Cardiovascular risk self-management in older people: Development and evaluation of an eHealth platform

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UITNODIGING
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van mijn proefschrift
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self-management in
older people
Development and evaluation
of an eHealth platform
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Amsterdam
U bent ook van harte
uitgenodigd op de receptie
na afloop van de promotie
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Cardiovascular risk self-management in older people: development and evaluation of an eHealth platform
Cathrien Beishuizen
Cardiovascular risk self-management in older people: development and evaluation of an eHealth platform

Cathrien R.L. Beishuizen
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Author contributions
Co-author affiliations
List of publications
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Acknowledgements (Dankwoord)
Chapter 1

General introduction
This thesis addresses how cardiovascular risk management (CVRM) could be provided to older people using eHealth. Due to global ageing, the number of people at risk of cardiovascular disease (CVD) will rise dramatically. Current CVRM programmes do not specifically address older people, although CVRM is effective until old age. In addition, effectiveness of current programmes is suboptimal, because they do not succeed in inducing long-term adherence to a healthy lifestyle and medication. It is also foreseen that the capacity of current programmes will not be sufficient to address all subjects (including older people) with elevated cardiovascular risk in the future. Novel prevention and risk management strategies are therefore urgently needed. eHealth is regarded a promising medium to provide self-management interventions. In this light, in the European study Healthy Ageing Through Internet Counselling in the Elderly (HATICE), an interactive internet-platform for CVRM in older people was developed. This platform is currently being tested in a large European RCT in Finland, France and the Netherlands.¹

The aims of this thesis were to develop an internet-platform for cardiovascular risk self-management in older people (the HATICE internet-platform) and to gain better understanding on how to engage older people in new forms of cardiovascular risk management.

CARDIOVASCULAR RISK MANAGEMENT IN OLDER PEOPLE: CURRENT SITUATION AND PRACTICE

Global ageing and cardiovascular disease: epidemiology

Currently, we live in times of large demographic transition due to global ageing. In 2011, the percentage (%) of people older than 60 years was 22 in Europe, 19 in North-America, 6 in Africa and 10 in Asia. In 2050, these percentages are projected to rise to 34, 27, 10 and 24, respectively.² This leads to enormous relative and absolute increases in numbers of older people worldwide. Consequently, this will induce large epidemiological changes of disease prevalences, characterized by age-dependent non-communicable diseases taking the place of communicable diseases worldwide.³

At old age, cardiovascular disease is the most prevalent non-communicable disease also causing the largest burden. According to the Global Burden of Disease (GBD) figures for 2010, this burden was estimated to be 173.9 million disability adjusted life years (DALYs), representing 30.3% of the total global burden of disease of the population of people 60 years and older. In 2030, this percentage is projected to have increased to 40.6%.⁴ In higher income countries, cardiovascular mortality rates decrease since the seventies, due to improved treatment options and implementation of primary prevention. This leads to enormous relative and absolute increases in numbers of older people worldwide. Consequently, this will induce large epidemiological changes of disease prevalences, characterized by age-dependent non-communicable diseases taking the place of communicable diseases worldwide.³

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and secondary prevention programmes. Morbidity rates are still rising, which can be understood as an effect of ageing, reduced mortality and the pandemic of unhealthy lifestyle and diabetes. In lower income countries, both mortality and morbidity rates are rising, which can be regarded as a result of improved socio-economical standards, because communicable disease become better controlled, life expectancies rise but people also adapt the unhealthy ‘Western’ lifestyle.\textsuperscript{15-20} These will

In Europe, cardiovascular mortality rates are declining: in Western and Northern Europe rates have been falling for over 30 years and since the millennium, rates are declining in the majority of European countries. Nevertheless, due to ageing there was an increase in absolute numbers of CVD cases. CVD is responsible for the largest loss of DALYs in Europe, as illustrated by a loss of 64.7 million DALYs in 2015 (23% of total burden of disease).\textsuperscript{6}

Also the incidence and prevalence of dementia is expected to rise enormously with global ageing.\textsuperscript{7} In 2010, the global burden of dementia in people aged 60 years and older was estimated 10.0 million DALYs, and this burden is projected to rapidly rise with 82.6% in 2030.\textsuperscript{6} In Europe, in 2015, the number of people with dementia was 10.5 million, and this number is expected to increase with 28% by 2030. Even larger increases are foreseen in low- and middle income countries.\textsuperscript{6}

Taking these trends together, it is expected that in the near future, the number of people at risk of cardiovascular disease or dementia will rise dramatically, also in Europe. This requires large flexibilities and unprecedented adaptations of health care systems.\textsuperscript{8}

Cardiovascular prevention and risk management becomes more important than ever. It can serve a dual goal in preventing both cardiovascular disease and dementia because cardiovascular disease and dementia share many risk factors.\textsuperscript{10-13} Ideally prevention initiatives result in non-occurrence of the diseases, but even if diseases are merely postponed, this will already substantially reduce their respective burden.

**CVRM at high age**

Although cardiovascular prevention is a lifelong assignment, current clinical guidelines recommend that the best time for CVRM for high-risk individuals to start is at middle age, because then modifiable cardiovascular risk factors (obesity, hypertension, diabetes mellitus, hypercholesterolemia, smoking and physical inactivity) start to become visible and elevated risk can still be minimized with lifestyle adaptations and, if indicated, medical treatment.\textsuperscript{14} However, a wealth of scientific publications strengthens the hypothesis that cardiovascular risk reduction is effective until very old age. Health benefits occur within a few years after a cardiovascular risk factor has been targeted, both with regard to primary and secondary prevention.\textsuperscript{15-20} These will
be relevant for many older people, if one considers that, for example, the average life expectancy in the Netherlands for a 80-year old individual is 8 years for a man and 10 years for a woman. Effects of CVRM are not limited to the prevention of CVD and, potentially, dementia, but are beneficial for healthy ageing in general. Clinical guidelines only recently started to include recommendations for CVRM in older people.24-22 Many clinical dilemmas specific for CVRM at older age are not yet fully addressed.22 These dilemmas include for example ideal target values for cardiovascular risk factor control, multimorbidity, polypharmacy, adverse events of drugs, frailty, shortened life expectancy and different priorities in health. These dilemmas need to be further studied to understand how to specifically address the needs of older people in CVRM programmes.

**Current practice of CVRM in Europe**

Most European countries have well implemented CVRM programmes following recommendations of the European guidelines on cardiovascular disease prevention, including population strategies and high-risk strategies.23 Cardiac rehabilitation programmes aimed at direct rehabilitation after suffering from an acute event, are generally implemented in secondary care settings by cardiologists.24 For the chronic management of these conditions, as well as for primary prevention, CVRM programmes are mostly implemented in the primary care setting.25 Often, primary care nurses (or practice nurses) deliver a substantial part of these programmes.26 In this thesis, we focus on CVRM in France, Finland and the Netherlands. Therefore, CVRM in these countries is described briefly.

**French cardiovascular risk management**

In France, CVRM is included in primary care and provided by general practitioners. National guidelines exist that address the different cardiovascular risk factors.27 National health campaigns exist to raise awareness for, for example, smoking cessation, physical activity and signs of stroke. General practitioners provide all care and monitoring themselves and do not delegate this to nurses. If indicated, patients are referred to a dietician or a psychologist (in case of smoking cessation), or to a medical specialist.

**Finnish cardiovascular risk management**

In Finland, cardiovascular risk management is included in primary care. In addition, a tradition of public campaigning exists to raise people’s awareness. Several national primary care guidelines exist addressing the different cardiovascular risk factors, including recommendations for primary and secondary prevention.28-31 In close

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collaboration with general practitioners, practice nurses monitor patients with diabetes, hypertension and dyslipidaemia, as described in these national guidelines. In Finland, occupational health facilities are also largely developed and offer preventive health care services in parallel to the primary care system. They also work with nurses and follow the same guidelines.

**Dutch cardiovascular risk management**

In the Netherlands, cardiovascular risk management is included in primary care provided by general practitioners. A national comprehensive cardiovascular risk management guideline provides a tool for calculation of the individual cardiovascular risk and recommendations for both primary and secondary prevention. In case of suffering an acute cardiovascular event, patients first follow an intensive rehabilitation programme, after which they are referred back to the general practice. In the general practice, practice nurses provide a substantial part of cardiovascular risk management, under supervision of a general practitioner, including diabetes care, which has been detailed in several regional and national guidelines and work descriptions. 32-35

**Current and future problems of CVRM programmes**

Current CVRM programmes face several problems. A big gap exists between the scientific promise and the reality of CVRM effectiveness. This is illustrated by the EUROASPIRE IV survey on therapeutic target achievements in coronary patients in Europe. At a median time (interquartile range) of 1.4 years (0.9-1.9 years) after a coronary event, 42.7% of the participants had hypertension (blood pressure ≥140/90mmHg) and 42% had hypercholesterolaemia (low-density lipoprotein(LDL)-cholesterol ≥2.5mmol/L. 36 Similar findings were obtained when evaluating Europeans at high risk of CVD. 37 This also holds for older people from Dutch general practice populations, as was shown in the preDIVA-study: there is ample room for improvement of the cardiovascular risk profiles of older people with and without CVD (Figure 1). 38 The preDIVA-study will be further described at the end of this introduction.

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Figure 1 Percentages of cardiovascular risk factors in people aged 70-78 participating in preDIVA.
From: Suzanne A Ligthart et al; *Eur J Prev Cardiolog* 19, 1365-1372.
BMI, body mass index; CVD, cardiovascular disease; Hyperlipidaemia, total cholesterol ≥5.0 mmol/l in primary prevention group, low-density lipoprotein >2.5 mmol/l in secondary prevention group; No sports, including no recreational walking/bicycling tours; SBP, systolic blood pressure (mmHg); Smokers, current smokers.

One important patient-related factor is that lifelong adherence to a healthy lifestyle and medical treatment is difficult to achieve and requires an enduring health behaviour change. The process of health behaviour change has been studied and theorised extensively, but in daily life, inducing and maintaining health behaviour change remains a large challenge. Another problem that current programmes face are the expanding costs of healthcare if the number of people eligible for CVRM will rise. Therefore, further research is required to study which CVRM strategies work best to stimulate enduring health behaviour change, which strategies work for older people and which strategies are fit to manage the increasing numbers of people at risk.
Self-management
In the last decades, new perspectives have been developed towards more optimal and ‘future-proof’ CVRM. Alongside the development towards patient-centered care, shared decision making and patient empowerment, one strategy is to adopt patient self-management in CVRM. In self-management, the patient takes an active role in setting treatment goals and managing his health and the health care professional takes a supporting role, providing all education and tools needed to stimulate the patient’s autonomy. This approach requires that patient and health care professional see each other as equals that both bring expertise essential for optimal management of the condition of the patient. The idea is that in this way, the patient obtains self-efficacy, becomes a problem solver of his own health condition and is intrinsically motivated towards lasting health behaviour change that results in therapeutic control of his condition, because he sets his own priorities, he is in control, and makes a conscious comparative assessment of the consequences of his decisions.

Two tools that health professionals can use in supporting patient self-management and health behaviour change are the ‘Stages of Change’-model and ‘Motivational Interviewing’. The ‘Stages of Change’-model was developed by Prochaska and DiClemente in the nineties. The model consists of five motivational stages (precontemplation, contemplation, preparation, action, maintenance and relapse) that together form the process of behaviour change. If health care professionals adapt their support to match the stage the patient is in, this will help the patient in moving towards the next stage.

‘Motivational Interviewing’ was developed by Miller and Rollnick in the nineties for supporting patients in quitting from alcoholism and was later developed for other health behaviour problems including smoking. It is defined as “a directive, client-centered counselling style for eliciting behaviour change by helping clients to explore and resolve ambivalence”. Self-management has been elaborated and studied most extensively in the context of diabetes, but also fits CVRM. It has been shown effective for control of individual CV risk factors, for example the control of hypertension and management of anti-coagulation therapy. It has also been shown effective in cardiac rehabilitation programmes. It has been less extensively studied in the context of primary prevention and in older populations. Its long-term effectiveness also needs to be further elucidated.
eHealth

Concurrently, the field of eHealth is being developed and rapidly expands the possibilities of healthcare. eHealth is a buzz word and policymakers, scientists, doctors and enterprises all have high expectations of eHealth. Large investments are being done both publicly and privately. eHealth is an umbrella term and can be very broadly defined as:

“Health services and information delivered or enhanced through the Internet and related technologies.”

The European Commission defined eHealth in their eHealth Action Plan 2012-2020 as:

“eHealth is the use of ICT in health products, services and processes combined with organisational change in healthcare systems and new skills, in order to improve health of citizens, efficiency and productivity in healthcare delivery, and the economic and social value of health. eHealth covers the interaction between patients and health-service providers, institution-to-institution transmission of data, or peer-to-peer communication between patients and/or health professionals.”

A few examples of applications of eHealth are: electronic health record systems, teleconsultations for tele-dermatology or tele-radiology, home tele-monitoring systems and wearable monitoring devices, educational health portals and online patients support groups. In this thesis, we focus on one particular form of eHealth, namely, patient-centered internet-platforms, that can be defined as:

“Systematic treatment/prevention programmes, usually addressing one or more determinants of health (frequent health behaviours), delivered largely via the internet (although not necessarily exclusively web-based), and interfacing with an end-user.”

Patient-centered internet-platforms are very suitable to deliver self-management interventions because of the possibilities for education, interactivity and monitoring. Once the platform has been developed, the self-management intervention could be delivered to a very large number of patients are relatively low costs. This makes web-based platforms very attractive tools for innovative CVRM. In fact, over the last fifteen years, many internet-platforms have been developed. In the beginning, most interventions focussed on control of single cardiovascular risk factors. Meta-analyses evaluating interventions targeting smoking, hypertension, overweight, and diabetes mellitus II in adult populations found small significant effects on improvements of intermediate outcomes (control of the risk factor itself), when comparing interventions to usual care. Overall, effects of internet interventions were smaller than of face-to-face interventions. Internet interventions that targeted
multiple lifestyle components for improvement of the cardiovascular risk profile were not superior to usual care. To date, little is known about the potential effectiveness of internet-platforms for older people, since only few platforms have been developed specifically for older people.

The research field of internet-platforms is relatively young and is still facing a number of teething problems. A common pitfall is that the interventions studied are not being described in a standardised way. This makes it difficult to compare interventions and identify the most effective components. Many internet-platforms are developed and offered on the market as health-application without robust evaluation of their effectiveness. Linked to this issue is the fact that digital developments go so fast that they can be hardly robustly tested in randomised controlled trials. Last, an often reported problem faced are high dropout rates. To enhance effective implementation of interventions, it is important to involve the target population throughout the development process. In this young field, many issues warrant further study. In this thesis we try to address the following questions: how to optimally develop an internet-platform that targets multiple cardiovascular risk factors? How to design an internet-platform specifically for older people? How can the process of self-management and health behaviour change best be supported online? How can sustained adherence to internet-platforms be stimulated?

OLDER PEOPLE AND INTERNET USE

Today, internet has become part of every domain of our lives. Access to internet is almost becoming a necessary premise for successful participation in society. For example, in 2015, the Dutch tax department aimed to work towards a complete transition from paper mail to digital communication with citizens regarding tax payment. Worldwide, many older people are still digitally illiterate. The current generation of older people did not grow up with computers and only became familiar with the internet at relatively old age. Many people feel internet technologies are developing faster than they can keep pace with. This often puts people off in engaging with new technologies or makes them feel uncertain when using them. In the European Union, a ‘digital divide’ exists between younger and older generations regarding internet use. However, the percentage of people aged 55-74 using internet at least once a week increased rapidly from 32% in 2009 to 57% in 2016. Older people use the internet mostly for emailing, looking up information on goods and services and reading the news. Seeking health information is the fourth most frequent activity on the web.

These promising numbers make it likely that, in the near future, the problem of a computer illiterate older generation will gradually disappear, and therefore, it is possible that there will be no ‘digital divide’ between younger and older generations regarding internet use in the near future. These promising numbers make it likely that, in the near future, the problem of a computer illiterate older generation will gradually disappear, and therefore, it is possible that there will be no ‘digital divide’ between younger and older generations regarding internet use in the near future.
not necessary to develop applications specifically for older people. Still, other age-related problems that can hamper internet use (such as sensory problems or cognitive impairment) will continue to exist. Since not many internet applications have been developed specifically for older people, research on how older people use these applications is also still in its infancy. Studies show that older people use and understand websites and applications in a different way than young people, as illustrated with the following examples:

- older people often have sensory and motor impairments that complicate use of applications, but applications can be made more senior-friendly with rather simple ‘lay-out’ solutions such as using bigger font size, contrasting colours, simple navigation, and large buttons to facilitate clicking;
- older people easier get lost on websites due to limited navigation skills, but are able to navigate well with a static navigation menu;
- older people seem to have more difficulty to filter for relevant information. When a lot of information is available, they have a tendency to read everything;
- (age related) cognitive impairment can negatively affect older people’s digital skills.

To facilitate older people in using applications and websites, these should be designed with these specific age-related problems in mind.

**CONTEXT OF THIS THESIS**

This thesis was conducted in the context of two studies:

- the Healthy Ageing through Internet Counselling in the Elderly (HATICE)-study;
- the Prevention of Dementia by Intensive Vascular Care (preDIVA)-study.

**The Healthy Ageing through Internet Counselling in the Elderly (HATICE)-study**

The HATICE-study aims to develop and test a coach-supported interactive internet-platform for self-management of cardiovascular risk factors in older people to improve the cardiovascular risk profile and reduce the risk of cardiovascular disease and cognitive decline. This thesis describes the development and evaluation of this platform. The HATICE consortium consists of clinical research teams of five European universities (University of Amsterdam (the Netherlands), University of Cambridge (UK), Karolinska Institutet (Sweden), University of Eastern Finland (Finland) and the University of Toulouse (France)) and two ICT companies (Vital Health Software (the Netherlands) and Novapten (France)). The platform was developed in close collaboration with these specific age-related problems in mind.

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collaboration with the private company Vital Health Software. Additional general objectives of the platform were:

- the platform should target older people with multiple cardiovascular risk factors and/or disease
- the platform should be implementable in different European countries, compatible with different health care systems and of added value to different health care structures.

Currently, the platform is being tested in a pragmatic, multi-national, multi-centre, prospective, randomised, open-label blinded endpoint (PROBE) trial with 18-months intervention and follow-up. The trial is being performed in the Netherlands, Finland and France. People aged 65 and older with at least two cardiovascular risk factors and/or a history of cardiovascular disease and basic Internet skills (ability to do a Google search and send an email) were eligible to participate. People were randomised to the intervention group (the interactive internet-platform with coaching) or to the control group (a static ‘sham’ platform). Primary outcome was defined as a composite score of the effects on systolic blood pressure, low-density-lipoprotein and body mass index. Secondary outcomes included the effect on lifestyle-related risk factors, incident cardiovascular disease, mortality, cognitive functioning, mood and cost-effectiveness. Recruitment started in March 2015. By July 2016, 2,725 people were included. Follow-up is expected to be completed in February 2018.

The Prevention of Dementia by Intensive Vascular Care (preDIVA)-study

For this thesis, data from the preDIVA-trial were used to study determinants of dropout from and non-adherence to a nurse-led CVRM programme for older people. The preDIVA trial was a Dutch cluster RCT with 6-year intervention and follow-up in a primary care setting. Briefly, the study assessed the effects of nurse-led intensive vascular care on prevention of dementia in a sample of 3,526 community-dwelling older people aged 70-78 without dementia. Participants were randomised to the intervention group (nurse-led intensive vascular care) or to the control group (usual care). The intervention consisted of 4-monthly consultations with the practice nurse at the general practice for assessment of the cardiovascular risk profile (blood pressure, LDL-cholesterol, weight, smoking habits, diet and physical activity). Based on these assessments, and following a protocol adhering to the Dutch primary care cardiovascular risk management guidelines, the practice nurse provided individually tailored lifestyle advice and optimised cardiovascular medical treatment. Outcome assessments took place at 2-yearly intervals. Follow-up was completed in March 2015.
This thesis is divided in two parts. Aim of part 1 is to describe the development of an internet-platform for cardiovascular risk self-management in older people (the HATICE internet-platform). In order to create an evidence-based platform the development process included several phases. In chapter 2, we report the results of a systematic review and meta-analysis to answer the question whether internet-interventions for CVRM in older people are effective in reducing cardiovascular risk and disease. In chapter 3, we report the results of an international focus group study with Dutch and Finnish primary care nurses. In this study we discussed nurses’ experiences and practices with behaviour change support for CVRM and the integration of their practices into a coach-supported internet-platform. Chapter 4 provides a synthesis of the developmental phases of the HATICE internet-platform, its evaluation in an international pilot study and a description of the final product. Aims of part 2 of this thesis were to gain better understanding on how to engage older people in new forms of cardiovascular risk management. In chapter 5, we report the outcomes of a qualitative study with Dutch participants of the HATICE trial to evaluate the internet-platform. We focussed on participants’ experiences that were perceived to influence their engagement with the internet-platform and assessed participants’ views on implementation of the platform in the primary care setting. In chapter 6, we report the outcomes of a study into engagement of older people with a CVRM programme from another angle, by quantitatively evaluating determinants of dropout and non-adherence in the preDIVA trial. In chapter 7 we discuss the main findings of the different studies, methodological considerations, potential clinical implications and directions for future research.
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PART I

Development of an internet-platform for cardiovascular risk self-management in older people
Chapter 2

Web-based interventions targeting cardiovascular risk factors in middle-aged and older people: a systematic review and meta-analysis

ABSTRACT

Background Web-based interventions can improve single cardiovascular risk factors in adult populations. In view of global ageing and the associated increasing burden of cardiovascular disease, older people form an important target population as well.

Objectives In this systematic review and meta-analysis, we evaluate whether web-based interventions for cardiovascular risk factor management reduce the risk of cardiovascular disease in older people.

Methods Embase, Medline, Cochrane and Cinahl were systematically searched from 1995 to November 2014. Search terms included cardiovascular risk factors and diseases (specified), web-based interventions (and synonyms) and randomised controlled trial. Two authors independently performed study selection, data-extraction and risk of bias assessment. In a meta-analysis, outcomes regarding treatment effects on cardiovascular risk factors (blood pressure, HbA1C, LDL-cholesterol, smoking status, weight and physical activity) and incident cardiovascular disease were pooled with random effects models.

Results 57 studies (n=19,862) fulfilled eligibility criteria and 47 studies contributed to meta-analysis. A significant reduction in systolic blood pressure (-2.66 mmHg; 95%CI, -3.81 to -1.52), diastolic blood pressure (-1.26 mmHg; 95%CI, -1.92 to -0.60), HbA1c level (-0.13 %; 95%CI, -0.22 to -0.05), LDL-cholesterol level (-2.18 mg/dL; 95%CI, -3.96 to -0.41), weight (-1.34 kg; 95%CI, -1.91 to -0.77) and an increase of physical activity (standardised mean difference 0.25; 95%CI, 0.10 to 0.39) in the web-based intervention group was found. The observed effects were more pronounced in studies with short (<12 months) follow-up and studies that combined the internet-application with human support (blended care). No difference in incident cardiovascular disease was found between groups (6 studies).

Conclusions Web-based interventions have the potential to improve the cardiovascular risk profile of older people, but the effects are modest and decline with time. Currently, there is insufficient evidence for an effect on incident cardiovascular disease. A focus on long-term effects, clinical endpoints and strategies to increase sustainability of treatment effects is recommended for future studies.
INTRODUCTION

The field of eHealth is expanding the potential of contemporary medicine. Global ageing and its associated burden of cardiovascular disease may expand the scope for innovative internet interventions. Current cardiovascular risk management programs in primary care will become too expensive and, although they are highly effective in research settings, their effectiveness is markedly lower in daily life. This evidence-practice gap has several causes. Adherence to life-long lifestyle and medication regimens is a serious challenge, illustrated by long-term adherence rates in chronic diseases that average as low as 50%. Web-based interventions are cheap, have a wide reach, and they enable self-management. This renders web-based interventions potentially powerful and scalable tools to enhance sustained adherence in cardiovascular risk management.

Older people form an important target population because cardiovascular risk reduction appears effective until old age. In 2012, 42% of European people aged between 55 and 74 years used the internet and this number is increasing. Meta-analyses showed that web-based interventions targeting single cardiovascular risk factors can induce improvements in adult populations. However, optimal cardiovascular prevention and risk management practice, as affirmed by the European Society of Cardiology and the American Heart Association, requires targeting the complete cardiovascular risk profile. This is particularly applicable for older people, who often have multiple risk factors or already suffered a cardiovascular event. A comprehensive approach would increase the value of web-based interventions for daily practice. Currently, little is known about the effectiveness of web-based interventions in older people.

In this systematic review and meta-analysis, we aim to answer the question whether web-based interventions for cardiovascular risk factor management reduce cardiovascular risk and disease in older people.

METHODS

Search strategy and selection of eligible studies
We performed a systematic literature search for randomised controlled trials (RCT) on web-based interventions in older people targeting one or more cardiovascular risk factors and/or disease. Methods were predefined in a research protocol using the PRISMA checklist and the Systematic Reviews Guidelines of the Center of Reviews and Dissemination (Supplementary Appendix 1). We defined web-based interventions as web-based participant-centered treatment or prevention programmes delivered via the internet and interacting with the participant in a tailored fashion.
Internet had to be the main medium through which the intervention was delivered, but other media (phone, face-to-face) could be included too. We excluded the following eHealth interventions: telemonitoring, telemedicine, and mobile phone-mediated interventions. The target of the intervention had to be one or more cardiovascular risk factors and/or cardiovascular disease. Thus, we included interventions for both primary and secondary prevention of cardiovascular disease. The target population had to have a mean age of 50 years or older and could have a mixed level of cardiovascular risk (one or more cardiovascular risk factors or established cardiovascular disease).

Main outcomes of interest were incident cardiovascular disease (myocardial infarction, angina pectoris, heart failure, stroke or transient ischemic attack, and peripheral arterial disease), cardiovascular mortality and overall mortality, and changes in cardiovascular risk factors including blood pressure (BP), glycated haemoglobin $\text{A}_1c$ ($\text{HbA}_1c$), low-density lipoprotein (LDL) cholesterol, smoking status, weight, level of physical exercise, or a composite cardiovascular risk score.

We performed a comprehensive literature search in the EMBASE, Medline, CINAHL, and Cochrane databases from 1995 onward (because the internet was not widely available before then). Key search terms were cardiovascular risk factors and diseases (separate diseases and risk factors specified), terms related to aspects of cardiovascular risk management (e.g., diet, exercise, BP control), web-based interventions (including all definitions and synonyms), and RCT/review/meta-analysis. The search was last updated on November 3, 2014 by CRB. The comprehensive search strategy is provided in Supplementary Appendix 2. Studies were included if (1) they were on web-based interventions targeting cardiovascular risk factors and/or disease, (2) study design was a RCT, (3) at least 50 patients were included, (4) mean age was at least 50 years, (5) the duration of the intervention was four or more weeks and follow-up was three or more months, (6) at least one of the outcomes of our interest was reported, and (7) language was English. Study selection was performed by two independent researchers (CRB and BS) by means of screening of titles and abstracts, and thereafter reading full texts on the basis of the inclusion criteria. If two publications described the same trial, the paper that reported the primary outcomes of the trial was included. Disagreements were resolved by discussion or by a third investigator (ER). We assessed reviews and meta-analyses encountered with our search strategy to check for additional relevant articles.

**Data extraction**

Two reviewers (BS and CRB) extracted data using a predefined data extraction form (Supplementary Appendix 3) for half of the included articles and checked each other’s results. Extracted information included study characteristics, patient baseline...
Web-based interventions targeting cardiovascular risk factors in middle-aged and older people

characteristics, characteristics of the intervention and control conditions, and available data on clinical and intermediate outcomes. For BP, glucose control, weight, lipids, and physical activity level, we extracted all baseline and follow-up levels, change scores or mean differences. Corresponding authors were contacted if needed. We used an adapted Cochrane Risk of Bias Tool to evaluate randomisation procedures, representativeness of study populations, blinding of outcome assessors (blinding of participants was usually not possible due to study design), completeness of outcome data, and completeness of reporting.

Meta-analysis
For categorical variables, we calculated odds ratios (ORs) with 95% confidence intervals (95% CIs). We estimated pooled ORs with Mantel-Haenszel random-effects models. For continuous outcomes, mean differences (MDs) or standardised mean differences (Hedges’ g effect sizes) with 95% CI were calculated. We estimated pooled effects with DerSimonian and Laird random-effects models. All HbA1c values were converted to percentages. All LDL cholesterol values were converted to mg/dL. All weight values were converted to kg. For level of physical activity, which was assessed with various instruments, we calculated standardised mean differences (SMDs) and 95% CI. If MDs or SMDs were reported, we included them directly in the pooled analyses. If not, we calculated change scores (difference between baseline and follow-up within group) or values assessed at follow-up. If values were measured at multiple time points, we used the values recorded at the last follow-up contact.

For studies with multiple arms, we included only one intervention arm in the meta-analysis in order not to create “unit-of-analysis” error by double counting the control group. Where possible, we selected the internet-only intervention arm. No data were imputed.

We estimated pooled effects for all single cardiovascular risk factors. To address the overall question of efficacy of web-based interventions for cardiovascular risk factor management, we evaluated the effect on cardiovascular composite scores, clinical outcomes (cardiovascular morbidity and mortality), and pooled the standardised primary outcomes of all studies. We used the primary outcomes as defined by the authors of the studies.

Funnel plots were inspected to assess for potential publication bias. Statistical heterogeneity was assessed using Q and I² tests. We explored reasons for heterogeneity by jackknife analysis and subgroup analyses. We assessed the following factors in subgroup analyses: study duration (predefined, short term [<12 months] versus long term [≥12 months]), type of cardiovascular prevention (primary versus secondary)
Chapter 2

RESULTS

Study selection
The search yielded 5,251 papers after removal of duplicates. We did not identify additional studies by searching reference lists. After screening of titles and abstracts, 462 papers remained. Review of these full texts resulted in 57 RCTs (corresponding with 84 papers) that fulfilled the selection criteria and were included in the systematic review. We contacted 16 authors to request additional data: nine authors responded and three authors complied with our request. Out of this final selection, 47 studies could be included in the meta-analysis (see Figure 1 for PRISMA flowchart).

Study characteristics
The 57 RCTs included 19,862 individuals (Tables 1-5). Study sample size ranged from 61 to 2,140 participants. Median study duration was 9 months (interquartile range [IQR] 6, range 3–60 months). The mean dropout rate was 15% (range 0%–62%). The mean age of the study populations ranged from 50 to 71 years. In only seven studies [22], and type of intervention (internet only or “blended” [internet application combined with human support]). Subgroup analyses were performed on the studies used for the analysis on primary outcomes only. The latter subgroup analysis (on type of intervention) consisted of two separate analyses, one to evaluate the internet-only interventions versus the control conditions and one to evaluate the blended interventions versus control conditions. In case a study tested both types of interventions with a multiple-arm design, the appropriate arm was included for each analysis. In addition, we performed a mixed effects meta-regression using the unrestricted maximum likelihood method to explore the association between study duration and effect size (standardised primary outcome). Last, we performed sensitivity analyses for the different domains of the risk-of-bias assessment by repeating the analysis on standardised primary outcomes in subgroups of studies with low risk of bias versus studies with an unclear or high risk of bias. For this analysis, we wanted to include all studies that contributed to one of the meta-analyses. Therefore, we complemented the sample of studies with defined primary outcomes that were cardiovascular risk factors of interest with studies that had not defined their primary outcome. If there was no defined primary outcome, we used the cardiovascular risk factor that was targeted most directly in the intervention studied. We used Review Manager 5.2 to draw the risk-of-bias assessment figure and to calculate standard deviations (SDs) or 95% CIs in cases where only standard errors (SEs) were available in the original data. We used Microsoft Office Excel version 10, SPSS version 20, and Comprehensive Meta Analysis version 2.2.064 for the statistical analyses.
were all participants older than 50 years of age. All participants had an increased risk of cardiovascular disease: 46 studies conducted primary prevention (control of cardiovascular risk factors or diabetes) and 11 studies conducted secondary prevention. In 41 studies, the intervention targeted a single cardiovascular risk factor; in 16 studies, multiple risk factors were addressed. We found no studies on interventions for smoking cessation meeting our inclusion criteria. In most studies, the primary outcome was change in a specific cardiovascular risk factor targeted by the intervention. Sixteen studies reported on clinical outcomes including new cardiovascular events and mortality rates as a part of adverse event monitoring. All interventions included lifestyle education and were participant-centered. Forty-four studies stimulated self-management by means of goal setting and self-monitoring. Half of interventions were stand-alone internet-platforms and the other half were “blended” [i.e., the platforms were supported by a nurse or another health care professional]. Intervention usage was reported by 22 studies. The median percentage of participants logging in to the intervention platform was 72% (range 33%-100%).
Table 1: Characteristics of the studies included for the systematic review: interventions targeting diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and study length</th>
<th>Participants</th>
<th>Age (years), mean (SD)</th>
<th>Sex (% female)</th>
<th>Intervention</th>
<th>Control</th>
<th>Primary; secondary outcomes</th>
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<tbody>
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<td>Bond 2010</td>
<td>2-arm RCT, USA; 6 m</td>
<td>62 people</td>
<td>67.2 (6.0)</td>
<td>45</td>
<td>Website: education, self-monitoring (glucose, exercise, weight, BP, medications), forum, nurse support (email, chat)</td>
<td>Standard diabetes care</td>
<td>HbA1c, BP, weight, total cholesterol, HDL cholesterol</td>
</tr>
<tr>
<td>IDEATEL 2000-2010</td>
<td>2-arm RCT, USA; 60 m</td>
<td>1655 Medicare recipients with DM</td>
<td>70.9 (6.7)</td>
<td>63</td>
<td>Online home telemedicine: nurse support (video chat), Web portal for self-monitoring (glucose, BP, education)</td>
<td>Standard diabetes care</td>
<td>HbA1c, systolic BP, diastolic BP, total cholesterol, LDL cholesterol</td>
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<td>D-net 2010</td>
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<td>320 people</td>
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<td>Website: (1) Self-management (glucose), coach support, (2) education, forum, (3) and (4) combined</td>
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<td>My path 2010</td>
<td>3-arm RCT, USA; 12 m</td>
<td>465 Medicare recipients with DM, BMI ≥29 kg/m² or 31 CV risk factor, Internet</td>
<td>58.4 (9.2)</td>
<td>50</td>
<td>Website: for computer-assisted self-management(CASM): goal setting, monitoring (HbA1c, BP, cholesterol, forum, education, (2) CASM: social support (coach, group session)</td>
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<td>104 people</td>
<td>63.5 (7.6)</td>
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<td>Website: self-management (glucose, BP, education, reminders@phone), care manager support</td>
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<td>Mobile DM 2011</td>
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<td>246 physicians with 161 people with DM and HbA1c ≥7.5%</td>
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<td>Ayal 2011</td>
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<td>125 people</td>
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<td>Website: risk profile, messaging to research, daily glucose monitoring</td>
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<td>Online personal health record: education, diabetes care plan, agenda, messaging, prescription skills</td>
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<td>151 people with DM, HbA&lt;sub&gt;1c&lt;/sub&gt; 8.5% from veteran health services</td>
<td>(1) Self-monitoring via phone (BP, gluc); (2) website; (3) website with links to other DM websites; usual care</td>
<td>60.2 (10.8)</td>
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<td>2-arm RCT; USA; 12 m</td>
<td>83 people with DM2, HbA&lt;sub&gt;1c&lt;/sub&gt; 7.0% and Internet from clinic: 65% with 2 CV risk factors</td>
<td>Electronic medical record: self-monitoring (glucose, exercise, diet, medication), support by care manager, usual care visits</td>
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* Abbreviations: BP: blood pressure; CASM: computer-assisted self-management; CASP: computer-assisted self-management + problem solving treatment; CV: cardiovascular; DM: diabetes mellitus; DM2: type 2 diabetes mellitus; GP: general practitioner; HbA<sub>1c</sub>: glycated hemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein. For studies with more than 2 arms, this arm was used for all analyses. For studies with more than 2 arms, this arm was used for the subgroup analysis on blended interventions.

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Table 2: Characteristics of the studies included for the systematic review: interventions targeting blood pressure

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<th>Age (years), mean</th>
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<th>Control</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
<th>Follow-up length</th>
<th>Primary prevention?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nolan 2013</td>
<td>2-arm RCT, USA; 2-arm RCT, USA; 2-arm RCT, USA</td>
<td>778 people with hypertension</td>
<td>59.1 (8.5)</td>
<td>52</td>
<td>Online BP self-monitoring</td>
<td>Usual care</td>
<td>Change in ambulatory BP</td>
<td></td>
<td>6 m</td>
<td>No</td>
</tr>
<tr>
<td>Bove 2013</td>
<td>2-arm RCT, USA; 2-arm RCT, USA; 2-arm RCT, USA</td>
<td>378 people with hypertension</td>
<td>56.5 (7.4)</td>
<td>56</td>
<td>Telemonitoring unit + web</td>
<td>Usual care</td>
<td>Change in ambulatory BP</td>
<td></td>
<td>6 m</td>
<td>No</td>
</tr>
<tr>
<td>Nolan 2013</td>
<td>2-arm RCT, USA; 2-arm RCT, USA; 2-arm RCT, USA</td>
<td>241 people with hypertension</td>
<td>59.6 (13.6)</td>
<td>59</td>
<td>Website + telephone system: BP action plan website: written educational material</td>
<td>Usual care</td>
<td>Change in ambulatory BP</td>
<td></td>
<td>6 m</td>
<td>No</td>
</tr>
<tr>
<td>Madsen 2008</td>
<td>2-arm RCT, Denmark; 2-arm RCT, Denmark; 2-arm RCT, Denmark</td>
<td>528 people with hypertension</td>
<td>55.5 (11.7)</td>
<td>58</td>
<td>E-newsletters</td>
<td>Usual care</td>
<td>Change in ambulatory BP</td>
<td></td>
<td>6 m</td>
<td>No</td>
</tr>
<tr>
<td>Magid 2013</td>
<td>2-arm RCT, USA; 2-arm RCT, USA; 2-arm RCT, USA</td>
<td>201 people with hypertension</td>
<td>55.9 (11.7)</td>
<td>58</td>
<td>Written education material, usual care</td>
<td>Usual care</td>
<td>Change in ambulatory BP</td>
<td></td>
<td>6 m</td>
<td>No</td>
</tr>
<tr>
<td>Horgan 2013</td>
<td>2-arm RCT, Canada; 2-arm RCT, Canada</td>
<td>117 people with hypertension</td>
<td>60.3 (11.5)</td>
<td>60</td>
<td>Written education material</td>
<td>Usual care</td>
<td>Change in ambulatory BP</td>
<td></td>
<td>6 m</td>
<td>No</td>
</tr>
<tr>
<td>McKinstry 2013</td>
<td>2-arm cluster RCT, UK; 2-arm cluster RCT, UK</td>
<td>348 people with hypertension</td>
<td>60.7 (11.2)</td>
<td>60</td>
<td>Written education material</td>
<td>Usual care</td>
<td>Change in ambulatory BP</td>
<td></td>
<td>6 m</td>
<td>No</td>
</tr>
<tr>
<td>Thiboutot 2013</td>
<td>2-arm RCT, Canada; 2-arm RCT, Canada</td>
<td>100 people with hypertension</td>
<td>60.5 (11.9)</td>
<td>60</td>
<td>Written education material, usual care</td>
<td>Usual care</td>
<td>Change in ambulatory BP</td>
<td></td>
<td>6 m</td>
<td>No</td>
</tr>
<tr>
<td>McKinstry 2013</td>
<td>2-arm cluster RCT, UK; 2-arm cluster RCT, UK</td>
<td>500 patients with hypertension</td>
<td>60.5 (11.9)</td>
<td>60</td>
<td>Written education material</td>
<td>Usual care</td>
<td>Change in ambulatory BP</td>
<td></td>
<td>6 m</td>
<td>No</td>
</tr>
<tr>
<td>McKinstry 2013</td>
<td>2-arm cluster RCT, UK; 2-arm cluster RCT, UK</td>
<td>500 patients with hypertension</td>
<td>60.5 (11.9)</td>
<td>60</td>
<td>Written education material</td>
<td>Usual care</td>
<td>Change in ambulatory BP</td>
<td></td>
<td>6 m</td>
<td>No</td>
</tr>
<tr>
<td>McKinstry 2013</td>
<td>2-arm cluster RCT, UK; 2-arm cluster RCT, UK</td>
<td>500 patients with hypertension</td>
<td>60.5 (11.9)</td>
<td>60</td>
<td>Written education material</td>
<td>Usual care</td>
<td>Change in ambulatory BP</td>
<td></td>
<td>6 m</td>
<td>No</td>
</tr>
<tr>
<td>McKinstry 2013</td>
<td>2-arm cluster RCT, UK; 2-arm cluster RCT, UK</td>
<td>500 patients with hypertension</td>
<td>60.5 (11.9)</td>
<td>60</td>
<td>Written education material</td>
<td>Usual care</td>
<td>Change in ambulatory BP</td>
<td></td>
<td>6 m</td>
<td>No</td>
</tr>
</tbody>
</table>

**Notes:**
- For studies with more than 2 arms, the arm was used for all analyses.
- For studies with more than 2 arms, the arm used for the subgroup analysis on blended interventions was used for the subgroup analysis on blended interventions.
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Table 3 Characteristics of the studies included for the systematic review: interventions targeting weight loss and weight loss maintenance

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and study length</th>
<th>Participants</th>
<th>Age (years), mean (SD)</th>
<th>Sex (%)</th>
<th>Intervention</th>
<th>Control</th>
<th>Primary; secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appel 2010</td>
<td>3-arm RCT; USA; 24 m</td>
<td>415 people with obesity, ≥1 CV risk factor, Internet from 6 primary clinics</td>
<td>54 (10.2)</td>
<td>64</td>
<td>(1) Website + mobile coach support education, self-monitoring (weight, diet, exercise), reminder, doctor informed; (2) 1 + in-person support</td>
<td>1 (or 2) meetings with coach, brochure with websites for weight loss</td>
<td>Change in weight from baseline to 24 m</td>
</tr>
<tr>
<td>Bennett 2012</td>
<td>2-arm RCT; USA; 24 m</td>
<td>365 obese people with hypertension from 3 clinics</td>
<td>54.6 (10.9)</td>
<td>69</td>
<td>Website interactive voice response system: self-monitoring weight, setting, coach support (phone), group sessions, education</td>
<td>Self-help booklet</td>
<td>Change in weight at 24 m</td>
</tr>
<tr>
<td>Bennett 2010</td>
<td>2-arm RCT; USA; 3 m</td>
<td>101 obese people with hypertension from 1 day</td>
<td>54.4 (11.1)</td>
<td>48</td>
<td>Website: goal setting, self-monitoring, behavioral skills education, forum, coach support (online, phone, face-to-face)</td>
<td>Folder on healthy weight, usual care</td>
<td>Change in weight at 12 weeks</td>
</tr>
<tr>
<td>Kinschewsky 2011</td>
<td>2-arm RCT; USA; 2 m</td>
<td>100 overweight people, Internet via flyers/internet</td>
<td>50.3 (0.9)</td>
<td>70</td>
<td>Website: target body weight, monitoring, behavioral tips, videos, weight baseline, tailored feedback, reminders</td>
<td>Wait list, people get access to website after 12 weeks</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Webber 2010</td>
<td>2-arm RCT; USA; 4 m</td>
<td>66 women, BMI 25–40, Internet from advertisements</td>
<td>50.0 (0.9)</td>
<td>100</td>
<td>Website: weight loss tips, lessons, message board, self-monitoring (weight, diet), chat room</td>
<td>All features of intervention except for online chat sessions</td>
<td>Not defined; weight, BMI, diet, exercise</td>
</tr>
<tr>
<td>R-LITE 2013</td>
<td>3-arm RCT; USA; 15 m</td>
<td>241 people with a BMI ≥25, metabolic syndrome from 1 clinic</td>
<td>52.9 (10.6)</td>
<td>47</td>
<td>(1) Website + 2 lifestyle classes; (2) website: self-monitoring (weight, exercise), messaging, DV D with lifestyle classes</td>
<td>Usual care</td>
<td>Change in BMI from baseline to 15 m</td>
</tr>
<tr>
<td>POWER 2014</td>
<td>4-arm RCT; UK; 12 m</td>
<td>179 people with BMI ≥30 kg/m² or ≥28 kg/m²; CV risk factors from 5 GPs</td>
<td>52.1 (13.2)</td>
<td>66</td>
<td>(1) Website: self-management website monitoring (weight), message board, coaching (email/phone); (2) 1 + nurse contact; (3) 1 + 7 nurse contacts</td>
<td>Usual care</td>
<td>Weight at 12 m</td>
</tr>
</tbody>
</table>

*Abbreviation: BMI: body mass index; CV: cardiovascular; GP: general practitioner; PA: physical activity. For studies with more than 2 arms, this arm was used for all analyses. For studies with more than 2 arms, this arm was used for the subgroup analysis on blended interventions. Control arm consists of same interactive Internet-platform as intervention arm.

Table 4 Characteristics of the studies included for the systematic review: interventions targeting weight loss and weight loss maintenance

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and study length</th>
<th>Participants</th>
<th>Age (years), mean (SD)</th>
<th>Sex (%)</th>
<th>Intervention</th>
<th>Control</th>
<th>Primary; secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stop Regain 2010</td>
<td>3-arm RCT; USA; 18 m</td>
<td>314 people with 10% weight loss in 2 years, via advertisements</td>
<td>51 (0)</td>
<td>81</td>
<td>(1) Website: self-monitoring, expert chat; (2) face-to-face self-monitoring via phone, weekly group sessions</td>
<td>(3) Newsletters</td>
<td>Weight gain at 18 m</td>
</tr>
<tr>
<td>WLM 2008</td>
<td>2-phase</td>
<td>2-arm RCT; USA; 30 m</td>
<td>103 people with ≥4 kg previous weight loss, hypertension, Internet via messages/phone</td>
<td>55.6 (9.7)</td>
<td>63</td>
<td>(1) Website: goal setting, setting action plan, self-monitoring (weight, PA, diet), education, bulletin board, reminder, support (email/phone); (2) personal contact (phone + face-to-face)</td>
<td>Printed lifestyle guidelines, 1 visit with coach</td>
</tr>
</tbody>
</table>

*Abbreviation: BMI: body mass index; CV: cardiovascular; GP: general practitioner; PA: physical activity. For studies with more than 2 arms, this arm was used for all analyses. For studies with more than 2 arms, this arm was used for the subgroup analysis on blended interventions. Control arm consists of same interactive Internet-platform as intervention arm.
### Table 4: Characteristics of the studies included for the systematic review: interventions targeting physical activity and cholesterol

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and study length</th>
<th>Participants</th>
<th>Age (years), mean (SD)</th>
<th>Sex (% female)</th>
<th>Intervention</th>
<th>Control</th>
<th>Primary/secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richardson 2011</td>
<td>2-arm RCT; USA; 4 m</td>
<td>324 patients from clinic; 1.2% CHD, 20% DMD, 61% BMI ≥30</td>
<td>52.0 (14.4)</td>
<td>65</td>
<td>Website + control + online community forum</td>
<td>Website: pedometer, tailored feedback</td>
<td>Change in average daily step count, patient attrition</td>
</tr>
<tr>
<td>Reid 2011</td>
<td>2-arm RCT; Canada; 12 m</td>
<td>223 patients with a recent CHD event; Internet via 2 cardiac centers</td>
<td>56.4 (9.0)</td>
<td>16</td>
<td>Website: tutorials, exercise plans, self-monitoring, specialist support</td>
<td>Usual care, education booklet</td>
<td>Mean steps per day</td>
</tr>
<tr>
<td>Ferrey 2010</td>
<td>2-arm RCT; Australia; 6 m</td>
<td>106 inactive random; 58% overweight</td>
<td>52.0 (4.6)</td>
<td>72</td>
<td>Website: behavioral strategies, goal setting, self-monitoring, advice, bulletin board, news</td>
<td>Website with minimal interactivity</td>
<td>No defined; physical activity, website use</td>
</tr>
<tr>
<td>Active after 55 2013</td>
<td>2-arm RCT; USA; 3 m</td>
<td>405 sedentary people with Internet via senior centers’ websites</td>
<td>60.3 (4.9)</td>
<td>69</td>
<td>Website: education, goal setting, exercise planning; 11 online exerceses, self-monitoring, reminder</td>
<td>Website with minimal interactivity</td>
<td>No defined; physical activity, BMI</td>
</tr>
<tr>
<td>HEART 2014</td>
<td>2-arm RCT; New Zealand; 6 m</td>
<td>171 people with stable CHD, Internet from 2 hospitals</td>
<td>60.2 (9.2)</td>
<td>19</td>
<td>Exercise prescription, behavioral strategies, Website videos, self-monitoring (reminders), education, reminders</td>
<td>Usual care</td>
<td>Change in peak oxygen uptake from baseline to 6 m</td>
</tr>
<tr>
<td>Phillips Direct Life 2015</td>
<td>2-arm RCT; Netherlands; 5 m</td>
<td>235 inactive people with Internet through local media</td>
<td>64.8 (2.9)</td>
<td>41</td>
<td>Website: goal setting, self-monitoring (exercise), e-coach feedback</td>
<td>Waitlist control</td>
<td>Change in physical activity</td>
</tr>
<tr>
<td>Subic 2014</td>
<td>3-arm RCT; USA; 3 m</td>
<td>114 sedentary people through media and Internet</td>
<td>63.0 (7.0)</td>
<td>24</td>
<td>(1) Pedometer; (2) website + pedometer: exercise strategies, goal setting, self-monitoring (exercise/feedback, forum)</td>
<td>No intervention</td>
<td>Endothelial function, vascular stiffness, step count, exercise</td>
</tr>
<tr>
<td>Peels 2013</td>
<td>5-arm cluster RCT; Netherlands; 12 m</td>
<td>2410 people from 6 municipal regions, 85% overweight</td>
<td>63.2 (8.4)</td>
<td>51</td>
<td>(1) Printed feedback report; (2) 1 + local exercise tips; (3) Web-based feedback report; (4) 3 + local exercise tips</td>
<td>Waitlist control</td>
<td>Physical activity</td>
</tr>
</tbody>
</table>
Table 4 Continued.

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Bloch(^a) 2006 (^m)</th>
<th>3-arm RCT</th>
<th>USA; 6 m</th>
<th>171 employees with increased cholesterol, DM or CHD</th>
<th>54.8 (9.4) —</th>
<th>(i) Website + financial reward; (ii) website + 4 classes, nurse support (phone)</th>
<th>Website, 10-year CVD score, monitoring, goals, tailored info</th>
<th>LDL cholesterol change at 6 m</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>live well 2013 (^b)</td>
<td>2-arm RCT</td>
<td>USA; 3 m</td>
<td>61 people with LDL cholesterol ≥3.37 mmol/L, Internet from primary clinics</td>
<td>52.0 (12.8)</td>
<td>75 Web-based rate-your-plate assessment, written educational material, Website: goal setting, self-monitoring, reminders</td>
<td>Web-based rate-your-plate assessment</td>
<td>Not defined; cholesterol, weight, Framingham risk score</td>
</tr>
</tbody>
</table>

*Abbreviations: BMI: body mass index; CHD: coronary heart disease; CVD: cardiovascular disease; DM: diabetes mellitus; DM2: type 2 diabetes mellitus; LDL: low-density lipoprotein. \(^a\)Control arm consists of same interactive Internet-platform as intervention arm. \(^b\)For studies with more than 2 arms, this arm was used for all analyses.
Table 5: Characteristics of the studies included for the systematic review: interventions targeting multiple risk factors

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and study length</th>
<th>Participants</th>
<th>Age (years), mean (SD)</th>
<th>Sex (% female)</th>
<th>Intervention</th>
<th>Control</th>
<th>Primary/secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live well 2013&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2-arm RCT; UK, 6 m</td>
<td>108 heart patients living in deprived areas</td>
<td>62.9 (6.0)</td>
<td>33</td>
<td>eHealth portal: glossary, education, local community links, discussion forum</td>
<td>No access to the eHealth portal</td>
<td>Not defined; behavior change (exercise, smoking, diet)</td>
</tr>
<tr>
<td>Lindley 2008&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2-arm cluster RCT; USA, 30 m</td>
<td>282 patients with chronic heart disease needing nursing care</td>
<td>64.0 (12.7)</td>
<td>39</td>
<td>Personal health record: education, monitoring, communication, goal setting, email, bulletin board</td>
<td>Usual care as the home care agencies were to provide</td>
<td>Satisfaction with nursing care</td>
</tr>
<tr>
<td>Heartcare II 2010&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3-arm RCT; USA, 12 m</td>
<td>423 senior university employees with Internet, 3.2% overweight, 46% obese</td>
<td>51.0 (7.0)</td>
<td>82</td>
<td>(1) Coach for Web-based risk assessment, lifestyle plan, email, phone or in-person contact; (2) website: risk profile assessment, advice, goal setting, action planning</td>
<td>Printed list of health promotion programs</td>
<td>Not defined; diet, exercise, weight</td>
</tr>
<tr>
<td>Hughes 2011&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2-arm RCT; UK, 6 m</td>
<td>104 patients with CHD or heart failure from 10 hospitals, 201 GPs, 64.0 (9.4)</td>
<td>62.3 (10.4)</td>
<td>25</td>
<td>Website + nurse: education, self-monitoring, discussion group, links contact (email, phone or mail), dominion</td>
<td>Usual care</td>
<td>Not defined; weight, exercise, BP, lipid profile, new CV events</td>
</tr>
<tr>
<td>Sordahl 2008&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3-arm cluster RCT; UK, 16 m</td>
<td>14 churches with 1071 members: 57% overweight, 60% sodatory</td>
<td>51.4 (3.5)</td>
<td>67</td>
<td>(1) Website: education, goal setting, knowledge test; (2) 1 + pulpit support</td>
<td>Wellness condition</td>
<td>Nutrition improvement, physical activity</td>
</tr>
<tr>
<td>Winett 2007&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3-arm RCT; Netherlands, 12 m</td>
<td>330 patients with CVD, 2 risk factors, Internet via 2 hospitals</td>
<td>59.9 (8.4)</td>
<td>25</td>
<td>Website: risk profile, self-monitoring (BP, cholesterol), treatment goals, messages, news, medication changes</td>
<td>Usual care by specialist or GP, receiving baseline risk profile</td>
<td>Relative change in Framingham heart risk score after 1 year</td>
</tr>
<tr>
<td>Vemovvi 2012&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2-arm RCT; Canada, 9 m</td>
<td>146 people with increased CV risk, Internet from 14 GPs</td>
<td>63.0 (10.5)</td>
<td>45</td>
<td>Website: tailored information, diet tool, bulletin board</td>
<td>Usual care</td>
<td>Not defined; BMI, BP, lipid profile</td>
</tr>
<tr>
<td>Vethofslon 2004&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2-arm RCT; USA, 12 m</td>
<td>107 patients with heart failure, Internet via clinic</td>
<td>56.0 (-)</td>
<td>23</td>
<td>Online medical record (clinical notes, laboratory reports, notes, education, nurse support)</td>
<td>Usual care</td>
<td>Change in self-efficacy domain</td>
</tr>
<tr>
<td>Rons&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2-arm RCT; USA, 12 m</td>
<td>465 people with CVD risk &gt;10% via community, clinic, churches</td>
<td>61.0 (10.0)</td>
<td>46</td>
<td>Online telomere medicine: laboratory and medication review, self-monitoring (BP, weight, pedometer, feedback), education, own doctor involved</td>
<td>4-months meetings with nurse; review data from high-kick</td>
<td>Reduction in Framingham 10-year CV Risk score</td>
</tr>
</tbody>
</table>

Table 6: Characteristics of the studies included for the systematic review: interventions targeting multiple risk factors

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and study length</th>
<th>Participants</th>
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<th>Intervention</th>
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<td>Live well 2013&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2-arm RCT; UK, 6 m</td>
<td>108 heart patients living in deprived areas</td>
<td>62.9 (6.0)</td>
<td>33</td>
<td>eHealth portal: glossary, education, local community links, discussion forum</td>
<td>No access to the eHealth portal</td>
<td>Not defined; behavior change (exercise, smoking, diet)</td>
</tr>
<tr>
<td>Lindley 2008&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2-arm cluster RCT; USA, 30 m</td>
<td>282 patients with chronic heart disease needing nursing care</td>
<td>64.0 (12.7)</td>
<td>39</td>
<td>Personal health record: education, monitoring, communication, goal setting, email, bulletin board</td>
<td>Usual care as the home care agencies were to provide</td>
<td>Satisfaction with nursing care</td>
</tr>
<tr>
<td>Heartcare II 2010&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3-arm RCT; USA, 12 m</td>
<td>423 senior university employees with Internet, 3.2% overweight, 46% obese</td>
<td>51.0 (7.0)</td>
<td>82</td>
<td>(1) Coach for Web-based risk assessment, lifestyle plan, email, phone or in-person contact; (2) website: risk profile assessment, advice, goal setting, action planning</td>
<td>Printed list of health promotion programs</td>
<td>Not defined; diet, exercise, weight</td>
</tr>
<tr>
<td>Hughes 2011&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2-arm RCT; UK, 6 m</td>
<td>104 patients with CHD or heart failure from 10 hospitals, 201 GPs, 64.0 (9.4)</td>
<td>62.3 (10.4)</td>
<td>25</td>
<td>Website + nurse: education, self-monitoring, discussion group, links contact (email, phone or mail), dominion</td>
<td>Usual care</td>
<td>Not defined; weight, exercise, BP, lipid profile, new CV events</td>
</tr>
<tr>
<td>Sordahl 2008&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3-arm cluster RCT; UK, 16 m</td>
<td>14 churches with 1071 members: 57% overweight, 60% sodatory</td>
<td>51.4 (3.5)</td>
<td>67</td>
<td>(1) Website: education, goal setting, knowledge test; (2) 1 + pulpit support</td>
<td>Wellness condition</td>
<td>Nutrition improvement, physical activity</td>
</tr>
<tr>
<td>Winett 2007&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3-arm RCT; Netherlands, 12 m</td>
<td>330 patients with CVD, 2 risk factors, Internet via 2 hospitals</td>
<td>59.9 (8.4)</td>
<td>25</td>
<td>Website: risk profile, self-monitoring (BP, cholesterol), treatment goals, messages, news, medication changes</td>
<td>Usual care by specialist or GP, receiving baseline risk profile</td>
<td>Relative change in Framingham heart risk score after 1 year</td>
</tr>
<tr>
<td>Vemovvi 2012&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2-arm RCT; Canada, 9 m</td>
<td>146 people with increased CV risk, Internet from 14 GPs</td>
<td>63.0 (10.5)</td>
<td>45</td>
<td>Website: tailored information, diet tool, bulletin board</td>
<td>Usual care</td>
<td>Not defined; BMI, BP, lipid profile</td>
</tr>
<tr>
<td>Vethofslon 2004&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2-arm RCT; USA, 12 m</td>
<td>107 patients with heart failure, Internet via clinic</td>
<td>56.0 (-)</td>
<td>23</td>
<td>Online medical record (clinical notes, laboratory reports, notes, education, nurse support)</td>
<td>Usual care</td>
<td>Change in self-efficacy domain</td>
</tr>
<tr>
<td>Rons&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2-arm RCT; USA, 12 m</td>
<td>465 people with CVD risk &gt;10% via community, clinic, churches</td>
<td>61.0 (10.0)</td>
<td>46</td>
<td>Online telomere medicine: laboratory and medication review, self-monitoring (BP, weight, pedometer, feedback), education, own doctor involved</td>
<td>4-months meetings with nurse; review data from high-kick</td>
<td>Reduction in Framingham 10-year CV Risk score</td>
</tr>
</tbody>
</table>
### Table 5 Continued.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Country</th>
<th>Sample Size</th>
<th>Population Characteristics</th>
<th>Follow-up</th>
<th>Intervention Details</th>
<th>Comparator Details</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bove 2011</td>
<td>2-arm RCT; USA, 12 m</td>
<td>385 people with CHD risk score ≥10% but no CVD</td>
<td>Framingham 10-year CHD risk score at 4 and 12 m</td>
<td>Website: CHD risk calculator, advice, education, action planning, goal setting; Same CHD risk calculator, but via phone. Framingham 10-year CHD risk score at 4 and 12 m.</td>
<td>62.0 (7.8)</td>
<td>48</td>
<td>CVD risk assessment, website: 6 modules with risk assessments, goal setting, education. Printed information on CVD: Not defined; Framingham 10-year CHD risk score at 4 and 12 m.</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Keyufing 2014</td>
<td>2-arm RCT; USA, 3 m</td>
<td>96 people with CVD or DM from primary clinics</td>
<td>CVD risk assessment, website: 6 modules with risk assessments, goal setting, education. Printed information on CVD: Not defined; Framingham 10-year CHD risk score at 4 and 12 m.</td>
<td>Same CHD risk calculator, but via phone. Framingham 10-year CHD risk score at 4 and 12 m.</td>
<td>36.1 (12.2)</td>
<td>67</td>
<td>Website: CHD risk calculator, advice, education, action planning, goal setting, self-monitoring, email/letter with experts. Usual care with GP. Change in systolic BP, weight and 10-year CVD risk score.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zollig 2014</td>
<td>2-arm RCT; UK, 6 m</td>
<td>95 people with stable angina, Internet from 9 GPs</td>
<td>Website: CHD risk assessment, education, goal setting, self-monitoring, email/letter with experts. Usual care. Printed report for patient and doctor. Printed lifestyle guide.</td>
<td></td>
<td>66.2 (6.2)</td>
<td>25</td>
<td>Website: CHD risk calculator, advice, education, action planning, goal setting, self-monitoring, email/letter with experts. Usual care with GP. Change in systolic BP, weight and 10-year CVD risk score.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activate your Heart 2014</td>
<td>2-arm RCT; USA, 6 m</td>
<td>101 people with BMI ≥26, elevated BP via electronic health records</td>
<td>Website: CHD risk calculator, advice, education, action planning, goal setting, self-monitoring, email/letter with experts. Usual care. Printed report for patient and doctor. Printed lifestyle guide.</td>
<td></td>
<td>56.9 (7.0)</td>
<td>42</td>
<td>Website: CHD risk calculator, advice, education, action planning, goal setting, self-monitoring, email/letter with experts. Usual care with GP. Change in systolic BP, weight and 10-year CVD risk score.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e-Care 2014</td>
<td>2-arm RCT; USA, 6 m</td>
<td>513 employees + families 45% overweight and 48% obese</td>
<td>Website: CHD risk calculator, advice, education, action planning, goal setting, self-monitoring, email/letter with experts. Usual care. Printed report for patient and doctor. Printed lifestyle guide.</td>
<td></td>
<td>60% older than 50 years</td>
<td>79</td>
<td>Website: CHD risk calculator, advice, education, action planning, goal setting, self-monitoring, email/letter with experts. Usual care. Printed report for patient and doctor. Printed lifestyle guide.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greene 2012</td>
<td>2-arm RCT; Canada, 12 m</td>
<td>46 GPs with 51 people with DM, at CV risk factor</td>
<td>Personal Web-based profile overview for DM/CVRM care. Automated telephone reminders, summary for doctor, doctor involved</td>
<td></td>
<td>60.7 (12.5)</td>
<td>49</td>
<td>Website: CHD risk calculator, advice, education, action planning, goal setting, self-monitoring, email/letter with experts. Usual care. Printed report for patient and doctor. Printed lifestyle guide.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halfbrook 2009</td>
<td>2-arm RCT; Australia, 9 m</td>
<td>436 people with DM, Internet via DM network</td>
<td>General website with home page and contact page only.</td>
<td></td>
<td>58.2 (10.3)</td>
<td>48</td>
<td>Website: CHD risk calculator, advice, education, action planning, goal setting, self-monitoring, email/letter with experts. Usual care. Printed report for patient and doctor. Printed lifestyle guide.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: BMI: body mass index; BP: blood pressure; CHD: coronary heart disease; CV: cardiovascular; CVD: cardiovascular disease; CVRM: cardiovascular risk management; DM: diabetes mellitus; GP: general practitioner. For studies with more than 2 arms, this arm was used for all analyses. For studies with more than 2 arms, this arm was used for the subgroup analysis on blended interventions.*
Quality assessment
Methodological quality of the included studies varied (Supplementary appendix 4). Most studies adequately described the randomisation and allocation concealment procedures. Due to the nature of the interventions, none of the studies had a double-blind design. In 20 studies, outcome assessors were blinded. 27 29 30 34-40 42 52 54 57 59 61 64 67
In 19 studies, blinding was not mentioned or unclear 28 31 33 41 44 46 54 56 60 63 65 69 71 74 76 77
and in 18 studies, outcome assessors were not blinded. 32 35 37 42 45 52 54 56 58 59 62 63 64 66 67 70 72 73 75 79 82

Effect of web-based interventions on single risk factors
Of the 57 studies included in the systemic review, 47 studies 26-32 34-42 44-53 55-60 62 64-68 70 73 74 76-79 81 82 provided sufficient information to be included in the meta-analysis. The mean age of the study populations of these 46 studies had the same range as the complete sample of 57 studies.

Systolic and diastolic blood pressure
The pooled analysis showed a significant reduction in both systolic and diastolic BP favouring the intervention (26 studies; n=7,720; Figure 2 and 3). For systolic BP, the weighted mean difference was −2.66 mm Hg (95% CI −3.81 to −1.52; I²=53%). For diastolic BP, the weighted mean difference was −1.26 mm Hg (95% CI −1.92 to −0.60; I²=46%).

Figure 2 Effect on systolic blood pressure (26 studies)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Duration (months)</th>
<th>Sample size</th>
<th>Methods for web-study</th>
<th>Difference in mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Control</td>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>Krachmalny et al. 2011</td>
<td>3</td>
<td>43</td>
<td>45</td>
<td>1.62</td>
</tr>
<tr>
<td>Fisher &amp; colleagues 2012</td>
<td>3</td>
<td>184</td>
<td>106</td>
<td>2.00</td>
</tr>
<tr>
<td>Shi et al. 2014</td>
<td>3</td>
<td>31</td>
<td>41</td>
<td>-1.00</td>
</tr>
<tr>
<td>Zeller 2014</td>
<td>3</td>
<td>67</td>
<td>40</td>
<td>-1.00</td>
</tr>
<tr>
<td>Acikgoz et al. 2014</td>
<td>6</td>
<td>40</td>
<td>42</td>
<td>2.23</td>
</tr>
<tr>
<td>Vehni 2015</td>
<td>6</td>
<td>31</td>
<td>31</td>
<td>-0.00</td>
</tr>
<tr>
<td>Vehni 2015</td>
<td>6</td>
<td>31</td>
<td>31</td>
<td>-0.00</td>
</tr>
<tr>
<td>v-ADEP 2016</td>
<td>12</td>
<td>139</td>
<td>162</td>
<td>0.00</td>
</tr>
<tr>
<td>Zeller 2016</td>
<td>12</td>
<td>120</td>
<td>118</td>
<td>-0.00</td>
</tr>
<tr>
<td>Klopfer et al. 2014</td>
<td>12</td>
<td>164</td>
<td>106</td>
<td>2.00</td>
</tr>
<tr>
<td>Minami et al. 2016</td>
<td>12</td>
<td>61</td>
<td>69</td>
<td>2.00</td>
</tr>
<tr>
<td>Morelli et al. 2017</td>
<td>12</td>
<td>25</td>
<td>90</td>
<td>2.00</td>
</tr>
<tr>
<td>Nair et al. 2019</td>
<td>12</td>
<td>123</td>
<td>123</td>
<td>-0.00</td>
</tr>
<tr>
<td>Tiwari et al. 2019</td>
<td>12</td>
<td>282</td>
<td>218</td>
<td>0.00</td>
</tr>
<tr>
<td>Vehni 2012</td>
<td>12</td>
<td>186</td>
<td>108</td>
<td>-1.00</td>
</tr>
<tr>
<td>E-UHET 2013</td>
<td>12</td>
<td>186</td>
<td>108</td>
<td>-1.00</td>
</tr>
<tr>
<td>Agarwal 2011</td>
<td>24</td>
<td>139</td>
<td>108</td>
<td>2.00</td>
</tr>
<tr>
<td>Bouveret 2012</td>
<td>24</td>
<td>165</td>
<td>163</td>
<td>-0.00</td>
</tr>
<tr>
<td>Pfeiffer et al. 2010</td>
<td>24</td>
<td>189</td>
<td>189</td>
<td>-3.73</td>
</tr>
<tr>
<td>Pfeiffer et al. 2010</td>
<td>24</td>
<td>189</td>
<td>189</td>
<td>-3.73</td>
</tr>
<tr>
<td>Estimated</td>
<td>24</td>
<td>189</td>
<td>189</td>
<td>-3.73</td>
</tr>
</tbody>
</table>

Systolic blood pressure (mmHg) | | | | |
| Intervention | Control | Lower | Upper | |
| Krachmalny et al. 2011 | 3 | 43 | 45 | 2.66 | -3.81 | -0.60 |
| Fisher & colleagues 2012 | 3 | 184 | 106 | 2.00 | -2.00 | -1.41 |
| Shi et al. 2014 | 3 | 31 | 41 | -6.85 | 4.85 |
| Zeller 2014 | 3 | 67 | 40 | -1.00 | -3.10 | 0.10 |
| Acikgoz et al. 2014 | 6 | 40 | 42 | -4.73 | 9.19 |
| Vehni 2015 | 6 | 31 | 31 | -10.36 | 10.36 |
| Vehni 2015 | 6 | 31 | 31 | -10.36 | 10.36 |
| v-ADEP 2016 | 12 | 139 | 162 | -4.83 | 4.83 |
| Zeller 2016 | 12 | 120 | 118 | -9.06 | -1.84 |
| Klopfer et al. 2014 | 12 | 164 | 106 | -1.00 | -1.00 |
| Morelli et al. 2017 | 12 | 25 | 90 | -7.94 | 11.94 |
| Nair et al. 2019 | 12 | 123 | 123 | -1.00 | -1.00 |
| Tiwari et al. 2019 | 12 | 282 | 218 | -3.06 | 3.06 |
| Vehni 2012 | 12 | 186 | 108 | 0.00 | -0.06 |
| E-UHET 2013 | 12 | 186 | 108 | -0.06 | -0.06 |
| Agarwal 2011 | 24 | 139 | 108 | 0.06 | -0.06 |
| Bouveret 2012 | 24 | 165 | 163 | 0.06 | -0.06 |
| Pfeiffer et al. 2010 | 24 | 189 | 189 | -0.06 | -0.06 |
| Pfeiffer et al. 2010 | 24 | 189 | 189 | -0.06 | -0.06 |
| Estimated | 24 | 189 | 189 | -0.06 | -0.06 |

Figure 2 Effect on systolic blood pressure (26 studies)

Figure 2 Effect on systolic blood pressure (26 studies)
Glycated haemoglobin A₁c
A significant reduction in HbA₁c level favouring the intervention among patients with type 2 diabetes mellitus was found (21 studies; n=6,518; Figure 4). The weighted mean difference for HbA₁c was −0.13% (95% CI −0.22 to −0.05; I²=74%). The jackknife procedure did not reveal one particular study responsible for high heterogeneity.
Figure 4 Effect on glycated haemoglobin (21 studies)

Weight

Fifteen studies tested interventions for weight loss and two studies tested interventions for maintenance of weight loss. The pooled analysis (17 studies; n=3,713; Figure 5) showed a significant reduction in weight favouring the intervention (weighted mean difference –1.34 kg, 95% CI –1.91 to –0.77; I²=61%). A sensitivity analysis leaving out the two studies on weight loss maintenance resulted in a similar effect size and level of heterogeneity. The jackknife procedure identified three studies contributing considerably to heterogeneity. 35 42 59

Figure 4 Effect on glycated haemoglobin (21 studies)

Weight

Fifteen studies tested interventions for weight loss and two studies tested interventions for maintenance of weight loss. The pooled analysis (17 studies; n=3,713; Figure 5) showed a significant reduction in weight favouring the intervention (weighted mean difference –1.34 kg, 95% CI –1.91 to –0.77; I²=61%). A sensitivity analysis leaving out the two studies on weight loss maintenance resulted in a similar effect size and level of heterogeneity. The jackknife procedure identified three studies contributing considerably to heterogeneity. 35 42 59
Figure 5 Effect on weight (17 studies)

Low-density lipoprotein cholesterol

A small but significant reduction in LDL cholesterol favouring the intervention was found (17 studies; n=5,035; Figure 6; weighted mean difference −2.18 mg/dL, 95% CI −3.96 to −0.41; I²=44%).

Figure 6 Effect on low-density lipoprotein cholesterol (17 studies)
Physical activity

Fourteen studies \((n=4,444; \text{Figure 7})\) reported the effect on physical activity. Eight studies used self-reported physical activity levels in minutes per week, five studies used daily step counts obtained from pedometers, and one study measured physical activity with accelerometers. Because of the differences in measurement instruments, we calculated standardised mean differences. A small significant difference in increase of physical activity levels was found in favour of the intervention \((\text{weighted standardised mean difference} \, 0.25, \, 95\% \, \text{CI} \, 0.10-0.39; \, I^2=81\%)\), but heterogeneity was high. The jackknife procedure identified one study driving a substantial part of heterogeneity; without this study, \(I^2\) was 68%.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Duration (months)</th>
<th>Sample size</th>
<th>Statistics for each study</th>
<th>Hedges' (g) and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active after 55 2013</td>
<td>3</td>
<td>125 180</td>
<td>-0.83</td>
<td>-1.07 -0.60</td>
</tr>
<tr>
<td>Philips Direct Life 2013</td>
<td>3</td>
<td>107 109</td>
<td>-0.58</td>
<td>-0.86 -0.31</td>
</tr>
<tr>
<td>Subac 2014 gr3 vs c</td>
<td>3</td>
<td>29 41</td>
<td>-1.00</td>
<td>-1.50 -0.50</td>
</tr>
<tr>
<td>HEART2014</td>
<td>6</td>
<td>85 86</td>
<td>-0.18</td>
<td>-0.48 0.11</td>
</tr>
<tr>
<td>Activate your heart 2014</td>
<td>6</td>
<td>35 40</td>
<td>-0.33</td>
<td>-0.79 0.12</td>
</tr>
<tr>
<td>Ferris 2009</td>
<td>6</td>
<td>52 54</td>
<td>-0.06</td>
<td>-0.43 0.32</td>
</tr>
<tr>
<td>Long 2010</td>
<td>6</td>
<td>366 238</td>
<td>-0.06</td>
<td>-0.22 0.10</td>
</tr>
<tr>
<td>Diabetes in Check 2014</td>
<td>9</td>
<td>195 202</td>
<td>-0.01</td>
<td>-0.21 0.19</td>
</tr>
<tr>
<td>Red 2011</td>
<td>12</td>
<td>115 108</td>
<td>-0.19</td>
<td>-0.45 0.07</td>
</tr>
<tr>
<td>Peels 2013</td>
<td>12</td>
<td>422 411</td>
<td>-0.09</td>
<td>-0.23 0.04</td>
</tr>
<tr>
<td>Keyshowing 2014</td>
<td>13</td>
<td>166 170</td>
<td>0.14</td>
<td>-0.06 0.36</td>
</tr>
<tr>
<td>REDDEM 2013 CASM vs c</td>
<td>12</td>
<td>96 150</td>
<td>-0.40</td>
<td>-0.65 -0.14</td>
</tr>
<tr>
<td>Hughes 2011 gr2 vs c</td>
<td>12</td>
<td>112 120</td>
<td>-0.02</td>
<td>-0.28 0.23</td>
</tr>
<tr>
<td>Winet 2007 gr1 vs c</td>
<td>15</td>
<td>310 291</td>
<td>-0.19</td>
<td>-0.39 0.01</td>
</tr>
</tbody>
</table>

Favour intervention  Favours control

-0.50   0.00   1.00   2.00

Figure 7 Effect on physical activity (14 studies)

Effect of web-based interventions on overall cardiovascular risk profile, cardiovascular morbidity, and mortality

Cardiovascular composite scores

Nine studies \((n=2,321; \text{Figure 8})\) reported a cardiovascular composite score. Five studies reported the Framingham 10-year cardiovascular disease risk score, three studies reported the Framingham 10-year coronary heart disease risk score, and one study reported a clinical composite score based on number of cardiovascular risk factors on target \((\text{BP}, \text{HbA}_1c, \text{body mass index, LDL cholesterol, physical activity, albuminuria,})\).
foot ulcers, and smoking). Because of the differences between the composite scores, we calculated standardised mean differences. A small significant improvement of the cardiovascular composite scores was found (weighted standardised mean difference –0.10, 95% CI –0.18 to –0.02; I²=0%).

<table>
<thead>
<tr>
<th>Cardiovascular composite scores (Hedges's g)</th>
<th>Study name</th>
<th>Duration (months)</th>
<th>Sample size</th>
<th>Statistics for each study</th>
<th>Hedges's g and 95% CI</th>
<th>Intervention</th>
<th>Control</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phillips Direct Life 2013</td>
<td>3</td>
<td>107</td>
<td>159</td>
<td>Intervention: 0.60, Standard error: 0.08</td>
<td>0.48</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zulily 2014</td>
<td>3</td>
<td>47</td>
<td>49</td>
<td>Intervention: 0.60, Standard error: 0.08</td>
<td>0.48</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eCare 2014</td>
<td>6</td>
<td>44</td>
<td>46</td>
<td>Intervention: 0.60, Standard error: 0.08</td>
<td>0.48</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holbrook 2009</td>
<td>6</td>
<td>236</td>
<td>241</td>
<td>Intervention: 0.60, Standard error: 0.08</td>
<td>0.48</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bova 2011</td>
<td>12</td>
<td>193</td>
<td>193</td>
<td>Intervention: 0.60, Standard error: 0.08</td>
<td>0.48</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPower-D 2013</td>
<td>12</td>
<td>170</td>
<td>162</td>
<td>Intervention: 0.60, Standard error: 0.08</td>
<td>0.48</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keyes/ing 2014</td>
<td>12</td>
<td>186</td>
<td>186</td>
<td>Intervention: 0.60, Standard error: 0.08</td>
<td>0.48</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venosso 2012</td>
<td>12</td>
<td>106</td>
<td>109</td>
<td>Intervention: 0.60, Standard error: 0.08</td>
<td>0.48</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live and Look 2013</td>
<td>15</td>
<td>31</td>
<td>29</td>
<td>Intervention: 0.60, Standard error: 0.08</td>
<td>0.48</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 8 Effect on cardiovascular composite scores (9 studies)

General effect of web-based interventions on cardiovascular risk factors

Finally, we pooled the primary outcomes of the 37 studies (n=11,021; Figure 9) that defined a primary outcome (systolic BP: 7 studies; HbA₁c: 13 studies; weight: 8 studies; physical activity: 6 studies; cardiovascular composite score: 3 studies). The weighted standardised mean difference was –0.24 (95% CI –0.31 to –0.16; I²=69%) in favour of the intervention. The jackknife procedure revealed that one study somewhat influenced the heterogeneity; without this study, heterogeneity dropped to 64%. The funnel plot (Supplementary Appendix 3) indicated that small studies reporting large effects might be overrepresented. The Egger’s test confirmed that the funnel plot was not symmetrical (p=0.01).
**Cardiovascular morbidity and total mortality**

Six studies (n=1,904; 1 short-term and 5 long-term studies) reported on cardiovascular event rates. The mean length of the studies was 13 months (range 6-24 months). The pooled analysis showed no difference in rate between groups (pooled OR 0.75, 95% CI 0.39-1.42; I²=27%; Figure 10). Total mortality rates were reported in 13 studies; in five studies, no deaths occurred and in the other eight studies, there were no differences between groups.

**Figure 9 General effect on primary outcomes (37 studies)**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Outcome</th>
<th>Duration (months)</th>
<th>Sample size</th>
<th>Statistic for each study</th>
<th>Hedge's g and 95% CI</th>
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<tr>
<td>Intervention</td>
<td>Control</td>
<td></td>
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<tr>
<td>-----------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
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<td>Weight</td>
<td>3</td>
<td>43</td>
<td>-0.71 (95% CI 0.18-1.23)</td>
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<tr>
<td></td>
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<tr>
<td>Hume 2009</td>
<td>Weight</td>
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<td>81</td>
<td>-0.79 (95% CI 0.10-1.37)</td>
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<td>Weight</td>
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<td>31</td>
<td>-0.97 (95% CI 0.07-1.75)</td>
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<tr>
<td>Oetzel 2012</td>
<td>Weight</td>
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<td>311</td>
<td>-0.32 (95% CI 0.04-0.60)</td>
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<tr>
<td>Abdal 2011</td>
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<td>3</td>
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<td>Hemkani 2014</td>
<td>Weight</td>
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<td>-0.38 (95% CI 0.01-0.77)</td>
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<tr>
<td>Leung 2012</td>
<td>Weight</td>
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<td>596</td>
<td>-0.17 (95% CI 0.02-0.33)</td>
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<td>Bois 2011</td>
<td>Weight</td>
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<td>84</td>
<td>-0.34 (95% CI 0.00-0.68)</td>
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<tr>
<td>Mulder 2014</td>
<td>Weight</td>
<td>3</td>
<td>194</td>
<td>-0.18 (95% CI 0.00-0.37)</td>
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<tr>
<td>Meller 2009</td>
<td>Weight</td>
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<td>133</td>
<td>-0.36 (95% CI 0.10-0.63)</td>
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<td>Ashworth 2014</td>
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<tr>
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<td>Weight</td>
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<td>162</td>
<td>-0.70 (95% CI 0.37-1.02)</td>
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<tr>
<td>Meller 2014</td>
<td>Weight</td>
<td>3</td>
<td>62</td>
<td>-0.34 (95% CI 0.00-0.68)</td>
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<tr>
<td>Meller 2013</td>
<td>Cardiovascular event</td>
<td>3</td>
<td>156</td>
<td>-0.70 (95% CI 0.37-1.02)</td>
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<tr>
<td>Meller 2014</td>
<td>Cardiovascular event</td>
<td>3</td>
<td>62</td>
<td>-0.34 (95% CI 0.00-0.68)</td>
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<tr>
<td>Rehfeld 2014</td>
<td>Cardiovascular event</td>
<td>3</td>
<td>156</td>
<td>-0.70 (95% CI 0.37-1.02)</td>
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<tr>
<td>Meller 2013</td>
<td>Total mortality</td>
<td>3</td>
<td>156</td>
<td>-0.70 (95% CI 0.37-1.02)</td>
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<tr>
<td>Meller 2014</td>
<td>Total mortality</td>
<td>3</td>
<td>62</td>
<td>-0.34 (95% CI 0.00-0.68)</td>
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<tr>
<td>Rehfeld 2014</td>
<td>Total mortality</td>
<td>3</td>
<td>156</td>
<td>-0.70 (95% CI 0.37-1.02)</td>
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<td>Meller 2013</td>
<td>Cardiovascular event</td>
<td>3</td>
<td>156</td>
<td>-0.70 (95% CI 0.37-1.02)</td>
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<td>Meller 2014</td>
<td>Cardiovascular event</td>
<td>3</td>
<td>62</td>
<td>-0.34 (95% CI 0.00-0.68)</td>
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<td>Rehfeld 2014</td>
<td>Cardiovascular event</td>
<td>3</td>
<td>156</td>
<td>-0.70 (95% CI 0.37-1.02)</td>
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<tr>
<td>Meller 2013</td>
<td>Total mortality</td>
<td>3</td>
<td>156</td>
<td>-0.70 (95% CI 0.37-1.02)</td>
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<tr>
<td>Meller 2014</td>
<td>Total mortality</td>
<td>3</td>
<td>62</td>
<td>-0.34 (95% CI 0.00-0.68)</td>
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<tr>
<td>Rehfeld 2014</td>
<td>Total mortality</td>
<td>3</td>
<td>156</td>
<td>-0.70 (95% CI 0.37-1.02)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: G² = 114.80, df = 36, p < 0.01, I² = 59.8%.

**Figure 10** General effect on primary outcomes (37 studies)

**Cardiovascular morbidity and total mortality**

Six studies (n=1,904; 1 short-term and 5 long-term studies) reported on cardiovascular event rates. The mean length of the studies was 13 months (range 6-24 months). The pooled analysis showed no difference in rate between groups (pooled OR 0.75, 95% CI 0.39-1.42; I²=27%; Figure 10). Total mortality rates were reported in 13 studies; in five studies, no deaths occurred and in the other eight studies, there were no differences between groups.

**Figure 9 General effect on primary outcomes (37 studies)**
Subgroup analyses

Results are summarised in Table 6. Within the analysis of pooled primary outcomes, the intervention effect was more pronounced in the short-term studies (15 studies; n=2,934; standardised mean difference −0.43, 95% CI −0.57 to −0.29; I²=69%) than in the long-term studies (22 studies; n=8087; standardised mean difference −0.12, 95% CI −0.19 to −0.06; I²=41%). The same pattern was found for all other outcomes except for LDL cholesterol (Supplementary appendix 6). There were no substantial differences in effect size between studies on primary prevention versus secondary prevention. To further explore the studies targeting primary prevention, we compared studies with populations of relatively low age (not all participants older than 50 years, n=29) with studies with populations of older age (all participants older than 50 years, n=4). The pooled effect size was larger for the studies with younger participants (Hedges’ g=−0.30) than for the studies with relatively younger participants (Hedges’ g=−0.23), but the confidence intervals overlapped largely. We repeated the analysis of pooled primary outcomes on the sample of studies testing an internet-only and a blended intervention. The intervention effect was more pronounced in the sample of blended studies (26 studies; n=7,538; standardised mean difference −0.33, 95% CI −0.43 to −0.22; I²=78%) compared to the sample of internet-only studies (14 studies; n=4,280; standardised mean difference −0.15, 95% CI −0.23 to −0.07; I²=40%).
Table 6 Subgroup analyses within the analysis of standardized primary outcomes

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N of studies</th>
<th>Hedges' $g$</th>
<th>95% CI</th>
<th>$I^2$</th>
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<tr>
<td><strong>Duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short (&lt;12 months)</td>
<td>15</td>
<td>–0.43</td>
<td>–0.57, –0.29</td>
<td>69%</td>
</tr>
<tr>
<td>Long (≥12 months)</td>
<td>22</td>
<td>–0.12</td>
<td>–0.19, –0.06</td>
<td>41%</td>
</tr>
<tr>
<td><strong>Type of prevention</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary (including diabetes control)</td>
<td>33</td>
<td>–0.23</td>
<td>–0.32, –0.17</td>
<td>72%</td>
</tr>
<tr>
<td>Secondary</td>
<td>4</td>
<td>–0.20</td>
<td>–0.34, –0.06</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Primary prevention: age subgroups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not all older than 50 years</td>
<td>29</td>
<td>–0.23</td>
<td>–0.33, –0.14</td>
<td>72%</td>
</tr>
<tr>
<td>All older than 50 years</td>
<td>4</td>
<td>–0.10</td>
<td>–0.51, –0.09</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Internet only vs control</strong></td>
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<tr>
<td></td>
<td>14</td>
<td>–0.15</td>
<td>–0.23, –0.07</td>
<td>40%</td>
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<tr>
<td><strong>Bleeding vs control</strong></td>
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<tr>
<td></td>
<td>26</td>
<td>–0.33</td>
<td>–0.43, –0.22</td>
<td>79%</td>
</tr>
</tbody>
</table>

* Subgroup analysis performed in the sample of studies that was used for the analysis of primary outcomes.

Subgroup analysis performed on the sample of studies that targeted primary prevention (including diabetes control). Subgroup analysis performed on the sample of studies that evaluated an internet-only intervention.

In case a study tested multiple arms, the appropriate arm was included in the analysis. Subgroup analysis performed on the sample of studies that evaluated a blended intervention. In case a study tested multiple arms, the appropriate arm was included in the analysis.

Meta-regression analysis

Because of the fairly consistent finding that treatment effects were higher in short-term studies than in long-term studies, we performed a mixed effects meta-regression analysis to explore the association between study duration and effect size. The effect size seemed to become smaller in studies with longer follow-up, although the association was not significant (Hedges’ $g$ = –0.321 + 0.006 months; $p$ = .07). After removal of one outlier study 14, that had a very long follow-up (5 years), the effect size significantly decreased over time in studies lasting 3 to 32 months (Hedges’ $g$ = –0.415 + 0.015 months; $p$ = .008; Figure 11).
Web-based interventions targeting cardiovascular risk factors in middle-aged and older people

Sensitivity analyses for the risk-of-bias assessment
We performed sensitivity analyses for each of the six domains of bias assessed with the adapted Cochrane Risk of Bias Tool by comparing the standardised primary outcomes of the studies with the low risk and unknown/high risk of bias (Supplementary appendix 7). There were no significant differences in pooled effect sizes in any of the domains except for the domain random sequence generation, in which the pooled effect was significantly larger in the subgroup of studies with unknown/high risk of bias.

DISCUSSION
In this systematic review and meta-analysis, we found for people with elevated cardiovascular risk, web-based interventions lead to improvement of systolic and diastolic BP, HbA1c, weight, LDL cholesterol, physical activity levels, and cardiovascular risk composite scores. Only seven studies included participants all aged 50 years or older. Therefore, our conclusions apply for the population in middle age and beyond. Effects were more pronounced over the short term (study duration <12 months) and in studies that tested a blended intervention (combination of an internet application and human support). We found no evidence for an effect on incident cardiovascular disease.

Our findings on single cardiovascular risk factors are consistent with conclusions of other meta-analyses in younger adult populations. We found a significant reduction in systolic BP of 2.66 mm Hg. A reduction of 3 mm Hg in systolic BP can...
lead to an 8% reduction in annual stroke mortality rate and a 5% reduction in annual coronary heart disease mortality rate\(^5\). We found a reduction of LDL cholesterol of 2.18 mg/dL (converted=0.06 mmol/L). A reduction of 0.5 mmol/L in LDL cholesterol for at least two years can lead to a reduction in coronary heart disease events of 20%\(^6\). Theoretically, assuming a linear relation, a reduction of 0.06 mmol/L could lead to a 2.4% reduction of coronary heart disease events. Thus, the effects on internet interventions on BP reduction and, to a lesser extent, LDL cholesterol reduction, can be clinically relevant at the population level if reductions are maintained. In addition, we evaluated the effect on the complete cardiovascular risk profile and prevention of cardiovascular disease, which has not been performed before. One other systematic review without meta-analysis that evaluated internet interventions for lifestyle change in older people reported that interventions with multiple components are more effective than interventions with a single component\(^4\).

We found that the beneficial effects of web-based interventions decline over time and effects are larger when interventions are combined with human support. Decreasing adherence over time was reported in several studies included in our meta-analysis and could be an important contributor to the decreasing effect over time. We were unable to formally test this because information on adherence and engagement was only reported by 22 studies and definitions varied widely. The identified effect moderators are not specific to web-based interventions for cardiovascular risk factors\(^5\)\(^6\)\(^7\). Maintenance of behavioral change is notoriously complex and best achieved in longer studies with intensive interventions, more face-to-face, and more follow-up contacts. However, such interventions lead to high attrition rates, probably reflecting selection of the most motivated participants\(^5\). A careful balance should be sought between effectiveness and implementability when designing cardiovascular risk management interventions, whether or not an internet-based approach is used.

Our results do not show a beneficial effect of web-based interventions on incident cardiovascular disease. Although the declining effect over time could play a role, more likely explanations for these findings are the limited follow-up time of the studies to detect these outcomes (mean length of the studies was 13 months) and the fact that these outcomes were not the primary focus of these studies. Because of the latter, data collection may not have been systematic and adjudication of the data by an independent committee may be lacking. Therefore, we cannot draw strong conclusions from these findings.

The results of this study should be interpreted with caution because of several limitations. The methodological quality of the studies was fair, but none of the studies was double blind, rendering them prone to performance bias. Only 20 studies had a blinded lead to an 8% reduction in annual stroke mortality rate and a 5% reduction in annual coronary heart disease mortality rate\(^5\). We found a reduction of LDL cholesterol of 2.18 mg/dL (converted=0.06 mmol/L). A reduction of 0.5 mmol/L in LDL cholesterol for at least two years can lead to a reduction in coronary heart disease events of 20%\(^6\). Theoretically, assuming a linear relation, a reduction of 0.06 mmol/L could lead to a 2.4% reduction of coronary heart disease events. Thus, the effects on internet interventions on BP reduction and, to a lesser extent, LDL cholesterol reduction, can be clinically relevant at the population level if reductions are maintained. In addition, we evaluated the effect on the complete cardiovascular risk profile and prevention of cardiovascular disease, which has not been performed before. One other systematic review without meta-analysis that evaluated internet interventions for lifestyle change in older people reported that interventions with multiple components are more effective than interventions with a single component\(^4\).

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The results of this study should be interpreted with caution because of several limitations. The methodological quality of the studies was fair, but none of the studies was double blind, rendering them prone to performance bias. Only 20 studies had a blinded
outcome assessment, so detection bias may also be present. Because the sensitivity analyses for the risk-of-bias assessment did not reveal significant differences between the low risk and unknown/high risk-of-bias subgroups, except for the domain of random sequence generation, we think that our findings have not been largely affected by these potential sources of bias. Another limitation is the substantial heterogeneity in several of the meta-analyses that is, in part, explained by two effect modifiers: study duration and intervention type. Patient groups with a higher burden have a larger window of opportunity for improvement potentially resulting in larger intervention effects 89, which could also have contributed to heterogeneity. We could not draw firm conclusions on the difference between primary and secondary prevention, because only four studies on secondary prevention were included in this analysis. Last, there is a potential for publication bias and small study bias. Most of the studies with small sample sizes reported large effects and similar studies with null findings did not appear in the funnel plots (Supplementary appendix 5).

Strengths of our study are the comprehensive search strategy, the quantitative meta-analysis, and the assessment of the effect of web-based interventions for all cardiovascular risk factors using both intermediate and clinical outcomes. Our search strategy was comprehensive because we used a broad definition of web-based interventions and only excluded telemedicine and mobile phone interventions. It was not always possible to set web-based interventions apart from telemedicine and mobile phone interventions. As long as the web-based programme was the main component of the intervention, we judged the study eligible for our systematic review. By pooling the effect sizes on all different cardiovascular risk factors, we aimed to assess the overall effect of an internet-based approach for people with increased risk of cardiovascular disease. This approach provides insight into the overall potential of internet-based interventions in this field. Although basic computer literacy as an inclusion criterion probably led to selection of participants with a relatively high socio-economic status, several studies included in the meta-analysis focused on people from medically underserved areas. Therefore, the external validity of the results might be acceptable and may be generalisable to middle-aged and older primary care populations with an increased risk of cardiovascular disease.

Our results show that web-based interventions can be effective in improving the cardiovascular risk factor profile of middle-aged and older people, but effects are modest and can only have clinical relevance on the population level if sustained over time. Considering the current interest and focus on eHealth by policy makers, funding agencies, and a myriad of research and patient organisations, 89 90 it is important to evaluate the actual evidence base objectively. Unrealistic expectations of the
effectiveness of web-based interventions obscure the true challenges that have to be overcome first, including testing interventions that were designed specifically for older people, improving methodological robustness of studies, and improving sustainability of effects. On the macro level, trials can assess sustainability by prolonging follow-up, recording clinical events, and measuring surrogate cardiovascular outcomes (e.g., BP, cholesterol levels, and weight) at multiple time points (e.g., at 6, 12, 24, and 36 months). On the micro level, adherence should be evaluated by studying intervention usage through time with standardized evaluation methods. Sustainability is of particular importance because long-term effects are required for primary and secondary prevention to truly contribute to the prevention of cardiovascular disease. Web-based interventions combined with human support are more promising than internet-only interventions.
ACKNOWLEDGEMENTS

We thank R. Spijker, medical librarian at the Academic Medical Centre of Amsterdam, for his assistance in designing and conducting the search and M Siervo, lecturer in Nutrition and Ageing at the Institute for Ageing and Health, Newcastle University, for his advice on our statistical analysis plan. We also thank the study authors (LA Volk, CC Quinn, and JD Ralston) who provided additional data.

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Conflicts of Interest

None declared.

ABBREVIATIONS

95%CI  95% confidence interval  
BP     blood pressure  
BMI    body mass index  
C      cholesterol  
CHD    coronary heart disease  
CV     cardiovascular  
CVD    cardiovascular disease  
CVRM   cardiovascular risk management  
DM     diabetes mellitus  
GP     general practitioner  
HbA1C  glycated haemoglobin  
IQR    interquartile range  
LDL-cholesterol low density lipid cholesterol  
MD     mean difference  
OR     odds ratio  
PA     physical activity  
RCT    randomised controlled trial  
SD     standard deviation  
SE     standard error  
SMD    standardised mean difference  
W      weight loss  
WM     weight loss maintenance  

95%CI  95% confidence interval  
BP     blood pressure  
BMI    body mass index  
C      cholesterol  
CHD    coronary heart disease  
CV     cardiovascular  
CVD    cardiovascular disease  
CVRM   cardiovascular risk management  
DM     diabetes mellitus  
GP     general practitioner  
HbA1C  glycated haemoglobin  
IQR    interquartile range  
LDL-cholesterol low density lipid cholesterol  
MD     mean difference  
OR     odds ratio  
PA     physical activity  
RCT    randomised controlled trial  
SD     standard deviation  
SE     standard error  
SMD    standardised mean difference  
W      weight loss  
WM     weight loss maintenance
REFERENCES


61. Webber KH, Tate DF, Michael Bowling J. A randomized comparison of two motivationally enhanced Internet behavioral weight loss programs. Behaviour research and therapy 2008;46(9):1090-5.
Chapter 2


Chapter 2


Web-based interventions targeting cardiovascular risk factors in middle-aged and older people

SUPPLEMENTARY APPENDICES

Supplementary appendix 1 Research protocol

Systematic review 'Internet-interventions targeting cardiovascular risk factors and diseases' (working title)

CRL Beishuizen, E Richard, E P Moll van Charante and BCM Stephan 18-02-2013

1. Background

- Globally cardiovascular disease is the nr 1 cause of death and disability and in Europe is the nr 1 cause of death among >65 year olds (WHO and Eurostat).
- Ongoing rise of the older aged population in developed countries is resulting in larger demands and increased pressure on healthcare resources.
- Different kinds of treatment exists (pharmacological, non-pharmacological, single- and multi-component interventions). Drugs (e.g., anti-hypertensive medications, statins) are effective when studied in large RCT's 2, 3. Multi-component intensive cardiovascular risk management programmes are widely implemented in primary care to address lifestyle (e.g., diet and physical activity). These intensive programs address multiple risk factors and are generally driven by a caregiver such as a nurse or a physician. Some of these programs have been proven to be effective in high-risk groups in research-settings 4, 5. In real life, however, lifestyle improvement is not easy to reach, due to difficulties with motivation and adherence (reference).
- Need for new approaches to promote adherence/compliance to cardiovascular risk management programs.
- In the last decennium the internet as a vehicle for treatment has become a field of interest for researchers and policymakers.
- Elderly and the internet: in 2012, 42% of the European people aged 55-74 used the internet and this number is on the rise (Eurostat).
- Internet-interventions in various diseases, state of the art. In Psychiatry for example, many validated applications for depressive and anxiety disorders are already being used.
Web-based interventions targeting cardiovascular risk factors in middle-aged and older people

• Quite a few reviews about internet-interventions targeting one cardiovascular risk factor exist. Only few reviews about internet-interventions exist that simultaneously target multiple risk factors or multi-morbidity. Results of these reviews are mixed.
• In the last 2 years, large randomized controlled trials analyzing the effect of internet-interventions addressing multiple cardiovascular risk factors have been executed.
• The aim of this review is to evaluate the current evidence for efficacy of internet-interventions in elderly populations targeting cardiovascular risk factors and/or disease. We will compare internet-only with blended (e.g., internet combined with another intervention type such as caregiver support) care approaches.
• Cost-effectiveness will also be studied.

2. Review question and PICOS

Main question:
• In the elderly, are internet-interventions that target cardiovascular risk factors and/or disease effective on indirect (e.g., surrogate/intermediate) and clinical outcomes of cardiovascular disease?

Secondary questions:
• Are there differences in effectiveness between different types of interventions (e.g., purely internet vs. blended (such as combined with a caregiver for example, a nurse or physician))?
• What are the internet-intervention-usage statistics (as in: how often do people log on) and adherence rates?
• What is the effect of internet-interventions on outcomes such as quality of life and patient satisfaction?
Chapter 2

3. Definitions
Cardiovascular risk factors were defined as: hypertension, diabetes mellitus, hypercholesterolemia, smoking, obesity, adiposity or overweight/obese (BMI>25 kg/m²), lack of physical exercise, a positive family history for cardiovascular disease and atherosclerosis or arteriosclerosis.

Cardiovascular disease was defined as: myocardial infarction, angina pectoris, heart failure, stroke or transient ischemic attack and peripheral arterial disease.

Internet-intervention was defined as: a web-based intervention, addressing the cardiovascular risk profile of the patient, providing one or more of the following: interactive educational material about cardiovascular risk factors and diseases, possibilities for self-monitoring and self-management of disease, prescription of medication, interactive feedback system with caregiver (physician, nurse or pharmacist), possibilities for goal setting with regard to risk profile, online community with peers.

4. Inclusion criteria
All randomized controlled trials evaluating internet-based interventions in participants aged 50 years and older targeting cardiovascular risk factors and/or disease. Sample size has to be above n=50. Included language was English. Patient characteristics, randomization, intervention, attrition and dropout have to be mentioned. If two publications describe one identical trial, data of the most relevant publication with the lowest chance of bias will be used.
In addition, we will study reviews and meta-analyses on this topic, in order to describe the existing body of evidence and to compare references listed in the articles with our search results and check for missed relevant articles.

**Checklist selection criteria**

1st selection on title/abstract:
- Internet-intervention for cardiovascular risk factors and/or disease
- Randomized controlled trial, review +/- meta-analysis
- N ≥ 50
- Population age ≥ 50 years

2nd selection on full text:
- Adequate randomisation
- Adequate description of patient characteristics (age and sex)
- Adequate description of intervention provided
- Duration of intervention ≥ 4 weeks and follow-up ≥ 3 months
- Adequate description of attrition and dropout rates
- At least one of the outcomes described above is studied

**Exclusion criteria**
- Design articles not reporting results
- RCT’s about telemonitoring or telemedicine, defined as: using remote telecommunications to monitor the patients vital signs or disease symptoms or for diagnostics
- RCT’s evaluating a computer-intervention without an internet-component

**5. Search strategy**

A pilot search in Pubmed and Google will be performed to encounter as many definitions of internet-intervention as possible.

The following databases will be consulted:
- Embase, Medline (including Pubmed), Cinahl
- Clinical trials.gov and WHO ICTRP

Searchterms (see also comprehensive list):
- Cardiovascular diseases (Mesh and ti/ab) and separate diseases specified (Mesh and ti/ab)
- Cardiovascular risk factors (Mesh and ti/ab) and separate risk factors specified (Mesh and ti/ab)
6. Study selection
Studies will be selected by screening of titles and abstracts using the 1st selection criteria defined above. Thereafter full papers will be assessed in detail using the 2nd selection criteria mentioned above.

Study selection will be done by two independent researchers. In the event of missing data the decision may be taken to contact authors of primary studies. Disagreements will be resolved by discussion or by a third independent investigator.

If necessary, the selection process will be piloted to further refine and clarify the inclusion criteria. This will be documented, just as the whole study selection process, reasons for exclusion and disagreements and solutions.

7. Quality assessment
Quality of the studies will be assessed for the risk of bias and other general issues related to study quality using the following criteria, based on Cochrane Handbook for Systematic reviews of Interventions and the Systematic Reviews Guidelines of the Centre of Reviews and Dissemination:

- Study design appropriate for research objective
- Generation of allocation sequence
- Allocation concealment
- Double - blinding (not possible inherent to intervention), but were outcome assessors blind to treatment allocation?
- Description of intervention clear
- Statistical analyses, if a cluster-RCT was performed, was the statistical analysis appropriate?
- Completeness of data/completeness of reporting
- Handling of dropouts/attrition
- Intention to treat analysis

8. Data extraction
Data will be extracted using a data extraction form (provided). If necessary, during extraction, due to advancing insight, more details on one topic will be extracted from all included studies.
9. Data synthesis

We plan to use a quantitative approach to data synthesis. If not enough quantitative data is provided, we will contact the authors of the primary study for more information.

Due to differences between studied interventions, we expect high heterogeneity between studies. Q and I-squared tests will be used to test for heterogeneity. If necessary, we will only combine primary studies using similar interventions or similar patient-groups for meta-analysis to reduce heterogeneity. If sufficient studies are identified sensitivity analysis will be carried out to take into account the influence of other variables e.g., study quality. Funnel plots will be used to assess for evidence of bias. Study quality will be evaluated using the criteria specified in the Cochrane Risk of Bias Tool assessing the following domains: measurement protocols, incomplete data outcome and selective reporting etc.

First, for surrogate outcomes (BP, BMI, HbA1c etc), we will calculate mean differences and their 95% confidence intervals. For the clinical endpoints, dichotomous in nature, we will calculate relative risks. For qualitative data (such as quality of life, adherence and patient satisfaction), a descriptive analysis will be given. Second, we will calculate pooled effect sizes using a fixed- and random effects model. Then, we will compare the models to test their robustness.

We can analyse what is the pooled effect size of a type of intervention on outcome (risk factor modelling or clinical outcome, or quality of life). We can also analyse what are the different effect sizes for a single risk factor or clinical outcome depending on type of intervention (pure internet or blended).
REFERENCES

Supplementary appendix 2 Comprehensive search strategy

OvidSP Embase 1980 to Present

d.d.: 26-02-2013
Line#  Term
1  exp cardiovascular disease/
2  exp heart infarction/
3  exp cerebrovascular accident/
4  exp diabetes mellitus/
5  exp heart failure/
6  exp hypertension/
7  "smoking and smoking related phenomena"/ or exp cigarette smoke condensate/
     or exp smoking/ or exp smoking regulation/ or exp tobacco smoke/
8  exp obesity/
9  exp sedentary lifestyle/
10 laziness/
11 exp hypercholesterolemia/
12 exp arteriosclerosis/
13 exp angina pectoris/
14 exp familial hypertrophic cardiomyopathy/
15 exp cardiovascular risk/
16 exp exercise/ or exp physical activity/
17 (physical adj activity).ti,ab,kw.
18 exp nutrition education/ or exp nutrition/
19 nutrition.ti,ab,kw.
20 exp diet/
21 exp blood pressure regulation/
22 (blood pressure adj (monitoring or regulation or control)).ti,ab,kw.
23 exp blood glucose monitoring/
24 exp home monitoring/
25 exp weight reduction/
26 (weight adj loss).ti,ab,kw.
27 (exercise or walking) adj program).ti,ab,kw.
28 (vascular adj2 risk).ti,ab,kw.
29 cholesterol.mp. or exp cholesterol/
30 (heart adj2 (infarct* or attack or failure or disease)).ti,ab,kw.
31 (cardiovascular adj2 (risk or risks or disease$)).ti,ab,kw.
stroke.ti,ab,kw.
(high adj blood pressure).ti,ab,kw.
hypertension.ti,ab,kw.
smoking.ti,ab,kw.
cerebrovascular.ti,ab,kw.
diabetes.ti,ab,kw.
sedentary.ti,ab,kw.
arteriosclerosis.ti,ab,kw.
cardiomyopathy.ti,ab,kw.
exp peripheral occlusive artery disease/
(peripheral adj2 arter* adj disease).ti,ab,kw.
exp atherosclerosis/
atherosclerosis.ti,ab,kw.
obese.tw.
overweight.tw.
or/1-46
exp telemedicine/ or exp Internet/
internet.ti,ab,kw.
(ehealth or e-health).ti,ab,kw.
telemedicine.ti,ab,kw.
telehealth.ti,ab,kw.
(mobile adj health).ti,ab,kw.
((internet or web or computer) adj2 intervention).ti,ab,kw.
(web-based adj2 tool).ti,ab,kw.
mhealth.ti,ab,kw.
(social adj media).ti,ab,kw.
exp social media/
facebook.ti,ab,kw.
apps.ti,ab,kw.
(ONLINE adj2 COMMUNITY).ti,ab,kw.
telemonitoring.ti,ab,kw.
web 2.ti,ab,kw.
mhealth.ti,ab,kw.
e-mail.ti,ab,kw. or exp e-mail/
(computer or internet) adj assisted adj therapy).ti,ab,kw.
web-site.ti,ab.
or/48-67
47 and 48
Web-based interventions targeting cardiovascular risk factors in middle-aged and older people

70 animal tissue/
71 animal model/
72 animal experiment/
73 exp invertebrate/
74 exp animals/
75 animal cell/
76 nonhuman/
77 or/70-76
78 human/ or normal human/ or human cell/
79 77 and 78
80 77 not 79
81 69 not 80
82 meta-analysis.tw.
83 systematic review.tw.
84 MEDLINE.tw.
85 pubmed.tw.
86 or/82-85
87 81 and 86
88 (random$ or crossover$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or allocat$).ti,ab.
89 crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
90 (Trial or comparison).ti.
91 or/88-90
92 81 and 91
93 limit 92 to (conference abstract or conference proceedings or “review”)
94 92 not 93
95 limit 94 to yr=“1995 -Current”
96 limit 87 to yr=“1995 –Current”

70 animal tissue/
71 animal model/
72 animal experiment/
73 exp invertebrate/
74 exp animals/
75 animal cell/
76 nonhuman/
77 or/70-76
78 human/ or normal human/ or human cell/
79 77 and 78
80 77 not 79
81 69 not 80
82 meta-analysis.tw.
83 systematic review.tw.
84 MEDLINE.tw.
85 pubmed.tw.
86 or/82-85
87 81 and 86
88 (random$ or crossover$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or allocat$).ti,ab.
89 crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
90 (Trial or comparison).ti.
91 or/88-90
92 81 and 91
93 limit 92 to (conference abstract or conference proceedings or “review”)
94 92 not 93
95 limit 94 to yr=“1995 -Current”
96 limit 87 to yr=“1995 –Current”
Supplementary appendix 3
Data-extraction form
Data extraction form Review 'Internet-interventions for cardiovascular risk management'
CRL Beishuizen, 26-04-2013

Source
- Date of extraction
- Study ID
- Review author ID
- Citation
- Author details
- Abstract/ description
- Aim/objective of study

Methods
- Study design
- Total study duration
- Allocation sequence concealment
- Blinding
- Handling of dropouts/attrition
- Intention to treat analysis
- Recruitment strategy

Participants
- Total number
- Inclusion criteria
- Number included
- Number excluded
- Drop-outs
- Length of follow-up
- Age
- Sex
- Co-morbidity
- Socio-demographics
- Level of education
- Groups similar at baseline?

Intervention
- Number of intervention groups
- Description of intervention
- Description of control
- Duration of intervention
- Specified: group/individual, pure/blended, caregiver, education, self-management, goal-setting, peer-to-peer contact

Outcomes
- Of each outcome: (together in 1 cell)
  1. Baseline mean + sd
  2. After intervention + time point (mean+sd)
  3. Mean difference + sd
  4. Effect size estimate
  5. Sample size
- Surrogate endpoints (blood pressure control, glucose control (HbA1c), cholesterol, BMI, physical activity and smoking)
- Clinical outcomes (new cardiovascular events or cardiovascular disease, disability and mortality)
- Psychological outcomes (including depression)
- Behavioural outcomes
- Adherence to drugs
- Quality of life etc (patient satisfaction)
- Use of internet-intervention and adherence

Supplementary appendix 3
Data-extraction form
Data extraction form Review 'Internet-interventions for cardiovascular risk management'
CRL Beishuizen, 26-04-2013

Outcomes
- Of each outcome: (together in 1 cell)
  1. Baseline mean + sd
  2. After intervention + time point (mean+sd)
  3. Mean difference + sd
  4. Effect size estimate
  5. Sample size
- Surrogate endpoints (blood pressure control, glucose control (HbA1c), cholesterol, BMI, physical activity and smoking)
- Clinical outcomes (new cardiovascular events or cardiovascular disease, disability and mortality)
- Psychological outcomes (including depression)
- Behavioural outcomes
- Adherence to drugs
- Quality of life etc (patient satisfaction)
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Intervention
- Number of intervention groups
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Participants
- Total number
- Inclusion criteria
- Number included
- Number excluded
- Drop-outs
- Length of follow-up
- Age
- Sex
- Co-morbidity
- Socio-demographics
- Level of education
- Groups similar at baseline?
Results
• Number of participants in each group
• Sample size for each outcome
• Drop out and lost to follow-up
• Outcome data for each intervention group
• Estimate of effect with confidence interval
• Adverse events

Conclusions / discussion
• Key conclusions / discussion points & limitations of study authors
• Conclusion / discussion points of review author

Miscellaneous
• Funding source
• Conflict of interest reported
• References to other relevant studies
• Correspondence required?
• Extra comments by review authors

Quality-criteria / risk of bias
• Selection bias
• Performance bias
• Attrition bias
• Detection bias
• Reporting bias

Results
• Number of participants in each group
• Sample size for each outcome
• Drop out and lost to follow-up
• Outcome data for each intervention group
• Estimate of effect with confidence interval
• Adverse events

Conclusions / discussion
• Key conclusions / discussion points & limitations of study authors
• Conclusion / discussion points of review author

Miscellaneous
• Funding source
• Conflict of interest reported
• References to other relevant studies
• Correspondence required?
• Extra comments by review authors

Quality-criteria / risk of bias
• Selection bias
• Performance bias
• Attrition bias
• Detection bias
• Reporting bias
### Supplementary appendix 4 Summary of risk of bias assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Passive control</td>
<td>✔</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>✔</td>
</tr>
<tr>
<td>2</td>
<td>Random sequence</td>
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<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>✔</td>
</tr>
<tr>
<td>3</td>
<td>Allocation concealment</td>
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<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>✔</td>
</tr>
<tr>
<td>4</td>
<td>Blinding of outcome assessors</td>
<td>✔</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>✔</td>
</tr>
<tr>
<td>5</td>
<td>Incomplete outcome data</td>
<td>✔</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>✔</td>
</tr>
<tr>
<td>6</td>
<td>Selective reporting</td>
<td>✔</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>✔</td>
</tr>
</tbody>
</table>

- **Low risk of bias**
- **Unknown risk of bias**
- **High risk of bias**

1. Representative sample (selection bias)
2. Random sequence generation (selection bias)
3. Allocation concealment (selection bias)
4. Blinding of outcome assessors (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
Web-based interventions targeting cardiovascular risk factors in middle-aged and older people

Supplementary appendix 5 Funnel plots

S2.1: systolic BP
S2.2: diastolic BP
S2.3: Hba1C
S2.4: weight
S2.5: LDL-cholesterol
S2.6: physical activity
S2.7: cardiovascular composite scores
S2.8: new cardiovascular events
S2.9: pooled primary outcomes
### Supplementary appendix 6 Subgroup analysis: study-duration

<table>
<thead>
<tr>
<th></th>
<th>N of studies</th>
<th>Effect size</th>
<th>Lower 95%CI</th>
<th>Upper 95%CI</th>
<th>I²</th>
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<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>short (&lt;12 months)</td>
<td>12</td>
<td>-3.54</td>
<td>-5.66</td>
<td>-1.41</td>
<td>63%</td>
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<td>long (≥12 months)</td>
<td>14</td>
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<td>-3.12</td>
<td>-0.90</td>
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</tr>
<tr>
<td><strong>Diastolic BP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>short (&lt;12 months)</td>
<td>12</td>
<td>-1.82</td>
<td>-3.11</td>
<td>-0.54</td>
<td>60%</td>
</tr>
<tr>
<td>long (≥12 months)</td>
<td>14</td>
<td>-0.99</td>
<td>-1.62</td>
<td>-0.36</td>
<td>17%</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>short (&lt;12 months)</td>
<td>8</td>
<td>-0.23</td>
<td>-0.36</td>
<td>-0.10</td>
<td>82%</td>
</tr>
<tr>
<td>long (≥12 months)</td>
<td>13</td>
<td>-0.06</td>
<td>-0.21</td>
<td>0.08</td>
<td>69%</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>short (&lt;12 months)</td>
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<td>-1.86</td>
<td>-2.17</td>
<td>-1.00</td>
<td>70%</td>
</tr>
<tr>
<td>long (≥12 months)</td>
<td>10</td>
<td>-0.84</td>
<td>-1.53</td>
<td>-0.14</td>
<td>41%</td>
</tr>
<tr>
<td><strong>LDL-cholesterol (mg/dl)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>short (&lt;12 months)</td>
<td>5</td>
<td>-0.32</td>
<td>-1.33</td>
<td>0.69</td>
<td>9%</td>
</tr>
<tr>
<td>long (≥12 months)</td>
<td>12</td>
<td>-2.98</td>
<td>-5.60</td>
<td>-0.36</td>
<td>32%</td>
</tr>
<tr>
<td><strong>Physical activity (Hedges’ g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>short (&lt;12 months)</td>
<td>8</td>
<td>-0.37</td>
<td>-0.62</td>
<td>-0.11</td>
<td>86%</td>
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<td>-0.25</td>
<td>0.01</td>
<td>56%</td>
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<tr>
<td><strong>CV composite scores (Hedges’ g)</strong></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>short (&lt;12 months)</td>
<td>4</td>
<td>-0.18</td>
<td>-0.31</td>
<td>-0.05</td>
<td>0%</td>
</tr>
<tr>
<td>long (≥12 months)</td>
<td>5</td>
<td>-0.05</td>
<td>-0.16</td>
<td>0.03</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Primary outcomes (Hedges’ g)</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>short (&lt;12 months)</td>
<td>15</td>
<td>-0.43</td>
<td>-0.57</td>
<td>-0.29</td>
<td>69%</td>
</tr>
<tr>
<td>long (≥12 months)</td>
<td>22</td>
<td>-0.12</td>
<td>-0.19</td>
<td>-0.06</td>
<td>43%</td>
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Supplementary appendix 7 Risk of bias assessment: sensitivity analyses for the domains of risk of bias

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<tr>
<th>Domain</th>
<th>N of studies</th>
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<th>Lower 95%CI limit</th>
<th>Upper 95%CI limit</th>
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<td><strong>Representative sample</strong></td>
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<tr>
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<td>25</td>
<td>-0.25</td>
<td>-0.35</td>
<td>-0.16</td>
</tr>
<tr>
<td>Unclear / high risk</td>
<td>22</td>
<td>-0.26</td>
<td>-0.36</td>
<td>-0.15</td>
</tr>
<tr>
<td><strong>Random sequence generation</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>39</td>
<td>-0.20</td>
<td>-0.27</td>
<td>-0.14</td>
</tr>
<tr>
<td>Unclear / high risk</td>
<td>8</td>
<td>-0.53</td>
<td>-0.82</td>
<td>-0.24</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>37</td>
<td>-0.22</td>
<td>-0.29</td>
<td>-0.15</td>
</tr>
<tr>
<td>Unclear / high risk</td>
<td>10</td>
<td>-0.38</td>
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<td>-0.17</td>
</tr>
<tr>
<td><strong>Blinding of outcome assessment</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>15</td>
<td>-0.37</td>
<td>-0.50</td>
<td>-0.23</td>
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Chapter 3

Integrating nurses’ experiences with supporting behaviour change for cardiovascular prevention into a self-management internet-platform in Finland and the Netherlands

Cathrien Beishuizen, Ulrika Akenine, Barbera, Anna Rosenberg, Mandana Falalahpour, Edo Richard, Hilkka Soininen, Francesca Mangialasche, Miia Kivipelto, Jeannette Pols and Eric Moll van Charante

Submitted to the BMJ Open
ABSTRACT

Background: Global ageing is linked to an increased burden of cardiovascular disease (CVD) and dementia, which calls for better prevention strategies. Self-management and eHealth applications are regarded promising strategies to support prevention. In the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) study, an internet-platform with coaching has been developed for prevention of CVD and cognitive decline in older people in Europe.

Aim: We explored nurses’ experiences with behaviour change guidance for cardiovascular (CV) prevention to learn how to optimally integrate these into an online setting.

Design and setting: Qualitative study in the Netherlands and Finland among nurses experienced in CV prevention.

Methods: Focus groups were held in both countries. Discussions were audiotaped and transcribed. Data were thematically analysed following grounded theory.

Results: Finnish and Dutch nurses expressed similar experiences with supporting behaviour change for CV prevention but used different practical approaches, which was reflected in their recommendations for online-support. Both groups emphasised that online-support should be combined with human support and integrated in regular care. Finnish nurses had more confidence in patient self-management and remote communication than Dutch nurses, who emphasised the importance of face-to-face contact and preferred to keep the control on medical aspects of prevention.

Conclusions: Differences in CV prevention support of Dutch and Finnish nurses appear to reflect their local healthcare practices, which should be taken into account when designing internet-platforms for health self-management. Including cognitive health as a goal of CV prevention might stimulate people’s motivation for health behaviour change.
INTRODUCTION

Global ageing places an increasing demand on healthcare systems, partially due to the absolute rise in cardiovascular disease (CVD) and dementia cases. As these disorders share a number of risk factors, effective cardiovascular (CV) prevention could also lead to the prevention of dementia. CV prevention requires health behaviour change, the process of “initiating and maintaining behaviours that reduce health risks and control existent chronic disease”. In CV prevention, core behaviours consist of a healthy lifestyle (healthy diet, sufficient physical activity and non-smoking) and adherence to medication. Although the processes behind supporting health behaviour change have been theorised extensively, putting them into practice remains a challenge and novel, more effective, approaches are needed. Two strategies of current interest are self-management and eHealth. In self-management, the individual, instead of the healthcare professional, takes the lead in the management of his/her risk factors and adherence, and therefore in behaviour change. eHealth applications can easily support self-management and are attractive because of their wide reach, low-cost and suitability for health education. Although researchers and policymakers have high expectations of eHealth and self-management, little is known of how self-management and behaviour change are best stimulated and maintained online.

This project is part of the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) study, which includes a European randomised controlled trial testing a coach-supported internet-platform for self-management of cardiovascular risk factors in older people to prevent CVD and cognitive decline. In an international focus group study, we aimed to explore (1) nurses’ experiences and practices with behaviour change guidance for cardiovascular prevention, including the potential for dementia prevention, and (2) how to integrate their practices into a coach-supported internet-platform (the online-support setting). This study took place in Finland and the Netherlands, two of the three countries where the HATICE-study is ongoing. Since the HATICE project aims to develop an internet-platform that is implementable across all European healthcare systems, we also explored the influence of local healthcare practices.

METHODS

We performed an international qualitative focus group study following grounded theory. The COREQ-checklist is included for complete information on methodology (Appendix 1).
Participants and setting

Finnish and Dutch primary care nurses experienced in cardiovascular preventive care were eligible for this study and convenience samples were obtained. In Finland, we recruited occupational healthcare nurses because of their important role in preventive CV care. Nurses working in a semi-private healthcare centre in Kuopio (Eastern Finland) were invited and six female nurses consented to participate. Being occupational health nurses they cared mostly for patients in the working age. In the Netherlands, we recruited primary care nurses experienced in cardiovascular risk management. A group of 32 nurses working in general practices in two urban areas in the centre of the Netherlands was invited and seven female nurses consented to participate. The Dutch participating nurses cared for patients of all ages. Table 1 contains further characteristics.

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*abbreviations: CVD = cardiovascular disease, FI = Finland, prim = primary, sec = secondary, prev = prevention, NL = the Netherlands, DM = diabetes mellitus, COPD = chronic obstructive pulmonary disease

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*abbreviations: CVD = cardiovascular disease, FI = Finland, prim = primary, sec = secondary, prev = prevention, NL = the Netherlands, DM = diabetes mellitus, COPD = chronic obstructive pulmonary disease

Table 1 Characteristics of the participating Finnish and Dutch nurses
The study was presented to the medical ethics committee of the Academic Medical Centre in the Netherlands and a waiver was provided. In Finland, application for ethical approval nor a waiver were required. All participants provided written informed consent.

**Data collection**
We conducted one focus group in the Netherlands (autumn 2013) and one in Finland (December 2015). In each country, an experienced focus group moderator chaired the sessions, while an assistant-moderator noted non-verbal communication and summarised the discussions. The discussion was conducted using a topic list as reference (Box 1 and Appendix 2). After the Dutch session, the topic list was refined for the Finnish focus group. Both moderators first discussed the nurses’ activities in cardiovascular prevention and how they supported their patients in the process of behaviour change. The Finnish moderator also discussed the nurses’ experiences on prevention of dementia. In the second part, the HATICE internet-platform was presented (Box 2, a full description of the platform is reported elsewhere) and the nurses were asked how they would optimally support their patients in an online setting. Both sessions lasted approximately two hours. The discussions were audio-recorded and transcribed.

**Box 1 Main topics discussed**

**Part 1**
- Prevention of cardiovascular disease and dementia: attitude and experiences
- Good guidance of behaviour change
- Relationship with the patient

**Part 2**
- Attitude towards the internet-platform and online-support
- Role and responsibilities of the internet-coach
- Interaction with the patients online
Box 2 Key features of the HATICE internet-platform with coaching

- Patient-centred: the patient can login onto a personal portal to review and manage his/her personal cardiovascular risk profile
- Improving health knowledge: the patient can access educational modules about cardiovascular risk factors and lifestyle
- Goal setting and self-monitoring: the patient can set his/her own goals for behaviour change and monitor how he/she is doing by entering self-measurements or keeping a diary
- Coaching: the coach monitors the patient’s self-management and they can communicate online through messages

Coding and analysis

In each country, two researchers coded and thematically analysed the transcripts following grounded theory. Themes were derived from the data. Open coding and identification of initial themes was first performed by the two researchers independently. Thereafter, codes and themes were compared. Dissimilarities were discussed until consensus was reached. Initial theme structure was then discussed with the senior researchers involved. In Finland, since the researchers were not Finnish native speakers, the transcript was translated into English and cross-checked by the Finnish focus group moderator, who was a Finnish native fluent English speaker. In this way, the complete analysis of the Finnish data could be performed in English. After the initial analysis was performed locally, themes and corresponding quotations of the Dutch sessions were also translated into English. The two research teams then had two meetings to discuss the structure of main themes and categories. This analysis-phase was an iterative process, during which the researchers of both teams repeatedly returned to their data-files to add, merge and refine themes, until a definite theme structure was agreed on by all authors. During the iterative analysis-phase, the researchers discussed the themes and alternatives and it was proposed that the local health care context was of influence on the differences found between caring styles of the two groups of nurses. Therefore, the research teams introduced their local health care systems to each other and these insights were used in further interpretation of the findings. A summary of the final conclusions was returned to the participants for feedback.
Both Finland and the Netherlands have strongly developed primary care systems with an important gatekeeper function:

**The Finnish primary care system**

In Finland, health promotion and disease prevention have been the focus of healthcare policy for decades. Primary care is delivered by public healthcare centres but also through occupational health facilities.25-27 In many parts of Finland, healthcare centres cover large geographical areas that are sparsely populated and often have shortage of staff, contributing to long waiting lists and lack of personal continuity of care. All healthcare centres use electronic medical records to ensure continuity of care. Finland was the first European country to introduce a law (in 1993) defining the patient’s right to access to all medical information and the right to autonomy (patient’s informed consent for any medical treatment). Currently, a national patient data repository is under development to provide Finnish patients complete access to their own electronic medical record.28 Nurses have an important role in primary healthcare. They work in close collaboration with the general practitioners and have their own consulting hours to assess patients. Regarding cardiovascular prevention, they monitor patients with diabetes, hypertension and dyslipidaemia, as described in national guidelines.29-31 Finnish companies offer occupational health facilities to their employees, including both preventive and curative health services, which are delivered through semi-private healthcare centres that also work with nurses in a similar fashion as the public primary health care centres. Since waiting lists are long in public primary care, many employees direct themselves to these health services instead.

**The Dutch primary care system**

Key features of the Dutch healthcare system are access to care for everyone and solidarity through medical insurance.22-24 General practices form the core of primary care and general practitioners (GPs) are gatekeepers of the healthcare system, providing acute, chronic and preventive care. Since the Netherlands are densely populated, people often live at short distance from their general practice. In most general practices continuity of care is ensured by allocating the patient to one GP. In the Netherlands, informed consent is also ensured by law, but in daily practice, consent is often assumed and only explicitly discussed in case treatment options can have far-reaching consequences.32 Almost all GPs use electronic medical records. Patients have the right to inspect their medical records, but do not have complete access to them.

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Nurses have an important position in primary care in the Netherlands. Since several decades, GPs have delegated tasks to practice nurses, especially concerning chronic disease management. Currently, these nurses provide a substantial part of cardiovascular risk management care, including diabetes care, which has been worked out in several regional and national guidelines and work descriptions.\textsuperscript{9-36} Access to the GP is efficient, there are no waiting lists.\textsuperscript{37}

RESULTS

We present our findings in two sections: 1) nurses experiences and practices with supporting the process of behaviour change for cardiovascular prevention, including the potential for dementia prevention, and 2) their suggestions on how to integrate their experiences in an online-support setting.

Part 1: Nurses experiences and practices with supporting the process of behaviour change for cardiovascular prevention

We identified three main themes, that both the Finnish and Dutch nurses regarded as preconditions for behaviour change guidance in their patients: establishing a relation of trust, awareness and expectation management, and appropriate timing and monitoring. Both groups of nurses explained what skills they used to realise these preconditions, showing subtle differences between the groups.

Establishing a relationship of trust

According to both the Finnish and Dutch nurses, the basis of behaviour change support lied in establishing a relationship of trust with the patient: developing a good nurse-patient relationship in which the individual felt at ease and respected and comfortable enough to open up about lifestyle and behaviour issues:

“For lifestyle change, for prevention, a relationship based on mutual trust is pivotal. It is good to have a many years’ standing contact with people. Then you know what is going on in someone’s life and in that, some kind of trust will grow that people really start believing what you are saying to them. And then, over time, people will start practising healthy behaviours that maybe they had no intention to follow, in the beginning” (Dutch nurse 1)

Skills the nurses used to stimulate trust to grow, were personalising and tailoring their support to each patient:
“And you need to get a good picture of the situation, so that you don’t give the same information to everyone. That’s of no use. You need to think what the central issues are for this patient. What are the things he or she seems to have resources for? What are the goals that the client sets? What is the client able to do, and with what kind of intensity? What will the time span be like? And I also ask my client directly what kind of support does he or she wishes? I’m trying to offer what the client thinks he or she needs” (Finnish nurse 1)

Interestingly, the nurses had different preferences for modes of communication. The Dutch nurses emphasised face-to-face contact and in-person continuity. The Finnish nurses preferred an initial face-to-face consultation but were comfortable with further phone or email contact and did not regard this as less personal than face-to-face contact. Email contact also had advantages:

“But sometimes this kind of communication online could be less complicated…than face to face.” (Finnish nurse 5)

“I have noticed in my work that some people prefer contacting me by e-mail and not by phone. [others agree] On the phone they might think that they are disturbing or it’s a bad timing, but one can write an e-mail or something anytime.” (Finnish nurse 3)

Awareness and expectation management
A second precondition was awareness and expectation management: checking the patients’ level of knowledge and expectations regarding prevention and personal cardiovascular risk. Nurses thought that most patients had considerable knowledge of cardiovascular disease prevention, especially in Finland, due to a long standing tradition in community based cardiovascular prevention (the North-Karelia project). Nonetheless, both groups of nurses had the experience that people were not especially aware of their personal cardiovascular risk status:

“That’s it, isn’t it, for many people their health is not a concern yet. You can list them the facts, and they hear and read it everywhere, that it is unhealthy to have overweight and that they need to exercise more, but right now, they are not yet bothered by it.” (Dutch nurse 6)

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Because of this lack of a sense of urgency, the nurses regarded the ability to educate their patients about consequences of health behaviours an essential skill of their profession. Once awareness and motivation had grown, people often had unrealistic expectations and the nurses needed to act as “myth busters” (Finnish nurse 4):

“And when we are, however, not able to offer the magic pills or wonder tricks, the clients may sometimes be disappointed when all I can suggest is these boring methods: diet and physical activity. And we cannot offer them a magic solution.” (Finnish nurse 4)

Often, once people were motivated to change their health behaviours, they also tended to set unrealistic goals, which the nurses then had to reshape:

“Start small. Do not make it too big. If you are obese, many people do not like it to go to the gym, they think the gym is only for lovely slim figures. You cannot convince them that that’s not true. Therefore it is important: try things first yourself. What can you do with small steps at home by yourself, before going outside. You have to start liking exercise.” (Dutch nurse 3)

Lastly, the nurses actively prepared their patients for failures during the process of behaviour change, as these were seen as inevitable:

“I usually tell the patients that they’re allowed to fail; but even so, they are invited to, and they should come to the appointments. So then we can check the situation again, and set a new goal if needed.” (Finnish nurse 1)

With the Finnish nurses, coaching on cardiovascular risk was also related to the potential for dementia prevention. They suggested that many patients feared dementia and lacked knowledge about the disease and treatment and prevention options, creating a stigma towards this condition. The nurses were aware of the link between cardiovascular disease and dementia, but felt they lacked sufficient knowledge and training to provide proper support:

“Well, we have not had the knowledge of reasons for dementia for that long. And these connections haven’t been...the research is recent: well, at least more recent than the research about heart diseases.” (Finnish nurse 5)
They found that educating patients on the link between cardiovascular disease and dementia, would be a good starting point to raise awareness. Potentially, this could enhance motivation for CV prevention:

“What is good for the heart – and we know what’s good for the heart – is also good for the brain but not everyone knows this. I think this link would be good to be aware of: you protect your heart but also the most important part of your body which is the brain.” (Finnish nurse 4)

Appropriate timing and monitoring

The third precondition mentioned by the nurses was appropriate timing and monitoring: providing professional support at appropriate times and monitoring the progress of the patient towards behaviour change. Regular follow-up appointments stimulated adherence and motivation:

“After three months, your plan fades away, your goal, your motivation.” (Dutch nurse 3)

“...that there is a possibility for follow-up. Usually it motivates people when someone looks after you: how are you progressing, no matter if the target is, for example, smoking cessation or increasing of physical activity.” (Finnish nurse 5)

Monitoring ensured that the nurses could support their patients when experiencing obstacles or failures, although this could be difficult:

“Disappointments also play a role. For example: a guy with diabetes, he quit smoking but then his sugar levels went up and he needed to start with insulin. How do you explain that to him? Well, I challenge you to keep his attitude up and to maintain his motivation.” (Dutch nurse 5)

When discussing monitoring lifestyle behaviours both nurse groups attributed themselves a supportive role putting the patient in charge, because lifestyle was seen as the personal domain of the patient. However, regarding the medical components of preventive care (control of hypertension, diabetes and hypercholesterolemia), the Dutch nurses attributed a more directive role to themselves and the medical practice to
avoid mistakes and complications, whereas the Finnish nurses regarded their patients as capable of staying in charge.

**Part 2: Integrating the nurses’ strategies into an online-support setting**

After having identified the preconditions for optimal behaviour change support and the skills nurses use in their current practices, we demonstrated the latest version of the HATICE internet-platform\(^{24}\) and discussed the online-support setting. Both groups of nurses emphasised the importance of the aforementioned preconditions for optimal online support.

**Establishing a relationship of trust**

All nurses regarded the presence of a coach as essential to guarantee personal support. The Finnish nurses felt that online coaching could successfully establish a relationship of trust, provided that the coach was a real person:

> “Because of this social interaction on this website [the HATICE platform], the participant has a familiar and friendly person [as a coach] and not just some distant virtual coach who is a stranger. […] it’s good that this combines the real-life person with the online contact, maybe it feels more comfortable and familiar for the participant.” (Finnish nurse 4)

An initial face-to-face consultation with the patient could strengthen the establishment of a good relationship. Overall, for the Finnish nurses, online support was an obvious step forward in innovating healthcare:

> “Well at least I think that this is absolutely the trend [others nod and agree], that all the services will be at least partly available online for the patients. Partly like this [via internet] and partly with human contact. I think that it’s an inevitable part of future.” (Finnish nurse 1)

In contrast, the Dutch nurses could not imagine the platform and coach fully substituting their personal guidance:

> “The strength of our guidance is the personal contact we have with the patients. […] that enables us to give them some subtle support and give them a small push into the right direction. To delegate all of that to an online coach just like that, that seems difficult to me. Then all personal contact will disappear.” (Dutch nurse 7)

avoid mistakes and complications, whereas the Finnish nurses regarded their patients as capable of staying in charge.

**Part 2: Integrating the nurses’ strategies into an online-support setting**

After having identified the preconditions for optimal behaviour change support and the skills nurses use in their current practices, we demonstrated the latest version of the HATICE internet-platform\(^{24}\) and discussed the online-support setting. Both groups of nurses emphasised the importance of the aforementioned preconditions for optimal online support.

**Establishing a relationship of trust**

All nurses regarded the presence of a coach as essential to guarantee personal support. The Finnish nurses felt that online coaching could successfully establish a relationship of trust, provided that the coach was a real person:

> “Because of this social interaction on this website [the HATICE platform], the participant has a familiar and friendly person [as a coach] and not just some distant virtual coach who is a stranger. […] it’s good that this combines the real-life person with the online contact, maybe it feels more comfortable and familiar for the participant.” (Finnish nurse 4)

An initial face-to-face consultation with the patient could strengthen the establishment of a good relationship. Overall, for the Finnish nurses, online support was an obvious step forward in innovating healthcare:

> “Well at least I think that this is absolutely the trend [others nod and agree], that all the services will be at least partly available online for the patients. Partly like this [via internet] and partly with human contact. I think that it’s an inevitable part of future.” (Finnish nurse 1)

In contrast, the Dutch nurses could not imagine the platform and coach fully substituting their personal guidance:

> “The strength of our guidance is the personal contact we have with the patients. […] that enables us to give them some subtle support and give them a small push into the right direction. To delegate all of that to an online coach just like that, that seems difficult to me. Then all personal contact will disappear.” (Dutch nurse 7)
Awareness and expectation management
All nurses regarded the internet-platform as a suitable means to raise awareness and increase health-literacy. Managing expectations related to online support was considered very important, because misunderstandings could arise more easily through this mean. Therefore, the coach should explain what could be expected from the platform and their support:

“Communication is very important in the beginning, what is it we do and what do they expect from the goals.” (Dutch nurse 1)

Appropriate timing and monitoring
The nurses envisioned that online, the patient would be in charge of timing of support and monitoring of progress. The coach would have a reactive role, providing support in response to the patient’s demand. However, the nurses felt the coach also needed to be proactive, in case people showed signs of losing motivation. This would require insight in people’s platform activities:

“[…] the nurse can also see it [the diary] and check. If the participant fails to achieve the goals, the nurse can go back and check what might have been the problem.” (Finnish nurse 5)

Both groups thought the platform should be aligned to regular healthcare. The Finnish nurses envisioned that the online coach could work in the same fashion as the nurses currently did, targeting both lifestyle and medical components of their patient’s health. The Dutch nurses stressed that not everybody would be able to self-manage, especially when it concerned medical issues. Therefore, they preferred a platform focusing on lifestyle only, keeping the control of medical issues in the medical practice:

“I think 2 or 3 types of platform users will arise: people who really get the concept of self-management (and start coaching themselves), people who need the coach (and give the coach access to their complete profile) and a group in between, alerting the coach if a goal has not been met.” (Dutch nurse 2)
DISCUSSION

Summary and interpretation

In this international focus group study, we identified three main themes that both the Finnish and Dutch nurses emphasised as most important preconditions for behaviour change support in cardiovascular prevention, and potentially, prevention of cognitive decline: (1) establishing a relationship of trust, (2) managing awareness and expectations and (3) appropriate timing and monitoring of the process of behaviour change. They regarded these preconditions equally important for optimal online support and stressed that a coach providing human support and integration with regular care were essential elements to achieve this. They expressed, however, different ideas on its implementation (Figure 1).

As mentioned in the introduction, realising and maintaining health behaviour change is notoriously complex. This was confirmed by the nurses we interviewed, but their clinical experience provided us with clear preconditions for optimal behaviour change support. The nurses used slightly different approaches to fulfil these preconditions,
both in their current practice and in their ideas on online support. To establish a relationship of trust, the Dutch nurses relied more on face-to-face contact than the Finnish nurses, which appeared to make them more sceptical about the effectiveness of online coaching. The Finnish nurses took a mainly supportive role in monitoring whereas Dutch nurses emphasised a more directive role for themselves and the general practice, with regard to medical aspects of preventive guidance. As Box 3 shows, the aims of preventive care are very similar between Finland and the Netherlands, with similar roles for primary healthcare nurses. This may explain why the nurses came up with similar preconditions for optimal support of behaviour change. Nevertheless, the differences we found in their current approaches and in their ideas for online support may reflect differences in culture, local healthcare organisation and geography. For example, the nurses’ ideas about their own responsibilities and patient autonomy may be aligned to the way patient-autonomy is being shaped in the two healthcare systems as well as the description of nurses’ responsibilities in local cardiovascular risk management guidelines. The different attitudes on face-to-face contact can be understood from the perspective of geography. Finland is a large but very sparsely populated country and the Netherlands are a very small but densely populated country. The large distances between patient and health care provider in Finland can make telephone and email contact an attractive alternative for face-to-face consultations. Our results concerning dementia prevention are of special interest. The Finnish nurses liked the idea of including cognitive health as a goal for cardiovascular preventive care, as dementia was regarded a growing public health problem and a combined approach could enlarge people’s motivation to engage in behaviour change. However, the nurses felt they could not provide proper support, given their limited knowledge and training on one hand, and limited availability of conclusive scientific evidence on the other.

**Strengths and limitations**

The HATICE project is novel in its aim to develop a generic innovative cardiovascular prevention strategy for older people that can be used across European healthcare systems, especially since it involves eHealth. In qualitative research, international joint analyses are not common because of language barriers. To overcome these, we put much effort in the alignment of our research methodology. The frequent interactions and extensive meetings of the research teams enabled us to explore our findings in the context of the local health care systems. Since we only performed two focus groups and did not follow a strategy of purposive sampling, we cannot exclude that a wider range of views could have been collected. However, the striking similarities found in both countries and the consistency of our findings with previous literature mitigates fears that our samples were too limited. Furthermore, when reviewing a summary of
our findings, the nurses confirmed that their experiences and views were well reflected and did not add new ones, emphasising that the most relevant themes were captured. The patient populations of the Finnish and Dutch nurses were not identical with respect to age. However, since both groups of nurses had comparable experience with cardiovascular prevention and both countries have similar aims for cardiovascular prevention we deem the selection of these nurses appropriate for our research purpose. In addition, the variety in our samples regarding age and clinical experience was large.

**Comparison with existing literature**
The experiences of the nurses with behaviour change support were comparable to those described in other European qualitative studies and as described by Dutch patients. The positive attitude of the Finnish nurses on self-management of medical issues was consistent with another Finnish study about nurses’ and physicians’ perceptions on patients’ responsibilities in self-care. The reserved attitude of the Dutch nurses was also reflected in a survey among Dutch healthcare professionals, where 50% feared that patients’ direct access to their medical record would cause misunderstandings and unnecessary anxiety. Finally, the conviction of all nurses that a coach was essential to complement the internet-platform, is supported by a meta-analysis we performed showing that internet-interventions combined with human support were more effective than ‘stand-alone’ interventions.

**Implications for practice**
Finnish and Dutch nurses have similar experiences with and views on supporting behaviour change for cardiovascular prevention, but use different practical approaches towards their patients. Including the maintenance of cognitive health as a goal of cardiovascular prevention might augment people’s motivation to partake in health behaviour change. When introducing new forms of preventive healthcare that involve patient self-management, like internet-platforms, local healthcare practices are to be taken into account to achieve optimal engagement.
ADDITIONAL INFORMATION

Acknowledgements
We thank all Finnish and Dutch nurses for their participation in the study, Suzanne Ligthart, Carin Miedema, Paulien Vermunt, Floor Rooskens (respectively discussion moderator, assistant-moderator and assistants in transcription and coding for the Dutch meetings), Lotta Salo and Eija Pietilä (organisation and summary notes of the Finnish meeting) for their assistance to the study.

Funding
The research leading to these results has received funding from the European Union Seventh Framework Programme for the HATICE-project (FP7/2007-2013, grant agreement n° 305374) and the Multimodal preventive trials for Alzheimer’s Disease: towards multinational strategies – programme (MIND-AD: MIND-AD Academy of Finland (grant agreement n°291803), MIND-AD VTR, Kuopio University Hospital (grant agreement n°5772815) and MIND-AD Academy of Sweden (Swedish Research Council, 529-2014-7503)).

Ethical approval
In the Netherlands, the study was presented to the medical ethics committee of the Academic Medical Centre in the Netherlands and a waiver was provided. In Finland, application for ethical approval nor a waiver were required. Written informed consent was obtained from all participants in both countries.

Competing interests
The authors have declared no competing interests.

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REFERENCES


Appendix 1 COREQ checklist

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<td>FI: Rosenberg A</td>
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<td>6</td>
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<td>NL: there was an indirect relationship between research team and the participants, because the nurses had been involved in a previous research project of the research team in which 2 researchers (Ligthart S and Moll van Charante EP) were also involved; FI: no previous relationship established</td>
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Domain 2: Study design

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<td>Interview guide</td>
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<td>Methods and Appendix 1</td>
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## Domain 3: Analysis and Findings

| 24 | Number of data coders | NL: 2 | FI: 2 | Methods |
| 25 | Description of the coding tree | See figure 1 | Figure 1 |
| 26 | Derivation of themes | See body of text | Methods |
| 27 | Software | No special qualitative software was used |
| 28 | Participant checking | See body of text | Methods and discussion |
| 29 | Quotations presented | See body of text | Results section |
| 30 | Data and findings consistent | See body of text | Results section |
| 31 | Clarity of major themes | See body of text and figure 1 | Results section and discussion |
| 32 | Clarity of minor themes | Within the groups, the Dutch and Finnish nurses shared opinions and experiences on most topics. Between the Dutch and Finnish groups, some interesting differences in opinions and experiences were identified. We choose therefore to focus on these differences when presenting our results, but not on divergent cases within the groups. Minor themes were not discussed due to word limits.

Minor themes were not discussed due to word limits.

Results section and discussion
Appendix 2: Topic list

FOCUS GROUP nurses part ONE cardiovascular prevention

Overview part one | Topic (possible items) | Possible questions
--- | --- | ---
CVD prevention | Activities on CVD prevention | Do you currently conduct activities on CVD prevention?
Experiences / lessons learned | What are your experiences and lessons learned, especially regarding giving ‘medical’ guidance versus giving lifestyle guidance and regarding behavior change?
Dementia prevention | In the last decade, we got more and more indications from neurological research that risk factors for cardiovascular disease are also risk factors for dementia. So, possibly, reducing cardiovascular risk may also postpone or prevent dementia.
Attitude towards dementia prevention | What is your attitude / your ideas regarding dementia prevention?
Awareness of dementia risk and compliance to lifestyle change | Most people are not yet aware of the association between CV risk and dementia, but do seem to be very afraid of dementia. Do you think that more awareness would enhance compliance/adherence to lifestyle change? What are your ideas on this?
Relationship with participants and regular healthcare system | Guiding lifestyle change | Which factors could contribute to good guidance of lifestyle change?
Relationship with patient | What factors could contribute to a good relationship with your patient?
Relation with GP and regular practice assistant | How should the platform coach link with the patients’ GP and regular practice assistant/nurse (the regular healthcare system)?
Attitude towards internet intervention | What is your attitude towards a prevention program via the internet (with support from a coach)? How should the platform coach link with the patients’ GP and regular practice assistant/nurse (the regular healthcare system)?

FOCUS GROUP nurses part TWO The platform

Assistant moderator explains about MATICE and platform by showing the presentation with screen shots of the platform

Information required for support | Imagine yourself being a coach using the internet-platform.
Role and responsibilities | What kind of information regarding the participants do you need to be able to support them?
Responsibility goal setting | Who is responsible for goal setting (capability of patient)?
Role in lifestyle groups | How do you see your role in creating lifestyle groups and how can participation be encouraged?
Interaction with participants | Experience with motivational interviewing | Do you have experience with motivational interviewing, how could this technique be used by the coach?
Frequency of contact | How often would you like to have contact with your patients?

CVD prevention

Activities on CVD prevention | Do you currently conduct activities on CVD prevention?
Experiences / lessons learned | What are your experiences and lessons learned, especially regarding giving ‘medical’ guidance versus giving lifestyle guidance and regarding behavior change?
Dementia prevention

Attitude towards dementia prevention | What is your attitude / your ideas regarding dementia prevention?
Awareness of dementia risk and compliance to lifestyle change | Most people are not yet aware of the association between CV risk and dementia, but do seem to be very afraid of dementia. Do you think that more awareness would enhance compliance/adherence to lifestyle change? What are your ideas on this?
Relationship with participants and regular healthcare system | Guiding lifestyle change | Which factors could contribute to good guidance of lifestyle change?
Relationship with patient | Which factors could contribute to a good relationship with your patient?
Relation with GP and regular practice assistant | How should the platform coach link with the patients’ GP and regular practice assistant/nurse (the regular healthcare system)?
Attitude towards internet intervention | What is your attitude towards a prevention program via the internet (with support from a coach)? How should the platform coach link with the patients’ GP and regular practice assistant/nurse (the regular healthcare system)?

FOCUS GROUP nurses part THREE Dementia prevention

Overview part one | Topic (possible items) | Possible questions
--- | --- | ---
CVD prevention | Activities on CVD prevention | Do you currently conduct activities on CVD prevention?
Experiences / lessons learned | What are your experiences and lessons learned, especially regarding giving ‘medical’ guidance versus giving lifestyle guidance and regarding behavior change?
Dementia prevention | In the last decade, we got more and more indications from neurological research that risk factors for cardiovascular disease are also risk factors for dementia. So, possibly, reducing cardiovascular risk may also postpone or prevent dementia.
Attitude towards dementia prevention | What is your attitude / your ideas regarding dementia prevention?
Awareness of dementia risk and compliance to lifestyle change | Most people are not yet aware of the association between CV risk and dementia, but do seem to be very afraid of dementia. Do you think that more awareness would enhance compliance/adherence to lifestyle change? What are your ideas on this?
Relationship with participants and regular healthcare system | Guiding lifestyle change | Which factors could contribute to good guidance of lifestyle change?
Relationship with patient | Which factors could contribute to a good relationship with your patient?
Relation with GP and regular practice assistant | How should the platform coach link with the patients’ GP and regular practice assistant/nurse (the regular healthcare system)?
Attitude towards internet intervention | What is your attitude towards a prevention program via the internet (with support from a coach)? How should the platform coach link with the patients’ GP and regular practice assistant/nurse (the regular healthcare system)?

Focus on the prevention of cerebrovascular disease, the prevention of dementia, and the importance of early intervention. Discuss the role of coaches, the importance of collaboration with healthcare professionals, and the potential of online platforms to support lifestyle changes. 

Appendix 2:  Topic list

CVD prevention

Activities on CVD prevention | Do you currently conduct activities on CVD prevention?
Experiences / lessons learned | What are your experiences and lessons learned, especially regarding giving ‘medical’ guidance versus giving lifestyle guidance and regarding behavior change?

Dementia prevention

Attitude towards dementia prevention | What is your attitude / your ideas regarding dementia prevention?
Awareness of dementia risk and compliance to lifestyle change | Most people are not yet aware of the association between CV risk and dementia, but do seem to be very afraid of dementia. Do you think that more awareness would enhance compliance/adherence to lifestyle change? What are your ideas on this?

Relationship with participants and regular healthcare system

Guiding lifestyle change | Which factors could contribute to good guidance of lifestyle change?
Relationship with patient | Which factors could contribute to a good relationship with your patient?
Relation with GP and regular practice assistant | How should the platform coach link with the patients’ GP and regular practice assistant/nurse (the regular healthcare system)?
Attitude towards internet intervention | What is your attitude towards a prevention program via the internet (with support from a coach)? How should the platform coach link with the patients’ GP and regular practice assistant/nurse (the regular healthcare system)?
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<thead>
<tr>
<th>Mode of communication</th>
<th>Which mode of communication do you prefer? (phone, skype +/- web-cam, email, chat...)</th>
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<td>Network of support</td>
<td>What should be the role of the participant network of support in lifestyle change and how can this network be engaged?</td>
</tr>
<tr>
<td>Alerts / reminders</td>
<td>Do you like to receive automatic alerts/reminders when patients have alarming values or did not log-on?</td>
</tr>
</tbody>
</table>

Assistant moderator and moderator verify key messages from focus group

Moderator thanks nurses
Translating nurses' experiences with cardiovascular prevention into an internet-platform
Chapter 4

Development and validation of an interactive internet-platform for older people – the Healthy Ageing Through Internet Counselling in the Elderly study

Cathrien Beishuizen*, Susan Jongstra*, Sandrine Andrieu, Mariagnese Barbera, Matthijs van Dorp, Bram van de Groep, Juliette Guillemont, Francesca Mangialasche, Tessa van Middelaar, Eric Moll van Charante, Hilkka Soininen, Miia Kivipelto, Edo Richard

* These authors equally contributed to the work

Telemedicine and e-Health 2017 Feb;23(2):96-104
ABSTRACT

Background A myriad of web-based applications on self-management have been developed, but few focus on older people. In the face of global ageing, older people form an important target population for cardiovascular prevention. This article describes the full development of an interactive internet-platform for older people, which was designed for the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) study. We provide recommendations to design senior-friendly web-based applications for a new approach to multicomponent cardiovascular prevention.

Methods The development of the platform followed five phases: (1) conceptual framework; (2) platform-concept and functional design; (3) platform-building (software and content); (4) testing and pilot study; and (5) final product.

Results We performed a meta-analysis, reviewed guidelines for cardiovascular diseases and consulted end-users, experts and software developers to create the platform-concept and content. The software was built in iterative cycles. In the pilot study, 41 people aged ≥65 years used the platform for 8 weeks. Participants used the interactive features of the platform and appreciated the coach-support. During all phases adjustments were made to incorporate all improvements from the previous phases. The final platform is a personal, secured, and interactive platform supported by a coach.

Discussion When carefully designed, an interactive internet-platform is acceptable and feasible for use by older people with basic computer skills. To improve acceptability by older people, we recommend involving the end-users in the process of development, to personalise the platform and to combine the application with human support. The interactive HATICE platform will be tested for efficacy in a multinational randomised controlled trial (ISRCTN48151589).
INTRODUCTION

In the last decade, the development of web-based applications has expanded dramatically.1 A concurrent development in medicine is the promotion of patient-centred care and self-management.2 3 Web-based applications fit in this trend. They are a useful medium for patient-education, stimulation of behaviour change and enhancement of self-management. In addition, web-based interventions can be implemented on wide scale at low-cost and allow for tailoring, interactivity, and interpersonal communication and provide anonymity.4 5 This renders web-based interventions suitable to target common healthcare problems with high costs such as cardiovascular disease.

Web-based interventions targeting single cardiovascular risk factors in adult populations have shown to be effective.6-9 However, cardiovascular prevention guidelines recommend a comprehensive approach of the total cardiovascular risk profile.10 11 It is currently unknown whether web-based interventions targeting multiple risk factors are also effective.

With global ageing, older people form an important target population for cardiovascular prevention. Few web-based applications for cardiovascular risk management focus specifically on older people.12 13 The number of people aged 65-74 in the European Union using internet increased from 20% in 2009 to 42% in 2015, illustrating the high potential of web-based interventions in older populations. Since older people read, use and understand websites differently than young people, a thorough design process is required to ensure that a web-based application truly fits this older audience.14-16 In this article we aim to describe the full development, from idea to piloting and implementation, of an interactive internet-platform for older people to improve their cardiovascular risk profile through a multicomponent prevention strategy. We describe all development phases to facilitate others in building on our experiences and move the development of web-based applications further. In addition, we provide recommendations to design senior-friendly web-based applications for multicomponent cardiovascular prevention. This platform is especially designed for the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) trial.17 This is a pragmatic, multinational, multicentre, prospective, randomised, open-label blinded endpoint (PROBE) trial with 18-month intervention and follow-up. The aim of the HATICE trial is to evaluate the effectiveness of the interactive internet-platform to improve the cardiovascular risk profile of older people with elevated cardiovascular risk.

With global ageing, older people form an important target population for cardiovascular prevention. Few web-based applications for cardiovascular risk management focus specifically on older people.12 13 The number of people aged 65-74 in the European Union using internet increased from 20% in 2009 to 42% in 2015, illustrating the high potential of web-based interventions in older populations. Since older people read, use and understand websites differently than young people, a thorough design process is required to ensure that a web-based application truly fits this older audience.14-16 In this article we aim to describe the full development, from idea to piloting and implementation, of an interactive internet-platform for older people to improve their cardiovascular risk profile through a multicomponent prevention strategy. We describe all development phases to facilitate others in building on our experiences and move the development of web-based applications further. In addition, we provide recommendations to design senior-friendly web-based applications for multicomponent cardiovascular prevention. This platform is especially designed for the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) trial.17 This is a pragmatic, multinational, multicentre, prospective, randomised, open-label blinded endpoint (PROBE) trial with 18-month intervention and follow-up. The aim of the HATICE trial is to evaluate the effectiveness of the interactive internet-platform to improve the cardiovascular risk profile of older people with elevated cardiovascular risk.
METHODS

The concepts of the platform were developed by the HATICE-consortium. Close interaction between academic researchers and software builders was key in the development phase. Important spearheads were to design a generic platform that is widely implementable and easily adaptable to different countries and primary care systems. Simultaneously, it should serve as the electronic database for data collection and storage and comply with all security and privacy regulations for good clinical practice. The HATICE trial, including the platform, 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. The platform was developed following five phases as shown in Figure 1.

Figure 1 Phases of platform development

Phase 1: Conceptual framework
We based the conceptual framework of the interactive internet-platform on Bandura’s social-cognitive theory for self-management and behavioural change and its practical elaboration in the computerised self-regulatory system. Successful behavioural change and its maintenance depend on self-efficacy, managing outcome expectations, setting goals and dealing with barriers. In this system, people are supported in the development of self-regulatory skills in a blended way; by a computer platform and a person serving as online coach. The computer platform can provide an environment for learning, goal setting, action planning and progress monitoring. The coach evaluates what people are doing within the platform and provides feedback.

We based the HATICE platform on this theory, by combining a web-based interactive platform for self-management with a personal coach. This coach uses motivational...
interviewing techniques and the stages of change model as tools to provide feedback and stimulate behavioural change in a cyclic manner (Figure 2). We used Michie’s taxonomy for standardised definitions of the behaviour change aspects in our intervention.

Figure 2 Cycle of self-management supported by the platform and coaching
Numbers correspond with the definitions of behaviour change techniques from Michie’s taxonomy

Phase 2: Platform concept and functional design
We performed a systematic literature review and meta-analysis on the effectiveness of internet-interventions targeting cardiovascular risk factors in older people. In parallel, we conducted fourteen 4-hour brainstorm sessions with academic researchers and software developers to elaborate our concept and the functional design of the platform. We made schematic visualizations of the functionalities and architecture of the platform (wireframes). We discussed this first concept with an expert in health communication among older people, an expert in online lifestyle change, an expert in preventive cardiology and representatives of patient-organizations (Dutch Heart Foundation and the Dutch and Finnish Alzheimer Association).

We organised a total of 10 focus groups with people resembling the target population for the HATICE trial and nurses with experience in cardiovascular risk management in the three countries where the trial will take place (the Netherlands, Finland,
France). To resemble the target population, people had to be older and have elevated cardiovascular risk and basic computer skills. The participants and nurses were recruited from centres that participated in previous randomised controlled trials (RCTs) on cardiovascular risk prevention. During these focus groups, we discussed how an internet-platform could help people improve their lifestyle and which functions the platform should offer. We incorporated the results of the meta-analysis, expert meetings and focus groups into the final version of the functional design.

**Phase 3: Building**

*3a: Generating the platform content*

A prerequisite for platform content was that all information had to be evidence-based. We evaluated the European, French, Finnish and Dutch clinical guidelines on cardiovascular prevention and risk management\(^{23-27}\) and developed generic modules for cardiovascular risk profile evaluation, lifestyle support and pharmacological recommendations. To address the complete cardiovascular risk profile, the intervention focused on seven modifiable cardiovascular risk factors (hypertension, dyslipidaemia, diabetes mellitus, overweight, lack of physical exercise, smoking and unhealthy nutrition).\(^{28}\) We aimed to combine interactive modules with static information, both with a strong focus on self-management.

*3b: Building the platform-software*

The final version of the functional design served as the basis to build the platform-software. Software was built using Scrum, an agile software development method in which small parts of the software are built in iterations.\(^{29}\) We worked in semimonthly planning cycles in which functionalities of the platform were agreed on, developed by the software developers, tested by both developers and researchers and subsequently released. A secure hosting environment was created that complied with strict Good Clinical Practice\(^{29}\) privacy regulations covered within the local NEN 7510 standard.\(^{29}\)

*3c: Building the platform for the control-condition of the HATICE trial*

In the HATICE RCT, the interactive internet-platform will be compared to a control condition. Therefore, we built a separate control-platform. This platform only contains static information modules on the seven cardiovascular risk factors and lacks all (inter)active and self-management features of the interactive internet-platform. There will be no coach support for the control group.

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Phase 4: Testing and evaluation
Prior to the pilot we performed two testing sessions with Dutch older people representative for the target population. Using the thinking aloud principle\textsuperscript{30}, assignments were given to the participants. Tasks included for example: (1) find the website using the Uniform Resource Locator (URL) and log on, and (2) prioritise a risk factor and make a related healthy lifestyle goal. Problems discovered during the test sessions were solved and improvements were incorporated in the platform.

Pilot methodology
The pilot took place in the three countries to test acceptability and feasibility of the intervention and control platforms and the complete study logistics. Detailed study logistics and complete inclusion criteria of the HATICE trial are published elsewhere.\textsuperscript{17} Participants were aged $\geq 65$ years and had an elevated risk for cardiovascular disease and basic computer skills.

After eligibility screening, the participants visited the research nurse. They received a welcome email with their sign in details, a short explanation of the platform and a paper manual. Randomisation took place during the visit in a 2:1 ratio. We chose to oversample the intervention group because the main aim was to test the interactive intervention platform. After randomisation, participants assigned to the intervention group, made lifestyle improvement goals and received coach-support. Participants assigned to the control group received access to the static control platform. Follow-up was 8 weeks. After all participants had completed the pilot, an evaluation session was held in each participating country. Participants completed an evaluation questionnaire (Supplementary Appendix 1a+1b) about logistics, usability and acceptability.

Phase 5: End product for RCT
After incorporation of the adaptations identified during the pilot, the platform was considered ready for the RCT.
RESULTS

Phase 1, 2 and 3 (development)
The results from the meta-analysis showed that only few web-based applications are specifically designed for, and tested in, older people. In addition, web-based applications can induce small improvements in the cardiovascular risk profile, with larger effects for blended (computer/coach) interventions.

The brainstorm sessions and expert consultations yielded important insight into specific requirements for a platform for older people, including adaptation of font size and the need for a simple and consistent layout with large buttons. To easily absorb information, older people need the platform to be well-organised which can be enhanced by using basic distinctive colours and simple illustrations. Adaptation of default audio settings to people with hearing impairments is required. A concise site map and a limited number of web pages can facilitate navigation. To prevent loss of motivation, people need to be kept allied to the platform. If people do not login for approximately three weeks, their motivation might already be disappearing. The experts also advised that a memory training game and other interactive features might stimulate motivation to log on.

From all three countries, 40 older people with elevated cardiovascular risk and internet skills participated in the focus group sessions. In addition, seven Dutch nurses experienced in cardiovascular risk management participated in two sessions. The target population indicated that older people like to be able to ask questions to a coach via internet. The platform should have a positive appearance, focussing on health rather than disease, and provide practical and reliable information that is often difficult to find on websites. The nurses felt that, to provide adequate support, some face-to-face contact would be indispensable, and also that the platform had potentially added value in providing continuous support on lifestyle change (manuscript currently being prepared by the HATICE consortium).

Content of the intervention
In line with the suggestion to focus on health rather than disease, we renamed risk factors "health factors". The intervention starts with an evaluation of the personal cardiovascular risk profile, which is generated by the platform from information provided during the study visit. Together with the coach, the participant decides which health factor(s) to prioritise. By doing so, the platform adapts the content of the platform to these health factors and becomes tailored. For each health factor, participants can: (1) set and monitor lifestyle goals; (2) enter health factor-related value in providing continuous support on lifestyle change (manuscript currently being prepared by the HATICE consortium).

Larger effects for blended (computer/coach) interventions.

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measurements (e.g. blood pressure, weight, etcetera); and (3) view informative contents. We created a step-by-step procedure that guides the participant to the process of setting goals (Supplementary Appendix 2). The participant sets a target date for the goal and can choose to receive automated reminders. The participant can write messages to the coach using a secured mailbox within the platform. Apart from the virtual presence of the coach, several other aspects of the intervention stimulate (inter)active participation such as interactive information videos and lifestyle groups (Table 1). The lifestyle groups provide an opportunity to connect with other participants and perform healthy activities together in real life.

To keep participants allied to the platform, the coach is automatically alerted if participants refrain from logging on for more than 3 weeks. The coach will then contact the participant to stimulate motivation.

Table 1 Features that stimulate (inter)active platform use

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interactive information videos</td>
</tr>
<tr>
<td>Goal-setting module (Supplementary Appendix 2)</td>
</tr>
<tr>
<td>Reminder messages on the goal</td>
</tr>
<tr>
<td>Reminder messages for the coach when the platform was not used for 3 weeks by a participant</td>
</tr>
<tr>
<td>Automated feedback messages on measurements with a positive, motivating tone</td>
</tr>
<tr>
<td>Lifestyle groups</td>
</tr>
<tr>
<td>Cognitive training programme</td>
</tr>
</tbody>
</table>

Phase 4 (pilot results)

Study population

Recruitment for the pilot started in September 2014 and follow-up lasted until February 2015. In total, 41 participants were randomised (29 to the intervention group and 12 to the control group Figure 3). Baseline characteristics of the participants are presented in Table 2. The mean age (standard deviation – SD) of the participants was 69 (4.6) years and 44% were male. Almost half of the participants had a history of cardiovascular disease, including myocardial infarction, stroke, transient ischemic attack, peripheral artery disease, or angina pectoris. The mean number (SD) of cardiovascular risk factors was 2.4 (1.1) per participant.

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Figure 3 Pilot flowchart

Recruitment in the Netherlands, Finland and France
304 individuals invited

Screening and study visit

Randomisation 2:1

Intervention platform N=29

Control platform N=12

8 weeks

Evaluation session

Evaluation session

• Sign-in details
• Platform explanation by nurse
• Paper manual

Figure 3 Pilot flowchart

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304 individuals invited

Screening and study visit

Randomisation 2:1

Intervention platform N=29

Control platform N=12

8 weeks

Evaluation session

Evaluation session

• Evaluation questionnaire
• Exchange experiences
### Table 2: Baseline characteristics of all pilot study participants

<table>
<thead>
<tr>
<th></th>
<th>Total N=41*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>69 (4.6)</td>
</tr>
<tr>
<td>Male gender, N (% of total)</td>
<td>18 (44%)</td>
</tr>
<tr>
<td>Education Level*</td>
<td></td>
</tr>
<tr>
<td>Primary, N (% of total)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>Secondary, N (% of total)</td>
<td>17 (42%)</td>
</tr>
<tr>
<td>University, N (% of total)</td>
<td>12 (29%)</td>
</tr>
<tr>
<td>History of CVD, N (% of total)</td>
<td>20 (49%)</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>35 (85%)</td>
</tr>
<tr>
<td>Currently smoking*</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Diabetes Mellitus type 2*</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Dyslipidemia*</td>
<td>25 (61%)</td>
</tr>
<tr>
<td>Overweight*</td>
<td>20 (49%)</td>
</tr>
<tr>
<td>Lack of physical exercise*</td>
<td>14 (33%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of cardiovascular risk factors per participant, N (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

* Two missing values for this variable. 1 Hypertension: ≥140/90 mmHg for participants <80 years, ≥160/90 mmHg for participants ≥80 years, or on blood pressure-lowering agents. 2 Smoking: any kind of tobacco. 3 Diabetes: diagnosed by a general practitioner/specialist or on antidiabetic medication. 4 Dyslipidemia: total cholesterol ≥5.0 mmol/l, LDL-cholesterol ≥2.5 mmol/l, or on lipid-lowering agents. 5 Overweight: body mass index ≥30 kg/m² or waist circumference men ≥102 cm, women ≥88 cm. 6 Lack of physical exercise: below the World Health Organization norm of 150 min of intermediate exercise a week. Abbreviations: CVD, cardiovascular disease; SD, standard deviation. *Intervention group (n = 29) and control group (n = 12) combined.
Patterns of use of the website

Log-ins: The characteristics of platform use are given in Table 3. Participants logged in 357 times in total, of which 282 times by the intervention group and 75 times by the control group.

The coaches logged in 383 times over a total study period of 12 weeks.

Table 3 Feasibility parameters of the pilot study

<table>
<thead>
<tr>
<th>User statistics</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Total log-ins (N=41)</td>
<td>357</td>
</tr>
<tr>
<td>Intervention (N=29)</td>
<td>282 (79%)</td>
</tr>
<tr>
<td>Control (N=12)</td>
<td>75 (21%)</td>
</tr>
<tr>
<td>Total log-ins coach</td>
<td>383</td>
</tr>
<tr>
<td>Total N of messages sent by intervention group*</td>
<td>162</td>
</tr>
<tr>
<td>Total N of messages sent by coach/platform</td>
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</tr>
<tr>
<td>Total N of goals set*</td>
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<tr>
<td>Blood pressure</td>
<td>2</td>
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</tr>
<tr>
<td>Diabetes</td>
<td>0</td>
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<tr>
<td>Exercise</td>
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<td>0</td>
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<tr>
<td>Nutrition</td>
<td>4</td>
</tr>
<tr>
<td>Weight</td>
<td>9</td>
</tr>
<tr>
<td>Total N of measurements entered*</td>
<td>212</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>78</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0</td>
</tr>
<tr>
<td>Exercise</td>
<td>68</td>
</tr>
<tr>
<td>Smoking</td>
<td>0</td>
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<tr>
<td>Nutrition</td>
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<td>Weight</td>
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</tbody>
</table>

* Intervention group only
Messages: The participants sent in total 74 messages to their coach through the platform. The average content of the messages was about their personal goals and how to achieve them. Participants received a total of 162 messages, including tailored messages sent by the coaches and automatic reminders. The average content of the messages from the coaches was an answer to participants’ questions and coaching/motivating the participants in their lifestyle goal.

Goals and measurements: In total, 30 lifestyle improvement goals were set. The majority of the goals were related to improvement of exercise and weight.

A total number of 212 new measurements were entered, mostly pertaining to blood pressure (78), exercise (68), and weight (55). A mean (SD) number of 5.2 (10.3) measurements was entered per participant.

Evaluation session

All pilot participants were invited to the evaluation session and 27 (66%) participants attended. They liked the idea of the platform, but were uncertain what to expect from it. Passwords provided to login for the first time were too difficult. The majority of the participants considered an instruction video necessary. Setting a goal was difficult for participants, although most succeeded with guidance from the coach. Participants appreciated the interactive features of the platform, including goal setting with associated measurement entries and the interactive videos. The information about a healthy lifestyle was appreciated, but the participants liked to print the texts on paper, so an icon to facilitate printing would be useful. The platform did not work optimally with relatively old software and/or hardware. Communication with the coach was very much appreciated and felt very personal to everybody, even though there was no face-to-face contact after the study visit.

Phase 5 (final version of the platform)

The final version of the platform is a secured web-based platform with personalised, secured accounts, where participants can find seven key pages and functionalities as described in Table 4. We have been simplifying the randomly generated passwords. To limit the chances of getting lost on the platform, the navigation structure has been kept as flat as possible. The seven key pages contain functionality that may open a pop-up, but there is no navigation deeper into the platform. The self-monitoring tools and the goal diary have also been simplified.

We have been creating an introduction video to provide more guidance on use of the platform. The platform is now accessible on all computer devices (desktop computer, laptop and tablet) with all major operating systems (Windows®, Mac OS®) and
all major browser software (Internet Explorer®, Edge®, Safari®, Chrome® and Firefox®) including older versions. The final platform has a simple and consistent layout style with large font size, limited use of (different) colours, a static main menu that is visible on every page and clear “return”-buttons. The layout of one of the pages of the platform is shown in Figure 4.

Table 4 Key pages and functionalities of the HATICE intervention platform

<table>
<thead>
<tr>
<th>Platform page</th>
<th>Functionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home page</td>
<td>• Introduction video explaining how to use the platform</td>
</tr>
<tr>
<td></td>
<td>• Overview-homepage to navigate directly to the most important items of the</td>
</tr>
<tr>
<td></td>
<td>platform: personal health priorities, goals, new messages and personal</td>
</tr>
<tr>
<td></td>
<td>lifestyle groups</td>
</tr>
<tr>
<td></td>
<td>• Photograph of the coach</td>
</tr>
<tr>
<td>My health priorities</td>
<td>• Overview of personal health priorities and step-by-step procedure to</td>
</tr>
<tr>
<td></td>
<td>register a measurement</td>
</tr>
<tr>
<td></td>
<td>• Overview of goals and step-by-step procedure to set new goal</td>
</tr>
<tr>
<td></td>
<td>• Overview of achieved goals</td>
</tr>
<tr>
<td></td>
<td>• Summary of personal cardiovascular health profile</td>
</tr>
<tr>
<td>Lifestyle groups</td>
<td>• Personal lifestyle groups</td>
</tr>
<tr>
<td>Messages</td>
<td>• Messages inbox for interaction with coach</td>
</tr>
<tr>
<td></td>
<td>• Overview of other available groups</td>
</tr>
<tr>
<td>Advice and education</td>
<td>• Information, advice and tips and tricks on healthy lifestyle for each</td>
</tr>
<tr>
<td></td>
<td>health factor</td>
</tr>
<tr>
<td></td>
<td>• Educational videos for each health factor</td>
</tr>
<tr>
<td></td>
<td>• Peer-to-peer videos with personal stories of peers on lifestyle change</td>
</tr>
<tr>
<td>News</td>
<td>• Every month a new international or national news item on research highlights,</td>
</tr>
<tr>
<td></td>
<td>facts or activities related to preventive health</td>
</tr>
<tr>
<td>User support</td>
<td>• Help-buttons on every page explaining the users specific functionalities</td>
</tr>
<tr>
<td></td>
<td>• Help-assistance through email and phone</td>
</tr>
<tr>
<td></td>
<td>• In addition, paper instruction manual</td>
</tr>
</tbody>
</table>

Figure 4 Final version of platform – My health priorities/blood pressure – page
DISCUSSION

In this article we described the two years of designing, developing and piloting of an internet intervention platform to improve the cardiovascular risk profile in older people using a multicomponent intervention strategy. The pilot showed that this platform is acceptable and feasible for use by older people. Literature review and the meta-analysis\(^{13}\) revealed that blended web-based applications are associated with larger treatment effects than internet-only applications. Because of that we enhanced the platform with a coach who could communicate with the intervention group by secure interactive messaging in the platform. We think that this personal touch could strengthen motivation and adherence. The expert consultations and focus groups helped us to understand the barriers older people encounter when using the internet. Some barriers, such as readability of the website and privacy concerns were already known from previous research. Other barriers, like difficulty with website navigation and the preference for a positive tone, were new. The pilot enabled us to determine whether our platform had overcome those barriers and revealed new issues such as difficulties with the login procedure. Simplifying the login-procedure seems trivial, but for older people, this can make a huge difference in accessibility.

Over the coming years, the platform described in this article will be tested for efficacy in the HATICE RCT.\(^7\) It is crucial to not only design an evidence-based internet-platform, but to test it in a controlled setting as well. In this time of vast digital expansion, technical developments may outpace the research needed to evaluate them. Therefore, some researchers advocate the use of adaptive trial designs for more flexible form of testing.\(^{19}\) Although this seems appealing, we think that ultimately randomised controlled study designs are required to evaluate clinical effectiveness and utility.

Thorough communication between software developers, researchers and end-users is crucial in understanding each other’s visions and needs. The final platform needs a synthesis of the three different viewpoints (clinical trial setting, software capabilities, and senior friendliness). To accomplish acceptability for older people, we recommend starting with a theoretical backbone, involving the end-users in the entire process of development, and enhancing the application with human support.

If proven effective, the pragmatic design of the HATICE intervention, independent of existing healthcare structures, will facilitate easy and wide implementation throughout Europe. The tailor-made character of the platform is specifically suited to the needs of older individuals and fits with the current trend towards a more personalised and digital approach in medicine.

DISCUSSION

In this article we described the two years of designing, developing and piloting of an internet intervention platform to improve the cardiovascular risk profile in older people using a multicomponent intervention strategy. The pilot showed that this platform is acceptable and feasible for use by older people. Literature review and the meta-analysis\(^{13}\) revealed that blended web-based applications are associated with larger treatment effects than internet-only applications. Because of that we enhanced the platform with a coach who could communicate with the intervention group by secure interactive messaging in the platform. We think that this personal touch could strengthen motivation and adherence. The expert consultations and focus groups helped us to understand the barriers older people encounter when using the internet. Some barriers, such as readability of the website and privacy concerns were already known from previous research. Other barriers, like difficulty with website navigation and the preference for a positive tone, were new. The pilot enabled us to determine whether our platform had overcome those barriers and revealed new issues such as difficulties with the login procedure. Simplifying the login-procedure seems trivial, but for older people, this can make a huge difference in accessibility.

Over the coming years, the platform described in this article will be tested for efficacy in the HATICE RCT.\(^7\) It is crucial to not only design an evidence-based internet-platform, but to test it in a controlled setting as well. In this time of vast digital expansion, technical developments may outpace the research needed to evaluate them. Therefore, some researchers advocate the use of adaptive trial designs for more flexible form of testing.\(^{19}\) Although this seems appealing, we think that ultimately randomised controlled study designs are required to evaluate clinical effectiveness and utility.

Thorough communication between software developers, researchers and end-users is crucial in understanding each other’s visions and needs. The final platform needs a synthesis of the three different viewpoints (clinical trial setting, software capabilities, and senior friendliness). To accomplish acceptability for older people, we recommend starting with a theoretical backbone, involving the end-users in the entire process of development, and enhancing the application with human support.

If proven effective, the pragmatic design of the HATICE intervention, independent of existing healthcare structures, will facilitate easy and wide implementation throughout Europe. The tailor-made character of the platform is specifically suited to the needs of older individuals and fits with the current trend towards a more personalised and digital approach in medicine.
ACKNOWLEDGEMENTS
We would like to thank the HATICE-consortium, Julia van Weert, professor of health communication, Ron Peters, professor of cardiology, Pim Happel, software developer, all participants of the focus groups and testing sessions and the coaches from the pilot study for their contributions to the development of the platform.

Funding
The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 305374.

Author Disclosure Statement
AS reports grants from EU - FP7, grants from EU - JPND, grants from Beaufour Ipsen, and grants from France Alzheimer Association, during the conduct of the study; personal fees from Beaufour Ipsen Pharma, Pierre Fabre, Lilly, Nestlé, Sanofi, Servier; non-financial support from Biogen, Nutrition Santé, Pfizer, Icon; and other from AMPA Association, outside the submitted work.
All other authors have nothing to disclose.
REFERENCES

Chapter 4
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SUPPLEMENTARY MATERIAL

Supplementary appendix 1a: Pilot evaluation questionnaire for control group

Questions to evaluate in Baseline 2 pilot
If you tick an answer with a dotted line, please fill in your explanation

Recruitment
Was the participant information letter clear enough?
  o yes
  o no
If no; what I thought was unclear was: ...................................................

Blood samples
Was it clear to you which laboratory to take blood you should go to?
  o yes
  o No
If no; what I thought was unclear was: ...................................................

Time spent on questionnaires
Was the actual time you spent on a questionnaire in accordance with the time that was indicated at the beginning of the questionnaire?

Mood questionnaire (GDS):
  o Yes, approximately 10 minutes
  o No, approximately ….. minutes

Anxiety questionnaire (HADS-A):
  o Yes, approximately 10 minutes
  o No, approximately ….. minutes

Self-management questionnaire (Partners in Health):
  o Yes, approximately 10 minutes
  o No, approximately ….. Minutes
Physical activity questionnaire (CHAMPS):
- Yes, approximately 10 minutes
- No, approximately …… Minutes

Quality of life questionnaire (EQ5D):
- Yes, approximately 10 minutes
- No, approximately …… Minutes

Disability questionnaire (LLFDI):
- Yes, approximately 10 minutes
- No, approximately …… Minutes

Nutrition questionnaire:
- Yes, approximately 10 minutes
- No, approximately …… minutes

Where all the questions in the questionnaires clear to you?
You can look at all the questionnaires provided on paper. If there was more than one question unclear within one questionnaire, please put this on the dotted line. Also if you want to explain why it was unclear, put this on the dotted line.

Mood questionnaire (GDS):
- Yes, I understood every question
- No, question … wasn’t clear to me

Anxiety questionnaire (HADS-A):
- Yes, I understood every question
- No, question … wasn’t clear to me

Self-management questionnaire (Partners in Health):
- Yes, I understood every question
- No, question … wasn’t clear to me
Physical activity questionnaire (CHAMPS):
- Yes, I understood every question
- No, question … wasn’t clear to me

Quality of life questionnaire (EQ5D):
- Yes, I understood every question
- No, question … wasn’t clear to me

Disability questionnaire (LLFDI):
- Yes, I understood every question
- No, question … wasn’t clear to me

Nutrition questionnaire:
- Yes, I understood every question
- No, question … wasn’t clear to me

Questions to evaluate pilot in feedback session

Logistics
Did your log-in work every time?
- Yes
- No, but it was fixed quite easily
- No, this was a problem

Could you change your password easily?
- Yes
- No, because; .................................................................

Did the screening and baseline assessments take long?
- No, it was perfectly doable
- Yes, it took long, but that was expected and I didn’t mind
- Yes, it took too long, approximately … minutes
Usability of the platform
What did you think about the layout of the portal?
- good
- too crowded
- too bright/plain (put a circle around the one you mean)
- size of the text too small/big (put a circle around the one you mean)
- other: .................................................................

Did you get motivated to change your lifestyle by the information on the platform?
- Yes, it helped me in wanting to change my lifestyle
- No, what I would like to see differently is: .............................................................

Did the following motivate you to change your lifestyle:
Try to give every answer a rank from 1 (did not motivate me at all) to 5 (did motivate me very much)
- The advice and education section
- To see my own results in the platform
- Just the feeling of participating in the study
- The questionnaires
- I didn’t get motivated at all

Acceptability
Do you think the advice and education section was useful?
- Yes, it was useful
- Yes, but in addition to other websites I already know
- No, I do not think it is useful

Which part of the advice and education did you liked most?
- Text
- 5-minute information
- Quiz

How often did you use the platform?
Approximately …… times/month
Is there a way to motivate you to use the platform more often? .................................

Did the platform interest you enough to keep using it?
- yes
- no,
Supplementary appendix 1b: pilot evaluation questionnaire for intervention group

Questions to evaluate pilot in Baseline 2
If you tick an answer with a dotted line, please fill in your explanation

Logistics

Recruitment
Was the participant information letter clear enough?
- yes
- no
If no; what I thought was unclear was:....

Blood samples
Was it clear to you which laboratory you should go to?
- yes
- No
If no; what I thought was unclear was:...............................

Time spent on questionnaires
Was the actual time you spent on a questionnaire in accordance with the time that was indicated at the beginning of the questionnaire?
GDS (10 min):
- Yes, approximately 10 minutes
- No, approximately …… minutes

HADS-A (10 min):
- Yes, approximately 10 minutes
- No, approximately …… minutes

Partners in Health (10 min):
- Yes, approximately 10 minutes
- No, approximately …… Minutes
Development and validation of the HATICE internet-platform

CHAMPS (15 min.):
  o Yes, approximately 10 minutes
  o No, approximately …… Minutes

EQSD (5 min.):
  o Yes, approximately 10 minutes
  o No, approximately …… Minutes

LLFDI (10 min.):
  o Yes, approximately 10 minutes
  o No, approximately …… Minutes

Nutrition (10 min.):
  o Yes, approximately 10 minutes
  o No, approximately …… minutes

Where all the questions in the questionnaires clear to you?

You can look at all the questionnaires provide on paper. If there was more than one question unclear within one questionnaire, please put this on the dotted line.

GDS:
  o Yes, I understood every question
  o No, question … wasn’t clear to me
.................................................................

HADS-A:
  o Yes, I understood every question
  o No, question … wasn’t clear to me
.................................................................

Partners in Health:
  o Yes, I understood every question
  o No, question … wasn’t clear to me
.................................................................

GDS:
  o Yes, I understood every question
  o No, question … wasn’t clear to me
.................................................................

HADS-A:
  o Yes, I understood every question
  o No, question … wasn’t clear to me
.................................................................

Partners in Health:
  o Yes, I understood every question
  o No, question … wasn’t clear to me
.................................................................
CHAMPS:
o Yes, I understood every question
o No, question … wasn’t clear to me

................................................................................................................................

EQ5D:
o Yes, I understood every question
o No, question … wasn’t clear to me

................................................................................................................................

LLFDI:
o Yes, I understood every question
o No, question … wasn’t clear to me

................................................................................................................................

Nutrition:
o Yes, I understood every question
o No, question … wasn’t clear to me

................................................................................................................................

Questions to evaluate pilot in feedback session
Logistics
Log-in
Did your log-in work every time?
o Yes
o No, but it was fixed quite easily
o No, this was a problem

Could you change your password easily?
o Yes
o No, because; …………………………………………………………………………
………………………………………………………….

What did you think of the duration of the screening and baseline assessments?
o The duration was fine for me
o It took long, but that was expected and I didn’t mind
Development and validation of the HATICE internet-platform

They both took too long, approximately (screening) …… minutes and (baseline) …… minutes
One of the two took too long: **screening / baseline** (put a circle around the one you mean)

**Usability of the platform**
What did you think about the appearance (layout) of the portal?
- good
- too crowded
- too bright/plain (put a circle around the one you mean)
- size of the text too small/big (put a circle around the one you mean)
- other: ..........................................................

Did you get motivated to change your lifestyle by the information and goal setting on the platform?
- Yes, it helped me in wanting to change my lifestyle
- No, what I would like to see differently is; ..........................................................

Did the following motivate you to change your lifestyle:
*Try to give every answer a rank from 1 (did not motivate me at all) to 5 (did motivate me very much)*
- The coach
- The advice and education section
- To see my own results in the platform
- Just the feeling of participating in the study
- The questionnaires
- I didn’t get motivated at all

How often did you use the platform?
Approximately …… times/month
Is there a way to motivate you to use the platform more often? ..............................

**Acceptability**
Do you think the advice and education section was more useful than the coach?
- Yes, it was more useful than the coach
- No, but it is an addition to the coach
- No, I think only the coach is useful enough
Development and validation of the HATICE internet-platform

Chapter 4

Which part of the advice and education did you like most?
- Text
- 5-minute information
- Quiz
- Video

Did you appreciate the interaction with the coach?
*More than one answer is possible*
- Yes, it helped me to get motivated
- Yes, but I would have liked some more contact
- No, the response was too slow
- No, I hoped to get more personal coaching and advice
- No, I couldn’t find the messages in the platform

What did you think of the example goals?
- good, I found an example that fitted my situation
- good, the examples inspired me to make my own goal
- not good, I could not relate to the examples

Were you motivated to join a lifestyle group?
- yes, doing things together helped me to get motivated
- no, I didn’t like the activities of the lifestyle groups
- Other:....

Did the platform interest you enough to keep using it?
- yes
- no, because:....

Other suggestions for HATICE:
Supplementary appendix 2: Step-by-step procedure for goal setting

Step 1: Selecting a health factor

Step 2: Selecting a goal
- Choose from a list of predefined goals
- Or create your own goal

Step 3: Defining the goal
- Make an action plan
- Set a target date
- Automatic reminders

Step 1: Selecting a health factor

Step 2: Selecting a goal
- Choose from a list of predefined goals
- Or create your own goal

Step 3: Defining the goal
- Make an action plan
- Set a target date
- Automatic reminders
PART II

Engagement of older people in eHealth or nurse-led CVRM

PART II

Engagement of older people in eHealth or nurse-led CVRM
Engaging older people in an internet-platform for cardiovascular risk self-management: a qualitative study among Dutch HATICE participants

Tessa van Middelaar, Cathrien R.L. Beishuizen, Juliette Guillemont, Mariagnese Barbera, Edo Richard, Eric P. Moll van Charante, on behalf of the HATICE consortium
ABSTRACT

Objectives To study older peoples’ experiences with an interactive internet-platform for cardiovascular self-management, to assess which factors influence initial and sustained engagement. To assess their views on future use within primary care.

Design Qualitative semi-structured interview study, with thematic analysis.

Setting Primary care in the Netherlands.

Participants People ≥65 years with an increased risk of cardiovascular disease who used the ‘Healthy Ageing Through Internet Counselling in the Elderly’ (HATICE) internet-platform with remote support of a coach. Participants were selected using a purposive sampling method based on gender, age, level of education, cardiovascular history, diabetes, duration of participation and login frequency.

Results We performed 17 interviews with 20 participants, including three couples. In the initial phase, platform engagement was influenced by perceived computer literacy of the participants, user-friendliness, acceptability and appropriateness of the intervention, and the initial interaction with the coach. Sustained platform use was mainly facilitated by a relationship of trust with the coach. Other facilitating factors were regular automatic and personal reminders, clear expectations of the platform, incorporation into daily routine, social support and a loyal and persistent attitude. Perceived lack of change in content of the platform could work both stimulating and discouraging. Participants supported the idea of embedding the platform into the primary care setting.

Conclusions Human support is crucial to initial and sustained engagement of older people in using an interactive internet-platform for cardiovascular self-management. Regular reminders further facilitate sustained use and increased tailoring to personal preference is recommended. Embedding the platform in primary health care may enhance future adoption.
INTRODUCTION

In view of global ageing and the associated increasing burden of cardiovascular disease (CVD), prevention has become crucial. The effectiveness of preventive interventions is indisputable, even in old age. However, adherence to long-term lifestyle and medication regimens remains a daunting challenge. Average adherence rates for chronic illnesses are as low as 50%. Currently, in several countries, cardiovascular risk management programmes are implemented into primary care and delivered by practice nurses. EHealth, i.e., a method to deliver health services and information using the internet and related technologies, is a promising tool for delivery of prevention. It can enable self-management and improve the reach and sustainability of pre-existing preventive programs. In particular, an eHealth platform combined with human support (i.e., a blended approach) has shown beneficial effects on cardiovascular risk factors.

Previous research on eHealth interventions identified several important influential factors of engagement: personal motivation, incorporation into personal life, and quality of the eHealth intervention. However, it is unclear whether these are the same for initial and sustained engagement. For cardiovascular prevention, sustained engagement seems crucial, as the effectiveness of eHealth interventions on cardiovascular risk factors declines over time, especially after one year follow-up. Also, an eHealth intervention specifically targeted at older people should have a specific age-friendly design. It is important to assess the views of end users of an eHealth intervention to improve its chances of successful implementation.

Our primary aim was to study older peoples’ experiences with an interactive internet-platform for cardiovascular self-management, to assess which factors influence initial and sustained engagement. Our secondary aim was to assess older people’s views on implementation of such a platform in the primary care setting.

METHODS

Setting and participants

This qualitative study with semi-structured interviews was performed among participants of the ‘Healthy Ageing Through Internet Counselling in the Elderly’ (HATICE, ISRCTN48151589) trial. HATICE is designed to investigate whether an internet-platform for cardiovascular self-management can improve the cardiovascular risk profile. People ≥65 years with an increased risk of cardiovascular disease were recruited to participate in HATICE in the Netherlands, Finland and France. Computer illiteracy, defined as the inability to send an email, was an exclusion criteria for the trial.
Through a thorough design and validation process we developed the internet-platform for cardiovascular self-management, adapted to meet the specific requirements of older people. The intervention is based on Bandura’s social-cognitive theory for self-management and behaviour change and incorporated Michie’s taxonomy for standardised definitions of behaviour change interventions. The platform offers blended care by remote support of a health-coach trained in motivational interviewing techniques and the trans-theoretical (or stages of change) model. Participants can send messages and receive feedback from their coaches within the platform. Other functionalities of the platform include the ability to set lifestyle goals, record measurements (e.g., blood pressure, weight), receive information on cardiovascular risk and healthy lifestyle, and subscribe to lifestyle groups. The layout and navigation structure were kept simple to make the platform user-friendly for older people. The content was regularly updated with news items on relevant developments in cardiovascular prevention. The intervention was solely delivered via the platform, except for an initial in-person meeting with their coach at baseline, during which first lifestyle goals were set, and a phone call after 12 months follow-up.

This qualitative sub-study was only performed among Dutch intervention participants. They were purposively sampled on gender, age, level of education, history of CVD, diabetes, duration of participation, and login frequency. Participants that prematurely ended their participation were also invited. Twenty out of 32 participants that were invited by telephone were willing to partake in the interview. Main reasons for people to decline participation were lack of time and too little overall use of the platform, even though we specifically aimed to also include these participants. The HATICE trial and this qualitative sub-study were approved by the medical ethics committee of the Academic Medical Centre in the Netherlands. All participants provided written informed consent.

Data collection

Between July 2016 and January 2017 three researchers (TvM [MD], CB [MD] and Suzanne van Rhijn [MSc]) held semi-structured interviews following an interview guide (Appendix 1), focusing on participant experiences with the platform. We iteratively adapted the interview guide during the data collection period. For example, we decided to separately address initial and sustained use as distinct phases in the engagement and adoption of the intervention, as sustained engagement is especially challenging in lifestyle interventions. During the interviews, participants were asked to log onto the platform to stimulate the discussion. The final part of the interview guide focused on the interaction with regular care, during which participants were asked if they preferred the platform to be incorporated in primary health care.
interviewers all had experience with conducting qualitative interviews. Two of the interviewers (TvM and CB) were involved in the design and maintenance of the platform (the participants were not made aware of this) and one (SvR) in the logistical support of the trial. The interviewers and participants had no professional relationship prior to the interview. Participants were interviewed in private at their homes and the interviews lasted approximately 50 minutes. No repeat interviews were deemed necessary. Interviews were audiotaped and transcribed verbatim and during the interviews field notes were taken.

Coding and analysis
Two researchers (TvM and CB) thematically analysed the transcripts in an iterative process. First, each researcher independently coded transcripts following an inductive approach; next the researchers discussed each other’s codes to achieve inter-observer agreement. Subsequently, the researchers together categorized the codes to generate a structure of main themes and subthemes. Themes were derived from the data and were not hypothesised prior to data collection. At several points during the analysis process results were discussed with other team members to ensure independent interpretation. After the first seven interviews, the interview guide was adapted based on one of these discussions, leading to a better distinction between initial and sustained engagement with the platform. Questions about initial engagement were asked to all participants and about sustained engagement to participants who had been in the study for at least six months. After 17 interviews, data saturation was reached as no new (sub)themes or issues emerged.

RESULTS
We performed 17 interviews with 20 participants (Table 1). Three interviews took place with couples participating in the HATICE trial together, one of which had prematurely dropped out from the trial. The age of the participants ranged from 65 to 84 years. Ten (50%) participants had a history of CVD and six (30%) had diabetes. Length of participation in the trial ranged from short (2-3 months, n=8 [40%]), intermediate (7-11 months, n=6 [30%]), to long (14-17 months, n=6 [30%]).

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Table 1. Characteristics of the participants

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Gender</th>
<th>Age</th>
<th>Education level*</th>
<th>CVD</th>
<th>DM</th>
<th>FU duration (mo.)</th>
<th>Partner partic. in HATICE</th>
<th>Login frequency (per mo.)</th>
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<tr>
<td>1</td>
<td>M</td>
<td>73</td>
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<tr>
<td>2</td>
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<td>+ 0.5</td>
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<td>-</td>
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<td>-</td>
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</tbody>
</table>

*Low education level indicates primary education or lower secondary education; intermediate, upper secondary education and post-secondary non-tertiary education; high, short-cycle tertiary education.

** Interview 7 was performed with participants that had recently (prematurely) ended their participation in HATICE. Nr. indicates number; CVD, history of cardiovascular disease; DM, diabetes mellitus; FU, follow-up; mo, month; partic., participating; M, male; F, female.
Initial platform engagement

User-friendliness for older people

Participants found the layout of the platform clear and simple which facilitated platform use. However they stated that a more attractive platform could have encouraged them to log in more often:

“"You should have a website that makes you think, when you have some spare time at night or in the afternoon, why don’t I just have a look at HATICE." [P8]"

Technical difficulties in using the platform, for example login difficulties, discouraged participants. Also, the notion of being inexperienced or incompetent with a computer or with the internet could hamper exploration of the platform and platform use. Sometimes, participants, together with their coach, found creative ways to use the platform when this was considered difficult:

“"I'm not a computer freak. (…) Once I receive a message then I answer it. And then she [coach] says, you should also complete it in the category that it belongs to [measurement]. To me it is not easy to find that […] But then later I notice that she has neatly entered it [in the measurement functionality]. I think that’s fine." [P12]"

People who regarded themselves as inquisitive or eager to learn said this stimulated them in exploring the different functionalities of the platform.

Coach: the basis for a relationship of trust

For participants, trusting the coach was a prerequisite to talk about their health behaviours and potential lifestyle goals. The in-person baseline consultation with their coach was much appreciated, and formed a basis to build a relationship of trust. If the coach responded quickly and adequately to messages sent after the baseline visit, this stimulated platform engagement:

“"At first I wanted… I really had no… I mean, I was actually curious. I did not think well this will… for me… At a certain moment, also because of her [coach], I immediately received a message back and she stimulated me, she said ‘oh well done’ and I don’t know what more. That made me say, OK I will continue with this." [P12]"
Instead, if messages were not answered timely, participants became discouraged to continue using the platform. Some participants found personal contact through the messaging system insufficient to build a relationship and missed face-to-face or telephone contact.

Usefulness and perceived benefit of the intervention

During their first encounter with the platform, participants tended to focus on a small number of functionalities that appeared useful and relevant, and continued with these over time. This mostly concerned the messaging and measurement functionalities:

“When I receive an email I will go to the website and log in. And then I see what happened [message] and have a look. And sometimes I’m asked to complete a questionnaire and I do that. And other times, as is the case now, I’ll go to the practice nurse; well then I have my blood and urine tested, and I send those along [send results to the coach].” [P16]

Some participants reported affinity with self-management and self-measuring of cardiovascular risk factors. They perceived the measurement functionality as useful and appropriate, facilitating platform use. Conversely, limited affinity with self-management could form a barrier to use this functionality:

“And I absolutely do not want my own blood pressure monitor. I did not want that when it [blood pressure] was too high and I certainly do not want it now that it is too low. Because I get very uh… It will influence me and I don’t want that. I will not make myself crazy.” [P3]

Participants who were aware of their cardiovascular risk status, in some cases because of a previous CVD, deemed the content of the platform relevant. Participants with limited perceived need to improve their lifestyle did not see how the platform could help them and tended to make limited use of it:

“I notice that it’s about CVD. That is all fine, but I don’t have that [history of CVD], so I will not engage any further with it [the platform]. […] Indeed, if I do encounter it [CVD], than I would do it, but at this moment…” [P5]

Participants who already frequently visited their health care professional(s) stated they did not expect important additional benefit. Age also played a role as one of the
oldest participants no longer prioritised adapting a healthier lifestyle because of his old age. Participants rarely adjusted or replaced the goals that were set at baseline. Limited use was made of the suggestions for lifestyle groups; participants expressed several reservations related to this functionality, such as that they thought that signing up created an obligation to participate and that groups would be dominated by older people with very limited functionalities.

**Sustained platform engagement**

*Coach: long-term relationship of trust*

As mentioned above, the coach was important to stimulate initial use of the platform. The coach also appeared pivotal in sustained platform use. If participants felt connected to the coach, participants felt inclined to keep using the platform and adhere to goals for lifestyle changes:

“Yes, because the coach makes you try to accomplish certain things. [...] That would be more difficult without the coach. I don’t know if... every time with the website... no, I don’t think that that would work on its own [platform without coach].” [P9]

The message content was also important; a positive and personal tone could boost someone’s motivation. One interviewee had experienced a change in coach during the trial. He stated this did not clearly change his platform use, although it did negatively impact his connection with the coach.

**Reactive use of the platform**

In many interviews, participants expressed difficulty to take initiative in using the platform, and found it easier to use the platform in a reactive way, e.g. responding to automatic or personal reminders:

“Look, I like to participate in such a study, but... Perhaps I’m a bit more passive, that I think even if I have to have ten visits a year, that is fine. We will have a conversation; I will complete lists; that is all fine. But a website is... to figure things out, and to write things down, that is something... [Interviewer: Maybe you can call that initiative?] Yes I suppose that could be it.” [P14]
Participants who considered themselves as being loyal or persistent noted this stimulated sustained platform use:

“I was told to make contact once a month. And so I… It’s stated here in my iPad: remember HATICE, report! And so we plan to do that.” [P11]

Lifestyle change: expectations and experiences

Being motivated for lifestyle change was a reason to continue using the platform and vice versa. This could be related to the reason to participate in the HATICE trial. Some participants were aware that the trial entailed active participation and hoped that they might benefit from it. Others, who participated to contribute to scientific progress, seemed to expect a more passive participation; i.e. questionnaires or tests for which no self-initiative was required, and were not inclined to use the platform for self-management. Secondly, if people managed to reach their lifestyle goals and experienced its positive effects on their health, this stimulated sustained participation:

“Five kilometre laps. Yes, that is the minimum distance that I would like to walk each time. And I can achieve that quite nicely. And in that, I noticed that I started to feel healthier. That was really surprising. I always thought that I would stumble along through the rest of my life. And now I can… you get more fit. You have more enthusiasm to tackle things.” [P14]

In contrast, some participants felt setting a goal was an unpleasant burden. If they did not manage to reach their goal, they refrained from registering this on the platform or informing their coach, also, because they felt embarrassed or demotivated:

“You get sort of forced to… Because you had to make certain promises, like ‘I will make sure to exercise so many times a day’ and ‘I will make sure I will lose weight’. Those kinds of things. Yes, that went against my gut feeling. […] You were sort of embarrassed if you said, well I actually did not do anything.” [P7]

Participants appreciated the automatic feedback on entered measurements as it gave a reassuring feeling of having their health monitored. This facilitated regular logging in.
Incorporation into daily routines

Participants said that it was easier for them to keep using the platform if they had incorporated their platform use into their daily or weekly routine:

“Yes I like it. It works as a sort of support. In life you have all kinds of support systems, with your habits and your things, and this is one of them. It has become a part of… Yes well sometimes I can use it and sometimes I can’t. But it has become a part of everything.” [P2]

Disruption of daily routines, such as illnesses, negatively affected platform use. Social support, on the other hand, was an incentive for sustained use. This was especially true for couples participating in the HATICE trial together:

“I said, ‘We should do something.’ Then I started to fill those [questionnaires] in. And I said, ‘Are you going to do that?’ [Response partner:] ‘Yes I will do that, but I am very busy.’ I said, ‘It will only take a minute.’” [P10]

Another important factor that facilitated platform-adherence was that the platform could improve the perceived continuity of support in self-management. In contrast to nurse-led periodic consultations, which are typical of secondary cardiovascular prevention programs, the platform felt like a source of continuous support that they could direct to any time:

“I already visit the practice nurse, but there is a lot of time in between [visits] and then yes… Of course together we assess the results, look at it and discuss it. But when I’m gone, it [the support] is also gone. Unless, of course, it turns out that I have to… that it’s not quite OK. But then it’s gone again. And this is, the continuity that you’re always working on it, that is good.” [P2]

Some participants found using the platform was time-consuming, which worked as a barrier. This could occur because of the misconception that they were obliged to regularly add measurements. In contrast, if participants felt the platform did not take too much of their time they were inclined to keep using it.
Perceived lack of change in the platform

Most participants were not aware of any changes made to the platform content, although others noted that news items were regularly updated. While several participants appreciated the stable content, others would have liked to see more changes over time, to stimulate their sustained engagement:

“Well I read that [information on cardiovascular risk] a little in the beginning and then that is that. Well now... And that does not change. I’m almost certain that this is the same as it was 1,5 year ago. [...] So that is not inviting; to keep looking if there is something new.” [P15]

The coach could influence this by varying the themes of conversation.

Future implementation

Participants indicated that the level of incorporation into the regular health care system was limited, and therefore some of them felt the platform had no clear added value on top of the nurse-led cardiovascular risk management they already received within the primary health care. Regarding future implementation, participants felt positive toward incorporation of the platform into the existing primary care structure. Especially if the practice nurse were to become their coach, thus contributing to continuity of support, and if all measurements performed at home, and within primary and secondary care were integrated into the platform:

“The visit to the practice nurse is of course the real measurement. So I feel it’s important to keep that, because it monitors your health, or at least a part of your health. That is important. But if all those measurements could be incorporated into this study, that would of course be very positive, because than you can compare it over several years or you can use it to look things up.”[P9]

A concern of some of the participants was that this incorporation would lead to substitution of valued, in-person contacts with health care professionals by more anonymous exchange of messages via the platform. A participant suggested to add regular in-person visits with measurements to increase motivation, as a solution.
DISCUSSION

Summary
We have found that the support of a coach is crucial to initiate and sustain engagement of older people with an interactive internet-platform for cardiovascular self-management. Factors associated with initial platform engagement are perceived computer literacy, usability and anticipated benefits of the platform, with special attention to the computer skills and preferences of older people. Factors associated with sustained platform engagement are regular automatic and personal reminders, clear expectations, incorporation into daily routine, and social support (Box 1). Incorporation into primary healthcare could facilitate implementation of the platform and could improve the perceived continuity of support in self-management.

<table>
<thead>
<tr>
<th>Initial platform use</th>
<th>Sustained platform use</th>
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<tbody>
<tr>
<td>User-friendliness for older people</td>
<td>Coach: long-term relationship of trust</td>
</tr>
<tr>
<td>• Layout: simplicity, attractiveness (+/-)</td>
<td>• Personal connection (+)</td>
</tr>
<tr>
<td>• Technical difficulties (-)</td>
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</tr>
<tr>
<td>• Perceived computer literacy (+/-)</td>
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<tr>
<td>Coach: the basis for a relationship of trust</td>
<td>Reactive use of the platform* (+)</td>
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<tr>
<td>• In-person baseline consultation (+)</td>
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<tr>
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<tr>
<td>Usefulness and perceived benefit of the intervention</td>
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</tr>
<tr>
<td>• Affinity with platform functionalities (including self-management) (+/-)</td>
<td>• Setting a goal is burdensome (-)</td>
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<tr>
<td>• Awareness of cardiovascular risk (+/-)</td>
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<td>• Motivation for lifestyle change with increasing age (-)</td>
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<tr>
<td></td>
<td>• Incorporation into daily routine (+/-)</td>
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<td></td>
<td>Perceived lack of change in the platform (+/-)</td>
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Box 1 Themes and subthemes identified in the interviews of the facilitators (+) and barriers (-) in initial and sustained platform use
*Reactive use indicates the preference of participants to use the platform in response to automatic or personal reminders.
Chapter 5

Strengths and limitations
The main strength of our study is that through our purposive sampling method we included both participants with a short, intermediate and long follow-up duration. This contributed to a clear distinction in motives for initial and sustained engagement. We used an iterative analysis method with multiple analysis rounds and adaptation of the interview guide throughout the process. Also, we followed the consolidated criteria for reporting qualitative research (COREQ) guidelines to facilitate reproducibility of study results. A limitation of our study is that we only interviewed Dutch participants, potentially limiting the scope to the Dutch health care setting. Furthermore, the sample is prone to bias as our participants were willing to partake in both the HATICE trial and our qualitative sub-study. This could have led to selection of people with a relative positive view on the intervention and with a high education level. We minimised this potential bias by purposively sampling participants on education level and login frequency. Another possible source of bias is the fact that two of the interviewers and researchers analysing the data were involved in the development and maintenance of the platform. This could have influenced the intonation of questioning and interpretation of the data, however their knowledge of the platform could also have stimulated the discussion. Independent analysis was ensured by incorporation of several analysis rounds with other team members.

Comparison with existing literature
Part of our results are in line with previous studies on engagement with eHealth interventions, such as on the influence of usability, perceived benefit and expectations of the intervention and the incorporation into personal life. A new finding that is especially relevant for eHealth interventions on cardiovascular prevention is the crucial role of continuous support by a coach for sustained engagement. This has previously been described in a non-digital multi-domain preventive intervention. In our study, the initial in-person contact was important to establish a relationship of trust between the participant and coach. For most people maintenance of this relationship via a messaging system appeared to work well for a longstanding personal connection. The importance of this kind of blended care is emphasised by a meta-analysis showing a more pronounced effect on cardiovascular risk reduction. Despite the use of motivational interviewing techniques and coaches following the trans-theoretical model, it was difficult to engage people with a low perceived benefit of the intervention. In general, motivational interviewing techniques delivered through eHealth have proven effective in inducing behavioural changes. Nevertheless, a complete in-person approach might be preferable for participants in the pre-contemplation phase, when there is no intention to change behaviour, as even reading information about cardiovascular risk would be preferable for participants in the pre-contemplation phase, when there is no intention to change behaviour, as even reading information about cardiovascular risk.
A tailored platform
Our study shows that many aspects of multi-domain eHealth interventions rely heavily on personal preferences. The HATICE platform has been adjusted to the need for a personalised platform, by not imposing any obligations on which functionalities to use and giving participants the opportunity to tailor the frequency of automatic reminders to personal preferences. However, during the interviews, it appeared that people prefer an even more personalised platform. For instance, engagement was dependent on personal preference with regard to how much the content of the platform changes over time and the complexity of the platform changes, affinity with self-measurement, whether or not confrontation with lifestyle goals was appreciated, the ideal amount of time invested, and the optimal frequency of reminders. As suggested by Bandura et al. it might be useful to tailor the platform content and the way it is provided based on a participants readiness to change. This could for example be incorporated in a self-learning system that automatically tailors to personal characteristics, stages of change, needs and wishes.

Implications for practice
During the HATICE trial, the platform was offered independently from regular care. Participants mentioned this separation as a barrier to platform use and agreed with the suggestion to incorporate it into the current primary care structure. Preventive eHealth interventions provide the opportunity to optimize continuity in support of self-management and reach individual targets with limited resources. In addition, implementation may improve sustained engagement with such an intervention. Suggestions for this incorporation are to have the practice nurse work as coach, link measurements from electronic health records directly to the platform, and align
this with additional in-person visits for nurse-led cardiovascular risk management. Nevertheless, opportunities to implement the platform probably differ based on the health care system. It is therefore crucial to properly evaluate the health care context and views of end-users and health care professionals to support successful implementation. Especially in health care systems with long distances or low resources, a preventive eHealth intervention may provide opportunities to improve existing preventive care.
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Competing interest

None to declare.

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REFERENCES


Engaging older people in an internet-platform for cardiovascular risk self-management


Interview guide

Opening question: Could you tell me about your experiences with the HATICE platform?

1. Use, experiences and opinion about the platform

General
Did you ever log onto the platform? What pages do you usually visit when you are logged on? What do you use the most and why? What don’t you use and why? What do you think about the platform? Does the platform motivate you to change your lifestyle? Why?

Baseline
Why did you choose to participate in HATICE? Did your coach introduce you to the platform during the second visit? What did the coach mention about the platform? What was your first impression? What were you expectations of the platform? What was expected of you?

Initial phase
What were your first experiences with logging onto the platform? What parts of the platform did you use then? What appealed you to use the platform? And what repelled you to use the platform?

Adherence phase
How is that now? Do you use the platform differently now in comparison to the beginning? Why? Are there things that could have increased your use of the platform? If it would be possible, would you keep using the platform after the study ended? Why?

Coach
How do you experience the contact with your coach? What do you like? What don’t you like? Do you feel that the coach is of added value to the platform? Would you prefer having telephone contact with your coach?

2. Interaction with regular care

Do you feel that the platform is of added value to regular care? To what extend? Have you consulted your general practitioner/practice nurse about the platform (or are you going to)? Why? Would you like it if the general practitioner/practice nurse had insight into data from your personal platform? Why? If yes, what data would you like to share and what not? (If applicable) Are there advantages or disadvantages to the platform in comparison to the care of your practice nurse?
Determinants of dropout and non-adherence in a dementia prevention randomised controlled trial: the Prevention of Dementia by Intensive Vascular Care Trial


ABSTRACT

Objectives To explore and compare sociodemographic, clinical and neuro-psychiatric determinants of dropout and non-adherence in older people participating in an open label cluster-randomised controlled trial - the Prevention of Dementia by Intensive Vascular care (preDIVA) trial - over 6 years.

Design Secondary analysis.

Setting 116 general practices in the Netherlands.

Participants Community-dwelling individuals aged 70-78 years (N=2,994).

Intervention Nurse-led multidomain intervention targeting cardiovascular risk factors to prevent dementia.

Measurements The associations between participant baseline sociodemographic (age, sex, education), clinical (medical history, disability and cardiovascular risk) and neuro-psychiatric (depressive symptoms (Geriatric Depression Scale-15) and cognition (Mini-Mental State Examination)) characteristics and dropout from the trial and non-adherence to the trial intervention were explored using multilevel logistic regression models.

Results Higher age, poorer cognitive function, more symptoms of depression, and disability were the most important determinants of dropout of older people. The presence of cardiovascular risk factors was not associated with dropout but was associated with non-adherence. Being overweight was a risk factor for non-adherence, whereas people with high blood pressure or a low level of physical exercise adhered better to the intervention. The association of poorer cognitive function and symptoms of depression with dropout was stronger in the control group than in the intervention group, and vice versa for increased disability.

Conclusion In a large dementia prevention trial with 6-year follow-up, dropout was associated with higher age, lower cognitive function and symptoms of depression and disability at baseline. These findings can help to guide the design of future dementia prevention trials in older adults. The associations we found between cardiovascular risk factors and non-adherence need to be confirmed in other older populations receiving cardiovascular prevention interventions.
INTRODUCTION
Participation of older people in longitudinal research is a long recognised challenge. Older persons are often excluded from medical intervention trials because of comorbidity and greater risk of death leading to high all-cause dropout rates. However, with global population ageing and rising interest in healthy ageing, older people are becoming important subjects for intervention studies. In the field of dementia research, prevention trials are increasingly being performed. Midlife cardiovascular risk is strongly associated with an increased risk of developing dementia in later life, and is therefore used as treatment target in dementia prevention trials. The combination of aged population and long follow-up periods makes these trials prone to high dropout rates. Furthermore, adherence to cardiovascular prevention programs is generally low and therefore adherence to complex interventions by older people who continue participation in trials is an additional challenge.

High dropout rates affect the internal and external validity of study results and may induce biased outcomes because dropout is rarely completely random. Non-adherence is not random either and is particularly troublesome if people with the highest cardiovascular risk drop out. Mechanisms leading to both dropout and non-adherence may affect dementia prevention trials, hampering the straightforward interpretation of study results and the efficacy of the interventions. Better understanding of the mechanisms could help to reduce dropout and non-adherence in future intervention studies.

Dropout could potentially be prevented if its determinants were better understood. In intervention studies with older people, higher age and cognitive impairment are the only factors consistently associated with dropout. For other factors, including lower educational level, lower socio-economic status, comorbidity, lower self-rated health, depression, allocation to the control group and male sex, findings are inconsistent. Determinants of non-adherence to cardiovascular prevention programs have been mostly studied in the context of secondary prevention. Younger age, higher depression scores, lower beliefs in treatment benefits and logistic aspects such as distance to the program location have been most consistently associated. Findings for the cardiovascular risk load as a determinant for adherence are inconsistent.

The aim of the current analysis was to assess sociodemographic, clinical and neuropsychiatric determinants of dropout and non-adherence in a randomised controlled trial (RCT) of a nurse-led multidomain intervention targeting cardiovascular risk factors to prevent dementia. Potentially preventable dropout was focussed on. Determining groups at high risk of dropout or non-adherence can help to improve the design of future dementia prevention trials.

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Methods

Study background and participants
The Prevention of Dementia by Intensive Vascular care (preDIVA) trial was a cluster RCT with 6-year intervention and follow-up in a primary care setting. Briefly, the study assessed the effects of nurse-led intensive vascular care on prevention of dementia in a sample of 3,526 community-dwelling elderly adults. Primary outcomes were incident dementia and disability. All persons from 116 participating general practices aged 70-78 without a diagnosis of dementia or conditions impeding long-term follow-up were eligible and were invited to participate; 53% consented to participate. Participants were randomised to the intervention (nurse-led intensive vascular care) or control (usual care) group. The intervention consisted of consultations every four months with the practice nurse at the general practice for assessment of the cardiovascular risk profile (blood pressure, weight, smoking habits, diet and physical activity). Based on these assessments, and following a protocol adhering to the Dutch primary care cardiovascular risk management guidelines, the practice nurse provided customised lifestyle advice and optimised cardiovascular medical treatment. Outcome assessments took place at every other year. The medical ethical committee of the Academic Medical Centre, University of Amsterdam, The Netherlands, approved the study protocol (trial registration: ISRCTN29711771). All participants provided written informed consent.

Definitions of dropout and non-adherence
Dropout was defined as leaving the study before the final 6-year visit. Time of dropout was defined as the moment from which onwards no subsequent study visits were attended. Trial-completion was defined as having participated in the trial until the final visit. Participants who dropped out due to death or dementia were excluded from all analyses, because these were predefined study outcomes and this analysis focused on determinants of preventable causes of dropout. Non-adherence to the trial intervention was defined as not having attended on average at least two out of three yearly intervention visits (66%) during participation in the trial (recorded at the evaluation visits every other year).

Measurements
Associations between dropout, non-adherence and baseline sociodemographic characteristics (age, sex, level of education), symptoms of depression, cognition, disability, comorbidity and cardiovascular risk factors were explored. Education was categorised as low (< 7 years), intermediate (7-12 years) and high (> 12 years). Symptoms of depression were assessed using the 15-item Geriatric Depression Scale.
Determinants of dropout and non-adherence in a dementia prevention RCT

Scale (GDS-15). The apathy subdomain within the GDS-15 (GDS-3a) was also examined because apathy is a potential risk factor for withdrawal from clinical care. To disentangle apathy symptoms from depressive symptoms, the associations with the remaining 12 depression items (GDS-12d) were simultaneously assessed. Cognition was assessed with the Mini-Mental State examination (MMSE). Disability was assessed with the Academic Medical Centre Linear Disability Score (ALDS), a linear disability scale ranging from 0 to 100 on which higher scores indicate better functioning. Scores on all scales were included as continuous variables. History of myocardial infarction, stroke and type 2 diabetes mellitus and were assessed by interview and cross-checked in electronic medical records. Individual cardiovascular risk factors were operationalised as follows: high systolic blood pressure (≥ 160mmHg); high total cholesterol (≥ 6.5mmol/l); overweight (BMI ≥ 30kg/m²); active smoking, alcohol intake (none, moderate (0-1 unit/day for women and 0-2 unit/day for men) and high (>1 unit/day for women and > 2 units/day for men)) and a low level of physical exercise (< 150 minutes per week), measured by self-report using the Longitudinal Ageing Study Amsterdam (LASA) physical activity questionnaire.

Statistical analysis

The dropout analyses included both the intervention and control groups (studied both combined and separately). The analyses on non-adherence were performed only in the intervention group. Dropout and non-adherence patterns were assessed over time by calculating dropout and non-adherence rates for the entire study period and for each 2-year period between the outcome evaluation visits. Dropout rates were calculated by dividing the number of people who dropped out during the study period of interest by the number of active participants at the beginning of that study period. Non-adherence rates were calculated by dividing the number of non-adherent intervention participants in a study period of interest by the total number of active intervention participants during that study period.

Which variables were associated with dropout and non-adherence was first explored by running multilevel univariable logistic regression models for each of the two outcomes. A multilevel approach with random intercepts for general practice and healthcare centre was used because of the cluster design of the trial. Next, independent associations were assessed in multilevel multivariable logistic regression analyses using a backwards stepwise method. All co-variables were included in the initial multivariable models, given the inconsistent previous reports. Co-variables were manually removed one by one in order to obtain the most parsimonious model, allowing for a maximum 20% change in b-coefficients and for no significant difference at the 5% level in log-likelihoods between each step.

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Last, two sensitivity analyses were performed. To evaluate the robustness of the final multivariable models, they were reran in the samples of cases with complete data for only the co-variables maintained in the final multivariable models. These samples contained more cases than the samples used for the main multivariable analyses, because of the smaller set of co-variables for which data needed to be complete. To explore whether the timing of dropout was associated with different determinants, we reran the final multivariable regression models in subgroups of early and late dropout. Early dropout was defined as dropout between randomisation and the 2-year follow-up visit, and all other dropouts were considered late dropout. All analyses were performed with SPSS version 22 and STATA version 13.1 and only complete data were used.

RESULTS

Study participants

Of the 3,526 participants randomised in the preDIVA trial, 2,994 were included in the current analyses on dropout (Figure 1); 532 people were excluded from the analyses.

Figure 1: Study flowchart with selection of active participants and dropouts for the analysis

Abbreviations: GP; general practitioner
because they dropped out due to death (n = 354, 10%) or dementia (n = 146, 4%) or they had an unclear dropout-status (n=32, these participants stopped participating but did attend the final study visit upon invitation). The primary analysis of the preDIVA trial also included cases of dementia and death occurring after dropout, explaining the lower numbers reported here. Of the people included in the current analyses, 1,869 (53%) people participated until the final 6-year visit and 1,125 (37%) people actively dropped out for various reasons (listed in Figure 1). Data on adherence status were available for 1,293 people in the intervention group, 286 (22%) of whom were non-adherent. Adherence data were missing for 322 participants who dropped out prior to the 2-year outcome assessment, so these participants could not be included in the non-adherence analyses. Figure 2 shows the dropout and non-adherence rates during study follow-up. Whereas the dropout rate was highest in the beginning of the trial and thereafter declined, non-adherence appeared to increase over time.

Figure 2 Dropout and non-adherence rates during study follow-up

* Dropout rates were calculated by dividing the number of people that dropped out during the study period of interest by the number of active participants at the beginning of that study period.
§ Non-adherence rates were calculated by dividing the number of non-adherent intervention participants in a study period of interest by the total number of active intervention participants during that study period.
Adherence data were missing for participants that dropped out prior to the 2-year study visit, so these participants could not be included in the non-adherence analyses.

Baseline characteristics

Table 1 shows the sociodemographic and clinical characteristics of the completers and dropouts in the control and intervention groups, and table 2 shows the characteristics of the non-adherent and adherent participants. The differences between all groups were small. Mean age of the total study population was 74.3 years (SD 2.5) and 56% were female.
Table 1 Baseline characteristics of the dropouts and the completers, split by randomisation group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group (n=1,379)</th>
<th>Intervention group (n=1,615)</th>
<th>p-value*</th>
<th>Control group (n=1,379)</th>
<th>Intervention group (n=1,615)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Dropouts (n=318 (23%))</td>
<td>Completers (n=901 (62%))</td>
<td>N</td>
<td>Dropouts (n=677 (41%))</td>
<td>Completers (n=1,038 (64%))</td>
</tr>
<tr>
<td>Sociodemographics</td>
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</tr>
<tr>
<td>Age, mean (SD)</td>
<td>1,379</td>
<td>75 (3)</td>
<td>74 (2)</td>
<td>0.001</td>
<td>1,615</td>
<td>75 (2)</td>
</tr>
<tr>
<td>Gender (fem) (n,%):</td>
<td>1,379</td>
<td>283 (69%)</td>
<td>478 (63%)</td>
<td>0.049</td>
<td>1,615</td>
<td>340 (63%)</td>
</tr>
<tr>
<td>Education (n, %):</td>
<td>1,357</td>
<td>0.013</td>
<td>1.605</td>
<td>0.019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- low</td>
<td>138 (27%)</td>
<td>175 (21%)</td>
<td>154 (20%)</td>
<td>21 (22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- intermediate</td>
<td>406 (70%)</td>
<td>549 (62%)</td>
<td>369 (61%)</td>
<td>640 (65%)</td>
<td></td>
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<tr>
<td>- high</td>
<td>62 (12%)</td>
<td>127 (15%)</td>
<td>74 (12%)</td>
<td>145 (14%)</td>
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</tr>
<tr>
<td>Medical history and comorbidity</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>- heart disease, n, %</td>
<td>1,367</td>
<td>158 (31%)</td>
<td>210 (25%)</td>
<td>0.048</td>
<td>1,606</td>
<td>178 (28%)</td>
</tr>
<tr>
<td>- stroke, n, %</td>
<td>1,363</td>
<td>53 (10%)</td>
<td>70 (10%)</td>
<td>0.162</td>
<td>1,592</td>
<td>58 (10%)</td>
</tr>
<tr>
<td>- diabetes, n, %</td>
<td>1,379</td>
<td>86 (17%)</td>
<td>138 (16%)</td>
<td>77 (15%)</td>
<td>1,615</td>
<td>98 (16%)</td>
</tr>
<tr>
<td>ALDS, median, IQR</td>
<td></td>
<td>88.1 (85.6 – 89.5)</td>
<td>89.5 (87.6 – 89.5)</td>
<td>&lt;0.001</td>
<td>1,605</td>
<td>88.9 (85.8 – 89.5)</td>
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<tr>
<td>Depressive symptoms and cognition</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS-15, median, IQR</td>
<td>1,294</td>
<td>1 (0-3)</td>
<td>1 (0-2)</td>
<td>&lt;0.001</td>
<td>1,520</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>GDS-12D, median, IQR</td>
<td>1,323</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>&lt;0.001</td>
<td>1,549</td>
<td>0 (0-1)</td>
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<tr>
<td>GDS-3A, median, IQR</td>
<td>1,338</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>&lt;0.001</td>
<td>1,570</td>
<td>0 (0-1)</td>
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<tr>
<td>MMSE, median, IQR</td>
<td>1,377</td>
<td>28 (27 – 30)</td>
<td>29 (27 – 29)</td>
<td>&lt;0.001</td>
<td>29 (28 – 29)</td>
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<tr>
<td>Cardiovascular risk profile</td>
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</table>
Table 1 Continued.

<table>
<thead>
<tr>
<th></th>
<th>1,377</th>
<th>206 (40%)</th>
<th>308 (36%)</th>
<th>0.146</th>
<th>1,614</th>
<th>266 (44%)</th>
<th>430 (41%)</th>
<th>0.192</th>
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<tr>
<td>Systolic BP ≥ 160mmHg, n, %</td>
<td>1,356</td>
<td>67 (13%)</td>
<td>137 (16%)</td>
<td>0.159</td>
<td>1,573</td>
<td>80 (3%)</td>
<td>123 (13%)</td>
<td>0.661</td>
</tr>
<tr>
<td>Tot chol ≥ 6.5mmol/l, n, %</td>
<td>1,379</td>
<td>120 (23%)</td>
<td>197 (23%)</td>
<td>0.903</td>
<td>1,613</td>
<td>162 (7%)</td>
<td>244 (24%)</td>
<td>0.262</td>
</tr>
<tr>
<td>BMI ≥ 30kg/m², n, %</td>
<td>1,376</td>
<td>61 (12%)</td>
<td>101 (20%)</td>
<td>0.998</td>
<td>1,612</td>
<td>79 (13%)</td>
<td>111 (11%)</td>
<td>0.235</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1,372</td>
<td>0.064</td>
<td>1.604</td>
<td>0.137</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol intake, n, %</td>
<td>1,349</td>
<td>64 (13%)</td>
<td>84 (0%)</td>
<td>0.185</td>
<td>1,582</td>
<td>98 (17%)</td>
<td>115 (12%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Abbreviations: ALDS, AMC linear disability scale; IQR, interquartile range; GDS-15, geriatric depression scale; GDS-12D, 12 depression items of the GDS-15; GDS-3A, 3 apathy items of the GDS-15; MMSE, mini-mental state examination; BP, blood pressure; tot chol, total cholesterol level; BMI, body mass index.

*p-values derive from Student’s t tests for continuous variables if normally distributed (Age), Mann-Whitney-U tests for continuous variables if distributions are skewed (ALDS, GDS and MMSE) and Chi-square tests for categorical variables.
Table 2 Baseline characteristics of the non-adherent and adherent intervention participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intervention group (n=1,293)*</th>
<th>Non-adherent (n=286 (22%))</th>
<th>Adherent (n=1007 (78%))</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>1,293</td>
<td>74 (2)</td>
<td>74 (2)</td>
<td>0.545</td>
</tr>
<tr>
<td>Gender (fem) (n,% )</td>
<td>1,293</td>
<td>168 (59%)</td>
<td>560 (56%)</td>
<td>0.346</td>
</tr>
<tr>
<td>Education (n, %)</td>
<td>1,288</td>
<td>70 (25%)</td>
<td>217 (22%)</td>
<td>0.370</td>
</tr>
<tr>
<td>- low</td>
<td>70 (25%)</td>
<td>217 (22%)</td>
<td>0.370</td>
<td></td>
</tr>
<tr>
<td>- intermediate</td>
<td>179 (63%)</td>
<td>642 (64%)</td>
<td>0.370</td>
<td></td>
</tr>
<tr>
<td>- high</td>
<td>34 (12%)</td>
<td>146 (15%)</td>
<td>0.370</td>
<td></td>
</tr>
<tr>
<td><strong>Medical history and comorbidity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- heart disease, n, %</td>
<td>1,285</td>
<td>75 (27%)</td>
<td>286 (29%)</td>
<td>0.510</td>
</tr>
<tr>
<td>- stroke, n, %</td>
<td>1,279</td>
<td>25 (9%)</td>
<td>83 (8%)</td>
<td>0.789</td>
</tr>
<tr>
<td>- diabetes, n, %</td>
<td>1,293</td>
<td>47 (16%)</td>
<td>203 (20%)</td>
<td>0.139</td>
</tr>
<tr>
<td><strong>Depressive symptoms and cognition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS-15, median, IQR</td>
<td>1,221</td>
<td>1 (0 - 2)</td>
<td>1 (0 - 2)</td>
<td>0.262</td>
</tr>
<tr>
<td>GDS-12D, median, IQR</td>
<td>1,244</td>
<td>0 (0 - 1)</td>
<td>0 (0 - 1)</td>
<td>0.093</td>
</tr>
<tr>
<td>GDS-3A, median, IQR</td>
<td>1,257</td>
<td>0 (0 - 1)</td>
<td>0 (0 - 1)</td>
<td>0.471</td>
</tr>
<tr>
<td>MMSE, median, IQR</td>
<td>1,291</td>
<td>29 (28 - 30)</td>
<td>29 (27 - 29)</td>
<td>0.486</td>
</tr>
<tr>
<td><strong>Cardiovascular risk profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP &gt; 160mmHg, n, %</td>
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<td>108 (38%)</td>
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<td>0.250</td>
</tr>
<tr>
<td>Tot chol ≥ 6,5mmol/l, n, %</td>
<td>1,256</td>
<td>35 (13%)</td>
<td>127 (13%)</td>
<td>0.903</td>
</tr>
<tr>
<td>BMI ≥ 35kg/m², n, %</td>
<td>1,291</td>
<td>81 (28%)</td>
<td>241 (24%)</td>
<td>0.134</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1,290</td>
<td>36 (13%)</td>
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<td>0.334</td>
</tr>
<tr>
<td>Alcohol intake, n, %</td>
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<td>284 (28%)</td>
<td>0.548</td>
</tr>
<tr>
<td>- none</td>
<td>90 (31%)</td>
<td>284 (28%)</td>
<td>0.548</td>
<td></td>
</tr>
<tr>
<td>- moderate</td>
<td>139 (49%)</td>
<td>519 (52%)</td>
<td>0.548</td>
<td></td>
</tr>
<tr>
<td>- high</td>
<td>57 (20%)</td>
<td>196 (20%)</td>
<td>0.548</td>
<td></td>
</tr>
<tr>
<td>Exercise &lt;150min/week, n, %</td>
<td>1,267</td>
<td>42 (15%)</td>
<td>113 (11%)</td>
<td>0.122</td>
</tr>
</tbody>
</table>

Table 2 Baseline characteristics of the non-adherent and adherent intervention participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intervention group (n=1,293)*</th>
<th>Non-adherent (n=286 (22%))</th>
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<th>p-value</th>
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<td></td>
<td></td>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
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<td>642 (64%)</td>
<td>0.370</td>
<td></td>
</tr>
<tr>
<td>- high</td>
<td>34 (12%)</td>
<td>146 (15%)</td>
<td>0.370</td>
<td></td>
</tr>
<tr>
<td><strong>Medical history and comorbidity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- heart disease, n, %</td>
<td>1,285</td>
<td>75 (27%)</td>
<td>286 (29%)</td>
<td>0.510</td>
</tr>
<tr>
<td>- stroke, n, %</td>
<td>1,279</td>
<td>25 (9%)</td>
<td>83 (8%)</td>
<td>0.789</td>
</tr>
<tr>
<td>- diabetes, n, %</td>
<td>1,293</td>
<td>47 (16%)</td>
<td>203 (20%)</td>
<td>0.139</td>
</tr>
<tr>
<td><strong>Depressive symptoms and cognition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS-15, median, IQR</td>
<td>1,221</td>
<td>1 (0 - 2)</td>
<td>1 (0 - 2)</td>
<td>0.262</td>
</tr>
<tr>
<td>GDS-12D, median, IQR</td>
<td>1,244</td>
<td>0 (0 - 1)</td>
<td>0 (0 - 1)</td>
<td>0.093</td>
</tr>
<tr>
<td>GDS-3A, median, IQR</td>
<td>1,257</td>
<td>0 (0 - 1)</td>
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<td>0.471</td>
</tr>
<tr>
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<td>0.486</td>
</tr>
<tr>
<td><strong>Cardiovascular risk profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP &gt; 160mmHg, n, %</td>
<td>1,292</td>
<td>108 (38%)</td>
<td>418 (42%)</td>
<td>0.250</td>
</tr>
<tr>
<td>Tot chol ≥ 6,5mmol/l, n, %</td>
<td>1,256</td>
<td>35 (13%)</td>
<td>127 (13%)</td>
<td>0.903</td>
</tr>
<tr>
<td>BMI ≥ 35kg/m², n, %</td>
<td>1,291</td>
<td>81 (28%)</td>
<td>241 (24%)</td>
<td>0.134</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1,290</td>
<td>36 (13%)</td>
<td>107 (11%)</td>
<td>0.334</td>
</tr>
<tr>
<td>Alcohol intake, n, %</td>
<td>1,285</td>
<td>90 (31%)</td>
<td>284 (28%)</td>
<td>0.548</td>
</tr>
<tr>
<td>- none</td>
<td>90 (31%)</td>
<td>284 (28%)</td>
<td>0.548</td>
<td></td>
</tr>
<tr>
<td>- moderate</td>
<td>139 (49%)</td>
<td>519 (52%)</td>
<td>0.548</td>
<td></td>
</tr>
<tr>
<td>- high</td>
<td>57 (20%)</td>
<td>196 (20%)</td>
<td>0.548</td>
<td></td>
</tr>
</tbody>
</table>
Determinants of dropout and non-adherence in a dementia prevention RCT

Abbreviations: ALDS, AMC linear disability scale; IQR, interquartile range; GDS-15, geriatric depression scale; GDS-12D, 12 depression items of the GDS-15; GDS-3A, 3 apathy items of the GDS-15; MMSE, mini-mental state examination; BP, blood pressure; tot chol, total cholesterol level; BMI, body mass index.

Adherence-data were missing for 322 participants that dropped out prior to the 2-year study visit, so these participants could not be included in the non-adherence analyses.

Adherence-data were missing for 322 participants that dropped out prior to the 2-year study visit, so these participants could not be included in the non-adherence analyses.

Chi-square tests for categorical variables. Whitney-U tests for continuous variables if distributions are skewed (ALDS, GDS and MMSE) and Chi-square tests for categorical variables.

Multilevel univariable logistic regression analyses showed that in both randomisation groups, increasing age, lower ALDS-scores, higher GDS-scores and lower MMSE-scores were all significantly associated with higher dropout rates (Supplementary table S1). Symptoms of apathy were also associated with higher risk of dropout in both groups. Participants with higher levels of education were less likely to drop out. Intervention group participants with a low level of exercise were also less prone to dropout. The other parameters tested were not significantly associated with dropout. With regard to non-adherence, people with high systolic blood pressure or a low level of exercise were more likely to be adherent to the intervention and overweight people were more often non-adherent (Supplementary table S1, last column).

Univariable analyses on dropout and non-adherence

Multilevel univariable logistic regression analyses showed that in both randomisation groups, increasing age, lower ALDS-scores, higher GDS-scores and lower MMSE-scores were all significantly associated with higher dropout rates (Supplementary table S1). Symptoms of apathy were also associated with higher risk of dropout in both groups. Participants with higher levels of education were less likely to drop out. Intervention group participants with a low level of exercise were also less prone to dropout. The other parameters tested were not significantly associated with dropout. With regard to non-adherence, people with high systolic blood pressure or a low level of exercise were more likely to be adherent to the intervention and overweight people were more often non-adherent (Supplementary table S1, last column).

Univariable analyses on dropout and non-adherence

Multivariable analyses on dropout and non-adherence

Multivariable logistic regression analyses yielded three separate models for dropout and non-adherence respectively (Table 3). Regarding dropout, differences between the control group and the intervention group were small. The final model for the control group was more parsimonious but in both groups older age (per year increase; control: OR 1.06, 95%CI 1.01-1.11 and intervention: OR 1.07, 95%CI 1.02-1.12) and a lower MMSE-score (per point decrease; controls: OR 1.23, 95%CI 1.14-1.32 and intervention: OR 1.07, 95%CI 1.00-1.15) remained the main factors independently associated with dropout. In the control group, a higher GDS-score (per point increase; OR 1.07, 95%CI 1.01-1.14) also remained significantly associated with dropout. In the intervention group, a lower ALDS-score (per point decrease; OR 1.06, 95%CI 1.03-1.09) was a risk for dropout. In the control group, the multivariable multilevel model did not have a significantly better fit than the one-level model (p=0.36), but this structure was maintained because of the clustered design of preDIVA and to facilitate a direct comparison with the intervention group. When repeating the multivariable analysis in the complete population (i.e. intervention and control groups combined; Supplementary table S2), the final model obtained reflected both the intervention
and the control model, as higher age, a lower MMSE-score, a higher GDS-score and a lower ALDS-score all remained significantly associated factors. When assessing symptoms of apathy and depression separately in the final models (Supplementary table S3), symptoms of apathy were no longer associated with dropout but the association with symptoms of depression remained. With regard to non-adherence, the most parsimonious model only contained high systolic blood pressure (OR 0.60, 95%CI 0.41–0.88), overweight (OR 1.84, 95%CI 1.22–2.79) and low level of exercise (OR 0.44, 95%CI 0.25–0.75) as significantly associated factors, which was consistent with the results of the univariable analyses.

Table 3: Determinants of dropout and non-adherence (final multivariable logistic regression models)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=1,196)</th>
<th>Dropout (n=1,403)</th>
<th>Non-adherence (n=1,129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fixed part</td>
<td>Random part</td>
<td>Fixed part</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>95%CI</td>
<td>p</td>
<td>95%CI</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.06</td>
<td>0.023</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>1.01 – 1.11</td>
<td>1.02 – 1.12</td>
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</tr>
<tr>
<td>Gender (female vs male)</td>
<td>1.20</td>
<td>0.04</td>
<td>0.94</td>
</tr>
<tr>
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<td>0.95 – 1.52</td>
<td>0.90 – 1.52</td>
<td>1.23</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.73</td>
<td>0.00</td>
<td>0.54</td>
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<tr>
<td></td>
<td>0.54 – 1.01</td>
<td>0.16 – 1.01</td>
<td>1.00</td>
</tr>
<tr>
<td>MMSE score (per point decrease)</td>
<td>1.23</td>
<td>0.001</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>1.14 – 1.32</td>
<td>1.00 – 1.15</td>
<td>1.00</td>
</tr>
<tr>
<td>GDS score (per point increase)</td>
<td>1.07</td>
<td>0.031</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>1.01 – 1.14</td>
<td>0.97 – 1.10</td>
<td>1.08</td>
</tr>
<tr>
<td>ALDS score (per point decrease)</td>
<td>1.02</td>
<td>0.151</td>
<td>1.05</td>
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<tr>
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<td>0.93 – 1.09</td>
<td>1.03</td>
</tr>
<tr>
<td>Systolic BP ≥ 160mmHg</td>
<td>1.17</td>
<td>0.040</td>
<td>0.93</td>
</tr>
<tr>
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<td>0.93 – 1.48</td>
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<td>1.00</td>
</tr>
<tr>
<td>BMI ≥ 30kg/m²</td>
<td>1.14</td>
<td>0.041</td>
<td>1.06</td>
</tr>
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<td>0.41 – 0.88</td>
<td>1.07</td>
</tr>
<tr>
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<td>0.00</td>
<td>0.65</td>
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<td>1.00</td>
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<tr>
<td>Alcohol intake</td>
<td>1.20</td>
<td>0.04</td>
<td>1.05</td>
</tr>
<tr>
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<td>0.99 – 1.52</td>
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<td>none vs moderate</td>
<td>0.66</td>
<td>0.023</td>
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</tr>
<tr>
<td></td>
<td>0.46 – 0.94</td>
<td>0.23 – 0.75</td>
<td>1.09</td>
</tr>
<tr>
<td>high vs moderate</td>
<td>0.66</td>
<td>0.023</td>
<td>0.46</td>
</tr>
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<td>0.46 – 0.94</td>
<td>0.23 – 0.75</td>
<td>1.09</td>
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<tr>
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<td>0.04</td>
<td>0.55</td>
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<td>0.46 – 0.84</td>
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Table 3: Determinants of dropout and non-adherence (final multivariable logistic regression models)

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<th>Dropout (n=1,403)</th>
<th>Non-adherence (n=1,129)</th>
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<td></td>
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<td>Random part</td>
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<tr>
<td></td>
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<td>OR</td>
<td>OR</td>
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<tr>
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<td>95%CI</td>
<td>p</td>
<td>95%CI</td>
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<tr>
<td>Age (per year increase)</td>
<td>1.06</td>
<td>0.023</td>
<td>1.07</td>
</tr>
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<td></td>
<td>1.01 – 1.11</td>
<td>1.02 – 1.12</td>
<td>1.02</td>
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<tr>
<td>Gender (female vs male)</td>
<td>1.20</td>
<td>0.04</td>
<td>0.94</td>
</tr>
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<td>0.90 – 1.52</td>
<td>1.23</td>
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<tr>
<td>History of diabetes</td>
<td>0.73</td>
<td>0.00</td>
<td>0.54</td>
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<td></td>
<td>0.54 – 1.01</td>
<td>0.16 – 1.01</td>
<td>1.00</td>
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<tr>
<td>MMSE score (per point decrease)</td>
<td>1.23</td>
<td>0.001</td>
<td>1.07</td>
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<td>0.041</td>
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</tr>
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<td>0.04</td>
<td>1.84</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>1.19</td>
<td>0.04</td>
<td>1.84</td>
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<tr>
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<td>0.46 – 0.84</td>
<td>0.39 – 0.75</td>
<td>0.95</td>
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</table>

and the control model, as higher age, a lower MMSE-score, a higher GDS-score and a lower ALDS-score all remained significantly associated factors. When assessing symptoms of apathy and depression separately in the final models (Supplementary table S3), symptoms of apathy were no longer associated with dropout but the association with symptoms of depression remained. With regard to non-adherence, the most parsimonious model only contained high systolic blood pressure (OR 0.60, 95%CI 0.41–0.88), overweight (OR 1.84, 95%CI 1.22–2.79) and low level of exercise (OR 0.44, 95%CI 0.25–0.75) as significantly associated factors, which was consistent with the results of the univariable analyses.
Abbreviations: ALDS, AMC linear disability scale; GDS, geriatric depression scale; MMSE, mini-mental state examination; BP, blood pressure; BMI, body mass index; GP, general practitioner; Var, variance; ICC, intraclass correlation.

* The following parameters were also included as co-variables in the multivariable model, but not maintained in the final model: gender, level of education, history of CVD, history of stroke, history of diabetes, level of systolic BP, level of total cholesterol, level of BMI, smoking status, level of physical activity. The multivariable model contains a level for health care center and general practice.

** The following parameters were also included as co-variables in the multivariable model, but not maintained in the final model: level of education, history of CVD, history of stroke, level of total cholesterol, level of physical activity.

*** The following parameters were also included as co-variables in the multivariable model, but not maintained in the final model: age, gender, level of education, history of CVD, history of stroke, history of diabetes, MMSE score, GDS score, ALDS score, level of total cholesterol, smoking status and alcohol intake.

**Sensitivity analyses**

Repeating the final models for dropout and non-adherence on the samples that had complete data for the retained co-variables did not alter conclusions (Supplementary table S4). Regarding dropout, for the intervention group MMSE-score was no longer significant, although the odds ratio remained similar. In addition, a history of diabetes was significantly associated with a lower risk of dropout. Last, we compared early and late dropout (Supplementary tables S5 and S6). Symptoms of depression were more strongly associated with early than with late dropout. A history of diabetes was found to prevent early dropout, while hypertension increased the risk. Otherwise, with regard to the variables most consistently associated with dropout in the analyses (higher age, lower MMSE-score and lower ALDS-score), timing of dropout did not make a difference.

**DISCUSSION**

In this large dementia prevention trial in older people, older age, poorer cognition, more symptoms of depression and disability were the most important determinants of dropout. Cardiovascular risk factors were not associated with dropout but some were associated with non-adherence. Overweight was a risk factor for non-adherence, whereas people with high blood pressure or a low level of physical exercise adhered better to the intervention. There was no indication that determinants of dropout are different with longer follow-up duration.

The absolute differences between the dropouts and completers and the adherent and non-adherent participants were small, suggesting that our results did not identify strong predictors of dropout or non-adherence. However, in addition to confirming the association of older age and poorer cognition with dropout in geriatric studies in
general, these findings provide evidence for symptoms of depression and disability as important determinants of dropout. The analysis did not confirm previously proposed determinants including sex, level of education, cardiovascular medical history and the cardiovascular risk factors. The investigation of symptoms of apathy in relation to dropout and non-adherence was an original aspect of our analysis. Although apathy can form a barrier to successful uptake of clinical care of various diseases, in the trial setting of preDIVA, we did not observe an independent association with dropout or non-adherence. A possible explanation for the lack of an independent association is that apathy often coincides with depression and has also been associated with cardiovascular comorbidity and risk, older age and functional and cognitive decline. The finding that poorer cognition and symptoms of depression were more strongly associated with dropout in the control group than in the intervention group, and vice versa for disability, are of interest. It may be that the personal attention from the intervention nurse was responsible for these differential findings. Findings from qualitative research in preDIVA completers and dropouts, that showed that the personal approach of the nurse was an important motivator to keep participating, corroborated this. The greater risk of dropout in people with greater disability in the intervention group may indicate that even this low intensity intervention became too demanding for more physically impaired participants. The finding that poorer cognition was more associated with dropout in the control group than in the intervention group is of importance for dementia prevention trials that select a measure of cognition as their primary outcome. Because of the selective loss of controls more prone to cognitive decline, intervention-effects could be underestimated in outcome assessments. In that case, dropout-retrieval may be essential for an unbiased interpretation of the main cognitive outcomes.

Dropout was relatively high (37%) in preDIVA but difficult to compare with similar trials since no other multi-domain nurse-led intervention trials of this duration exist. In drug trials with older people for the prevention of cardiovascular events and cognitive decline, dropout rates were approximately 20% to 25% at 5 year follow-up. This underlines that high dropout is inevitable in older populations. Nevertheless, neither its high dropout rates nor the occurrence of differential dropout affected the main result of the preDIVA trial because information regarding the primary outcome (incident dementia) was obtained for 98% of the participants, including the dropouts. This information was retrieved from general practitioner’s electronic health records. By selecting a clear clinical parameter (dementia) as primary outcome, preDIVA successfully by-passed the risk of the main outcome being influenced by attrition bias and there therefore is no need to adjust its main result for factors found to be associated with dropout. The same accounts for mortality, because information on survival was available for 99.8% of the participants.
An overall non-adherence rate to the preDIVA-intervention of 22% was found but non-adherence increased along study-follow-up. The external validity of these findings is likely to be high, because our intervention was well embedded in the daily practice of primary care. Therefore, similar adherence rates are expected if an intervention resembling this intervention were implemented in regular primary care. Our findings that cardiovascular risk factors do not predict dropout, but are associated with non-adherence, suggest that it was possible to reach the participants at highest risk, but that future trials should invest in increasing adherence in these people, especially in overweight older people. It seems plausible that these findings could at least partly translate to regular care as well. The suggestion of diabetes as a protective factor for dropout can be related to the pragmatic nature of the preDIVA trial, in which the same practice nurses often delivered both the preDIVA intervention and regular diabetes care. It is difficult to compare our findings to the literature because almost all previous research has been done in cardiovascular rehabilitation programs and results are mixed.21,22 Literature on determinants of adherence to primary prevention programs is limited: of the two studies identified only one evaluated cardiovascular risk factors but found no association with non-adherence.4 One British study in a mixed population of primary and secondary prevention candidates identified older age and treatment beliefs as determinants of adherence but did not study cardiovascular risk factors.31 PreDIVA can be best compared to the latter study, although the preDIVA population was on average ten years older.

This study has several limitations. In spite of the large number of potential determinants of dropout and non-adherence studied, the role of some additional factors possibly related to dropout and non-adherence including ethnicity, socio-economic status, marital status and comorbidity other than cardiovascular disease, could not be investigated. Socio-economic status may however been indirectly reflected in level of education. Likewise, the physical burden of any comorbidity will have been captured in lower ALDS-scores. Participants’ beliefs and perceptions of health in relation to non-adherence, which are frequently reported as important determinants, were not assessed.22 Another limitation was the missing data on adherence status for 322 early dropouts. This hampers a direct comparison with the dropout analysis and may explain why we did not find any association between non-adherence and age or symptoms of depression, which has been reported before.22 Nevertheless, because the non-adherence sample can be directly compared to the late dropout sample and determinants of early and late dropout were similar, this issue may be of minor concern. Last, instead of logistic regression, Cox regression analysis may have been more appropriate to analyse dropout,46 but it was not expected that this method would alter our conclusions since no differences were found between early and late dropout. Main strengths of this study have been the large number of both potentially important determinants of adherence and dropouts to the study. In spite of this large number of potentially important determinants, determinants of dropout and non-adherence including ethnicity, socio-economic status, marital status and comorbidity other than cardiovascular disease, could not be investigated. Socio-economic status may however been indirectly reflected in level of education. Likewise, the physical burden of any comorbidity will have been captured in lower ALDS-scores. Participants’ beliefs and perceptions of health in relation to non-adherence, which are frequently reported as important determinants, were not assessed.22 Another limitation was the missing data on adherence status for 322 early dropouts. This hampers a direct comparison with the dropout analysis and may explain why we did not find any association between non-adherence and age or symptoms of depression, which has been reported before.22 Nevertheless, because the non-adherence sample can be directly compared to the late dropout sample and determinants of early and late dropout were similar, this issue may be of minor concern. Last, instead of logistic regression, Cox regression analysis may have been more appropriate to analyse dropout,46 but it was not expected that this method would alter our conclusions since no differences were found between early and late dropout. Main strengths of this study have been the large number of both potentially important determinants of adherence and dropouts to the study.
analysis are the large sample size and long follow-up duration of preDIVA. In addition, the population-based approach of recruitment leads to high external validity of the findings for the general older population, as opposed to dementia prevention trials recruiting through memory or expert centers or via advertisements. To the knowledge of the authors, this is the first analysis comparing dropout and non-adherence in older people.

CONCLUSIONS

In a large dementia prevention trial, dropout and non-adherence were associated with different participant characteristics. The finding that poorer cognition and more symptoms of depression and disability increase the risk of dropout can help guiding the design of future dementia prevention trials in older adults. The associations found between cardiovascular risk factors and non-adherence need to be confirmed in other older populations subjected to primary or mixed cardiovascular prevention interventions.
Determinants of dropout and non-adherence in a dementia prevention RCT

ACKNOWLEDGMENTS

We would like to thank all participants of the preDIVA trial, all practice nurses and general practitioners involved and the research team responsible for trial-coordination, data-management and coordination of outcome adjudication (Carin E. Miedema, Suzanne A. Ligthart, Lisa S. Eurelings, Jan Willem van Dalen, Emma F. van Bussel and Marieke P. Hoevenaar-Blom). Last, we thank Marieke P. Hoevenaar-Blom for her support and advice on data-analysis.

Funding

The preDIVA trial was supported by the Dutch Ministry of Health, Welfare and Sport (grant number 50-50110-98-020), the Dutch Innovation Fund of Collaborative Health Insurances (grant number 05-234), and the Netherlands Organization for Health Research and Development (grant number 62000015). In addition, the research leading to these results was supported by the European Union Seventh Framework Programme (FP7/2007-2013, grant agreement number 305654; the Healthy Ageing Through Internet Counselling in the Elderly (HATICE)-project).

Conflict of Interest

The authors have no financial or any kind of personal conflicts with this paper.

Conflict of Interest

The authors have no financial or any kind of personal conflicts with this paper.
REFERENCES


### Supplementary table S1: Determinants of dropout and non-adherence (univariable logistic regression analyses)

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<tr>
<th>Parameter</th>
<th>Dropout (control)</th>
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<th>Non-adherence (intervention)</th>
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<td>1.04 - 1.14</td>
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<td>Education</td>
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<td>MMSE score (per point decrease)</td>
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<td>1.14 - 1.30</td>
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<td>0.284</td>
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<td>0.88</td>
<td>1.45</td>
<td>0.344</td>
<td>1.32</td>
<td>1.04</td>
<td>1.68</td>
<td>0.023</td>
<td>1.08</td>
<td>0.73</td>
<td>1.60</td>
<td>0.667</td>
</tr>
<tr>
<td>- high vs moderate</td>
<td>0.77</td>
<td>0.54</td>
<td>1.05</td>
<td>0.097</td>
<td>1.12</td>
<td>0.85</td>
<td>1.47</td>
<td>0.486</td>
<td>1.50</td>
<td>0.70</td>
<td>1.71</td>
<td>0.680</td>
</tr>
<tr>
<td>Exercise &lt; 150min/week</td>
<td>1.349</td>
<td>0.77</td>
<td>0.54 - 1.09</td>
<td>0.144</td>
<td>1.682</td>
<td>0.60</td>
<td>0.47 - 0.85</td>
<td>0.003</td>
<td>1.267</td>
<td>0.46</td>
<td>0.28 - 0.75</td>
<td>0.002</td>
</tr>
</tbody>
</table>

The univariable models included a level for health care center and for general practice (not shown).

Abbreviations: ALDS, AMC linear disability scale; GDS-15, geriatric depression scale; GDS-12D, 12 depression items of the GDS-15; GDS-3A, 3 apathy items of the GDS-15; MMSE, mini-mental state examination; BP, blood pressure; tot chol, total cholesterol level; BMI, body mass index.
Supplementary table S2: Determinants of dropout (final multivariable logistic regression model in the complete population, i.e. intervention and control group combined) (N=2,599)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (N=2,599)</th>
<th>95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed part</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.06</td>
<td>1.03 – 1.10</td>
<td>0.001</td>
</tr>
<tr>
<td>Gender (female vs male)</td>
<td>1.11</td>
<td>0.93 – 1.33</td>
<td>0.228</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- intermediate vs low</td>
<td>0.86</td>
<td>0.70 – 1.06</td>
<td>0.160</td>
</tr>
<tr>
<td>- high vs low</td>
<td>0.82</td>
<td>0.60 – 1.11</td>
<td>0.198</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.82</td>
<td>0.65 – 1.04</td>
<td>0.097</td>
</tr>
<tr>
<td>MMSE score (per point decrease)</td>
<td>1.14</td>
<td>1.08 – 1.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GDS score (per point increase)</td>
<td>1.05</td>
<td>1.00 – 1.10</td>
<td>0.033</td>
</tr>
<tr>
<td>ALDS score (per point decrease)</td>
<td>1.04</td>
<td>1.02 – 1.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP ≥ 160mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Random part</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care center</td>
<td>26</td>
<td>0.04 – 0.29</td>
<td>0.03</td>
</tr>
<tr>
<td>GP practice</td>
<td>115</td>
<td>0.01 – 0.20</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Randomisation was included as a covariable but not maintained in the final model. Other co-variables that were included but not maintained in the final model were: history of cardiovascular disease, history of stroke, level of total cholesterol, level of BMI, smoking status, level of physical activity and alcohol intake.

Abbreviations: ALDS, AMC linear disability scale; GDS, geriatric depression scale; MMSE, mini-mental state examination; BP, blood pressure; BMI, body mass index; GP, general practitioner; Var, variance; ICC, intraclass correlation.
Supplementary table S3: Determinants of dropout (final multivariable logistic regression models) – sensitivity analysis with three apathy items (GDS-3A) and 12 depression items (GDS-12D) of the Geriatric Depression Scale

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=1,196)</th>
<th>Intervention (n=1,403)</th>
<th>Fixed part</th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year increase)</td>
<td>1.06</td>
<td>1.01 – 1.11</td>
<td>0.021</td>
<td>1.07</td>
<td>1.02 – 1.12</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (female vs male)</td>
<td>-</td>
<td>-</td>
<td>1.21</td>
<td>0.95 – 1.54</td>
<td>0.125</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of diabetes</td>
<td>-</td>
<td>-</td>
<td>0.74</td>
<td>0.54 – 1.01</td>
<td>0.060</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE score (per point decrease)</td>
<td>1.23</td>
<td>1.14 – 1.32</td>
<td>&lt;0.001</td>
<td>1.07</td>
<td>1.00 – 1.15</td>
<td>0.046</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS-3A (per point increase)</td>
<td>1.01</td>
<td>0.87 – 1.19</td>
<td>0.857</td>
<td>0.94</td>
<td>0.81 – 1.09</td>
<td>0.415</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS-12D (per point increase)</td>
<td>1.10</td>
<td>1.00 – 1.20</td>
<td>0.041</td>
<td>1.08</td>
<td>0.98 – 1.18</td>
<td>0.112</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALDS score (per point decrease)</td>
<td>1.02</td>
<td>0.99 – 1.05</td>
<td>0.125</td>
<td>1.06</td>
<td>1.03 – 1.09</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP ≥ 160mmHg</td>
<td>1.18</td>
<td>0.94 – 1.49</td>
<td>0.163</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 30kg/m²</td>
<td>1.14</td>
<td>0.87 – 1.50</td>
<td>0.339</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently smoking</td>
<td>-</td>
<td>-</td>
<td>1.21</td>
<td>0.85 – 1.72</td>
<td>0.296</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>-</td>
<td>-</td>
<td>p overall= 0.076</td>
<td>p overall= 0.408</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none vs moderate</td>
<td>0.85</td>
<td>0.64 – 1.13</td>
<td>0.286</td>
<td>1.19</td>
<td>0.90 – 1.56</td>
<td>0.215</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high vs moderate</td>
<td>0.67</td>
<td>0.47 – 0.95</td>
<td>0.026</td>
<td>1.15</td>
<td>0.85 – 1.56</td>
<td>0.377</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random part</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>Variance</td>
<td>95%CI</td>
<td>ICC</td>
<td>N</td>
<td>Variance</td>
</tr>
<tr>
<td>Health care center</td>
<td>24</td>
<td>0.02</td>
<td>0.00 – 0.05</td>
<td>0.005</td>
<td>26</td>
<td>0.16</td>
<td>0.06 – 0.39</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>GP practice</td>
<td>53</td>
<td>0.05</td>
<td>0.00 – 0.19</td>
<td>0.02</td>
<td>62</td>
<td>0.00</td>
<td>0.00 – 0.00</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALDS, AMC linear disability scale; GDS-15, geriatric depression scale; GDS-12D, 12 depression items of the GDS-15; GDS-3A, 3 apathy items of the GDS-15; MMSE, mini-mental state examination; BP, blood pressure; BMI, body mass index; GP, general practitioner; Var, variance; ICC, intraclass correlation.
### Supplementary table S4: Determinants of dropout and non-adherence (final multivariable logistic regression models – rerun in the maximum samples)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=1,278)</th>
<th>Dropout Intervention (n=1,498)</th>
<th>Non-adherence Intervention (n=1,264)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed part</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>95%CI</td>
<td>OR</td>
<td>95%CI</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.07</td>
<td>1.02 – 1.13</td>
<td>0.004</td>
</tr>
<tr>
<td>Gender (female vs male)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>-</td>
<td>0.73</td>
<td>0.54 – 0.99</td>
</tr>
<tr>
<td>MMSE score (per point decrease)</td>
<td>1.21</td>
<td>1.13 – 1.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GDS score (per point increase)</td>
<td>1.08</td>
<td>1.02 – 1.15</td>
<td>0.010</td>
</tr>
<tr>
<td>ALDS score (per point decrease)</td>
<td>1.02</td>
<td>0.99 – 1.05</td>
<td>0.127</td>
</tr>
<tr>
<td>Systolic BP ≥ 160mmHg</td>
<td>-</td>
<td>1.12</td>
<td>0.90 – 1.40</td>
</tr>
<tr>
<td>BMI ≥ 30kg/m²</td>
<td>-</td>
<td>1.07</td>
<td>0.82 – 1.39</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>-</td>
<td>1.17</td>
<td>0.83 – 1.65</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>-</td>
<td>0.86</td>
<td>0.65 – 1.14</td>
</tr>
<tr>
<td>- none vs moderate</td>
<td>0.73</td>
<td>0.52 – 1.02</td>
<td>0.067</td>
</tr>
<tr>
<td>Exercise &lt;150min/week</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Random part</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Var</td>
<td>95%CI</td>
<td>N</td>
</tr>
<tr>
<td>Health care center</td>
<td>24</td>
<td>0.04</td>
<td>0.00 – 0.93</td>
</tr>
<tr>
<td>GP practice</td>
<td>53</td>
<td>0.04</td>
<td>0.00 – 2.18</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALDS, AMC linear disability scale; GDS, geriatric depression scale; MMSE, mini-mental state examination; BP, blood pressure; BMI, body mass index; GP, general practitioner; Var, variance; ICC, intraclass correlation.
Supplementary table S5: Determinants of early dropout in the complete population (final multivariable logistic regression model) (N=2,599)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (N=2,599)</th>
<th>Fixed part</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year increase)</td>
<td></td>
<td>1.06</td>
<td>1.02 – 1.11</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Gender (female vs male)</td>
<td></td>
<td>0.97</td>
<td>0.78 – 1.21</td>
<td>0.794</td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- intermediate vs low</td>
<td></td>
<td>0.83</td>
<td>0.65 – 1.07</td>
<td>0.157</td>
<td></td>
</tr>
<tr>
<td>- high vs low</td>
<td></td>
<td>0.94</td>
<td>0.64 – 1.38</td>
<td>0.745</td>
<td></td>
</tr>
<tr>
<td>History of diabetes</td>
<td></td>
<td>0.70</td>
<td>0.52 – 0.96</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>MMSE score (per point decrease)</td>
<td></td>
<td>1.15</td>
<td>1.08 – 1.22</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>GDS score (per point increase)</td>
<td></td>
<td>1.07</td>
<td>1.01 – 1.12</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>ALDS score (per point decrease)</td>
<td></td>
<td>1.02</td>
<td>1.00 – 1.04</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>Systolic BP ≥ 160mmHg</td>
<td></td>
<td>1.26</td>
<td>1.01 – 1.56</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>Random part</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care center</td>
<td>26</td>
<td>0.15</td>
<td>0.05 – 0.41</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>GP practice</td>
<td>115</td>
<td>0.10</td>
<td>0.03 – 0.32</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALDS, AMC linear disability scale; GDS, geriatric depression scale; MMSE, mini-mental state examination; BP, blood pressure; GP, general practitioner; Var, variance; ICC, intraclass correlation.

1: Early dropout: dropping out after the baseline visit until the period of the second study visit, compared to the people still in the study at least until visit 2 (excluding people with an unclear dropout status)
### Supplementary table S6: Determinants of late dropout in the complete population (final multivariable logistic regression model) (N=2,148)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (n=2,148)</th>
<th>Fixed part</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year increase)</td>
<td>1.05</td>
<td>1.01 – 1.10</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Gender (female vs male)</td>
<td>1.17</td>
<td>0.94 – 1.45</td>
<td>0.164</td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- intermediate vs low</td>
<td>0.91</td>
<td>0.70 – 1.21</td>
<td>0.468</td>
<td></td>
</tr>
<tr>
<td>- high vs low</td>
<td>0.77</td>
<td>0.52 – 1.13</td>
<td>0.199</td>
<td></td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.94</td>
<td>0.71 – 1.21</td>
<td>0.640</td>
<td></td>
</tr>
<tr>
<td>MMSE score (per point decrease)</td>
<td>1.10</td>
<td>1.03 – 1.17</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>GDS score (per point increase)</td>
<td>1.04</td>
<td>0.98 – 1.09</td>
<td>0.311</td>
<td></td>
</tr>
<tr>
<td>ALDS score (per point decrease)</td>
<td>1.04</td>
<td>1.01 – 1.06</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Systolic BP ≥ 160mmHg</td>
<td>1.04</td>
<td>0.84 – 1.31</td>
<td>0.723</td>
<td></td>
</tr>
<tr>
<td><strong>Random part</strong></td>
<td><strong>N</strong></td>
<td><strong>Variance</strong></td>
<td><strong>95%CI</strong></td>
<td><strong>ICC</strong></td>
</tr>
<tr>
<td>Health care center</td>
<td>26</td>
<td>0.10</td>
<td>0.02 – 0.58</td>
<td>0.03</td>
</tr>
<tr>
<td>GP practice</td>
<td>114</td>
<td>0.09</td>
<td>0.02 – 0.35</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALDS, AMC linear disability scale; GDS, geriatric depression scale; MMSE, mini-mental state examination; BP, blood pressure; GP, general practitioner; Var, variance; ICC, intraclass correlation.

\(^1\) Late dropout: dropping out after the second study visit in the period of the third and final study visit compared to the people that completed the study (excluding the people with an unclear dropout status)
This thesis focuses on how cardiovascular risk management (CVRM) can be provided to older people using eHealth. In part 1, we describe the development of the internet-platform for cardiovascular risk self-management in older people for the HATICE-study. In part 2, we aim to gain better understanding on engagement of older people in eHealth and nurse-led CVRM. This chapter summarises the main findings of this thesis and discusses these in the context of current literature. Furthermore, some methodological considerations, directions for future research and clinical implications are provided.

**PART 1: DEVELOPMENT OF AN INTERNET-PLATFORM FOR CARDIOVASCULAR RISK SELF-MANAGEMENT IN OLDER PEOPLE**

**Reviewing the literature**

In order to provide an evidence based foundation for the HATICE internet-platform, we first performed a systematic review and meta-analysis to answer the question whether internet-interventions for CVRM in older people are effective in reducing cardiovascular risk and disease (chapter 2). Although 57 RCTs could be included, only seven RCTs contained participants that were all above 50 years of age. Therefore, we concluded that internet-platforms specifically designed for older people are still scarce. Thus, the conclusions of our the meta-analysis apply to both middle-aged and older people with elevated cardiovascular risk. We found that internet-platforms lead to improvement of the individual cardiovascular risk factors systolic and diastolic blood pressure, LDL-cholesterol, HbA1c, weight, physical activity levels. These findings affirmed conclusions of other meta-analyses in younger adult populations.\(^1\) The reductions found in systolic blood pressure (mean difference \(-2.66\) mmHg (95% CI \(-3.81\) to \(-1.52\))) and LDL-cholesterol (mean difference \(-2.18\) mg/dL (95% CI \(-3.96\) to \(-0.41\))) were modest but could potentially translate into clinically relevant reductions of CV mortality or disease on a population level, if reductions were maintained over a longer period of time. CVRM is most effective when the complete CV risk profile is targeted.\(^2\) We could assess this with a meta-analysis of nine studies and found that internet-interventions also improved cardiovascular composite scores. We did not find an effect of the internet-interventions studied on cardiovascular event rates, but this was only reported in six studies with an average duration of 13 months. This finding was in contrast with the meta-analysis by Widmer et al, who did report a significant reduction in CVD outcomes by digital health interventions compared to usual care.\(^3\) However, these analyses cannot be directly compared to ours, because the latter also included mobile health and telecare devices and the CVD outcomes were more broadly defined, also including hospitalisations and all-cause mortality. We further...
evaluated the general effect of internet-platforms on cardiovascular risk factors, by pooling the standardised primary outcomes of all included studies that had defined a primary outcome (37 studies, n=11,021). We found a standardised mean difference of –0.24 (95% CI –0.31 to –0.16) in favour of the intervention. This effect-size can be interpreted as a small effect. In a further meta-regression, to assess the association between effect size and study-duration, we found that the beneficial effects on risk reduction declined over time. We hypothesised that declining effects over time could be associated with decreasing adherence. This was consistent with crumbling effect sizes. We hypothesised that declining effects over time could be associated with decreasing adherence. This was consistent with crumbling adherence rates reported in several of the included studies. Also in literature, difficulty to induce long-term adoption of internet-platforms is frequently reported and better adherence rates have been associated with positive outcomes. Lastly, from sub-group analyses, we could conclude that internet-platforms combined with human support (ranging from online communication to face-to-face meetings) are more effective than stand-alone digital interventions. This finding was consistent with research on interventions for diabetes self-management and strengthened our decision to include support by health coaches in the HATICE platform.

Consulting end-users
The importance of adding human support to an internet-platform was confirmed by the results described in chapter 3. Here we performed an international focus group study with seven Dutch and six Finnish primary care nurses, to learn from their experiences and practices with behaviour change support for CVRM and to discuss how to integrate their practices in a coach-supported internet-platform. We found that Finnish and Dutch primary care nurses with experience in CVRM had similar experiences in supporting health behaviour change in their patients. Both groups emphasised three preconditions needed for optimal behaviour change support: establishment of a relationship of trust, attention for awareness and expectation-management, and appropriate timing of support (matching the stage of change). These findings are in line with the preferences of older people for support in CVRM. However, small differences existed between the countries in the clinical practices the nurses used to meet these preconditions. The Finnish nurses for example had frequent consultations by phone, which was practical due to the large distances their patients needed to travel to their clinic. The Dutch nurses relied mostly on face-to-face contact. When discussing how health behaviour change support could be optimally provided online, both groups emphasised the importance of human support and integration with regular primary care. The Dutch nurses, however, were convinced that an internet-platform supported by a coach could never create the same strength of relationship they had built with their patients, and therefore they kept a slightly more reserved
attitude towards online support. Moreover, they only regarded the platform suitable for support of lifestyle changes. They argued that care of medical issues should remain in the general practice domain. In contrast, the Finnish nurses saw no limitations of a digital approach. They argued that a relationship of trust could just as well be induced through internet, provided that the platform would be combined with human support and incorporated in regular care. Furthermore, they had no objections to supporting both lifestyle aspects and medical aspects of CVRM in this fashion. We attributed the differences found to local differences in culture, health care structure and geography. The attitudes we found were consistent with descriptions of attitudes towards self-management and enhancing patient autonomy of Finnish and Dutch health care professionals in other studies. Self-management requires health care professionals to adopt a different attitude towards the patient. Perhaps the Finnish nurses are further ahead in adopting this attitude than the Dutch nurses.

**Synthesis of the platform**

In chapter 4, we described the full development of the interactive HATICE internet-platform. Apart from the literature review (chapter 2) and focus groups with nurses (chapter 3), the developmental process also involved focus groups with the target population (manuscript currently in preparation), extensive brainstorm sessions with the software developers of the company involved, consultations of experts in CVRM and communication with older patients and representatives of patients organisations and its evaluation in an international pilot study.

The final HATICE internet-intervention is a personalised, secured, interactive internet-platform for self-management of the lifestyle aspects of seven modifiable cardiovascular risk factors with support from a health coach. The developmental process and pilot resulted in a number of adaptations made to meet the specific needs of the target population (summarised in table 1). The support of the health coach included: initial face-to-face meetings for assessment of the cardiovascular risk profile, explanation of the platform and initial goal setting, continuous online support of health behaviour change in an empathic, positive and counselling fashion following the principles of Motivational Interviewing, referral to their general practitioner if cardiovascular risks required medical evaluation and, at 12 months, a follow-up telephone call to boost motivation.

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Table 1 Age-related problems and solutions in the HATICE intervention platform

<table>
<thead>
<tr>
<th>Age-related problems</th>
<th>Platform solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual impairments</strong></td>
<td>• Large font size</td>
</tr>
<tr>
<td></td>
<td>• Simple layout</td>
</tr>
<tr>
<td></td>
<td>• High contrast colour scheme</td>
</tr>
<tr>
<td><strong>Motor impairments</strong></td>
<td>• Large buttons</td>
</tr>
<tr>
<td></td>
<td>• No use of mouse hover-over</td>
</tr>
<tr>
<td><strong>Cognitive ageing</strong></td>
<td>• Content written in concise and easy-to-understand language</td>
</tr>
<tr>
<td></td>
<td>• Interact content to stimulate capturing information</td>
</tr>
<tr>
<td></td>
<td>• Information offered in text, interactive audio format and in videos</td>
</tr>
<tr>
<td><strong>Limited navigation skills</strong></td>
<td>• Concise site-map, limited to max. 3 levels of navigation</td>
</tr>
<tr>
<td></td>
<td>• Static main menu that remains visible on every page</td>
</tr>
<tr>
<td><strong>Drowning in information</strong></td>
<td>• Only showing information relevant for health priorities</td>
</tr>
<tr>
<td></td>
<td>• Concise information</td>
</tr>
<tr>
<td></td>
<td>• No linking to information outside the platform</td>
</tr>
<tr>
<td><strong>Login difficulties</strong></td>
<td>• Help-assistance through email and phone</td>
</tr>
<tr>
<td></td>
<td>• Simple passwords</td>
</tr>
<tr>
<td><strong>Feeling insecure about internet skills</strong></td>
<td>• Introduction video explaining how to use the platform</td>
</tr>
<tr>
<td></td>
<td>• Help-buttons on every page</td>
</tr>
<tr>
<td></td>
<td>• Help-assistance through email and phone</td>
</tr>
<tr>
<td></td>
<td>• Paper instruction manual</td>
</tr>
<tr>
<td><strong>Focus on health instead of disease</strong></td>
<td>• Positive tone of voice; e.g., health factors instead of risk factors</td>
</tr>
<tr>
<td></td>
<td>• Positive and empathic attitude of health coach</td>
</tr>
<tr>
<td><strong>Reliability concerns</strong></td>
<td>• Study being recommended by own general practitioner</td>
</tr>
<tr>
<td></td>
<td>• Face-to-face meeting with health coach</td>
</tr>
<tr>
<td></td>
<td>• Explanation that information is based on clinical guidelines</td>
</tr>
<tr>
<td></td>
<td>• Picture of the health coach</td>
</tr>
</tbody>
</table>

Self-management was facilitated in the following way: insight in personal risk profile, educational modules, ability to choose risk factors as priorities and create lifestyle goals, self-monitoring tools and online communication with the coach. The available functionalities corresponded with the different stages of change that participants could be in (table 2).
The platform was developed to function independently of regular primary care but to be easily implementable in existing care structures if proven effective. The platform intervention focussed on the lifestyle aspects of CVRM. Still, interactions with regular primary care were foreseen in case new cardiovascular risks were detected that required medical treatment. In that case, the health coach advised people to see their general practitioner.

The pilot (41 older participants from the Netherlands, Finland and France, 8 weeks) detected various teething problems such as the login procedure being regarded too complicated and the platform not working optimally in older internet browsers. The evaluation sessions revealed that participants had difficulty in creating lifestyle goals by themselves, but succeeded together with the coach. The self-monitoring tool was frequently used for measuring of blood pressure, weight and exercise level, but not at all for smoking and diabetes. The participants positively valued the coach support. In conclusion, the pilot showed that an interactive internet-platform is acceptable and feasible for use by older people with basic computer skills. Continuous interaction between researchers, software developers and end-users (both patients and health care professionals) was necessary to generate solutions for the detected problems that worked for all parties involved. Figures 1-3 provide an impression of the final platform.

### Table 2 Implementation of stages of change and self-management in the HATICE platform

<table>
<thead>
<tr>
<th>Stage of change</th>
<th>Functionality</th>
</tr>
</thead>
</table>
| Pre-contemplation | • Information on each health factor  
|                  | • Educational videos for each health factor |
| Contemplation    | • Summary of personal cardiovascular health profile  
|                  | • Peer-to-peer videos with personal stories of peers on lifestyle change |
| Preparation      | • Advice and tips and tricks on healthy lifestyle for each health factor  
|                  | • Suggestions for goals |
| Action           | • Step-by-step procedure to set new goal  
|                  | • Overview of health priorities and self-monitoring tools |
| Maintenance      | • Monitoring of progress, with positive toned automatic responses and regular feedback from health coach  
|                  | • Overview of achieved goals  
|                  | • Personal lifestyle groups |
| Relapse          | • Positive toned automatic responses in case of relapse  
|                  | • Communication with health coach |

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Figure 1 Final version of platform – homepage

Figure 2 Final version of platform – Goal setting page
Currently, there is still a dearth of scientifically tested internet-platforms for CV risk self-management that specifically target older people. Internet-platforms targeting people of middle-age and older can induce modest improvements of individual CV risk factors and the CV risk profile, but effects decline over time. Studies on effects of internet-interventions on incident CVD are limited in number and follow-up time, therefore there is currently insufficient evidence on effects on this pivotal outcome. Blended interventions (combining the internet-platform with human support) are more effective than stand-alone interventions. Primary care nurses from Finland and the Netherlands also emphasise the importance of human support when CVRM is integrated in an online setting. Human support is essential for the establishment of a relationship of trust, to manage people's expectations and for appropriate timing of support (matching the stage of change). When carefully designed with consultation of current literature and experts, continuous involvement of the end-users and pilot testing, it is possible to develop an internet-platform that is acceptable and feasible for use by European older people with basic computer skills and increased cardiovascular risk. We showed that older people start to actively use such a platform and use the different features. Based on the extensive developmental process, we propose several solutions for age-related problems associated with internet-platform use (table 1).

**Conclusions of part 1**

Currently, there is still a dearth of scientifically tested internet-platforms for CV risk self-management that specifically target older people. Internet-platforms targeting people of middle-age and older can induce modest improvements of individual CV risk factors and the CV risk profile, but effects decline over time. Studies on effects of internet-interventions on incident CVD are limited in number and follow-up time, therefore there is currently insufficient evidence on effects on this pivotal outcome. Blended interventions (combining the internet-platform with human support) are more effective than stand-alone interventions. Primary care nurses from Finland and the Netherlands also emphasise the importance of human support when CVRM is integrated in an online setting. Human support is essential for the establishment of a relationship of trust, to manage people's expectations and for appropriate timing of support (matching the stage of change). When carefully designed with consultation of current literature and experts, continuous involvement of the end-users and pilot testing, it is possible to develop an internet-platform that is acceptable and feasible for use by European older people with basic computer skills and increased cardiovascular risk. We showed that older people start to actively use such a platform and use the different features. Based on the extensive developmental process, we propose several solutions for age-related problems associated with internet-platform use (table 1).
PART 2: ENGAGEMENT OF OLDER PEOPLE IN EHEALTH OR NURSE-LED CVRM

In part 2 of this thesis, we studied engagement of older people with CVRM, by performing a qualitative evaluation study of the HATICE internet-platform (chapter 5) and a quantitative assessment of engagement with the intensive vascular nurse-support intervention from the preDIVA trial (chapter 6).

Engagement to the HATICE-platform

In chapter 5, we performed 17 interviews with 20 Dutch participants of the HATICE trial to evaluate their initial and long-term engagement with the platform. Regarding initial engagement (initial use of the platform and familiarising oneself with the platform), we identified as influential factors for use: perceived computer literacy, senior user-friendliness of the platform, acceptability and perceived appropriateness of the intervention and initial interaction with the health coach. In sustained engagement (using the platform for a longer period for self-management purposes), we found that establishment of a relationship with the coach was the most important factor, followed by the use of regular automatic and personal reminders, having clear expectations of the platform, incorporating the use of the platform into daily routine, getting social support and having a loyal and persistent attitude. Some of the factors identified have been described in literature before, such as platform user-friendliness, perceived benefits and expectations of the platform and incorporation into personal life. A novel finding was that coach support was identified as an important factor for both initial and sustained engagement, suggesting that one of the strengths of adding human support to an internet-platform may lie in inducing sustained engagement with the platform. With regard to the regular automatic and personal reminders from the platform, we found that participants preferred to use the platform in a ‘reactive’ way rather than in an ‘active’ way, i.e., to respond to reminders rather than to use the platform on one’s own initiative. This seems to resemble the way people use smartphone applications such as Facebook and Whatsapp. Electronic reminders have been proven an effective tool to increase adherence to medication and reduce cardiovascular risk, but if they are used too frequently, ‘alert fatigue’ can arise. Besides engagement we also discussed with the participants whether a platform like HATICE should be implemented in regular primary care. Participants were positive about this. In fact, they experienced it as a barrier that the HATICE-platform was offered independently from regular care. In their view, the alignment of the internet-platform to regular CVRM visits with the practice nurse would optimise continuity of care. This may improve engagement with the intervention, as has been suggested in literature on optimal diabetes management.

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Engagement to intensive nurse-led CVRM

We also evaluated engagement of older people with a non-digital CVRM intervention, by studying dropout from and adherence to intervention tested in the preDIVA trial (chapter 6). The preDIVA intervention consisted of 4-monthly consultations with the regular practice nurse at the general practice for intensive vascular care. This included assessment of the complete cardiovascular risk, provision of tailored lifestyle advice and optimization of medical treatment. In an exploratory analysis, we examined sociodemographic, clinical, and neuropsychiatric determinants of dropout and nonadherence. The clinical determinants included cardiovascular risk factors. In the analysis on dropout we focussed on dropout that could potentially be prevented and therefore, we excluded dropout due to death or dementia. Along study follow-up time, the dropout rate remained stable. The preventable dropout rate was stable along study follow-up. However, the non-adherence rate increased with a longer follow-up duration. We found that participants with, at baseline, a higher age, a lower level of cognition, more symptoms of depression or disability had the highest risk to drop out. Higher age and lower level of cognition were already known factors to be consistently associated with dropout.25 Symptoms of depression and disability have also been previously assessed but results on associations were inconsistent.25-26 Our findings provide additional evidence that symptoms of depression and disability are important determinants of dropout in older people. We also found that there was more dropout of people with symptoms of depression or lower cognition allocated to the control condition than to the intervention condition. In clinical practice, it may merit to give these people extra attention, since the findings of differential dropout could also suggest that the extra nurse contact stimulated these people to continue participation. The latter finding also seems important for other dementia trials. Selective loss of people in the control condition that are more prone to cognitive decline can lead to an underestimation of intervention-effects if the primary outcome is a cognitive screening measure. Solutions to reduce this risk of bias are taking a major clinical endpoint as primary outcome, such as diagnosis of dementia, and putting effort in dropout-retrieval. Next to dropout, we also assessed determinants of non-adherence to the intervention. The same factors were assessed but different associations were found. The factors associated with dropout did not emerge in the analysis on non-adherence, although in other studies associations between non-adherence to cardiac rehabilitation programs high age and symptoms of depression have been reported.27 Instead, being overweight was a risk factor for non-adherence, and elevated blood pressure and physical inactivity were associated with adherence. These findings are novel and need to be reproduced. Although the preDIVA intervention was offered in the context of an RCT, we think that the external validity of our findings is high, since the preDIVA population closely resembles a normal unselected population of...
community dwelling older people,29 and the intervention was integrated in regular primary care.

Conclusions of part 2
Qualitative research with participants of the HATICE trial showed that interaction with a health coach was regarded an important factor to stimulate engagement with the HATICE platform, both for initial and long-term engagement. Other important factors were senior user-friendliness of the platform, perceived appropriateness of the intervention, use of automatic and personal reminders, motivational status and incorporation of platform use into daily routine. Quantitative analysis of dropout and non-adherence to the preDIVA intervention showed that people at advanced age, with lower levels of cognition, with symptoms of depression or functional disabilities are more prone to dropout from nurse-led CVRM. Differential dropout rates were found for symptoms of depression and lower levels of cognition, where controls with these characteristics dropped out more often than intervention participants. These findings need to be taken into account in the design of future dementia trials when choosing cognitive outcomes. In clinical practice, it may merit to give patients with these characteristics extra attention to keep them allied, since the findings might indicate that the extra nurse contact stimulated them to keep participating.

METHODOLOGICAL CONSIDERATIONS

Meta-analysis: limits and possibilities of the pooled standardised effects analysis
In the meta-analysis, one method we used to evaluate the general effect of internet-platforms on cardiovascular risk factors, was pooling the standardised primary outcomes of all included studies. This original approach may initially look like a comparison of apples and oranges. However, when inferences based on this analysis are limited to the intention of the analysis, being to estimate the overall effect of internet-platforms on cardiovascular risk factors, and one keeps in mind that the analysis only tells us what the direction of the effect is and what order of effect size can potentially be expected on a cardiovascular risk factor in general, we regard the analysis not only valid, but also informative. In addition, this method provided further opportunities for sufficiently powered analyses on heterogeneity and risk of bias. The heterogeneity analyses provided insights on declining effects with increasing study duration and convincing evidence that blended interventions induced larger effects than internet-only interventions. Bias assessment in systematic review and meta-analysis can be undertaken in several ways. Sometimes scales are used and summary...
scores are calculated. The Cochrane Collaboration discourages this practice because it is not transparent and its validity is low.\textsuperscript{20, 31} Frequently used is the Cochrane Risk of Bias assessment tool to uniformly assess the risk of bias in seven domains (selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases) in RCTs.\textsuperscript{31} Recommendations are provided to summarise the domain assessments within studies or across studies using the well-known distinctions ‘low risk of bias’, ‘unclear risk of bias’ and ‘high risk of bias’. The way bias is judged and summarised is a subjective process, depending on the interpretation of the assessor. The Cochrane Collaboration therefore recommends that this is performed blindly. The Cochrane Collaboration recommends to judge a study to be overall low risk of bias if all key domains are judged to be of low risk of bias. Studies have an unclear risk of bias if one or more domains are judged unclear. And studies have a high risk of bias if one or more key domains have a high risk of bias. In meta-analyses, a common procedure is to exclude all studies that are overall evaluated as having an unclear or high risk of bias. Next, sensitivity analyses can be performed to assess quantitatively how the low quality studies influence the outcome. Limitations of this method are that it is not possible to take into account that studies may have very different bias profiles. We therefore chose another approach by looking at each domain of bias separately. We performed sensitivity analyses assessing differences in pooled standardised effect size for each domain of bias that we regarded key for our research question. In our opinion, this enables a nuanced, transparent and more objective bias assessment. This method may be useful for other meta-analyses if risk of bias is very much spread over different domains in the included studies.

**Qualitative research in an international setting**

We performed a qualitative study in an international setting. This imposes an extra challenge to distinguish ‘real’ differences between the nurses’ practices and recommendations from differences in language and culture. We therefore took much time to comprehend each other’s primary care systems and the direct context in which the nurses work. We also put effort in translating all the relevant documents to English and had extensive meetings with the research teams. We did not include French nurses in our sample, although the HATICE platform is also being tested in France, since no nurses are currently engaged in CVRM care.

**Optimal development of internet-platforms**

During the development of the HATICE-platform, we realised how difficult it is to robustly develop and scientifically test an internet-platform in the fast changing world of digital development. At the time the HATICE-trial will be completed, part

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of the lay-out and functionalities will appear out-dated. One option to allow for more flexibility is the use of adaptive trial designs. This may enable more rigorous software updates during the ongoing trial. In this way the functionalities will be kept up-to-date while the principle content of the intervention will not change. This approach also has adverse effects, because most older people with limited computer skills may become confused by small lay-out changes and thus, this approach could induce extra disengagement.

**Mixed methods**
In this thesis, different research designs were used to develop the internet-platform and to study engagement with different forms of CVRM. This can be regarded as a mixed methods approach. The most important conclusions from this thesis were drawn from both quantitative and qualitative research and were further explored with qualitative research. We therefore provide an example of the synergy effect of combining quantitative and qualitative methods. This is especially appropriate for novel research fields involving health behaviour.

**DIRECTIONS FOR FUTURE RESEARCH**

**Recommendations for the development of future internet-platforms for older people**
Based on the developmental process of the HATICE-platform we offer a set of solutions for age-specific problems in using eHealth applications (table 1). An internet-platform for older people can be further personalised if the platform is adapted to the specific age related problems, for example adjusted to level of visual acuity, digital literacy or cognitive performance.

To prevent reinventing the wheel, the development of medical internet-platforms for older people may benefit from more cross-pollinations with other fields that develop eHealth applications. To stimulate engagement, best practices from application designers and online marketing might also be useful for medical applications. The application development industry has become very successful in developing applications, such as Facebook, Whatsapp, WeChat, Pinterest and Wordfeud, that are even considered addictive. An important mechanism that is used by these apps is habit-forming. Potentially, health applications can adopt these strategies, since internet-platforms for self-management may be most effective if they induce habit-forming as well.

Another suggestion to stimulate engagement with internet-platforms for CVRM is to facilitate ‘reactive’ use. One way to do this is to offer the functionalities of the platform...
in a more sequential form, adapting what is offered to the stage of change that the participant is in (table 2) and reducing the number of functionalities the participant can choose from. This was in fact already suggested by Albert Bandura in the practical elaboration of his social-cognitive theory for self-management and behavioural change. In combination with the use of electronic reminders, the patient is guided through the intervention, instead of having to explore everything him/herself. One may argue if stimulating ‘reactive’ use is still compatible with self-management as originally defined. Medical ethics philosopher Maartje Schermer makes a distinction between concordant self-management and compliant self-management. Concordant self-management matches the original definition of self-management (as described in the introduction of this thesis), aiming to empower patients to become well-informed problem solvers of their conditions and lives, supported by their health care providers. In compliant self-management, the educational and empowering aspects of self-management are less self-evident and the patient self-monitors his/her symptoms following suggestions from his/her health care provider. The health care provider reacts on the data provided and adjusts the therapy if needed, but the patient only executes the management but does not necessarily learn from it. This type of self-management may be stimulated with the ongoing development of technologies for monitoring that becomes more and more automated. This may impress as eHealth development taking the wrong turn. However, we do not think that facilitating ‘reactive’ use of our internet-platform will hamper ‘concordant’ self-management. The whole internet-intervention is centered around the motivational status of the user, and the user him/herself decides on what goals to set and how to monitor them. Furthermore, the use of motivational interviewing techniques by the health coach is specifically aimed to stimulate concordant self-management as well. Furthermore, it is also possible that ‘concordant’ self-management more easily leads to lack of commitment than ‘compliant’ self-management, especially in people with only minor elevated cardiovascular risk. This was mentioned by the interviewed participants in chapter 5, they preferred reactive use, because they found it difficult to self-initiate everything. Possibly, different combinations of ‘concordant’ and ‘compliant’ self-management are optimal for different patients, as was also suggested by one of the nurses interviewed in chapter 3:

“I think 2 or 3 types of platform users will arise: people who really get the concept of self-management (and start coaching themselves), people who need the coach (and give the coach access to their complete profile) and a group in between, alerting the coach if a goal has not been met.” (Dutch nurse 2)
Recommendations for future trials testing internet-platforms for older people

Based on our systematic review we recommend that future trials testing internet-platforms for older people specifically include older populations. Sustainability of effectiveness of the interventions can be better assessed by including prolonged follow-up intervals. Moreover, this would allow for measuring major clinical outcomes such as cardiovascular disease. Individual changes in levels of cardiovascular risk factors (blood pressure, cholesterol levels, weight) over time should be analysed in relation to adherence rates. More standardised descriptions of interventions and standardised evaluation methods will facilitate comparisons of interventions.

The HATICE RCT was designed with the aim to evaluate the clinical effectiveness of the HATICE internet-platform. The multi-component intervention was considered a ‘black box’. First, its effectiveness on improving the cardiovascular risk profile needs to be assessed and, hopefully, established. Next, it can be assessed which components of the intervention make it successful. However, if the RCT fails to demonstrate effectiveness, questions will rise regarding its implementation and it will be attempted to analyse the components of the intervention more in depth. We hope that this thesis has provided some starting points for further fine-tuning of the intervention. Internet-platforms for CVRM in older people may benefit from implementation research, “to understand what, why, and how interventions work in “real world” settings and to test approaches to improve them.” (Peters DH et al. BMJ 2013).

It is difficult to test an intervention for improvement of CVRM in a context of care were CVRM is already quite good and still being intensified, as is the case in the Netherlands, Finland and France. A strategy can be to target high-risk populations in countries with less developed CVRM programs, because these people have the largest window of opportunity. Furthermore, health care systems in these countries may profit most from the incorporation of eHealth applications. Because of these reasons, the AMC study group, together with the HATICE consortium initiated Prevention of Dementia using Mobile phone Applications (PRODEMOS). In this large scale project, the implementation of an mHealth dementia prevention intervention for people aged 55 years and older at increased risk for dementia will be tested in deprived area’s in the UK and in China. The mHealth dementia prevention intervention will build on the HATICE intervention adapted to a smart phone, and adapted to be socio-culturally appropriate in these different settings.

Recommendations for future trials testing internet-platforms for older people

Based on our systematic review we recommend that future trials testing internet-platforms for older people specifically include older populations. Sustainability of effectiveness of the interventions can be better assessed by including prolonged follow-up intervals. Moreover, this would allow for measuring major clinical outcomes such as cardiovascular disease. Individual changes in levels of cardiovascular risk factors (blood pressure, cholesterol levels, weight) over time should be analysed in relation to adherence rates. More standardised descriptions of interventions and standardised evaluation methods will facilitate comparisons of interventions.

The HATICE RCT was designed with the aim to evaluate the clinical effectiveness of the HATICE internet-platform. The multi-component intervention was considered a ‘black box’. First, its effectiveness on improving the cardiovascular risk profile needs to be assessed and, hopefully, established. Next, it can be assessed which components of the intervention make it successful. However, if the RCT fails to demonstrate effectiveness, questions will rise regarding its implementation and it will be attempted to analyse the components of the intervention more in depth. We hope that this thesis has provided some starting points for further fine-tuning of the intervention. Internet-platforms for CVRM in older people may benefit from implementation research, “to understand what, why, and how interventions work in “real world” settings and to test approaches to improve them.” (Peters DH et al. BMJ 2013).

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General discussion  Chapter 7

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CLINICAL CONSIDERATIONS – HOW TO SHAPE ONLINE SELF-MANAGEMENT OF CVRM FOR OLDER PEOPLE IN PRIMARY CARE?

We found compelling evidence that internet-platforms for CVRM work better if combined with human support. Furthermore, both the interviewed nurses and HATICE participants recommended to incorporate the internet-platform into the regular primary care setting. We first need to await the results of HATICE on the clinical effectiveness of the intervention, but one can already discuss potential benefits and drawbacks of the incorporation into regular care. An important benefit of incorporating the platform into regular care was formulated by the HATICE participants interviewed in chapter 5:

“I already visit the practice nurse, but there is a lot of time in between [visits] and then yes… Of course together we assess the results, look at it and discuss it. But when I’m gone, it [the support] is also gone. […] And this is, the continuity that you’re always working on it, that is good. ” [P2]

Thus, combining periodic face-to-face nurse visits with in-between use of the platform could augment the perceived continuity of support in self-management. By enhancing patients’ commitment with the goals set, this may potentially also stimulate long term engagement with health behaviour change. Other benefits are that it provides a safe context for the internet-platform to target both the lifestyle and medical aspects of CVRM, rather than the lifestyle aspects only, as is the case in the current HATICE-platform. One could hypothesis that online self-management interventions that also target medical aspects of CVRM are more powerful but may induce more adverse events. In the systematic review and meta-analysis (chapter 2), most of the included internet-interventions targeted both lifestyle and medical aspects of CVRM but some interventions only targeted lifestyle aspects of CVRM. Unfortunately, no subgroup analysis was performed to compare their effectiveness on CV risk reduction. In line with this issue, one could consider whether the person supporting the internet-platform should have a medical background or not. If an internet-platform is incorporated into regular primary care, it seems most obvious to attribute the support to a primary care nurse that is already dealing with CVRM. The interviewed Dutch and Finnish primary care nurses also suggested such an approach (chapter 3). In countries where primary care is organised differently, like in France, this role might fit other health care providers better. However, the interviewed HATICE participants (chapter 5) were very positive about the support provided by the HATICE health coaches who did not have a medical background. Possibly, a non-medical context of the platform

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contributes to a focus on health instead of disease, and a positive tone of voice. The preference for this positive attitude was one of the findings from the focus groups we performed with older Dutch, Finnish and French people in the developmental process of the HATICE-platform (briefly mentioned in chapter 4, manuscript currently under preparation). Further, people preferred a coaching attitude to a patronising attitude when it concerned lifestyle advice. This was also emphasised in a qualitative study with preDIVA participants evaluating the preDIVA intervention: lifestyle was regarded as something personal and should be discussed in dialogue. Last, people feared that internet-interventions would completely substitute face-to-face care. This fear is not unfounded considering the foreseen large rises in people in need of CVRM in the near future. However, the conclusions from this thesis indicate that human support is an essential element to increase the efficacy of eHealth applications. Perhaps, based on the level of cardiovascular risk (primary or secondary prevention), interventions could have different intensities, saving more intensive programs with more periodic face-to-face meetings for people with the highest risk.
REFERENCES


This thesis describes how self-management of the cardiovascular risk profile could be offered to older people using eHealth.

In chapter 1 we describe the background and aims of this thesis. Global ageing contributes to the fact that in the near future the number of people with cardiovascular disease or with elevated risk will rapidly increase. Older people (people aged 65 years and older) form an important target group because they are often at high risk for cardiovascular disease and they will still benefit from interventions that reduce the risks. Current cardiovascular risk programmes do not yet completely address the specific needs of older people. Moreover, current cardiovascular risk programmes are not future-proof yet, because they do not have the capacity to support everybody at risk and their effectiveness in daily practice is markedly lower than expected based on scientific evidence. An important factor related to this is the fact that it is notoriously difficult to adhere to a lifelong healthy lifestyle and medication use. This requires an enduring health behaviour change. Innovative strategies are needed to make cardiovascular risk management more future-proof. Self-management is a promising strategy to stimulate adherence. EHealth provides many opportunities to provide online self-management programmes to large groups of patients. Older people do not yet use the internet as massively as younger people, but in Europe, the number of older people that frequently uses the internet is increasing rapidly. The European project ‘Healthy Ageing Through Internet Counselling in the Elderly’ (HATICE) therefore aims to develop an internet-platform for cardiovascular self-management in older people. The studies described in this thesis have been performed in the context of HATICE. In part 1 we describe the development of an internet-intervention for cardiovascular self-management in older people (the HATICE-platform). In part 2 we describe research on engagement of older people in innovative forms of cardiovascular risk-management.

PART 1: DEVELOPMENT OF AN INTERNET-PLATFORM FOR CARDIOVASCULAR RISK SELF-MANAGEMENT IN OLDER PEOPLE

In chapter 2 we present the results of a systematic review and meta-analysis on randomised controlled trials (RCTs) testing the effectiveness of internet-interventions for cardiovascular risk management in older people. We found 57 studies that fulfilled inclusion criteria. The first conclusion was that research on internet interventions specifically targeting older people is still scarce; in only 7 out of the 57 trials, all participants were aged 50 years and older. In the other included trials, the mean age of the populations was 50 years or older. 47 out of the 57 studies could be used for the meta-analysis. The meta-analyses showed that the internet interventions lead to...
small but significant improvements of the cardiovascular risk factors: blood pressure, LDL-cholesterol, weight and amount of physical activity. Compared to the control group, the systolic blood pressure in the intervention group was on average 2.66 mmHg (95%-confidence interval: -3.81 to -1.52 mmHg) lower and the level of LDL-cholesterol was on average -0.06 mmol/l lower (95%- confidence interval: -0.10 to 0.01mmol/l) lower. No difference was found between the groups in incidence of new cardiovascular events. However, this was measured in only six studies with a relatively short follow-up interval (on average 13 months). In further analyses, we found that the beneficial effects of the internet-interventions are smaller with longer study duration. Our hypothesis is that this may be mediated by reduced adherence to the intervention. Finally, we found that studies that combined the internet-intervention with human support induced larger effects than stand-alone interventions. We concluded therefore that internet-interventions have a beneficial effect on improvement of the cardiovascular risk profile, but that this effect is modest and declines with time. Future research should focus on interventions specially targeting older people, interventions combined with human support, maintenance of effects and measuring major clinical endpoints.

In chapter 3 we present the results of one of the sequential steps in the development of the internet-platform. Here, we performed an international focus group study with six Finnish and seven Dutch primary care nurses that were experienced in cardiovascular risk management. We investigated their experiences with supporting health behaviour change for cardiovascular risk management. Next, we asked how they envisioned this guidance could be provided with a coach-supported internet-platform. The Finnish and Dutch nurses indicated three preconditions for good support of health behaviour change: building a relationship of trust, awareness and expectation management, and appropriate timing of support (matching the stage of change). To accomplish these preconditions the Finnish and Dutch nurses used largely the same practical approaches, but there were also small differences. The Finnish nurses were accustomed to frequent consultations by telephone, because their patients often lived at considerable distances. Further, the Finnish nurses took a supporting role with regard to both lifestyle and medical components of cardiovascular risk management. The Finnish nurses relied on telephone-contact and the Dutch nurses more on face-to-face contact. For the Dutch nurses, frequent face-to-face contact was essential for the development of a relationship of trust. They interacted with their patients in a supportive fashion when it concerned lifestyle but in case of medical issues, their attitude was more directive, because they found that these matters belonged to the responsibility of the general practice. Next, we discussed how an internet-intervention could provide optimal support for health behaviour change for cardiovascular risk management. Both groups of nurses...
emphasised that an online intervention should be combined with human support and implemented in regular care. The Dutch nurses had a reserved attitude, they were not convinced a relationship of trust could be realised with mostly online contact. They also suggested that such a platform should only target lifestyle, because they regarded it more safe to limit the medical guidance to the general practice. The Finnish nurses had a more embracing attitude towards online cardiovascular risk management, regarding it a logical development towards the future of medicine, provided that human support was ensured and the first contact was face-to-face. We concluded that the differences in practical approaches and attitudes towards the internet-platform were associated with differences in geography, culture and local primary care organisation. Possibly, Finnish nurses are further ahead in adopting a self-management stimulating attitude than the Dutch nurses.

In chapter 4 we describe the complete development process of the internet-platform and the pilot in which we tested platform feasibility among 41 older people from the Netherlands, Finland and France. The development process included systematic literature research (described in chapter 2), evaluation of clinical guidelines and health behaviour theories, discussions with experts in communications with older people and in cardiology, meetings with representatives of patient organisations, extensive brainstorm sessions by researchers and software developers, consultations with end-users (older people and nurses (described in chapter 3)), testing sessions with older people and the international pilot study. The final platform is a personalised, secured, interactive internet-platform for self-management of the lifestyle components of seven modifiable cardiovascular risk factors (hypertension, overweight, elevated cholesterol levels, smoking, unhealthy diet, physical inactivity and diabetes) with support from a health coach. The development process and the pilot resulted in a series of recommendations for a senior-friendly internet-platform. These recommendations included: big font size, a simple lay-out, a limited amount of webpages to simplify navigation, clear and concise information texts, no links to locations outside of the platform, simple login procedure and a positive tone of voice focusing on health instead of disease. The pilot revealed that the login procedure needed to be simplified further and that the platform was not accessible easily from outdated browsers. During the pilot, participants self-monitored their blood pressure, weight and level of exercise. The self-monitoring functionalities for smoking cessation and diabetes were not used. During the evaluation session people were positive about the platform, emphasising mostly the support from the health coach.

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PART 2: ENGAGEMENT OF OLDER PEOPLE IN EHEALTH OR NURSE-LED CVRM

In chapter 5 we present the results of an interview study with 17 Dutch participants of the HATICE trial. In the interviews, it was discussed how the participants used the internet-platform in order to identify factors associated with engagement with the internet-platform. We distinguished initial and sustained engagement. The following factors stimulated initial engagement: computer self-efficacy (trust in your own computer skills), platform senior user friendliness, acceptability and perceived appropriateness of the intervention and initial interaction with the health coach. For sustained engagement, building a relationship of trust was the most important factor. Other stimulating factors were regular automatic and personal reminders, having clear expectations of the platform, incorporating the use of the platform into daily routine, getting social support and having a loyal and persistent attitude. These findings confirm the importance of incorporating human support into an internet-platform for older people, and suggest this may enhance engagement with the intervention. The participants further preferred the internet-platform to be implemented into regular primary care. If a practice nurse would adopt the role of health coach, this could augment continuity of care, which potentially would also lead to enhanced engagement to therapy.

In chapter 6 we present research into engagement of older people with another cardiovascular risk management intervention, the nurse-led intensive vascular care intervention. This intervention was tested in the Prevention of Dementia by Intensive Vascular Care (preDIVA) trial. This randomised controlled trial included 3,526 Dutch community dwelling older people and investigated whether 6 years of intensive vascular care provided to older people could prevent dementia. We explored factors associated with dropout from the trial and with non-adherence to the intervention. We found that higher age, lower levels of cognition, symptoms of depression and disability were associated with a higher risk on dropout. In the control group, more people with lower levels of cognitions and/or symptoms of depression dropped out than in the intervention group. This finding may be important for other dementia prevention trials to take into account, because this differential dropout could bias study outcomes. A solution is to choose a major clinical endpoint (such as incidence of dementia) or to invest in dropout retrieval. This was both done in the preDIVA trial. The findings of this research also suggest that, in clinical practice, it may merit to regularly see older people with these characteristics to stimulate engagement with care. The factors associated with dropout were not associated with non-adherence. We found that people with overweight were more often non-adherent and, on the other hand, people associated with dropout were not associated with non-adherence. We found that higher age, lower levels of cognition, symptoms of depression and disability were associated with a higher risk on dropout. In the control group, more people with lower levels of cognitions and/or symptoms of depression dropped out than in the intervention group. This finding may be important for other dementia prevention trials to take into account, because this differential dropout could bias study outcomes. A solution is to choose a major clinical endpoint (such as incidence of dementia) or to invest in dropout retrieval. This was both done in the preDIVA trial. The findings of this research also suggest that, in clinical practice, it may merit to regularly see older people with these characteristics to stimulate engagement with care. The factors associated with dropout were not associated with non-adherence. We found that people with overweight were more often non-adherent and, on the other hand, people...
with hypertension or physical inactivity were more often adherent to the intervention. These findings are novel and need to be reproduced. We expect the external validity of our findings to be large, because the preDIVA population constitutes a good reflection of a normal Dutch population of older people and because the intervention was offered in the setting of people's own general practices.

In chapter 7 we discuss the main findings of this thesis, some methodological considerations, recommendations for future studies and for clinical practice. The main findings are: (1) there exist only few internet-interventions for cardiovascular self-management that specifically have been developed for older people; (2) internet-interventions for cardiovascular risk self-management have a beneficial effect on reducing cardiovascular risk, but effects are modest and decline with time; (3) internet-interventions for cardiovascular self-management are more effective if combined with human support; (4) provided that the developmental process was meticulous with close involvement of the end-users, an internet-intervention can be developed that is feasible and acceptable to use for older people; (5) the additional value of human support of an internet-intervention may lay in, among other factors, the establishment of a relationship of trust and increasing engagement of the participants with the intervention; (6) integration of an internet-platform into regular care could contribute to continuity of care; (7) participants with lower levels of cognition and/or symptoms of depression have a higher risk to dropout from a dementia prevention trial, this risk is more pronounced for control group participants than for intervention group participants.

Worldwide, health care systems face large challenges due to the large increase in people with cardiovascular disease or at elevated risk. This thesis provides starting points on how to develop an eHealth application for cardiovascular self-management for older people. The results of this thesis indicate that human support forms an essential component of internet-interventions to increase their effectiveness. Currently, the effectiveness of the HATICE-platform is being tested in a large randomised controlled trial with 2,725 older participants in the Netherlands, Finland and France.

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Addendum

Dutch summary (Nederlandse samenvatting)
Author contributions
Co-author affiliations
List of publications
PhD portfolio
About the author
Acknowledgements (Dankwoord)
DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)

Dit proefschrift beschrijft onderzoek naar zelfmanagement van het cardiovasculair risicoprofiel door ouderen en de mogelijkheden die eHealth daarbij biedt. Met andere woorden: hoe kunnen we ouderen met behulp van online hulpmiddelen ondersteunen om zo te leven dat ze minder last krijgen van hart- en vaatziekten?

In hoofdstuk 1 lichten we de achtergrond en doelstellingen van dit proefschrift toe. De wereldwijde vergrijzing draagt eraan bij dat in de nabije toekomst het aantal mensen met hart- en vaatziekten of een verhoogd risico hierop snel zal toenemen. Ouderen (mensen met een leeftijd van 65 jaar en ouder) vormen een belangrijke doelgroep in deze populatie, want zij hebben vaak een verhoogd risico op hart- en vaatziekten en zij hebben nog steeds veel profijt van een interventie die het risico verlaagt. In de praktijk is dit nog niet altijd even goed zichtbaar. In de huidige programma’s voor cardiovasculair risicomanagement wordt nog maar beperkt aandacht besteed aan ouderen. Tevens zijn de huidige cardiovasculaire risicomanagement programma’s nog niet voorbereid op de toekomst; ze hebben onvoldoende capaciteit om alle toekomstige mensen met een verhoogd risico op hart- en vaatziekten zorg te bieden. Daarnaast zijn ze ook minder effectief in de dagelijkse praktijk dan men op basis van wetenschappelijk onderzoek mag verwachten. Een factor die hierbij een belangrijke rol speelt, is dat het erg moeilijk is om een gezonde leefstijl en het trouw innemen van medicatie een leven lang vol te houden. Dat vergt een gedragsverandering die vervolgens vastgehouden moet worden.

Er zijn innovatieve strategieën nodig om cardiovasculair risicomanagement toekomstbestendig te maken, bijvoorbeeld op het gebied van zelfmanagement eHealth. Zelfmanagement wordt als een veelbelovende strategie gezien om therapietrouw te bevorderen. EHealth biedt veel mogelijkheden om zelfmanagementprogramma’s online aan te bieden aan grote groepen patiënten. Onder ouderen is het internetgebruik nog niet zo wijdverspreid als onder andere leeftijdsgroepen, maar het aantal ouderen dat internet gebruikt in Europa stijgt snel. Het Europese project ‘Healthy Ageing Through Internet Counselling in the Elderly’ (HATICE) heeft daarom als doel een internetplatform te ontwikkelen voor cardiovasculair zelfmanagement bij ouderen. De onderzoeken in dit proefschrift zijn gedaan in het kader van HATICE. In deel 1 beschrijven we de ontwikkeling van een internetplatform voor cardiovasculair zelfmanagement bij ouderen (het HATICE-platform). In deel 2 beschrijven we onderzoek naar de betrokkenheid van ouderen bij eHealth en cardiovasculair risicomanagement.

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DEEL 1: ONTWIKKELING VAN EEN INTERNET-INTERVENTIE VOOR CARDIOVASCULAIR ZELFMANAGEMENT BIJ OUDEREN

In hoofdstuk 2 presenteren we de resultaten van een systematisch literatuuronderzoek naar de effectiviteit van internetinterventies voor cardiovasculair risicomanagement bij ouderen, die onderzocht werden in gerandomiseerde gecontroleerde onderzoeken. We vonden 57 onderzoeken die voldeden aan onze inclusiecriteria. De eerste conclusie was dat er nog maar weinig internetinterventies specifiek voor ouderen onderzocht zijn, in slechts zeven onderzoeken waren alle deelnemers ouder dan 50 jaar. In de andere onderzoeken was de gemiddelde leeftijd 50 jaar of ouder. 47 van de 57 onderzoeken konden gebruikt worden voor meta-analyses. We vonden bij deze analyses dat de internetinterventies leidden tot kleine maar significante verbeteringen van de volgende cardiovasculaire risicofactoren: bloeddruk, LDL-cholesterolwaarde, gewicht en hoeveelheid lichamelijke activiteit. Ten opzichte van de controlegroep was de systolische bloeddruk in de interventiegroep gemiddeld -2,66 mmHg lager (95%-betrouwbaarheidsinterval: -3,81 - -1,52 mmHg) en de LDL-cholesterolwaarde gemiddeld -0,06 mmol/l lager (95%-betrouwbaarheidsinterval: -0,10 - -0,01 mmol/l). We vonden geen significante verschil in het aantal nieuwe hart- en vaatziekten tussen de groepen met en zonder internetinterventie. Dit was echter slechts in zes onderzoeken gemeten die een betrekkelijk korte duur hadden (gemiddeld 13 maanden). In verdere analyses vonden we dat de effecten van de internetinterventies kleiner zijn bij een langere onderzoeksduur. Onze hypothese is dat een afname in betrokkenheid bij de interventie hierbij een rol speelt. Als laatste vonden we dat onderzoeken, waarin de internetinterventie gecombineerd werd met ondersteuning door een zorgverlener, een groter effect hadden dan de interventies die op zichzelf stonden. We concludeerden daarom dat internetinterventies een gunstig effect hebben op verbetering van het cardiovasculair risicoprofiel, maar dat het gaat om een bescheiden effect dat afneemt in de tijd. Toekomstig onderzoek zou zich moeten richten op interventies speciaal voor ouderen, op interventies gecombineerd met menselijke ondersteuning, op de duurzaamheid van effecten en het meten van klinische uitkomsten.

In hoofdstuk 3 presenteren we de resultaten van een van de vervolgstappen in de ontwikkeling van het internetplatform. Hier deden we internationaal focusgroep onderzoek met zes Finse en zeven Nederlandse eerstelijnsverpleegkundigen die ervaring hadden met cardiovasculair risicomanagement. We onderzochten eerst wat hun ervaringen zijn met het stimuleren van hun patiënten tot een gezonde gedragsverandering in het kader van cardiovasculair risicomanagement. Vervolgens vroegen we ze hoe een internetinterventie dergelijke ondersteuning zou kunnen bieden.
De Finse en Nederlandse verpleegkundigen noemden hiervoor dezelfde drie voorwaarden: het opbouwen van een vertrouwensrelatie, het creëren van risicobewustzijn en realistische verwachtingen, en de gebeden ondersteuning afstemmen op de motivatie van de patiënt. Om deze voorwaarden te realiseren gebruikten de Finse en Nederlandse verpleegkundigen in grote lijnen dezelfde werkwijzen, maar er waren kleine verschillen. De Finse verpleegkundigen waren gewend om veel consulten telefonisch uit te voeren, onder andere vanwege de dunbevolking van hun regio. Zij waren ook gewend een ondersteunende rol aan te nemen bij zowel leefstijl-gerateerde als medische zaken. De Nederlandse verpleegkundigen vonden het essentieel om hun patiënten regelmatig echt te zien, om een vertrouwensband te kunnen opbouwen. Hun interactie met de patiënt was voor leefstijl-gerateerde zaken ook ondersteunend, maar wat betreft medische zaken vonden ze het belangrijk dat de huisartspraktijk hiervoor de verantwoordelijkheid behield.

Vervolgens bespreken we hoe een interventie via internet ondersteuning zou moeten bieden voor gedragsverandering ten behoeve van cardiovascular risicomangement. Beide groepen verpleegkundigen vonden de combinatie met menselijke ondersteuning essentieel, alsmede om zo’n internetinterventie te integreren in de reguliere zorg. De houding van de Nederlandse verpleegkundigen was enigszins terughoudend; het leek hen niet goed mogelijk om een vertrouwensband op te bouwen als de communicatie grotendeels online zou verlopen. Daarnaast vond het veiliger als het internetplatform zich alleen op de leefstijlaspecten van cardiovascular risicomangement zou richten. De Finse verpleegkundigen zagen een internetplatform voor cardiovascular zelfmanagement als een logische ontwikkeling richting de toekomst. Mits ondersteund door een zorgverlener en geïntegreerd met een echte kennismaking, hadden ze het idee via zo’n platform op dezelfde manier te kunnen werken als ze nu gewend waren. Wij concludeerden dat de verschillen in werkwijze waarschijnlijk berusten op verschillen in geografie, cultuur en plaatselijke organisatie van de eerstelijnszorg. Zelfmanagement vraagt zorgverlener een coachende rol aan te nemen in de relatie met de patiënt. Mogelijk hebben de Finse verpleegkundigen zich deze rol al iets meer eigen gemaakt dan de Nederlandse verpleegkundigen.

In hoofdstuk 4 beschrijven we het complete ontwikkelproces van het internetplatform en het pilotonderzoek waarin het platform gebruikt werd door 41 ouderen uit Nederland, Finland en Frankrijk. Het ontwikkelproces bestond uit literatuuronderzoek (beschreven in hoofdstuk 2), evaluatie van klinische richtlijnen en gedragswetenschappelijke theorieën, gesprekken met experts in communicatie met ouderen en in cardiologie, gesprekken met vertegenwoordigers van patiëntenorganisaties, uitgebreide brainstormsessies met wetenschappers en
softwareontwikkelaars, raadpleging van de doelgroepen (ouderen en verpleegkundigen (beschreven in hoofdstuk 3)), testmiddagen met ouderen en het pilotonderzoek. Het uiteindelijke platform is een gepersonaliseerd, beveiligd, interactief internetplatform voor zelfmanagement van de leefstijlaspecten van zeven modificeerbare cardiovasculaire risicofactoren (hoge bloeddruk, overgewicht, te hoog cholesterol, roken, ongezond dieet, te weinig beweging en diabetes) met ondersteuning door een gezondheidscoach. Het ontwikkelproces en de pilot leverde een reeks aanpassingen op om het platform zo gebruiksvriendelijk mogelijk voor ouderen te maken. Deze hielden onder andere in: groot lettertype, simpele lay-out, een platform dat bestaat uit een beperkt aantal webpagina’s om navigeren te versimpelen, informatieteksten zijn helder en bondig geformuleerd, geen links naar websites buiten het platform, simpele inlogprocedure en een positieve toon waarbij het platform gezondheid benadrukt in plaats van ziekte. Bij de pilot kwamen enkele kinderzakjes aan het licht zoals dat de inlogprocedure nog steeds te ingewikkeld was en het platform niet goed toegankelijk was op computers met verouderde browsers. Tijdens de pilot hielden veel deelnemers meteen bij voor bloeddruk, bewegen en gewicht, maar niemand hield dit bij voor diabetes en roken. In een evaluatiebijeenkomst uitten de deelnemers zich positief over het platform, waarbij zij met name de ondersteuning door de gezondheidscoach noemden.

DEEL 2: BETROKKENHEID VAN OUDEREN BIJ EHEALTH EN CARDIOVASCULAIR RISICOMANAGEMENT

In hoofdstuk 5 presenteren we de resultaten van een interviewonderzoek met 17 Nederlandse deelnemers van het HATICE-onderzoek. In de interviews werd besproken hoe de deelnemers het internetplatform gebruikten of gebruik hadden om zo factoren van invloed op betrokkenheid bij het internetplatform te identificeren. We maakten onderscheid tussen initiële betrokkenheid en langdurige betrokkenheid. De volgende factoren waren van stimulerende invloed op initiële betrokkenheid: vertrouwen in eigen computervaardigheden, gebruiksvriendelijkheid van het platform voor ouderen, mate waarin het platform als acceptabel en relevant wordt beschouwd en het eerste contact met de coach. Voor langdurige betrokkenheid was het opbouwen van een vertrouwensband met de coach de belangrijkste stimulerende factor. We identificeerden ook periodieke communicatieve en persoonlijke herinneringsberichten, het hebben van heldere verwachtingen van het platform, het inpassen van het platform in de dagelijkse routine, het ontvangen van sociale steun en een plichtgetrouwe persoonlijkheid als stimulerende factoren. Deze bevindingen bevestigen het belang van menselijke ondersteuning bij een internetplatform voor ouderen, wat mogelijk bijdraagt aan een grotere betrokkenheid bij de interventie. Deelnemers vonden verder dat het internetplatform geïmplementeerd moest worden in de reguliere eerstelijnszorg.

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Als een praktijkondersteuner de rol van coach op zich zou nemen, zou dit bijdragen aan de continuïteit van zorg, wat mogelijk therapietrouw aan de behandeling ook ten goede zou komen.

**In hoofdstuk 6** presenteren we het onderzoek naar de betrokkenheid van ouderen bij een andere cardiovascular risicomanagement interventie, namelijk intensieve vaatzorg door middel van frequentie bezoeken aan de praktijkondersteuner. Deze interventie werd onderzocht in het Preventie van Dementie via Intensieve Vaatzorg (preDIVA)-onderzoek. Dit was een gerandomiseerd gecontroleerd onderzoek met 3526 Nederlandse ouderen waarbij onderzocht werd of het geven van zes jaar intensieve vaatzorg aan ouderen dementia kan voorkomen. We keken naar factoren geassocieerd met onderzoeksuitval en met het niet voldoende deelnemen (therapieontrouw) aan de interventie. We vonden dat een hogere leeftijd, aanwijzingen voor een verminderde cognitie, symptomen van depressie en beperkingen in het dagelijks functioneren geassocieerd waren met een hoger risico op uitval uit het onderzoek. In de controlegroep vielen meer mensen uit met een verminderde cognitie en/of symptomen van depressie dan in de interventiegroep. Dit is een belangrijke bevinding waar andere dementieonderzoeken rekening mee moeten houden omdat deze ongelijke uitval de uitkomsten van onderzoeken kan vertekenen. Een oplossing kan zijn om een harde klinische uitkomstmee aan te kiezen (zoals incidentie van dementie) of te investeren in het terugzoeken van deelnemers die uitgevallen zijn. Dit is beide gedaan in het preDIVA-onderzoek. Dit onderzoek suggereert ook dat het mogelijk loont om in de klinische praktijk mensen met deze kenmerken regelmatig te zien om betrokkenheid bij de zorg te stimuleren. De factoren geassocieerd met onderzoeksuitval waren niet geassocieerd met therapieontrouw, maar we vonden wel dat deelnemers met overgewicht vaker therapieontrouw waren en deelnemers met hypertensie of lichamelijke inactiviteit juist vaker therapietrouw. Deze bevindingen zijn nieuw en moeten geregistreerd worden. We verwachten wel dat de externe validiteit van onze bevindingen groot is, omdat de preDIVA populatie een goede afspiegeling is van een normale populatie van Nederlandse ouderen, en omdat de interventie geïntegreerd in de huisartspraktijk werd aangeboden.

In **hoofdstuk 7** bediscussiëren we de belangrijkste bevindingen van dit proefschrift, enkele methodologische overwegingen, aanbevelingen voor toekomstig onderzoek en de klinische praktijk. De belangrijkste bevindingen zijn: (1) er zijn nog maar weinig internetinterventies voor cardiovascular zelfmanagement die specifiek zijn ontwikkeld voor ouderen; (2) internetinterventies voor cardiovascular zelfmanagement hebben een gunstig effect op het verlagen van het cardiovascular risico, maar de effecten zijn bescheiden en nemen af in de tijd; (3) internetinterventies voor cardiovascular
zelfmanagement zijn effectiever als zij gecombineerd worden met menselijke ondersteuning; (4) als een internetinterventie zorgvuldig wordt ontworpen met betrekking van de eindgebruikers leidt dit tot een acceptabel en gebruiksvriendelijk platform voor ouderen; (5) de meerwaarde van menselijke ondersteuning van een internetinterventie ligt onder andere in het opbouwen van een vertrouwensband en het vergroten van de betrokkenheid van deelnemers met het platform; (6) integratie van een internetplatform in de reguliere eerstelijnszorg kan bijdragen aan continuïteit van zorg; (7) deelnemers met een verminderde cognitie en/of symptomen van depressie hebben een groter risico om uit te vallen uit een dementie preventie onderzoek, dit risico is groter voor de controledeleenemers dan de interventiedeleenemers.

Gezondheidszorgsystemen wereldwijd staan voor grote uitdagingen door de snelle groei van het aantal mensen met hart- en vaatziekten of een verhoogd risico hierop. Dit proefschrift biedt aanknopingspunten hoe een eHealth applicatie voor cardiovasculair zelfmanagement voor ouderen ontworpen kan worden. De resultaten van dit proefschrift wijzen erop dat menselijke ondersteuning een essentieel onderdeel is om de effectiviteit van internetinterventies te vergroten. Momenteel wordt de effectiviteit van het HATICE-platform onderzocht in een groot gerandomiseerd gecontroleerd onderzoek waaraan 2,725 ouderen deelnemen in Nederland, Finland en Frankrijk.
AUTHOR CONTRIBUTIONS

Cathrien Beishuizen had full access to all the data presented in this thesis and takes responsibility for the integrity of the work as a whole. The relative contributions of co-authors are specified below:

Chapter 2
Edo Richard, Eric Moll van Charante, Willem van Gool, Carol Brayne, Miia Kivipelto, Sandrine Andrieu and Hilkka Soininen conceived the study. Cathrien Beishuizen, Blossom Stephan and Edo Richard wrote the study protocol and analysis plan. Cathrien Beishuizen and Blossom Stephan collected and extracted the data, with support from Edo Richard and Eric Moll van Charante. Cathrien Beishuizen performed the statistical analysis, supported by Blossom Stephan, Edo Richard, Wim Busschers and Willem van Gool. Cathrien Beishuizen and Edo Richard drafted the manuscript and all authors critically revised the manuscript for important intellectual content.

Chapter 3
Cathrien Beishuizen, Edo Richard, Eric Moll van Charante, Hilkka Soininen, Francesca Mangialasche and Miia Kivipelto designed the study. Cathrien Beishuizen, Mariagnese Barbera and Anna Rosenberg acquired the data. Cathrien Beishuizen, Ulrika Akenine, Mariagnese Barbera and Anna Rosenberg analysed the data. Cathrien Beishuizen, Ulrika Akenine, Mariagnese Barbera, Anna Rosenberg, Francesca Mangialasche, Eric Moll van Charante and Jeannette Pols were responsible for interpretation of the results. Cathrien Beishuizen drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

Chapter 4
Edo Richard, Eric Moll van Charante, Miia Kivipelto, Sandrine Andrieu, Hilkka Soininen en Bram van de Groep conceived the study. Matthijs van Dorp and Bram van de Groep developed the software. Cathrien Beishuizen, Susan Jongstra, Mariagnese Barbera and Juliette Guillemont acquired the data. Cathrien Beishuizen en Susan Jongstra analysed the data and drafted the manuscript. All authors critically revised the manuscript for important intellectual content.
Chapter 5
Tessa van Middelaar, Cathrien Beishuizen, Edo Richard and Eric Moll van Charante designed the study. Tessa van Middelaar and Cathrien Beishuizen acquired and analysed the data. Tessa van Middelaar, Cathrien Beishuizen, Eric Moll van Charante, Edo Richard, Juliette Guillemont and Mariagnese Barbera were responsible for interpretation of the data. Tessa van Middelaar and Cathrien Beishuizen drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

Chapter 6
Willem van Gool, Edo Richard and Eric Moll van Charante were responsible for the conception, design and conduct of the preDIVA trial and data collection. Cathrien Beishuizen, Edo Richard, Nicola Coley and Sandrine Andrieu wrote the study protocol and analysis plan. Cathrien Beishuizen performed the statistical analysis, with support from Nicola Coley. All authors were responsible for interpretation of the results. Cathrien Beishuizen drafted the manuscript. All authors critically revised the manuscript for important intellectual content.
Addendum

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**List of publications**

**This thesis**


**Other**


**PHD PORTFOLIO**

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PhD period: January 2013 – December 2017  
Name PhD supervisor: Prof. Dr. W.A. van Gool  
Co-promotores: Dr. E. Richard, Dr. E.P. Moll van Charante  
Department: Neurology, General Practice

**PHD TRAINING**

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<td>Innovation for Health Conference (Rotterdam)</td>
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<tr>
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### TEACHING

#### Lecturing

Lecture for 1st year Medical Information Sciences students: 'Development of an eHealth platform for older people'
- 2014, 2015: 1.0

Workshop for 3rd year Medical students: the neurological examination
- 2015: 0.5

#### Tutoring, Mentoring, Supervising

Floor Roosken (bachelor thesis, systematic review entitled: 'Lifestyle interventions in the elderly; what type is best to sustainably prevent cardiovascular diseases?')
- 2013-2014: 3

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PhD portfolio

### (Inter)national conferences

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ABOUT THE AUTHOR

Cathrien Regina Louisa Beishuizen (1985) was born and raised in Amsterdam. After graduating from the Ignatius Gymnasium in Amsterdam, she spent half a year in Perugia, Italy, to learn Italian. In 2004, she started her medical studies at the Academic Medical Center of the University of Amsterdam. In 2005 and 2006, she did a minor in Philosophy at the University of Amsterdam. Her interest in research developed during her research-internship at the Department of Experimental Immunology, where she studied effects of CD70 stimulation on humoral immune responses in mice (supervisors: prof. dr. R.A.W. van Lier and dr. K.J.P.M. van Gisbergen). During her medical studies, as a side job, she provided home care to older people, growing an affinity for older people. In 2009, she paused her medical studies to work one year as a volunteer teaching-assistant at the Department of Family and Community Health of the Medical Faculty of the Catholic University of Mozambique in Beira, Mozambique. Here, she developed an interest in prevention, public health and family medicine. Back in the Netherlands, she started her two year of clinical rotations, which she completed with an elective internship in Tropical Medicine in Turiani Hospital, Tanzania and a final internship in Internal Medicine in Spaarne Gasthuis (former: Kennemer Gasthuis), Haarlem. During the rotations she decided she wanted to become a general practitioner. She obtained her medical degree in 2012. At the beginning of 2013, she started her PhD research at the Department of Neurology and General Practice under supervision of prof. dr. W.A. van Gool, dr. E. Richard and dr. E. P. Moll van Charante. Here, she found many of her interests combined, including preventive health, older people and doing research in the context of primary care. In 2014, she was given the opportunity to spend 5 months as a visiting scholar at the University of Toulouse under supervision of prof. dr. S. Andrieu and dr. N. Coley, as an exchange within the HATICE-consortium.

Currently, Cathrien works as a resident in Geriatric Psychiatry at Zuiderpoort GGZinGeest, Haarlem. In march 2018, she starts her training to become a general practitioner at the Academic Medical Center of Amsterdam. Cathrien lives together with her partner Jochem Lybaart and their daughter Mercia.
ACKNOWLEDGEMENTS (DANKWOORD)

In januari 2013 begon ik aan dit promotietraject. Het was een ontzettend leuke en afwisselende tijd, waarin ik mij breed heb kunnen ontwikkelen als wetenschapper en als mens. Dankzij de veelzijdige bagage die het onderzoek mij bracht, voel ik me gesterkt om te beginnen aan de huisartsopleiding. Het promoveren ging niet zonder slag of stoot en de laatste loodjes waren zwaar. Zonder de hulp en steun van velen was het niet gelukt, waarvoor ik hen zeer dankbaar ben. Een aantal mensen wil ik in het bijzonder bedanken.

Graag wil ik iedereen die deelnam aan HATICE en PreDIVA hartelijk danken. Zonder jullie geen wetenschappelijk onderzoek. Ook de huisartspraktijken wil ik hartelijk danken voor hun deelname.

Beste prof. dr. van Gool, beste Pim, ik prijs mij een zeer gelukkige promovendus met jou als promotor en het was een groot voorrecht promovendus te zijn. Je liet me zien hoe tegelijk een integere en pragmatische wetenschapper te zijn. Ik heb heel veel bewondering voor je arbeidsethos, drive, nieuwsgierigheid, denkkracht en mentale flexibiliteit. Je gaf vrijheid maar was er altijd, en direct, als ik je hulp vroeg. Je oplossingen gaven helderheid, inzicht en inspiratie. Ik heb een heel goede herinnering aan de rondeleiding die je me gaf op Dijk en Duin, en het leidde tot een waardevol jaar aanlossen in de ouderenpsychiatrie. Dankjewel dat je oog had voor mijn gezin en me ook het laatste jaar duidelijk coachte dat het me lukte om het proefschrift af te ronden.


Edo, je grote betrokkenheid in het begin gaf mijn onderzoek een solide basis van waaruit HATICE en het proefschrift vanzelf vorm kregen. Ik heb van jou erg veel geleerd, maar het belangrijkste is helder formuleren en presenteren en natuurlijk om het simpel te houden. Ik vind het inspirerend hoe je HATICE hebt geleid en ervoor zorgde dat de doelstellingen werden gehaald, ook al was de Europese samenwerking soms behoorlijk uitdagend, en ik heb veel bewondering voor je enorme drive.

Eric, waar Edo de grote lijn in de gaten hield, zorgde jij voor de nodige verdieping. Ik vond de discussies die we hadden over onze kwalitatieve onderzoeksbevindingen ontzettend waardevol. Het is inspirerend te zien hoe je werk en privé combineert en

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ruimte maakt voor muziek. Ik ben erg blij dat ik je advies om een jaar te aniossen ter harte heb genomen, daardoor ben ik nu overtuigd klaar voor de huisartsopleiding.


Alle co-auteurs: hartelijk dank voor de inspirerende samenwerking. Dear Blossom, I very much enjoyed doing the systematic review and meta-analysis together with you, thank you very much for all your efforts.

De HATICE-onderzoeksprogramma in het AMC:

Lieve Susan, wij vormden een goed team, ondanks of (waarschijnlijk) dankzij onze verschillende eigenschappen, maar met eenzelfde gevoel voor humor. Ik heb veel bewondering voor je doelgerichtheid en het niet uit de weg gaan van verantwoordelijkheid. Ik ben van nature uit op harmonie, maar heb van jou geleerd een confrontatie aan te gaan en te staan voor je overtuigingen. Daarnaast wil ik je erg bedanken voor je zorgzaamheid. Het was fijn om met je te sparen en om lief en leed te delen en ik hoop dat wij dat in de toekomst blijven doen. Dankjewel dat je naast me wil staan als paranimf.

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Lieve Marieke, wat fijn dat jij met je kennis en kunde HATICE en preDIVA kwam versterken. Ik ben erg gesteld geraakt op je no-nonsense houding en je grote hart.

Lieve Carin, jij ziet geen enkele beer op de weg en krijgt alles gedaan. Ik heb veel geleerd van je creativiteit, onconventionele aanpak en levenshouding. Ik heb veel met je gelachen bij onze bezoeken aan de huisartspraktijken. Suzanne, door jou precisie en analytische skills hadden jij en Carin in no-time de logistiek van de HATICE-trial geprofessionaliseerd en werkten het als een geoliede machine. Dankzij jullie grote inzet en die van stille krachten Marije en Charlotte is de inclusie en praktische uitvoering van de trial zo succesvol verloopen. Ik ben jullie daar erg dankbaar voor.
Lieve coaches (Karina, Ursula, Irma, Anita, Imke, Floris en Marga), het was inspirerend om te horen hoe jullie met de deelnemers aan de slag gingen. Zoals ik in dit proefschrift betoog, maken jullie voor mensen het verschil waardoor het het waard wordt om een internetplatform als HATICE te gebruiken. Dank voor de fijne samenwerking. Floor, het was leuk en leerzaam om jou te begeleiden bij je bachelorscriptie. Veel dank voor al je hulp bij de focusgroepen.

Dear members of the HATICE consortium, it was very special and an honour to work together with you. It was not easy to develop an eHealth platform in four languages fitting the Finnish, French and Dutch culture, but we did it. I have fond memories of the General Assembly meetings. I would like to thank in particular prof. dr. Andrieu: dear Sandrine, thank you very much for your hospitality in Toulouse. I had a wonderful time at your department. Dear Nicola, I very much enjoyed working together with you on the dropout analysis. You taught me a lot. I am happy that you became a friend.


Lieve kamergenoten van H2-235 met wie ik kortere of langere tijd de spaarzame zuurstof in ons inpandige hok heb mogen delen: dank voor de inwijing in het promotiebestaan en voor alle gezelligheid. Dunja, Emma, Jan-Willem, Lisa, Rosanne en Max, het was altijd goed frustratie spuiten en lachen in onze kringgesprekken, en ik heb erg goede en hilarische herinneringen aan onze kamertijden.

Graag wil ik de medewerkers van de afdelingen Neuropsychologie en Huisartsenonderzoek van het AMC bedanken voor de leerzame onderwijsmomenten en wetenschappelijke discussies tijdens de vaatclub, journalclub en wetenschapsbesprekingen.

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Lieve vrienden, dank voor alle gezelligheid, betrokkenheid en steun. Ik kan niet iedereen persoonlijk bedanken, maar wil graag stilstaan bij een aantal vrienden.
Lieve Barbara, wij hebben een hoop afgespard, o.a. op de racefiets tijdens de vele rondjes Haarlemmerliede, waar ik ontzettend veel aan heb gehad. Ik zie je je ontwikkelen tot een echte academicus, en je zet mij aan tot groei. En ondertussen valt er gelukkig een hele hoop te lachen. Ik vind het een grote eer dat je me terzijde staat als paranimf.

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Lieve Jolien en Maaike, samen met Barbara vormen jullie voor mij een heel vertrouwd clubje, en een fijn klinkbord, hetzij voor ons persoonlijk wel en wee, hetzij voor onze professionele ontwikkeling, en natuurlijk bij het samen muziek maken.

Lieve Laura, Anne en Santje, dankjulliewel voor de earlijke en relativerende gesprekken die we met elkaar hebben. Wat fijn dat wij al zo lang vriendinnen zijn, en al onze grotere en kleinere gebeurtenissen in het leven met elkaar beleven. Ik hoop dat we dat altijd blijven doen.

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Lieve Kevin, Eelco en Vanessa, één van de leuke dingen van Jochem is dat hij zulke leuke vrienden heeft. We kunnen goed met elkaar praten over waar we tegenaan lopen in het leven, dat is heel waardevol voor mij.


Lieve Gerrie, al bijna 32 jaar ben jij onderdeel van onze familie, dat vind ik erg bijzonder en een groot goed. Je hebt een grote rol in mijn promotieonderzoek, als platformtester en rolmodel in een van de platformfilmpjes. En ‘gezond ouder worden’, dat bén jij. Daarmee ben je voor dit proefschrift ook een belangrijke inspiratiebron.
Lieve Sara, lieve zus, ik vind het fijn dat ik zoveel met jou kan delen en sparren, dat was altijd al, maar is des te meer zo omdat we allebei dokter zijn. Jouw wijze, nuchtere en relativerende levenshouding en je grote gevoel voor humor zijn voor mij heel belangrijk.

Lieve Berend, lieve grote kleine broer, zoals ik de afgelopen jaren een flinke ontwikkeling doormaakte, deed jij dat ook. En we haalden allebei ons rijbewijs. Ik heb het gevoel dat je je draai steeds meer vindt. Ik ben trots op je, wat fijn dat je mijn broer bent.

Lieve pap en mam, dankjewel dat jullie mij altijd steunen en me het vertrouwen geven dat ik het kan. Als het mij weleens boven het hoofd dreigt te groeien, helpen jullie me prioriteiten te stellen waardoor ik het weer op de rit krijg. De manier waarop jullie in het leven staan is voor mij een inspiratie. Dankjewel dat je me door de laatste loodjes heen hebt gecoacht.

Lieve Jochem, je bent mijn thuishaven waar ik rust en relativering vind, en inspiratie om van het leven iets moois te maken. Het afgelopen jaar was een pittige exercitie, dankjewel dat je je mannetje stond en mij zo steunde. Ik kan mijn geluk niet op samen met jou en Mercia.

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UITNODIGING
voor het bijwonen van de openbare verdediging van mijn proefschrift

Cardiovascular risk self-management in older people
Development and evaluation of an eHealth platform

donderdag 12 april 2018, 10:00
Agnietenkapel
Universiteit van Amsterdam
Oudezijds Voorburgwal 229
Amsterdam

U bent ook van harte uitgenodigd op de receptie na afloop van de promotie

Cathrien Beishuizen
c.r.beishuizen@amc.uva.nl

Paranimfen
Barbara Sjouke
Susan Jongstra
promotiecathrien@gmail.com