eHealth in cardiovascular risk management to prevent cognitive decline

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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 (Sys-tematic 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?

Figure 1. The HATICE research consortium

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(28). 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 therefor 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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