eHealth in cardiovascular risk management to prevent cognitive decline

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Cardiovascular diseases and dementia are diseases that have a major impact on our society. These diseases share a number of risk factors, including hypertension, hypercholesterolemia, smoking, diabetes mellitus, obesity and physical inactivity. One can imagine that even a small improvement in cardiovascular risk factor management in a large number of people can lead to a substantial beneficial effect on overall incident cardiovascular disease and maybe even postpone or prevent dementia. We can use eHealth to optimise cardiovascular risk management by developing internet interventions that focus on prevention. eHealth can also play an important role in improving research purposes. You can easily reach a wide audience, perform remote repeated measurements and provide patient-centred care at lower costs.

The aim of this thesis is to provide insight in the possibilities of cardiovascular prevention via eHealth and mHealth, and to show different aspects of cognitive functioning: assessing, predicting and preventing cognitive decline.

Susan Jongstra, 2017
eHealth
in cardiovascular risk management
to prevent cognitive decline

Susan Jongstra
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EHEALTH IN CARDIOVASCULAR RISK MANAGEMENT TO PREVENT COGNITIVE DECLINE

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Acknowledgements (Dankwoord)
They may forget your name, but they will never forget how you made them feel.

Maya Angelou
Chapter 1

GENERAL INTRODUCTION
Prevention of cardiovascular disease and dementia

The incidence of cardiovascular disease (CVD) has declined impressively in the last decades, but remains a major public health threat with still around 4 million deaths in Europe each year(1). This is almost 45% of all annual deaths in Europe, with a higher percentage of females than males(1). Another disease that also poses a major health problem, of which the incidence rate has not clearly declined, is dementia(2, 3). Dementia affects around 41 million people worldwide and the global prevalence of dementia is likely to double every 20 years, mainly due to the increased life expectancy(4). This is why dementia has been designated as a health priority by the G8 countries in 2013(5).

These two diseases with major impact on society share a number of risk factors, including hypertension, hypercholesterolemia, smoking, diabetes mellitus, obesity and physical inactivity(6, 7). We know that treating these risk factors (with medications or lifestyle adaptations) can be effective for the prevention of CVD(8, 9). One can imagine that even a small improvement in cardiovascular risk factor management in a large number of people can lead to a substantial beneficial effect on overall incident cardiovascular disease and thereby reduce the economic burden in health care costs(10). This is the so called the ‘prevention paradox’, which was described for the first time by Geoffrey Rose in 1981(11). As an example he suggested a reduced salt intake on population level to reduce the mean blood pressure. The effects of such a measure may not even be noticeable at an individual level, but the cardiovascular disease risk on population level reduces significantly.

Whereas the evidence that treating modifiable risk factors reduces the incidence of cardiovascular disease is very strong, this is not (yet) the case for the prevention of dementia. Based on observational studies, up to 30% of dementia cases are attributable to cardiovascular risk factors(12), but there is no direct evidence from randomised controlled trials (RCTs) to show that treatment of cardiovascular risk factors reduces dementia incidence(13).

There are many studies on targeting a single risk factor to reduce the incidence of cardiovascular disease(14-16). A lot of them are partly effective, although the question remains if we can accomplish greater risk reductions if we target more than one risk factor at the same time, in the same individual. Especially older adults are more likely to have more than one modifiable risk factor(17) and that made research take a turn in targeting not only one but multiple risk factors at a time. In particular secondary prevention is increasingly studied in a multifactorial way to prevent cardiovascular disease (e.g. the RESPONSE trial(18), the DEBATE trial(19) and the ADDITION-Europe trial(20)). Primary prevention is also very suitable for a
multifactorial approach(21). In theory, targeting multiple risk factors simultaneously should yield an additive effect on reducing the cardiovascular disease risk and perhaps even on the reduction of dementia risk, although randomised controlled trials in older adults targeting dementia are scarce and show mixed results(19-21). Over the last decade, three multifactorial prevention interventions have studied in RCTs in older adults with the primary aim to reduce dementia incidence or cognitive decline: the preDIVA (Prevention of Dementia by Intensive Vascular care)(22) trial, the FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) trial(23) and MAPT (Multidomain Alzheimer Preventive Trial)(24). These three studies also show inconsistent results. The FINGER study suggests that a multifactorial lifestyle intervention could improve or maintain cognitive functioning in older adults with high risk of dementia compared to the general population, but the effect size was very small and of uncertain clinical significance(23). The preDIVA study (nurse-led multidomain intervention to reduce dementia incidence) did not result in a reduced incidence of all-cause dementia in an unselected population of older adults. The preDIVA participants were not selected on high cardiovascular risk and this might be one of the reasons for the neutral overall findings(22). The window of opportunity in a country like the Netherlands with already high standards of usual care may therefore be limited, especially in an unselected population. In the MAPT trial no effect of multi-domain intervention in older persons who had a cognitive complaint or were deemed frail was shown(24).

**Modifiable cardiovascular risk factors and a healthy lifestyle in older adults**

Some cardiovascular risk factors simply cannot be modified, such as age, sex, ethnicity and family history. Fortunately, several risk factors can be affected by drug treatment or through lifestyle adaptions. These modifiable risk factors include hypertension, tobacco use, diabetes mellitus, physical inactivity, unhealthy diet, dyslipidaemia, overweight and obesity. In primary health care, a first step is usually to improve an unhealthy lifestyle and thereby directly or indirectly influence these modifiable risk factors. An unhealthy lifestyle can be described as one that is not compliant with the World Health Organisation (WHO) guidelines for different prominent health risk behaviours, such as being insufficiently active, eating insufficient fruit and vegetables, using tobacco or drinking too much alcohol.

We need to ask ourselves if it is useful and cost-effective to apply preventive strategies in older adults (above 65 years). It is difficult to motivate older adults in cardiovascular prevention programs and to keep them from dropping out(25). Is this age group too old for prevention of CVD and should we focus exclusively on the middle aged or even adolescents?
This thesis is written under the strong assumption that, with global ageing, older people form also an important target population for cardiovascular prevention. However, an important issue in cardiovascular risk management is the lack of evidence for the best approach and optimal target values for (frail) older adults (> 65 years)(26). There are clear national and international cardiovascular prevention guidelines(27) that mainly focus on younger adults, but it is questionable if these can or should also be applied to older adults. There are a couple of studies that suggest we cannot extrapolate the target levels for younger adults to older adults. For example, the INVEST study(28) found a U-shaped distribution of risk for cardiovascular events in adults ≥50 years with blood pressure, suggesting that not only high, but also a relatively low blood pressure can be hazardous. In contrast, the SPRINT study(29) suggests that even for people aged ≥75 years or older, a systolic blood pressure lower than 120 mmHg is the most optimal target for preventing cardiovascular events and death. With regard to dementia, there is insufficient evidence that blood pressure lowering can lead to lower dementia incidence rates(30). Some studies show a protective effect on cognition when treating high blood pressure(31), while other studies do not show this benefit(32, 33) or even show a potential harm in accelerating cognitive decline(34). It is not clear how these findings can be reconciled; is the actual value of the blood pressure decisive; is it merely the variability in blood pressure over time; or might it be the class of medication (e.g. calcium channel blocker or angiotensin receptor blocker)?:

The same inconsistencies appear to apply for the target values in older adults for Body Mass Index (BMI) and Low Density Lipoprotein (LDL) cholesterol(35, 36). Do we need to treat older individuals differently or not and if so, what is the age limit to do so and what are the exact target levels? Questions that warrant further study in the light of the current scarcity of available studies.

The reality of daily practice is that preventive target values are often not reached(37, 38), leaving room for a substantial improvement in the cardiovascular risk profile. Both patient and doctor factors play a role in this gap between evidence and practice(39). Patient self-management is a potentially powerful strategy to improve adherence to therapy in CVD risk reduction(40, 41). Specific patient characteristics can determine the strategies applied at the individual level. The possibility for tailor-made prevention programmes can empower individuals and improve adherence to pharmacological and non-pharmacological interventions(42).
eHealth

eHealth is a term that was rarely used before the beginning of this century, but is used on daily basis nowadays(43). It does not only include ‘Internet medicine’, but is used for everything related to computers, or actually everything related to the digital world and medicine. In the last decades the internet has expanded from the desktop to usage on a laptop, a tablet and the pocket sized smartphone, which makes internet available on every place we can think of. eHealth opened a world full of possibilities and related to that experts say the ‘e’ does not only stand for ‘electronic’, but can be supplemented with ‘efficiency’, ‘empowerment’, ‘education’, ‘enabling’, ‘ethics’ and ‘equity’(43).

As indicated above, a current development in medicine is the promotion of person-centred care and self-management(44, 45). A person-centred and autonomy supportive counselling approach is important in maintaining for example a lifestyle modification. Internet applications fit in this trend and in this last decade, the development of internet applications has expanded dramatically because of this(46). They are a useful medium for patient-self-education, stimulation of behaviour change and enhancement of self-management. In addition, internet interventions can be implemented on wide scale at low-cost and allow for tailoring, interactivity, interpersonal communication and provide anonymity(47, 48). This renders internet interventions suitable to target common health care problems with high costs such as cardiovascular disease and especially cardiovascular risk factors. Since the development of the Internet, several types of internet interventions have been offered to the population to modify unhealthy lifestyle behaviours for the prevention of cardiovascular disease(49-51). Although these developments appear very promising, several challenges are to be taken into account. Firstly, the evidence base for the value of eHealth in managing cardiovascular diseases is still weak and the best methods may not have been identified or developed yet(52). Secondly, the development of eHealth is often technically driven and not by the needs and expectations of health professionals and patients, and thirdly, connectivity between tools and systems are mostly lacking. Furthermore, there are major issues and concerns about privacy and data security(53). There is also a lack of cost effectiveness studies and regulation of reimbursement of eHealth which ultimately may turn out to be one of the biggest obstacles for the introduction of evidence-based eHealth applications into the health delivery system. These challenges are all the more reason to join international forces and start well designed internet interventions, with the highest standards of security and privacy, including participation of health professionals and patients and to perform cost-effectiveness analyses of these interventions.
**mHealth in research**

When talking about new vocabulary, mHealth is definitely a word that was not used until two decades ago and is a commonly used term nowadays. It overlaps with eHealth in a way that it includes digital health, but in the mobile form (that is where the ‘m’ stands for), including mobile phones with a special focus on smartphones, tablets, laptops and smartwatches. The reason of the fast evolution of mHealth concerns two main factors. First, healthcare systems of developing countries have multiple constraints. These include a growing population with large numbers of rural inhabitants, a high prevalence of diseases(54), low number of health care workers, and limited financial resources. Second, the recent rapid increase in mobile phone use in developing countries and smartphones in high-income counties plays an important role. This holds for use of mobile phones by healthcare workers, as well as in the total population. Because of this greater access to mobile phones, including in rural areas, and in all age categories, there is a huge potential of lowering costs to deliver and collect healthcare (information)(55). A great opportunity for research purposes, because lower costs, reaching a wide audience from all age groups and easily performing repeated measurements sounds almost too good to be true.

**eHealth for the prevention of cardiovascular disease**

The internet has become a major source of information for people of all ages, and its use among older people throughout Europe has increased dramatically(56, 57), making it a potentially suitable medium to reach all age groups. Together with the rise of eHealth this creates opportunities for well designed, well tested and large-scale prevention programmes. Internet interventions targeting single cardiovascular risk factors, such as for example blood pressure control, increasing physical activity, dietary control and smoking cessation have shown to be effective for reducing this specific risk factor (50, 58, 59), although effects are modest and the duration of effect is usually short. This makes the clinical significance of these effects unclear. Cardiovascular diseases are generally related to a combination of interrelated modifiable risk factors which potentiate each other. Cardiovascular prevention guidelines therefore recommend a comprehensive approach on the total cardiovascular risk profile(60, 61). It is currently unclear whether eHealth interventions focussing on multiple risk factors are also effective. It seems that small effects are reached in the multifactorial approach, but if these may ultimately translate into clinically relevant effects on major clinical endpoints because of the synergistic effect is doubtful(62). Another advantage of the multifactorial approach is that patients can choose the risk factor they are most motivated for to change (e.g. losing weight to control their BMI), but simultaneously work on other risk factors to accomplish their goal (e.g. more physical exercise to lose weight and a lower BMI can simultaneously
lower the blood pressure). A disadvantage of multiple lifestyle interventions is that it might be burdensome and overwhelming for patients to handle everything at the same time. A systematic review from Vegting et al. (63) demonstrates that the available internet interventions with a multifactorial approach do not show a clinically significant effect on cardiovascular risk factor reduction. They also state that it is difficult to compare the included studies because of the diversity in intervention programs and study design. It is therefore important that future multifactorial internet interventions focus on a combination of evidence based parts of the intervention, such as the combination of (digital) human support (e.g. a coach) and high privacy standards (50).

**eHealth and prevention for older adults**

Due to the increase of life expectancy and the increasing number of older people, there is an increasing need for the care and monitoring of frail, multi-morbid community-dwelling older people. When designing a trial on prevention of cardiovascular disease and dementia, the optimal age of the research population is a matter of debate. The benefits of higher efficacy in midlife (64, 65) are counteracted by the large sample size and long follow-up required to detect an effect on incident disease. The optimal time-window depends on the peak incidence age in the country or region of interest, and is in Europe probably somewhere in early late-life, around 60 years old (66).

Since older adults are an under investigated, but important target group for research and can still benefit from cardiovascular disease prevention, internet interventions can be suitable for the delivery of such a prevention program. Until a decade ago, the problem with internet interventions for older people was the low access and internet capabilities of the elderly. However, especially in Europe, internet use among older adults has risen sharply and this process is continuing to spread globally. The number of people aged 65-74 years in the European Union using internet increased from 20% in 2009 to 57% in 2016 (67), illustrating the high potential of web-based interventions in older populations. Specifically in the Netherlands these numbers are even higher, around 84% of the people aged 65-75 years and 51% of the people aged 75 years and older (57) have an internet connection at home.

There are only several internet interventions for cardiovascular risk management that focus specifically on older people (50). Since research shows that older people read, use and understand websites differently compared to young people (68), a thorough design process is required to ensure that an internet application truly fits the older audience to reach an effect (69).
Measuring cognitive decline

For cardiovascular diseases we can use measures that can give us a clear indication if the disease is there or not (CT-scan for stroke, electrocardiogram for myocardial infarction) or, for cardiovascular risk factors, if a value reaches the indicated target (e.g. measurement of blood pressure or serum cholesterol). For the clinical diagnosis of dementia we can use criteria described in internationally accepted guidelines, including the International Classification of Diseases and Related Health Problems (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Cognitive function can be quantified with several screening instruments measuring multiple cognitive domains, for example the Mini Mental State Examination (MMSE)(70) or the Montreal Cognitive Assessment (MoCA)(71). If indicated, a more extensive neuropsychological test battery can be used. Which magnitude of cognitive change can be considered clinically relevant is debatable. In addition, neuropsychological tests are influenced by other determinants such as mood and physical condition of the patient and the knowledge and skills of the examiner. For years researchers have been trying to optimize algorithms and to find the best measurements to detect, but also to predict cognitive decline and dementia. Given the time constraints of health care professionals and their perceived lack of knowledge and skills on this specific subject, short, easy-to-use instruments could strengthen the diagnostic work-up in primary care, given that the MMSE and the MoCa are not specifically designed to detect early stages of cognitive impairment(72). New opportunities appear to lie ahead when such tests could be combined with the latest technology and if we integrate it in our developing eHealth world. The use of the smartphone is one of the newest developments in mHealth and seems very promising in reaching a large audience and repeated testing in a research setting. We can use the smartphone to measure all kinds of lifestyle related determinants(73, 74), so it is also an attractive tool to measure our cognition on an easy and routinely basis. Obviously these kinds of tests must be well developed and validated before it can be implemented for actual use in clinical practice, but also for research purposes.
OUTLINE OF THIS THESIS

This thesis is divided in two parts.

Part one consists of two chapters (chapter two and three) both discussing (a part of) the development and design of the Healthy Ageing Through Internet Counselling in the Elderly – HATICE – trial. In chapter two we aim to give an overview and guideline of the development of an internet platform specifically designed for the prevention of cardiovascular disease (improvement of an unhealthy lifestyle) in older adults. We describe a step by step development process and this chapter points out the difficulties and pitfalls in this rapidly developing field of internet interventions. Chapter three is all about the design of the HATICE trial. In this pragmatic, multinational, multicentre, investigator initiated, prospective, randomised, open label with blinded end point trial we aimed to investigate whether a coach-supported interactive internet intervention to optimise self-management of cardiovascular risk factors in older individuals can improve the cardiovascular risk profile and reduce the risk of cardiovascular disease and cognitive decline. The effectiveness of the platform described in chapter two is being tested in this trial.

Part two is about cognition. Assessing, predicting and preventing cognitive decline or dementia. In the first chapter of this part, chapter four, we describe the results of a part of the iVitality proof-of-principle study - cognitive testing using a smartphone. For this study, we developed five cognitive tests suitable for the smartphone based on the equivalent validated conventional cognitive tests.

In chapter five, using data from the preDIVA (acronym for ‘prevention of dementia by intensive vascular care’) study, we aimed to investigate if a relatively new and internationally unknown test like the Visual Association Test (VAT) has incremental value in the prediction of cognitive decline and dementia in the primary care setting when there is a decline in MMSE score over time.

Chapter six is about the potentially preventive effect, with respect to cognitive performance, of antihypertensive medication withdrawal. As a somewhat controversial topic, in this chapter we review the literature about the withdrawal of antihypertensive therapy to prevent cognitive decline. Quitting medications in a world where we have endless options in treating hypertension can seem ridiculous, but might be a solution for other problems. This is a Cochrane systematic review that aims to entail a discussion of the balance between benefit and harm of antihypertensives in older people.
Chapter seven of this thesis provides a general discussion and evaluates the overall findings. It discusses methodological considerations, implications for clinical practice and directions for future research. An overall summary of this thesis is given in chapter eight.
REFERENCES


Part I

EHEALTH IN CARDIOVASCULAR RISK MANAGEMENT
"How can I type a capital letter 1?"

(Participant in one of the platform testing sessions, November 2014)
Chapter 2

DEVELOPMENT AND VALIDATION OF AN INTERACTIVE INTERNET PLATFORM FOR OLDER PEOPLE
THE HEALTHY AGEING THROUGH INTERNET COUNSELLING IN THE ELDERLY STUDY

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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 aging, 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 personalize the platform and to combine the application with human support. The interactive HATICE platform will be tested for efficacy in a multinational randomized controlled trial (ISRCTN48151589).
BACKGROUND

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, interpersonal communication and provide anonymity (4, 5). This renders web-based interventions suitable to target common health care 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 in a different way 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 paper 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, multi-national, multi-centre, prospective, randomised, open-label blinded endpoint (PROBE) trial with 18-months 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.
Chapter 2

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(18). The platform was developed following five phases as shown in Figure 1.

![Figure 1. Phases of platform development](image)

### 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 computerized self-regulatory system(19). 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 (20) and the stages of change model (21) as tools to provide feedback and stimulate behavioural change in a cyclic manner (Figure 2). We used Michie’s taxonomy for standardized definitions of the behaviour change aspects in our intervention (22).

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 (22)

**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 (13). In parallel, we conducted 14 four-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 organized focus groups with the target population and nurses with experience in cardiovascular risk management in the three countries where the trial will take place (the Netherlands, Finland and France). During these focus groups it was discussed how an internet platform could help people improve their lifestyle and which functions such a 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(10, 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)(10). 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(28). We worked in semi-monthly 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(18) 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 randomised controlled trial (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 interactive features of the interactive internet platform. There will be no coach support for the control group.
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, assignments were given to the participants. Tasks included for example: 1) Find the website using the Uniform Resource Locator (URL) and log on. 2) Prioritize 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. Participants were aged ≥65 years, had an elevated risk of developing cardiovascular disease and had 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 eight weeks. After all participants had completed the pilot, an evaluation session was held in each participating country. Participants completed an evaluation questionnaire about logistics, usability and acceptability.

Phase 5: End product for randomised controlled trial

After incorporation of the adaptations identified during the pilot, the platform was considered ready to be used in 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(13). Also, 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-organized 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, forty 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 focus groups with the target population indicated that older people liked to be able to ask questions to a coach via internet. They indicated that the platform should have a positive appearance, focusing on health rather than disease, and provide practical and reliable information that is often difficult to find on websites. The nurses felt that, in order to provide adequate support, some face-to-face contact would be indispensable, but also that the platform had potential 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) will be prioritized. 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 measurements (e.g. blood pressure, weight, etcetera); (3) view informative contents. We created a step-by-step procedure that guides the participant to the process of setting a lifestyle improvement goal (Supplement 1). The participant sets a target date for the goal and can choose to receive automated reminders about this goal. The participant can write a message to the coach via 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 video’s 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 three weeks. The coach will then contact the participant and tries to motivate the participant again.

Table 1

<table>
<thead>
<tr>
<th><strong>Features that stimulate (inter) active platform use</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Interactive information video’s</td>
</tr>
<tr>
<td>Goal-setting module (Supplement 1)</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 program</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 randomized (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) 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.

Figure 3: Pilot flowchart
Table 2. Baseline characteristics of the pilot study population

<table>
<thead>
<tr>
<th>Characteristic</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(^a)</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(^b)</td>
<td>35 (85%)</td>
</tr>
<tr>
<td>Currently smoking(^c)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Diabetes Mellitus type 2(^d)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Dyslipidaemia(^e)</td>
<td>25 (61%)</td>
</tr>
<tr>
<td>Overweight(^f)</td>
<td>20 (49%)</td>
</tr>
<tr>
<td>Lack of physical exercise(^g)</td>
<td>16 (39%)</td>
</tr>
<tr>
<td>No. of cardiovascular risk factors per participant, N (% of total)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>1</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>2</td>
<td>16 (39%)</td>
</tr>
<tr>
<td>3</td>
<td>14 (34%)</td>
</tr>
<tr>
<td>4</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>5</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

\(^a\) Two missing values for this variable
\(^b\) Hypertension: \(\geq 140/90\) mmHg for participants <80 years, \(\geq 160/90\) for participants \(\geq 80\) years, or on blood pressure-lowering agents
\(^c\) Smoking: any kind of tobacco
\(^d\) Diabetes: Diagnosed by a general practitioner/specialist or on antidiabetic medication
\(^e\) Dyslipidaemia: total cholesterol \(\geq 5.0\) mmol/L, LDL-cholesterol \(\geq 2.5\) mmol/L or on lipid-lowering agents
\(^f\) Overweight: body mass index \(\geq 30\) kg/m\(^2\) or waist circumference men \(\geq 102\) cm, women \(\geq 88\) cm
\(^g\) Lack of physical exercise: below the World Health Organisation norm of 150 min of intermediate exercise a week.

Patterns of use of the website

Number of 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>
<th></th>
</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 send by intervention group</td>
<td>74</td>
</tr>
<tr>
<td>Total N of messages send by coach/platform</td>
<td>162</td>
</tr>
<tr>
<td>Total N of goals set</td>
<td>30</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>2</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0</td>
</tr>
<tr>
<td>Exercise</td>
<td>13</td>
</tr>
<tr>
<td>Smoking</td>
<td>0</td>
</tr>
<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>
</tr>
<tr>
<td>Nutrition</td>
<td>10</td>
</tr>
<tr>
<td>Weight</td>
<td>55</td>
</tr>
</tbody>
</table>

**Number of messages**

The participants sent in total 74 messages to their coach via 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.

**Number of 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 were 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 on the use of the intervention platform 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 felt the need to print the texts on paper, so an icon for an easy way to print would be useful. The platform did not work optimally when relatively old software and/or hardware was used. Communication with the coach was very much appreciated and felt very personal to all participants, 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 the participant 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 participants 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 (with the menu page still visible at the background), but there is no navigation deeper into the platform. The self-monitoring tools and the goal diary have also been also 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>
</table>
| Home page         | Introduction video explaining how to use the platform  
|                   | Overview-homepage to navigate directly to the most important items of the platform: personal health priorities, goals, new messages and personal lifestyle groups  
|                   | Photograph of the coach  
| My health priorities | Overview of personal health priorities and step-by-step procedure to register a measurement  
|                   | Overview of goals and step-by-step procedure to set new goal  
|                   | Overview of achieved goals  
|                   | Summary of personal cardiovascular health profile  
| Lifestyle groups  | Personal lifestyle groups  
|                   | Overview of other available groups  
| Messages          | Messages inbox for interaction with coach  
| Advice and Education | Information, advice and tips and tricks on healthy lifestyle for each health factor  
|                   | Educational video’s for each health factor  
|                   | Peer-to-peer video’s with personal stories of peers on lifestyle change  
| News              | Every month a new international or national news item on research highlights, facts or activities related to preventive health  
| User support      | Help-buttons on every page explaining the users specific functionalities  
|                   | Help-assistance through email and phone  
|                   | In addition, paper instruction manual  

![Image of the HATICE intervention platform](image)

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

In this paper we described the design, development 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. The entire development process took two years of preparation time and effort.

The meta-analysis learned us that blended web-based applications associated with larger treatment effects than internet-only applications(13). This was one of the reasons why we combined the platform with a coach, also, because we think that the personal touch may 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 and comprehensibility of the website, and privacy concerns, were already known from previous research. Other barriers, like the fear of getting lost and the preference for a positive tone, were new. The pilot enabled us to evaluate if this platform had overcome those barriers and revealed other issues such as difficulties with the login procedure. Simplifying the login-procedure seems a triviality but, for older people, this can make a huge difference in accessibility of the platform.

Over the coming years, the platform described in this paper will be tested for efficacy in the HATICE RCT(17). 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 tend to advance faster than researchers can keep pace with. Therefore, some researchers advocate the use of adaptive trial designs to enable a more flexible form of testing(31). Although this seems appealing, we think that ultimately robust controlled study designs are required to evaluate clinical effectiveness and utility. Thorough communication between the 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) of these groups.

To accomplish acceptability for older people, we recommend to start with a theoretical backbone, to involve the end-users in the entire process of development, to personalise the platform and to combine the application with human support.
Chapter 2

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

Funding
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Author Disclosures
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CB has nothing to disclose. SJ has nothing to disclose. TvM has nothing to disclose. ER has nothing to disclose. EMvC has nothing to disclose. BvdG has nothing to disclose. MvD has nothing to disclose. FM has nothing to disclose. HS has nothing to disclose. JG has nothing to disclose. MB has nothing to disclose. MK has nothing to disclose.
REFERENCES

Development and validation of an interactive internet platform


SUPPLEMENT 1. STEP BY STEP PROCEDURE FOR GOAL SETTING

Step 1: Selecting a health factor
- Blood Pressure
- Cholesterol
- Exercise
- Weight
- Diabetes Mellitus
- Non Smoking
- Nutrition

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
“De zijt werkt niet…”

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

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

Susan Jongstra*, Cathrien Beishuizen*, 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, and Edo Richard

*These authors contributed equally

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ABSTRACT

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

Methods and analysis HATICE is a multi-national, multi-centre, prospective, randomised, open-label blinded endpoint (PROBE) trial with 18-months intervention. Recruitment of 2600 older people (>=65 years) at increased risk of cardiovascular disease will take place in the Netherlands, Finland and France. Participants randomised to the intervention condition will have access to an interactive internet platform, stimulating self-management of vascular risk factors, with remote support by a coach. Participants in the control group will have access to a static internet platform with basic health information. The primary outcome is a composite score based on the average z-score of the difference between baseline and 18 months follow-up values of systolic blood pressure, low-density-lipoprotein and body mass index. Main secondary outcomes include the effect on the individual components of the primary outcome, the effect on lifestyle related risk factors, incident cardiovascular disease, mortality, cognitive functioning, mood and cost-effectiveness.

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

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

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

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

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

Patient self-management is a potentially powerful strategy to improve adherence to therapy in CVD risk reduction(19, 20). Specific patient characteristics can determine the strategies applied at the individual level. Increasing knowledge about a healthy lifestyle and the possibility for tailor-made prevention programs can empower individuals and improve adherence with pharmacological and non-pharmacological interventions(21).
When designing a trial on prevention of cardiovascular disease and dementia, the optimal age-range of the target population is matter of debate. The benefits of higher efficacy in midlife are counteracted by the large sample size and long follow-up required to detect an effect on incident disease\(^2\). The optimal time-window depends on the peak incidence age, and is probably somewhere in late midlife or early late-life\(^2\).

The internet has become a major source of information for people of all ages, and its use among older people throughout Europe has increased dramatically, making it a potentially suitable medium for the delivery of widely implementable health care interventions\(^2\). Together with the rise of eHealth this creates opportunities for large-scale delivery of prevention programs encouraging self-management\(^2\).

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

**METHODS**

**Study design**

HATICE is a pragmatic, multi-national, multi-centre, investigator initiated, prospective, randomised, open-label blinded endpoint (PROBE)\(^2\), trial with 18-months intervention and follow-up. Due to the nature of the intervention, complete double blinding is not possible. Investigators evaluating outcome measures are blinded for the randomisation group and the primary outcome is based on objective parameters.

**Study population and recruitment**

The study population will consist of community-dwelling people aged 65 years or older who have two or more cardiovascular risk factors and/or manifest cardiovascular disease or diabetes mellitus. This leads to a mixed population with an indication for either primary or secondary prevention. Inclusion and exclusion criteria are listed in Table 1.
Table 1. Overview of inclusion and exclusion criteria

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

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

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

Recruitment started in March 2015.

**Intervention**

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

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

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

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

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

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

**Pilot**

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

The primary outcome is a composite score based on the average z-score of the difference between baseline and 18 months follow-up values of systolic blood pressure, low-density-lipoprotein (LDL) and body mass index (BMI). Several considerations have led to the decision for this outcome. First, a multi-domain outcome capturing the potential effect of our multi-domain intervention on a composite of risk factors was deemed appropriate. Second, no existing cardiovascular risk score can be applied to both primary and secondary prevention, whereas our pragmatic trial targets a mixed population with an indication for primary or secondary prevention. Third, we deemed it inappropriate to include any parameter based on patient-reported measures (e.g. physical activity questionnaire) in our primary outcome due to the risk of reporting bias; self-reported parameters were considered insufficiently reliable for the primary outcome.

Secondary outcomes

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

Study logistics

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

**Figure 2.** Study logistics

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

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

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

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

**Randomisation and blinding**

Participants are randomised during the baseline visit in a 1:1 ratio using central randomisation according to a computer generated randomisation sequence. We decided not to stratify for any characteristic, since the magnitude of the sample size, even within one country, renders any imbalance between the groups extremely unlikely (45, 46). In case of spouse/partner participation, partners will be allocated to the same treatment arm to prevent contamination. It is explained to participants that they are randomised to one of two internet-platforms to improve lifestyle, without further details.

The coaches who support the participants in the intervention group are not blinded. Outcome assessment at the end of study at month 18 will be done by an independent assessor blinded to treatment allocation.

**Safety**

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

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

STATISTICAL ANALYSIS

Sample size
We originally based our power calculation on proportions. With advancing insight we decided on a continuous primary outcome, resulting in a new sample size calculation, again taking into account the effect of participants randomised as couples. We base the new sample size calculation on the effect-sizes of the HATICE primary outcome as observed in the preDIVA and FINGER trials(14, 27). In the PreDIVA study the mean difference in z-score of the HATICE primary outcome between baseline and two year follow-up is 0.070 (p=0.002; intervention group -0.194 and control group -0.124). In the FINGER study this
mean difference is 0.041 (p=0.11; intervention group -0.128 and control group -0.087). To avoid the risk of being underpowered since the effect was non-significant in the FINGER study, we base our sample size calculation on an effect size of 0.06.

Based on the first 1000 recruitments, we estimate that 17.5% of the participants will be recruited as a couple. Couples can be considered the smallest possible clusters (n=2). Although intra-cluster correlation coefficients (ICC) in RCTs are typically below 0.05, the ICC for vascular and lifestyle-related risk factors within small clusters of relatives may be much higher, up to 0.25(47).

With 80% power, a 0.05 two-sided significance level, accounting for an estimated 14% attrition based on previous experiences in our own multi-domain prevention study(14), an ICC of 0.25(47) and an effect size of 0.06 the required sample size is estimated to be 2534 participants in total. To allow for unexpected factors we raise this to 2600.

Because the meaning of a difference in z-scores is difficult to interpret, we estimated the threshold for a clinically relevant difference in z-score by using the follow-up data in preDIVA for clinical outcomes. For this purpose we compared preDIVA participants who did develop CVD or dementia with those who didn’t during an average follow-up of 6.7 years. In preDIVA the change in z-score after 2 years was -0.205 in participants who developed CVD or dementia and -0.146 in participants who did not develop CVD or dementia. We therefore assume that a difference of 0.059 on the composite primary outcome of HATICE can be considered as clinically relevant.

**Data analysis**

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

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

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

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

Economic evaluation

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

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

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

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

**DISCUSSION**

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

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

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

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

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

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

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

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

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

Acknowledgements
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Competing Interests
Non declared

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Part II

COGNITIVE FUNCTIONING – ASSESSMENT, DEMENTIA RISK PREDICTION AND PREVENTION
Whenever I remembered my father who wants euthanasia and that he wants this, I feel like I’m killing him.

Until a doctor explains that she is for the patient what a guiding dog is for a blind person. The dog helps and protects, the blind is in control.

(Daughter of a patient with dementia who wants euthanasia)
Chapter 4

COGNITIVE TESTING IN PEOPLE AT INCREASED RISK OF DEMENTIA USING A SMARTPHONE APP
THE IVITALITY PROOF-OF-PRINCIPLE STUDY

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JMI\R mHealth and uHealth (2017 May 25); 5 (5)
ABSTRACT

Background Smartphone-assisted technologies potentially provide the opportunity for large-scale, long-term, repeated monitoring of cognitive functioning at home.

Objective The aim of this proof-of-principle study was to evaluate the feasibility and validity of performing cognitive tests in people at increased risk of dementia using smartphone-based technology during a 6 months follow-up period.

Methods We used the smartphone-based app iVitality to evaluate five cognitive tests based on conventional neuropsychological tests (Memory-Word, Trail Making, Stroop, Reaction Time, and Letter-N-Back) in healthy adults. Feasibility was tested by studying adherence of all participants to perform smartphone-based cognitive tests. Validity was studied by assessing the correlation between conventional neuropsychological tests and smartphone-based cognitive tests and by studying the effect of repeated testing.

Results We included 151 participants (mean age in years=57.3, standard deviation=5.3). Mean adherence to assigned smartphone tests during 6 months was 60% (SD 24.7). There was moderate correlation between the firstly made smartphone-based test and the conventional test for the Stroop test and the Trail Making test with Spearman $\rho=.3-.5$ ($P<.001$). Correlation increased for both tests when comparing the conventional test with the mean score of all attempts a participant had made, with the highest correlation for Stroop panel 3 ($\rho=.62$, $P<.001$). Performance on the Stroop and the Trail Making tests improved over time suggesting a learning effect, but the scores on the Letter-N-back, the Memory-Word, and the Reaction Time tests remained stable.

Conclusions Repeated smartphone-assisted cognitive testing is feasible with reasonable adherence and moderate relative validity for the Stroop and the Trail Making tests compared with conventional neuropsychological tests. Smartphone-based cognitive testing seems promising for large-scale data-collection in population studies.
INTRODUCTION

The global prevalence of dementia is likely to increase in the coming years, mainly due to the growing population with an increased life expectancy (1). To investigate interventions to prevent dementia, large sample sizes with long follow-up are required (2). Assessment of cognitive functioning over time is important for early detection of cognitive decline in longitudinal dementia prevention studies. Conventional neuropsychological examination is burdensome, time-consuming, and expensive and therefore hardly feasible in large-scale studies with long follow-up. To get informed about cognitive functioning without the need for full neuropsychological examination, innovative solutions are required.

New technology is rapidly adopted by older generations, illustrated by a steady increase in the Internet and smartphone use over the last years (3). Using smartphone technology, remote monitoring of health parameters such as physical activity and blood pressure have already been widely studied and found feasible, also in older populations (4,5). Smartphones are likely to be the principal platform for the development of the next generation of clinical care and research (6). Smartphone-assisted cognitive testing would provide the ability to assess cognitive functioning rapidly and repeatedly in a noninvasive manner, at a convenient moment, and without generating high costs. Experience with smartphone use during a clinical cognitive assessment has already been tested (7), paving the way to integration in a home setting. Feasibility and validity of smartphone-based cognitive testing has been described, although narrowed down to specific patient groups or a specific cognitive test (8-11). Despite these advances made in conducting smartphone research, little is known in terms of the feasibility and validity of applying multiple cognitive tests using smartphone-based technologies for clinical research in larger populations. Implementation of an app is only feasible if participants are compliant (12) and the technical performance is optimal (13).

The aim of this study was to investigate the feasibility and validity of a cognitive test battery using smartphone-assisted technology in healthy adults, during a 6 months follow-up period.
Chapter 4

METHODS

Study Participants

We recruited participants at increased risk of cognitive decline and dementia, operationalized as a parental history of dementia (14). These persons are highly motivated to participate in a monitoring study to support preventive strategies for dementia, and therefore suitable for a proof-of-principle study (15).

Participants were included if: [1] they were 50 years or older, [2] at least one of their parents was diagnosed with any form of dementia, [3] they knew how to handle and were in possession of a smartphone with iOS or Android (version 2.3.3 or higher) software, [4] they had no dementia or any other cognitive disorder, and [5] they had no medical history of stroke or transient ischemic attack.

Participants were recruited through advertisements at memory outpatient clinics, nursing homes, general practices, and using the communication channels (website and newsletter) of the Dutch Alzheimer Foundation. People were asked to contact the study center and if all of the inclusion criteria were met, participants received detailed study information in print and an appointment for baseline measurement was made. Enrollment and follow-up took place from September 2013 to January 2015. Written informed consent was obtained from all participants at the baseline study visit. The study was approved by the medical ethical committee of Leiden University Medical Center (LUMC), the Netherlands.

iVitality Platform

iVitality is a web-based research platform that consists of a website, a smartphone-based app, and sensors that are connected with or already integrated in the smartphone to measure health characteristics including cognitive function, blood pressure (4), physical activity (integrated pedometer), and lifestyle (with questions about health and mood). The smartphone-based app was installed during the baseline assessment and the sensors were activated if participants were officially included in the study, until the end of follow-up. Participants could log on to the website to overlook the measurements and results of their performance on the app. Participants received alerts from the iVitality smartphone app to perform a test or measurement (eg, cognitive test or blood pressure) on their smartphone.
Study Design

Participants visited the study center at LUMC or Academic Medical Center (AMC) at baseline, where they received information about the study and the smartphone-based app was installed and explained. During this visit, baseline measurements were performed by a study physician or research nurse. Afterwards, during a 6 month follow-up period, participants received messages on their smartphone, reminding them to voluntarily perform a specific cognitive test (Table 1). Alert moments were chosen in a way that every test had at least four reminder moments evenly spread during the 6 month follow-up period. Table 1 indicates on what day since baseline the message was sent for every test to every individual participant. The smartphone app collected data from the tests and provided feedback to the participant by showing the results of their measurements. A secured Internet connection transferred the data to the website and the database of the study center.

<table>
<thead>
<tr>
<th>Table 1. Message moment per cognitive test during follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weeks in study</strong></td>
</tr>
<tr>
<td>Memory-Word Day</td>
</tr>
<tr>
<td>Trail Making test Day</td>
</tr>
<tr>
<td>Stroop Day</td>
</tr>
<tr>
<td>Reaction Time test Day</td>
</tr>
<tr>
<td>Letter-N-Back Day</td>
</tr>
</tbody>
</table>

Baseline Measurements

In preparation for the first visit to the study center, all participants completed a web-based questionnaire including questions about level of education, medical history, and medication use. The study physician measured parameters including weight, height, and blood pressure of all participants.

Cognitive function at baseline was tested using five neuropsychological tests to assess global cognitive function, executive function, attention, and immediate and delayed recall. The mini-mental state examination (MMSE) (16) was used to evaluate global cognitive function. The
15-Word Verbal Learning test (15-WVLT) (17) was used to assess immediate and delayed recall. The Trail Making test (TMT) (18), parts A and B, were used to measure attention and executive function. The Stroop-Color-Word test (19) was used to test selective attention.

**Smartphone-Based Cognitive Tests**

Five digital versions of cognitive tests were developed for the iVitality smartphone app based on existing neuropsychological tests, but carefully adapted for smartphone use.

The Memory-Word test was based on the 15-WVLT (17). A series of 10 words with a fixed time pace was presented to the participants, which they were instructed to remember. Directly afterwards, participants were displayed a list of 20 words, including the 10 words which were presented before, mixed with 10 new words. Participants had to press "yes" or "no" for recognition. Each correct and incorrect response was recorded.

The TMT, based on the original TMT part A and B (18), consisted of four parts of increasing complexity in which participants had to make a trail connecting 12 circles. In part 1, the circles contained numbers in ascending order (1-2-3), part 2 contained letters in ascending order (A-B-C), part 3 contained numbers and letters alternating in ascending order (1-A-2-B), and in part 4, numbers and letters had to be connected alternating and in opposing order: numbers ascending, letters descending (1-Z-2-Y). The total time for each part was recorded. This last part was added to decrease the ceiling effect in a cognitively healthy population.

The Stroop color-word test was based on the original Stroop test (19). In the smartphone version, 30 items were presented in all three parts. Names of colors in black letters (part I), colored blocks (part II) or names of colors in other colored letters (part III) were presented together with multiple-choice answers. Total time to complete each part was recorded.

The Reaction Time test consisted of two parts: in part 1, participants were requested to touch the screen of the smartphone as soon as a presented green box turned blue. In part 2, the green box was again presented, but turned into either a blue or red box. The participants had to touch the screen as soon as possible, only if the blue box appeared. At one random instance an enlarged blue box was presented, as a measure of the startle time. In all parts, the time was recorded between the box turning blue and the moment the participant touched the screen in milliseconds. The time between presenting the enlarged blue box and pressing the screen was recorded as the startle (reaction) time in milliseconds.
The Letter-N-Back test, based on the original N-back test (20), consisted of four parts. A series of letters on the screen of the smartphone was presented in a sequential order. In part 1 (0-back), participants had to touch the screen when the letter “X” appeared (in total 11 items presented); for part 2 (1-back), participants had to touch the screen when the letter that was displayed, was the same as the previous one (in total 11 items presented); in part 3 (2-back), participants had to touch the screen when a letter that was displayed was the same as the one before the previous one (in total 15 items presented); and in part 4 (3-back), they had to touch the screen when the letter that was displayed was the same as the one that was presented before the previous 2 letters (in total 20 items presented). Each correct and incorrect response was recorded.

Prior to each test, a short explanation was displayed. Screenshots of the tests are shown in Supplement 1.

Statistical Analyses

Characteristics of the study participants are reported as mean (SD) for continuous variables and as number (%) for categorical variables.

Feasibility was evaluated by the technical performance of the app and adherence to perform cognitive tests on a smartphone. Validity was studied by assessing the correlation between conventional and smartphone cognitive tests, and the effect on performance of repeated cognitive tests on a smartphone.

For each participant and each test, we assessed adherence during follow-up. Adherence was defined as the actual performance of cognitive test measurements within 1 week of the reminder received through the smartphone app. The technical performance was defined as the ability to function as developed on every participant’s smartphone.

To assess the relative validity of the first performed smartphone test compared with the conventional Stroop and TMT, we calculated the correlation coefficient. Since the test results were generally not normally distributed, we used Spearman correlation coefficient. To investigate systematic differences between conventional and smartphone cognitive tests, we computed z-scores for both and visualized the values in a Bland-Altman plot.

In a sensitivity analysis, we assessed the correlation between the score on the conventional test at baseline and the mean score of all attempts a participant had made on a specific smartphone-based test, to account for (technical) difficulties in the first attempt and a learning curve. In a
Chapter 4

second sensitivity analysis, we assessed the correlation between the conventional Stroop test and the first smartphone attempt without many mistakes. The participant needed to score at least half of the answers correct, and if not, the following score (of the next attempt) was taken. Since no conventional version of the Letter-N-Back test and the Reaction Time test were done at baseline, we could not assess the relative validity for these tests.

To assess potential learning effects after repeated testing, performance over time on the smartphone cognitive tests were visualized graphically. We analyzed the linear trend in test performance with each attempt using a linear mixed effects model with a random intercept and random slope for attempt within each subject (MIXED procedure). To investigate selective dropout, we performed an additional analysis on the effect of repeated testing including only those participants who performed 9 tests or more.

All analyses were performed using IBM SPSS software (version 23).

RESULTS

Baseline Characteristics

The flowchart for inclusion of participants is shown in Figure 1. The study population consisted of 151 participants. Two participants discontinued the study immediately after baseline visit because of technical issues with their smartphone, so they do not have smartphone measurements. During the follow-up period of 6 months, 12 participants (8%, 12/149) discontinued the study.

Baseline characteristics are shown in Table 2. Mean age was 57.3 (SD 5.3) years and 71% (107/151) were female. The most commonly used smartphone types were iPhone and Samsung. Almost 60% (88/151) of the participants had a high education level. None of the participants had an MMSE score below 27 points. More details about the other baseline characteristics are published elsewhere (4,15).
The iVitality Proof-of-Principle Study

Registration for iVitality-POP study
N=195

Inclusion iVitality-POP study
N=151

Discontinued study
N=12 (7.9%)
Reasons:
N=2 technical issues
N=10 personal circumstances

Completed follow-up
N=139

Figure 1. Flowchart inclusion of study participants

Table 2. Baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Study participants (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>57.3 (5.3)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>107 (70.9)</td>
</tr>
<tr>
<td>Highest education level, n (%)</td>
<td></td>
</tr>
<tr>
<td>Low (&lt;7 years)</td>
<td>16 (10.6)</td>
</tr>
<tr>
<td>Middle (7-12 years)</td>
<td>44 (29.1)</td>
</tr>
<tr>
<td>High (&gt;12 years)</td>
<td>88 (58.3)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>26.4 (4.0)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), mean (SD)</td>
<td>138 (18.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg), mean (SD)</td>
<td>85 (10.8)</td>
</tr>
<tr>
<td>MMSE³, median (interquartile range)</td>
<td>29 (29-30)</td>
</tr>
</tbody>
</table>

³Missing data for n=3 participants.
³MMSE: mini mental state examination.
Adherence

Adherence to the test program of the five smartphone-based cognitive tests during a 6 month follow-up is shown in Figure 2. Adherence was highest for the Reaction Time test (67%) and slightly lower for the other tests (62% for the Stroop test, 61% for the Memory-Word test, 61% for the Letter-N-Back test, and 48% for the Trail Making test). During the 6 month follow-up, adherence slightly decreased for all tests. Mean adherence per participant was 60% (SD 24.7). When investigating the data for the percentage of participants (calculated from total N=151) who made a test at least once during follow-up, irrespective of timing relative to the reminder, this was 98% for the Reaction Time test, 97% for the Stroop test, 95% for the N-back test, 94% for the Memory-Word test, and 89% for the TMT.

![Figure 2. Adherence to smartphone-based cognitive tests](image)

Relative Validity of the Smartphone Test Compared With the Conventional Test

Raw test scores of the conventional tests at baseline and the firstly performed smartphone tests are described in Supplement 2. Since the smartphone-based tests were based on the conventional tests but not identical, direct comparison between the raw test scores is not possible using absolute values.
The association between the conventional cognitive test made at baseline and the corresponding firstly performed cognitive test on the smartphone is shown in Table 3. There was moderate correlation between the smartphone-based test and the conventional test for the Stroop test (panel 3) and the TMT with $\rho=0.5$ and 0.4 respectively.

The sensitivity analysis in which we investigated the correlation between the conventional test and the mean score of all performed corresponding smartphone tests during follow-up showed higher correlation coefficients for both tests compared with the correlation with the first performed cognitive test (Table 3).

<table>
<thead>
<tr>
<th>Test</th>
<th>n</th>
<th>Conventional versus first performed smartphone test</th>
<th>Conventional versus mean score of all performed smartphone tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$\rho$</td>
<td>$P$ value</td>
</tr>
<tr>
<td>Stroop panel 1</td>
<td>146</td>
<td>0.36</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Stroop panel 2</td>
<td>146</td>
<td>0.31</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Stroop panel 3</td>
<td>146</td>
<td>0.50</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>TMT c numeric</td>
<td>135</td>
<td>0.38</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>TMT c alphanumeric</td>
<td>135</td>
<td>0.39</td>
<td>&lt;.001b</td>
</tr>
</tbody>
</table>

$^a$CC: correlation coefficient.  
$^b$Significant at the <.001 level  
$^c$TMT: Trail Making test.

The number of mistakes made by the participants in the conventional Stroop test was very low and randomly distributed, and therefore not accounted for in the analysis. The number of mistakes in the smartphone-based Stroop test was accounted for in a sensitivity analysis (Supplement 3). This showed a higher correlation coefficient for all three panels compared with the correlation with the first performed cognitive test when not accounted for mistakes (panel 1: $\rho=0.39$, panel 2: $\rho=0.33$, and panel 3: $\rho=0.57$).
Chapter 4

Figure 3. Systematic differences between conventional and smartphone-based cognitive tests in a Bland-Altman-plot. All values are standardised (in scores)
The Bland-Altman plots of tests which showed moderate correlation (Figure 3) show that the difference between the measurements was randomly distributed over the mean of the measurements. However, inspection of the Bland-Altman plot suggests that for the TMT (numeric and alphanumeric), correlation decreases with increasing time needed to complete the test.

**Repeated Cognitive Testing**

The trend in test scores for each smartphone-based test is shown in Figure 4. With increasing number of test repeats, the number of participants contributing to the data decreased since each test was actively offered 4 times during the study, so any excess number of performed tests is on participants’ initiative. The performance on the Stroop test improved for each panel with almost 1 sec per attempt (panel 3: beta=-.93, P<.001) and the reversed alphanumeric TMT improved with 1.8 sec per attempt (beta=-1.81, P<.001). The performance on the N-back, the Memory-Word, and the Reaction Time test remained virtually stable over time.

The sensitivity analysis in participants who performed the tests at least nine times showed similar results (Supplement 4).
Figure 4. Effect of repeated cognitive tests on smartphone
Number below the x-axis represent the number of participants performing that attempt. Boxes in the right upper corner of each graph represent the estimate (β) with confidence interval (CI). Significant results are marked with *. The coloured lines in N-back graph represent the maximum obtainable score per part.
Abbreviations: P=panel, tn=true negatives, tp=true positives, n=numeric, a=alphabetic, an=alphanumeric, ran=reverse alphanumeric, rt=reaction time, srt=selective reaction time, st=startle time.
DISCUSSION

Principal Findings

Our study shows that smartphone-based cognitive testing in cognitively healthy adults over 50 years of age is feasible and that motivated research participants are reasonably adherent to regular testing following an alert on their smartphone. Of the cognitive tests developed in iVitality, the smartphone-based Stroop test and the TMT have a moderate correlation with conventional tests. Repeated testing leads to improved test scores with increasing number of tests performed, suggesting a learning effect for the Stroop test and the TMT.

Adherence to smartphone tests in trial setting varies between studies (17%-90%) (21-23). These mixed percentages can be explained by the broad definition of adherence in smartphone interventions considering different frequencies, lengths, and intensities of use. Adherence of our participants is relatively good (60%) compared with these studies. The high frequency of reminders the participants received not only for the cognitive tests, but also for the other measurements in the iVitality POP study, could have caused a certain degree of alarm fatigue. This could have reduced the adherence and might explain the variability in adherence in our study. Participants were most adherent to the Reaction Time test. Potential reasons are that the test is easy, not very time-consuming, and does not require processing of information. Only 2 participants (1.3%) could not perform the smartphone tests because of technical problems. This suggests that repeated smartphone-based neuropsychological testing outside the context of a research center is also technically feasible.

Few studies have been performed to validate cognitive testing using a smartphone, usually in the context of a specific disorder or healthy young people (8,10,22). The moderate correlations in our study for the attention and executive function tasks are comparable with correlations found in a other study investigating cognitive smartphone apps focusing on working memory and perceptual speed (24). Another Stroop smartphone app was already validated to diagnose covert hepatic encephalopathy (9), but was not compared with the conventional Stroop test (19). The moderate association found between the conventional Stroop test and a smartphone Stroop test was not found before (22). This is also the first study investigating the TMT on a smartphone compared with the conventional version (25) with a moderate correlation.

The correlation coefficient increases for all smartphone-based tests with more attempts and when leaving the scores out from participants who made many mistakes in the smartphone Stroop test (Supplement 3), implicating that technical challenges while performing the test may have to be overcome. Our participants received short digital instructions prior to the
smartphone-based tests in an attempt to limit the influence of technical issues. Nevertheless, the first attempt could be less reliable because of misunderstanding. The mean performance reduced random measurement error and therefore resulted in stronger associations. Especially for the Stroop test we noticed that some participants made a lot of mistakes in the first attempt (more than half of the answers were incorrect), indicating misunderstanding and implicating the need for more explanation on beforehand in further research.

In line with our findings, another study that also developed a Letter-N-Back test and Reaction Speed test for the smartphone did not observe a learning effect over time (22). The fact that we did not find an improvement on performance in the Memory-Word, Letter-N-Back, and Reaction Speed tests can be due to the ceiling effect in our sample of participants without any cognitive complaints.

Limitations
This proof-of-principle study has several limitations. We selected participants with a parental history of dementia and therefore they are highly motivated to participate. This may have introduced a selection bias toward better adherence, which reduces the external validity. Another limitation is that we could not validate every smartphone test to a conventional test administered at baseline. Future studies must try to develop a more comparable smartphone test. Strengths of this study are the relatively large sample size for a proof-of-principle study, the moderate level of adherence, and the validation of part of the tests to conventional neuropsychological tests.

CONCLUSIONS
Taken together, the results of this proof-of-principle study show that smartphone cognitive testing in healthy older individuals is feasible and yields valid test results. It allows for repeated testing to observe changes over time while reducing the need for face-to-face contact, making it time-efficient, less burdensome for research participants, and less expensive. The tests should be considered as screening tests to detect changes over time, rather than replacing conventional neuropsychological test batteries. It may be particularly useful for large-scale data-collection in population studies with long follow-up requiring repeated testing.
Before implementation of this type of tests, further research should focus on criterion validity
to investigate whether the tests adequately pick up cognitive decline both cross-sectionally
as well as longitudinally. To reduce a potential learning effect, alternative versions of the
tests could be developed, although for longitudinal research this is less important since the
learning effect seemed to wane in our study.
Acknowledgments
The authors thank Dr AJM de Craen†, clinical epidemiologist, Dr BA Schmand, professor of neuropsychology, Dr WA van Gool, professor of neurology, and Dr EP Moll van Charante, general practitioner, for their comments on the analysis plan and interpretation of the data.

Funding
This project was supported by the Dutch Ministry of Health, Welfare and Sport and was enabled by ZonMw (NGI/NWO 050-060-810 project 627002001). The authors Susan Jongstra and Edo Richard received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement No. 305374.

Conflicts of Interest
None declared.
REFERENCES


SUPPLEMENT 1

Screenshots of cognitive test on smartphone

Stroop test panel 1

Stroop test panel 3

Memory-Word test

Trail making test

N-back test (0-back)

N-back test (1-back)
Mean test results of conventional cognitive tests at baseline and first made cognitive test on a smartphone

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Conventional mean (SD)</th>
<th>Digital Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroop</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop panel 1 total time (sec)</td>
<td>43.53 (6.2)</td>
<td>31.78 (7.6)</td>
</tr>
<tr>
<td>Stroop panel 2 total time (sec)</td>
<td>54.41 (8.8)</td>
<td>31.46 (5.8)</td>
</tr>
<tr>
<td>Stroop panel 3 total time (sec)</td>
<td>83.09 (17.0)</td>
<td>34.59 (6.2)</td>
</tr>
<tr>
<td><strong>Trail making test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail making test numeric (sec)</td>
<td>26.64 (8.8)</td>
<td>15.22 (8.6)</td>
</tr>
<tr>
<td>Trail making test alphabetical (sec)</td>
<td>-</td>
<td>14.45 (5.3)</td>
</tr>
<tr>
<td>Trail making test alphanumeric (sec)</td>
<td>57.8 (18.1)</td>
<td>22.37 (16.5)</td>
</tr>
<tr>
<td>Trail making test reversed alphanumeric (sec)</td>
<td>-</td>
<td>33.86 (23.7)</td>
</tr>
<tr>
<td><strong>Word learning test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word learning test # correct trial 1</td>
<td>5.89 (1.7)</td>
<td>-</td>
</tr>
<tr>
<td>Word learning test # correct trial 2</td>
<td>8.35 (2.1)</td>
<td>-</td>
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<tr>
<td>Word learning test # correct trial 3</td>
<td>9.82 (2.3)</td>
<td>-</td>
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<tr>
<td>Word learning test # correct trial 4</td>
<td>10.61 (2.1)</td>
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<td>Word learning test # correct trial 5</td>
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<td>Word learning test # correct delayed</td>
<td>9.42 (2.7)</td>
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<td>Word learning test # correct recognition positive</td>
<td>14.34 (1.2)</td>
<td>-</td>
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<tr>
<td>Word learning test # correct recognition negative</td>
<td>14.56 (0.9)</td>
<td>-</td>
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<tr>
<td>Word learning test # true positives</td>
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<td>8.32 (1.5)</td>
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<tr>
<td>Word learning test # true negatives</td>
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<td>9.54 (0.7)</td>
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<tr>
<td><strong>Reaction speed test</strong></td>
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</tr>
<tr>
<td>Reaction speed test reaction time (sec)</td>
<td>-</td>
<td>0.52 (0.3)</td>
</tr>
<tr>
<td>Reaction speed test selective reaction time (sec)</td>
<td>-</td>
<td>0.57 (0.3)</td>
</tr>
<tr>
<td>Reaction speed test startle reaction time (N=127)</td>
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<td>0.47 (0.4)</td>
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<td><strong>Letter N-back test</strong></td>
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<tr>
<td>Letter N-back test 0-back correct</td>
<td>-</td>
<td>10.61 (0.8)</td>
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<tr>
<td>Letter N-back test 1-back correct</td>
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<td>10.10 (1.2)</td>
</tr>
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<td>Letter N-back test 2-back correct</td>
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<td>13.91 (1.1)</td>
</tr>
<tr>
<td>Letter N-back test 3-back correct</td>
<td>-</td>
<td>18.00 (1.4)</td>
</tr>
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</table>
SUPPLEMENT 3

Relative validity of the first performed cognitive test without many mistakes compared with the conventional cognitive test at baseline

<table>
<thead>
<tr>
<th>Test</th>
<th>N</th>
<th>ρ correlation coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroop panel 1</td>
<td>145</td>
<td>0.39</td>
<td>&lt;0.000*</td>
</tr>
<tr>
<td>Stroop panel 2</td>
<td>145</td>
<td>0.33</td>
<td>&lt;0.000*</td>
</tr>
<tr>
<td>Stroop panel 3</td>
<td>138</td>
<td>0.57</td>
<td>&lt;0.000*</td>
</tr>
</tbody>
</table>
SUPPLEMENT 4

Effect over time for repeated cognitive tests (only for the participants who made the test at least 9 times)

Stroop test

N=12

Time to complete test (sec)

Attempt

Panel 1 □ Panel 2 ■ Panel 3 ▲

Trail Making test

N=11

Time to complete test (sec)

Attempt

numeric □ alphabetic ■ alphanumeric ▲ reverse alphanumeric

Memory test

N=9

Number of correct items

Attempt

true negatives □ true positives ■

Reaction time test

N=23

Mean time (sec)

Attempt

mean reaction time □ mean selective reaction time ■ startle time
“Are these tests really going to tell you if I have memory problems or even dementia? I will only have to name the things you said a minute ago!”

(Quote of a participant during the MMSE test, December 2015)
Chapter 5

IMPROVING PREDICTION OF DEMENTIA IN PRIMARY CARE
THE INCREMENTAL VALUE OF THE VISUAL ASSOCIATION TEST TO THE MINI MENTAL STATE EXAMINATION – A COHORT STUDY

Susan Jongstra, Willem A. van Gool, Eric P. Moll van Charante, Jan-Willem van Dalen, Lisa S.M. Eurelings, Edo Richard, Suzanne A. Ligthart

Manuscript submitted
ABSTRACT

Background The Mini-Mental-State-Examination (MMSE) is one of the most widely used instruments to screen for cognitive defects. This instrument alone is not sensitive enough to recognise early symptoms of dementia in primary care. We aimed to investigate whether Visual Association Test (VAT) results improve the predictive value for the development of dementia of MMSE score changes in the course of two years.

Methods Participants were from the preDIVA-trial (n=2690). Using MMSE change scores over two years and VAT scores we assessed the predictive values of a diagnosis of dementia in the 4-6 years following. We performed logistic regression analysis adjusted for age and education.

Results Dementia developed in 157 (5.9%) participants. A decline of ≥2 in total MMSE score is associated with an odds ratio of 3.55 (95% CI 2.5-5.0) compared to a stable or improved MMSE. Participants with a ≥2 MMSE score decline over time and an additional imperfect VAT score had an odds ratio of 9.55 (5.9-15.4) for future dementia. A decline of one point in MMSE score is associated with an increased risk of dementia if the VAT score is imperfect.

Conclusion Administering the VAT in persons with only a small decline on the MMSE over a two year period has substantial incremental value for identification of those who are at increased risk of dementia. This simple test may help distinguishing older persons who need further cognitive examination and counselling from those in whom a watchful waiting policy is justified.
INTRODUCTION

Nowadays 47.5 million people worldwide suffer from dementia(1). Dementia is associated with increased disability, dependency and mortality(2) and has impact on different levels, affecting the wellbeing of the patient and posing a great burden on caregivers and society at large(1). A timely diagnosis of dementia is important as it will allow for tailored counselling of patients and caregivers, it enables access to specific information, resources and support, as well as early access to appropriate symptomatic treatment(s) (3-5). To screen for cognitive impairment, various diagnostic instruments are used. Although new screening instruments have been developed over the last years, the Mini Mental State Examination (MMSE)(6) is still widely used(7). In spite of its limitations, including limited sensitivity for early stages of cognitive impairment(8), many doctors use it on a regular basis and it is also widely used in clinical research. The MMSE has high test-retest reliability(9, 10), which has led researchers to using it for measuring changes in cognition over time, even though it was never developed for this purpose(11). However, when screening for dementia the meaning of a decline of only one or two points on the total MMSE score over a one to two year timeframe is unclear. This leads to the question whether such a decrease on the total MMSE score should invite further investigation and whether such a decrease heralds incipient cognitive decline. If further investigation would be warranted, non-invasive tests to distinguish between normal ageing and early signs of dementia are preferable(12-14).

The Visual Association Test(VAT) might be useful for this purpose. It is a test of associative memory and very sensitive to detect impaired anterograde memory(15), without bias based on language skills. It has particularly good test characteristics for the detection of early signs of Alzheimer’s disease, the most common form of dementia. It comprises a cued recall test using associations of pictorial material, to assess deterioration in episodic memory. The VAT is very quick (2-3 minutes) and easy to administer.

The preDIVA study(prevention of dementia by intensive vascular care) is the only study in which both the MMSE and the VAT have been administered repeatedly during long-term follow-up in cognitively intact older people, thus allowing for analysis of their discriminatory power for the early detection of dementia.

In this paper we aimed to investigate the predictive value of MMSE score changes in the course of two years for the development of dementia during the 4-6 years to follow and whether the score on the VAT improves the predictive value.
METHODS

Participants
The study sample was drawn from the preDIVA trial(16). This was a cluster-randomized controlled trial with a mean follow-up of 6.7 years to assess the efficacy of nurse-led intensive vascular care on the prevention of dementia in a primary care population. Between May 2006 and March 2009, 3526 community-dwelling older individuals aged 70–78 years were included. Exclusion criteria at baseline were prevalent dementia and disorders or circumstances expected to hinder long-term participation and follow-up. Carefully instructed practice nurses carried out all measurements. A detailed description of the preDIVA study design and procedures has been published elsewhere(16, 17). For the present analyses the population is considered as a cohort, irrespective of randomization group. Since this study aimed to assess predictive values for future dementia during long-term follow up, participants were excluded from this analysis if they dropped-out in the first two years of the intervention, were diagnosed with dementia within the first two year of follow-up or within three months after the two-year follow-up assessment.

The Medical Ethics Committee of the Academic Medical Center in Amsterdam approved the study and all participants signed informed consent before enrolment.

Dementia diagnosis
For all participants, cognitive status was assessed during all follow-up measurements, supplemented by available clinical information from general practitioners’ electronic health records including reports on hospital admissions, outpatient diagnostic evaluations by geriatricians, neurologists, psychiatrists, neuroimaging, and/or neuropsychological examinations. For all participants (including dropped out participants) cognitive status was checked at the end of the study (after 6 to 8 years of follow-up). An independent outcome adjudication committee including neurologists, old age psychiatrists, geriatricians, cardiologists, and family physicians, evaluated dementia diagnoses blinded for treatment group. As a quality check and to minimise the risk of false-positive diagnoses, all dementia diagnoses were re-evaluated after one year(16).

MMSE and VAT
The Dutch version of the MMSE(18) was used in all measurements with a maximum obtainable score of 30 points. To determine change over time in MMSE scores, we compared the scores at baseline to the two-year follow-up measurement score.
The VAT test (version VAT A)(15) consisted of six association cards showing two interacting objects (e.g. an ape holding an umbrella, Figure 1). The participants were asked to name both objects on the cards and they were not told to remember the objects (incidental leaning). There are also six cue cards showing only one of the objects. Cued recall is tested without delay by showing the six cue cards and asking the participants to identify the missing object. One point is given if the response is sufficiently clear to distinguish the target object from the other objects used in the test. The maximum score is 6 points (one per card).

For the present analysis we used the VAT scores at the two-year follow-up assessment (and not the change in score over time).

Figure 1. Pictures used in the Visual Association Test. Ape with umbrella on the left and the cue card on the right.

**Statistical analysis**

Participants were included in the analysis if data were available for both the MMSE at baseline and at two-year follow-up, and VAT at two-year follow-up. MMSE score difference was calculated by subtracting the baseline total MMSE score from the two-year follow-up total MMSE score. We performed logistic regression analysis with diagnosis of dementia as dependent variable and with dichotomised MMSE difference (stable or improvement ≥-1 versus decline ≤-2 over time) and dichotomised VAT score (optimal score 6 versus imperfect score ≤5) as independent variables separately. This strict cut-off for the VAT score was chosen since
the study concerned a healthy (older) population and therefore it was expected that the performance would be optimal if cognition was intact. We adjusted all analyses for age and educational level, since both factors are known possible confounders for the relation between MMSE score and dementia. We have chosen for a logistic regression since we were interested in the cumulative risk over time rather than the specific timing of dementia onset. In addition, we performed logistic regression analysis for dementia predicted by combined MMSE difference and VAT scores, categorised into four groups (ΔMMSE≥-1 and VAT=6; ΔMMSE≥-1 and VAT≤5; ΔMMSE≤-2 and VAT=6; ΔMMSE≤-2 and VAT≤5).

Finally, we assessed the percentage of dementia cases per category of MMSE difference (from ≤-3 to ≥3), both overall and separately for participants with a maximum VAT score (6 points) and for participants with a lower VAT score (≤5 points).

For all analyses SPSS software (version 23) was used.

RESULTS

Study population

In total, 2690/3526 (76.3%) participants without dementia completed baseline and two-year follow-up measurements and were included in the present analysis. The most frequently occurring reasons for drop-out were withdrawal on own request or relocation, described in more detail elsewhere(16). Fourteen participants were excluded because they were diagnosed with dementia within the first two years of follow-up or within three months after the two-year follow-up visit. Baseline characteristics are summarized in Table 1. Mean age was 73.7 (SD 2.4) years and most of the participants (63.5%) had an intermediate education level (7 to 12 years).

Follow-up with respect to dementia diagnosis was available for 2648 participants (98.4%) after a median follow-up time of 6.7 years. Dementia developed in 157 (5.9% 95% confidence interval (CI) 5.0-6.8%) of this group.

The results of the logistic regression analysis are shown in Table 2. The odds ratio of the MMSE difference score (stable score versus decline) over two year is 3.55 (95% CI 2.5 to 5.0). The odds ratio of the dichotomized VAT score is comparable (3.28 95% CI 2.4 to 4.6). Adjusting for age or education did not significantly change these odds ratios.
### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Study population at baseline (N=2690)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (SD)</td>
<td>73.7 (2.4)</td>
</tr>
<tr>
<td>Sex male, n (%)</td>
<td>1212 (45.6)</td>
</tr>
<tr>
<td>Educational level&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Low (&lt;7 years), n (%)</td>
<td>591 (22.5)</td>
</tr>
<tr>
<td>Intermediate (7-12 years), n (%)</td>
<td>1672 (63.5)</td>
</tr>
<tr>
<td>High (&gt;12 years), n (%)</td>
<td>368 (14.0)</td>
</tr>
<tr>
<td>Race Caucasian, n (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2555 (96.2)</td>
</tr>
<tr>
<td>MMSE score at baseline, median (IQR)</td>
<td>29 (27-29)</td>
</tr>
<tr>
<td>VAT score at baseline, median (IQR)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6 (5-6)</td>
</tr>
</tbody>
</table>

<sup>a</sup> 24 missings  
<sup>b</sup> 40 missings  
<sup>c</sup> 14 missings  
Baseline characteristics of the study participants are reported as mean (standard deviation) or median (inter quartile range) for continuous variables and as number (percentage) for categorical variables.

### Table 2. Risk of dementia

<table>
<thead>
<tr>
<th></th>
<th>n/N</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>Adjusted* OR (95% CI)</th>
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<tbody>
<tr>
<td>ΔMMSE over 2 year&lt;sup&gt;1&lt;/sup&gt;</td>
<td>57/402&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3.55 (2.5 to 5.0)</td>
<td>&lt;0.001</td>
<td>3.45 (2.4 to 4.9)</td>
</tr>
<tr>
<td>VAT at 2 year FU&lt;sup&gt;2&lt;/sup&gt;</td>
<td>97/919&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3.28 (2.4 to 4.6)</td>
<td>&lt;0.001</td>
<td>3.14 (2.2 to 4.4)</td>
</tr>
<tr>
<td>MMSE and VAT combined&lt;sup&gt;4&lt;/sup&gt;:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE stable + perfect VAT&lt;sup&gt;3&lt;/sup&gt;</td>
<td>40/1466</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MMSE stable + imperfect VAT&lt;sup&gt;3&lt;/sup&gt;</td>
<td>60/680</td>
<td>3.23 (2.1 to 4.9)</td>
<td>&lt;0.001</td>
<td>3.08 (2.0 to 4.7)</td>
</tr>
<tr>
<td>MMSE decline + perfect VAT&lt;sup&gt;3&lt;/sup&gt;</td>
<td>20/203</td>
<td>3.61 (2.1 to 6.3)</td>
<td>&lt;0.001</td>
<td>3.46 (2.0 to 6.1)</td>
</tr>
<tr>
<td>MMSE decline + imperfect VAT&lt;sup&gt;3&lt;/sup&gt;</td>
<td>37/142</td>
<td>9.55 (5.9 to 15.4)</td>
<td>&lt;0.001</td>
<td>9.14 (5.6 to 14.9)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Adjusted for age and educational level  
<sup>2</sup> Score: ≤-2 versus ≥-1  
<sup>3</sup> Score: ≤5 versus >5  
<sup>4</sup> Scores of ΔMMSE and VAT combined. Reference category is best performing group: participants with ΔMMSE≤-1 and VAT=6  
Abbreviations: MMSE= Mini Mental State Examination; VAT= Visual Association Test; n= number of dementia cases; N= number at risk; B= beta coefficient; OR= odds ratio; CI= confidence ratio; FU= follow-up

For the analyses with participants categorised into four groups based on combined MMSE difference and VAT score (Table 2), the best performing group (ΔMMSE ≤-1 and VAT =6) was used as reference group. The group of participants that had lower scores on both tests
(ΔMMSE ≤-2 and VAT ≤5) had highest risk for incident dementia with an odds ratio of 9.55 95%CI 5.9 to 15.4 compared to those with a stable or improving MMSE change score or a perfect score on the VAT.

Figure 2. a+b. On the left side of the x-axis are the participants who improved in total MMSE score and the participants on the right side decreased in MMSE score over two years.
The percentage of participants diagnosed with dementia per MMSE change score is shown in Figure 2a. Of those who were stable or improved on the MMSE score, the risk of developing dementia varied (2.4% to 6.4%) around the average risk of 5.9%. A two or three points decline on MMSE score, however, was associated with an increased risk of developing dementia of 10.1% and 20.8% respectively (Figure 2a), significantly higher than the overall risk of developing dementia.

When comparing dichotomized VAT scores at the two-year assessment per MMSE change category (Figure 2b), groups with imperfect VAT scores (≤5) all had substantially higher percentages of incident dementia (Figure 2a). An imperfect VAT score increased the predictive value of a two or three points decrease on the MMSE substantially from 10.1% to 14.4% and from 20.8% to 29.3% respectively. Even in those who have a decline of 1 point on the MMSE score, an imperfect score on the VAT doubles the risk to 12.2% (95%CI 7.5 to 17.0). In contrast, the risk of developing dementia for participants with a two or three point decrease on the MMSE score and a perfect VAT score is not significantly different from the average risk of the cohort as a whole (Figure 2b).

**DISCUSSION**

Among non-demented community-dwelling older people, a decline of two or more points on the MMSE score over two years reflects an increased risk of all-cause dementia compared with those with a stable or improved score or lower decrease. This increased risk was not affected by age or educational level. VAT scores have additional value in discriminating persons with and without increased risk of dementia, especially in individuals with a (minor) decline in MMSE score. The VAT administered without the MMSE does not seem to have this additional value compared to the MMSE difference score alone in this population.

The clinical significance of changes over time in MMSE scores has been subject of debate, because a change in MMSE score over time can be explained by several causes. Small changes may result from various factors including measurement errors, learning effects, ageing and regression to the mean and therefore may not necessarily reflect true cognitive changes(13, 14). Our results are consistent with these findings. Although in our results two or more points decrease on the MMSE score does reflect an increased risk of dementia, still the vast majority of participants (about 80%) with such a score change did not develop dementia over the four years to follow. There are no studies that analysed the additional value of the VAT after performing the MMSE, while the MMSE seems unreliable in predicting and detecting (early) dementia(8),
whereas the VAT is especially developed for this purpose. Other studies show that the VAT has a higher specificity and positive predictive value to detect dementia compared to other cognitive tests (19), even in the preclinical phase (15). In our analyses, performing the VAT as an additional test in participants with a decline of only one point or more in MMSE score, was associated with a significant and clinically meaningful increased risk of dementia if the VAT score is imperfect.

A formal comparison with other methods that have been suggested for prediction of dementia is beyond the scope of the present study. However, a global comparison of the effect size (Cohen’s d of 1.24, based on the odds ratio of 9.55 (table 2) (20) found in the present analysis for the combination of MMSE change with VAT compares quite well with effect sizes reported in a meta-analysis of levels in cerebrospinal fluid (CSF) of total tau, phosphorylated tau and amyloid-beta-42 ranging from 0.91 to 1.11 or the effect size of medial temporal lobe atrophy on magnetic resonance imaging (MRI) of 0.75 (21). This approximate comparison based on studies with numerous methodological differences suggests that a direct comparison in a single cohort of the various predictive methods is warranted. Especially, because performing a VAT in individuals with a declining MMSE will be far more cost-effective and is associated with much less burden to patient and carer than doing a lumbar puncture for cerebrospinal fluid examination or making a MRI scan (22, 23) which requires at least one extra visit.

**Strengths and limitations of this study**

This study has several limitations. Participants were only included in the analysis if they performed the MMSE at baseline and at two-year follow-up, and the VAT at two-year follow-up. This has led to a smaller sample than the original study and possibly to selection bias. For this paper, only version A of the VAT was used. Originally, the VAT consisted only of the VAT A version, with promising results in detecting dementia (15). VAT B (six extra association cards) could be added to further increase the sensitivity of the test in participants with a maximum score at the VAT A. The strengths of this study are the large sample size, the long follow-up period, the blinded adjudication of dementia diagnoses (including a one year follow-up after the diagnosis of dementia), completeness of follow-up on all-cause dementia (16) and clinical perspective assessing instruments that can be administered easily in daily practice.
CONCLUSION

We have shown that administering the VAT in persons with a decline of only one point or more on the MMSE over a two year period has substantial incremental value for identification of those who are at increased risk of dementia. Administration of the VAT to those who decline on the MMSE in primary care may help distinguishing those who need a further cognitive examination, counselling or potentially referral to a memory clinic from those in whom a watchful waiting policy is justified.
Acknowledgements
The authors want to thank the preDIVA participants and nurses for their work and participation. Also, we want to thank dr. M. Hoevenaar-Blom for her statistical advice.

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Declaration of competing interests
Nothing to declare.
REFERENCES

"Why do you care about my blood pressure if you do not know my heart rate?"

(Quote of a participant during the evaluation session of the pilot, November 2015)
Chapter 6

ANTIHYPERTENSIVE WITHDRAWAL FOR THE PREVENTION OF COGNITIVE DECLINE
A COCHRANE SYSTEMATIC REVIEW

Susan Jongstra, Jennifer K Harrison, Terry J Quinn, Edo Richard

Cochrane Database Systematic Reviews; 2016 Nov 1
ABSTRACT

Background Clinical trials and observational data have variously shown a protective, harmful or neutral effect of antihypertensives on cognitive function. In theory, withdrawal of antihypertensives could improve cerebral perfusion and reduce or delay cognitive decline. However, it is also plausible that withdrawal of antihypertensives may have a detrimental effect on cognition through increased incidence of stroke or other vascular events.

Objectives To assess the effects of complete withdrawal of at least one antihypertensive medication on incidence of dementia, cognitive function, blood pressure and other safety outcomes in cognitively intact and cognitive impaired adults.

Search methods We searched ALOIS, the specialised register of the Cochrane Dementia and Cognitive Improvement Group, with additional searches conducted in MEDLINE, Embase, PsycINFO, CINAHL, LILACS, Web of Science Core Collection, ClinicalTrials.gov and the World Health Organization Portal/ICTRP on 12 December 2015. There were no language or date restrictions applied to the electronic searches, and no methodological filters were used to restrict the search.

Selection criteria We included randomised controlled trials (RCTs) and controlled clinical trials (CCTs) provided they compared withdrawal of antihypertensive medications with continuation of the medications and included an outcome measure assessing cognitive function or a clinical diagnosis of dementia. We included studies with healthy participants, but we also included studies with participants with all grades of severity of existing dementia or cognitive impairment.

Data collection and analysis Two review authors examined titles and abstracts of citations identified by the search for eligibility, retrieving full texts where needed to identify studies for inclusion, with any disagreement resolved by involvement of a third author. Data were extracted independently on primary and secondary outcomes. We used standard methodological procedures expected by Cochrane.

The primary outcome measures of interest were changes in global and specific cognitive function and incidence of dementia; secondary outcomes included change in systolic and diastolic blood pressure, mortality, adverse events (including cardiovascular events, hospitalisation and falls) and adherence to withdrawal. The quality of the evidence was evaluated using the GRADE approach.
Main results We included two RCTs investigating withdrawal of antihypertensives in 2490 participants. There was substantial clinical heterogeneity between the included studies, therefore we did not combine data for our primary outcome. Overall, the quality of included studies was high and the risk of bias was low. Neither study investigated incident dementia.

One study assessed withholding previously prescribed antihypertensive drugs for seven days following acute stroke. Cognition was assessed using telephone Mini-Mental State Examination (t-MMSE) and Telephone Interview for Cognitive Status (TICS-M) at 90 days as a secondary outcome. The t-MMSE score was a mean of 1.0 point higher in participants who withdrew antihypertensive medications compared to participants who continued them (95% confidence interval (CI) 0.35 to 1.65; 1784 participants) and the TICS-M was a mean of 2.10 points higher (95% CI 0.69 to 3.51; 1784 participants). However, in both cases the evidence was of very low quality downgraded due to risk of bias, indirectness and evidence from a single study. The other study was community based and included participants with mild cognitive impairment. Drug withdrawal was for 16 weeks. Cognitive performance was assessed using a composite of at least five out of six cognitive tests. There was no evidence of a difference comparing participants who withdrew antihypertensive medications and participants who continued (mean difference 0.02 points, 95% CI -0.19 to 0.21; 351 participants). This evidence was of low quality and was downgraded due to risk of bias and evidence from single study.

In one study, the systolic blood pressure after seven days of withdrawal was 9.5 mmHg higher in the intervention compared to the control group (95% CI 7.43 to 11.57; 2095 participants) and diastolic blood pressure was 5.1 mmHg higher (95% CI 3.86 to 6.34; 2095 participants). This evidence was low quality, downgraded due to indirectness, because the data must be interpreted in the context of the wider study looking at glyceryl trinitrate administration or not, and evidence from a single study. In the other study, systolic blood pressure increased by 7.4 mmHg in the withdrawal group compared to the control group (95% CI 7.08 to 7.72; 356 participants) and diastolic blood pressure increased by 2.6 mmHg (95% CI 2.42 to 2.78; 356 participants). This was moderate quality evidence, downgraded as evidence was from a single study. We combined data for mortality and cardiovascular events. There was no clear evidence that antihypertensive medication withdrawal affected adverse events, although there was a possible trend to increased cardiovascular events in the large post-stroke study (pooled mortality risk ratio 0.88, 95% CI 0.72 to 1.08; 2485 participants; and cardiovascular events risk ratio 1.29, 95% CI 0.96 to 1.72). Certain prespecified outcomes of interest (falls, hospitalisation) were not reported.
Authors' conclusions The effects of withdrawing antihypertensive medications on cognition or prevention of dementia are uncertain. There was a signal of a positive effect in one study looking at withdrawal after acute stroke but these results are unlikely to be generalisable to non-stroke settings and were not a primary outcome of the study. Withdrawing antihypertensive drugs was associated with increased blood pressure. It is unlikely to increase mortality at three to four months' follow-up, although there was a signal from one large study looking at withdrawal after stroke that withdrawal was associated an increase in cardiovascular events.
BACKGROUND

Hypertension (blood pressure above a recommended value) is a common clinical condition with a well-established causal role in cardiovascular disease(1). Hypertension is particularly prevalent in older age; more than half of the population over the age of 50 years, and approximately 80% of the population older than 80 years have hypertension(2, 3). The protective effect of antihypertensive treatment against cardiovascular events and premature mortality is well established(4, 5). The evidence to support treatment of hypertension in healthy older adults is robust(6). Evidence for benefit of antihypertensive therapy in frail older adults with comorbidities and geriatric syndromes including cognitive and functional decline is limited, and some data suggest potential for harm, with studies describing association between antihypertensive therapy and higher mortality(7), and serious injuries arising from falls(8).

The evidence for antihypertensive therapy in people with cognitive impairment or dementia, and the impact of this treatment on cognition is uncertain, with conflicting results in published data and no meta-analysis possible due to heterogeneity(9). Data have variously shown a protective, harmful or neutral effect of antihypertensives on cognition. One study with almost 5000 older adults, suggested no detrimental effect of antihypertensive treatment on cognitive function in people with existing cognitive problems(10). Two other large studies did not show a reduction of incident dementia in people treated with antihypertensive medications(11, 12). However, other work suggested a protective effect of antihypertensive treatment on vascular-induced dementia(13), while another study reported potential for antihypertensive medication to accelerate cognitive decline(14).

These seemingly conflicting trial data may be explained by the complex relationship between blood pressure and cognition over the life course. Hypertension in middle-age is a risk factor for incident dementia, driven at least in part by cerebrovascular disease(15). However, the association between blood pressure and dementia at an older age is inverse(16, 17). Several years before dementia onset, a decrease in blood pressure can be seen(18), and low blood pressure is associated with cognitive decline in the years after diagnosis(19), although the direction of causality is unknown. Several mechanisms were proposed to underlie this decrease in blood pressure in the years before the diagnosis of dementia, including autonomic dysregulation as symptom of neurodegeneration(20). The arteriosclerotic and age-related changes to cerebral blood flow autoregulation in older people could also result in cerebral hypoperfusion, potentially influencing cognitive functioning(17).
Thus, the evidence base for cognitive benefits of hypertension treatment in midlife is compelling, but the evidence for cognitive effects of hypertension treatment in older age is less clear. The Cochrane systematic review on hypertension treatment in elderly people showed that adherence to treatment is limited and a considerable proportion of older people discontinue treatment, due to adverse effects, in particular when the level of prescribed treatment increased(5). Taking all this into account, there is a concern that antihypertensive medication may have potential for harm in people with cognitive impairment/dementia and it may negatively influence cognitive functioning. There is an associated debate regarding the benefit of withdrawing antihypertensive therapy in older adults, since the risk-benefit ratio of treatment might be different at differing ages and with different classes of antihypertensive medications(21).

It would be interesting for patients, carers and policymakers if withdrawal of antihypertensive medications has a positive effect on cognitive functioning, since this might possibly lead to a decrease in dementia incidence and thus major health cost savings. Reducing medication use will also contribute to less healthcare expenditures. Such withdrawal may take place in isolation, or may be part of a wider medication review or deprescribing exercise. Deprescribing is “the process of tapering or stopping drugs, aimed at minimizing polypharmacy and improving patient outcome” and is a growing area with observation and trial evidence(22). Older adults(23), care home residents(24), and people with advanced dementia(25) are all populations in whom inappropriate prescribing is thought to be common with scope for improvements through deprescribing or electronic systems for medication review.

The purpose of this systematic review was to summarise all available evidence on cognitive effects of withdrawal of antihypertensive medications and associated benefits and harms in adults (including healthy adults and people with prevalent cognitive decline).

**Description of the condition**

We have focused on the implications of antihypertensive medication on cognitive functioning, including cognitive decline and dementia. Cognitive decline is often accompanied by deterioration in emotional control, social behaviour or motivation. The number of people living with cognitive impairment not classified as dementia is probably even higher, but no exact data on this exist. The term 'mild cognitive impairment' (MCI) refers to a 'syndrome defined as cognitive decline greater than expected for an individual’s age and education level but that does not interfere notably with activities of daily life’(26). Although rates of conversion from MCI to dementia vary, it is thought that people with MCI are at an increased
risk of developing dementia(27). Dementia is a syndrome that is caused by a variety of brain diseases of typically chronic and progressive in nature. The dementia syndrome involves disturbances of memory combined with other impairments multiple of brain function, such as language, thinking, orientation, perception and behaviour. These impairments occur to such a degree that they negatively affect the performance of everyday activities. Although the incidence of dementia is thought to be declining in Western countries(28), the prevalence is increasing due to the ageing world population meaning larger numbers of people are living with dementia(29). Worldwide, 47.5 million people were estimated to be affected in 2015 and it is anticipated that this figure will double by 2030, resulting in high costs and considerable burden to individuals and societies(30).

**Description of the intervention**

In this review, we identified and appraised randomised controlled trials (RCTs) and controlled clinical trials (CCTs) which evaluated the cognitive consequences of withdrawal of antihypertensive treatment in adults. For this review, we defined ‘antihypertensive treatment’ as the use of any drug with any blood pressure lowering effect, prescribed for any indication.

Major classes of antihypertensive drugs include thiazide diuretics, beta-blockers, drugs inhibiting the renin-angiotensin system, calcium channel blockers, direct vasodilators, centrally active drugs and others. The different classes of antihypertensive drugs have differential effects on some outcomes, and it is possible that they have differential effects on cognition. Some studies have suggested that especially calcium channel blockers(31) and diuretics(32, 33) may have a protective effect on cognition, but this has not been shown in a RCT.

**How the intervention might work**

There are plausible theoretical reasons why withdrawal of antihypertensive therapy may have a beneficial effect on cognition. One of these reasons might be autonomic dysregulation as symptom of neurodegeneration(20). Another theory is about arteriosclerotic and age-related changes to cerebral blood flow autoregulation in older adults, resulting in cerebral hypoperfusion(17) and potentially influencing cognitive functioning. Equally, withdrawal of antihypertensive therapy may accelerate cognitive decline through incident stroke or progression of small vessel disease. Interventions to completely withdraw at least one antihypertensive medication in people with and without cognitive problems may also reduce adverse effects and improve quality of life for the patient and carer. However, they may also cause withdrawal symptoms such as
'rebound' tachycardia with withdrawal of beta-blocker, headache, agitation and nausea(34). Therefore, we have examined trials which evaluate effects of antihypertensive withdrawal, contributing to the evidence base in this area.

**Why it is important to do this review**

Contemporary guidelines for blood pressure management in older adults focused on indications for treatment and choice of treatment. It is possible that withdrawal of antihypertensive medication in certain older-adult populations may have beneficial effects on cognition or rates of incident dementia, or both. A cost saving intervention (drug withdrawal) that impacts on cognition would have important individual and public health implications. Drug withdrawal might also decrease the burden of polypharmacy. This burden is usually accompanied with minor and major adverse events, so withdrawal of drugs may have a positive impact. A synthesis of all relevant data moves us closer to adopting evidence-based interventions, or identifies the evidence gaps that require further original research. In general, studies that address the effect of withdrawal of drugs in adult populations are highly relevant to prevent unnecessary and potentially harmful treatments. It is recognised that the initiation and continuation of inappropriate medications is known to negatively impact on the safety of patients(35), thus medication withdrawal has the potential to improve safety, provided it does not come with additional greater risks. Finally, improved understanding of medication withdrawal is of particular interest to patients who should be active participants in any deprescribing process. Exploring and addressing their concerns and understanding is critical in successful withdrawal(36), and improving the evidence base behind recommendations is a key component of this.

**Objectives**

To assess the effects of complete withdrawal of at least one antihypertensive medication on incidence of dementia, cognitive function, blood pressure and other safety outcomes in cognitively intact and cognitive impaired adults.
METHODS

Criteria for considering studies for this review

Types of studies
We selected studies if they met the following criteria: RCTs comparing withdrawal of antihypertensive medications with continuation of the medications. We also included CCTs that meet other inclusion criteria. An outcome measure assessing cognitive function or dementia diagnosis had to be clearly defined.

Types of participants
Participants were aged 18 years and over. Participants must have been taking the antihypertensive medications for a minimum of one month irrespective of indication.

Participants could reside in any healthcare setting (including acute hospitals, nursing and residential homes, and the community). We included healthy participants and participants with all grades of severity of existing dementia or cognitive impairment.

Types of interventions
Withdrawal of any medication with blood pressure lowering effects (see list of relevant medications included in Supplement 1) with no restriction to duration of follow-up.

Types of outcome measures
Primary outcomes
• Cognitive impairment or rates of incident dementia in cognitively intact and cognitively impaired adults.
• Cognition in the short-term in adults with or without established cognitive impairment.

Cognitive function quantified with a recognised assessment instrument including multiple cognitive domains, for example (but not limited to) Folstein’s Mini Mental State Examination (MMSE)(1), Montreal Cognitive Assessment (MoCA)(2), more extensive neuropsychological testing, or formal clinical diagnosis of dementia according to current internationally accepted guidelines, for example (but not limited to) International Classification of Diseases and Related Health Problems (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).
Secondary outcomes

- Changes in systolic and diastolic blood pressure.
- Rates of (serious) adverse events across the included studies. These included mortality, cardiovascular events, early (within first eight weeks) and late (post-six months) adverse effects (e.g. falls and hospitalisation).
- Adherence to withdrawal of the antihypertensive medications. We defined adherence to withdrawal as participants remaining off medication for the duration of the study or at least six months, whichever was longer.

Search methods for identification of studies

We used the electronic databases listed below to search for relevant studies regardless of language, personnel, research setting or date of publication.

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group’s (CD-CIG) specialised register on 12 December 2015.

ALOIS is maintained by the Trials Search Coordinator for the CDCIG, and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy older adult populations. The studies are identified through:

- monthly searches of a number of major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO and LILACS;
- monthly searches of a number of trial registers: ISRCTN; UMIN (Japan’s Trial Register); the World Health Organization (WHO) portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others);
- quarterly search of the Cochrane Central Register of Controlled Trials (CENTRAL); and
- six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses and Australasian Digital Theses.

To view a list of all sources searched for ALOIS see AboutALOIS on the ALOIS website (www.medicine.ox.ac.uk/alois).
Details of the search strategies run in healthcare bibliographic databases, used for the retrieval of reports of dementia, cognitive improvement and cognitive enhancement trials, can be viewed in the ‘Methods used in reviews’ section within the editorial information about the Cochrane Dementia and Cognitive Improvement Group.

We ran additional searches in MEDLINE, Embase, PsycINFO, CINAHL, LILACS, Web of Science core collection, ClinicalTrials.gov and the WHO Portal/ICTRP to ensure that the search was as comprehensive and up-to-date as possible. See Supplement 2 for the search strategy that we used to retrieve reports of trials from MEDLINE (via the OvidSP platform).

Searching other resources
In case of incomplete reports or conference abstracts, we conducted further searches for connected papers and, if necessary, we contacted authors to obtain missing information.

We handsearched the reference lists of the relevant articles that we retrieved and searched for non-MEDLINE listed journals. We also searched the Science Citation Index for articles citing key references. We emailed two North American research groups with active deprescribing research programmes to check we had not missed any relevant studies.

Data collection and analysis

Selection of studies
Phase 1: two review authors (SJ and JH) independently performed searches and screening of identified studies. We independently examined titles and abstracts of citations obtained from the searches and discarded obviously irrelevant articles. At this stage, we were overly inclusive; we retrieved for further assessment any article that suggested a relevant study.

Phase 2: from the potentially relevant articles in Phase 1, two review authors (SJ and JH) independently selected studies (based on the full-text format) for inclusion. We resolved disagreement on study inclusion by consensus or third party adjudication (ER).

We detailed the study selection process in a PRISMA(3) flow diagram (Figure 1).
Figure 1. PRISMA Study flow diagram

Data extraction and management

Two review authors (SJ and JH) independently performed data extraction using a prespecified data extraction form and entered the data into Review Manager 5 software (40). In case of discrepancies, we involved a third review author (ER) until we reached consensus.

We created and used a specific data extraction form, including source, methods, participants, interventions, outcomes, results, funding source and declarations of interest according to the Cochrane Handbook for Systematic Reviews of Interventions guidance (41).

One review author (SJ) entered the data into Review Manager 5, which were checked for accuracy by a second review author (JH) (40).
Assessment of risk of bias in included studies

Two review authors (SJ and JH) independently assessed the internal validity of each included study. We described the risk of bias of all included studies in the Characteristics of included studies table and narrative. We used the Cochrane 'Risk of bias' tool for assessment and we used seven standard criteria: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting and other risk of bias (41). We assessed every study for each of the seven criteria and reported the information in a 'Risk of bias' table in Figure 2.

Figure 2. Cochrane 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

Measures of treatment effect

We used mean differences (MD) or standardised mean differences (SMD) with 95% confidence intervals (CI) for continuous outcomes, and risk ratios (RR) with 95% CIs for the analysis of dichotomous outcomes.
Scales that are commonly used in dementia trials are often coded ordinally. We treated the
data measured with scales comprising of more than 10 categories as continuous variables
assuming a normal distribution.

**Unit of analysis issues**
The unit of analysis was the person undergoing the withdrawal of an antihypertensive
treatment. As defined in our protocol, we considered for each study whether groups of
individuals were randomised together to the same intervention (i.e. cluster-randomised
trials), whether individuals underwent more than one intervention (e.g. in a cross-over
trial) or whether there were multiple observations for the same outcome (e.g. repeated
measurements, recurring events).

**Dealing with missing data**
For each outcome measure, we sought data on every participant assessed. To allow an
intention-to-treat analysis, we sought the data irrespective of compliance, whether the
participant was subsequently deemed ineligible, or otherwise excluded from treatment or
follow-up. We did not use data from titration phases prior to the randomised phase to assess
safety or efficacy. We made a qualitative judgement as to whether to exclude studies if the
impact of missing data was too large.

**Assessment of heterogeneity**
We considered clinical heterogeneity between trials (participants, interventions and
outcomes) when deciding whether to synthesise data. Statistical heterogeneity was considered
by using the I² test (41). We considered heterogeneity of 30% to 60% as moderate, 50% to 90%
as substantial and 75% to 100% as considerable. We made a decision on the appropriateness of
meta-analysis based on statistical and clinical heterogeneity.

**Assessment of reporting biases**
We searched for non-published as well as published studies in databases and trial registries,
to avoid publication bias. To avoid language bias, we did not employ language restrictions for
included studies. Where there are multiple publications from one study, we only included the
primary publication to address duplicate publication bias.

**Data synthesis**
We decided on suitability of meta-analysis for each outcome by a qualitative assessment
(including statistical and clinical heterogeneity) of the included studies.
We conducted data synthesis and analyses using Review Manager 5 software (40). We planned to use RRs and a random-effects model to combine outcomes across trials for a meta-analysis. The weighting factor for each study would be the inverse of the within-study variance plus a between-study variance component.

**Subgroup analysis and investigation of heterogeneity**

If we had identified 10 or more trials that contributed to the analyses of primary outcomes, we planned to perform stratified analyses of the primary effectiveness outcome according to the following trial characteristics: presence versus absence of dementia or cognitive impairment at baseline, age and type/class of antihypertensive treatment (thiazide diuretics, angiotensin converting enzyme inhibitors (ACE-I), etc.).

**Data presentation - ‘Summary of findings’ tables**

We used the GRADE approach to assess the quality of the supporting evidence behind each estimate of treatment effect (42, 43). We presented key findings of the review including a summary of the amount of data, the magnitude of the effect size and the overall quality of the evidence, in a ‘Summary of findings’ table, created using GRADEproGDT software (44). We preselected the following outcomes: cognitive impairment (incident dementia (clinical diagnosis) and change in a validated cognitive test score); change in systolic and diastolic blood pressure; mortality; cardiovascular events; falls; hospitalisation and adherence to withdrawal. Following guidance from the CDCIG editorial team, we decided to exclude change in systolic and diastolic blood pressure and adherence to withdrawal outcomes from presentation in the table.

**Sensitivity analysis**

We planned to perform a sensitivity analysis for pooled results based on methodological quality. We also planned to perform sensitivity analyses without CCTs (if identified) to look at the effect of these studies and to avoid risk of bias from the non-randomised design. These sensitivity analyses could not be performed due to the inclusion of only two studies, so there was not enough data to pool.
## Summary of findings for the main comparison

**Patient or population:** adults with cognitive impairment/dementia and cognitively intact populations  
**Setting:** any setting  
**Intervention:** antihypertensive withdrawal for the prevention of cognitive decline  
**Comparison:** antihypertensive continuation  

<table>
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<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
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<td><strong>Incident dementia – not measured</strong></td>
<td>n/a</td>
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<td>-</td>
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</tr>
<tr>
<td><strong>Cognition (at 90 days): t-MMSE score</strong></td>
<td>The mean t-MMSE score was 9</td>
<td>The mean t-MMSE score in the intervention group was 1 point higher (0.35 to 1.65)</td>
<td>1784² (1 RCT) Bath 2015</td>
<td>⊠ΟΟΟ very low³,4,5</td>
<td>Lower scores indicate worse cognitive function. Participants with acute stroke after 7 days of antihypertensive withdrawal</td>
</tr>
<tr>
<td><strong>Composite cognitive function</strong> (change over 16 weeks)</td>
<td>The mean change in cognitive function was 0.01 points lower</td>
<td>The mean change in cognitive function in the intervention group was 0.02 points higher (0.19 lower to 0.23 points higher)</td>
<td>351² (1 RCT) Moonen 2015</td>
<td>⊠ΟΟΟ low³,5</td>
<td>Lower total scores indicate worse cognitive functioning. Participants with MCI</td>
</tr>
<tr>
<td><strong>Mortality (at 3 to 4 months’ follow-up)</strong></td>
<td>Study population RR 0.88 (0.72 to 1.08)</td>
<td>RR 0.88 (0.72 to 1.08)</td>
<td>2485 (2 RCTs)</td>
<td>⊠ΟΟΟ moderate⁴</td>
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*Absolute effects are expressed as numbers needed to treat (NNT) where appropriate.
### Cardiovascular events (at 3 to 4 months' follow-up)

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<tr>
<th>Study population</th>
<th>RR 1.29 (0.96 to 1.72)</th>
<th>2485 (2 RCTs)</th>
<th>low*&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td>61 per 1000</td>
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<td>(59 to 105)</td>
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### Falls – not measured

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<td>-</td>
</tr>
</tbody>
</table>

### Hospitalisations (at 4 months' follow-up)

<table>
<thead>
<tr>
<th>Study population</th>
<th>RR 0.85 (0.36 to 2.06)</th>
<th>388 (1 RCT)</th>
<th>low&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>53 per 1000</td>
<td>45 per 1000</td>
<td>Moonen 2015</td>
<td></td>
</tr>
<tr>
<td>(19 to 109)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; MCI: mild cognitive impairment; n/a: not available; RR: risk ratio; t-MMSE: telephone Mini-Mental State Examination.

**GRADE Working Group grades of evidence**

- **High quality**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate quality**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low quality**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low quality**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1. Telephone Mini-Mental State Examination Score range 0 to 22 points.
2. Based on number alive at 90 days; data not available by group on number assessed.
3. Downgraded due to risk of performance bias arising from participants and personnel not being blinded.
4. Downgraded due to indirectness as majority of study participants were people with acute stroke.
5. Downgraded as evidence from single study.
6. Compound overall cognitive score presented. Included components were: time to complete Trail Making Test parts A and B; Interference score of the abbreviated Stroop Color-Word Test; Immediate and Delayed Recall on the 15-word verbal learning test; Visual Association Test and Letter Digit Substitution Test. Compound scores were computed by converting the raw scores of each test to standardized z scores ((test score - mean)/ standard deviation) and calculating the mean z scores across the tests in each compound.
7. Data missing for three in the intervention and two in the control group.
8. Downgraded due to imprecision.

---

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; MCI: mild cognitive impairment; n/a: not available; RR: risk ratio; t-MMSE: telephone Mini-Mental State Examination.
RESULTS

Description of studies

Results of the search
The electronic searches performed on 12 December 2015 retrieved 10,989 results. After initial de-duplication two review authors (SJ and JH) independently assessed the remaining 10,970 references for relevance. We received no information for further published or unpublished studies from experts or manufacturers. We excluded 10,894 references that were not relevant on title and abstract screening. Two review authors (SJ and JH) independently assessed 76 full-text articles and conference abstracts for eligibility. Seventy-three articles did not meet our inclusion criteria and were excluded. We included three articles referring to two trials (Bath 2015 (45); Moonen 2015(46)). The selection process is summarised in the PRISMA diagram (Figure 1).

Included studies
We identified two trials for inclusion with 2490 randomised participants (45, 46). Bath 2015 is known as the ‘Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for the management of high blood pressure in stroke (ENOS) study’. Moonen 2015 is known as the ‘Discontinuation of antihypertensive treatment in elderly people on cognitive functioning (DANTE) study’. We did not contact the authors of either of the included studies since this was not deemed necessary.

Participants
The ENOS study randomised 4011 participants, although only 2097 participants were included in the antihypertensive withdrawal substudy, as the remainder were not taking antihypertensive medication before admission (45). Participants who were included in the antihypertensive withdrawal substudy had a more severe phenotype than those who were not taking antihypertensive drugs before randomisation; they were older, more likely to be women, had higher rates of vascular risk factors and were less likely to have a normal premorbid Rankin Scale score. The DANTE study randomised 393 participants (46). The populations recruited into the two studies were clinically distinct. In Bath 2015, all participants had to have experienced an acute stroke, while in Moonen 2015, all participants had MCI (defined as an MMSE score between 21 and 27) and taking antihypertensive medications. The mean age of participants in the DANTE study was 81 years (46), in comparison with 73 years in the ENOS study (45). Moonen 2015 only included people aged 75 years and older. Men
were 39% to 42% of the study population in DANTE in comparison with 50% to 52% of the study population in ENOS. Both studies reported comorbidities at baseline and these seemed comparable between intervention and control groups (45, 46).

Systolic blood pressure was higher at baseline in the ENOS study at 166 mmHg to 168 mmHg (45) in comparison to 147 mmHg to 148 mmHg in the DANTE study, whose eligibility criteria limited systolic blood pressure to 160 mmHg (46).

Moonen 2015 assessed cognitive status at baseline and follow-up, while in Bath 2015, cognitive status was unknown at baseline and only evaluated at follow-up. One study excluded people with dementia (46). Only one study reported level of education at baseline, which was comparable between groups (46). Both studies included participants taking any classes of antihypertensive treatment. Most participants in both studies were taking more than two antihypertensive medications, more than 60% of participants in DANTE (46) and more than 50% of participants in ENOS (45). Diuretic use was higher in DANTE (54%) than ENOS (16%) and ACE-I use was lower in DANTE (35%) than ENOS (48%).

**Setting**

The two clinical settings also varied. Bath 2015 was a large international multicentre study conducted in acute hospital settings, recruiting participants at hospital admission. More than 60% were recruited in the UK, with the remainder worldwide (45). Moonen 2015 was conducted in primary care in the Leiden region of the Netherlands, with participants recruited by general practitioners (GPs).

**Interventions and comparators**

The interventions reported in each of the studies vary in duration of antihypertensive withdrawal from seven days (45) to three months (46).

Bath 2015 was a parallel-group design RCT with four groups. The entire sample was randomised to receive a glyceryl trinitrate (GTN) patch (intervention) or no patch (control). All participants who were taking antihypertensive medications prior to admission (2097/4011 participants) were then additionally randomised to stop their antihypertensive medications (intervention) or to continue pre-existing antihypertensive medications (control). Both the GTN intervention and antihypertensive withdrawal were for the first seven days following an acute stroke admission. Thereafter medications could be prescribed or reintroduced as clinically indicated.
Moonen 2015 was a parallel-group design RCT with two groups. Over an initial six-week period, antihypertensive medications were withdrawn by the participant's GP using a withdrawal algorithm designed by the study authors. This was done provided systolic blood pressure did not exceed 180 mmHg. Medication withdrawal was completed within four weeks from randomisation and continued for a period of three months thereafter.

**Funding sources**
The UK Medical Research Council funded Bath 2015 and a grant from the Program Priority Medicines for the Elderly, the Netherlands Organization for Health Research and Development, funded Moonen 2015.

**Excluded studies**
We excluded 77 publications, conference abstracts and registered trials and presented the reasons for exclusion in the Characteristics of excluded studies table. Reasons for study exclusion were: wrong study design (not an RCT or CCT); wrong outcome measure (lack of cognitive outcome measure used); wrong comparator (the study did not compare participants withdrawing antihypertensive medications with participants continuing them); wrong intervention (participants were not randomised to withdraw or continue antihypertensive medications) and study protocol (planned work without results reported; none met our eligibility criteria for inclusion as ongoing studies).

**Risk of bias in included studies**
Overall, the quality of included studies was high (see Characteristics of included studies table, Figure 2), with the exception of high risk for performance and attrition bias in both studies.

**Allocation**
Both studies were at low risk of selection bias as they used a central computerised randomisation procedure for allocation of participants. Stratification was used to ensure that the groups were balanced and key parameters appeared adequately divided between intervention and control groups in each study.
Antihypertensive withdrawal for the prevention of cognitive decline

Blinding
Both studies were at high risk of performance bias as neither masked the participants or medical personnel associated with the study to the treatment allocation. No placebo medications were administered to participants who had usual antihypertensive therapy withdrawn. Since the outcome measurement in each of the two studies was blinded, this minimised the effect of bias on the different outcome measures.

Both studies were at low risk of detection bias as outcome assessment was conducted independently of the study team and assessors were masked to the treatment allocation of the participants.

Incomplete outcome data
Overall, the risk of attrition bias was low for both studies because they applied an intention-to-treat analysis. With respect to the primary outcome of this review, cognitive performance, both studies were at high risk for attrition bias. We graded this as high risk for attrition bias according to the GRADEproGDT 2015 guidelines and reported this in Summary of findings for the main comparison. Although both studies presented an intention-to-treat analysis for their results, not all surviving participants received cognitive testing at follow-up and the studies did not report the reasons to account for missing data. Bath 2015 reported cognitive assessment on 1272 (telephone Mini-Mental State Examination (t-MMSE) score) and 1179 (Telephone Interview for Cognitive Status (TICS-M) score), although 1784 survived at 90 days. Moonen 2015 reported the intention-to-treat analysis for 356 participants, while they randomised 388 participants. From those 356 participants, data were missing for three in the intervention group and two in the control group for their primary outcome (overall cognitive function).

Selective reporting
Both studies were at low risk of reporting bias as outcomes were reported as described in the published protocols. The protocol for Moonen 2015 was included in the published paper as a supplemental appendix and the analysis plan for Bath 2015 was published separately.

Other potential sources of bias
Both studies were at low risk for other potential sources of bias as none were identified.

Effects of interventions
See: Table summary of findings for the main comparison for an overview of the results.
Primary outcomes

Incident dementia

Neither study evaluated the presence of incident dementia at follow-up.

Change in cognitive test scores

Cognitive function (at 90 days)

Bath 2015 report data at 90 days for cognitive assessment conducted via the telephone. The numbers assessed in each group were not reported and so the denominator used was the number alive at 90 days. It is recognised this is an overestimate as the number alive at 90 days was 1784, whereas the number who received a t-MMSE was 1272 and the TICS-M was 1179.

The t-MMSE score was a mean of 1.0 point higher in participants who withdrew antihypertensive medications compared to participants who continued them (95% CI 0.35 to 1.65; 1784 participants). The TICS-M was a mean of 2.10 points higher (95% CI 0.69 to 3.51; 1784 participants) (Figure 3; Figure 4). However, in both cases, the evidence was of very low quality (downgraded due to risk of bias from missing cognitive outcome data, evidence from a single study and indirectness).

Figure 3. Forest plot of comparison: 1 Cognitive function (at 90 days)
1.1 Telephone Mini-Mental State Examination score

Figure 4. Forest plot of comparison: 1 Cognitive function (at 90 days)
1.2 Modified Telephone Interview for Cognitive Status score
Change in cognitive performance (over 16 weeks)

Moonen 2015 report data for 351/388 participants on their primary outcome of cognitive performance using a composite of at least five out of six cognitive tests. A higher score represented a better cognitive performance. There was no evidence of a mean difference in cognitive performance between participants who withdrew antihypertensive medications than participants who continued (MD 0.02 points, 95% CI -0.19 to 0.23; 351 participants) (Figure 5). This evidence was of low quality (downgraded due to risk of bias from missing cognitive outcome data and evidence from a single study).

Figure 5. Forest plot of comparison: 2 Change in cognitive function (over 16 weeks)

2.1 Composite score

Each of the six cognitive tests were reported independently for 356/388 randomised participants. There was no evidence of change in cognitive performance in participants who withdrew medications using the MMSE score (MD 0.34 points, 95% CI -0.08 to 0.76; 356 participants); the 15-Word Verbal Learning Immediate Recall score (MD 0.24 points, 95% CI -0.66 to 1.14; 356 participants); the Delayed Recall score (MD 0.16 points, 95% CI -0.29 to 0.61; 356 participants); or the Visual Association Test score (MD 0.14 points, 95% CI -0.17 to 0.45; 356 participants). This evidence was low quality (downgraded due to risk of bias from missing cognitive outcome data and evidence from a single study).

There was no evidence of change in cognitive performance in participants who withdrew medications using the Stroop Interference score (MD -2.22 points, 95% CI -9.62 to 5.18; 356 participants) or the Trail Making Tests score (MD 10.06 points, 95% CI -2.20 to 22.32; 356 participants). In both cases, evidence was very low quality (downgraded due to risk of bias from missing cognitive outcome data, imprecision and evidence from a single study).
Secondary outcomes

Blood pressure at seven days
Systolic and diastolic blood pressure was assessed in 2095/2097 participants in Bath 2015, with missing data for the other two participants. After seven days, systolic blood pressure was 9.5 mmHg higher in the intervention compared to the control group (95% CI 7.43 to 11.57; 2095 participants) and diastolic blood pressure was 5.1 mmHg higher (95% CI 3.86 to 6.34; 2095 participants). This evidence was low quality (downgraded due to indirectness from the ability to interpret these data within the wider study looking at GTN administration or not and evidence from a single study).

Change in systolic blood pressure (over 16 weeks)
Mean change in systolic and diastolic blood pressure was evaluated for the 356 participants in Moonen 2015. Systolic blood pressure increased by 7.4 mmHg in the withdrawal group compared to the control group (95% CI 7.08 to 7.72; 356 participants) and diastolic blood pressure increased by 2.6 mmHg (95% CI 2.42 to 2.78; 356 participants). This was moderate quality evidence (downgraded due to evidence from a single study).

Adverse events

Mortality
Both studies reported data on mortality at follow-up (16 weeks and 90 days) including all randomised participants for one study (45), and missing data on five randomised participants in the other (46). There was no evidence that antihypertensive medication withdrawal affected mortality at follow-up (RR 0.88, 95% CI 0.72 to 1.08, I² = 0%; 2485 participants; 2 studies; moderate quality evidence (downgraded due to indirectness)) (Figure 6).

Cardiovascular events
Both studies reported on cardiovascular events during follow-up. Moonen 2015 reported only myocardial infarction, while Bath 2015 reported myocardial infarction, sudden cardiac death and other cardiovascular events. We pooled the results and there was no evidence of effect of antihypertensive medication withdrawal on the incidence of cardiovascular events (RR 1.29, 95% CI 0.96 to 1.72; I² = 0%; 2485 participants; 2 studies; low quality evidence (downgraded due to imprecision and indirectness)) (Figure 7).
Antihypertensive withdrawal for the prevention of cognitive decline

### Figure 6. Forest plot of comparison: Adverse events

#### Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>All withdrawal</th>
<th>All continuation</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td></td>
</tr>
<tr>
<td>5.1.1 Mortality within 90 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bahn 2015</td>
<td>148 167</td>
<td>1044 1653</td>
<td>0.88 (0.72, 1.08)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1044 1653</td>
<td></td>
<td>0.88 (0.72, 1.08)</td>
</tr>
<tr>
<td>Total events</td>
<td>146</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 1.29 (P = 0.23)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Cardiac events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>All withdrawal</th>
<th>All continuation</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td></td>
</tr>
<tr>
<td>5.2.1 Any cardiovascular events within 90 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bahn 2015</td>
<td>96 1044</td>
<td>1044 1653</td>
<td>1.29 (0.97, 1.72)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1044 1653</td>
<td></td>
<td>1.29 (0.97, 1.72)</td>
</tr>
<tr>
<td>Total events</td>
<td>96</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 1.73 (P = 0.08)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Myocardial infarction within 16 weeks

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>All withdrawal</th>
<th>All continuation</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td></td>
</tr>
<tr>
<td>Moonen 2015</td>
<td>1 1</td>
<td>186 189</td>
<td>0.65 (0.06, 15.05)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>189 189</td>
<td></td>
<td>0.65 (0.06, 15.05)</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 0.04 (P = 0.97)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Total (95% CI)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>All withdrawal</th>
<th>All continuation</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td></td>
</tr>
<tr>
<td>5.2.2 Myocardial infarction within 16 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moonen 2015</td>
<td>96 1044</td>
<td>1044 1653</td>
<td>1.29 (0.96, 1.72)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1044 1653</td>
<td></td>
<td>1.29 (0.96, 1.72)</td>
</tr>
<tr>
<td>Total events</td>
<td>96</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 0.09 (P = 0.99)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Falls

Neither study report data on incidence of falls.

### Hospitalisations

Moonen 2015 reported incident hospitalisations. There was no evidence that antihypertensive withdrawal reduced the risk of incident hospitalisations (RR 0.85, 95% CI 0.36 to 2.06; 388 participants; low quality evidence (downgraded due to imprecision and evidence from a single study)).
Adherence to withdrawal

Bath 2015 reported adherence to allocated withdrawal or continuation for the entire seven-day period of study. Data were available for 2095/2097 included participants in the continue versus stop arm. A total of 810/1044 participants in the intervention group adhered to stopping antihypertensive therapy compare to 610/1051 participants in the control group adhered to continuation of antihypertensive therapy. Adherence to allocated treatment was higher in participants withdrawing from antihypertensive medication than participants stopping (RR 1.34, 95% CI 1.26 to 1.42; 2095 participants; low quality evidence (downgraded due to indirectness and as results from a single study)).

Moonen 2015 reported no data on adherence to withdrawal of antihypertensive medications.

DISCUSSION

Summary of main results

Despite a clear increase in blood pressure in the withdrawal groups of both studies, there was no effect on cognition after seven days or 16 weeks. There was also no effect on cardiovascular events or mortality during the relatively short follow-up in the two studies. The overall quality of the data from the two included studies was high(45, 46). However, with respect to our primary outcome measure, cognitive function, we downgraded evidence when applying GRADE methodology(44). For both studies, there was a risk of bias introduced from missing cognitive outcomes data and analyses of cognition could not be pooled, meaning data in each case were from a single study. Therefore, we considered the evidence to be low quality for Moonen 2015 and very low quality for Bath 2015 as this was also considered indirect. To put these results in context, it is important to state that our assessment of quality was in relation to our specific study question and is not a statement on the quality of the included trials themselves.

Dementia and cognitive performance

Neither study evaluated development of incident dementia following medication withdrawal. This lack of evidence for a key question of interest to this review may reflect the short follow-up periods used in both studies (90 days and 16 weeks). This outcome measure is likely to require longer-term surveillance of recruited participants, but would be of particular interest for the DANTE study that included a population considered to have MCI(46).
The data on cognitive performance is difficult to interpret with different results depending on the cognitive measure used. Furthermore, determining the clinical significance of the changes observed is key. Bath 2015 contains very low quality evidence of improvement in cognitive performance at 90 days of follow-up; however, we do not know the baseline cognitive function of the included participants and cannot ascertain the effect of the acute event (stroke) and the other intervention studied (nitric oxide) from the effect of antihypertensive withdrawal for a seven-day period. There is also a risk of a survival bias being introduced through the study design, as only participants alive and able to complete cognitive assessment at 90 days were included. Participants who had died or could not be assessed in the telephone assessment were excluded and this reflects the lower numbers in the cognitive analyses. We had to use a proxy denominator in the form of ‘alive at 90 days’ to incorporate the cognitive data. This overestimates the numbers assessed and reduces confidence in the result presented. Moonen 2015 used a composite cognitive score as their primary outcome and we found low quality evidence that there was no evidence of effect on cognitive performance in participants who withdrew medications over the 16-week study period, compared to participants who continued.

**Blood pressure**

We found low quality evidence from one study and moderate quality evidence from the other study that systolic and diastolic blood pressure rise following cessation of antihypertensive medications when compared to participants who continue therapy. This clinically plausible result is consistent; however, it does not appear to be matched with any evidence of increased mortality (moderate quality evidence) or cardiovascular events (low quality evidence). The evidence for treating hypertension in older adults has been established in randomised trials and is known to reduce cardiovascular morbidity and mortality(5).

**Adverse events and safety**

A rise in blood pressure may have been anticipated to lead to a rise in adverse events. We found no evidence of a significant increase in cardiovascular events (low quality evidence) or mortality (moderate quality evidence) in either study. We recognise that the studies had a relatively short period of follow-up (months) and that it would take years of follow-up to be certain that the drug withdrawal interventions had no effect on cardiovascular events. Accepting this major caveat, as detailed in our protocol, we pooled data from the available studies for common endpoints of mortality and cardiovascular events. These pooled data...
suggested no evidence of effect of antihypertensive medication withdrawal on the incidence of cardiovascular events or mortality across the studies, albeit the ENOS study (45) contributes almost all the data.

Adherence to withdrawal

The results on adherence to withdrawal are difficult to interpret as they could only be extracted from one study (45), and this also evaluated the effects of another medication (GTN) which may lower blood pressure. It is difficult to conclude what effect this had on the adherence of participants allocated to either arm of the study. Data were not reported for participants who recommenced medications in Moonen 2015 despite the inclusion of criteria for re-introduction of medications.

Overall completeness and applicability of evidence

Only one of the studies identified for inclusion in the review aligned with our study question of interest, namely to examine the cognitive effects of antihypertensive medication withdrawal (46). Cognition was a secondary outcome measure used by Bath 2015, whose primary question of interest was the safety and efficacy of nitric oxide in the context of acute stroke, with or without continuing existing antihypertensive therapy. This affects the extractable data available and limits the ability to compare the two interventions.

Furthermore, although both populations were at high risk of cognitive decline, the mechanism for these was clinically distinct. Bath 2015 recruited people hospitalised for acute stroke who were recruited into an intervention study of nitric oxide. Here the expected rationale for withdrawing antihypertensive medication would be to maintain or augment blood pressure during an acute (seven-day) period following stroke where it may be plausible to anticipate cerebral perfusion is acutely compromised (48). Moonen 2015 recruited community-dwelling older adults with evidence of reduced cognitive performance where withdrawing medication could be considered to improve cerebral blood flow where brain perfusion may be chronically impaired (49). Both represent questions of clinical uncertainty and areas of variation in practice.

The procedure for medication withdrawal in Moonen 2015 was described in full in the supplementary material, overseen by the participants’ GPs. The procedure used by Bath 2015 was not clearly described. Many participants in the control group also experienced withdrawal of their medication as a consequence of impaired swallow following acute stroke, for part or all of the seven-day period and only 67.8% of participants were adherent for all seven days.
A particular limitation of the data presented is the inability to combine cognitive scores and blood pressure data due to the variations in reporting between the papers. One argument is that the populations were too distinct to pool data. However, if we are to make best use of all available clinical trial data, greater effort must be made in the reporting of outcomes using a more standardised approach. Even if the data had been presented in the same format, we could not have pooled scores as the measures used and the interventions itself were heterogeneous. This is an area of interest beyond the scope of this review, reflected in international efforts to standardise outcome measure reporting (50). Additionally, for some of the cognitive outcome measures used in the included studies (t-MMSE in Bath 2015 and cognitive composite score in Moonen 2015), the clinical significance of change in the cognitive test scores is uncertain and this makes a result difficult to interpret on a population level.

Also, neither study focused on the withdrawal of one particular antihypertensive drug (class). Participants were allowed to stop their previously described antihypertensive medications irrespective of the class. We planned to do a subgroup analysis for the different classes of antihypertensives, but due to a lack of data, this could not be done.

Finally, the extent of excluded studies in relation to those eligible for inclusion is important to explore. Two common reasons included the design of the study, principally those identified were observational in design and the lack of use of any cognitive outcome measure at follow-up. The search strategy for this review was comprehensive and designed to incorporate all studies looking at the withdrawal of antihypertensive medications. However, current indexing does not readily identify medication withdrawal studies and this is an additional issue which would benefit from further collaborative work to more easily identify deprescribing studies.

**Quality of the evidence**

Data from the two RCTs (2135 participants) could not be pooled for analysis of change in cognitive test score. Evidence was of low quality in relation to cognitive performance. Evidence was downgraded in Moonen 2015 due to risk of bias from incomplete outcome data and assessment of cognitive outcomes and evidence being from a single study. Evidence from Bath 2015 was downgraded to very low quality for the same risk of bias and evidence from a single study plus the indirectness associated with the comparison between blood pressure lowering with GTN and potential interaction with the intervention studied (namely antihypertensive medication withdrawal) as we could not establish who was in the GTN and placebo study arms.
Chapter 6

Data from the two RCTs (2135 participants) could not be pooled for analysis of change in blood pressure due to the different reported measures included and clinically distinct periods evaluated. There was low quality evidence of mean systolic and diastolic blood pressure being higher after seven days in participants who stopped antihypertensive medications compared to participants who continued them in Bath 2015, downgraded due to risk of indirectness from the other intervention under study (GTN administration) and evidence from a single study. There was moderate quality evidence of mean rise in both systolic and diastolic blood pressure after 10 weeks of follow-up after antihypertensive medication withdrawal (total study period 16 weeks) in Moonen 2015, downgraded as evidence was from a single study. On the basis of two RCTs (2485 participants) there was no evidence of effect on mortality or cardiovascular events. However, evidence for mortality was downgraded to moderate quality due to the risk of indirectness associated with the majority of the participants being people with acute stroke compared to community dwellers with MCI. The evidence for cardiovascular events was low quality in view of the same indirectness plus imprecision in the result.

Adherence to withdrawal could only be assessed in one study (2095 participants) and the evidence here was considered low quality, downgraded due to indirectness from the potential use of GTN and the evidence being from a single small study.

No data were available on incidence of dementia or falls.

**Potential biases in the review process**

This review has followed Cochrane procedures and there were only minor amendments to the review process from those stated in the protocol, outlined in Differences between protocol and review.

**Agreements and disagreements with other studies or reviews**

Cognitive impairment is considered as a significant factor in deprescribing decision-making by geriatricians(51) and the lack of evidence for people with established dementia needs to be addressed. Much of the developing evidence in this area is not class-specific and is targeted at reducing the overall burden of unnecessary medication use, particularly in the frail older-adult population(52). One limitation of our approach may be the focus on a single drug class, although this benefits from clarity in observing the effect of withdrawal on drug-specific outcome measures.
Antihypertensive medication withdrawal is a topic of interest not only limited to cognitive effects. We await the results of a UK feasibility study of antihypertensive medication withdrawal for people with dementia(53).

There are other systematic reviews that have been looking to the protecting effects of antihypertensive medications on cognition(54-56), most of them showing a protective effect of one or more drug classes. Despite these results, it is also important to look at the effect on cognition with drug withdrawal, since this reduces the polypharmacy and is more cost-effective than continuing or introducing drugs.

This review is one of a suite of Cochrane Reviews, looking at withdrawal of specific drug(s) or drug classes in the context of cognition. An additional Cochrane Review, describing antihypertensive withdrawal with a non-cognitive focus is underway and will provide complementary data.

**Authors’ conclusions**

*Implications for practice*

It is uncertain whether withdrawal of antihypertensive medications has an influence on cognition or can prevent dementia or cognitive impairment in healthy adults or adults with impaired cognition. Withdrawing antihypertensive drugs was associated with increased blood pressure levels. It is unlikely to increase mortality at three to four months’ follow-up, although there was a signal from one large study looking at withdrawal after stroke that withdrawal was associated an increase in cardiovascular events.

*Implications for research*

Review of the included and excluded studies suggests possible avenues for future drug withdrawal study design and conduct. For our primary focus of antihypertensives and cognition, further research should include older people and have suitably long follow-up to capture changes in rates of cognitive decline or incident dementia. A classical randomised controlled trial (RCT) design can be used for deprescribing, just as it can for studies of new drugs, although the need for a placebo or an alternative treatment in the withdrawal group is debatable. For studies of withdrawal of a drug class, such as antihypertensives, matched placebos would be almost impossible to achieve for all different kinds of antihypertensive treatment. Ideally, new RCTs looking at withdrawal of antihypertensives (or other drugs) should standardise their cognitive and other outcome measures. There are many ways to
measure cognitive function, but these are not always comparable since they may measure different cognitive domains. This heterogeneity precludes comparisons between studies and complicates meta-analysis.

Deprescribing medications in general is becoming a major subject for new research projects (deprescribing.org)(57). Optimising medication through deprescribing can be a vital part of managing chronic conditions, reducing adverse effects and improving outcomes, including cognitive outcomes. The deprescribing rubric includes many approaches, withdrawal of all but essential drugs; withdrawal of drugs considered to have increased risk in older adults; withdrawal of drug classes and withdrawal of single agents. Each approach is suited to a particular research question. For future studies looking at antihypertensive withdrawal, a focus on one type (class) of drug may be preferable, as cognitive effects may vary with drug class and withdrawal studies which are too broad may miss important class-specific effects. The heterogeneity in approach to drug withdrawal that is included in the umbrella term ‘deprescribing’ complicates systematic review. To progress the de-prescribing agenda, we need agreed descriptive terms for the various approaches. As the literature on deprescribing research increases, it may help future reviews if search filters for this study methodology are developed.
Acknowledgements
We would like to acknowledge the valuable input of Sue Marcus (Managing Editor, Cochrane Dementia and Cognitive Improvement Group (CDCIG)) and Anna Noel-Storr (Information Specialist, CDGIG) who designed the search strategy and conducted the search.

Declaration of interest
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External sources
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References to studies included in this review


REFERENCES


44. GRADEproGDT. Hamilton (ON): GRADE Working Group, McMaster University; 2015.


Antihypertensive withdrawal for the prevention of cognitive decline


107. ISRCTN31208535. A clinical trial to test amlodipine as a new treatment for vascular dementia. 2014.


SUPPLEMENT 1

All medications with antihypertensive function (irrespective of indication)

- Loop diuretics: bumetanide, ethacrynic acid, furosemide, torsemide
- Thiazide diuretics: epitizide, hydrochlorothiazide and chlorothiazide, bendroflumethiazide, xipamide
- Thiazide-like diuretics: indapamide, chlorthalidone, metolazone
- Potassium-sparing diuretics: amiloride, triamterene
- Dihydropyridines: amlodipine, cilnidipine, felodipine, isradipine, lercanidipine, levamlodipine, nicardipine, nifedipine, nimodipine, nitrendipine, barnidipine, lacidipine, arandipine, azelnidipine, benidipine, clevidipine, darodipine, efonidipine, manidipine, nifuglipine, nilvadipine, nisoldipine, nitrendipine, oxodipine, prandipine
- Non-dihydropyridines: diltiazem, verapamil
- ACE-inhibitors: captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril, benazepril, zofenopril, imidapril, cilazapril
- Angiotensin II receptor antagonists: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, azilsartan, fimasartan
- Beta blockers: atenolol, metoprolol, nedolol, nebivolol, oxprenolol, pindolol, propranolol, timolol, bisoprolol, acebutolol, celiprolol, esmolol, sotalol
- Alpha blockers: doxazosin, phentolamine, indoramin, phenoxybenzamine, prazosin, terazosin, tolazolin, ketanserin, urapidil, fentolamin
- Mixed Alpha + Beta blockers: carvedilol, labetalol
- Vasodilators: hydralazine, minoxidil
- Renin Inhibitors: aliskiren
- Aldosterone receptor antagonists: eplerenone, spironolactone
- Alpha-2 adrenergic receptor agonists: clonidine, guanabenz, guanfacine, methyldopa, moxonidine, guanethidine, megamylamine
- Other: magnesium sulfate
## SUPPLEMENT 2

### Search strategies

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### Antihypertensive withdrawal for the prevention of cognitive decline

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Antihypertensive withdrawal for the prevention of cognitive decline

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5. CINAHL (EBSCOhost) [searched 12 December 2015]

S1 TX antihypertensive* OR "antihypertensive*" OR "angiotensin converting enzyme inhibitor*"
S2 TX "AT 2 receptor block*" OR "AT 2 receptor antagonist*" OR ARB OR ARBs OR acei OR ace-i
S3 TX "adrenergic beta antagonist*" OR "adrenergic alpha antagonist*" OR "beta block*" OR "alpha block*" OR diuretic* OR "calcium channel blocker*" OR CCB OR CCBs
S4 TX chlorothiazide OR chlorothalidone OR hydralazine OR hydrochlorothiazide OR minoxidil OR captopril OR enalapril OR fosinopril OR lisinopril OR ramipril
S5 TX losartan OR irbesartan OR candesartan OR eprosartan OR valsartan OR olmesartan OR telmisartan OR amlodipine OR diltiazem OR felodipine OR nicardipine OR nifedipine OR nisoldipine OR verapamil OR alpenrolol OR atenolol OR metoprolol OR nadolol OR oxprenolol
S6 TX pindolol OR propranolol OR labetalol OR prazosin OR spironolactone OR triamterene OR bumetanide OR furosemide OR indapamide OR frusemide OR di- azoxide OR eplerenone OR amiloride OR clonidine OR methyldopa OR isradipine OR xipamide OR barnidipine OR lacidipine OR aranidipine OR azelniidine
S7 TX benidipine OR clevidipine OR darodipine OR efondipine OR manidipine OR nifudipine OR nilvadipine OR nisoldipine OR nifedipine OR oxodipine OR pranidipine OR zofenopril OR imidapril OR cilazapril OR azilsartan OR fimasartan OR bisoprolol OR acebutolol OR celiprolol OR esmolol OR solotol OR ketanserin OR urapidil OR lentiolamin OR minoxidil OR "magnesium sulphate"
S8 (MH "Hypertension")
S9 (MH "Diuretics")
S10 (MH "Angiotensin II Type I Receptor Blockers") OR (MH "Sodium Channel Blockers") OR (MH "Calcium Channel Blockers")
S11 (MH "Hydralazine")
S12 (MH "Captopril")
S13 TX withdraw*
S14 TX cessat*
S15 TX reduce* OR reducing* OR reduct*
S16 TX taper*
S17 TX stop*
S18 TX "carr* on" OR continuation
S19 TX "come off " OR "taken off"
S20 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S21 S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19
S22 S20 AND S21
S23 (MH "Randomized Controlled Trials")
S24 TX placebo
### Chapter 6

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<td>[searched 12 December 2015] <strong>TOPIC:</strong> (antihypertensive* or &quot;antihypertensive*&quot; or &quot;angiotensin converting enzyme inhibitor&quot;* or &quot;AT 2 receptor block&quot;* or &quot;AT 2 receptor antagon&quot;* or ARB or ARBs or acei or ace-I or &quot;adrenergic beta antagonist&quot;* or &quot;adrenergic alpha antagonist&quot;* or &quot;beta block&quot;* or &quot;alpha block&quot;* or diuretic* or &quot;calcium channel blocker&quot;* or CCB or CCBs or chlorothiazide or chlorthalidone or hydralazine or hydrochlorothiazide or minoxidil or captopril or enalapril or fosinopril or lisinopril or ramipril or losartan or irbesartan or candesartan or eprosartan or valsartan or olmesartan or telmisartan or amlodipine or dihydralazine or nicardipine or nifedipine or nimodipine or verapamil or alprenolol or atenolol or metoprolol or nadolol or exprenolol or pindolol or propranolol or labetalol or prazosin or spironolactone or triamterene or bumetanide or furosemide or indapamide or frusemide or diazoxide or eprenolone or amiloride or clonidine or methylpenta or isradipine or zipamidine or ranipidine or aranipidine or azelnipidine or benidipine or clevidipine or darodipine or efondipine or manidipine or niguilidine or nifidipine or nifedipine or nitrendipine or oxodipine or prandipine or zofenopril or imidapril or cilazapril or azilsartan or finasartan or bisoprolol or amlodipine or siroliprol or esmolol or sotalol or ketanserin or urapidil or fentolamin or minoxidil or &quot;magnesium sulphate&quot;) AND <strong>TOPIC:</strong> (withdraw* or reduce or stop* or taper* or cessat* or reduction) AND <strong>TOPIC:</strong> (cognition or cognitive or &quot;executive function&quot;* or memory or dementia or alzheimer*) AND <strong>TOPIC:</strong> (random* or trial or placebo or &quot;double-blind*&quot; or &quot;single-blind*&quot; or RCT or &quot;control group&quot;) <strong>Timespan:</strong> All years. Search language=Auto</td>
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<td>7. LILACS (BIREME)</td>
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<td>#3urapidil or fentolamin or minoxidil or &quot;magnesium sulphate&quot;</td>
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<td>#5MeSH descriptor: [Hypertension] explode all trees</td>
<td>10985</td>
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<tr>
<td>#6or #2 or #3 or #4 or #5</td>
<td>#7reduce* or stop* or taper* or cessat* or withdraw*</td>
<td>111</td>
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<tr>
<td>#8and #7</td>
<td>#9cognit*</td>
<td>4</td>
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<tr>
<td>#10dement*</td>
<td>#11MeSH descriptor: [Cognition] explode all trees</td>
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<tr>
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<td>#13memory</td>
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<tr>
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<td>#15or #9 or #10 or #11 or #12 or #13 or #14</td>
<td>(&quot;angiotensin converting enzyme inhibitor* OR antihypertensive OR antihypertensives) AND (cognition OR cognitive OR dementia)</td>
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<td>#16or #15 and #8</td>
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9. Clinicaltrials.gov
(www.clinicaltrials.gov) [searched 12 December 2015]
Interventional studies: ("angiotensin converting enzyme inhibitor* OR antihypertensive OR antihypertensives) AND (cognition OR cognitive OR dementia) Recruitment status: ALL

10. ICTRP Search Portal
(apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; Clinical-Trials.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service – Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register] [searched 12 December 2015]
Recruitment status: ALL

TOTAL before de-duplication and first assess 13307
TOTAL after de-duplication 10985
## Characteristics of included studies - Bath 2015

### Methods
- **Design:** randomised controlled parallel group trial
- **Date of study:** 20 July 2001 to 14 October 2013
- **Sample size calculation:** yes, needed 1750 for primary outcome
- **Inclusion criteria:** adults with a clinical stroke syndrome with limb weakness lasting at least 1 hour (i.e. not likely to be a transient ischaemic attack), residual limb weakness at the time of enrolment, with onset <48 hours, conscious (Glasgow Coma Scale >8), systolic blood pressure in range 140 mmHg to 220 mmHg inclusive on the basis of at least 1 of the 3 baseline prerandomisation measures, independent prior to stroke (premorbid mRS <2) and capable of a meaningful consent, or assent from a relative or carer if the person was unable to give meaningful consent (e.g. in cases of dysphasia, confusion or reduced conscious level)
- **Exclusion criteria:** a definite need to start (e.g. for thrombolysis), continue or stop blood pressure lowering drugs; need for, or contraindication to, glyceryl trinitrate; coma (Glasgow coma scale score <8); pure sensory stroke; isolated dysphasia; preceding moderate or severe dependency (mRS score 3 to 5); confounding neurological or psychiatric disease; a disorder mimicking stroke (e.g. hypoglycaemia, Todd’s paresis); liver dysfunction (international normalised ratio >1.5, aminotransferase >3 times normal concentrations) or renal dysfunction (creatinine >3 times normal concentrations); severe concomitant medical disorder; pregnancy or breastfeeding; previous participation in the ENOS trial; planned surgical intervention or participation in another trial within 2 weeks

### Participants
- **Number in study:** 2097
- **Country:** international multicentre
- **Setting:** acute hospitalisation for stroke
- **Age mean (SD):** 73 (11) years
- **Sex:** intervention 52% men; control 50% men
- **Comorbidity:** assessed and comparable at baseline
- **Level of education:** not reported
- **Dementia:** cognitive status not assessed at baseline

### Interventions
- **Intervention:** withdrawal of pre-existing antihypertensive medications for 7 days following stroke
- **Control:** continue pre-existing antihypertensive medications following stroke

### Outcomes
- **Measured at 90 days:**
  - t-MMSE
  - TICS-M
  - Blood pressure
  - Mortality
  - Adherence to withdrawal
  - Serious adverse events (including myocardial infarction)

### Notes
- **Funding source:** UK Medical Research Council
- **Declaration of interest:** “We declare no competing interests”
<table>
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<th>Risk of bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
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<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Comment: they used stratification and minimisation to ensure that the groups were balanced for prognostic factors, and the random element reduced predictability</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Central computer based system.</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Comment: not blinded for participant or personnel if the antihypertensive medication was stopped</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Comment: they applied an intention-to-treat analysis. For primary outcome of this review: 1778 participants alive at 90 days’ follow-up and so eligible for cognitive assessment. Results table reported t-MMSE data for 1272 participants and TICS-M data for 1179 participants - no explanation provided for missing assessment data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Comment: outcomes reported as described in published protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
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</tbody>
</table>
### Characteristics of included studies - Moonen 2015

#### Methods
- **Design:** randomised controlled parallel group trial
- **Date of study:** 26 June 2011 to 23 August 2013
- **Sample size calculation:** yes, 400 participants required for primary outcome
- **Inclusion criteria:** aged ≥ 75 years, used antihypertensive treatment, systolic blood pressure ≤ 160 mm Hg and had an MMSE score of 21 to 27
- **Exclusion criteria:** a clinical diagnosis of dementia, use of antihypertensives for reasons other than hypertension, current angina pectoris, cardiac arrhythmia, heart failure, myocardial infarction or a coronary reperfusion procedure < 3 years ago, a history of stroke or transient ischaemic attack or a limited life expectancy

#### Participants
- **Number in study:** 393
- **Country:** the Netherlands
- **Setting:** community primary care
- **Age mean (SD):** intervention 81.1 (4.3) years; control 81.5 (4.6) years
- **Sex:** intervention 77% men; control 70% men
- **Comorbidity:** assessed and comparable at baseline
- **Level of education:** assessed and comparable at baseline
- **Dementia:** people with existing dementia were excluded

#### Interventions
- **Intervention:** discontinuation of antihypertensive medications over a 6-week period after randomisation using a withdrawal algorithm with outcome assessment at 16 weeks
- **Control:** blood pressure medication continued. Blood pressure recorded at 6 and 10 weeks post-randomisation and at 16 weeks

#### Outcomes
- **Measured after 16 weeks:**
  - Overall cognition (compound score): computed if 5 of the following 6 test were available: Stroop-Colour Word Test and Trail Making Test for executive functioning, 15-Word Verbal Learning Test and Visual Association Test for (immediate and delayed) verbal and picture memory and Letter-Digit Substitution Test for psychomotor speed
  - MMSE for global cognitive functioning
  - Blood pressure
  - Mortality
  - Adherence to withdrawal
  - Serious adverse events (including infarction, hospitalisations)

#### Notes
- **Funding source:** this study was supported by a grant from Program Priority Medicines for the Elderly, the Netherlands Organization for Health Research and Development (Project 113101003)
- **Declaration of interest:** “None reported”
### Risk of bias

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<th>Authors' judgement</th>
<th>Support for judgement</th>
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<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Participants were randomly assigned, in a 1:1 ratio, to parallel discontinuation (intervention group) or continuation (control group) of antihypertensive treatment. The allocation was generated by a central computerized randomisation procedure in a 1:1 ratio in stratified block randomisation.”</td>
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<td>Quote: “Stratified block randomisation was used (with block sizes of 4 per general practice) to ensure that intervention and control participants were equally distributed within general practices. Concealment of treatment allocation was ensured by a central computerized randomisation procedure.”</td>
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<td>Blinding of outcome assessment (detection bias)</td>
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<td>Quote: “At baseline and at the follow-up 16 weeks after randomisation, blood pressure was measured and cognitive, psychological, and general daily functioning were assessed by trained blinded research personnel during home visits. Study outcomes … were assessed in a standardized manner by research personnel masked to the allocated intervention.”</td>
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<td>Low risk</td>
<td>Comment: intention-to-treat analysis in both groups. However, cognitive assessment data missing for primary outcome without explanation provided</td>
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<td>Low risk</td>
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**SUPPLEMENT 4**

**Characteristics of excluded studies**

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**RCT:** randomised controlled trial
Chapter 7

GENERAL DISCUSSION
This thesis comprises a number of studies that are all related to at least two of the four themes: eHealth, cardiovascular risk management, older adults or cognition. **Part I** focusses primarily on the first three themes and describes the processes leading to and the design of a large international randomised controlled trial; Healthy Ageing Through Internet Counselling in the Elderly (HATICE). An ambitious international trial, specifically designed for older adults (≥65 years) and, as such, an important addition to existing healthcare and cardiovascular risk management strategies. **Part II** of this thesis focuses on cognition, or actually the degradation of cognition (cognitive decline and dementia), in connection with the other three themes named before. In the present chapter, the main findings of this thesis will be summarised and discussed in the context of the current knowledge and literature. Furthermore, I will discuss the implications for clinical practice and future research.

**PART I EHEALTH IN CARDIOVASCULAR RISK MANAGEMENT**

**Improvement of cardiovascular risk factors in older adults**

The focus on older adults as exemplified in this thesis is based on the following considerations. Different from the initial name of our trial (Healthy Ageing Through Internet Counselling in the Elderly - HATICE), we changed the vocabulary to 'older adults', because the use of 'elderly' may have a patronizing ring to it and therefore should be avoided if possible. In order to refrain from this we decided to use the term 'older adults' in referring to our study subjects throughout this thesis.

Globally and in particular in Europe, the older population is growing, with a specific rapid increase in the number of oldest old persons (aged ≥85 years)(1). This ageing population is growing because of the increased life expectancy, but strikingly, the number of years we live a healthy life free of any disability, is declining(1). This development is likely to have a considerable impact on society as a whole: most directly with respect to the different health and care needs and demands of the older adults. That is the reason why we think the focus in research should also be on older, relatively under investigated populations, to not only live a longer, but also a longer healthier life.

As the baseline data of the preDIVA (Prevention of Dementia by Intensive Vascular care) trial(2) convincingly document, there is a clear window of opportunity for cardiovascular prevention in older people(3). Almost two thirds of the trial population (community dwelling older adults aged 70-78 years) had two or more modifiable cardiovascular risk factors. Moreover, it has been repeatedly documented that treating older adults for these risk factors
is still beneficial (4, 5), at least for the reduction of cardiovascular disease. However, it is still not clear whether or not interventions aimed to improve cardiovascular risk profiles also hold promise for preventing cognitive decline or dementia, with inconclusive trial results (2, 6, 7).

A major problem in cardiovascular prevention for older adults (aged >70 years) is the lack of consensus on and evidence for cut-off scores in national and international guidelines (8). Within the HATICE project we compared European cardiovascular risk management guidelines (9) and found that this lack in evidence is at least Europe wide, with the upper age limit in e.g. the Finnish CVD guideline of 74 years, but in the European guideline (8) only 65 years. In older adults the cut-off scores for when to treat the separate risk factors with drugs or other interventions also differs importantly according to the guidelines of the different European countries. This state of affairs clearly illustrates the need for more internationally oriented research in cardiovascular prevention in older adults. The lack of research in this higher age group might be due to the fear of side effects. A low blood pressure (because of treatment with antihypertensive medications) can lead to falls or a reduced blood perfusion of the brain (10, 11) and thereby increase the overall risk of mortality or disability. Polypharmacy might also be one of the reasons to just not treat the older adult in the context of prevention, because more medications increases the risk of drug interactions and iatrogenic complications (12). This further complicates treatment decisions in older people, especially when no clear directives are available.

Self-management and goal setting for behaviour change

One of the most difficult challenges in lifestyle improvement for the prevention of cardiovascular disease is maintaining the behaviour change for a long period of time (13). Especially for the older adult it can be very difficult to change things that they are used to do their entire life and that are sometimes even in contrast with what they had learned in the past (e.g. until the 1950s, doctors approved of smoking for a healthy life). There is wealth of literature on optimal strategies for sustained lifestyle change. A relatively new development of the last decade is the focus on self-management (or patient-empowerment): let the participants be in control of their own health. Recent research shows that the use of goal setting and self-monitoring of behaviour (using a pedometer, or registering blood pressure or food intake) helps people to improve their cardiovascular risk profile (14). A person-centred and autonomy supportive counselling approach is important in maintaining this lifestyle. Effective self-management support is not equivalent to just telling participants what to do. It means acknowledging the participants’ central role in their care, one that fosters a sense of responsibility for their own health (14).
A high cardiovascular risk can be regarded as a chronic illness as well, just as cardiovascular disease itself. Hypertension, dyslipidaemia, overweight, are all risk factors that can go unnoticed by the participant, but seriously increase the risk of cardiovascular diseases and can therefore be seen as a silent potential disease as well. Awareness of these risk factors can stimulate health improvement and reduce the overall cardiovascular risk. Individuals with obesity and additional cardiovascular risk factors for example can receive dietary counselling to reduce their risk of cardiovascular disease(15). An evidence based way to reduce the modifiable cardiovascular risk factors. The HATICE platform and randomised controlled trial (RCT) (chapter 2 and 3) stimulate self-monitoring of these (and other) risk factors. By means of online goal setting with the support of a coach we hope to create self-awareness and create the optimal condition to improve the cardiovascular risk profile.

**Internet use for cardiovascular risk management**

The fact that internet use among all age groups is rising(16) creates the opportunity to reach large populations by using eHealth and might even help to guide older adults towards a longer healthier life in their own homes. The increase in accessibility of the internet can help patients, but also caregivers in terms of medical information availability and time efficiency (e.g. not having to travel long distances). In chapter 2 we argued that the biggest pitfall in internet interventions is the rapidly evolving technology in this field. This may lead to many eHealth intervention strategies, all without sound evidence of their efficacy. It takes time to develop a well-designed product, especially if it needs to fit a relatively unexperienced user group, such as the older population. The development of the HATICE internet platform lasted around two years and its efficacy is now being tested in the randomised controlled HATICE trial. The process of developing a well-designed intervention platform is time consuming, in the first place because a large number of different experts were involved:

- the end-users, who should be consulted in a focus group, testing group or with the thinking aloud principle(17);
- experts, for example patient organisations or people specialised in communicating with older adults;
- software developers, for the technical part;
- researchers, to ultimately guarantee evidence based interventions.

All four groups are essential in this process and need to work together to build an optimal working platform ready for efficacy testing.
Important in cardiovascular prevention by lifestyle improvement is using a coaching approach of the health care worker and to build a personal relationship with the participant.(18). An important finding from the focus groups with potential participants of HATICE is a seemingly obvious barrier in this coaching: the negative, normative and directive tone of voice in the advices that can be given. ‘Lose weight!’, ‘exercise more!’ ‘take your medications as prescribed’, ‘don’t eat too much sugar’ are based on widely accepted knowledge, but a more gentle way of conveying these very same messages may increase their efficacy. Obvious indeed, but this positive tone of voice is also important in vocabulary. Renaming ‘risk factor’ to ‘health factor’ made a huge difference for the focus group participants, because they felt they were working on their health, rather than being warned for increased risks of chronic diseases. These suggestions might specifically hold for older adults, since they have to change long-standing habits calling for the most tailored approach that can be provided.

A meta-analysis by Beishuizen et al. about internet-interventions aimed at improving cardiovascular risk factors showed that internet-interventions with a blended (human/computer) approach were associated with larger treatment effects than internet-only interventions(13). This seems like a comforting result, that even though our world is rapidly digitalising, we still need the human input to reach a better effect on our health. In this review there were only studies included investigating a single risk factor, so it might be that a multifactorial approach of treating risk factors can reach an even greater effect. However, the question remains if these kind of blended interventions are cost-effective if the human involvement is still necessary, and a lack in cost-effectiveness analyses in internet interventions provides no clear answer. In the HATICE trial we test this kind of blended approach to improve the cardiovascular risk profile and hopefully, the HATICE cost-effectiveness analysis can give us an answer in the future.

Internet use among older adults

We discovered known and unknown barriers encountered by older adults using a prevention platform during the focus groups and iterative testing sessions while developing the HATICE platform. A known barrier for older adults is privacy and the importance that personal health information is not accessible for everyone. An unknown barrier was the difficulty of dealing with solutions to protect this privacy, for example with passwords and login procedures. A secured platform taking privacy matters into account should still be accessible, not complicating the login procedure too much, because of limited internet literacy in this older age group. Obviously, reliable, secure and effective login procedures are important prerequisites for any trial in this field.
Difficulties associated with internet illiteracy in older adults might be a problem that will resolve itself in a couple of decades. This may hold true for the long process of development: with increasing internet literacy, fewer specific adaptations for older adults shall be needed. Nevertheless, according to the Administration on Aging, 45% of older adults aged 65 to 69 have some degree of disability and this increases to 74% for those 80 years or older(19). So older adults need to deal with other problems than younger adults do, for example because of the need for hearing and vision aids. It is not likely that his will change in the coming decades. Colouring and use of flashing objects need to be limited(20-22), and other characteristics of platform design, such as fonts, graphics, background images, navigation, and search mechanism may prevent older adults from taking advantage of online health resources if not especially for them designed. This holds true for an internet platform, but also for applications used on a tablet or smartphone.

The challenge in primary outcome(s)

When designing a trial, one of the most important elements that needs to be carefully considered is the primary outcome for obvious methodological reasons as a properly defined primary outcome will reduce the risk of false-positive outcomes resulting from the statistical testing of many outcomes, and it will reduce the risk of a false-negative outcome by providing the basis for the sample size calculation for an adequately powered study(23).

The primary outcome of the HATICE RCT (chapter 3) is a unweighted composite score based on the average z-score of the difference between baseline and 18 months follow-up of the three measurable risk factors systolic blood pressure, low-density-lipoprotein (LDL) and body mass index (BMI). The reason why we decided not to use validated cardiovascular risk scores such as the Framingham(24) or the SCORE (Systematic COronary Risk Evaluation) (25) is because these scores were developed for populations specifically with or without manifest cardiovascular disease, while the HATICE study population consisted of both participants with and without a cardiovascular history. This choice was deliberately made because lowering the cardiovascular risk is important for both groups, together representing a large potential target population. To date, no validated risk scores exist that can harbour risks of primary as well as secondary prevention populations, warranting a different outcome measure for both groups combined. Hence, we preferred an HATICE risk score over established risk scores that would not match our study population as a whole, accepting the fact this score has not been validated externally.
Ideally we would have chosen a clinically robust primary outcome like mortality, incident cardiovascular disease or dementia. However, from the previous three major trials (preDIVA, MAPT and FINGER) and from observational cohort data, we learned that we would have needed extensive follow-up for these outcome measures with a large sample size and this combination was not deemed feasible within the timeframe of the HATICE study. Extended observational follow-up for the HATICE RCT may enable us to analyse these measures as secondary outcomes in the future.

Another important reason why we chose the current, composite primary outcome was because of the 'unbiased' measurability of the three included risk factors. Systolic blood pressure and body mass index (height and weight) are measured by a trial nurse blinded for treatment allocation and low-density lipoprotein is measured in a (fasted) blood serum sample all according to a strict study protocol. Other risk factors (lack of physical exercise, unhealthy diet or smoking) are generally measured through self-report instruments and thereby potentially prone to reporting bias. Especially regarding lifestyle improvement, study participants may feel inclined to want to report increased physical activity, increased consumption of fruit and vegetables and reduced or even quitted smoking. After careful consideration we decided not to weigh the different components of the risk score, even though their contribution to the overall risk is probably not equal. No data are available to support any decision on weighing these factors, rendering it impossible to make an appropriate weighing factor.

Combining three variables into one composite outcome measure gave rise to questions on the appropriate sample size calculation. What could be regarded as a minimum clinically relevant effect? Since we use a new composite score in the HATICE RCT, the potential treatment effect for this outcome was unknown, as was the minimally clinically important difference. We analysed the effect of our outcome measure with the data of preDIVA(2) and FINGER(7), calculated the clinical relevance and based our sample size calculation on these measures, to deal with our non-standardised primary outcome. In the preDIVA study the mean difference in z-score of the HATICE primary outcome between baseline and two year follow-up was 0.070 (p=0.002). In the FINGER study this mean difference was 0.041 (p=0.11). To avoid the risk of being underpowered since the effect was non-significant in the FINGER study, we based our sample size calculation on an effect size of 0.06, closer to the results found in preDIVA.

The correct size of the study sample optimizes the number of participants needed to detect the minimum treatment effect that is clinically relevant. Minimizing a sample size of a study has the advantage of reducing costs, enhancing feasibility, and has ethical implications. A
downside to this is that you minimize too much and not catch the treatment effect. We actually expanded our sample size based on the calculated treatment effect, to minimize the risk of missing an effect.

**International collaborations and sharing data in research**

International data sharing is increasingly promoted, because it has many advantages: it increases power, creates transparency and ensures disclosure(26). On the contrary, there are many policy, privacy, and practical issues that need to be addressed in order to make data sharing practical and useful for research purposes. The HATICE research group is an example of such an international collaboration including researcher partners from five different European countries (The Netherlands, Sweden, Finland, the United Kingdom and France, figure 1). The collaboration of this research group started April 2011 with the European Dementia Prevention Initiative(27) (EDPI, www.edpi.org) and agreements about data sharing were made, since there were three major ongoing trials running in The Netherlands preDIVA(2), France MAPT(6) and Finland FINGER(7)) that had comparable study aims to prevent dementia by treating modifiable cardiovascular risk factors. A comprehensive data sharing platform was built to be able to compare study variables and outcomes and to initiate new analyses on the combined data set. Although this may sound obvious, this initiative was all but straightforward, demanding huge efforts in terms of planning, personnel/manpower, repeated discussions and negotiations to arrive at a functional, shared platform with data from all three trials. Slightly different trial designs, with different tests and measures at different time points with sometimes different values for the same measurement all had to be aligned. For some measures we questioned whether sharing data would go at the cost of too much modification and were still sufficiently useful for an appropriate interpretation of the findings. Thus, we concluded that, although efforts to share data seem justified and of added value, they are certainly challenging and by no means uncomplicated.

Highly ranked journals as for example the British Medical Journal, the Lancet and PLoS Medicine all promote or already require as a prerequisite for manuscripts considered for publication, for authors to share the coded patient data underlying the study results(26). A great development to create more transparency and the possibility of independent confirmation of results, but the question is legitimate if these kind of data sets are interpretable for a fellow researcher?
With our experience within the HATICE research group and the shared data platform we can confirm this might lead to misinterpretation and would require a lot more documents and explanation than a single public dataset. Sharing data between research groups or as requirement of a journal will only work if:

1. there are clear agreements and good collaborations between the owner of the data (researcher, sponsor, financer);
2. the analyser of the data, under the additional requirements that;
3. the dataset is well structured and provided with explanation for proper interpretation, and;
4. arrangements about publication of the data are made (authorships, finances, etcetera).

**The expected outcome of HATICE**

At this moment the HATICE RCT is still ongoing and is expected to end towards the beginning of 2018, when the last 18 months follow-up measurements are scheduled. The final results of the HATICE trial will show whether an internet platform supported by a coach
to improve the cardiovascular risk profile is (cost-)effective on modifiable cardiovascular risk factors, and perhaps also on cardiovascular disease. It may yield clues on the pathway towards cardiovascular risk management strategies with enhanced, digital support in- or outside the health care structures. Beneficial effects could facilitate further implementation approaches within the 'tested' countries (The Netherlands, Finland and France) and explore the possibilities in other European countries or even beyond. Neutral findings may not preclude the possibility to find positive leads within subgroups and send us in a good direction for the future.

**Figure 2.** The HATICE logo

**PART II COGNITIVE FUNCTIONING – ASSESSMENT, DEMENTIA RISK PREDICTION AND PREVENTION**

**mHealth in research**

Besides all the advantages of mHealth in research, there is an important downside to this development as well: mHealth has raised serious legal issues because a lack (of compliance with) privacy and data protection laws. mHealth systems often collect a broad range of information and more continuously than is collected in traditional clinical settings. Online data sharing makes sensitive personal health-related data vulnerable for risks in privacy, information may be out in the open. Therefore, it is paramount that new mobile health applications go through a thorough and robust development cycle to guarantee that it complies with all prevailing international privacy and data protection laws. In Chapter 2, we have tried to develop a guideline for such a development cycle (in five phases), which can be used for mHealth applications as well.
Large healthcare organisations value the importance of mHealth as well and recognise the usefulness in healthcare solutions and research opportunities, but also point out the importance of evidence of effect (see quote 1).

"The responsibility for generating evidence should not fall solely only on the product developers. The research and clinical communities also must help to generate these needed data. Our review of the evidence to date, even with its flaws and limitations, clearly demonstrates the great potential that mobile technologies can have to aid in lifestyle modification. Thus, clinicians should not conclude that mobile technologies are generally unproven and thus can be ignored. The current absence of evidence should not be used as evidence of an absence of effectiveness."
- The American Heart Association

Quote 1. American Heart Association.

mHealth and cardiovascular disease in older adults

A recent systematic review showed that mHealth technology has a positive effect on the secondary prevention of CVD with possible improvement of adherence to evidence-based therapy(29). It is conceivable that the findings from this study are an underestimation of the current mHealth potential, since most of the included studies in this meta-analysis used older mHealth technology such as text messaging, which already promotes an older model of care delivery without interactive feedback. As mentioned before, the eHealth/mHealth world is evolving so rapidly that literature cannot keep up.

Despite the increase in smartphone usage by older adults, at least 25% of smartphone users aged >65 years have never downloaded an application to their device(30). Older people tend not to use smartphones as designed and resort to older technologies such as text messaging. Small buttons on a smartphone, swiping on a tablet and losing track in navigation are all features that limit the older adult in the use of applications(31).

The iVitality study (chapter 4) was designed as a proof-of-principle study to monitor blood pressure(32) and cognition with the aim of implementing this approach in a large-scale RCT on the prevention of cognitive decline and dementia. Many challenges still have to be
overcome in terms of adherence and relative validity of the smartphone-based cognitive tests, but the results were promising in usage of the application by the older adult because of the simplicity of the tests and extensive instructions of the whole application.

iVitality shows that smartphone-based cognitive testing allows for repeated testing to observe changes over time while reducing the need for face-to-face contact, making it time-efficient, less burdensome for research participants and less expensive. The tests should be considered as screening tests to detect changes over time, rather than replacing conventional neuropsychological test batteries. It may be particularly useful for large-scale data-collection in population studies with long follow-up requiring remote repeated testing. Therefore, usage in the future of these kind of applications to collect data about cognition can help research and screening opportunities to the next level.

**Cognitive assessment: the use of screening instruments**

In 2013, the Alzheimer’s Association developed ten recommendations for improving the early detection and clinical care for dementia(33). One of these recommendations involves the implementation of cognitive screening in general practice as part of personalised healthcare. However, before such implementation can take place, some issues should be addressed. For example, from what age should we than start screening, with what reliable, validated screening instrument(s) and how to deal with the bias of age and education? Literature states that screening instruments alone have insufficient specificity to diagnose dementia when used in a comprehensive screening program with high misdiagnosis rates(34), especially when used for older adults with and without memory complains(35). When estimating the feasibility of cognitive screening in general practice the following issues should be taken into account: the incidence of dementia/cognitive impairment in that population; the sensitivity and specificity of the test; the advantage for people identified correctly as having the diagnosis (true-positives); the disadvantage for people misdiagnosed (false-negatives); and the costs of the test, difficulty and time of administration(36).

Actually, there is no shortage of quick, predictive cognitive tests for dementia in the literature. Is it really necessary to add another test to the Montreal Cognitive Assessment (MoCA)(37), the Memory Impairment Screen (MIS)(38), Addenbrooke’s Cognitive Examination III (ACE-III)(39), or the General Practitioner Assessment of Cognition (GPCOG)(40)? In chapter 5 we wanted to investigate whether a specific test for visual memory, which is one of the earliest cognitive domains affected by Alzheimer’s Disease, could have added value after a cognitive screening instrument has been used. We showed that administering the Visual Association
Test (VAT) in persons with a decline of one point or more on the MMSE over a two year period has substantial incremental value for identification of those who are at increased risk of dementia. One could argue even more in favour of the VAT, for its several outstanding characteristics: it is one of the few instruments specifically validated within a primary care population, not influenced by language skills(41), does not need informant information, and it can quite easily be transformed in a mHealth application.

In chapter 5 we also performed a global comparison of the effect sizes of different methods in predicting dementia. It suggests that the effect size of the VAT additional to the MMSE change score over time (Cohen’s d of 1.24) is comparable to the effect sizes found in a meta-analysis of levels in cerebrospinal fluid (CSF) of total tau, phosphorylated tau and amyloid-beta-42 ranging from 0.91 to 1.11 and the effect size of medial temporal lobe atrophy on magnetic resonance imaging (MRI) of 0.75(42). A comparison that must be interpreted cautiously, but it shows combining cognitive tests can be as useful as more invasive ways to identify a population at increased risk that can be monitored over time. Performing a VAT in individuals with a declining MMSE is likely to be more cost-effective and is associated with much less burden to patient and carer than doing a lumbar puncture for cerebrospinal fluid examination or making a MRI scan(43, 44).

Polypharmacy in older people with cardiovascular disease

With all the prevention opportunities for cardiovascular disease, partially with medications as antihypertensives and cholesterol lowering drugs, the potential problem of polypharmacy arises. This holds especially for older adults who tend to suffer from more than one cardiovascular risk factor and have a higher incidence of cardiovascular disease. In developed countries, around 90% of persons aged 65 years and older are taking at least one prescribed medication (not only restricted to cardiovascular disease)(45). With older age, the constitution of the body changes, resulting in altered metabolism, absorption, and elimination of medications, and consequently are less tolerated(46). Each treatment recommended by a national or international cardiovascular guideline for (the prevention of) cardiovascular disease might be rational and evidence based in the middle aged population, but the combination of all these can have a negative influence on older adults suffering from several chronic conditions. A patient-centred approach has the potential to avert this harmful influence especially if this is based on evidence for efficacy of the treatment (if available), combined with information on the prognosis of the patients’ disease or condition, and on relevant interactions with other medications and coexisting morbidity(12). The purpose is to attain an optimal therapeutic balance through increasing benefits and decreasing harms
by stimulating adherence to the most essential treatments. Doctors should consider to stop therapies that are not essential or potentially harmful in order to decrease the risk of side effects of specific medication or drug interactions due to polypharmacy (47). In this context chapter 6, about antihypertensive withdrawal for the prevention of cognitive decline, was written. We could not conclude that withdrawal of (one) antihypertensive medication is beneficial or harmful for the preservation of cognition. This lack of evidence might be because of the lack of (comparable) studies we could include, but might also be due to the short follow-up of the included studies and therefore missing the ultimate effect.

We urge the importance of withdrawal trials because optimising medication through deprescribing can be a vital part of managing chronic conditions as cardiovascular disease and dementia, reducing adverse effects and improving outcomes. In this developing world of medical improvement we should not only focus on the benefits of new medications, but also on the implications and potential harms for specific patient groups.
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Chapter 8

SUMMARY
In chapter one we introduced the rationale and background of this thesis. This thesis is divided in two parts: (1) eHealth in cardiovascular risk management and (2) Cognitive functioning – assessment, dementia risk prediction and prevention. All chapters have a connection with at least two of the four following themes: eHealth, older adults, management of cardiovascular risk factors (prevention) and cognition.

The Netherlands is one of the frontrunners in internet use. High internet penetration across all age groups and educational levels creates an opportunity to deliver (preventive) healthcare at home via the internet. This is what we call eHealth nowadays. Other countries, especially in Europe, follow rapidly in spreading internet access and this gives us the opportunity to develop and validate internet interventions to improve and prevent major health problems like cardiovascular disease and dementia.

PART I EHEALTH IN CARDIOVASCULAR RISK MANAGEMENT

In chapter two of this thesis we describe the extensive, profound and time-consuming process of developing an internet platform for the prevention of cardiovascular disease in older adults. A clear overview and guideline divided into five phases from the first thoughts to the final end product is provided. Phase one is about the conceptual framework, and this explains that the beginning of this process (building a platform) cannot start without a fundamental basis substantiated by literature. We describe that a blended approach to motivate people for a better lifestyle seems to work best, combining automated digital contact with actual human support. Phase two describes the platform concept and functional design. In this phase we brought the three most important parties together to fulfil the needs and possibilities of the platform (end users, health care researchers and software developers). It is crucial to understand the end users: what do they expect, what motivates them and what are they capable of in terms of computer use. The software developers provide the required technology and the researchers design the study to test the actual effectiveness of the platform. Phase three describes the building of the platform and its content; the latter based on the most recent literature and international health guidelines. Phase four shows the results of the international pilot study (N=41) in the testing and evaluating stage. Phase five is about the end product of the platform, ready to test in a randomised controlled trial (which is described in chapter three).
In *chapter three* we present the rationale and design of the HATICE trial (Healthy Ageing Through Internet Counselling in the Elderly). The HATICE trial is a pragmatic, multinational, multicentre, investigator initiated, prospective, randomised, open-label blinded end point (PROBE) trial with 18 months intervention and follow-up. In this study, researchers from three different European study groups collaborate based on their shared experience with large clinical dementia prevention trials (preDIVA, FINGER and MAPT). This previous experience was translated into the development of the interactive internet platform as described in chapter 2 to be tested in this RCT. This platform is aimed at optimising self-management of cardiovascular risk factors in older individuals. The aim of the HATICE trial is to investigate whether this coach-supported interactive internet platform can improve the cardiovascular risk profile and reduce the risk of cardiovascular disease and cognitive decline. Recruitment of 2725 participants aged 65 years and older with at least two cardiovascular risk factors or manifest cardiovascular disease (primary and secondary prevention) took place in three European countries (The Netherlands, Finland and France). The older population as target group for cardiovascular prevention through the internet is chosen with care, since this is a population that is usually overlooked in such trials, but can profit from cardiovascular prevention. The primary outcome is a composite score based on the difference between baseline and 18 months follow-up values of systolic blood pressure, low-density-lipoprotein and body mass index, which are measurable risk factors not amenable to reporting bias. In addition to clinical outcomes including cardiovascular disease and cognitive decline, cost-effectiveness is an important secondary outcome, which is pivotal in the rapidly developing world of eHealth.
PART II COGNITIVE FUNCTIONING – ASSESSMENT, DEMENTIA RISK PREDICTION AND PREVENTION

In chapter four, we present the results of the cognitive testing part in the iVitality study. We show that it is technically feasible to perform repeated cognitive tests on a smartphone and that adherence of older people with an increased risk of developing dementia, because they have a family history of dementia, is reasonable. We used several cognitive tests, which are based on existing paper and pencil cognitive tests. It is a challenge to make a smartphone-based cognitive test that measures exactly the same cognitive domain and is comparable to the validated conventional test. The relative validity of some of the tests compared to the conventional neuropsychological tests was only moderate. However, performance of the participants improved with repeated measures and this improved the relative validity as well. The performance improvement was mostly due to technical difficulties at the start of the study rather than an actual learning effect. We conclude that smartphone-based cognitive testing seems very promising for modern, future, large-scale data-collection in population studies.

In chapter five we present the added predictive value of a neuropsychological test of visual memory (Visual Association Test, VAT) over and above a cognitive screening instrument (Mini Mental State Examination, MMSE) based on data from the preDIVA trial (Prevention of Dementia by Intensive Vascular Care). PreDIVA is a large randomised controlled trial performed in the primary care setting to assess whether intensive vascular care can prevent or postpone dementia in community-dwelling older adults (>70 years old). For the study described in this chapter, we considered the study as a cohort (N=2690). We assessed whether the score on the VAT could improve prediction of who will develop dementia in the next 4-6 years of those who have a decrease of their score on the MMSE after two years of follow-up. In total, dementia developed in 157/2690 (5.8%) participants and a decline of two or more points in total MMSE score over two years was associated with an odds ratio of 3.55 (95% confidence interval 2.5-5.0) for developing future dementia. Strikingly, participants with a decline of two or more points on their MMSE score and an additional imperfect VAT score (5 points or less) had an odds ratio of 9.55 (95% CI 5.9-15.4) for developing future dementia. Whereas those with a decline on the MMSE score and a maximum score on their VAT had an odds ratio of 3.61 (95% CI 2.1-6.3) for developing future dementia. It seemed that such a short, simple test as the VAT has substantial incremental value for distinguishing older individuals that are at increased risk of developing dementia.
High blood pressure (hypertension) is one of the most important risk factors for developing cardiovascular diseases, but also dementia. Some fear that blood pressure reduction may lead to cerebral hypoperfusion and as such actually will increase the risk of dementia, which is supported by observational data showing an increased risk of dementia in those with a low blood pressure. To test the hypothesis that a low blood pressure by antihypertensive medications might be harmful for cognitive performance, in chapter 6 we systematically reviewed the literature regarding the effects of complete withdrawal of at least one antihypertensive medication on the incidence of dementia and cognitive decline. Unfortunately, high quality research in this topic is scarce and only two studies could be included in this Cochrane review. Neither of these two studies investigated incident dementia, so no conclusions about the effect of developing dementia could therefore be drawn. Cognition was measured in both studies in a very different way, precluding meta-analysis, but withdrawal of antihypertensive medications did not show a significant effect on cognition in either study.

In chapter 7 we present and discuss the main findings of this thesis in context of the latest literature and potential clinical implications for future research.
Appendices

DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)
AUTHOR CONTRIBUTIONS
CO-AUTHOR AFFILIATIONS
LIST OF PUBLICATIONS
PHD PORTFOLIO
ABOUT THE AUTHOR
ACKNOWLEDGEMENTS (DANKWOORD)
Dutch summary (Nederlandse samenvatting)

In hoofdstuk één worden de achtergrond en rationale van dit proefschrift toegelicht. Nederland is wereldwijd een van de koplopers in internettoegang en -gebruik. De grote beschikbaarheid van internet voor alle leeftijdsgroepen van verschillende opleidingsniveaus biedt de mogelijkheid tot het leveren van (preventieve) gezondheidszorg op afstand, ook wel aangeduid met de term eHealth. Hiermee kan een groot gedeelte van de (zorgafhankelijke) populatie bereikt worden. Ook andere landen, met name in Europa, volgen snel in deze ontwikkeling van internettoegang en -gebruik. Dit biedt de mogelijkheid voor het ontwikkelen van gevalideerde eHealth interventies die gebruikt kunnen worden om het risico op ernstige aandoeningen zoals dementie en hart- en vaatziekten te verminderen of zelfs te voorkomen.

Het doel van dit proefschrift is om inzicht te geven in de mogelijkheden van cardiovasculaire preventie via eHealth en mHealth en tevens verschillende manieren van management en beoordeling van cognitie weer te geven. Dit proefschrift is verdeeld in twee delen: (1) eHealth in het kader van cardiovasculair risicomanagement en (2) beoordeling van risico en risicomanagement ten aanzien van cognitieve achteruitgang. Beide delen en daarmee ook de afzonderlijke hoofdstukken hebben een verband met ten minste twee van de volgende vier thema’s: eHealth, cardiovasculair risicomanagement, ouderen en cognitie.

Deel I Ehealth in cardiovasculair risicomanagement

In hoofdstuk twee van dit proefschrift beschrijven we het uitgebreide, intensieve en tijdrovende proces van de ontwikkeling van een internet platform voor de preventie van cardiovasculaire ziekten bij ouderen. Er wordt een overzicht gegeven, vanaf de eerste gedachten in vijf fases leidend tot het uiteindelijke eindproduct. Fase één betreft het conceptuele raamwerk, waarin we beschrijven dat voorafgaand aan de ontwikkeling van een internet platform uitgebreid literatuuronderzoek nodig is als fundament. Uit dit literatuuronderzoek blijkt dat een gecombineerde aanpak van puur digitaal, geautomatiseerd contact ondersteund door menselijk contact het beste werkt bij het motiveren tot leefstijl aanpassingen. Fase twee beschrijft het platformconcept en het functionele ontwerp. In deze fase brachten we de drie belangrijkste partijen samen (eindgebruikers (ouderen), wetenschappers uit de gezondheidszorg en softwareontwikkelaars) om zo goed mogelijk behoeften en mogelijkheden van het platform op elkaar af te stemmen. Het is cruciaal om de eindgebruikers te begrijpen: wat verwacht men van een dergelijk platform, wat motiveert
gebruikers en hoe gaan zij om met de computer en het internet. De softwareontwikkelaars zorgen voor de benodigde technologie en de wetenschappers ontwikkelen het onderzoek om de effectiviteit van een dergelijk platform te testen. Fase drie beschrijft het daadwerkelijke bouwen van het platform tegelijkertijd met het creëren van de inhoud, gebaseerd op de meest recente literatuur en internationale richtlijnen. In fase vier, de test- en evaluatiefase, laten we de resultaten van de internationale pilot studie zien gebaseerd op 41 ‘proef’-gebruikers uit verschillende landen. Fase vijf verwijst naar het platform als eindproduct, klaar om te testen in een gecontroleerd, gerandomiseerd onderzoek (omschreven in hoofdstuk drie).

In hoofdstuk drie wordt de rationale en het ontwerp van de HATICE studie beschreven (Healthy Ageing Through Internet Counselling in the Elderly – gezond oud worden door begeleiding via internet voor ouderen). De HATICE studie is een pragmatische, prospectieve, gerandomiseerde, open-label studie met een geblindeerde eindpuntmeting. De studie wordt uitgevoerd in Nederland, Finland en Frankrijk in meerdere centra, met 18 maanden interventie en vervolg. Deze studie is geïnitieerd door onderzoekers van drie verschillende Europese studiegroepen, allen gespecialiseerd en ervaren in grote klinische dementie preventie studies (preDIVA, FINGER en MAPT). Deze ervaringen zijn vertaald in de ontwikkeling van een interactief internet platform, zoals beschreven in hoofdstuk twee, dat getest wordt in deze gerandomiseerde studie. Het platform is ontwikkeld om zelfmanagement van de cardiovasculaire risicofactoren in ouderen te optimaliseren. Het doel van de studie is om te onderzoeken of het interactieve HATICE internet platform - dat ondersteund wordt door coaches - het cardiovasculaire risicoprofiel kan verbeteren om uiteindelijk zo het risico op cardiovasculaire ziekten en cognitieve achteruitgang te verminderen. In 14 maanden werden in de drie deelnemende landen 2725 deelnemers van 65 jaar en ouder met minstens twee cardiovasculaire risicofactoren of een manifeste cardiovasculaire ziekte bereid gevonden om aan de studie deel te nemen. Deze doelgroep voor primaire en secundaire cardiovasculaire preventie via internet werd zeer bewust gekozen, aangezien dit een doelgroep is die in onderzoek veelal miskend wordt, terwijl deze groep ouderen wel goed van cardiovasculaire preventie zou kunnen profiteren. De primaire uitkomstmaat van deze studie is een samengestelde score gebaseerd op het verschil in systolische bloeddruk, lagedichte-lipoproteïne (LDL) cholesterol en body mass index (BMI) tussen het begin van de studie en na 18 maanden. Dit zijn drie cardiovasculaire risicofactoren die niet beïnvloedbaar zijn door selectieve onder- of overrapportage. In aanvulling op klinische uitkomstmaten zoals cardiovasculaire ziekten en cognitieve achteruitgang, is de kosteneffectiviteit een belangrijke secundaire uitkomstmaat en cruciaal in de snelle ontwikkeling van eHealth. Naar verwachting zullen begin 2018 alle metingen kunnen worden afgereed.

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DEEL II BEoordeling van risico en risicomanagement om cognitieve achteruitgang te voorkomen

In hoofdstuk vier presenteren we de resultaten van de onderzochte cognitieve testen uit de iVitality studie. We laten zien dat het technisch mogelijk is om herhaald cognitieve testen uit te voeren op een smartphone (een mobiele telefoon met uitgebreide computermogelijkheden). Tevens wordt er door de deelnemers met een licht verhoogd risico op dementie (gebaseerd op het feit dat bij ten minste één ouder de diagnose dementie werd gesteld) redelijk trouw gehoor gegeven aan de volgens het studieprotocol voorgeschreven timing van de testen. We hebben verschillende cognitieve testen op de smartphone gebruikt die gebaseerd zijn op conventionele, gevalideerde, ‘pen en papier’ neuropsychologische testen. Het is een uitdaging om cognitieve testen voor de smartphone te maken die precies hetzelfde cognitieve domein meten en die goed vergelijkbaar zijn met de gevalideerde conventionele test. De relatie van sommige onderzochte cognitieve smartphone testen was matig in vergelijking met de conventionele testen. Echter, de resultaten van de deelnemers verbeterden naarmate ze de testen vaker uitvoerden en dit verbeterde tevens de relatie validiteit. De verbetering in resultaten kwam voornamelijk door technische moeilijkheden die overwonnen moesten worden en waarschijnlijk niet door een leereffect. We concluderen in dit hoofdstuk dat cognitieve testen uitgevoerd op de smartphone veelbelovend zijn voor moderne grootschalige dataverzameling in grote toekomstige populatiestudies.

In hoofdstuk vijf presenteren we de aanvullende voorspellende waarde van een neuropsychologische test van het visuele geheugen (Visuele Associatie Test, VAT) na het uitvoeren van een bekend cognitief screenings instrument (Mini Mental State Examination, MMSE). De data gebruikt voor dit onderzoek komt van de preDIVA studie (Prevention of Dementia by Intensive Vascular Care – preventie van dementie door intensieve vasculaire zorg). PreDIVA is een grote gerandomiseerde, gecontroleerde studie onder thuiswonende ouderen (70-78 jaar aan de start van het onderzoek) om door middel van intensieve vasculaire zorg uitgeoord in de huisartspraktijk, dementie te voorkomen of uit te stellen. Voor de studie die wordt beschreven in dit hoofdstuk, hebben we de deelnemers van preDIVA als cohort beschouwd (N=2690). We hebben onderzocht of de score van de VAT de voorspellende waarde verbetert voor het ontwikkelen van dementie in de komende 4-6 jaar voor degenen bij wie de MMSE score daalde in de eerste twee jaar van de studie. In totaal ontwikkelden 157 van de 2690 (5.8%) geïncludeerde deelnemers dementie. Een daling van twee of meer punten op de MMSE score over twee jaar tijd was geassocieerd met een odds ratio van 3.55 (95% betrouwbaarheidsinterval (BI) 2.5-5.0) op het ontwikkelen van dementie in de toekomst. Een
opvallende bevinding was dat deelnemers met een daling van twee of meer punten op de MMSE score over twee jaar tijd gecombineerd met een suboptimale score op de VAT (5 punten of minder) een odds ratio hadden van 9.55 (95% BI 5.9-15.4) op het ontwikkelen van dementie in de toekomst. Deelnemers met een vergelijkbare daling van de MMSE score en de maximale score op de VAT (6 punten) hadden een odds ratio van 3.61 (95% BI 2.1-6.3) op het ontwikkelen van dementie in de toekomst. Hieruit blijkt dat een korte en eenvoudige test zoals de VAT een substantiële toegevoegde waarde kan hebben bij het onderscheiden van ouderen met een verhoogd risico op het ontwikkelen van dementie.

Hoge bloeddruk (hypertensie) is een van de belangrijkste risicofactoren voor het ontwikkelen van cardiovasculaire ziekten, maar ook voor het ontwikkelen van dementie. Sommigen vrezen dat een bloeddrukverlaging kan leiden tot cerebrale hypoperfusie en daarmee het risico op dementie juist kan verhogen. Dit wordt in de literatuur tevens ondersteund door observationele data die een verhoogd risico op dementie laten zien bij mensen met een lage bloeddruk. Om de hypothese te testen dat een lage bloeddruk door gebruik van antihypertensiva cognitieve functies nadelig beïnvloedt, hebben we in hoofdstuk zes de literatuur systematisch onderzocht met betrekking tot de effecten van het stoppen van ten minste één antihypertensivum op de incidentie van dementie en cognitieve achteruitgang. Helaas is kwalitatief hoogwaardig onderzoek naar dit onderwerp schaars en konden wij slechts twee studies includeren in deze Cochrane review. Geen van deze twee studies hebben het nieuw voorkomen van dementie in de eigen studiepopulatie onderzocht, dus wij konden geen conclusies trekken over het effect op het ontwikkelen van dementie. Cognitie werd in de beide studies op zeer verschillende manieren gemeten, wat een meta-analyse onmogelijk maakte. Het stoppen van antihypertensieve medicatie had echter in de afzonderlijke studies geen significant effect op de cognitie.

In hoofdstuk zeven worden de belangrijkste bevindingen van dit proefschrift samengevat en bediscussieerd in de context van de meest recente wetenschappelijke literatuur en de implicaties voor toekomstig onderzoek worden uiteengezet.
AUTHOR CONTRIBUTIONS

Chapter 2: SJ, CB were responsible for the drafting of the manuscript. ER, MK, SA, HS, EPMvC and BvG were responsible for the study conception. MvD and BvdG were responsible for the software development. All authors critically revised the manuscript and approved the final version for publication.

Chapter 3: ER and SJ were responsible for the drafting of the manuscript. ER, MK, SA, HS, CB, WAvG, EPMvC and BvG were responsible for the study conception. All authors were responsible for the study design and provided professional or statistical support. All authors critically revised the manuscript and approved the final version for publication.

Chapter 4: SPM and LWW designed the study. SJ was responsible for the drafting of the manuscript. RC converted the data. SJ did the analysis with statistical support of MPH. All authors critically revised the manuscript and approved the final version for publication.

Chapter 5: WAvG designed the study. SJ conducted the statistical analysis and literature search and wrote the article. All authors contributed intellectually to the writing or revising of the manuscript, and approved the final version for publication.

Chapter 6: SJ and JH conducted study selection, data extraction, data analysis and produced an initial draft of the review, amended in accordance with TQ and ER’s comments. ER assisted in resolving any conflicts in study selection. TQ and ER provided supervision and support to SJ and JH, revising the review drafts in preparation for submission. All authors approved the final version of the manuscript for publication.
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LIST OF PUBLICATIONS

This Thesis


Improving prediction of dementia in primary care - the incremental value of the Visual Association Test to the Mini Mental State Examination – a cohort study. S Jongstra, WA van Gool, EP Moll van Charante, J van Dalen, LSM Eurelings, E Richard, SA Ligthart, manuscript submitted


Other

Appendices


PHD PORTFOLIO

Name: Susan Jongstra
PhD period: January 2014 – December 2016
Promotor: Prof. Dr. W.A. van Gool
Copromotores: Dr. E. Richard, Dr. E.P. Moll van Charante
Department: Neurology

PHD TRAINING

General courses

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**TEACHING**

**Lecturing**

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**Tutoring, mentoring, supervising**

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**PARAMETERS OF ESTEEM**

Nominated VasCog 2016 Young Investigator Poster Award 2016
ABOUT THE AUTHOR

Susan Jongstra (1986, Maarssen, the Netherlands) graduated in 2004 from Broklede College in Breukelen. Afterwards, she studied psychobiology at the Faculty of Science, Mathematics and Informatics of the University of Amsterdam. In addition, she started to study medicine at the Academic Medical Center in Amsterdam in 2006.

In 2010, for her medical research internship, Susan spent five months at the Department of Neurobiology of the Karolinska Institutet in Stockholm, Sweden. After two years of clinical rotations she travelled to Paramaribo, Suriname, for one of her final internships in Emergency Medicine. She obtained her medical degree cum laude in 2013.

After graduation, Susan has worked for one year as a resident at the Neurology Department of the Spaarne Hospital (currently Spaarne Gasthuis), Hoofddorp. In 2014, she started her PhD research on cardiovascular prevention with eHealth at the Department of Neurology under supervision of Dr. Edo Richard, Dr. Eric P. Moll van Charante and Prof. dr. W.A. van Gool. During her PhD research, she became even more fascinated with the complex world of neurons and brain. As a result, in January 2017, Susan has started her training to become a neurologist at the Academic Medical Center in Amsterdam.
ACKNOWLEDGEMENTS (DANKWOORD)

Toen ik in november 2013 een onverwacht mailtje van Edo Richard kreeg over een mogelijk promotietraject in het AMC had ik nooit kunnen denken dat ik drieënhalf jaar later mijn proefschrift zou verdedigen. Vele hoogtepunten, maar zeker ook dieptepunten hebben dit promotietraject gekenmerkt. Promoveren was voor mij de methode om mijzelf en anderen nog beter te leren kennen. Dat mijn promotietraject uiteindelijk tot een opleidingsplaats in het AMC heeft mogen leiden is de kers op de taart. Naast het mooiste, liefste en leukste nieuwe kersje in mijn leven dan….

Allereerst wil ik alle deelnemers van HATICE, preDIVA en iVitality bedanken voor deelname aan het wetenschappelijk onderzoek. Zonder deelnemers geen data en zonder data geen promotie. Zeker op oudere leeftijd deelnemen kan soms een hele opgave zijn, maar gelukkig is die bereidwilligheid er voor deze studies genoeg geweest.


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Appendices


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