROTOCOL SIGNATURE SHEET

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1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

(S)AE	**(Serious) Adverse Event**
ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
BMI	**Body Mass Index**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CRF	**Case Report Form**
CV	**Curriculum Vitae**
CVD	**Cardiovascular Disease**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
GLM	**General Linear Model**
GP	**General Practitioner**
HATICE	**Healthy Aging through Internet Counseling of the Elderly**
HELIUS	**Healthy Life in an Urban Setting**
HIC	**High Income Country**
HIPAA	**Health Insurance Portability and Accountability Act**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
LMIC	**Low Middle Icome Country**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
NDPI	**Netherlands Dementia Prevention Initiative**
PRODEMOS	**Prevention of Dementia by Mobile Phone Applications**
RCT	**Randomized Controlled Trial**
RUDAS	**The Rowland Universal Dementia Assessment Scale**

SES	**Socioeconomic status**
SMART goal	**Simple Measurable Achievable Realistic and Time-bound goals**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

2. SUMMARY

Rationale: The prevalence of dementia is expected to increase in the coming decades, especially among lower socio-economic status (SES) and migrant communities. This emphasizes the need for prevention, particularly given the absence of curative treatments. Around 40% of dementia is associated with potentially modifiable risk factors. Mobile health (mHealth) interventions targeting multiple risk factors simultaneously may help reducing dementia risk. The MIND-PRO study adapts and tailors a previously developed mobile app for populations with low-SES and/or migration background in the Netherlands.
Objective: To evaluate effectiveness and implementation of a new mHealth intervention to improve lifestyle and reduce dementia risk factors through self-management with remote coaching.
Study design: Single-center, investigator-initiated, prospective, open-label blinded endpoint randomized controlled type 2 hybrid implementation-effectiveness trial with a 12 months intervention to demonstrate proof of concept for both effectiveness and implementability.
Study population: People aged 50-75 years, of low SES and/or migration background in the Netherlands, with one or more dementia risk factors and who have a smartphone.
Intervention (if applicable): Use of a coach-supported culturally adapted app for self-management of dementia risk factors (i.e. obesity, inactivity, hypertension, hypercholesterolemia, unhealthy diet, smoking). The app allows goal-setting, monitoring, and self-measurements (weight, blood pressure, exercise, …). Evidence-based education modules, interactive videos, and personalized news related to risk factors are included. An ethnic-matched lifestyle coach skilled in motivational interviewing provides remote support. The control condition is the use of a static app with general health advice, without any interactive features. The platform adheres to healthcare security standards (NEN 7510, HIPAA, GDPR).
Main study parameters/endpoints: The primary effectiveness outcome is a composite score of systolic blood pressure, non-HDL cholesterol, and BMI. The difference between baseline and 12-month follow-up values will be analyzed continuously using z-scores. Additionally, implementation outcomes will be weighed against each other using mixed methods. These outcomes will be operationalized as coverage, acceptability, adoption, appropriateness, feasibility, fidelity, implementation costs, and sustainability
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The risks of participating are negligible, because it is a non-invasive study which may lead to a healthier lifestyle, potentially reducing the risk of dementia. There will be three study visits which can occur at the research site or at the participant's home. Participants are asked to provide blood samples (finger-prick) on two occasions (at t0 and t12) and blood pressure and weight are measured. Using the smartphone app does not involve other risks than an active lifestyle in general. The intervention does not involve medical treatments.

3. INTRODUCTION AND RATIONALE

Dementia is characterized by progressive deterioration in cognitive function beyond the expected consequences of biological ageing (1). Its global prevalence is expected to rise the coming decades, due to population ageing and growth (2). Especially people living in low- and middle-income countries (LMIC) and people of lower socio-economic status (SES) and/or migration background in high-income countries (HIC) will be overrepresented (2, 3).

In the Netherlands, dementia will grow to become the most important cause of death by 2050 and will be the illness with the greatest financial burden on society (4). On a micro level, dementia affects not only those who suffer from it but also their family and friends because of the increased care and attention their loved ones will require (4). Given the absence of curative treatment, interventions aimed at dementia prevention may mitigate the rising demand for dementia care. (5).

The strongest known risk factor for dementia is age. However, dementia is not the inevitable consequence of biological ageing (6). Up to 40% of dementia is associated with modifiable risk factors, including high blood pressure, physical inactivity, unhealthy diet, overweight, and smoking (7). Even a modest reduction of 10% in these risk factors can potentially decrease the incidence of dementia, especially in communities with lower socioeconomic status and/or a migration background, where these risk factors are more prevalent (8). Poorer overall health habits and restricted access to healthcare may help to explain this in part (9). Modifying lifestyle factors can potentially reduce the risk of developing dementia and improve overall brain health. (10).

Since the presence of multiple risk factors may pose an additive or even synergistic effect on dementia risk, targeting several risk factors simultaneously may be more effective (11, 12). Multidomain interventions via the implementation of mHealth interventions (mobile health application), have shown to be effective for improving glycemic control in diabetic patients, increase physical activity, enhance mental health, diet quality, and nutrition (13). The widespread use of mobile phones, coupled with increasing access to the internet via mobile devices, presents a unique opportunity for leveraging mHealth to reach underserved populations, such as low-SES and migrant communities. These populations are often difficult to reach and engage in traditional preventive programs due to a range of barriers, including financial constraints, language barriers, and lack of transportation. By utilizing mobile

technology, mHealth can provide accessible health services, overcoming these barriers and helping those who need it most.

Despite the increasing use of mHealth, knowledge on its successful implementation in vulnerable populations is scarce and has shown to be challenging, especially in low-SES and migrant populations (14-16). We seek to bridge this knowledge gap by deploying a coach-supported mHealth intervention aimed at reducing dementia risk in these populations. The intervention is based on the experiences of the Prevention of Dementia by Mobile Phone Applications (PRODEMOS) project (17) and the Healthy Aging through Internet Counseling of the Eldery (HATICE) project (18). In the MIND-PRO project we will built on the lessons learned from the PRODEMOS (17, 19, 20) and HATICE (18, 21, 22) trials, to further adapt a mobile phone application and tailor it to a population with a migration background and/or low-SES in the Netherlands.

4. OBJECTIVES

The overall aim is to investigate whether a coach-supported mHealth intervention for lifestyle improvement can reduce the risk of dementia in those with low SES and/or a migration background aged 50-75 years.

The specific objectives are to investigate:

- The effectiveness of a coach-supported mHealth intervention for lifestyle improvement to reduce the risk of dementia in those with low SES and/or a migration background aged 50-75 years.
- The implementation of this coach-supported mHealth intervention for dementia prevention, operationalised as the coverage, acceptability, adoption, appropriateness, feasibility, fidelity, costs, and sustainability.

5. STUDY DESIGN

The study is a single-centre, investigator initiated, prospective, open-label blinded endpoint randomized controlled trial with 12 months intervention. The study will be conducted in the Netherlands. We will use a type 2 hybrid implementation-effectiveness design to show proof of concept for effectiveness and implementability using a composite of three objectively measurable dementia risk factors as a composite effectiveness outcome (23).

6. STUDY POPULATION

6.1 Population

People aged between 50 and 75, of low SES and/or migration background in the Netherlands, with one or more dementia risk factors and in possession of a smartphone are eligible for participation.

Target population explained:

- Dementia prevention is likely more effective among people with risk factors for dementia. Since individuals with cardiovascular disease (CVD) already have a high risk for dementia, people with a history of CVD are also eligible, irrespective of risk factors.
- The optimal age-range for risk reduction is unknown. We have taken a pragmatic approach, targeting individuals aged between 50 and 75 years (24). Most dementia risk factors exert their strongest detrimental effect in midlife, therefore improving the dementia risk profile in midlife rather than late-life is likely to be most effective for the prevention of cognitive decline and dementia in late-life (25, 26).

- In high income countries, individuals of low SES have an elevated risk of future dementia (27), partly due to unfavorable risk profiles, in combination with limitations in health care access, poorer social networks and different attitudes and beliefs about (preventive) health practices (28, 29). There is more room for reducing dementia risk than in persons of high SES who tend to have better-controlled risk factors.
- The prevalence of dementia in non-western immigrant groups is higher compared to native populations in high-income countries (3, 30). Like in persons of low-SES, there is more room for improvement of dementia risk in people with a migration background, compared to native populations of high-SES.
- In this study, we specifically focus on people with a Turkish or Hindustani background and Dutch-origin individuals with a lower socio-economic status, because previous research has shown that the risk of dementia is increased in these populations. It is not feasible to adapt the intervention for all ethnicities within the current study. The reason we chose these specific groups is that they already participate in the HELIUS study and are therefore relatively easily accessible and will be more likely to participate in our study. Naturally, we are aware that the results of this study cannot simply be translated to other ethnic groups. It is conceivable that we will also see similarities between the groups, building on previous versions of the intervention, which were tested in France, Finland, the Netherlands, the UK and China (HATICE and PRODEMOS studies). If the intervention appears to be effective, this may help to ultimately develop the intervention for other groups of people with a migration background.

6.2 Inclusion criteria

To be eligible to participate in this study, a subject must meet all of the following criteria:

- Age ≥ 50 years ≤ 75 years;
- Basic level of literacy in Dutch;
- Possession of a smartphone;
- Turkish or South-Asian Surinamese background; OR Dutch background with low SES, operationalised using educational level and occupational status, as previously performed in the Healthy Living in an Urban Setting (HELIUS) study;
    - HELIUS is an observational cohort study dedicated to health in the largest migrant populations of Amsterdam, including the host population itself (n=25.000) (31). All participants in HELIUS that will be contacted for the MIND-PRO study, have agreed to be contacted for other studies.

- Increased risk of dementia based on:
  1. ≥ one dementia risk factors defined as:
     - Hypertension, defined by any of the following:
       - Diagnosis by specialist or general practitioner.
       - Currently on anti-hypertensive drugs.
       - Baseline blood pressure: ≥ 140/90 mmHg;
     - Dyslipidaemia, defined by any of the following:
       - Diagnosis by specialist or general practitioner
       - Use of lipid-lowering drugs
       - Baseline total cholesterol ≥5.0 mmol/L
     - Diabetes mellitus, defined by any of the following:
       - Diagnosis by specialist or general practitioner
       - Use of any blood glucose-lowering medication
     - Active smoking (use of any sort of tobacco in any quantity)
     - Overweight, defined by any of the following:
       - Body mass index (BMI) ≥ 30
       - Waist circumference men ≥ 102 cm, women ≥ 88 cm
     - Lack of physical exercise, defined as below the World Health Organization (WHO) norm (five times a week 30 minutes or a total of 150 minutes per week of intermediate exercise)
     - Depression
       - Currently on anti-depressive medication or receiving psychotherapy for depression
       - History of treatment (i.e. drug therapy or psychotherapy) for depression
  2. **OR** Manifest cardiovascular disease, as diagnosed by specialist or general practitioner.

6.3 Exclusion criteria

- Previously diagnosed with dementia by a specialist or general practitioner
- A score below the cut-off score of 21 on the Rowland Universal Dementia Assessment Scale (RUDAS) (32, 33), a validated dementia screening method specifically developed to be less susceptible to cultural, linguistic, and educational biases (34). The RUDAS is available in multiple languages, including Dutch and Turkish.

- Any condition expected to limit 12 months compliance and follow-up, including metastasised malignancy or other terminal illness
- Any impairment interfering with operation of a smartphone
- Participating in another RCT on lifestyle behavioural change
- Present alcohol or illicit drug abuse; binge drinking is not an exclusion criterion – this is a potential target for behaviour change.

6.4 Sample size calculation

We calculated the sample size based on the expected effect of the intervention on our primary effectiveness outcome (a composite z-score of the objectively measurable risk factors systolic blood pressure, BMI and non-HDL cholesterol) in those with low education as a proxy for low SES. In participants in the HATICE trial with a low educational level, the mean difference between intervention and control participants in change from baseline was 0.107 (pooled SD 0.454) for the composite z-score after 1.5 years. In the preDIVA trial, the difference in composite z-score between people with low SES developing dementia and those who did not during 6-8 years of follow up was 0.096 . We therefore consider a mean difference in change of 0.107 as potentially clinically relevant with respect to the risk of dementia. For specific migrant groups few data are available. With 277 participants per treatment arm, we will have 80% power (with alpha set at 0.05) to detect a 0.107 (pooled SD 0.454) difference on our primary outcome (z-score of systolic blood pressure, BMI and non-HDL cholesterol). To adjust for an anticipated drop-out of 20% in this specific target population we will recruit 692 participants.

7. TREATMENT

7.1 Study name

MIND-PRO will be the (inter)national and publication name of the study. MIND-PRO is an acronym for ‘mHealth INtervention for Dementia PRevention through lifestyle Optimisation’.

7.2 Design of the intervention

Factors relating to culture, language, or health literacy may contribute to the level of engagement in prevention programs for individuals with low SES and/or a migration background (30). Developing better tailored preventive interventions may increase their effectiveness for reduction of the risk of dementia, and may improve recruitment, retainment, and assessment of effectiveness.

We will build upon our experiences from the preceding HATICE (18, 21, 22) and PRODEMOS trials (17, 19, 20). In the context of these projects, and another recent interview study with Turkish migrants on risk factors and prevention in our group (van Apeldoorn et al, submitted), we are designing the intervention which takes cultural aspects of health, health perception, and views on prevention into account, based on the PRODEMOS app. This is done in co-creation with the target populations. This will result in a mHealth intervention adopted to the wishes and needs of our target population and optimized for use in this RCT. The process of co-creating the app will be described in a qualitative study reviewed by the Ethical Committee of Amsterdam UMC (METC-number 2023.0578).

7.3 Description of intervention and control condition

The intervention is aimed at lifestyle behavioural change using a mHealth intervention (app), supported by a coach. Participants randomized to the intervention arm will have access to an interactive mobile app that facilitates self-management of dementia risk factors (hypertension, dyslipidaemia, active smoking, overweight, lack of physical exercise). After secure login, the app shows the participants' dementia risk profile, based on baseline assessment. Participants can set goals for lifestyle change, monitor these goals, and enter self-measurements of for example weight, blood pressure and physical exercise. Furthermore, the app contains evidence-based education modules (both static and interactive), educational videos which will be developed within the project, and news items that are arranged according to personal risk factors (extensive experience from previous projects will be used). The participants will be supported by an experienced lifestyle coach trained in motivational interviewing who will be matched to the ethnicity of the participants as much as possible. The coaches will help to formulate simple, measurable, achievable, realistic and time-bound (SMART) goals.

Those randomized to the control condition will have access to an app which is similar in appearance but lacks any interactive features and does not provide coach-support. It will contain general information on how to live a healthy lifestyle.

The MIND-PRO app will be based on the existing Patient Journey app (Interactive Studios). Development of the content is a collaboration between our academic team and Interactive Studios. It is primarily designed for smartphone use but will also be made accessible via tablet and will be compatible with Android and iOS operating systems. The MIND-PRO app is designed

following earlier experience with app design for lifestyle improvement to reduce dementia risk in the PRODEMOS project (17) and HATICE study (18), which included all development phases from conceptual framework until testing in pilot studies and eventually in two large RCTs.

All education and advice the participants receive will be based on contemporary (inter)national guidelines on risk factor management. The coach directs a participant to their own general practitioner in case of an indication for (drug) treatment (based on entered measurements) or any other indication to see a doctor. To make sure participation in MIND-PRO does not interfere with ongoing primary or secondary care, a PDF print-out and e-mail function for the participant will be available, so that information on dementia risk factors collected in MIND-PRO can be easily presented to any treating physician. There will be no direct link between the MIND-PRO app and any electronic health record, to avoid confusion about the status of MIND-PRO as a stand-alone dementia risk reduction intervention. Coaches in MIND-PRO will not prescribe or give direct advice about medications.

The mHealth intervention will be built in accordance with the highest security requirements in healthcare. It will comply with NEN 7510, the Health Insurance Portability and Accountability Act (HIPAA) and General Data Protection Regulation (GDPR). Since the app also serves as an electronic Case Report Form (CRF), data will be stored according to the current good clinical practice guidelines. The data will be stored centrally at a server in the Netherlands, hosted by a certified Microsoft datacenter which is completely compatible with the highest standards of data management in medical research. Data collected via the app is not stored on the device, other than variables that indicate which function was last used in the app (e.g. chat function, library or home page) and last time you opened the app and which health goal is active. The Patient Journey app in which the MIND-PRO intervention is developed is currently used in regular patient care in the Netherlands across a range of disciplines.

7.4 Role of the coach

The main job of the coach is to share current knowledge to the participants on the importance of dementia risk factor control and work with participants to develop personalised goals, and then to reach these with positive change in their lifestyle behaviours. The coach can review risk profiles and can help to prioritise risk factors and to set goals according to the participants' level of motivation and self-efficacy. For this purpose, all coaches will receive training in motivational interviewing techniques. Since we know that personal contact can contribute to the bond of trust

between coach and participant, the coach will be present at the baseline visit to set an initial health goal together with the intervention participant and to explain how to use the app. Subsequently, there will only be online contact via chat or video calling. The frequency of contact depends on the needs of the participants and the phase of lifestyle change and is expected to be between once a week and once a month.

We will recruit at least 3 coaches who have experience in guiding people through lifestyle change. We will look for 1 Dutch, 1 Turkish and 1 Hindustani lifestyle coach who have completed at least an MBO (middelbaar beroepsonderwijs) education in the fields of healthcare and welfare, or similar. Each coach will guide approximately 100 participants in the intervention group.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Primary study parameter/endpoint

This is a type 2 hybrid implementation-effectiveness randomised controlled trial. There is a primary effectiveness outcome and there are several primary implementation outcomes.

1. Effectiveness: composite score of systolic blood pressure, non-HDL cholesterol, and BMI. We will use the z-score of the difference between baseline and 12 months follow-up values to be analysed as continuous variables, as previously done in the HATICE trial (18).

   Rationale for this outcome: Due to the long time lag between exposure (risk factors) and dementia onset, incident dementia cannot be used as outcome (35). A dementia risk score can be used as proxy for proof of concept of effectiveness on dementia risk. To avoid reporting bias, we use a composite outcome including three objectively measurable variables from dementia risk scores appropriate to capture the potential effect of our multidomain intervention.

2. Implementation of the mHealth intervention: We will measure multiple aspects of implementation using mixed methods:
   - Coverage: Comparison of characteristics participants with eligible/source population
   - Acceptability: Satisfaction with the application e.g. user-friendliness, credibility, content, complexity (qualitative & quantitative research methods).
   - Adoption: intention, initial decision, or action to try or employ the mHealth intervention (quantitative analysis of the utilisation, usage and uptake of the mHealth intervention)
   - Appropriateness: qualitative analysis of the perceived fit or relevance of the mHealth intervention in the target population.
   - Feasibility: qualitative analysis to what extent the mHealth application can be carried out in a low socio-economic setting and in a population with a migration background.
   - Fidelity: qualitative evaluation of the degree to which the mHealth application is implemented as intended, compared to the original design.

- Costs: analysis of the implementation costs related to the app and coaching time will be part of a health economic analysis.
- Sustainability: quantitative evaluation of the extent to which the mHealth application is being used and incorporated during the 12 months of the implementation trial.

8.1.2 Secondary study parameters/endpoints

The questionnaires used to assess the secondary outcomes are presented in **table 2 below**.

- Change in CAIDE dementia risk score between baseline and follow-up(36) (see Appendix 2)
- Change in individual modifiable components of the CAIDE risk score between baseline and follow-up (i.e. blood pressure, BMI, total cholesterol, physical activity(37))
- Disability(38)
- Depressive symptoms(39)
- Intervention costs
- Cost-effectiveness
- Cognitive functioning, assessed with culturally-sensitive cognitive screening tests, the RUDAS (The Rowland Universal Dementia Assessment Scale) and the Box Task(40).
- Digital measures for social daily functioning measured by BeHapp (remote behavioural monitoring app) (see Appendix 1.) Only in a subgroup of participants willing to install the BeHapp app; separate consent will be asked on the informed consent form.

Domain	**Questionnaire(s)**
1. Physical exercise	Self- administered short International physical activity questionnaire (IPAQ-SF)
2. Disability	WHO Disability Assessment Schedule 2.0 (WHODAS 2.0, 12-item)
3. Depressive symptoms	Geriatric Depression Scale 15-item (GDS-15)

Table 2. Self-assessment questionnaires

8.2 Randomization, blinding and treatment allocation

Randomization will take place in the app using a computer algorithm in a 1:1 manner. Participants will be blinded to treatment allocation. Participants will be informed that random allocation will be to one of two different smartphone apps, and that the study is on reducing the risk of dementia. Partners who also participate in MIND-PRO will automatically be allocated to the same treatment arm, to avoid contamination. Together those two partners allocated to the same treatment arm form the smallest conceivable cluster. Based on our experience in the HATICE and PRODEMOS study, this does not affect the power of the study. Multi-level analysis yielded the same results as single-level analysis. Outcome assessment will be performed by an independent assessor who is blinded to treatment allocation. The coaches who support participants in behavior change are, due to the nature of the intervention, not blinded. A certain level of unblinding during outcome assessment is conceivable, since a participant could express details about participation of the MIND-PRO app specifically to the outcome assessor. It is unlikely that this will influence the components of the primary outcome, including blood pressure, non-HDL cholesterol and BMI as these are objectively measured.

8.3 Study procedures

We will use our extensive experience in recruiting large samples for prevention RCT's in the Netherlands (preDIVA n=3.526), Europe (HATICE n=2724, of which 1471 in NL) and low SES populations in the UK (PRODEMOS, n=600). Initially we will recruit through the HELIUS cohort study (31). All HELIUS participants that will be contacted by MIND-PRO gave informed consent to be contacted for future related studies. There were 24.780 participants who participated at baseline of HELIUS. Of these,11.035 participated in the follow-up assessment between 2019 and 2021. Potentially eligible participants, based on the risk factor information available in the HELIUS cohort at the follow-up assessment, will receive an invitation email or mail from the HELIUS research team, in which they will be informed about the study and asked whether they are willing to participate in the study. Approximately 2140 potential participants will receive an initial invitation. The information in the (e)mail will be sent in Dutch for Dutch and Surinamese and in Turkish and Dutch to those with a Turkish background. Those who do not respond are called by phone to explain the study and ask whether they are willing to participate. All who are interested and potentially eligible, will have a pre-screening call to check eligibility.

Those eligible and willing to participate, are invited for a screening visit, during which the informed consent form will be signed, and additional measurements (weight, blood pressure, non-HDL cholesterol and cognitive assessment with RUDAS and Box Task) will be done. At the end of the screening visit the MIND-PRO app will be downloaded and participants will be explained on how to fill in the self-assessment questionnaires in the app. After the screening visit, a second appointment will be made for the baseline visit during which the self-assessment questionnaires will be evaluated and completed and they will be randomized to either the intervention or control group. Screening and baseline visits will take place at one of our research locations, closest to their home (e.g. a research location in Amsterdam West or Amsterdam UMC, location AMC). The research assistants that will contact and screen the potential participants will be trained and culturally matched as much as possible. If preferred, visits can also take place at home of the participants.

In case we do not meet our target recruitment sample size in the HELIUS population who came to the HELIUS follow-up visit, we will consult the HELIUS board to discuss other options with regard to reaching participants. For example, contacting all HELIUS participants who only attended the HELIUS baseline visit. Furthermore, If we are not able to recruit sufficient participants via the HELIUS cohort, we will continue recruitment via GP practices. For this we will collaborate with a number of GP practices in areas of Amsterdam with a high percentage of inhabitants from Turkish and Surinamese descent. We have extensive experience recruiting via selected GP practices. In preDIVA we recruited 3526 older persons via GP practices. Alongside recruiting via GP practices, we will start recruiting participants via community centres in neighbourhoods which house a large number of immigrants and residents with lower socioeconomic status.

<u>Invitation mail/e-mail:</u>

- Containing the participant information form

<u>Pre-screening call (15 minutes):</u>

- Explanation about MIND-PRO
- Assessing smartphone possession and literacy
- Assessing exclusion criteria
- Obtain information about medical history
- Obtaining general information including demographics and medication use

- If willing to participate, planning of screening visit 2 weeks later

Screening visit (60 minutes):

- Answering questions
- Sign Informed Consent (IC)
- Physical measurements (height, weight, waist & hip circumference, blood pressure)
- Test cholesterol with point-of-care test (finger-prick)
- Administering the RUDAS and Box Task
- Download and install the MIND-PRO application
- Instructions on how to fill in the self-assessment questionnaires (see **table 2**), with the research assistant available to assist.

Participants are requested to fill out the self-assessment questionnaires (see **table 2**). In case they have trouble filling them out, the questionnaires can be completed with the assessor during the baseline visit.

Baseline visit (40 minutes):

- Evaluation and completion of self-assessment questionnaires
- If the participants are willing to install the BeHapp app for assessment of the secondary outcome related to social interaction, they will also download the BeHapp app
- Randomization to intervention or control arm
- Intervention group: Review risk profile, shared decision on risk factors to target, motivational interviewing on lifestyle improvement, intervention app explanation by coach. Advice to visit the GP in case any of the baseline assessment values exceed current GP practice guidelines for any (non-)pharmacological intervention
- Control group: Review risk profile, control app explanation and advice to visit the GP in case any of the baseline assessment values exceed current GP practice guidelines for any (non-)pharmacological intervention.

Online or phone assessment after 6 months:

Participants will be requested to fill out a questionnaire that is provided in the app. This questionnaire contains questions on adverse events, including incident CVD, doctor visits, and hospital admissions. Those who do not fill out the questionnaires, will be called and the

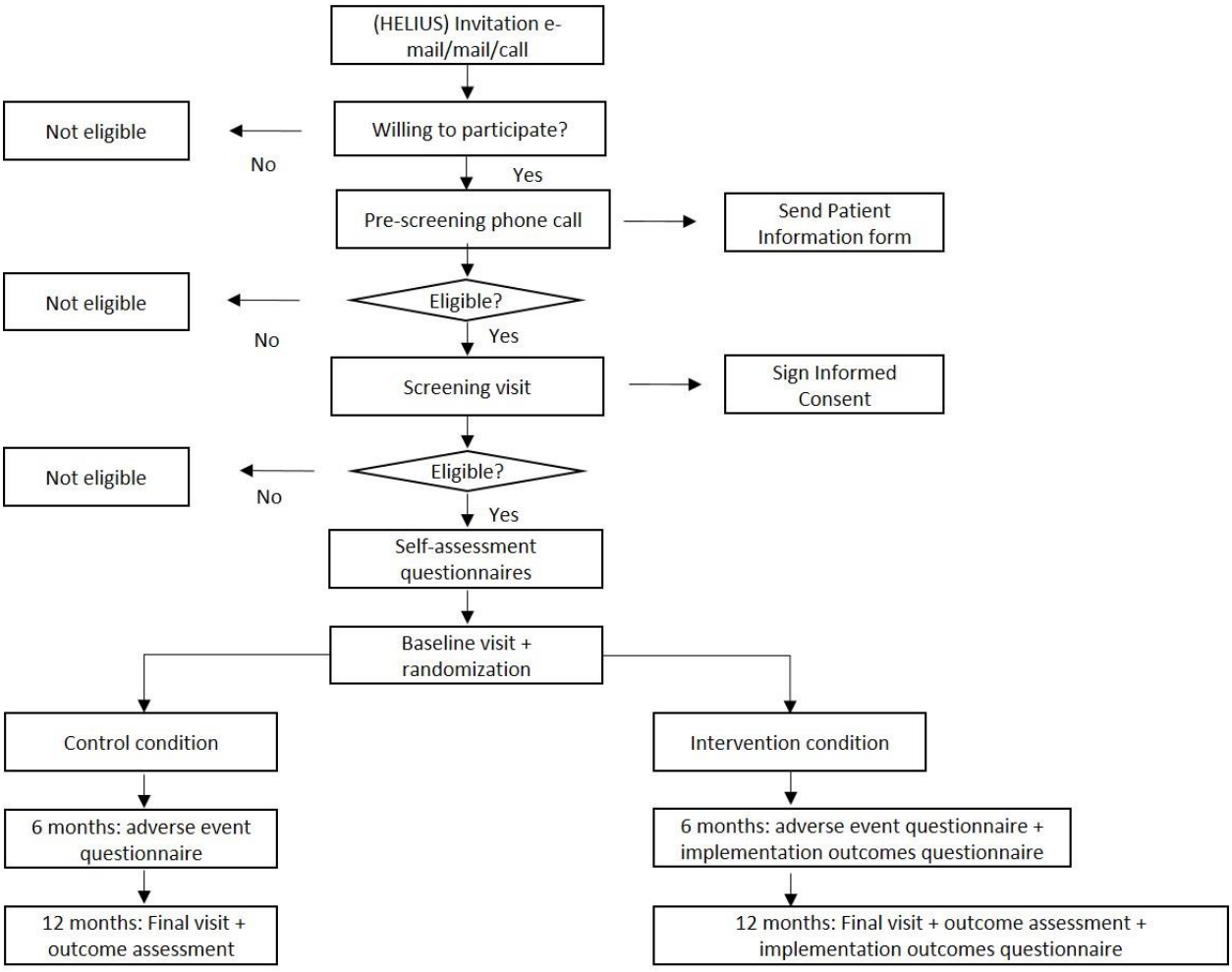
questionnaires will be administered by an assessor. Also all participants in the intervention group will be asked to fill out a questionnaire in the app about the implementation outcomes. For the qualitative analysis of the implementation outcomes, a selection of approximately 30 participants from the intervention group will be asked to participate in an interview covering the implementation outcomes.

Final visit at 12 months (30 minutes):

- Evaluation and completion of self-assessment questionnaires for all participants, and implementation outcomes questionnaire in intervention group participants
- Check prefilled adverse event data based on 6-months questionnaire (to avoid double counting)
- Obtain information about newly developed disease since baseline visit
- Physical measurements (height, weight, blood pressure)
- Test cholesterol with point-of-care test (finger-prick)

The baseline and final visit will be performed by an independent assessor, blinded to treatment allocation.

Figure 1: Flowchart study procedures



8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

8.5 Specific criteria for withdrawal (if applicable)

Not applicable

8.6 Follow-up of subjects withdrawn from participation

The reason for withdrawal will be recorded if subjects are willing to provide one. Subjects will be asked whether they agree with a follow-up assessment in person or by phone at the end of the study. This is to minimize bias introduced by selective drop-out. If the participant cannot be

contacted personally, e.g. in case the participant has developed aphasia due to stroke, we will contact their general practitioner, unless the participant had not consented to further inquiry through their general practitioner during follow-up on the informed consent form. A separate question on the permission to be contacted at the end of the study in case of cessation of participation will be asked. Participants who do not log in at all after the baseline visit will be approached by telephone, to ask if they are willing to attend the final visit, to contribute to the primary analysis according to the intention to treat principle.

8.7 Premature termination of the study

No specific criteria for premature termination of the study are defined. No serious safety issues are expected to arise, due to the nature of the intervention. Considering the duration of the follow-up (12 months), the expected effects, the outcomes used and the non-invasive character of the intervention, no interim analysis is planned.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. Considering the nature of the intervention this is considered very unlikely.

9.2 vAEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Because the intervention consists of advice on a healthy lifestyle and no direct prescription of drugs or any other invasive intervention is involved, direct adverse events caused by the intervention are unlikely. At a general level, only adverse events with clinical consequences will be registered, including cardiovascular disease (stroke or myocardial infarction), number of hospital admissions, number of emergency room visits, (temporary) institutionalization, and mortality. For the health economics analyses, two additional questions will be ask regarding number of visits to a general practitioner or paramedics (such as dietitian or physiotherapist).

AEs will be monitored using a six-monthly questionnaire embedded in the mHealth application. All participants are requested to fill out the form and the reported adverse events are cross-checked by an assessor using available data or, with permission, by consulting the participants' GP. This permission will explicitly and separately be asked in the informed consent procedure. If the participants do not fill in the online questionnaire, they will receive a reminder within 7 days via the app. If they still do not respond, an assessor will try to contact the participants by phone.

Due to the non-invasive nature of the current intervention and the very low expected number of AEs, no other AEs are registered. If the intervention leads to serious AEs (e.g. falls because of increased exercise or lowered blood pressure levels), this is expected to result in additional doctor visits, Accident and Emergency services (A&E) visits or hospitalizations, and will be detected in the six month questionnaires and during 12 months follow-up visit

9.2.2 Serious adverse events (SAEs)

No SAEs directly due to our intervention are expected, due to the nature of the intervention.

9.3 Follow-up of adverse events

Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.4 Data Safety Monitoring Board (DSMB) / Safety Committee

There will be no independent Data Safety Monitoring Board (DSMB) or Safety Committee installed, because the study brings a negligible risk to the participants.

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

The MIND-PRO study has one primary effectiveness outcome: a composite score of objectively measurable dementia risk factors (systolic blood pressure, non-HDL cholesterol, and BMI). The primary effectiveness outcome is the difference between the 12 months composite Z score and the baseline composite Z score ((ZSBP + Zldl-cholesterol + ZBMI)/3). For the primary analyses we will use a univariate general linear model (GLM) taking clustering of the intervention into account to assess the effect on the composite Z score within ethic group. If needed, we will adjust for baseline imbalances. A per protocol analysis will be performed. If feasible, exploratory subgroup analyses on the primary outcome will be performed for country of origin, sex, age group, history of CVD and diabetes. Multiple imputation of the primary effectiveness outcome will be done in a sensitivity analysis. For the implementation objectives we will assess implementation of the mHealth application with a series of implementation outcomes, as summarized in **table 3** to evaluate the implementation of the mHealth intervention.

Table 3. Summary of implementation research methods and outcomes

Method	Implementation outcome[7]	Measurements	Population	When measured
Quantitative	Coverage	(Non)response rates, comparison characteristics participants with eligible/source population	Potential target population	At baseline
	Adoption	Quantitative analysis of the utilisation, usage and uptake -> e.g. logins, goals setting, sending messages	All intervention participants	After 1 month (data features)
	Appropriateness	Short questionnaire of perceived fit or relevance*	All intervention participants	After 6 months and at study end
	Acceptability	Short questionnaire of agreeability, user-friendliness, credibility, complexity, content*	All Intervention participants	After 6 months and at study end
	Feasibility	The extent to which the mHealth intervention can be carried out	All intervention participants	After 6 months and at study end
	Fidelity	Degree to which the mHealth application is implemented compared to the original protocol	All intervention participants	At the end of the study
	Sustainability	Adherence, dropout, data features (time spent in the app)	All intervention participants, dropouts	Data features throughout the study
	Implementation cost	Implementation costs (see cost effectiveness analysis plan in Appendix 2)	n.a.	After 6 months and at end of study
Qualitative	Appropriateness	Perceived fit or relevance of the intervention	Intervention participants**; coaches	After 6 months
	Acceptability	Agreeability, user-friendliness, credibility, complexity, content	Intervention participants**; coaches	After 6 months
	Feasibility	Practical and social barriers/ facilitators related to the feasibility of the intervention	Intervention participants**; coaches	After 6 months
	Fidelity	Degree to which the mHealth application is implemented compared to the original protocol	coaches	After 6 months
	Sustainability	Adherence	Coaches	After 6 months

*We used several questions from the validated mHealth App Usability Questionnaire for Interactive mHealth Apps (MAUQ), where applicable to our intervention(41)
**30 participants (10 Dutch, 10 Turkish, 10 South-Asian Surinamese) will be invited for an interview on the implementation outcomes.

10.2 Secondary study parameter(s)

The effect on the CAIDE dementia risk score and it's individual components (blood pressure, BMI, non-HDL cholesterol, physical activity), and the Behapp digital endpoint for daily general movement (distance moved) will be analyzed using general linear models taking clustering of the intervention within ethnic group into account.
In addition, as an exploratory analysis, longitudinal data of Behapp endpoints will be assessed towards daily changes over time. For that purpose, time series analysis will be performed to detect trends in this longitudinal data as a function of intervention.
Self-assessment scales for disability, depressive symptoms and cognitive functioning, which are mostly ordinal, will also be analyzed as linear scales if characteristics of the instruments allow. In case a self-assessment instrument has a defined cut-off for the presence or absence of a condition, such as for instance the case of the geriatric depression scale, chi square statistics will be used. Poisson regression or zero-inflated models may be applied to distributions resembling count or zero-inflated data. A description of the cost-effectiveness analysis can be found in Appendix 3.

10.3 Interim analysis (if applicable)

Considering the relatively short duration of the study, the expected low rate of direct clinically relevant outcomes, the limited short-term consequences of a difference on our primary outcome and the fact that sustainability of any possible effect over a longer period of 6 months is an important outcome, no interim analysis is planned.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version of 2013) and in accordance with the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), The Dutch Medical Research Involving Human Subjects
Act (WMO). Data management, monitoring and reporting of the study will be performed in accordance with the ICH GCP guidelines. Technicians and data managers of Interactive Studios will perform central data management using a Microsoft SQL server. This database program is designed to meet industry regulations, including ISO 27001 and the Dutch NEN7510 norm.

11.2 Recruitment and consent

The MIND-PRO study is part of the research project 'Netherlands Dementia Prevention Initiative' (NDPI), which launched in December 2022, funded by ZonMw. NDPI is part of the National Dementia Strategy of the Dutch Ministry of Health, Welfare and Sports and aims to promote dementia risk reduction and brain health, specifically in hard-to-reach and vulnerable groups in society. Within this consortium, barriers and facilitators for reaching and engaging the target population of our study are investigated using qualitative interviews and semi-quantitative questionnaires. Results will be used to facilitate recruitment of our relatively hard-to-reach target population, in addition to the previous (qualitative) studies we already performed on this topic (19-21). For recruitment we will be using the infrastructure of the Healthy Life in an Urban Setting (HELIUS) study, which is an observational cohort study dedicated to health in the largest migrant populations of Amsterdam, including the host population itself (n=24.780) (31). Also see section 6.3 *Study procedure* for a detailed description of the recruitment strategy.

As this study will be focussed on individuals with a low SES and/or migration background we will adapt our informed consent form and participant information form to their literacy level and language.

11.3 Benefits and risks assessment, group relatedness

Participants in the intervention group may benefit from participation, since improving lifestyle may reduce their risk of dementia or may have other health benefits. The control group will not be disadvantaged, since they will receive care as usual according to current guidelines and whether using the mHealth app is really beneficial is unknown (clinical equipoise, hence an RCT).

All relevant findings gathered during the baseline assessment will be communicated to the participant and the participants' general practitioner (with consent of the participant).
There is no risk involved in using the mHealth app. Engaging in a healthier lifestyle is generally not associated with increased risk. Learning about elevated risk factors may lead to anxiety, however the risk factors we assess are not disease markers and are generally accepted markers of risk as used in daily primary care.

11.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. For the WMO clinical trial participants insurance waiver will be applied due to the negligible risk participation in the study caries.

11.5 Incentives

People who travel to one of the research locations for the screening or baseline visit are offered a free local public transport day card to compensate them for he travel costs they incurred.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The study will be conducted according to the principles of the Declaration of Helsinki (version of 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts. Data management, monitoring and reporting of the study will be performed in accordance with GCP guidelines.
Identifiable data will also be accessed by the assessors to arrange appointments at the research office or in the home of the participant. All staff will undergo training in data protection. The data will be stored on whole drive encrypted computers which are also password protected. Physical data such as consent forms will be stored in locked filing cabinets, in locked rooms, within locked buildings which are accessible only to the staff working there.

Data management will take place centrally at the Department of Public and Occupational Health (Amsterdam UMC, location AMC) in close collaboration with Interactive Studios and will be archived and stored for the next 15 years, in accordance to GCP guidelines. Hosting of the mHealth platform, which also includes data management for all data collected in the project (the CRF is integrated in the platform) will take place at a secure server in the Netherlands, meeting all required security standards. Only de-identified data will be stored at the secure server in the Netherlands, in line with the current GDPR regulations.

Participant's data are coded with a unique number (Participant Identification Number: PIN). The code is structured as follows: first number for ethnicity (7=Turkish, 8=Surinamese, 9=Dutch), 2 digits for recruitment origin (01=second HELIUS survey round, 02=first HELIUS survey round, 03=general practitioner or community centre), 4 digits for participants number. The key to this code is known by the coordinating research centre. The coordinator at AMC and one senior researcher will have access to this code.

12.2 Monitoring and Quality Assurance

After approval by the METC of the Amsterdam UMC, a meeting with a Clininal Research Associate (CRA) will take place. During this intake, the different potential risks during the research will be discussed. Based on this information a monitoring plan, specific for the study, will be drafted by the CRA. Monitoring will be done in-house by the Clinical Monitoring Centre (CMC) (in Appendix 4).

12.3 Amendments

All amendments will be notified to the METC that gave a favourable opinion. No amendments are foreseen.

12.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last participant's last visit. The investigator will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The investigator intends to publish the data from this study efficiently and timely in renowned peer-reviewed journals with a preference for open access journals.
The guidelines for authorship are based on the rules of the International Committee of Medical Journal Editors (ICMJE). These rules are followed by the key general medical journals (BMJ, Lancet, NEJM and JAMA). The ICMJE states that all persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. The first and last authors should take responsibility for the integrity of the work, from inception to published article.

13. STRUCTURED RISK ANALYSIS

Use of the intervention platform is not expected to be associated with health risks other than the risks older people experience in general when having an active lifestyle. The intervention-platform focuses on healthy lifestyle by supporting participants' self-management. The app by no means intends to replace primary care. The coach that supports the app will ensure that proposed goals, action plans and activities are feasible and safe. It will be explicitly communicated that MIND-PRO does not replace any regular primary or secondary care. In case of any condition requiring medical attention, including medication changes of any kind, there are strategies in place for the participant to be referred to their own doctor (e.g., by the coach or study PI).

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15. Appendix

15.1 Appendix 1 - Description of BeHapp, a secondary endpoint

One of the secondary outcomes of the MIND-PRO study is the effect on passively monitored social functioning using a smartphone application (Behapp).

Behapp has been developed and is operated by The University of Groningen to provide a remote, unobtrusive, and objective measure of sociability and social exploration in a longitudinal daily-life manner. Behapp is a mobile app (Android & iOS) conceptualized for mobile passive monitoring of human subjects and does not require any input from the participant.

Behapp measures several aspects of social behavior using different data modalities, which are collected through a smartphone carried by study participants (42, 43). Once installed, the application continuously monitors communication and exploration patterns in participants as a function of social acts (e.g., number of text messages sent and received, number and duration of phone calls), social exploration (e.g., number of unique places visited based on GPS location updates), and general smartphone usage. Social functioning is constructed using the several smartphone app modalities which include proxy measures for 1) exchange with other individuals, and the diversity of communication partners, and 2) movement within the social context using GPS. Using these proxy measures, social withdrawal is quantified by a lower number (e.g., when compared to the general public's distribution) in less visits to locations and reduced time travelling and a reduction in communication through phone and social media use.

An important advantage over existing methods to measure social functioning is that Behapp circumvents the issue of subjectivity in behavioral assessments given that no active input is required from the participant, other than installing the application and providing some baseline information.

The Behapp research platform is designed and developed with security and user privacy as top-priority. The platform is based on a zero-trust architecture and consistently applies the principle of least privileges. All study-data is end-to-end encrypted and kept isolated from publicly connected network resources. The study-data is geo-redundantly stored in data centers placed in EU member states and fully backed-up on a daily basis. All data is processed in line with the

GDPR and the Schrems II ruling. Additionally, the platform as a whole has been audited by the security team at Sogeti Nederland B.V. in 2023, no identifiable participant data was found to be at risk. An in-depth explanation of Behapp, as well as the privacy and security measures deployed by Behapp are described, in detail in a previous study (41).

From the participants' perspective all data is encrypted before being stored locally on the participant's device and cleared after each successful upload. This data is uploaded at 2-hour intervals to central Behapp servers (only if there is a Wi-Fi connection), after which the encrypted data is immediately deleted from the participant's device. Furthermore, Behapp does not record any information about the content of any spoken or written messages. Prior to sending data to the research database Behapp irretrievably obfuscates any information related to any individual interacting with the participant. Obfuscation allows our researchers to determine whether the same instance (person or device) has been recorded more than once while preventing them from directly identifying the recorded instance.

Lastly, the use of Behapp in vulnerable populations, including those with Alzheimer's Disease and schizophrenia was approved by the METC of the University of Groningen (file numbers 2021.0751)

15.2 Appendix 2 – CAIDE risk score

Scoring of the CAIDE dementia risk score (37)

	Model 1				Model 2			
	β coefficient	p	OR (95% CI)	Score	β coefficient	p	OR (95 % CI)	Score
Age								
<47 years	0 (reference)		1	0	0 (reference)		1	0
47–53 years	1·084	0·013	2·958 (1·261–6·938)	3	1·155	0·009	3·175 (1·331–7·572)	3
>53 years	1·762	0·000	5·825 (2·192–15·476)	4	1·874	0·000	6·513 (2·365–17·935)	5
Education								
≥10 years	0 (reference)		1	0	0 (reference)		1	0
7–9 years	0·910	0·055	2·485 (0·982–6·291)	2	1·149	0·025	3·155 (1·155–8·620)	3
0–6 years	1·281	0·006	3·599 (1·453–8·913)	3	1·587	0·002	4·890 (1·833–13·043)	4
Sex								
Women	0 (reference)		1	0	0 (reference)		1	0
Men	0·470	0·097	1·599 (0·919–2·784)	1	0·438	0·133	1·549 (0·875–2·743)	1
Systolic blood pressure								
≤140 mm Hg	0 (reference)		1	0	0 (reference)		1	0
>140 mm Hg	0·791	0·015	2·206 (1·169–4·161)	2	0·817	0·013	2·263 (1·186–4·317)	2
Body-mass index								
≤30 kg/m²	0 (reference)		1	0	0 (reference)		1	0
>30 kg/m²	0·831	0·006	2·296 (1·263–4·173)	2	0·608	0·059	1·837 (0·977–3·453)	2
Total cholesterol								
≤6·5 mmol/L	0 (reference)		1	0	0 (reference)		1	0
>6·5 mmol/L	0·631	0·046	1·879 (1·012–3·491)	2	0·460	0·156	1·585 (0·839–2·992)	1
Physical activity*								
Active	0 (reference)			0	0 (reference)		1	0
Inactive	0·527	0·072	1·693 (0·953–3·009)	1	0·579	0·057	1·783 (0·983–3·236)	1
APOE ε4 status								
Non-ε4					0 (reference)		1	0
ε4					0·890	0·002	2·434 (1·390–4·265)	2
Follow-up time	0·093	0·014			0·093	0·019		
Intercept	-7·642	0·000			-8·203	0·000		

The score for each factor is the β coefficient multiplied by 2·5 and rounded to the closest integer. *Active people have leisure time physical activity at least twice a week; inactive people exercise less often than twice a week.

Table 2: **Logistic regression models for dementia risk in 20 years, according to the risk factor profiles at middle age and the risk scores derived from the β coefficients**

15.3 Appendix 3 – Health economics

A key challenge in dementia primary prevention interventions in midlife or early late-life is the long duration before an effect is expected on the outcome dementia. Mathematical model-based simulation studies can be used to extrapolate short-term trial outcomes by synthesizing data from multiple sources (e.g., trial for effectiveness on risk factor and cohort studies on association between risk factor and dementia onset). The health economic evaluation in this study is closely linked to a project of the parallel BIRD-NL consortium (42). In BIRD-NL, a health economic microsimulation model will be developed based on the existing models MISCAN (dementia) and PRODEMOS (dementia and cardiovascular disease) studies. The basis of this model is a dementia-free survival function and a mortality function, both by age, sex and SES. Updated evidence on the association between modifiable risk factors and dementia onset, and non-modifiable factors (migration background) and dementia onset will be used to adjust the dementia-free survival function. Possible interactions with age, sex and SES will be included in the model. The model will simulate the annual incidence of dementia onset and death, and produce the outcomes life expectancy, person-years with dementia, QALYs and costs.

The mHealth intervention will be implemented into the model (after basic model development in the BIRD-NL consortium). This will be done in terms of the target population (Dutch persons aged 50+ with low SES and/or migration background) and intervention effect. The model will simulate the dementia onset in the usual care strategy of individuals using the relative risk corresponding to each factor's risk status. The mHealth intervention effect is reflected by copying the baseline population characteristics and apply the effect observed from the current trial on each modifiable risk factor (e.g., a difference in score between baseline and follow-up, between control and intervention arm). The model will simulate the 'mHealth in addition to usual care' strategy using the same procedure as for the usual care strategy.

As the current RCT only covers a 1-year follow-up period, experts within the NDPI consortium will be asked for evidence (or, if unavailable, their opinion) on plausible estimates of long-term effectiveness endurance beyond the trial follow-up period. These assumptions will be implemented in the model. Intervention costs will be obtained from estimates on coaching time and mHealth app operationalization costs recorded as secondary outcome during this trial.

These simulations will result in the proportion of the starting population with a history of dementia and mortality (and cardiovascular disease) over lifetime. The simulated data will be combined with estimates from literature on health-related quality of life and care costs related to dementia (and cardiovascular disease) to estimate the cumulative lifetime QALYs and costs for the 'usual care' strategy and 'mHealth in addition to usual care' strategy. This allows to estimate the incremental cost-effectiveness ratio of the mHealth intervention.

Uncertainty will be addressed by univariate sensitivity analysis (e.g., using different assumptions on beyond-trial effectiveness endurance).

Results will be published open-access following international CHEERSII reporting guidelines.

15.4 Appendix 4 – Monitoring

Amsterdam UMC
Universitair Medische Centra

Bevestiging aanvraag voor centrale monitoring CMC

Studie (acroniem):	M I N D - P R O
NL-nummer:	NL84958.018.23
Verrichter:	Amsterdam UMC
Afdeling:	Public and Occupational health
Hoofdonderzoeker:	Edo Richard
Uitvoerend onderzoeker:	Anne Roos van der Endt
Type studie:	☐ Geneesmiddelenonderzoek ☐ Medisch hulpmiddelen onderzoek ☐ Voeding onderzoek ☒ Overig WMO-plichtig onderzoek
Mono of multicenter:	☒ Monocenter ☐ Multicenter *Indien multicenter, aantal sites (inclusief locatie AMC):*
Risico:	☒ Verwaarloosbaar ☐ Matig ☐ Hoog
Aantal patiënten:	692
Beoogde startdatum:	01-04-2023

Bovengenoemde studie zal worden gemonitord door monitors van het Clinical Monitoring Center (CMC). Na goedkeuring van de METC nemen wij met u contact op om een intake te plannen.

Op de intranetpagina van het CMC treft u een rekenmodel aan waarmee u – afhankelijk van risico, type onderzoek en studieduur – kunt uitlezen hoeveel monitoringvisites mogelijk worden gepland en welke kosten - bij multicenter onderzoek - daaraan verbonden zijn. Zie pagina Monitoring (de link naar het **Rekenmodel monitoring** staat in de rechterkolom op de pagina).

Stuur dit aanvraagformulier naar: cmc_diensten@amsterdamumc.nl. Binnen +/- 2 werkdagen ontvangt u dit formulier getekend retour.

Bij deze bevestig ik de aanvraag van monitoring van bovengenoemde studie door het CMC:

Naam: Saskia Hendriks Datum: 19-9-2023

Handtekening: Digitaal ondertekend door S.Hendriks
Datum: 2023.09.19 13:44:49 +02'00'