eHealth in cardiovascular risk management to prevent cognitive decline

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De zijt werkt niet…

(Dutch quote from an email of a participant indicating that the website did not work on his computer, February 2015)
Chapter 3

HEALTHY AGEING THROUGH INTERNET COUNSELLING IN THE ELDERLY
THE HATICE RANDOMISED CONTROLLED TRIAL
FOR THE PREVENTION OF CARDIOVASCULAR DISEASE AND COGNITIVE IMPAIRMENT

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*These authors contributed equally

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Chapter 3

ABSTRACT

Introduction 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 an coach supported interactive internet platform, can improve the cardiovascular risk profile and reduce the risk of cardiovascular disease and cognitive decline.

Methods and analysis HATICE is a multi-national, multi-centre, prospective, randomised, open-label blinded endpoint (PROBE) trial with 18-months intervention. Recruitment of 2600 older people (>=65 years) at increased risk of cardiovascular disease will take place in the Netherlands, Finland and France. Participants randomised to the intervention condition will 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 will have access to a static internet platform with basic health information. The primary outcome is 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 and body mass index. Main secondary outcomes include the effect on the individual components of the primary outcome, the effect on lifestyle related risk factors, incident cardiovascular disease, mortality, cognitive functioning, mood and cost-effectiveness.

Ethics and dissemination The study was approved by the medical ethics committee of the Academic Medical Center in Amsterdam, the Comité de Protection des Personnes Sud Ouest et Outre Mer in France and the Northern Savo Hospital District Research Ethics Committee in Finland. We expect that data from this study will result in a manuscript published in a peer-reviewed clinical open access journal.

Trial registration Controlled-Trials.com registration number ISRCTN48151589 registered September 2014.
BACKGROUND

Despite impressive reductions of its incidence in many countries, cardiovascular diseases (CVD) continue to be a major public health issue with over 4 million deaths in Europe each year(1). In parallel, the global prevalence of dementia is likely to increase in the coming years, mainly due to increased life expectancy(2). CVD and dementia share a number of risk factors including hypertension, hypercholesterolemia, smoking, diabetes, obesity and physical inactivity(3, 4). Treatments targeting most of these risk factors are effective for the prevention of CVD(5-7). Even small improvements of vascular risk factor management in a large population, can lead to a large effect on incident cardiovascular disease at the population level(8) and substantial reductions in health care costs(9).

Although up to 30% of dementia cases are attributable to modifiable (mostly cardiovascular) risk factors(10), there is currently insufficient evidence from randomised controlled trials (RCT) that treatment will also reduce dementia incidence. Vascular risk factors rarely occur in isolation. It is plausible that targeting multiple risk factors simultaneously can have an additive effect on the reduction of the risk of CVD and dementia, but RCTs targeting the older population are rare and with mixed results(11-13). However, the recently published large RCT ‘Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)’, suggest that a multidomain lifestyle intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population(14).

In spite of clear guidelines for cardiovascular risk management mainly for younger adults(15), but also applied on older adults, the sobering reality of daily practice is that target values are often not reached(16, 17), leaving room for a substantial improvement. Both patient and doctor factors play a role in this gap between evidence and practice(18). Innovative strategies to improve cardiovascular risk management are therefore urgently needed.

Patient self-management is a potentially powerful strategy to improve adherence to therapy in CVD risk reduction(19, 20). Specific patient characteristics can determine the strategies applied at the individual level. Increasing knowledge about a healthy lifestyle and the possibility for tailor-made prevention programs can empower individuals and improve adherence with pharmacological and non-pharmacological interventions(21).
When designing a trial on prevention of cardiovascular disease and dementia, the optimal age-range of the target population is matter of debate. The benefits of higher efficacy in midlife are counteracted by the large sample size and long follow-up required to detect an effect on incident disease(22). The optimal time-window depends on the peak incidence age, and is probably somewhere in late midlife or early late-life(23).

The internet has become a major source of information for people of all ages, and its use among older people throughout Europe has increased dramatically, making it a potentially suitable medium for the delivery of widely implementable health care interventions(24). Together with the rise of eHealth this creates opportunities for large-scale delivery of prevention programs encouraging self-management(25).

In the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) trial we investigate whether a coach-supported interactive internet intervention to optimise self-management of cardiovascular risk factors in older individuals can improve the cardiovascular risk profile and reduce the risk of cardiovascular disease and cognitive decline.

**METHODS**

**Study design**

HATICE is a pragmatic, multi-national, multi-centre, investigator initiated, prospective, randomised, open-label blinded endpoint (PROBE)(26), trial with 18-months intervention and follow-up. Due to the nature of the intervention, complete double blinding is not possible. Investigators evaluating outcome measures are blinded for the randomisation group and the primary outcome is based on objective parameters.

**Study population and recruitment**

The study population will consist 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 prevention. Inclusion and exclusion criteria are listed in Table 1.
### Table 1: Overview of inclusion and exclusion criteria

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

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

Recruitment takes place in the Netherlands, Finland and France. Based on a pilot study (later described) and experience from previous trials(14, 27, 28) we expect a response rate of approximately 10%. In the Netherlands recruitment will take place through registration lists of all individuals ≥65 years registered in primary care practices. In Finland recruitment will take place by inviting individuals from the population registry based on age, by selecting participants from previous population-based surveys, as was previously done to recruit for RCTs(29), and by advertisements in local media, patient organizations and their websites and health care centres. In France participants will be enrolled from various sources. In addition to recruitment through general practitioners (GP), prevention centres, cardiovascular risk factors consultations and the geriatrics department and memory clinics in the Toulouse area, participants will also be recruited through mailing lists and advertisements in local media, seniors clubs and conferences.
People aged ≥65 years will receive an information letter and are invited to apply through a country specific website or emailing or calling the local study centre. Those interested will receive a pre-screening telephone call. If eligible, people are invited to attend the first screening visit.

Recruitment started in March 2015.

**Intervention**

Participants randomised to the intervention condition will have access to an interactive internet platform, specifically designed for use by older people (Figure 1). The platform is in the participants own language (Finnish, French or Dutch) and facilitates self-management of vascular and lifestyle related risk factors, including blood pressure, overweight, physical inactivity, diet, smoking, diabetes and hypercholesterolemia. After secure login, a participant can view his/her own cardiovascular risk profile created through baseline measurements. At the interactive part of the platform, the participants can set a personal goal for lifestyle change, make a corresponding action plan, monitor goals by entering data (e.g. blood pressure or a food diary), join lifestyle activity groups and correspond with their coach, whom they have met in person at the baseline assessment. In addition, participants can find health information in static and interactive education-modules, watch peer videos on lifestyle change, and use a program for cognitive training.

The platform and the guidance provided by the coach are based on current European and national guidelines for cardiovascular risk management(15). When indicated, this is adapted to national guidelines from one of the three countries where participants are recruited. Due to the heterogeneous population in this trial, which includes participants with elevated cardiovascular risk with or without established CVD, primary as well as secondary prevention guidelines will be applied. The HATICE intervention platform does not replace existing health care in any way, but is offered as an add-on.

The platform is supported by a coach trained in motivational interviewing. All coaches in all three countries work according to a coach protocol set up by the research team. Guided by the preferences of the participant, the coach provides remote support by assisting in realistic goal-setting according to the ‘specific, measurable, attainable, realistic and time bound’ (SMART) principle(30). Communication between the participant and the coach is through a messaging system within the platform. The coach receives automatic alerts when participants
enter measurements or when a participant has not been active on the platform for more than 3 weeks. The coach advises the participant to log in at least once a week, but this is not compulsory.

There are regular national and international meetings with the coaches and the research team to discuss the intervention and to solve discrepancies between countries and coaches.

Participants randomised to the control condition will have access to an internet platform with only the static information on cardiovascular risk factors, but lacking interactive features and the support of a coach.

Figure 1. Screenshot of intervention portal (simulated values, participant and coach)

Pilot

Between September 2014 and February 2015 a pilot study was conducted in the three participating countries with a total of 41 participants, in order to test the trial procedure and the platform. We adjusted the protocol and the platform where needed, according to the feedback of the end users; e.g. enlargement of electronic buttons, more guidance on the use of the platform (e.g. introduction video and more instructions from the coach) and more positive tone of voice (e.g. ‘health factor’ instead of ‘risk factor’).
Primary outcome

The primary outcome is 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). Several considerations have led to the decision for this outcome. First, a multi-domain outcome capturing the potential effect of our multi-domain intervention on a composite of risk factors was deemed appropriate. Second, no existing cardiovascular risk score can be applied to both primary and secondary prevention, whereas our pragmatic trial targets a mixed population with an indication for primary or secondary prevention. Third, we deemed it inappropriate to include any parameter based on patient-reported measures (e.g. physical activity questionnaire) in our primary outcome due to the risk of reporting bias; self-reported parameters were considered insufficiently reliable for the primary outcome.

Secondary outcomes

Main secondary outcomes include the difference between baseline and month 18 on the individual components of the primary outcome, the difference in lifestyle related risk factors (physical exercise, diet, smoking status), the difference in estimated 10-year cardiovascular disease risk based on the Framingham cardiovascular disease risk score (measured at 18 months), cardiovascular risk factors, aging and dementia risk-score (CAIDE)(31), incident cardiovascular disease, mortality, disability, cognitive functioning, incident dementia, physical fitness, mood and cost-effectiveness. The clinical outcomes stroke, myocardial infarction, angina pectoris, peripheral arterial disease, dementia and death will be adjudicated by an independent outcome committee in each country.

Study logistics

The overall study logistics are shown in Figure 2. In this trial, each participant will make three visits to the study centre. After the pre-screening by telephone, the first (screening) visit will take place. Informed consent will be signed by every participant. Eligibility criteria will be checked by recording blood pressure, weight, height, hip and waist circumference, cognition (Mini Mental State Examination(32)) and medical history. Blood pressure will be measured twice with an Omron M6 Comfort (HEM-7321-E) device in resting sitting position. After this visit the participants are requested to fill in seven online self-assessment questionnaires at home: Community Healthy Activities Model Program for Seniors (CHAMPS) physical activity questionnaire(33), a nutrition questionnaire (adapted from ePredice(34)), 15-item Geriatric Depression Scale (GDS)(35), Late Life Function and Disability Instrument (only disability part)(36), EuroQol EQ5D-3L(37), Hospital Anxiety and Depression Scale (only anxiety part)(38), and...
part)(38) and the Partners in Health scale(39) (participant rated self-management measure). Validated versions of these questionnaires in the local languages (Finnish, French, Dutch) will be used, whenever available. If not, the validated English version of the questionnaire was translated according to the proper translation guideline(40) into the three languages.

**Figure 2.** Study logistics

Before the baseline visit, a fasting blood sample will be drawn for determining blood glucose, glycated haemoglobin, cholesterol spectrum, C-reactive protein and DNA storage. DNA will be stored locally, but is considered as one biobank. During the second (baseline) visit, which will take place approximately two weeks after the screening visit, all outcome assessment instruments will be applied. Physical functioning will be assessed using the short physical performance battery(41). Medication use and results of blood tests will be recorded. Cognitive function in different domains will be tested using the Stroop test(42), auditory verbal learning
test(43, 44) and semantic verbal fluency test (animal naming). For the intervention group this visit will be concluded with a motivational interview by the coach and an explanation of the platform to facilitate its use.

At 12 months, the participants are requested to fill in all seven online self-assessment questionnaires again and will receive a telephone evaluation call. Participants from both groups will be called and medication lists will be checked. The participants from the intervention group will have an additional interview with a strong focus on their motivation with their own coach.

At the end of study visit at 18 months all parameters assessed during screening and baseline visits and the online questionnaires are recorded again by an independent assessor, blinded to treatment allocation.

The electronic case report forms (eCRF) are built into the platform and only available for the assessors and researchers. All data will be coded, to assure confidentiality. Data will be managed in one central server for all three countries.

Randomisation and blinding

Participants are randomised during the baseline visit in a 1:1 ratio using central randomisation according to a computer generated randomisation sequence. We decided not to stratify for any characteristic, since the magnitude of the sample size, even within one country, renders any imbalance between the groups extremely unlikely(45, 46). 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.

Safety

The intervention is considered low-risk, since no drugs are prescribed and only lifestyle advice and support is provided. Serious adverse events (SAE) resulting from the intervention are not expected. No data safety and monitoring board is installed. Adverse events are however monitored using a 3-monthly questionnaire to be filled in online by the participant in both treatment arms. If the participant is not able to fill in the questionnaire due to a medical
condition, the informant will be contacted to fill in the questionnaire. This questionnaire is automatically generated and concerns new cardiovascular events (myocardial infarction, stroke, transient ischemic attack, angina pectoris, peripheral arterial disease, diabetes mellitus), general practitioner visits, and institutionalisation. A logistic algorithm was designed to optimise data collection on adverse events and endpoint during the study (Figure 3) and minimise missing data on outcomes.

Figure 3. Periodic endpoint and adverse events check questionnaire during trial
C=coach or research assistant, P=participant, AE=adverse event, AEQ=adverse event/endpoint questionnaire, CVD=cardiovascular disease

STATISTICAL ANALYSIS

Sample size
We originally based our power calculation on proportions. With advancing insight we decided on a continuous primary outcome, resulting in a new sample size calculation, again taking into account the effect of participants randomised as couples. We base the new sample size calculation on the effect-sizes of the HATICE primary outcome as observed in the preDIVA and FINGER trials(14, 27). 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(47).

With 80% power, a 0.05 two-sided significance level, accounting for an estimated 14% attrition based on previous experiences in our own multi-domain prevention study(14), an ICC of 0.25(47) 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 raise this to 2600.

Because the meaning of 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 develop CVD or dementia with those who didn’t during an average follow-up of 6.7 years. In preDIVA the change in z-score after 2 years was -0.205 in participants who developed CVD or dementia and -0.146 in participants who did not develop CVD or dementia. We therefore assume that a difference of 0.059 on the composite primary outcome of HATICE can be considered as clinically relevant.

**Data analysis**

For the primary analyses we will use a univariate general linear model to assess the effect on the primary outcome. All analyses will be according to the intention-to-treat principle. No imputation of the primary outcome will be made for the primary analysis. If there are significant differences in baseline characteristics, these will be adjusted for in secondary analyses. We will evaluate country, centre and coach differences and if indicated, this will also be adjusted for in secondary analyses.

The effect on the individual variables of the composite outcome (i.e. blood pressure, BMI, LDL) and on the 10-year cardiovascular disease risk calculated using the Framingham risk score will be analysed using general linear models. Since the Framingham risk score is heavily influenced by age, the calculation of the risk score after 18 months will be done using the
baseline age, in order to prevent obscuration of a true treatment effect by increasing age. For clinical dichotomous secondary outcomes, including incident cardiovascular disease and mortality, standard Cox-proportional hazards models will be used.

Self-assessment scales, which are mostly ordinal, will be analysed as linear scales where possible. If a self-assessment instrument has a defined cut-off for the presence or absence of a condition, (e.g. the GDS) chi square statistics will be used.

The full statistical analysis plan will be produced prior to the data analysis.

**Economic evaluation**

The economic evaluation of this trial will be performed as a cost-effective analysis (CEA) with the costs per patient with a reduced risk of CVD and cognitive decline as outcome parameter. Additionally, a cost-utility analysis (CUA) will be performed with the costs per quality adjusted life year (QALY) as outcome parameter. A health care perspective will be taken with a comparative assessment of the most relevant medical costs. These include the costs of hospital visits, emergency room visits, visits to the general practitioner or a physician and institutionalisation for the two study groups. We will take the additional costs associated with implementing this intervention into account. Due to the inclusion criteria for age, the vast majority of participants will be retired and therefore costs of loss of productivity are not taken into account. Unit costing will be based on national guidelines for costing in health care research.

The EQ-5D-3L will be used to generate health status scoring profiles over time and this will be transposed into QALY’s. Incremental cost-effectiveness analyses will be performed to estimate the extra costs per additional patient with a reduced risk of CVD and cognitive decline as well as the extra costs per QALY. Country-specific subgroup analyses will be performed to account for differences in health care delivery.

Depending on the outcomes of the CEA and CUA it will be assessed whether a modelling scenario of internet counselling with a lifetime horizon is opportune and if so, how it should be elaborated.

The opportunity arises if the intervention proves effective, the health states at the end of the 18 months of follow-up differ between the groups and such difference in health states is expected to have an impact on need for health care for the remainder of their lifetime. If so, the groups will continue to differ by their costs of health care and the costs per QALY may shift for the
better. If the 18-months costs per QALY are already acceptable against existing standards of societal willingness to pay per QALY at the time of analysis and further improvement is expected, then no modelling scenario is needed to underpin reimbursement decisions. If the costs per QALY are unacceptable despite proven effectiveness, then modelling is needed to find out the impact of the lifetime perspective on the cost-effectiveness acceptability of the lifestyle internet platform. Modelling of costs and QALYs from a lifetime perspective combines study and literature data on costs and QALYs in different stages of cardiovascular disease and/or cognitive impairment on the one hand with literature data on risks (hazard rates) of disease progression. If modelling seems opportune, then the current study will include the design for a subsequent modelling study.

DISCUSSION

In HATICE, we will study the effect of an internet intervention to improve lifestyle related risk factors for CVD, with the aim to improve the whole cardiovascular risk profile and preventing cardiovascular mortality and morbidity, including cognitive decline. The wide and still growing access and use of the internet offers an excellent possibility to deliver an eHealth intervention in a scalable and cost-effective way. By focusing on the perspective of older people during the development phase, we have built an intuitive, easy to use platform, allowing for widespread use among older adults with only limited computer skills. The pilot of this study showed that the platform was easy to use and appreciated by the participants.

Improvement in physical activity can already be reached by regular walking, exercise groups and brief exercise advice by mail in a cost-effective way(48). A Cochrane meta-analysis showed that interactive computer-based interventions are effective for weight loss and weight maintenance(49). Also, support and self-management in changing lifestyle leads to improved health outcomes(50, 51), and a stronger long-term effect(52). Using an innovative interactive approach based on the stimulation of self-management with coach support in HATICE can potentially lead to scalable and cost-effective methods to contribute to healthy ageing and the prevention of cardiovascular disease and cognitive decline.

The choice of primary outcome was carefully made. A clinically relevant outcome parameter, such as incident cardiovascular disease or dementia, would have required a longer follow-up or a significantly larger sample size, both not deemed feasible. As such HATICE can be considered a large proof-of-principle trial. HATICE is a pragmatic trial, targeting a mixed population and delivering primary and secondary prevention. This precludes the use of one
of the established cardiovascular risk scores (e.g. Framingham(53), SCORE(54), which are validated for either primary or secondary prevention) as a primary outcome. Despite its limitations, a combined z-score of measurable risk factors is in our opinion the best reflection of an effect on the cardiovascular risk profile in a heterogeneous population with different risk factors present at baseline.

The different source populations will result in differences in characteristics of participants from the three countries. This resulting heterogeneity increases external validity of the results to a wider population and will allow for secondary analyses on the effect of the intervention in different populations.

The effects of the intervention can be quite different in each of the participating countries, since the implementation of cardiovascular risk management in these three countries is organised differently. The extensive experience of the research team in the different participating countries with large randomised prevention trials (FINGER(14), MAPT(28) and PreDIVA(27)) in older populations facilitates the execution of this large RCT.

Although many older people use the internet nowadays, those who feel confident enough to participate in an eHealth trial might be higher educated. This will influence the generalizability and will have to be taken into account when interpreting the results particularly when assessing effect on cognition.

In our primary outcome we have included BMI. Although this may not be the best anthropometric parameter to reflect the risk of cardiovascular disease associated with obesity, it is the least subject to bias during assessment (as opposed to waist circumference or waist-hip ratio).

In spite of the blinded outcome assessment at the final follow-up visit, a certain degree of unblinding due to participant’s expression of experiences with the platform might occur.

The pragmatic design of the intervention, independent of existing health care structures, will facilitate easy and wide implementation throughout Europe, if proven effective. The tailor-made character of the intervention specifically suited to the needs of older individuals fits with the current development towards a more personalised approach in medicine.
Ethical approval and dissemination
The study was approved by the medical ethics committee (MEC) of the Academic Medical Center in Amsterdam, the Comité de Protection des Personnes (CPP) Sud Ouest et Outre Mer in France and the Northern Savo Hospital District Research Ethics Committee in Finland. Results from this study will be published in a peer-reviewed journal electronically and in print.

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Competing Interests
Non declared

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