Statistical analysis plan

MIND PRO trial

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Contents

1. Background

The Mobile Health (mHealth) Intervention for Dementia Prevention through lifestyle Optimisation (MIND-PRO) study addresses the increasing prevalence of dementia among populations with lower socioeconomic status (SES) and a migrantion background. The study aims to evaluate the effectiveness and implementation of an mHealth app designed for self-managed lifestyle modifications with remote coaching to reduce dementia risk factors.

This Analysis plan will be used as a work description for all the persons who are involved in the analyses of the MIND PRO trial (ISRCTN92928122).

2. Study 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.

3. 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.

Study 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.

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 self-reported educational attainment in the Netherlands or in the country of origin, specifically defined as i) none, or only primary education', (ii) 'lower vocational or lower secondary education', (iii) 'intermediate vocational or intermediate or higher secondary education' as previously collected in HELIUS.
- Manifest cardiovascular disease, as diagnosed by specialist or general practitioner OR ≥ 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

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) [1, 2], a validated dementia screening method specifically developed to be less susceptible to cultural, linguistic, and educational biases [3]. 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.

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.

Randomisation procedures

Randomization will take place in the app using a computer algorithm in a 1:1 manner, stratified by ethnicity. Participants will be informed that they are randomized to one of two different smartphone apps, that can provide support in changing their lifestyle to reduce the risk of dementia. Partners who also participate in MIND-PRO will automatically be allocated to the same treatment arm to limit contamination. Outcome assessment will be performed by an assessor who is blinded to treatment allocation. The coaches who support participants in behaviour 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. Participants are therefore instructed to not discuss the intervention with the assessors. If any unblinding occurs, its impact is likely limited since our primary outcome consists solely of objectively measured parameters.

More information about the intervention and the measurements can be found in the trial protocol.

Study outcomes

Primary outcomes

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 [4].

   Rationale for this outcome: Due to the long time lag between exposure (risk factors) and dementia onset, incident dementia cannot be used as outcome [5]. 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.

Secondary outcomes

The questionnaires used to assess the secondary outcomes are presented in **table 1 below**.

- Change in CAIDE dementia risk score between baseline and follow-up[6] (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[7])
- Disability[8]
- Depressive symptoms[9]
- 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[10].
- Digital measures for social daily functioning measured by BeHapp (remote behavioural monitoring app). 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 1. Self-assessment questionnaires

4. Statistical Analysis

General

Prior to analysis, all data will be checked for missing values and miscoding, and univariate analyses will be performed to compare the distribution of variables and to identify abnormalities/outliers.

Primary and secondary outcomes will be analysed according to the "intention to treat" principle for all participants who underwent baseline assessment and subsequent randomization and with available outcome data.

Primary outcomes

The primary effectiveness outcome is the difference between the composite Z score after 12 months and the baseline composite Z score ($(Z_{SBP} + Z_{non\text{-}HDL\text{-}cholesterol} + Z_{BMI})/3$). The baseline mean and SD will be used to calculate composite Z scores at both time points to be able to detect a change. For the primary analyses we will use a linear mixed effects model with individual observations nested within ethnic groups operationalized by a random intercept and/or slope (dependent on best model fit).

Implementation of the intervention will be analysed with graphically portray of the Likert scales for the questionnaires and we will perform thematic analyses for the in-depth interviews.

Sensitivity analyses

Sensitivity analyses will only be done for effect of the intervention on the composite Z score of SBP, non-HDL cholesterol and BMI.
If needed, we will explore the impact of any baseline imbalances by including imbalanced factors as covariate in a sensitivity analysis. A per protocol analysis will be done, based on uptake within the first month and continued use during the whole intervention period. Finally, we will conduct a sensitivity analysis using multiple imputation.

Predefined subgroup analyses

Exploratory subgroup analyses will only be done for effect of the intervention on the composite Z score of SBP, non-HDL cholesterol and BMI.
Exploratory separate analyses on the effect of the intervention on the primary outcome will be performed for ethnic group, sex, age group, history of CVD and diabetes. Interaction terms will be included to test

for between-subgroup differences in intervention effects. A p value of 0.10 is regarded significant interaction.

Secondary outcomes

The effect on the CAIDE dementia risk score and its individual components (i.e. blood pressure, BMI, non-HDL cholesterol, physical activity) will be analysed using the same model as for the primary analysis*.

In addition, as an exploratory analysis, the effect on daily changes in general movement will be assessed based on the data collected with the BeHapp application[11-13]. For that purpose, time series analysis will be performed to detect trends in this longitudinal data as a function of intervention, accounting for clustering within ethnicities.

Scales for disability, depressive symptoms and cognitive functioning, mostly ordinal, will also be analyzed as linear scales* if the data characteristics allow. Poisson regression or zero-inflated models may be applied to distributions resembling count or zero-inflated data.

A description of the cost-effectiveness analysis will be given in a separate analysisplan on ISRCTN.

* The same model as used for the primary analysis will be employed for linear secondary outcomes: a linear mixed effects model with individual observations nested within ethnic groups operationalized by a random intercept and/or slope (dependent on best model fit for primary outcome).

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