eHealth in cardiovascular risk management to prevent cognitive decline
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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.

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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)\cite{70} or the Montreal Cognitive Assessment (MoCA)\cite{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\cite{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\cite{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.
Chapter 1

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.
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