Analysis plan HATICE trial

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1. Background

Cardiovascular disease and dementia share a number of risk factors including hypertension, hypercholesterolemia, smoking, obesity, diabetes and physical inactivity. The rise of eHealth has led to increasing opportunities for large-scale delivery of prevention programs encouraging self-management. The aim of this study is to investigate whether a multi-domain intervention to optimise self-management of cardiovascular risk factors in older individuals, delivered through a coach supported interactive internet platform, can improve the cardiovascular risk profile and reduce the risk of cardiovascular disease and cognitive decline.

HATICE is a multi-national, multi-centre, prospective, randomised, open-label blinded endpoint (PROBE) trial with 18-months intervention. In total 2725 older people (>=65 years) at increased risk of cardiovascular disease were recruited from the Netherlands, Finland and France. Participants randomised to the intervention condition have access to an interactive internet platform, stimulating self-management of vascular risk factors, with remote support by a coach. Participants in the control group have access to a static internet platform with basic health information.

This Analysis plan will be used as a work description for all the persons who are involved in the analyses of the HATICE trial (ISRCTN48151589).

2. Study Objectives

Primary Objective:

To investigate whether a multi-domain intervention to optimise self-management of cardiovascular risk factors in older individuals, delivered through a coach supported interactive internet platform, can improve the cardiovascular risk profile. This cardiovascular risk profile is summarized in a composite score based on the average Z score of the difference between baseline and 18 months follow-up values of systolic blood pressure, low-density-lipoprotein (LDL) and body mass index (BMI).

Secondary Objectives:

To evaluate the effects of the intervention on:

- the change between baseline and month 18 on the individual components of the primary outcome and other biological risk factors
- the change in estimated 10-year cardiovascular disease risk based on the 'Framingham cardiovascular disease risk score' (comparable to other studies) and 'SCORE OP' (developed in a very large population of European elderly and internally validated)
- the change in lifestyle related risk factors (physical exercise, diet, smoking status)
- the change in estimated dementia risk based on available and validated risk scores, including the 'cardiovascular risk factors, aging and dementia risk-score' (CAIDE)
- incident cardiovascular disease and all-cause mortality
- disability
- cognitive functioning
- incident dementia
- physical fitness
- mood
- self-efficacy
- cost-effectiveness[1]

The clinical outcomes stroke, myocardial infarction, angina pectoris, dementia and death will be adjudicated by an independent outcome committee in each country.

[1] Analyses on cost-effectiveness are outside the scope of this analysis plan

3. Study Design

This chapter briefly describes the study design of the HATICE trial. More details are available from Richard et al[1].

The intervention

Participants randomised to the intervention condition have access to an interactive internet platform, stimulating self-management of vascular risk factors, with remote support by a coach. Participants in the control group have access to a static internet platform with basic health information. Participants are randomised during the baseline visit in a 1:1 ratio using central randomisation according to a computer generated randomisation sequence. In case of spouse/partner participation, partners will be allocated to the same treatment arm to prevent contamination. It is explained to participants that they are randomised to one of two internet-platforms to improve lifestyle, without further details. The coaches who support the participants in the intervention group are not blinded. Outcome assessment at the end of study at month 18 will be done by an independent assessor blinded to treatment allocation.

Study population

Recruitment took place in the Netherlands, Finland and France. The study population consists of community-dwelling people aged 65 years or older who have two or more cardiovascular risk factors and/or manifest cardiovascular disease or diabetes mellitus. This leads to a mixed population with an indication for either primary or secondary cardiovascular prevention. Inclusion and exclusion criteria are listed in the overview on the next page and Table 1 shows the distribution of screening/ baseline characteristics by country.

Inclusion criteria	Exclusion criteria
• **Age ≥65 years** • **Available informant** • **≥2 cardiovascular risk factors defined as:** ▪ hypertension, defined by any of the following: - diagnosis by specialist or GP* - currently on anti-hypertensive drugs - baseline BP*: if <80 years; ≥140/90 mmHg; if ≥80 years: systolic BP ≥160 mmHg ▪ dyslipidaemia, defined by any of the following: - diagnosis by specialist or GP* - currently on lipid-lowering drugs - total cholesterol ≥5.0 mmol/L and/or LDL ≥2.5mmol/L ▪ overweight, defined by any of the following: - BMI* ≥30 kg/m^2 - waist circumference men ≥102 cm, women ≥88 cm ▪ active smoking ▪ lack of physical exercise defined as below the WHO* norm of 30 minutes of intermediate exercise, 5 times a week **AND/OR** • **History of cardiovascular disease:** stroke/transient ischemic attack, myocardial infarction, angina pectoris and/or peripheral arterial disease. (diagnosis by specialist or GP) • **Diabetes mellitus** (diagnosis by specialist or GP)	• Previously diagnosed dementia • MMSE* score <24 • Any condition expected to limit 18-months compliance and follow-up • Computer illiteracy, defined as unable to send an email • Severe (visual) impairment interfering with operating a computer

*GP = general practitioner; BP = blood pressure; LDL = low-density-lipoprotein; BMI = body mass index; WHO = World Health Organisation; MMSE = Mini Mental State Examination

Table 1. Distribution of screening/ baseline characteristics HATICE trial by country

Characteristic	N	All (n= 2725)	Netherlands (n= 1472)	France (n= 368)	Finland (n= 885)
Demographics					
Age, y, median (IQR)	2725	69 (67-73)	69 (67-74)	70 (67-74)	68 (66-70)
Male sex, n (%)	2725	1429 (52.4)	817 (55.5)	228 (62.0)	384 (43.3)
Partner participates, n (%)	2725	420 (15.4)	360 (24.5)	0 (0)	60 (6.8)
Educational level, n (%)					
Basic	2725	781 (28.7)	621 (42.2)	49 (13.3)	111 (12.5)
Post-secondary non-tertiary	2725	823 (30.2)	396 (26.9)	107 (29.1)	320 (36.2)
Tertiary	2725	1121 (41.1)	455 (30.9)	212 (57.6)	454 (51.3)
Cardiovascular history, n (%)*	2713	827 (30.3)	507 (34.4)	105 (28.5)	215 (24.3)
Cardiovascular risk factors					
Hypertension, n (%)**	2725	2148 (78.8)	1180 (80.2)	276 (75.0)	692 (78.1)
Dislipidemia, n (%)***	2724	2604 (95.5)	1420 (96.5)	351 (95.4)	833 (94.0)
Obesity (BMI>=30 kg/m2), n (%)	2725	1015 (37.2)	565 (38.4)	112 (30.4)	338 (38.1)
Diabetes Mellitus, n (%)	2723	604 (22.2)	368 (25.0)	54 (14.7)	182 (20.5)
Smoking, n (%)	2725	270 (9.9)	170 (11.5)	40 (10.9)	60 (6.8)

* Any of angina pectoris, myocardial infarction or stroke

** either high bloodpressure (if < 80 years: >= 140/90 mmHg; if >= 80 years: >= 160/90), self-reported hypertension diagnosis, or self-reported anihypertensive usage

*** either LDL >= 2.5, total cholesterol >=5, self-reported dyslipidemia diagnosis, or self-reported cholesterol lowering drugs

Sample size calculation

We base the sample size calculation on the effect-sizes of the HATICE primary outcome as observed in the preDIVA and FINGER trials. In the PreDIVA study the mean difference in Z score of the HATICE primary outcome between baseline and two year follow-up is 0.070 (p=0.002; intervention group -0.194 and control group -0.124). In the FINGER study this mean difference is 0.041 (p=0.11; intervention group -0.128 and control group -0.087). To avoid the risk of being underpowered since the effect was non-significant in the FINGER study, we base our sample size calculation on an effect size of 0.06.

Based on the first 1000 recruitments, we estimate that 17.5% of the participants will be recruited as a couple. Couples can be considered the smallest possible clusters (n=2). Although intra-cluster correlation coefficients (ICC) in RCTs are typically below 0.05, the ICC for vascular and lifestyle-related risk factors within small clusters of relatives may be much higher, up to 0.25[49].

With 80% power, a 0.05 two-sided significance level, and accounting for an estimated 14% attrition based on previous experiences in our own multi-domain prevention study[14], an ICC of 0.25 [49] and an effect size of 0,06 the required sample size is estimated to be 2534 participants in total. To allow for unexpected factors we raised this to 2600.

Finally, we included 2725 participants in the HATICE trail.

Measurements

Figure 1 shows the logistics of the measurements. After the screening, seven digital questionnaires are filled out by the participants at home. All participants fill out every three months an adverse event questionnaire. After 12 months an assessment is performed by telephone. Before the 18 months assessment, again the seven self-assessment questionnaires are filled out at home. More information about the measurements can be found in the protocol paper that was published in BMJ open.[1]

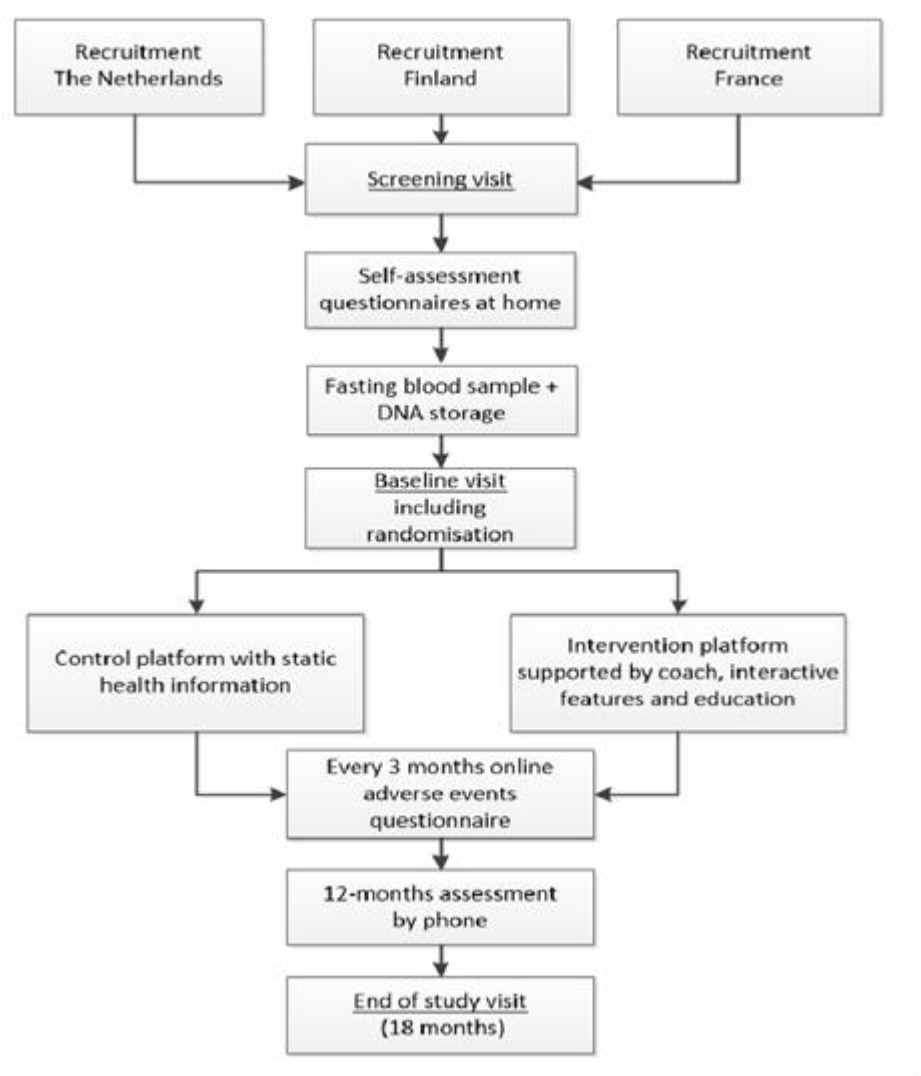

Figure 1: logistics of the measurements

5. 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 outcome

The primary outcome is the difference between the 18 months composite Z score and the baseline composite Z score $((Z_{SBP} + Z_{ldl\text{-}cholesterol} + Z_{BMI})/3)$. The means and SDs used to calculate composite Z scores are based on the baseline mean and SD of the intervention and control groups from the three countries combined.

For the primary analyses we will use a univariate general linear model (GLM) to assess the effect on the composite Z score. The primary outcome will not be imputed in case it is missing as part of the primary analysis.

If needed, we will adjust for baseline imbalances and take clustering of the intervention within country, centre and coach into account.

Sensitivity analyses

- A per protocol analysis will be performed.
- If one of the variables needed to calculate composite Z scores is missing either at baseline or at the final assessment, no change in composite Z scores can be calculated for the primary analyses. In a sensitivity analysis, we will use multiple imputation for the individual variable (e.g. LDL at 18 month).

Clinical relevance of Z score difference:

Because a difference in Z scores is difficult to interpret, we estimated the threshold for a clinically relevant difference in Z score by using the follow-up data in preDIVA for clinical outcomes. For this purpose we compared preDIVA participants who did with those who did not develop CVD or dementia during an average follow-up of 6.7 years. In preDIVA the change in Z score for the HATICE primary outcome after 2 years was -0.146 in participants who developed CVD or dementia and -0.205 in participants who did not develop CVD or dementia. We therefore assume that a difference of 0.06 or more on the composite primary outcome of HATICE can be considered clinically relevant.

Predefined subgroup analyses

Separate analyses on the primary outcome will be performed for

- Country (Finland, France, the Netherlands)
    - Due to cultural differences the intervention may have differential effects across the participating countries. Furthermore, small differences in expertise or organisation may have impacted the effectiveness of the intervention. For example, in The Netherlands for the coaches it was not obliged to have a (para-) medical degree and in France the screening and baseline assessments were not performed by the coaches themselves (coaches stepped in as of the motivational interviewing part).

- Gender (male/female)
    - Lifestyle change may have different effects on CV risk factors by gender; possibly women are more likely to change their lifestyles. On the other hand, men may be more computer literate.

- Age group
    - Lifestyle change may have different effects on CV risk factors by age group; possibly in the oldest old the window of opportunity for prevention is smaller

- Education
    - A higher level of education may be associated with a larger effect on CV risk, e.g. through a higher adherence to the intervention.

- Participation with partner
    - Effects in participants who participate with partner may be larger as couples can stimulate and support each other in behavioural changes

- History of CVD or diabetes at baseline
    - Participants with a history of CVD or diabetes at baseline are more likely to be involved in disease management programs, with less room for improvement of CV risk factor levels than participants without CVD/DM2.

- Self-efficacy (measured by Partners in Health –PIH)
    - If self-efficacy is low, intervention may be less successful

- Consistent coaching
    - Compliance to the intervention may be lower with changes in coaches.

For the subgroup analyses, additional interaction terms will be included to test for between-subgroup differences in intervention effects.

Secondary outcomes

The effect on the change during 18 months in **continuous factors measured at baseline and at M18** will be analysed using general linear models (GLM). These are the individual biological risk factors,

Framingham CVD risk score, SCORE OP, CAIDE risk score, waist circumference, HbA1c within diabetics, blood lipids, disability (LLFDI), Z scores of cognitive tests[2], physical fitness (SPPB total score), and mood (HADS and GDS)

The effect on the change in **continuous factors measured at baseline, M12 and M18**, will be analysed using a linear multiple measurements model taking into account the measurement at 12 and 18 months. These are physical activity (CHAMPS B), diet (MEDAS), and self-efficacy (PIH).

For the effect on the change in **dichotomous variables measured at baseline, M12 and M18** a multiple measurements model taking into account the measurement at 12 and 18 months will be used. These are adherence to WHO guidelines, defined as 'at least 2.5 hours of at least moderate intense activity per week', and smoking cessation.

The effect on **time-to-event data** will be analysed by standard Cox-proportional hazards models with time since inclusion as the timescale. These are incident cardiovascular disease, mortality and dementia.

6. Evaluation of adherence to the internet intervention ('user statistics')

To address the adherence to the internet intervention, we will show the number of logins and goals that were set by the intervention participants, as well as the messages between coaches and participants.

References

1. Richard, E., et al., *Healthy Ageing Through Internet Counselling in the Elderly: the HATICE randomised controlled trial for the prevention of cardiovascular disease and cognitive impairment.* BMJ Open, 2016. **6**(6): p. e010806.

[2] Unadjusted Z scores will be standardised to the baseline mean and SD at each timepoint for cognitive functioning according to MMSE, Stroop 1-3 (time in seconds), ratio stroop 3/ stroop 2, Rey Recall (# words), Rey Recognition (# yes + no) and Verbal Fluency. Also a composite-score based on average Z score from the 8 tests (Z scores with higher scores suggesting better performance) will be calculated.