Towards dementia prevention

Risk factors and lifestyle behaviour change

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Towards dementia prevention: risk factors and lifestyle behaviour change

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General introduction

The focus of this thesis is the prevention of dementia in middle-aged and older adults by targeting lifestyle-related risk factors for dementia. Dementia is a syndrome characterised by progressive cognitive impairments, behavioural and personality changes that interfere with daily functioning. It has serious physical, psychosocial and economic consequences for the people living with dementia, their caregivers and for society as a whole[1]. Due to global ageing, the number of 55 million people living with dementia today is expected to increase to over 130 million in 2050. Much of the increase will occur in low- and middle-income countries (LMIC)[2].

Although the clinical picture of dementia has been recognised for centuries, views on its pathophysiology have shifted over the years, as I will describe in more detail in ***chapter 2*** of this thesis. It is currently perceived that both genetic factors, such as carrying the ApoeE4 allele, and vascular factors are involved in the development of brain pathologies, including plaques, tangles and vascular lesions[3-5]. These pathologies increase the likelihood of developing dementia[6], but can only in part explain the onset and course of the disease.

In absence of curative treatment options, primary prevention may be an important strategy to delay dementia onset and thereby reduce its future prevalence[7, 8]. Observational studies suggest that dementia is associated with multiple potentially modifiable factors, which could serve as a target for prevention. These modifiable risk factors include blood pressure, Body Mass Index (BMI) and dyslipidaemia[9-14], diabetes mellitus[15], smoking[16], physical inactivity[17], cognitive inactivity[18], poor diet[19] and low educational attainment[20]. Due to the high prevalence of these risk factors and their interactions, even modest improvements on the individual level may lead to a substantial reduction of dementia cases at the population level[21].

Dementia prevention trials

To date, intervention studies that aim to reduce dementia risk by targeting individual risk factors have shown inconsistent results. As exposure to a combination of modifiable risk factors may yield a synergistic effect on dementia risk[22, 23], several multi-domain interventions, targeting multiple dementia risk factors simultaneously, have been performed over the past years. The preDIVA trial compared the effect of intensive nurse-led multi-domain cardiovascular care with care as usual on dementia and disability outcomes in 3526 older adults. After 6-8 years, no significant effect was observed on both outcomes[24]. Two other large multi-domain intervention studies using cognitive functioning as primary

outcome showed inconsistent results with slightly more improvement of the intervention compared to the control condition over 2-3 years[25, 26]. Thus, despite promising results from observational studies, these three trials have failed to provide convincing evidence that multi-domain interventions reduce the risk of cognitive decline and incident dementia, although point-estimates consistently suggest a small protective effect.

There are several potential explanations for the gap between results from observational studies and dementia prevention trials, as I will discuss in ***chapter 2***. It is conceivable that the lack of effect in the three trials was explained by a relatively high age, ranging from 60 to 78 years, which may have been too high to detect an effect of the intervention. Another potential explanation is the small window for risk factor improvement, as all three trials were performed in high-income countries (HIC) with high-quality cardiovascular risk management[27]. We took these and other methodological issues that have been associated with the design of dementia prevention trials into account for the design of the multi-domain Prevention Of Dementia Using Mobile Phone Applications (PRODEMOS) trial, aiming to include 2400 participants in the United Kingdom (UK) and China. PRODEMOS participants are aged between 55 and 75 years, have an increased dementia risk and have a low socioeconomic status (SES) (in the UK only). They are randomised between a coach-supported smartphone application, facilitating self-management of dementia risk factors, and a control application without a coach and lacking other interactive features. The main outcome is the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score, assessed after 18 months of intervention[28]. For this proof-of-concept study, we aimed to select individuals who are not too old to benefit from the intervention. Also, we selected individuals with an elevated dementia risk in underserved populations to further increase the potential efficacy. I will discuss the design of the PRODEMOS randomised controlled trial in more detail in ***chapter 3***.

Towards a tailored intervention

Long-term adherence to lifestyle and medication regimens is one of the main challenges of lifestyle-related prevention strategies, illustrated by sustained adherence rates of approximately 50% in chronic diseases[29, 30]. Patient self-management and digital health are two key elements of the PRODEMOS intervention that may have the potential to enhance long-term adherence to the intervention[31].

In self-management, patients actively manage their health, whereas healthcare workers take a supportive role, offering health education and other tools needed to stimulate the patient's autonomy[32, 33]. Self-management behaviours are likely affected by patient characteristics such as ethnicity and educational level[34, 35]. For example, needs regarding lifestyle support and barriers for healthy behaviours appear to differ between people with low and high SES[36-38]. In order to develop an effective lifestyle intervention, it is necessary to tailor the intervention to the needs and wishes of the target population[39]. Targeting two different populations in the PRODEMOS trial (i.e. older adults in Beijing, China, and low-SES older adults in the UK), we involved both target groups in the very early phases of study development. ***Chapters 4*** and ***5*** of this thesis describe two interview studies, assessing the attitudes and views on healthy lifestyle interventions for the prevention of dementia among older people with low SES in the Netherlands and older people in Beijing, respectively.

Digital health is another novel approach to potentially facilitate adherence to lifestyle interventions. Web-based interventions are relatively cheap and widely available[40], and have the potential to improve cardiovascular risk factors in middle-aged and older adults[41]. The Healthy Ageing Through Internet Counselling in the Elderly (HATICE) trial recently demonstrated that a coach-supported internet intervention can improve cardiovascular risk factors in older adults[42]. As smartphone penetration rates are rising worldwide[43], mobile health (mHealth) interventions are increasingly viewed as a promising method for health delivery in underserved populations[44], including populations in LMIC and populations with low SES in HIC. However, the evidence available to date suggests that long-term engagement with mHealth lifestyle interventions is often low[45, 46], and the frequency of using a health app typically declines rapidly over time[47]. As a certain degree of engagement is needed for intervention effectiveness, developing an intervention that can successfully reach and engage the target population over a longer period of time is one of the main challenges in the PRODEMOS project. Involving end-users and prioritising their needs during the development process has been associated with more appropriate app design and success of the intervention[48, 49]. ***Chapter 6*** describes the development of the PRODEMOS mHealth intervention, attempting to optimise engagement intensity and duration by involving end-users and other stakeholders throughout the process.

Dementia risk factors in old age

While in midlife dementia risk is associated with high values for cardiovascular risk factors including blood pressure, cholesterol and BMI, these relationships are less straightforward later in life. In late life, these relationships may follow an inverse or U-shaped curve, with both high and low values imposing increased dementia risk[9, 12, 50-56]. The exact nature of these contrasting relationships is still unclear, however, as they have been described for a variety of risk factors and outcomes such as cardiovascular disease and mortality, they may reflect an overarching phenomenon involving all these risk factors simultaneously. Possibly, low values for these risk factors are signs of a state of impaired homeostasis across a range of physiological processes and organ systems, contributing to the development of dementia. Alternatively, the relationship between low values for cardiovascular risk factors and dementia onset may be retro-causal, with low values being early manifestations of neurodegeneration. Other explanations, related to study methodologies, may be conceivable, such as the competing risk of death or survival bias, wherein participants who survive to old age despite high values of cardiovascular risk factors may be less susceptible to their potential negative effects.

To date, it is unknown whether older adults with a combination of low values for cardiovascular risk factors have a further increased dementia risk than can be explained by a dose-response relationship. Better identification of older adults at increased dementia risk is important in clinical practice, as current prevention guidelines rely on risk factors in midlife. Using data from the Prevention of Dementia by Intensive Vascular care (preDIVA) observational extension (POE) study, we assessed the relationships of low blood pressure, low BMI and low non-high density lipoprotein (non-HDL) cholesterol with dementia risk, and whether the combination of these factors signal increased risk beyond the sum of their individual associations (***chapter 7***).

Antihypertensive medication and dementia risk

The high prevalence and widely available treatment options render hypertension in particular a suitable target for dementia prevention strategies. A recent meta-analysis of 14 RCTs found that blood pressure lowering with antihypertensive medication (AHM) is associated with a reduced risk of dementia and cognitive decline as compared with control[57]. Beside blood pressure-lowering effects, certain AHM classes may have class-specific beneficial effects on dementia

risk[58-62]. Angiotensin receptor blockers (ARBs) and certain calcium channel blockers (CCBs), which are most consistently associated with a decreased dementia risk, stimulate angiotensin 2 and angiotensin 4 receptors in the brain, potentially reflecting neuroprotective effects[63, 64]. For selection of a first-choice antihypertensive agent, current hypertension guidelines often leave room for the physician's own preference. Therefore, if observations on a potential protective effect of these AHM groups on dementia incidence can be further validated, this could contribute to further personalization of hypertension management.

It is to date unclear whether the associations between use of ARBs and CCBs and dementia risk are sustained over long periods, because most findings are based on studies with a maximum follow-up of seven years[62]. The POE study yields longitudinal data on AHM use over up to twelve years of follow-up, allowing for assessment of both short- and long term associations between use of different AHM classes and dementia risk. ***Chapter 8*** describes the associations between use of CCBs, ARBs and AT II-stimulating AHM as a group (i.e. thiazides, dihydropyridine CCBs and ARBs) with dementia, compared with use of other classes, over seven and more than ten years of follow-up.

Part I of this thesis addresses the self-management of lifestyle-related dementia risk factors and the potential supportive role for digital health. The studies in part I are performed in preparation of the currently ongoing PRODEMOS trial (Box 1). **Part II** focuses on risk factors for dementia in old age, and on the relationship between use of specific antihypertensive medication classes and dementia in older adults. For the studies described in part II, we used data gathered in the (POE) study (Box 1).

Box 1. Overview of preDIVA and PRODEMOS study, which were the basis for this thesis

	preDIVA	**PRODEMOS**
Sample size	3,526	2,400[a]
Study period	2006-2018	2021-2023
Recruitment area	The Netherlands	United Kingdom and Beijing, China
Age range	70-78	55-75
Main inclusion criteria	Not demented	Not demented; ≥2 dementia risk factors[b]; smartphone possession; low SES[c]
Randomisation	Cluster randomisation	Individual randomisation
Intervention condition	Nurse-led intensive vascular care	Interactive, coach-supported smartphone application, facilitating self-management of dementia risk factors
Control condition	Care as usual	Static smartphone application without coach support
Intervention period	6-8 years	18 months
Follow-up period	6-8 years; 10-12 years[d]	18 months
Primary outcome	Dementia; disability	CAIDE dementia risk score; implementation outcomes
Main secondary outcomes	Cardiovascular disease; vascular factors; cognitive decline; depression	Cost-effectiveness; all-cause mortality; dementia; MCI; stroke; individual components of CAIDE

[a] planned sample size; [b] dementia risk factors include insufficient physical activity, active smoking, depression, manifest cardiovascular disease, diabetes mellitus, hypertension, obesity, and dyslipidaemia; [c] applies to UK only, defined as living in a postal code area ranked as equal to or less than the lowest 3rd decile of the Index of Multiple Deprivation; [d] follow-up period of preDIVA was 6-8 years, follow-up period of preDIVA observational extension was 10-12 years. CAIDE = Cardiovascular Risk Factors, Aging and Dementia; MCI = mild cognitive impairment; SES = socioeconomic status.

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PART I

Lifestyle behaviour change to prevent dementia using mHealth

2

A population perspective on the prevention of dementia

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Abstract

The global number of people living with dementia is expected to increase to 130 million in 2050. Based on extensive evidence from observational studies, it is estimated that about 30% of dementia cases may be attributable to potentially modifiable risk factors. This suggests that interventions targeting these factors could perhaps delay or prevent the onset of dementia. Since the vast majority of people with dementia live in low- and middle-income countries, such interventions should preferably be easy and affordable to implement across a wide range of health care systems. However, to date, results from dementia prevention trials do not provide convincing evidence that treatment of these risk factors reduces the risk of dementia. The current paper aims to give an overview of available evidence for the potential for dementia prevention. In particular, we discuss methodological issues that might complicate the development of effective prevention interventions and explore the opportunities and challenges for future dementia prevention research. Currently, several ongoing and planned trials are testing the effect of multi-domain interventions on dementia risk in high-risk populations. It is desirable that future dementia strategies also target the wider population, through interventions on the individual, community, and population level, in order to constrain the growing prevalence of dementia worldwide.

Changing perspectives on late-life dementia

The clinical picture of dementia has been recognized for centuries, but throughout time the theories on its causes have varied widely. Dementia received specific attention in 1907, when Alois Alzheimer wrote his famous case report "About a peculiar disease of the cerebral cortex"[1]. His findings of plaques and tangles in the brain of a 51-year old patient with progressive cognitive problems were included in a leading psychiatry textbook by Emil Kraepelin, and the condition was referred to with the term "Alzheimer's disease" (AD)[2]. From then on, AD was considered to be a rare condition, causing dementia through plaques and tangles in relatively young people. Cognitive decline in the last decades of life, at the time referred to as senile dementia, was considered to be attributable to atherosclerosis, and stroke and was thought of as a distinct condition[3].

From the early seventies onwards, perceptions of the pathogenesis of senile dementia shifted from vascular mechanisms to AD pathology, based on the discovery of extensive amounts of extracellular amyloid depositions (plaques) and intracellular depositions of hyperphosphorylated tau-protein (tangles) in the brains of older people with dementia[4]. Consequently, the sharp distinction between pre-senile and senile dementia faded. In the early nineties, it was discovered that the specific e4 allele of Apolipoprotein E (APOEε4) was associated with both early- and late-onset dementia[5, 6], supporting the hypothesis that Alzheimer's disease was the predominant cause of both early- and late-onset dementia. At this time, vascular dementia was still considered a separate, less frequent cause of dementia.

The role of vascular pathology in the development of late-life dementia regained interest in the late nineties, when several epidemiologic and radiologic studies reported a strong relationship of cardiovascular risk factors and disease with impaired cognitive functioning[7, 8]. These findings were supported by neuropathological findings. Examination of the brains of 102 elderly nuns suggested a strong interaction effect on cognitive functioning between the presence of AD pathology and lacunar strokes[9]. A large autopsy study in a population-based cohort in the United Kingdom, with a median age of 85 at death, showed that most dementia patients had a mixture of cerebrovascular and AD pathology, whereas subjects without dementia often had a considerable level of pathologies as well, or no pathologies at all[10]. Since then, numerous epidemiologic studies have investigated the relationship between vascular risk factors or vascular disease, and stroke development, and late life dementia[11-13]. Based on several more recent studies, it is perceived that the presence and mutual interaction of genetic factors,

such as carrying the APOEε4 allele, and vascular factors are involved in the development of multiple brain pathologies, including amyloid plaques, tangles containing hyperphosphorylated tau, and different vascular lesions[14-16]. These brain pathologies all increase the likelihood to develop mild cognitive impairment (MCI) and dementia[17], but they are not sufficient to fully explain either onset, course, or specific clinical symptoms.

Exploring the window of opportunity for dementia prevention

The concept of dementia caused by multifaceted brain disease implies a wide range of possible strategies for dementia prevention and treatment. The need for such strategies is emphasized by the large number of people living with dementia worldwide, which is expected to rise from 47 million in 2015 to over 130 million in 2050, largely due to the increasing life expectancy[18]. It is estimated that 90% of dementia patients are older than 75 years, and 75% are older than 80 years of age[19]. Strategies to prevent dementia among people without the disease could perhaps delay its onset and reduce the prevalence of dementia[20]. Since it is expected that by 2050 68% of all people with dementia live in low- and middle-income countries (LMIC)[18], such strategies should ideally be easy and inexpensive to implement on a large scale across a wide variety of health care systems.

Observational studies suggest a number of modifiable factors that are associated with dementia risk and could serve as a target for prevention. Elevated blood pressure, body mass index (BMI), elevated total cholesterol levels[21-26], diabetes mellitus[27], current smoking[28], depression[29], physical inactivity[30], cognitive inactivity[31], poor diet[32], and low educational attainment[33] are well-established factors that are independently associated with an increased risk of dementia. Even small improvements of the modifiable dementia risk factors on the individual level have the potential to lead to a substantial reduction of dementia cases at the population level, due to the high global prevalence of these risk factors[34]. By calculating population-attributable risks for seven well-established dementia risk factors (diabetes mellitus, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment), and taking inter-relatedness into account, it was estimated that 30% of all dementia cases worldwide can be attributed to these potentially modifiable risk factors[35], with low educational attainment, smoking, and physical inactivity carrying the strongest risk. This suggests a large window of opportunity for dementia prevention.

The high prevalence of these modifiable factors raises the question of whether population-based prevention strategies could reduce the prevalence of dementia. Over the years, many community programs have been designed to reduce cardiovascular disease (CVD) risk. Controlled before–after studies have shown that, in general, these programs can be effective at improving cardiovascular risk factors and, in some cases, reducing incident CVD and mortality[36]. Although risk factors are largely similar for CVD and dementia, no comparable studies have been performed to study the effect of community prevention programs on cognitive functioning or dementia. However, five large studies have compared dementia occurrence between two time points in well-defined geographical areas. Four of five studies showed a slight reduction of dementia prevalence, which could potentially be attributed to population-level investments, including improved education and better prevention and treatment of vascular conditions[37].

Dementia prevention trials

In the last two decades, several intervention studies have been performed to test the hypothesis that dementia can be delayed or prevented by improving individual risk factors or the overall dementia risk profile in people free from cognitive impairment at baseline. We distinguish single-domain interventions, targeting a single risk factor, and multi-domain interventions, targeting multiple dementia risk factors simultaneously. Below, we will discuss these studies with dementia as a primary or secondary outcome.

Single-domain interventions

Although the list of potential interventions is very long[38], we will restrict our overview to the interventions for which most robust evidence from clinical trials and meta-analyses is available. As such, we do not intend to be exhaustive here.

Treatment of hypertension may reduce the risk of dementia via blood pressure lowering mechanisms, but also through other, perhaps antihypertensive class-specific, effects[21, 39-41]. Results of hypertension trials have been encouraging, but are still inconclusive. A meta-analysis of four placebo-controlled trials of antihypertensive treatment with incident dementia as a primary outcome showed a combined risk ratio of 0.87 (95% CI 0.76 to 1.00; N = 16,595 individuals; n = 786 dementia cases), favouring treatment[42]. A more recent meta-analysis included nine blood pressure-lowering trials, including two lifestyle interventions, with a median follow-up of 3.9 years. The pooled risk ratio for incident dementia was 0.93 (95% CI 0.84 to 1.02; N = 57,682; n = 2131 dementia cases)[43]. The recently published

Systolic Blood Pressure Intervention Trial: Memory and Cognition in Decreased Hypertension sub-study (SPRINT-MIND) assessed whether intensive blood pressure treatment with any agent, aiming for levels lower than 120 mmHg, could reduce incident dementia compared with standard blood pressure control, aiming for levels lower than 140 mmHg, in over 9000 patients (50+) with hypertension. The trial was ended prematurely because of beneficial effects on cardiovascular events and all-cause mortality in the intervention group. Pre-planned secondary analyses showed no significant effect on probable dementia (HR 0.83; CI 0.67 to 1.04; N = 8563; n = 325 dementia cases), but a significant reduction of incident MCI (HR 0.81; CI 0.69 to 0.95; N = 8563; n = 640 probable MCI cases) after a median intervention period of 3.3 years and a median follow-up period of 5.1 years[44]. Taken together, despite promising results from observational studies[21], these two meta-analyses and recent RCT failed to provide convincing evidence that dementia can be delayed or prevented with blood pressure treatment, but point estimates consistently suggest a potential preventive effect.

Type 2 diabetes mellitus (T2DM) may increase dementia risk through different mechanisms including cerebrovascular damage, insulin resistance, and mitochondrial dysfunction[45, 46]. A recent systematic review identified seven randomized controlled trials to assess the effects of different T2DM treatment strategies on cognitive function and incident dementia[47]. Three studies were included in the efficacy analyses and used cognitive function or incident dementia as outcome measure. All three studies were at unclear risk of bias. Two of these studies compared intensive glycaemic control versus standard glycaemic control[48, 49]. There was no significant difference between the two groups with regard to the number of participants who declined by at least 3 points on the mini-mental state examination (MMSE) over five years (RR 0.98; CI 0.88 to 1.08; N = 11,140 individuals; 1 study), incident dementia (RR 1.27; CI 0.87 to 1.85; N = 11,140 individuals; n = 109 dementia cases; 1 study)[49], or MMSE score after 40 months (MD –0.01; CI –0.18 to 0.16; N = 2794 individuals; 1 study)[48]. The third study compared glibenclamide with repaglinide. After 12 months, a small advantage of glibenclamide on MMSE score was found (MD –0.90; CI –1.68 to –0.12; N = 156 individuals; 1 study)[50].

Despite observational evidence[43, 44], to date no trials have shown beneficial effects of cholesterol-lowering treatment on dementia risk. A systematic review identified two RCTs that compared the effect of a statin versus placebo on cognitive decline and incident dementia among individuals with increased cardiovascular risk. Both studies had a low risk of bias. No difference was found with regard to incident dementia (OR 1.00; CI 0.61 to 1.65; N = 20,536; n = 62 dementia cases; 1 study) between simvastatin and placebo. No effect of simvastatin or pravastatin was

found on cognitive function, assessed by five different cognitive tests[51]. According to current guidelines, a very high percentage of participants between 40 and 75 years old are eligible for statin prescription, with the aim to prevent cardiovascular disease[52]. Although the prevention of stroke can be expected to lower the risk of dementia, there is no direct evidence for this effect so far.

Physical activity is thought to decrease dementia risk through multiple mechanisms, including increased neurogenesis, angiogenesis, and synaptic plasticity and anti-inflammatory effects[53]. Moreover, physical activity can have beneficial effects on other factors that are associated with dementia risk, including obesity, dyslipidaemia, and high blood pressure. A recent systematic review investigated 32 trials with a follow-up of more than 6 months, to assess the effectiveness of physical activity interventions on cognitive function among adults without a diagnosis of cognitive impairment. Included studies targeting only physical activity involved aerobic training (six studies, 531 individuals), resistance training (three trials, 315 individuals), and tai chi (one trial, 93 individuals). Evidence from these trials was insufficient to draw any conclusion about a beneficial effect on cognitive function[54]. Because of the beneficial effects of physical activity on obesity and the risk of CVD, public health campaigns and public health initiatives to facilitate physical activity are widely applied. To date, whether this will reduce the risk of dementia remains uncertain.

Multi-domain interventions

Exposure to a combination of modifiable dementia risk factors may have a synergistic effect on risk of cognitive decline and dementia[55, 56]. Therefore, multi-domain interventions, targeting more than one risk factor, may be a more appropriate approach to study dementia prevention. In the past decade, several multi-domain trials have been performed, testing varying interventions across a wide range of sample sizes and follow-up times. We will discuss the main multi-domain intervention studies in terms of sample size and follow-up time with dementia, MCI, or cognitive decline as primary end-point (Table 1).

Table 1. Multi-domain dementia prevention trials

	preDIVA	FINGER	MAPT
Sample size	3,526	1,260	1,680
Age range	70-78	60-77	70+
Main inclusion criteria	Not demented[b]	Dementia risk score ≥6[a] Cognitive performance at mean or slightly lower level	Not demented[b] Memory complaints or limitations in daily living or slow gait speed
Intervention	Nurse-led intensive vascular care	Diet advice, exercise, cognitive training and vascular care	Cognitive training, advice on physical activity and nutrition, and vascular care +/- omega 3 polyunsaturated fatty acids
Intervention period	6-8 years	2 years	3 years
Follow-up period	6-8 years	2 years	3 years
Primary outcome	Dementia; disability[d]	Cognitive function[c]	Composite z-score of 4 cognitive tests[e]
Main secondary outcomes	Cardiovascular disease; vascular factors; cognitive decline; depression	Vascular and lifestyle factors; depressive symptoms; disability	Physical performance; depression

FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive impairment and Disability; MAPT: Multidomain Alzheimer Prevention Study; preDIVA: prevention of dementia by intensive vascular care. a assessed with Cardiovascular Risk Factors, Aging and Dementia risk score; b defined as no clinical diagnosis and a Mini-Mental State Examination > 23; c assessed with the Neuropsychological Test Battery; d assessed with the AMC Linear Disability Score; e items from the Free and Cued Selective Reminding test, Mini-Mental State Examination, Digit Symbol Substitution Test, and Category Naming Test.

The Dutch prevention of Dementia by Intensive Vascular Care (preDIVA)[57] cluster-randomized trial compared the effect of a 6-year, intensive, nurse-led multi-domain cardiovascular care intervention with usual care on the cumulative incidence of dementia and disability. 116 General practices were randomly assigned to one of the conditions. 3526 individuals without dementia, aged 70–78 years, participated. After a median follow-up of 6.7 years, primary outcome data were obtained in more than 98% of the participants. No significant effect was found of the intensive cardiovascular care on incident dementia (HR 0.92; CI 0.71 to 1.19; N = 3454 individuals; n = 233 dementia cases) and disability.

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)[58] compared the effect of a multi-domain intervention, including nutritional guidance, physical activity, cognitive training, and monitoring of modifiable dementia risk factors, with general health advice (control group) on cognitive function, assessed with an extensive neuropsychological test battery (NTB). 1260 Individuals without dementia, aged 60–77 years, with an increased dementia risk in terms of six or more points on the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score, were randomly assigned to either of the treatment arms. After two years, the intervention group showed a slightly

larger improvement on the standardized NTB compared with the control group (between-group difference in change score per year 0.022; CI 0.002 to 0.042; N = 1190 individuals).

The French Multidomain Alzheimer Preventive Trial (MAPT)[59] studied the effects of omega 3 polyunsaturated fatty acids and the effect of a multi-domain intervention, consisting of group sessions targeting cognitive training, physical activity, and nutrition on cognitive function. Participants were eligible when they were 70 years or older and either had subjective memory complaints, limitations in one instrumental activity of daily living, or slow walking speed. 1680 Participants were randomly assigned to one of four groups: the multi-domain intervention combined with omega 3 polyunsaturated fatty acids, the multi-domain intervention with placebo, and omega 3 polyunsaturated fatty acids with no other intervention or placebo alone. After three years, there were no significant differences in cognitive function, assessed with a composite score of four cognitive tests, between any of the treatment groups and the placebo alone group: between-group differences were 0.093 (95% CI 0.001 to 0.184; N = 1525 individuals) for combined intervention, 0.079 (95% CI –0.012 to 0.170; N = 1525 individuals) for the multi-domain intervention plus placebo group, and 0.011 (95% CI –0.081 to 0.103; N = 1525 individuals) for the omega 3 polyunsaturated fatty acids group.

Explaining the gap between observational and interventional studies

A substantial gap exists between the results from many observational studies, suggesting optimism, and the rather sobering results from dementia prevention trials. Hence, it could be that vascular factors have an association, rather than a causal relationship, with dementia risk. However, most of Hill's criteria for causation, such as consistency and plausibility[60], are met. Although the current evidence does not support a protective effect of preventive interventions for dementia, particularly for hypertension, there is a rather consistent signal in the direction of a preventive effect. Moreover, it is conceivable that methodological issues, which have been associated with the design of dementia prevention trials[61-63], lead to type II errors, masking "true" effects of multi-domain interventions, and causing apparent inconsistency with observational evidence.

Age of the target population and J-shaped curves

An important issue when designing a dementia prevention trial is the optimal age range of the target population. A target population that is too young would

require infeasible follow-up periods or sample sizes, due to the low incidence of dementia in younger age. Conversely, a target population that is too old would probably lead to decreased efficacy of the intervention, because the relationship between some risk factors and dementia becomes more complex with age[63]. The association between blood pressure during late-life and dementia is suggested to follow a U- or J-shaped curve, with both high and low values imposing increased dementia risk[64]. This is consistent with ample research on the relationship between blood pressure and cardiovascular disease[65]. With regard to BMI, a similar J-shaped relation with dementia risk is suggested in late-life, with elevated BMI levels being associated with lower, and being underweight with increased, dementia risk[66], suggesting a similar type of J-shaped curve as with blood pressure. Likewise, high total serum cholesterol concentrations in late-life have been associated with decreased dementia risk[24, 67]. It is unclear when the directions of these associations change. Nevertheless, it is conceivable that the target populations from the three multi-domain interventions described above, with age-ranges 60–77, 70+, and 70–78 years, respectively, were too old to benefit from the interventions. These complex relationships pose a major challenge for future dementia prevention trials. Clearly, one size does not fit all, but with regard to age, it is currently unclear what the optimal target values for blood pressure, BMI, and cholesterol might be.

Risk profile of the target population

The level of quality and accessibility of standard preventive care that is available for the target population affects the degree of contrast a trial may yield. Subgroup analyses of the preDIVA study show the strongest effects of the intervention in participants with untreated hypertension and in participants without history of cardiovascular disease[57]. It could well be that an effect of the intervention was not found in the three multi-domain intervention trials, because high-quality cardiovascular risk management was already available for both intervention and control participants. As such, future studies may need to target populations at high risk who lack access to high-quality preventive health care. Policymakers and health organisations alike may need to actively target those persons that are typically not represented in clinical trials, but are at highest risk.

Hawthorne and Treatment Effects in the Control Condition

Another challenge is the observed improvement on primary and secondary outcomes of the control group in some multi-domain intervention studies[57, 58]. This is illustrated by the decrease in blood pressure in both study arms of the preDIVA trial. The mean difference in systolic blood pressure between baseline and follow-up was 8.3 mmHg in the intervention group and 4.6 mmHg in the control group,

Tabel 2. Planned and ongoing multi-domain dementia prevention trials

	HATICE	Impact of Lifestyle Modification on Prevention of Dementia	MYB	PRODEMOS
Start of recruitment	March 2015	March 2016	May 2018	January 2020
Sample size	2,725	3,600	8,500	2,400
Recruiting countries	NL, Finland, France	Thailand	Australia	UK, China
Age range	65+	45-75	55-77	55-75
Main inclusion criteria	Not demented[a]; ≥2 cardiovascular risk factors	Thai nationality; no diagnosis of dementia, diabetes, COPD, cancer or CVD	No diagnosis of dementia or severe depression	Not demented[a], ≥2 dementia risk factors
Intervention	Coach-supported Internet platform for self-management of cardiovascular risk factors	Coach-supported computer program on diet, physical activity, alcohol drinking and smoking	Digital modules on physical activity, nutrition, peace of mind, and brain training	Coach-supported smartphone app for self-management of dementia risk factors
Intervention period	1.5 years	3 years	3 years	1.5 years
Follow-up period	1.5 years	10 years	3 years	1.5 years
Primary outcome	Composite z-score of SBP, LDL cholesterol and BMI	Incident dementia	Global cognition composite domain score[b]	CAIDE score; implementation outcomes
Main secondary outcomes	Individual factors from composite score; incident CVD	Incident T2DM, CVD, cancer, COPD, mortality	Incident dementia; dementia risk	Individual components of CAIDE score; disability; cost-effectiveness

BMI: body mass index; CAIDE: Cardiovascular Risk Factors, Aging and Dementia risk score; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; HATICE: Healthy Aging Through Internet Counselling in the Elderly; Impact of Lifestyle Modification on Prevention of Dementia: Impact of Lifestyle Modification on Prevention of Dementia, Chronic Kidney Disease, Diabetes, Chronic Obstructive Pulmonary Disease, Cancers and Cardiovascular Disease in a Thai General Population: Cluster Randomized Controlled Trial; LDL: low-density lipoprotein; MYB: Maintain Your Brain; NL = The Netherlands; PRODEMOS: Prevention Of Dementia Through Mobile Phone Applications; SBP: systolic blood pressure; T2DM: type 2 diabetes mellitus; UK = United Kingdom. [a]defined as Mini-Mental State Examination > 23; [b] Maintain Your Brain Battery.

suggesting initiation of treatment by a general practitioner or specialist or changes in lifestyle behaviour by the participant following the baseline measurements. Additionally, changed behaviour of participants or healthcare professionals as a reaction to the awareness of the study (Hawthorne effect) is likely to play a role[68]. Both mechanisms could mask the "true" contrast between the intervention and control condition, leading to type II errors.

Competing risk of death

Age is the most important risk factor for dementia. Starting at the age of 60, the incidence of dementia doubles with every 6.3 years increase in age[18]. It is likely that, due to shared risk factors, dementia prevention trials have beneficial effects on cardiovascular endpoints, and, as a consequence, on mortality. Therefore, effective multifactorial interventions could paradoxically increase dementia incidence rates when death is delayed. If not taken into account, this could lead to serious underestimation of the effectiveness of dementia prevention interventions.

Future directions

Strategies to deal with limited statistical power

When designing dementia prevention trials, sufficiently large sample sizes and/or long follow-up periods are paramount to reach statistical power, due to the time lag between the optimal timing of the intervention and dementia onset. Hence, given these preconditions, funding dementia prevention trials will remain a daunting challenge.

One potential approach towards longer follow-up is open label extension of studies, as was done in the Syst-Eur trial[13]. However, selective attrition will be a complicating factor for such observational extensions. Another strategy to overcome lack of power is to collaborate with other (international) research groups, enabling the design of multi-national trials and pooling of data of previous trials where possible and appropriate. An example is the European Dementia Prevention Initiative (EDPI) consortium, a collaboration of five European institutes, including the three research groups involved in the FINGER, MAPT, and preDIVA trials, respectively[69]. A third strategy could involve selection of a primary outcome that is likely to emerge earlier in life than dementia onset. Examples are cognitive impairment, existing dementia risk scores, or biomarkers presumed to reflect biological processes eventually leading to dementia. However, the uncertain association between biomarkers and cognition renders this a suboptimal primary outcome with regard to clinical relevance. A fourth solution could be to exclusively

target individuals with an increased dementia risk who are still free from cognitive impairments. Numerous strategies exist to estimate dementia risk, including the use of biomarkers, imaging[70], family history[71], and dementia risk scores[72, 73]. Obviously, from a population perspective, the use of (invasive) biomarkers is not feasible, certainly not in LMIC, but simple and readily available risk markers such as a positive family history or the presence of multiple dementia risk factors can be applied on a large scale at low cost. Some researchers have also used signs of cognitive decline to indicate high dementia risk. However, the latter approach is accompanied by a relatively high risk of including individuals with an early stage of dementia, in whom the intervention is less likely to be effective[74]. A fifth approach could be to target populations with poor access to preventive healthcare quality, such as in LMIC. These populations could be a promising target for lifestyle interventions, since the incidence of dementia is relatively high and the peak incidence is at younger age than in high-income countries (HIC)[18]. Moreover, the prevalence of dementia risk factors in these countries is higher than in HIC[75].

Ongoing and planned multi-domain dementia prevention trials

For successful implementation in LMIC, dementia prevention interventions should ideally be easily available, accessible, and affordable. These criteria are often met by web-based interventions, such as electronic health (eHealth) and mobile health (mHealth), especially because the majority of the world population uses internet these days and in countries with limited internet access it is increasing rapidly[76]. Four currently ongoing or planned multi-domain interventions will be testing the effectiveness of such digital dementia prevention interventions (Table 2).

The ongoing multi-national Healthy Aging Through Internet Counselling in the Elderly (HATICE) trial, performed by the EDPI consortium, is comparing a coach-supported, interactive internet platform, stimulating self-management of cardiovascular risk factors, with a sham platform without interactive features, for 18 months. The study population consists of approximately 2724 individuals, aged 65 years or older, and with an increased cardiovascular risk. The primary endpoint is a composite cardiovascular risk score, including systolic blood pressure, low-density-lipoprotein, and BMI. Cognitive function is a secondary outcome[77].

An ongoing cluster-randomized trial in Thailand with 3600 participants is comparing a three-year digital, coach-supported lifestyle modification intervention on four domains (diet, physical activity, alcohol drinking, and smoking) with care as usual. Participants are eligible when they are between 45 and 75 years of age and do not have a diagnosis of dementia, chronic kidney disease, diabetes, chronic obstructive pulmonary disease, cancer, or CVD. The primary outcome, measured

after ten years, is incident dementia. Cognitive function, assessed with the MMSE, is one of the secondary outcomes[78].

The Maintain Your Brain (MYB) trial is comparing a digital platform with interactive modules on physical activity, diet, mental health, and cognitive training with a digital platform containing static information about dementia risk factors. The study population will consist of approximately 8500 individuals, recruited through an existing Australian cohort of non-demented community dwelling individuals aged between 55 and 77 years. The primary outcome, measured after three years, is cognitive change on a composite score of cognitive functioning. Secondary outcomes are incident dementia and change in dementia risk[79].

The planned Prevention Of Dementia Through Mobile Phone Applications (PRODEMOS) trial, initiated by the EDPI consortium, takes place in the United Kingdom (UK) and in Beijing, China[80]. A total of 2400 individuals, aged 55–75 years, with an increased dementia risk profile, and of low socioeconomic status in the UK, are randomized between a coach supported, interactive smartphone application, stimulating self-management of dementia risk factors; and a sham application without interactive features. The primary endpoint, measured after 18 months, is the CAIDE dementia risk score.

World Wide Fingers is an interdisciplinary network that arose from the FINGER trial. The multi-domain lifestyle intervention showed a modest beneficial effect on cognitive function after two years in a Finnish geriatric population. The same intervention is going to be tested in the United States, in rural China, in Singapore, and in several European countries[81].

Population-based approaches

Most of the ongoing trials are testing individual interventions in specific high-risk populations. However, the majority of dementia cases occur in individuals with low or intermediate risk[82]. It is therefore desirable that future dementia prevention strategies also target the wider population. Interventions targeting (a subgroup of) the population as a whole require different strategies. In addition to the individual level, primary prevention can be delivered at the community or the population level. Public health interventions that target common risk factors, such as discouraging smoking and encouraging a healthier lifestyle, can be implemented at several levels, and may include media campaigns, legislative changes, and preventive measures in working spaces and the community. Evaluating the effects of such interventions is complex, and may require different approaches than the classical parallel group randomised controlled trial. In addition to alternative

methodologies to evaluate effectiveness, measures related to implementation will have to be taken into account, and such studies may require alternative large-scale governmental funding. Since risk factors for dementia largely overlap with risk factors for CVD, implementation in existing healthcare would probably benefit from an integrated approach, targeting dementia, CVD, and other non-communicable diseases[83].

Conclusions

Although results from observational studies suggest optimism, to date, results from dementia-prevention trials do not provide convincing evidence that treatment of these risk factors reduces the risk of dementia. However, some interventions, especially in intensive hypertension management, appear promising in the reduction of dementia risk and cognitive decline. Taking into account that the majority of dementia cases occur in LMIC, interventions should be easy and affordable to implement. Currently, several ongoing trials are testing the effectiveness of eHealth and mHealth interventions in high-risk individuals. Further implementation research on broadly available preventive interventions in the general population is warranted, to achieve global impact on dementia prevalence.

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3

Prevention of Dementia using Mobile Phone Applications (PRODEMOS): protocol for an international randomised controlled trial

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Abstract

Introduction

Profiles of high risk for future dementia are well understood and are likely to concern mostly those in low-income and middle-income countries and people at greater disadvantage in high-income countries. Approximately 30%–40% of dementia cases have been estimated to be attributed to modifiable risk factors, including hypertension, smoking and sedentary lifestyle. Tailored interventions targeting these risk factors can potentially prevent or delay the onset of dementia. Mobile health (mHealth) improves accessibility of such prevention strategies in hard-to-reach populations while at the same time tailoring such approaches. In the current study, we will investigate the effectiveness and implementation of a coach-supported mHealth intervention, targeting dementia risk factors, to reduce dementia risk.

Methods and analysis

The prevention of dementia using mobile phone applications (PRODEMOS) randomised controlled trial will follow an effectiveness–implementation hybrid design, taking place in the UK and China. People are eligible if they are 55–75 years old, of low socioeconomic status (UK) or from the general population (China); have ≥2 dementia risk factors; and own a smartphone. 2400 participants will be randomised to either a coachsupported, interactive mHealth platform, facilitating selfmanagement of dementia risk factors, or a static control platform. The intervention and follow-up period will be 18 months. The primary effectiveness outcome is change in the previously validated Cardiovascular Risk Factors, Ageing and Incidence of Dementia dementia risk score. The main secondary outcomes include improvement of individual risk factors and cost-effectiveness. Implementation outcomes include acceptability, adoption, feasibility and sustainability of the intervention.

Ethics and dissemination

The PRODEMOS trial is sponsored in the UK by the University of Cambridge and is granted ethical approval by the London–Brighton and Sussex Research Ethics Committee (reference: 20/ LO/01440). In China, the trial is approved by the medical ethics committees of Capital Medical University, Beijing Tiantan Hospital, Beijing Geriatric Hospital, Chinese People's Liberation Army General Hospital, Taishan Medical University and Xuanwu Hospital. Results will be published in a peer-reviewed journal.

Introduction

With global ageing, the prevalence of dementia is expected to increase to over 130 million in 2050, especially in low-income and middle-income countries (LMIC) and in people from low socioeconomic status (SES) background in high-income countries (HIC)[1, 2]. Strategies need to be developed that aim to reduce the risk of dementia—many of which will be at community and population level, but those that are individually based must be effective, affordable and easily implementable across various healthcare settings.

Up to 40% of dementia cases are estimated to be attributable to potentially modifiable risk factors[3], of which 10%–20% are cardiovascular risk factors including hypertension, midlife obesity, dyslipidaemia, diabetes, smoking and physical inactivity[4-6]. To date, intervention studies aiming to reduce dementia risk by targeting one or more of these risk factors have shown inconsistent results[7, 8]. Results from randomised controlled trials (RCT) on blood pressure-lowering treatment have suggested a beneficial effect on dementia risk, although not consistently and convincingly[9-11]. Since the presence of multiple risk factors may pose an additive or even synergistic effect on dementia risk[12, 13], targeting several risk factors simultaneously may be more effective. The only study to date designed to address this question using dementia as primary outcome did not show a statistically significant effect after 6–8 years of intervention, although subgroup analysis suggested benefit for those with untreated hypertension at baseline[14].

A considerable challenge when designing a dementia prevention trial is the time lag between the optimal timing of the intervention and the onset of dementia. Using incident dementia as primary outcome requires large sample sizes and/or long follow-up periods to reach statistical power[15, 16]. Dementia risk scores could be used as a proxy, especially in trials with follow-up periods up to several years. Another challenge, possibly explaining the neutral results of intervention studies so far, is the small window for risk factor improvement given a background of high-quality cardiovascular risk management in HIC where these studies were performed[17]. This lends further support for targeting people in LMIC and low-SES populations in HIC.

Digital health interventions have the potential to improve cardiovascular risk factors in middle age and beyond, especially when offered with human coaching (blended care)[18]. In the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) trial, we recently demonstrated that a coach-supported internet intervention facilitating self-management of cardiovascular risk factors can reduce

older adults' cardiovascular risk over a static control platform, both in high and low socioeconomic participant subgroups[19]. Currently, digital health interventions are increasingly offered through smartphones. Smartphone penetration rates are especially high in HIC[20], also among people with low SES. In 2018, 67% of people with the lowest SES in UK owned a smartphone[21]. Approximately 40%–50% of the LMIC population is connected to mobile internet[20, 22], with rates up to 60% in China[23]. This renders mobile health (mHealth) a promising method for health delivery in underserved populations, including the improvement of cardiovascular risk factors[24, 25].

We have developed a coach-supported mHealth intervention to reduce dementia risk by addressing common cardiovascular risk factors via lifestyle changes, building on the existing HATICE internet platform. Our aim is to assess the effectiveness and implementation of this smartphone intervention on dementia risk in older people at increased risk of dementia from a low-SES population in the UK and from the general population in Beijing, China.

Methods

Study design

Prevention of dementia using mobile phone applications (PRODEMOS) is a multinational, prospective, randomised, open-label blinded endpoint trial with 18-month intervention and follow-up. The study follows a hybrid effectiveness–implementation design, taking a dual focus on assessing effectiveness and implementation outcomes[26, 27]. The Amsterdam University Medical Centre (Amsterdam UMC) is the coordinating centre.

Study population and recruitment

The study population will consist of community-dwelling older adults aged 55–75 years old, of low SES in the UK and of any SES in China, who have ≥2 dementia risk factors and own a smartphone. Low SES in the UK is operationalised as living in a postal code area ranked as equal to or less than the lowest third decile of the index of multiple deprivation[28]. Eligibility criteria are similar for both countries, except for criteria for obesity, based on differences in national prevention guidelines[29] (box 1).

Recruitment will take place in the Eastern Clinical Research Network (National Institutes of Health Research) region of the UK and in the Beijing and Tai'an cities, China. In the UK, recruitment has started in January 2021 and will be undertaken

by approximately 10–15 general practioner (GP) practice. A random computer selection of participants living in the designated postal code areas meeting the age criterion and having ≥1 known dementia risk factor according to the GP registry will be approached through an information letter, inviting them to contact the local study centre. In China, participants will be recruited from seven hospitals through advertisements on hospital websites, targeted recruitment via local social media (WeChat) or direct approach by nurses and physicians. In China, recruitment is expected to start mid-2021.

Intervention and control condition

Central to our study is the PRODEMOS platform, which interconnects the assessor portal, the participant app and the coach portal (figure 1). The assessor portal facilitates blinded collection of baseline and outcome assessments for all participants. The intervention and control condition are both delivered through a smartphone app, which, in the case of intervention participants, allows communication with the coach portal. Data from the assessor portal, participant app and coach portal can be extracted through a researcher portal and stored in a central database. The PRODEMOS platform was built in close collaboration between software developers and researchers from Amsterdam UMC, University of Cambridge, Brighton and Sussex Medical School, Capital Medical University in Beijing, health coaches and representatives of the target population from both countries. The internet platform previously used in the HATICE trial served as the basis for the PRODEMOS platform[30]. In addition to the transition of the participants' end into a mobile app, adjustments were made to the platform in repeated cycles of interaction with end users. In an iterative process, experiences, needs and wishes from the target population and health coaches regarding the app and coach support, gained through interviews and focus groups, served as a guideline for further development.

Box 1. Overview of in- and exclusion criteria.

Inclusion criteria

- Age ≥ 55 years ≤ 75 years
- Living in a postal code area ranked as equal to or less than the lowest 3rd decile of IMD[a]
- Good proficiency of the national language (English in UK, Mandarin in China)
- Possession of a smartphone
- ≥ 2 Dementia risk factors:
- Insufficient physical activity (self-reported intermediate or vigorous activity of < 150 minutes per week)
    - Active smoking (self-reported use of any sort of tobacco in any quantity)
    - Depression:
        - Current diagnosis by specialist or GP or;
        - History of treatment for depression (i.e. drug therapy or psychotherapy)
    - Manifest cardiovascular disease, as diagnosed by specialist or GP
    - Diabetes mellitus:
        - Diagnosed by specialist or GP or;
        - Use of insulin or other blood glucose-lowering medication
    - Hypertension:
        - Diagnosed by specialist or GP or;
        - Use of blood pressure-lowering medication or;
        - Mean of baseline blood pressure measurements of ≥ 140 (systolic) or ≥ 90 (diastolic)
    - Obesity:
        - BMI ≥ 30 (UK), ≥ 28 (China) or;
        - Baseline waist circumference ≥ 102 cm (men in UK), 90 cm (men in China), 88 cm (women in UK), 85 cm (women in China)
    - Dyslipidemia:
        - Diagnosed by specialist or GP or;
        - Use of lipid-lowering medication or;
        - Baseline total cholesterol ≥ 5.0 mmol/L[a]

Exclusion criteria

- Manifest dementia, as diagnosed by specialist or GP
- MMSE < 24 (participants with ISCED level of > 1), MMSE <21 (participants with ISCED level of 1)
- Any condition expected to limit 18-months follow-up, including metastasized malignancy or other terminal illnesses
- Smartphone illiteracy, defined as not being able to send a message from a smartphone
- Visual impairment interfering with operation of a smartphone
- Participating in another RCT on behaviour change
- Present severe alcohol or illicit drug abuse

[a] Applies only to participants in United Kingdom. BMI = Body Mass Index; GP = general practitioner; IMD = Index of Multiple Deprivation; ISCED = International Standard Classification of Education; MMSE = Mini Mental State examination; RCT = Randomised Controlled Trial; UK = U=1 ofnited Kingdom.

Participants have only access to one of two versions of the participant app. Participants randomised to the intervention condition will have access to an interactive smartphone application in their own language (English in the UK and Mandarin in China). The intervention app facilitates coach-supported self-management of seven dementia risk factors, including overweight, unhealthy diet, insufficient physical activity, smoking, hypertension, dyslipidaemia and diabetes. Participants can set personal goals for lifestyle change, following the specific, measurable, achievable, realistic and time-bound principle. Participants receive automated reminders to enter measurements (eg, number of steps and blood pressure) for these goals, facilitating progress monitoring. The intervention participants will receive support from an experienced lifestyle coach, who is trained in motivational interviewing and works according to a coach protocol based on current guidelines for risk factor management. Regular training sessions in each country will enhance uniformity in coaching procedures, taking cultural differences into account. During the baseline visit, after randomisation, the coach discusses the participant's dementia risk profile, and a first lifestyle goal will be set through the app. After the baseline visit, all communication between the participant and coach will take place through the messaging functionality. Through the coach portal, the coach can view goals and measurements, send tailored education modules, and offer remote support to facilitate sustainable behaviour change.

Participants randomised to the control condition will have access to the control app, which is similar in appearance but only contains education material, lacking interactive features and coach-support. During the baseline visit, control participants will receive concise feedback on their risk profile.

The PRODEMOS intervention in its current design is positioned as add-on to existing care.

Primary and secondary outcomes

Following a type II hybrid design, primary outcomes for effectiveness and implementation are equally important. The primary effectiveness outcome is the change in the Cardiovascular Risk Factors, Ageing and Incidence of Dementia (CAIDE) dementia risk score between baseline and 18-month follow-up[31]. The main secondary effectiveness outcomes include change in the individual modifiable components of the primary outcome, change in ten-year cardiovascular disease (CVD) risk, cost-effectiveness and certain clinical outcomes such as incidence of mild cognitive impairment (MCI) and dementia. The operationalisation of all effectiveness outcomes is listed in table 1.

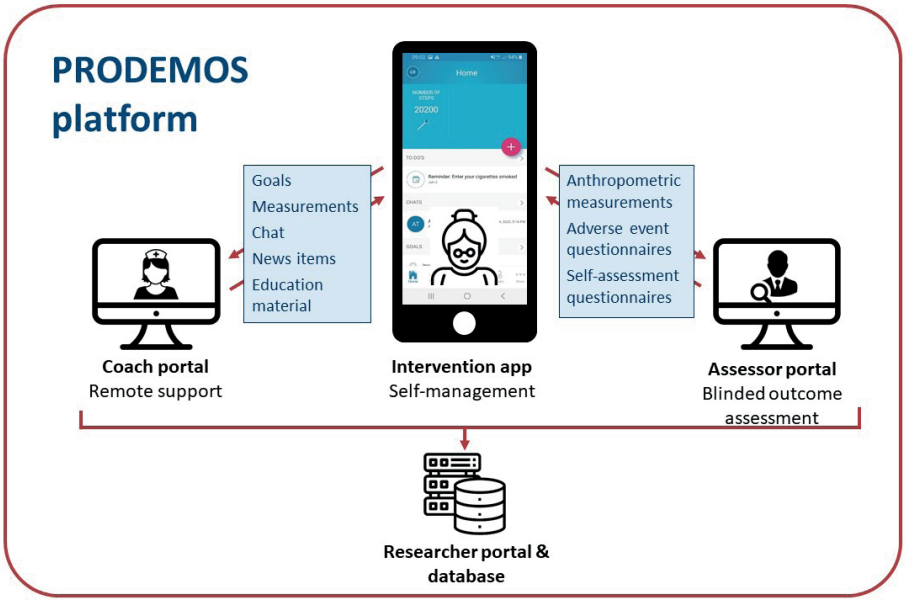

Figure 1. Overview of the PRODEMOS platform and its functionalities

Main features of coach portal: viewing and adjusting details of goals and measurements; sending and receiving chat messages to and from participants; sending education- and news items. Main features of intervention app: setting and adjusting goals; entering measurements; sending and receiving chat messages to and from coach; reading education- and news items automatically pushed by platform or received from coach; receiving periodic adverse event questionnaires and self-assessment questionnaires. Main features of assessor portal: blinded collection of participant data through electronic CRFs and questionnaires. The control application has similar connections with the assessor portal and the researcher portal / database, but is not connected to the coach portal.

Implementation outcomes include acceptability, adoption, appropriateness, feasibility, fidelity, coverage, sustainability and costs of the implementation. User statistics, including data on goals set, messages sent and education items read, will be analysed to assess adoption and sustained use of the platform. In-depth interviews with participants and coaches will focus on user experiences, particularly with respect to barriers and facilitators for (sustained) platform use. All implementation outcomes and evaluation methods are shown in table 2.

Table 1. Effectiveness outcomes

Primary outcome		
CAIDE score (range 0-15), which is comprised of and calculated from:		**Points**
Age	<47 years	0
	47-53	3
	>53	4
Education	≥10 years	0
	7-9 years	2
	<7 years	3
Gender	Female	0
	Male	1
Systolic blood pressure	≤140 mmHg	0
	>140 mmHg	2
BMI	≤30 kg/m^2	0
	>30 kg/m^2	2
Total cholesterol	≤6.5 mmol/L	0
	>6.5 mmol/L	2
Physical activity [a]	Yes	0
	No	1
Secondary outcomes		
Individual modifiable components of the CAIDE score[b]	Estimated 10-year cardiovascular risk	
Number of uncontrolled risk factors	LIBRA dementia risk score	
Active smoking	Number of hospital admissions	
Medication adherence	Diet [e]	
Number of drugs	Disability [f]	
Incident dementia[c]	Anxiety [g]	
Incident MCI[c]	Self-management [h]	
Incident cardiovascular disease[c,d]	Depressive symptoms [i]	
Incident diabetes[c]	Quality of life [j]	
All-cause mortality	Cost-effectiveness	

[a] assessed according to WHO standard for physical activity of at least 150 minutes per week; [b] physical activity assessed with the International Physical Activity Questionnaire Short Form; [c] self-reported and cross-checked with GP file; [d] Defined as myocardial infarction or stroke; [e] assessed with short-form food frequency questionnaire (UK) and China Kadoorie Biobank food frequency questionnaire (China); [f] assessed with the WHO Disability Assessment Schedule; [g] assessed with the Hospital Anxiety and Depression Scale – Anxiety; [h] assessed with the Partners In Health; [i] assessed with the Geriatric Depression Scale; [j] assessed with the ICEpop CAPability measure for Adults and EuroQol 5 dimensions 3 levels. BMI = Body Mass Index; CAIDE = Cardiovascular Risk Factors, Aging and Dementia; LIBRA = Lifestyle for Brain Health; MCI = Mild Cognitive Impairment; UK = United Kingdom.

Table 2. Summary of implementation research methods and outcomes

Method	Outcome	Measurement	Population[a]	Timing of assessment
Quantitative	Coverage	(Non)response rates, comparison characteristics of participants with eligible population	Potential target population	At baseline
	Adoption	Utilisation, usage, and uptake	Intervention participants, coaches	After two weeks
			Intervention participants, coaches	After 3 months and at study end
	Appropriateness	Short questionnaire of perceived fit or relevance in the target population and the coaches		After 3 months and at study end
	Acceptability	Short questionnaire of agreeability, user-friendliness, credibility	Intervention participants, coaches	Throughout the study
	Sustainability	Adherence, dropout	Intervention participants, dropouts[b]	N.a.
	Cost	Implementation costs	N.a.	
Qualitative	Feasibility	The extent to which the mHealth intervention can be carried out → practical and social barriers/facilitators	Intervention participants, dropouts[b], coaches	After 3 months and at study end
	Appropriateness	Perceived fit or relevance in the target population	Intervention participants, dropouts[b], coaches	After 3 months and at study end
	Acceptability	Agreeability, user-friendliness, credibility	Intervention participants, dropouts[b], coaches	After 3 months and at study end
	Fidelity	Degree to which the mHealth application is implemented compared to the original protocol	N.a.	After the study

[a] For all analyses a Chinese and UK population will be involved. b Study dropouts will be asked to participate in a short exit-interview. mHealth = mobile health. AE = adverse event.

Study logistics and data collection

The trial design is visualised in figure 2. All participants will receive one phone call and make three visits to a study venue during the study. Data are collected in electronic case report forms that are accessible through the assessor portal (figure 1).

Eligibility criteria that can be assessed remotely will be checked by a local research team member through the screening phone call. During the subsequent screening visit, informed consent will be obtained, and final eligibility will be assessed by administering the Mini-Mental State Examination; measuring blood pressure, Body Mass Index, waist circumference and total cholesterol (capillary blood sample in the UK; venous blood sample in China); and assessing physical activity, smoking behaviour and a brief medical history. Weight will be measured with a calibrated scale; blood pressure will be measured twice with a calibrated, automated blood pressure device. Screening visits will be performed by (GP) nurses and local research team members specifically trained to perform these measurements and will take place at the GP surgery or a nearby community venue. Standard operating procedures will be used to achieve uniform measurements within and between countries.

After the screening visit, all participants will fill in eight self-assessment questionnaires in the PRODEMOS app. These questionnaires will be used to assess secondary outcomes (ie, physical activity, quality of life, well-being, disability, depressive symptoms, self-management, anxiety and diet; table 1) and potential barriers for lifestyle behaviour change, which can inform coaches to tailor their coaching strategy. Seven of these questionnaires (ie, International Physical Activity Questionnaire–Short Form, EuroQol Five Dimensions, ICEpop CAPability Measure for Adults, WHO Disability Assessment Schedule 2.0, Geriatric Depression Scale (GDS), Partners In Health and Hospital Anxiety and Depression Scale–Anxiety) have been externally validated in both Western and Chinese populations[32-45]. Owing to obvious cultural differences, we decided to use two different diet questionnaires that were validated in the UK and Chinese population, respectively (Short-Form Food Frequency Questionnaire and Kadoorie Biobank Food Frequency Questionnaire)[46, 47].

The baseline visit will be conducted face-to-face by the health coach at the GP practice or local community venue. During this visit, self-assessment questionnaires are reviewed, relevant medical history and medication use are recorded, and participants are randomly assigned to one of the treatment

conditions. Only intervention participants will set a first lifestyle goal together with the coach, according to their dementia risk profile.

All participants will receive periodic adverse event (AE) questionnaires in the app, assessing incident dementia, MCI, CVD and diabetes. All self-reported outcomes will be verified with the participant's treating physician.

After 18 months, the questionnaires and all measurements performed during the screening and baseline visit are repeated during the final visit.

Randomisation and blinding

After completion of the baseline assessments, participants will be individually randomised in a 1:1 ratio, stratified by country, using a central, computer-generated sequence. Participating cohabiting partners will be allocated to the same study condition. Complete blinding of participants is not possible, owing to the nature of the intervention. Participants will be informed that they will be randomised to one of two lifestyle apps, without further details. All outcome assessments will be done by an independent assessor unaware of treatment allocation.

Safety and privacy

Due to the nature of the intervention, serious AEs are unlikely to occur, and we consider the intervention low risk. A data safety and monitoring board is not installed.

Some precautions are taken to optimise participant safety. First, regardless of their study allocation, participants will be referred to their GP or treating physician if deemed necessary based on their baseline or outcome parameters and local guidelines. Second, AEs will be monitored through three 6 monthly questionnaires, for which participants will receive notifications on their smartphone and reminders through email (UK) or SMS (China). If the participant is not able to fill in the questionnaire, an informant can be contacted. A blinded researcher will, with explicit permission gained through the informed consent procedure, cross-check all reported AEs by consulting the participant's GP or treating physician. Third, the PRODEMOS platform is built in accordance with the highest security requirements in healthcare. It complies with NEN 7510, the Health Insurance Portability and Accountability Act, ISO 133485 and General Data Protection Regulation.

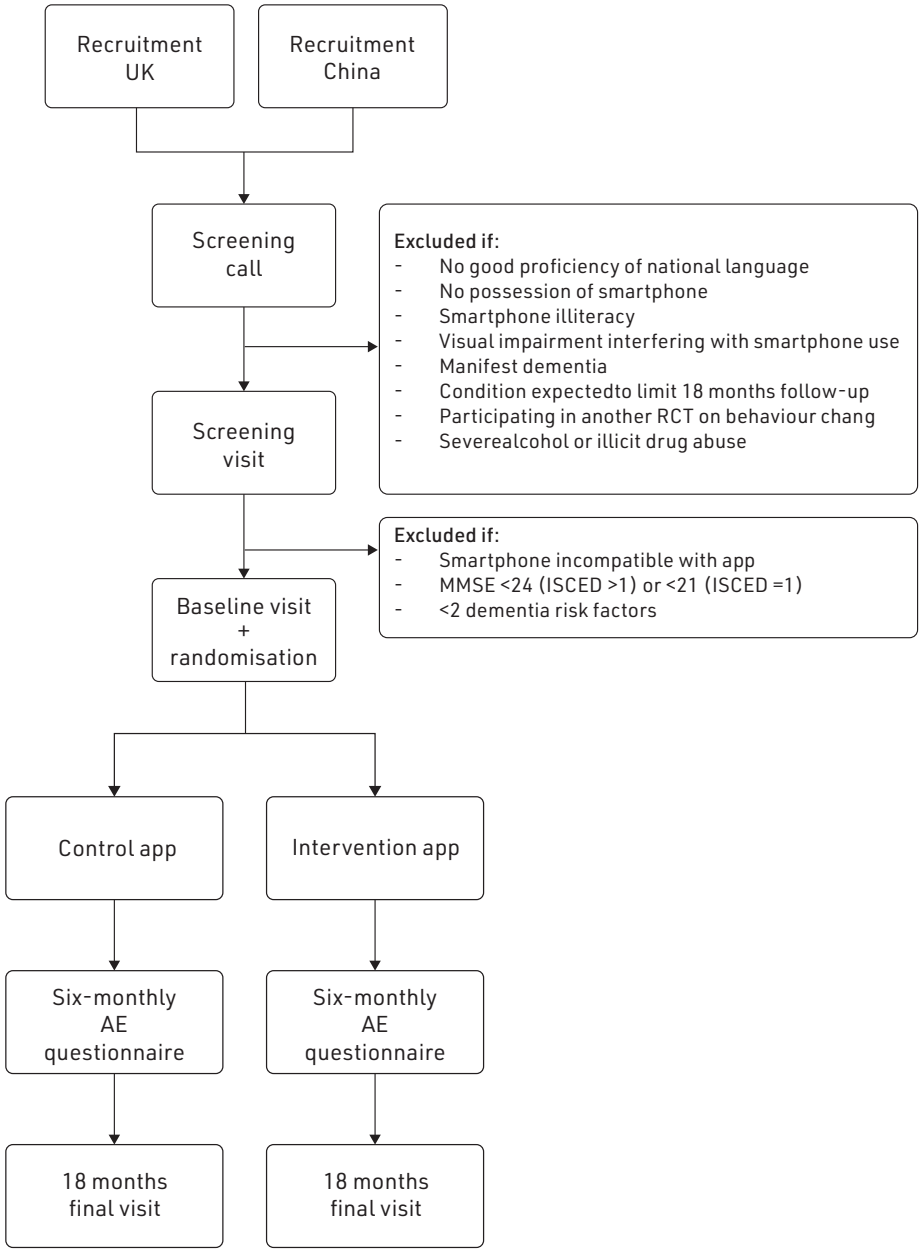

Figure 2. Trial design

AE = Adverse Event; ISCED = International Standard Classification of Education; MMSE = Mini-Mental State Examination; UK = United Kingdom.

Protocol adjustments due to COVID-19 pandemic

As a result of the COVID-19 pandemic and related local research restrictions, certain adjustments have been made to the original study protocol as published on the International Standard Randomised Controlled Trial Number Register (ISRCTN). First, recruitment was planned to start in early 2020 but had to be suspended until January 2021. Second, as it is difficult to predict the development of the pandemic and associated restrictions, we have slightly amended the study protocol to allow for flexible measurement procedures at baseline that can be operationalised in either one or two face-to-face visits and for a flexible intervention duration of 12–18 months. However, we will strive for a follow-up period of 18 months in as many participants as possible.

Patient and public involvement

We have received valuable input into the design of the study and mHealth platform from multiple interactive sessions with GPs, health coaches, researchers, representatives of people living with dementia, community leaders and policy makers. Needs and views regarding the intervention were assessed through interviews and focus groups with potential end users in both countries. All patient-facing material used in the UK has been reviewed by potential end users. Qualitative evaluations of the pilot study with research staff, coaches and patient participants were used to refine the intervention and study procedures.

Statistical analysis

Sample size

The CAIDE Score will be used as primary effectiveness outcome. We decided to use a difference of 0.186 points on the CAIDE Score between the average of both study groups as a minimum target threshold, because this difference was observed in the Prevention of Dementia by Intensive Vascular Care trial after two years (p=0.005; intervention group=−0.290±1.47 SD and control group=−0.104±1.36 SD). Attrition after two years of follow-up was 21% in this study. 14 With 80% power, a 0.05 two-sided significance level, accounting for 21% attrition, and a mean difference in change in CAIDE of 0.186, the required sample size is estimated to be 2319 participants. To allow for unexpected factors, we raised this to 2400.

Data analysis

The effect on the CAIDE Score will be analysed using linear mixed-effect models according to the intention-to-treat principle, taking clustering within partner pairs and country into account by testing best fit for random intercept and/or

slope. If needed, we will adjust for baseline imbalances and take clustering of the intervention within centre and/or coach into account. No imputation of the CAIDE Score will be done for the primary analysis. In sensitivity analyses, we will use multiple imputation to assess the impact of missing items needed to calculate the CAIDE Score, provided there are no indications that the variables are missing not at random, and a per protocol analysis for those adherent to the intervention will be performed. Moreover, we will explore the interaction of intervention duration with the effect of the invention by adding an interaction term (intervention duration*randomisation group) to the main model. This will give insight into the potential additional intervention effect in participants with a follow-up time of less than 18 months.

Subgroup analyses will be performed for country, sex, age group, having a history of CVD, number of risk factors, willingness to change lifestyle (assessed with one question during the baseline visit), participation with(out) a participating partner, having the same coach during the full length of the study and the number of goals set. For all these factors, interaction terms will be included to test for between-subgroup differences in intervention effects.

The effect on individual modifiable components of the CAIDE Score and 10-year CVD Risk Scores will be analysed using linear mixed-effect models according to the intention-to-treat principle, taking clustering within partner pairs and country into account. Self-assessment scales, which are mostly ordinal, will be regarded as linear scales if there are at least four categories and the 'distance' between the categories can be regarded equal. Poisson regression or zero-inflated models may be applied to distributions resembling count or zero-inflated data. The choice of the final model will be a compromise between optimal fit and interpretability of the results for a general clinical public.

Prevalence ratios will be used for self-assessment instruments with defined cut-offs for the presence or absence of a condition, for example, 'depressive symptoms' for a GDS >5. For (clinical) dichotomous outcomes, such as incident CVD, dementia or mortality, Cox proportional hazard models will be used with time using baseline as timescale. A sensitivity analysis will be performed using age as timescale.

The full analysis plan, including the health economic analysis plan entailing the cost–consequence analysis of the within-trial results, the cost-effectiveness analyses and the cost–utility analysis and hypotheses for the subgroup analyses, is published on the ISRCTN website: http:// www.isrctn.com/ISRCTN15986016.

Pilot study

Between December 2019 and March 2020, a 6-week pilot study was conducted in the Brighton and Sussex area, the UK. Since the main aim was to test study logistics and functionality of the intervention app, participants were randomised in a 3:1 (intervention/control) ratio. An invitation letter was sent to 600 potentially eligible patients from two GPs. The response rate was 14.8% (n=89), of whom 21 participants (3.5%) could be included. The main reasons for exclusion were not living in the designated postal code area and having less than two dementia risk factors. Participants had a median age of 69 years old, and 12 (57%) were men. Fifteen participants were allocated to the intervention group and six to the control group.

During the pilot study, 10 of 15 intervention participants set at least one goal (range: 1–8 goals). Goals were set in five domains, including physical activity, healthy diet, body weight, blood pressure and cholesterol. Six of ten participants entered goal-related measurements (range: 2–243 measurements). All intervention participants used the chat functionality to consult the coach. In total, 278 messages were sent back and forth, that is, on average three messages per intervention participant per week.

The pilot study was evaluated through qualitative sessions with the participants and coaches. The main adjustments based on the participants' feedback included improvements to the chat functionality (allowing attachments and larger font size), simplification of the functionality to enter and view measurements, setting the first goal together with the coach and more detailed instructions for app use through an instruction video and written manual. Based on feedback from the coaches, we improved the functionalities for population management in the coach portal, including an input screen to make notes about individual participants and a functionality to send education material to (groups of) participants.

A similar pilot study will be conducted in China, to test platform functionality and study logistics in all seven participating trial centres.

Discussion

In the PRODEMOS study, we will investigate the implementation of a self-management mHealth intervention with remote coaching and its effect on dementia risk over 18 months. We will target people aged 55–75 years old with elevated dementia risk of low SES in the UK and of any SES in the Beijing and

Tai'an cities in China, as these populations are usually not reached by preventive strategies and may benefit the most. User data and qualitative analysis of our pilot study suggest that our mHealth application, after further adaptations to improve attractiveness and usability, is now ready to be studied in older adults who are interested in participating in a study on lifestyle change to lower their overall dementia risk.

The HATICE trial has shown that a coach-supported internet platform can improve cardiovascular risk factors in European elderly. Although we build on these experiences, the modality (ie, app instead of internet platform) and target population are different. The resulting uncertainty that there would be a similar benefit of our intervention renders the use of a hybrid effectiveness–implementation design highly suitable[27].

Strengths

Chronic disease risk is largely affected by socioeconomic factors, including psychological, cultural and economic characteristics, requiring preventive strategies that take these aspects into account[48]. In PRODEMOS, we aim to support individuals by offering intensive human support through the app and by aligning the intervention with the healthcare system. In order to eventually embed a complex prevention intervention into primary healthcare, it is crucial to involve and consult all stakeholders, such as GPs, practice nurses, and end users[49]. In the current hybrid effectiveness–implementation study, we take some first steps to explore the possibilities and challenges for embedding the intervention in existing healthcare. This study will provide concrete evidence of the scale of the change that might be achieved for individuals at risk, whether and how this approach is taken up within diverse populations.

The PRODEMOS study is designed as one trial, recruiting participants in two different countries, increasing the external validity of the results. Overall, both countries will follow the same research protocol and highly similar standard operating procedures and will investigate similar interventions. Through semi-structured interviews among the elderly in Beijing and the UK, we learnt that needs and wishes regarding lifestyle behaviour change through mHealth are largely similar (manuscripts currently being drafted). Therefore, the Chinese and UK intervention will share the same functionalities and coaching procedures. Given obvious cultural-related and healthcare-related differences, certain aspects of the study logistics, lifestyle support and layout of the app had to be culturally adjusted. In a pre-planned subgroup analysis, we will assess both effectiveness and implementation outcomes for both countries separately.

Limitations

The study may yield some limitations. First, the optimal age range for trials on dementia risk reduction is unknown[15]. There is a trade-off between potentially more effective treatments in midlife and the chance to detect treatment effects on cognitive outcomes in late life.4 As in the current study, we are assessing both a dementia risk score and clinical outcomes; we have taken a pragmatic approach, targeting individuals aged 55–75 years old[15].

Second, change in CAIDE dementia risk score is not easily translated into incidence of dementia. However, although not specifically designed as RCT outcome measure, the CAIDE Score can detect change over time[50].

A third potential limitation is that, owing to the nature of the intervention, blinding of the participants is only partly possible. A certain degree of contamination might occur, especially in communities that live closely together. The study logistics and intervention are designed in such a way as to limit contact between participants after randomisation.

Finally, the results of the baseline measurements will be revealed to all participants, potentially leading to treatment effects in both study conditions. Also, behaviour of participants and their treating physicians may change in both study conditions as a reaction to the awareness of being part of the study (Hawthorne effect). Both mechanisms will perhaps mask (part of) the 'true' contrast in dementia risk between the intervention and control condition.

For the planned health economic analyses, we will rely on economic modelling, based on the intermediate outcomes reflecting risk of dementia and CVD and assumptions on their causality with the clinical endpoints dementia and CVD, because the study is not designed nor powered to detect an effect on these clinical endpoints.

The high prevalence of dementia, lower provision of high-quality cardiovascular preventive care in LMIC and lower uptake of such programmes in Western lowSES populations require affordable and straightforward preventive strategies. If proven effective and implementable, our pragmatic smartphone intervention facilitates widespread use and reduction of dementia risk for hard-to-reach populations across the globe.

Ethics and dissemination

The PRODEMOS trial is sponsored in the UK by the University of Cambridge and is granted ethical approval by the London–Brighton and Sussex Research Ethics Committee (reference: 20/LO/01440). In China, the trial is approved by the medical ethics committees of Capital Medical University, Beijing Tiantan Hospital, Beijing Geriatric Hospital, Chinese People's Liberation Army General Hospital, Taishan Medical University and Xuanwu Hospital. Data will be exported in a pseudonymised format according to prevailing guidelines on good clinical practice in both countries. Only anonymised data will be exchanged between the UK, China and the Netherlands. The exported data will be stored centrally on a protected server in the Netherlands, which is compatible with the highest standards of data management in medical research. Results will be published in a peerreviewed journal.

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4

Attitudes and views on healthy lifestyle interventions for the prevention of dementia and cardiovascular disease among older people with low socioeconomic status: a qualitative study

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Abstract

Objectives

Individuals with a low socioeconomic status (SES) have an increased risk of cardiovascular disease (CVD) and dementia, partly due to the high prevalence of unhealthy behaviours in this population. Interventions targeting lifestyle-related risk factors can potentially delay or prevent CVD and dementia onset. In this study, we explore the attitudes, experiences and views of low SES older adults on healthy lifestyles for the prevention of CVD and dementia. We also aim to study the potential role for coach-supported mobile health (mHealth) use, facilitating the development of the Prevention of Dementia using Mobile Phone Applications (PRODEMOS) intervention.

Design and setting

We performed semi-structured interviews and used thematic analysis to analyse the data. Recruitment took place through multiple general practices in the Netherlands.

Participants

Dutch non-demented adults aged ≥55, at increased risk of dementia, who possess a smartphone. Participants were purposively sampled on age, sex, and history of CVD and diabetes.

Results

Between May 2018 and June 2019, we performed 19 interviews. Five main themes were: 1) participants perceived little influence on their future health, 2) the sacrifices of healthy lifestyles outweighed the potential benefits, 3) physical complaints or disease could prompt behaviour change, 4) participants perceived they had limited self-efficacy to change their behaviour and 5) the social network had an important role in behaviour change. Needs regarding mHealth support were an easy-to-use smartphone application with trustworthy health information, which is provided in a non-obligatory way.

Conclusions

Low SES older adults may benefit from lifestyle interventions that aim to improve self-efficacy levels by (remote) human support. Appropriateness and attractiveness of such interventions may increase when taking into account the participant's own autonomy, and when emphasizing the direct gains of lifestyle changes for daily life. Moreover, involving the social network may be a valuable approach when developing lifestyle interventions for low SES older adults.

Introduction

Individuals with a low socioeconomic status (SES) have a substantially increased risk of cardiovascular disease (CVD)[1] and dementia[2] compared to their high SES counterparts. One of the explanations for this difference is the high prevalence of unhealthy behaviours among low SES individuals, including smoking, unhealthy diet, and insufficient physical inactivity[3,4]. This suggests that lifestyle interventions targeting cardiovascular risk factors may have particular potential to delay or prevent CVD and dementia onset in low SES populations.

Digital health-supported lifestyle programs are emergent strategies for the delivery of interventions to hard-to-reach populations, given the rapidly increasing availability of internet around the world[5]. Previously, a meta-analysis suggested that the cardiovascular risk profile of middle-aged and older people could be improved by web-based lifestyle interventions, especially when combined with human support[6]. More recently, the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) trial showed that a coach-supported digital lifestyle intervention can improve the cardiovascular risk profile of older European adults[7].

Building on experiences gained from the HATICE trial, the Prevention of Dementia using Mobile Phone Applications (PRODEMOS) trial will assess the effectiveness and implementation of a coach-supported mobile health (mHealth) platform, facilitating self-management of risk factors to reduce dementia risk in older people with a low SES background in the UK[8]. Effectively reaching low SES populations is challenging, as they generally tend to benefit less[9,10] and are more likely to drop out[11] of intervention studies. Also, barriers for healthy behaviours and needs regarding lifestyle support appear to differ from those with high SES[12-14]. Therefore, tailoring of our lifestyle intervention to their needs and preferences is crucial to effectively reach and engage low SES participants[15-17].

In the current qualitative study, we aim to explore the attitudes, experiences and views of Dutch low SES older adults on healthy lifestyles for the prevention of dementia and CVD. We also aim to study the potential role for coach-supported mHealth use, facilitating development and further adaptation of the PRODEMOS mHealth intervention.

Methods

Participants and setting

Participants were recruited through six general practices in the Netherlands, covering both rural and urban areas. Eligibility criteria were age ≥55 years, a low SES background, smartphone possession, and increased risk of dementia (defined as the presence of ≥2 dementia risk factors, i.e. history of CVD, diabetes, hypertension, overweight, dyslipidaemia, depression, insufficient physical activity and current smoking).Participants were purposively sampled on age, sex, living situation and history of CVD and diabetes. Overall eligibility was assessed by the general practitioner and validated through a screening phone call by one of the researchers. We verified the participants' educational level as a proxy for SES and only included those with an International Standard Classification of Education (ISCED) level of ≤2 (comparable with primary school or lower secondary education as highest completed educational level). In total, 19 out of 27 eligible individuals were willing to participate in the study. Written informed content was obtained before the start of each interview for all participants.

Data collection

Between May 2018 and June 2019, three researchers (EE, MH, and MHB) performed semi-structured interviews. The interviewers had no professional or other type of relationship with the participants. The professional backgrounds of the researchers (i.e. medical doctor (EE, MH) and dietician (MHB)) were not actively mentioned, to reduce the risk of socially desirable answers.

The interview guide (Supplement 1) comprised questions about experiences and attitudes regarding lifestyle behaviour change in relation to dementia and CVD prevention, and about needs for and views on the potential role for mHealth. When deemed necessary, we iteratively adapted the guide based on experiences during the interviews. Examples of such adjustments are adding questions on the role of religion and financial resources in disease prevention.

Interviews took place at the participants' homes, to avoid potential undesirable effects of a medical setting on participants' response. Interviews lasted approximately 45 minutes (range 25-60 minutes), were audiotaped and transcribed verbatim. Transcripts were enriched with field notes taken during the interviews. Participants were offered the opportunity to contact the research team in a later stage if they had further remarks or questions regarding the study, or if they wanted to withdraw participation. According to the Dutch law, the study was not required to undergo review by a Medical Research Ethics Committee.

Coding and analysis

Data were thematically analysed following the six phases as described by Braun and Clarke[18]. The first two steps of analysis were concurrent with the interviews.

1. All researchers (EE, MH, MHB, and EMvC) familiarized themselves with the data by thoroughly reading the transcripts. The researchers involved in initial coding (EE, MH, and MHB) additionally listened to the audiotapes of the interviews.

2. Initial coding was done using MaxQDA in sets of 2-3 interviews. Each interview was independently coded by EE and by either MH or MHB. Initial codes of each set of interviews were compared and discussed until any disagreements were resolved, resulting in a new set of codes. We used a data-driven approach, coding the content of the entire dataset.

3. After reaching data saturation and finishing initial coding, EE, MH, and MHB independently searched for potential themes by combining codes in MaxQDA. In a face-to-face meeting, all printed codes were visually mapped and organized into themes. In a face-to-face discussion with EMvC, these themes and their potential interrelationships were discussed.

4. EE and EMvC reviewed the candidate themes and subthemes. Some themes were merged, whereas other themes were refined or split into multiple themes. EE reread all initial codes, to judge whether the themes were a good representation of the data.

5. Narratives for each theme were written by EE, describing the themes and subthemes. MH, MHB, and EMvC reviewed the narratives, and made adaptations to the names and arrangement of the themes where deemed appropriate.

6. Narratives were enriched by illustrative examples, which were selected by EE, MH, and MHB, and reviewed by EMvC.

Patient and Public Involvement

Patients and/or the public were not involved in the design or conduct of this study.

Results

We performed 19 semi-structured interviews. Participants were aged 55-77 years. Twelve participants had a history of CVD. Demographics of participants are presented in table 1.

Table 1. Socio-demographic characteristics and medical history of included participants.

Characteristic		**N=19**
Age (year)	Median [range]	67 [55-77]
Sex (female)	N (%)	8 (42)
Born in the Netherlands (yes)	N (%)	17 (89)
History of CVD (yes)	N (%)	12 (63)
History of diabetes (yes)	N (%)	11 (58)
Living situation	N (%)	
With partner		11 (58)
With other		1 (5)
Alone		7 (37)

CVD = cardiovascular disease.

In line with our research question, we will present the results in two sections. Part I describes the attitudes, experiences and views regarding healthy lifestyles for prevention of CVD and dementia. We identified five key themes: 1) little perceived influence on future health, 2) sacrifices outweigh the potential benefits, 3) physical complaints or disease can prompt behaviour change, 4) limited self-efficacy on behaviour change and 5) important role for the social network. In part II, we will address the needs and views regarding lifestyle support and the potential role of coach-supported mHealth.

Part I: Attitudes, experiences and views regarding healthy lifestyles for disease prevention

1. Little perceived influence on future health

Many participants felt that they had little or no influence on their future health or disease onset, because it is largely predestined. Health and disease were often seen as a matter of (bad) luck or as something that is decided by a higher spirit or genetic predisposition, rather than a risk that can be affected by choices in lifestyle behaviour.

> *"I do my best in life and I try to be positive and it's all in the Lord's hands. […] And who knows, tomorrow I cross a road without seeing a car approaching,*

and then you're gone too. [...]Living a healthier lifestyle to avoid diseases, I don't know about that."

Moreover, some participants did not recognise a potential effect of (un)healthy behaviours on disease risk, based on previous experiences. Participants often related to anecdotes of relatives or friends who used to have a healthy lifestyle but eventually got ill, or people who had become very old in spite of their unhealthy behaviours, to question the assumed relation between healthy lifestyles and favourable health outcomes.

"I see people who say: 'If you smoke, you'll get lung cancer.' Blah blah blah. I mean, my grandfather smoked his whole life. He lived to 87 years old. He didn't die from lung cancer."

2. Sacrifices outweigh potential benefits

Many participants stated that making sacrifices, such as depriving oneself from tasty foods and alcohol, or engaging in physical activities that were not deemed enjoyable, as disproportionate to the potential benefits of such healthy behaviours. Participants often referred to the potential benefit of healthy behaviours as "perhaps living a year or two longer", without considering potential positive effects on the quality of life. Especially with ageing, having a pleasant life in the present seemed to be more meaningful than potential future gains from a healthy lifestyle.

"But I can't bring myself to go to the gym and work up a sweat for an hour there."

"And we're all gonna go at some point anyway, so at that point I'd rather be able to say I had a comfortable life than a longer one."

3. Physical complaints or disease can prompt behaviour change

In retrospect, many participants found it difficult to pinpoint what had made them initiate working on a healthy lifestyle, but often they referred to a specific moment in time, when something 'clicked' for them, causing them to flip a switch.

-"And how did you manage to stick with it [quit smoking]?"

"[...]someone flipped a little switch in me. If you don't want to, it's not gonna happen. Then nothing will work."

-"But what was that switch?"

"I don't know. But yeah, suddenly you really want it. And you're fully behind it [...]You have to flip that little switch."

For some participants, becoming ill, such as getting a CVD or diabetes, was the spark that set off behaviour change, to prevent further deterioration or relapse of the disease. This seemed to be especially the case for smoking. Sometimes, lifestyle advice from healthcare workers shortly after diagnosis was a trigger for such behaviour change.

"I smoked like a chimney. And never touched another cigarette since that day [heart attack]."

"Yeah, because at first the surgeon who cut open my groin, she just said [...]"Are you ever gonna be done with that stupid smoking habit?" I'll never forget that. [...]she saw right away that I was a pretty heavy smoker. [...]At that point I said to myself: "I'm done [smoking]."

For other participants, physical discomfort caused by unhealthy behaviours rather than a formal disease was an incentive to change. Examples are breathing problems caused by smoking, or being unable to tie shoelaces due to obesity.

"[...]I can hardly tie my shoelaces. And look, that annoys the hell out of me. But now I've been wearing slippers for 3 months [...]so now I'm not annoyed. And soon I'm gonna have to wear my shoes again, and maybe that will cause to flip a switch."

"I don't quit smoking for lung cancer or anything. [I quit] for myself. For my [takes a deep breath] wheezing. And my [coughs loudly] during the night"

4. Limited self-efficacy on behaviour change

Breaking with habits is a daunting challenge

For some participants changing behaviour felt like a major hurdle, especially when unhealthy lifestyles had become a long-standing habit.

"Well, look, at some point it just turned into a habit, the smoking. [...]You just need something in your mouth."

Some participants said that they were aware that they should change long-lasting habits, and knew how they should change, but found it hard to put knowledge into action.

"We know bloody well that all that fried fish isn't good for me, actually. […]And we also know well enough that we should be eating healthy fish. It shouldn't be fried. […]No, [it's] not about knowing better, it's about living habits."

Disappointing results have a demotivating effect

Participants who had previously initiated behaviour change mentioned that their progress declined after some time. For many of them, this had a demotivating effect on their (future) attempts to change their lifestyle.

"At some point […]it [weight] uhh kind of stays the same. And it won't go down any more. And then, that's the moment for me […]it falters."

5. Important role for the social network

The importance of maintaining autonomy

Some participants took issue with others meddling with their lifestyle behaviour. They stressed that unsolicited lifestyle advice could even have a counterproductive effect on their motivation to change. Some people preferred advice from people in the inner circle, such as a partner, to advice from people who are less familiar, such as healthcare professionals.

"I ain't letting anyone tell me what to do. […]If they're gonna tell me: "you have to…" then I'm gonna do the opposite."

"My coach is on the other side of the [kitchen] table. Really, I'm serious. […] She [spouse] is the only one who's advice I'll take."

Family and close friends can prompt behaviour change

Some participants mentioned that their attempts to change their lifestyle behaviour were triggered by people from their inner social circle. In some cases, negative feedback by close family members caused feelings of embarrassment, sparking efforts to quit smoking or lose weight.

-"And do you remember why you suddenly thought: I need to lose weight?"

"My daughter. […]I noticed that at some point she started […]walking a few metres behind me. And that she was kind of like, I don't wanna become like my mother. And then I was like, I don't want that."

Having a healthy lifestyle is easier when done together with peers

For many participants, living closely together with peers following healthy lifestyles or aiming to improve them, made it easier to adopt similar behaviours.

-"Were there things that helped you abstain?"

"*The home front really. No smoking at home."*

Some participants tried to make changes to their lifestyle by changing their behaviour together with friends or family. Such peers could provide increased incentive to stick to the intended behaviour.

"*Well, I happened to have a buddy. […]So I'd meet them at the gym. And then uh, "Did you smoke?" "No." "No, me neither." You know. […] And then you can deal with it."*

Especially in the case of physical activity, participants looked for peers who had approximately the same age, and had similar impairments or goals. A safe environment with mutual understanding for each other's health situation was deemed imperative to successfully involve in physical exercise together.

"I do feel very […]safe. […]I'm not good at running. And uhh, when you're like: "Phew" and you sit down for a moment. Nobody will be like: "Hey, come on!!""

Part II: Potential role for coach-supported mHealth use

We explored the potential added value of a coach-supported mHealth intervention to facilitate lifestyle behaviour change, as part of the development of the PRODEMOS platform.

Professional lifestyle support

For some participants, previous lifestyle coaching from a healthcare professional had made it easier to change their behaviour, due to the added impetus to achieve lifestyle goals.

-"And that coach at the time, from the doctor…how was she able to guide you in the quitting process?"

"Yeah…that's what a big stick does. Because you have to show up like every week. […]I mean, then you can't be like: I smoked."

Some participants indicated that healthcare professionals should be careful when offering lifestyle advice. Language used should be not too coercive, but rather friendly and open to the participant's own views.

> *"Don't start telling me what to do or what not to do [...]"*
>
> ***-"And what would the ideal approach look like?"***
>
> *"That you give people ideas: "Have you considered this?" Or: "Have you tried that?""*

Several participants mentioned that consistent and trustworthy health information is an important facilitator for behaviour change. Especially in the case of diet, contradictory information could cause a sense of insecurity, hampering attempts to improve their diet.

> *"One moment you can't have an egg, the next you can have three a day, so to speak... [...]And then this or that is bad, and the other causes cancer [...]It drives me completely nuts."*

Limited faith in professional guidance

Despite the experienced difficulties, participants were sometimes reluctant to seek or accept professional guidance when changing their behaviour. Some had little faith in professional support due to previous, unsuccessful experiences. Others expressed they had no need for support, because they felt their knowledge was already sufficient and feared interference with their own choices.

> *"Yeah but I only went there [dietician] once or twice. That really doesn't work. Well, doesn't work, I mean, you know what to do by yourself"*

The platform should be easy-to-use

Although participants were selected on their smartphone possession, they had often limited confidence in their digital skills and foresaw to need detailed instructions and intensive support when introduced to a new app.

> *"If you're going to introduce this [app], you'd really have to educate a group of people, like how do you use something like that?"*

Other participants expressed that health information and other support from the coach should be easy-to-read, avoiding medical language.

"[The app has to be] understandable! Don't go tossing around big words and medical terms and all that."

Discussion

Summary of main findings

In this study on attitudes, experiences and views on healthy lifestyles and prevention of CVD and dementia among Dutch low SES older adults, we identified five main themes. First, participants perceived they had limited influence on their future health. Genetic predisposition or faith were considered to be more important determinants of health than own lifestyle behaviours. Second, following a healthier lifestyle was associated with sacrifices on diet or physical exercise that outweighed their potential health benefits, especially with ageing. Third, feedback from the body in terms of illness or physical discomfort could serve as a trigger for behaviour change. Fourth, self-perceived efficacy on behaviour change was limited, especially when previous attempts had been disappointing. Fifth, the social network was of paramount importance to trigger and maintain changes towards healthy behaviours. Finally, provided that the platform is easy-to-use and coach-support is trustworthy and presented in a non-obligatory way, mHealth support may be an acceptable and appropriate strategy to facilitate lifestyle behaviour change in low SES older adults who own a smartphone.

Interpretation of findings and comparison with literature

Our finding that low SES older adults have little confidence that behaviour changes will yield better health outcomes, may be explained by their perceived lack of influence on future health outcomes. A survey on attitudes and beliefs on healthy lifestyles among 2728 adults suggested that low SES individuals less frequently think about the future and foresee a shorter life expectancy than high SES adults. Both characteristics were associated with more unhealthy behaviours, probably reflecting a lack of motivation to change[19]. In line with our own findings, low SES has been associated with a strong external health locus of control[20] and strong beliefs in the impact of predestination on health, rather than their own efforts[19].

Although financial costs, i.e. expenses, are a commonly described barrier for healthy behaviours among low SES adults[12, 13], the notion that costs in a more figurative sense, i.e. sacrifices needed to live healthily, outweigh the potential health benefits, appears to be less well-known. In a previous study on perspectives towards lifestyle-related secondary CVD prevention, older adults often preferred current quality of life to potential future gains of healthy behaviours, or were only inclined

to involve in lifestyle behaviour change when positive effects of these efforts on quality of life were clearly noticeable on the short term[21]. Other studies described that living healthily comes more easily for those used to healthy behaviours, and vice versa[13, 22]. In our study, for many participants healthy diet and regular physical activity were not part of their daily lives. Perhaps, getting more familiar with certain healthy behaviours could partly reduce their negative attitudes.

It has been previously reported that, especially in the lower SES groups, physical impairments or disease onset can prompt behaviour change[13, 21, 23]. In our study, also less severe symptoms, such as physical or practical discomfort caused by overweight, rather than disease onset itself, could serve as a trigger.

The expressions of low self-efficacy on behaviour change we observed are in line with several previous studies on low SES and older adults[21, 24-26]. Low self-efficacy usually decreases the chance of successful behaviour change, and unsuccessful attempts further decrease motivation to make renewed attempts[27]. Although participants in our study were generally not inclined to seek or accept professional support, lifestyle interventions and –support, tailored to their needs and wishes, may have the ability to break this cycle by increasing participants' self-efficacy levels[28, 29].

In line with our own results, previous qualitative studies reported that, regardless of participants' SES, engaging in physical exercise becomes easier and more pleasant when peers are involved[13, 22]. A focus group study comparing attitudes towards healthy lifestyles between low and high SES adults reported that low SES adults in particular expressed the need for peers to be of the same age with comparable health complaints. Similarly, regarding nutritional advice, low SES adults had the most outspoken preference for group-oriented approaches[13].

The Attitudes, Social influence and self-Efficacy (ASE) model is a theoretical framework that aims to explain behavioural intentions[30] and is based on the Theory of Planned Behaviour[31]. It suggests that attitudes, social influence and self-efficacy affect behavioural intentions. Personal barriers and skills subsequently affect the transition into actual behaviour. We feel that our results largely fit into the ASE model, as the perceived lack of influence on future health and sacrifices accompanying healthy behaviours represent 'attitudes', the important role for peers represents 'social influence', and the expressions of limited self-confidence clearly link with 'self-efficacy'.

Strengths and limitations

A main strength of our study is the purposive sample, consisting of older adults who differ in age, living situation, and CVD and diabetes history, contributing to an overview of existing experiences, attitudes and views on healthy lifestyles for disease prevention among low SES older adults in the Netherlands.

A potential limitation of this study is that we only included participants living in the Netherlands. As healthcare systems vary widely in preventive care delivery across countries, applicability of our findings may be limited to low SES populations in countries with similar social services and care provision. Second, GP's were specifically asked to invite low SES individuals, which may have inflated the number of individuals from the lowest SES levels. A final limitation may be that the PRODEMOS intervention was still in the early phase of development when the interviews were performed. The lack of an advanced prototype prohibited an in-depth exploration of specific needs and preferences regarding the functionalities and layout of the mHealth intervention.

Implications for practice

As self-efficacy levels seemed to be modest at best, low SES older adults may benefit from lifestyle interventions that include human support and aim to increase self-confidence and perceived self-efficacy levels. Appropriateness and attractiveness of such interventions may increase when provided in a non-obligatory way, taking into account the participant's own autonomy. As motives to change tend to focus on concrete, short-term goals rather than prevention of future disease, lifestyle advice should ideally emphasize the direct gains of such changes for daily life. Moreover, lifestyle information for low SES older adults should be easy-to-follow, unambiguous, and trustworthy. Given that peer support is an important factor for initiation and sustainability of behaviour change, involving peers may be a valuable approach when developing lifestyle interventions for low SES older adults. As smartphone interventions allow participants to use the intervention in a flexible way, remote coaching using an mHealth application may be a promising strategy to engage low SES adults, provided that it fits their needs, is easy-to-use and comes with extensive and sustained support.

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Supplementary material

Supplement 1: interview guide, translated from Dutch

Introduction of participant

Before we get started, I want to get to know you a little better. Would that be ok?

- Could you please tell me something about yourself and your health? *[I.e. marital status; (grand) children; family; friends; working status; former job(s); hobbies; daily activities?]*
    - Are you happy with your current lifestyle?

View on self-management of a healthy lifestyle

- How do you view your lifestyle?
    - How healthy do you live? Can you give this a grade? Why not lower? What is going well? What doesn't go so well? What do you need to live healthily?
    - Have you ever tried to change certain aspects of your lifestyle, i.e. your diet, physical activity, smoking?
    - What habit did you change? When was that? Why then? Was there a certain trigger? How did it go?
    - Was it easy for you to persist in your new habit? What factors made it easy? *[what kind of rewards, rewards on short/long term, support from peers?]*
    - Did you sometimes have a hard time to persist in your new habit? What factors made it difficult? What did you do when you were having a hard time? Which external factors, such as financial constraints, were barriers for you?
- Did you ask for support of others?
    - Who did you ask for support? Why? (How) did that help you?
- Do you have any experiences with such coaching?[*i.e. diabetes nurse; cardiovascular nurse etc.]*

- What does he/she help you with? What aspects do you like? Are there aspects you dislike?

Experiences with / views on cardiovascular disease & dementia

I'd like to know what your experiences are with cardiovascular disease, such as heart attacks.

- Could you tell me something about your own experiences with cardiovascular disease, or experiences of family / friends with CVD? *[I.e. consequences of cardiovascular disease for daily life, perceived causes of disease]*

- How do you see your own risk to suffer (again) from such disease? Do you fear that?

- How do you see your own influence on your CVD risk? How do you think you can influence that?

Another disease we study is dementia.

- What are your experiences with dementia? Family? Friends? *[I.e. consequences of dementia for daily life, perceived causes of disease]*

- How do you perceive your own risk to suffer from dementia?

  - Do you think you can influence your own dementia risk? How? When?

In recent years research has established that dementia is partially caused by the same risk factors as CVD. So dementia risk is increased for people who smoke cigarettes or people with obesity or hypertension etc.

- For some people, this knowledge could perhaps change their motivation to change their lifestyles. For others, this knowledge doesn't seem to change their motivation to change. Would this knowledge change your motivation to change your lifestyle?

View on sustained lifestyle changes through mHealth / lifestyle apps + remote coach

Like I said in my introduction, we aim to design a smartphone or tablet app that could help you to improve your lifestyle if you so wish and to decrease cardiovascular risk.

- Do you have a smartphone?
    - What do you use your smartphone for? When do you use it? *[use at home, or also use in public transport / while shopping etc.]*
    - What things do you prefer to do with your computer / laptop / tablet instead of your smartphone? Why?
- Have you ever used your smartphone to improve your lifestyle? *[I.e. apps to count calories; to improve physical activity; quit smoking].*
    - What kind of app / website was that? When did you start using it? How did that go? How did the app help you? What aspects did you like? What did you dislike? Why did you stop using the app?
- What kind of lifestyle app would you want to use?
    - What should such an app be able to do for you?
        - How do you view peer contact?
    - What would withhold / stop you from using the app?
    - How would you use it? Only when at home, or also outside the house? Would you prefer an app for smartphone or tablet? Or both? Why?
    - How would you prefer to receive feedback? *[Automatic? SMS? Message from coach?]*
- Would a lifestyle coach embedded in that app be of any help?
    - Why would(n't) that be helpful? What do you expect from such coaching?
    - How would you like to stay in contact with the coach? How often? How important is face-to-face contact for you?

- How important is it of you that the coach has a medical background?

- How would you like it if the coaching through the app is performed by your nurse practitioner / diabetes nurse? What are advantages? What are potential pitfalls?

End of interview

We have come to the end of our interview. Thanks so much for your help!

– Are there any things that you would want to add? Do you have any questions? We'd like to invite you in the near future to join one or two panel discussions to test the app we're building, so that we can see if it meets your wishes. Would you be willing to join? *[Write down e-mail address]*

5

Needs and views on healthy lifestyles for the prevention of dementia through mobile health (mHealth) interventions in China: a qualitative study

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Abstract

Objectives

Over the coming decades, China is expected to face the largest worldwide increase in dementia incidence. Mobile health (mHealth) may improve the accessibility of dementia prevention strategies, targeting lifestyle-related risk factors. Our aim is to explore the needs and views of Chinese older adults regarding healthy lifestyles to prevent cardiovascular disease (CVD) and dementia through mHealth, supporting the Prevention of Dementia using Mobile Phone Applications (PRODEMOS) study.

Design

Qualitative semi-structured interview study, using thematic analysis.

Setting

Primary and secondary care in Beijing and Tai'an, China.

Participants

Older adults aged 55 and over without dementia with an increased dementia risk, possessing a smartphone. Participants were recruited through seven hospitals participating in the PRODEMOS study, purposively sampled on age, sex, living area, and history of CVD and diabetes.

Results

We performed 26 interviews with participants aged 55-86 years. Three main themes were identified: valuing a healthy lifestyle, sociocultural expectations, and need for guidance. First, following a healthy lifestyle was generally deemed important. In addition to generic healthy behaviours, participants regarded certain specific Chinese lifestyle practices as important to prevent disease. Second, the sociocultural context played a crucial role, as an important motive to avoid disease was to limit the care burden put on family members. However, time-consuming family obligations and other social values could also impede healthy behaviours such as regular physical activity. Finally, there seemed to be a need for reliable and personalised lifestyle advice and for guidance from a health professional.

Conclusions

The Chinese older adults included in this study highly value a healthy lifestyle. They express a need for personalised lifestyle support in order to adopt healthy behaviours. Potentially, the PRODEMOS mHealth intervention can meet these needs through blended lifestyle support to improve risk factors for dementia and CVD.

Introduction

China has the largest population of people with dementia worldwide. The rapidly increasing incidence of dementia is expected to seriously challenge the Chinese public and healthcare system in the coming decades[1-3]. Observational studies have shown an association of lifestyle-related risk factors with dementia in people aged 65 and over[4]. An estimated 40% of dementia cases might be attributable to these risk factors[5], suggesting the potential to delay or even prevent dementia if these risk factors are successfully addressed.

For successful implementation in China, including its underserved rural areas, such dementia prevention interventions should be inexpensive and easily accessible. Digital health interventions may meet these criteria, given the wide and increasing availability of internet[6, 7]. As in China the internet is most frequently accessed through smartphones[8], digital health interventions offered as mobile health (mHealth) may be most feasible. The Prevention of Dementia using Mobile Phone Applications (PRODEMOS) study will assess the effectiveness and implementation of a coach-supported mHealth intervention to reduce overall dementia risk in older people in the United Kingdom (UK) and Beijing, China[9]. The development of this application builds on the internet platform used in the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) trial, which recently demonstrated that a coach-supported internet intervention leads to a modest improvement of cardiovascular risk profile of older adults in three European countries[10]. For PRODEMOS, the mHealth intervention will be adjusted according to the needs and wishes from the target population.

Despite a growing interest in risk factor management through mHealth, little is known about needs and views of Chinese older adults regarding lifestyle behaviour change and the potential role of mHealth. With the steep increase in unhealthy lifestyles, dementia and cardiovascular disease (CVD)-related mortality in China, this has become an urgent, national priority[11, 12]. In the current study, we aim to explore the knowledge, experiences, attitudes, needs, and views of Chinese older adults regarding healthy lifestyles for the prevention of dementia and CVD through mHealth. The results of this study will facilitate development and cultural adaptation of the PRODEMOS intervention.

Methods

PRODEMOS trial

The current qualitative study is part of the PRODEMOS randomised controlled trial (RCT). The PRODEMOS RCT aims to include 1200 older adults both in the UK and in China, with an increased dementia risk. Participants are randomised between a coach-supported mHealth intervention and care-as-usual. Main functionalities of the intervention app are similar to the HATICE platform (i.e. setting lifestyle goals, entering measurements, receiving coach-support through the chat functionality, and receiving interactive education). Dementia risk and implementation outcomes are assessed after 18 months[9].

Participants

For this qualitative study, participants were recruited through a phone call or WeChat (a common Chinese social media platform) by doctors or village leaders within the catchment areas of seven Chinese hospitals participating in the PRODEMOS study. Centres varied regarding type of care offered (general vs. specialist) and location (Beijing, urban Tai'an, and rural Tai'an area). Eligibility criteria were largely similar to the PRODEMOS study protocol: aged 55+, possession of a smartphone, non-demented, and with increased risk of dementia. Increased dementia risk was defined as ≥2 dementia risk factors, i.e. history of CVD or diabetes, hypertension, obesity, dyslipidaemia, depression, insufficient physical activity, and active smoking[8]. Participants were recruited based on their medical records, or when they visited the hospital for their regular medication prescription, and were purposively sampled on age, sex, living area, history of CVD and diabetes, and educational level. 26 out of 35 invited individuals were willing to participate in the study. Written informed consent was obtained before the start of each interview. The ethic committee of the Capital Medical University (CMU), Beijing, approved the study.

Data collection

Between February and December 2019, we performed semi-structured interviews in sets of 3-6 interviews. An interview guide (Supplement 1) was composed by researchers from CMU, Edith Cowan University, and Amsterdam UMC. It included questions about knowledge, experience, attitudes, needs, and views regarding healthy behaviours in general, their potential role in the prevention of dementia and CVD, and the perceived window of opportunity for mHealth and coach-support. Every interview was preceded by a short introduction on the PRODEMOS study. If deemed necessary, we made adjustments to the interview guide after each set of interviews (e.g. adding questions about Traditional Chinese Medicine

(TCM) and the preferred background of the coach). Nine researchers (JZ, XL, BJ, HL, WZ, JL, YN, YY, XX), performed the interviews. XL is a professor in General Medicine and has broad experience with qualitative research. BJ, HL, WZ, JL, YN, YY, and XX are medical doctors and received training in qualitative research from EMvC. To minimise between-interviewer variation, interviewers were asked to adhere to the interview guide as much as possible. The principal researcher (JZ, PhD student) attended all interviews to make field notes, and to ensure that all topics of the interview guide were sufficiently discussed. EE attended six and EMvC attended four interviews in person, with live translations into English by a professional translator. The interviews took place in the participating centres, local community venues, or at the participant's house. The interviews lasted 35-90 minutes, were audio-recorded, and transcribed verbatim. Data collection was finished once data saturation had been reached.

Coding and analysis

Thematic analysis was performed by five researchers (JZ, XZ, MS, EMvC, and EE) following the six phases as described by Braun and Clarke[13].

1. Transcripts were translated into English and shared with the Amsterdam UMC researchers. After each set of interviews, transcripts were thoroughly read by the researchers in their own language. JZ, MS and EE discussed all transcripts. A licensed translator (LB) attended to make sure that all transcripts were fully understood and appropriately translated.

2. Initial coding was performed by two researchers from CMU (JZ and XZ) independently using the MaxQDA software for qualitative research. After coding each set of interviews, codes were compared and discussed until disagreements were resolved, resulting in a new set of codes. EMvC and EE reviewed the coding of each interview during video-meetings with JZ, MS, XZ, and LB. A Dutch medical doctor with extensive knowledge of the Chinese culture and language (RT) was involved in interpretation of the findings.

3. After initial coding of all interviews, researchers from CMU and Amsterdam UMC independently searched for potential themes. Potential themes and their interrelationship were discussed during several online video-meetings, and during a face-to-face meeting in Beijing.

4. Potential themes were reviewed and organised into thematic maps. LB attended the online discussions to verify consistency with the original meaning of the texts.

All transcripts were re-read by JZ and EE to ensure that the themes were a good representation of the data.

5. Narratives were written for each theme by JZ and EE independently. The narratives were discussed with EMvC and MS. The names and arrangement of themes and subthemes were refined accordingly.

6. Illustrative examples were selected by JZ and EE, and were translated into English by LB.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

We performed 26 semi-structured interviews. Participants were aged 55-86. Demographics and medical history of the participants are presented in Table 1.

We identified three key themes: "valuing a healthy lifestyle", "sociocultural expectations", and "need for guidance". The themes and subthemes are listed in table 2.

1. Valuing a healthy lifestyle

Why it is important to live a healthy lifestyle

Many participants stressed that a healthy lifestyle is important, emphasizing the relationship between a healthy lifestyle and CVD. Some interviewees felt that living healthily could reduce the risk of future dementia. Physical activity, a healthy diet, and refraining from smoking or drinking alcohol were considered healthy behaviours.

> *-"I think the reason why my elder brothers passed away so early is that they smoked and did not exercise. [...] Only now I realise that it's not healthy to stay up late and do no exercise. Maybe they didn't realise it at that time."*

Some participants mentioned more specific, Chinese healthy behaviours, including taking footbaths, spinning walnuts, and having a balanced temperament.

Table 1. Socio-demographic characteristics and medical history of included participants.

Characteristic		**N=26**
Age (year)	Median [range]	64 [55-86]
Sex (female)	N (%)	13 (50)
Retired (yes)	N (%)	17 (65)
History of CVD (yes)	N (%)	9 (35)
History of diabetes (yes)	N (%)	13 (50)
Education level[a]	N (%)	
Primary school and below		1 (4)
Junior high school		8 (31)
Senior high school		9 (35)
College and above		8 (31)
Living situation	N (%)	
With spouse only		9 (35)
With spouse + other family		15 (58)
Alone		2 (8)
No. of risk factors[b]	N (%)	
1 or 2		8 (31)
3		12 (46)
4 or more		6 (23)
Region	N (%)	
Beijing		21 (81)
Urban Tai'an[c]		2 (8)
Rural Tai'an		3 (12)

[a]Primary school = ISCED level of 1; Junior high school = ISCED level of 2; Senior high school = ISCED level of 3; College and above = ISCED level of > 4. [b]Risk factors include diabetes mellitus, insufficient physical activity according to WHO criteria, active smoking, hypertension, dyslipidemia, obesity, and depression. [c]City in Shandong province with 5.5 million inhabitants. CVD = cardiovascular disease.

Table 2. Key themes and subthemes.

1.	**Valuing a healthy lifestyle**
	Why it is important to live a healthy lifestyle
	Experiences on improving lifestyle behaviour change
	The role of Traditional Chinese Medicine
2.	**Sociocultural expectations**
3.	**Need for guidance**
	Finding reliable, useful information
	Need for a tailored health plan and personalised support

-"It is said that spinning walnuts can activate blood vessels. I reckon it's good for preventing cerebrovascular diseases."

Some participants mentioned that, at older age, a healthy lifestyle becomes less important, because disease may already have developed.

-"I often drink alcohol, eat meat and sometimes pickled vegetables. I think these are not so good, but I feel I found out too late. The underlying diseases already developed."

Other participants mentioned that health is largely determined by destiny or genetic predisposition rather than by lifestyle behaviours.

-"I don't know [about risk factors for dementia]. But sometimes it is your fate to get sick, this has to do with genes."

Experiences on improving lifestyle behaviour

All participants had experience with lifestyle behaviour change, often triggered when a participant experienced illness. Confrontation with diseases, such as CVD or diabetes, could be a motivator to quit smoking or make changes to their diet. Also, the disease or death of a close friend or relative could be a trigger to change behaviour.

-"I quit smoking after I got sick. [...] I quit smoking straight after I had a myocardial infarction."

-"A friend from the past has cancer, which is a huge alert for us [to smoke or drink less alcohol]"

Some participants started to change their behaviour after they found out about abnormal values during regular health-checks, for example for blood pressure and cholesterol.

-"There was a time when my blood pressure was really high [...]. Then I quit smoking and started drinking less alcohol."

The role of Traditional Chinese Medicine (TCM)

Some participants used TCM to stay healthy, such as acupuncture and Tai Chi. Such activities could go hand-in-hand with other lifestyle changes, such as changes in diet. Moreover, some participants mentioned that they used medicinal

TCM to stay healthy, although most participants mentioned use of medicinal TCM to treat rather than prevent disease. Some participants did not use medicinal TCM because, in their experience, the effect of TCM comes too slow.

> *-"I practiced Tai Chi, and now we also practice Yi Jin Gong and Ba Duan Jin every morning. Since my father is in his eighties, it's more suitable for him to do this kind of low-intensity exercise. I do the same exercise together with him."*

> *-"I don't use traditional Chinese medicine very often because it works too slowly. When my blood pressure is high, the effect will be too slow after taking it. The problem of high blood pressure cannot be solved by traditional Chinese medicine."*

2. Sociocultural expectations

Participants mentioned that support from their family and friends can be helpful to start or maintain healthy behaviours. For some, the social environment was the drive to change behaviour, as they tried to quit smoking or drinking because others urged them to do so.

> *-"There is no need to be told by others because I know how to do this [a healthy lifestyle], but I don't want to do it. However, I'm especially willing to do it when my children say it once in a while."*

Similarly, family members could take the lead in lifestyle support, for example by cooking and eating healthier food for the sake of the spouse's health.

> *-"Previously, I cooked whatever he liked to eat, [...] but since he suffered from myocardial infarction, I cook with the principle of less meat, less fat and less salt."*

Participants mentioned that engaging in change together can facilitate behaviour change. Some participants went walking or square dancing together with friends, family members or people living in the same neighbourhood, and reminded each other of the intended behaviour. Drinking or smoking behaviour could also be influenced by the social environment, although sometimes in a more unconscious way.

-"[...] we live in the company dormitory in which there are more than 200 households. We often make an appointment to walk together. It really works."

-"I think it has a lot to do with the crowd. It helps if you're dealing with people who are willing to change. If there are four people, of whom three of us don't smoke and only I smoke, then I will smoke less, but if everyone does, I will smoke more. [...] Others certainly influence me."

Also, the *digital* social network could be of support. Almost all participants had experiences with use of one or more lifestyle-related mini-programs (comparable to apps) offered by WeChat. Examples of such programs are platforms for health-related knowledge exchange and lifestyle groups where peers can support each other to live healthily. For some participants, comparing their own results (i.e. number of steps) with the results of others, could serve as an impetus to further increase their efforts.

-"I think one of the best things about my participation in this weight loss program is that there is a WeChat Group. Especially when I just joined, it was also a stimulant for me to see others exercise in the group."

My son enables WeChat Sports for me. [...] When it is time, I will go out for a walk. After the walk, I will compare my steps with others. It is like a task, it motivates me.

Many interviewees had important family responsibilities, such as taking care of their grandchildren or their ill or disabled spouse and/or parents. The need to take care of others was often a motive to stay healthy, as participants feared to burden others with these care tasks or become a burden to others if they themselves would develop disease. Apart from being a motive, time-consuming family responsibilities were sometimes a barrier for healthy behaviours, such as physical activity.

-"If we are in good health, the burden on our children will be less. Otherwise, [...] our children's burden will increase."

-" It feels like I'm spending too much time taking care of my family, and then neglect my own health. I feel the family burden is too heavy."

Some participants experienced conflicts between the choice for improved lifestyle behaviours and meeting social expectations, as participants seemed to associate smoking and drinking alcohol with hospitality. Participants mentioned difficulties to forbid guests to smoke in the house, leading to secondary smoking, especially when guests were not part of the inner social circle. Moreover, some participants were inclined to accept cigarettes or drinks, as a courtesy, when offered by others.

-"It annoys us if guests smoke in our house, my husband says not to let them come in our house in the future. But once the guests have arrived, how can we say that they cannot come?"

"[...] if my son-in-law comes over, I won't tell him not to smoke here. I can persuade my son and daughter, but not my son-in-law."

3. Need for guidance

Finding reliable, useful information

Most participants were willing to improve their lifestyle behaviour but did not know how to achieve this all by themselves. Most interviewees obtained their health information from TV or WeChat, yet often questioned its general reliability and applicability to their personal (health) situation.

-"I just think there's too much information on Baidu [Chinese search engine, comparable to Google], sometimes it's not all correct and sometimes it doesn't fit my disease condition."

Participants expressed a need for comprehensive information about the CVD risk factors or diseases they suffered from, and personalised advice on how to improve these conditions.

-"I need guidance from others. It should be based on my actual situation, instead of just telling me how to do, which may be harmful to me. I hope it will be a personalised guidance focusing on me."

Need for a tailored health plan and personalised support

Participants called for a health plan, suited to their needs and abilities. Such a plan would need to be quite clear-cut, for example about what, when and how much one should eat in their specific situation.

-"[I need information] for example, how to do exercise; when and how long do I need to sleep? In terms of meals, it should be specific: what to eat, what I can eat and the most important is how much to eat, requiring a refined recipe."

On the other hand, some participants mentioned that guidance should not be too strict, because making too major changes at once would be unrealistic.

-"Other people can give me advice. I'll follow it if I think it works, but it should not be too strict. For example, if you tell me I can't eat meat for a week, I can't do that."

Ideally, lifestyle advice should be given by a health professional best qualified for this task. Some participants felt that this was best done by doctors, given their expertise on the complex interplay of disease, medication, and lifestyle behaviours. However, many interviewees realised that doctors often lack the time to provide intensive lifestyle support. Some felt that nurses could take on the role of competent lifestyle coaches, provided that they would be supervised by doctors.

-"I think nurses may be less professional, but provide better service. Nurses may be more patient in communicating with others, but less knowledgeable than doctors."

-"If nurses are unable to answer questions, I believe [...] doctors can provide guidance. Moreover, you don't have to answer me in real time, just give me guidance after your discussion."

Discussion

Summary of main findings

In this study on perspectives regarding healthy lifestyles to reduce dementia and cardiovascular risk among Chinese older adults, we identified three main themes. First, following a healthy lifestyle was generally regarded important. In addition to generic healthy behaviours, participants considered certain specific Chinese behaviours healthy, including tai chi, and acupuncture. Second, sociocultural context played an important role in lifestyle behaviour change. The main motive to stay healthy was to limit the burden put on family members, because, by Chinese tradition, children often take care of their elderly parents and (retired) parents take care of grandchildren. However, family responsibilities may also impede

healthy behaviour such as regular physical activity. Moreover, other Chinese social values, such as being hospitable to guests by allowing them to adhere to smoking and drinking habits, sometimes conflicted with own intended health behaviours. Third, participants often regarded information on TV and WeChat as too generic or incorrect. There seemed to be a need for reliable and personalised lifestyle advice and guidance from a health professional.

Comparison with existing literature

The interviewees appeared well aware of the relationship between lifestyle and chronic disease risk. This finding is in contrast with a survey performed in 2013 among 925 elderly living in Jinan, China, suggesting that participants had limited knowledge on and awareness of the relationship between lifestyle behaviour and chronic disease risk[14]. Moreover, comparable studies on health literacy in general showed lower rates among people of higher age groups[15, 16]. Since we specifically aimed for participants with known vascular risk factors, this may have led to selection of people with increased awareness for (secondary) disease prevention, as was also found in a cross-sectional study comparing 46,000 Chinese people with and without CVD[17]. Another explanation may be that, in recent years, prevention of dementia and CVD has become central to the agenda of Chinese policymakers. The 2008 healthcare reform has strongly focused on improving preventive healthcare and health education[18, 19], for example through large-scale health promotion through TV programs, and several public health strategies to discourage cigarette smoking and reduce salt intake in larger cities such as Beijing[7, 20]. This increased public attention may have contributed to interviewees' awareness of healthy lifestyles in the prevention of diseases.

Our interviewees indicated that being accommodating to guests sometimes conflicted with their own healthy behaviours. This finding is in accordance with results from a focus group study in Beijing, where adults (30+) believed that smoking and drinking alcohol were necessary to earn respect from their guests[21]. In the Chinese culture, drinking alcohol - traditionally as an important part of special celebrations and festivals - and sharing tobaccos are common ways to show respect, especially in rural areas[22, 23]. China's most recent national health policy 'Healthy China 2030' focuses especially on promotion and popularization of healthy lifestyles. Perhaps, with continuous public attention, and alcohol and tobacco control strategies that take cultural aspects into account, healthy behaviours will more and more become part of Chinese sociocultural habits, starting in younger and urban communities[24].

Our participants expressed a need for professional guidance, which is in accordance with a previous qualitative study among Chinese rural adults. They were highly motivated to change their behaviour but were unable to succeed without professional support[21]. In China, many health-related information is available on Chinese internet. However, the needs of end-users are not always met, as they find it difficult to judge the validity of health information on the internet[25]. Moreover, existing apps often lack personalised and professional guidance[26, 27]. China has approximately two doctors per 1000 inhabitants, compared to 3.6 in the European Union[21, 28]. Although our interviewees often considered doctors most qualified for lifestyle support based on their expertise, some realise that doctors may lack the time to meet their needs. For many participants, lifestyle support given by a nurse or other healthcare professional would therefore be acceptable, especially when supervised by a doctor.

Strengths and limitations

A strength of our study is our purposive sample with participants who differ regarding their CVD history, living situation, and education level. This approach gave us an extensive overview of the potential attitudes, needs and wishes of Chinese older adults living in the Greater Beijing area. We were able to build on previous qualitative research experiences on evaluating lifestyle coaching and use of digital self-management applications in Europe[29-32]. In order to overcome cultural and language barriers, a licensed interpreter was involved in the translations of all interview transcripts and multiple in-depth discussions of our (preliminary) findings with the Chinese partners and other experts in Chinese culture and language. Furthermore, the interview guide was aimed at discussing examples from daily experiences to limit the chance of socially desirable answers. We followed the consolidated criteria for reporting qualitative research guidelines to improve the interpretation and reproducibility of our results[33].

A limitation of our study is that most of our interviewees lived in the urban Beijing area. This limits our scope to urban older adults, where there are considerable differences between urban and rural areas in China regarding healthcare and awareness for disease prevention[19, 34, 35]. Another potential limitation is that some interviewers and interviewees had a doctor-patient relationship. This may occasionally have led to selective questions or socially desirable answers. We have deliberately decided on this approach, because, in Chinese culture, private issues, including lifestyle behaviours, are most easily discussed with people who are well trusted. An independent researcher was present at all interviews to standardise the interviews.

Implications for practice and research

Despite high awareness for disease prevention and motivation to adopt a healthy lifestyle, Chinese older adults expressed a strong need for tailored lifestyle support from a health professional. With approximately 67% of inhabitants owning a smartphone in 2020, China is in the top 10 countries with highest smartphone coverage[36]. There are many Chinese smartphone applications and mini-programs to help individuals adopt a healthier lifestyle. However, only very few have been scientifically studied or validated[37]. Fuelled by the findings of our study, we have tried to adjust the PRODEMOS intervention to the needs and wishes of the Chinese target population. The PRODEMOS app will be embedded as a mini-program in the WeChat environment. Results from other apps or mini-programs, such as step counters, will be automatically transferred to the PRODEMOS mini-program. If desired, participants can choose traditional Chinese options to work on their healthy lifestyle, including tai chi and square dancing, although our intervention, which focuses on lifestyle rather than medication use, does not include advice on medicinal TCM. To facilitate peer support, the platform will enable participation of a spouse and other cohabitating relatives in the same study arm, and offers 'peer videos', showing experiences of other older adults who changed their lifestyle behaviours. Based on the needs and wishes for coaching, PRODEMOS participants will receive trustworthy health information and personalised coaching, tailored to the participant's health condition and social environment. To optimally fit into Chinese current practice, coaching in PRODEMOS will be performed by nurses, with supervision from a doctor. Coaches will be specifically trained to provide lifestyle advice that matches well with daily routines of participants, involving relevant peers. Specific attention will be paid to sociocultural values, such as time constraints due to family responsibilities, which may complicate (sustained) behaviour change.

The mHealth intervention will be tested in an RCT in the greater Beijing area in the coming years. Facilitating a personalised approach, it has the potential to support Chinese older adults to improve their lifestyle related risk factors for CVD and dementia.

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Supplementary material

Supplement 1: interview guide, translated from Chinese

1. Introduction

My name is [name] and I work for [institution]. We are doing research on a healthy lifestyle. We are currently developing a smartphone application that should help people aged 55 years or older to live healthier, in order to decrease their risk to live healthier. There will also be a coach involved to help people with this. We want to understand what the wishes are of people aged 55 or older. I have conversations with some of those people and you are one of them. Thank you very much for participating in this interview!

We would like to talk with you about your lifestyle, for instance about your physical exercise, your diet and other habits. Our research subject is dementia. Dementia is an old age disease. For that reason we're looking for older people to talk with. We would like to talk with you about this disease. The interview will be about your experiences, so please tell us whatever you can think of. Everything you will tell us important and interesting for us. The interview will take about 45 minutes and will be audio taped. Before we start, I'd like to let you know that we will not share the information with other people outside our research team. The audio tapes will anonymously be stored in our office.

2. Demographics

a) Date of birth

b) Place of birth

c) Place of residence

d) Living situation: living on your own / living with a partner / living with (grand) children / living with others

e) Level of education

f) (Former) profession

3. Introduction of participant

Before we get started, I want to get to know you a little better. Would that be ok? Happy to tell you about me as well if you like. This is to discuss what your daily life looks like.

a) Could you please tell me something about your daily life?

    a. What do you do on a regular day? Do you still work? What kind of work do you do? Do you have hobbies? Do you regularly see friends or family?

    b. Are you happy with your daily life, or are there things you'd like to change? Many people experience stress, for example due to their work. Do you experience any occupational stress? Or are there any other stress factors that have considerable influence on your daily life?

4. View on self-management of a healthy lifestyle

As I told you, we are doing research on a healthy lifestyle. I'd like to talk with you about your habits that are related to your health, such as smoking and physical activity. Is that ok?

a) Can you tell me something about your lifestyle behaviour?

    a. Are you physically active? What kind of activities do you do?

    b. What does your diet look like? Describe me what kind of food you eat during the day. Do you cook yourself, or does somebody else cook for you?

    c. Do you smoke tobacco? What kind of tobacco do you smoke? How much do you smoke? At what age did you start?

    d. Do you drink alcohol? What kind of alcohol do you drink? How much do you drink? At what age did you start drinking?

b) Everybody has certain behaviour or habits that are healthy or unhealthy. Some people try to change certain behaviour into more healthy behaviour. Have you ever tried to change certain aspects of your behaviour? [to researcher: please ask that apply, according to their habits mentioned previously]

    a. Have you ever tried to become more physically active (for example in order to lose weight)?

i. Why did you try that? Was there a trigger?

ii. How did you do that?

iii. Did you manage to increase your physical activity? What aspects made it hard to increase your physical activity? [for researcher: think of work-related stress, caring for others, financial problems, environmental aspects etc.] What aspects helped you to increase your physical activity? [for researcher: think of support from others, support from healthcare workers, seeing results etc.]

b. Have you ever tried to change your diet into a more healthy diet (for example to lose weight)? i. Why did you try that? Was there a trigger?

ii. What did you change / How did you do that?

iii. Did you manage to change your diet? What aspects made it hard to change your diet? [for researcher: think of work-related stress, caring for others, financial problems, environmental aspects etc.] What aspects helped you to change your diet? [for researcher: think of support from others, support from healthcare workers, seeing results etc.]

c. Did you ever try to stop smoking tobacco? i. Why did you try that? Was there a trigger?

ii. How did you do that?

iii. Did you manage to quit smoking? What aspects made it hard to quit smoking? [for researcher: think of work-related stress, caring for others, financial problems, environmental aspects etc.] What aspects helped you to quit smoking? [for researcher: think of support from others, support from healthcare workers, seeing results etc.]

d. Did you ever try to stop drinking alcohol? i. Why did you try that? Was there a trigger?

ii. How did you do that?

iii. Did you manage to quit / decrease drinking? What aspects made it hard? [for researcher: think of work-related stress, caring for others, financial problems, environmental aspects etc.] What aspects helped you to quit/decrease drinking? [for researcher: think of support from others, support from healthcare workers, seeing results etc.]

e. Have you ever tried other aspects of your behaviour?

i. What did you change?

ii. Why did you try that? Was there a trigger?

iii. How did you do that? Was it successful? What aspects made it hard? [for researcher: think of work-related stress, caring for others, financial problems, environmental aspects etc.] What aspects helped you? [for researcher: think of support from others, support from healthcare workers, seeing results etc.]

c) Did you ask for support of others, when you tried to change your behaviour? [please relate to one or more attempts to change behaviour mentioned by the participant]

a. [if no] Why didn't you ask for support? Were you hesitant / embarrassed to ask somebody? Or was there nobody available? Have you considered to ask anybody for support?

b. [if yes] Who did you ask for support? Why did you ask this specific person? Could he/she help you to continue your behaviour change? How did he/she do this?

5. Risk of cardio- and/or cerebrovascular disease and dementia.

As I told you in the beginning, we are currently developing a smartphone application that should help people to live more healthy, in order to decrease their risk to develop dementia and other disease, such as cardiovascular disease and cerebrovascular disease. I'd like to talk with you about these diseases.

a) Do you know people with dementia? Or do you know something about dementia?

a. What do you know about this disease?

b. How do you see your own risk to develop dementia? Do you fear that?

c. Do you have the feeling that there is anything you can do to prevent dementia? Are there things you do to prevent dementia?

b) Do you know people who suffer from cardio- or cerebrovascular disease, such as a heart attack or stroke?

c) Do you yourself suffer from such disease?

a. [If no] Do you know what risk factors you have? How do you see your own risk to suffer from such disease? Do you fear that? Do you have the feeling that there is anything you can do to prevent such disease? Are there things you do to prevent cardio- and cerebrovascular disease?

b. [If yes] How do you see your own risk to suffer again from such disease? Do you fear that? Do you have the feeling that there is anything you can do to prevent such disease? Are there things in your behaviour you have changed since the cardio- or cerebrovascular disease?

d) Do you have cardiovascular risk factors?

a. Are you overweight? [If yes] since when are you overweight?

b. Do you have high blood pressure? [If yes] How long do youknow that you have highblood pressure? Do you use antihypertensive medication?

i. Tell me about the use of the medication? How often do you use it? Do you use different drugs? Do you have difficulties taking the medication?

c. Do you have high cholesterol? [If yes] How long do you know that you have high cholesterol? Do you use statins?

i. Tell me about the use of the statins? How often do you use it? Do you use different drugs? Do you have difficulties taking the medication?

d. Do you have diabetes? [If yes] How long do you know that you have diabetes? Do you know how diabetes is optimally controlled? What do you know about the target levels [of glucose or HbA1c]

i. Do you have medication for diabetes? How often do you use it? Do you use different drugs? Do you have difficulties taking the medication?

e) Can you think of other potential risk factors for cardiovascular disease, such as second hand smoking? [It can be hard to change lifestyle when the person(s) you live with has certain (unhealthy) behaviour. If somebody is living with a partner, other family members or roommates: Can you tell me something about the lifestyle and risk factors of your partner / familymember/ room mate? Do they smoke tobacco/ do they drink/ do they have certain less healthy diet habits? To what extent does that influence your own healthy behaviour? For example, is your partner /family member / roommate involved in cooking your meals?

6. View on sustained lifestyle changes through mHealth / lifestyle apps+ remote coach

Like I said in my introduction, we aim to design an app for the smartphone or tablet that could help you to improve your lifestyle behaviour and to decrease dementia risk.

a) Do you have a smartphone[mobile phone with apps, such as Wechat]?

a. What do you use your smartphone for? When do you use it?[use at home,or also use in public transport/while shopping etc.]

b. Do you need others (family or friends) to help you with the smartphone?

b) Do you haveother devices, such as desktop computeror laptop?

a. [If yes] What things do you prefer to do with your computer / laptop / tablet instead of your smartphone? Why?

c) Have you ever used your smartphone to improve your lifestyle? [I.e. apps to count calories; to improve physical activity; quit smoking].

a. What kind of app / website was that? When did you start using it? How did that go? How did the app help you? What aspects did you like? What did you dislike? Why did you stop using the app? Did you need others (family / friends) to help you with the app?

b. What would you worry about health management using this kind of app? What would you request or expect on this app?

d) How could an app help you?

a. Do you think that an app can help you to have a more healthy lifestyle? [If not] Why not?

b. For what kind of behaviour change would you use the app? [think of increasing physical activity, diet change, quit smoking/drinking etc.] Why? Are there any aspects you think you will never be able to change?

c. What should such an app be able to do for you?

i. Would you use the app to enter your behaviour (for example: physical activity) or the results (for example: your weight)? [If not] Why not?

ii. Would you like an app that facilitates contact with other people like you? [If yes] How would you use that function? [If not] Why not?

iii. Could the app help you by offering information about a healthy lifestyle, or do you prefer to search the internet yourself?

iv. Do you have other suggestions for the app to help you to improve your lifestyle?

e) The app we are currently developing will be linked to a remote coach.

a. What would you think of a lifestyle coach, that is attached to the app? Why would(n't) that be helpful? What do you expect from such coaching?

b. What do you consider important in such a coach? [education, approach etc.]

c. Is it important for you to have met the coach in real life? What is your preferred way to have contact with the coach? [Wechat / phone calls etc / face to face / video message etc.]

d. How often would you like to have contact with the coach?

e. How would you prefer to receive feedback? [Automatic? SMS? Message from coach?]

f. Do you use WeChat ? How long do you use WeChat on average?

f. Do you follow with interest (pay attention to) the WeChat Public Number or WeChat applet related to health care? Would you prefer us to guide your lifestyle through WeChat or App?

7. End of interview

We have come to the end of our interview. Thanks so much for your help!

- Are there any things that you would want to add? Do you have any questions?

5

6

Design and development of a mobile health (mHealth) platform for dementia prevention

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Abstract

Background

Mobile health (mHealth) has the potential to bring preventive healthcare within reach of populations with limited access to preventive services, by delivering personalized support at low cost. Although numerous mHealth interventions are available, very few have been developed following an evidence-based rationale or have been tested for efficacy. This article describes the systematic development of a coach-supported mHealth application to improve healthy lifestyles for the prevention of dementia and cardiovascular disease in the United Kingdom (UK) and China.

Methods

Development of the Prevention of Dementia by Mobile Phone applications (PRODEMOS) platform built upon the experiences with the Healthy Aging Through Internet Counseling in the Elderly (HATICE) eHealth platform. In the conceptualization phase, experiences from the HATICE trial and needs and wishes of the PRODEMOS target population were assessed through semi-structured interviews and focus group sessions. Initial technical development of the platform was based on these findings and took place in consecutive sprint sessions. Finally, during the evaluation and adaptation phase, functionality and usability of the platform were evaluated during pilot studies in UK and China.

Results

The PRODEMOS mHealth platform facilitates self-management of a healthy lifestyle by goal setting, progress monitoring, and educational materials on healthy lifestyles. Participants receive remote coaching through a chat functionality. Based on lessons learned from the HATICE study and end-users, we made the intervention easy-to-use and included features to personalize the intervention. Following the pilot studies, in which in total 77 people used the mobile application for 6 weeks, the application was made more intuitive, and we improved its functionalities.

Conclusion

Early involvement of end-users in the development process and during evaluation phases improved acceptability of the mHealth intervention. The actual use and usability of the PRODEMOS intervention will be assessed during the ongoing PRODEMOS randomized controlled trial, taking a dual focus on effectiveness and implementation outcomes.

Introduction

The projected worldwide increase in dementia prevalence is expected to largely occur in low- and middle-income countries and amongst hard-to-reach populations in highincome countries[1,2]. An estimated 30–40% of late-life dementia appears to be attributable to potentially modifiable risk factors, including smoking, insufficient physical activity, and unhealthy diet[3]. Interventions targeting these risk factors may have the potential to delay or prevent dementia onset and could be especially beneficial for vulnerable populations, given their high exposure to high risk of these behaviors[4,5].

The rapid increase of internet access through mobile devices may have the potential to bring preventive healthcare within reach of large groups of people who have limited access to preventive services[6]. Mobile health (mHealth) applications can contribute to personalized care and remote delivery of health messaging and services, at low cost and on a global scale[7,8]. Seizing the business opportunity healthcare applications have mushroomed, rising to over 90 000 in app stores in the first quarter of 2020[9,10]. However, very few of these have been developed following an evidence-based rationale, or have been tested for efficacy in a (randomized controlled) trial. While the conceptualization and architecture of such mHealth interventions are key aspects of development with respect to its perceived usability, uptake, and ultimately success, guidelines to design mHealth interventions for vulnerable populations are not readily available[11].

In the Prevention of Dementia using Mobile Phone Applications (PRODEMOS) trial, we will assess the effectiveness and implementation of a coach-supported mHealth platform to reduce dementia risk over a period of 18 months. The study population will consist of 1,200 older adults with low socioeconomic status (SES) from the United Kingdom (UK) and 1,200 older adults from Beijing, China, all with 2 or more lifestyle factors at levels associated to an increased dementia risk[12]. In this article, we describe the development of the PRODEMOS mHealth intervention, from general idea to platform design, and from prototype to pilot study. We make specific recommendations on mHealth design for vulnerable populations, based on extensive interactions with the target population and other important stakeholders, including health care professionals, software developers, and researchers.

Methods

Context of PRODEMOS Study

The platform described in this paper was designed as part of the PRODEMOS trial. Development of the PRODEMOS platform built on the Healthy Aging Through Internet Counseling in the Elderly (HATICE) eHealth platform, which was designed and piloted between 2013 and 2016 and proven effective for lowering cardiovascular risk amongst European older adults in a randomized controlled trial (RCT)[13, 14]. The coach-supported HATICE platform enabled self-management of cardiovascular risk factors, integrating European guideline recommendations on prevention of cardiovascular disease (CVD) and principles of Bandura's social-cognitive theory of self-management and behavioral change[15].

In PRODEMOS, we will focus on dementia prevention, however, with up to 50% of modifiable risk factors for dementia being cardiovascular risk factors we were still able to incorporate experiences and evidence from the HATICE trial[3, 16, 17]. Given the rising smartphone penetration rates worldwide[18], and because especially in LMIC people tend to access and use the internet through smartphones rather than personal computers[19], we decided to develop the PRODEMOS platform as an mHealth intervention. The PRODEMOS platform is built to facilitate the self-management of risk factors for dementia, including overweight, hypertension, high cholesterol, diabetes, unhealthy diet, smoking, and insufficient physical activity. In line with the HATICE platform, PRODEMOS participants are able to set SMART (Specific, Measurable, Achievable, Realistic, Timely) lifestyle goals, enter measurements, read goal-related education materials, and receive personalized lifestyle- and goal setting support via chat messaging from a remote coach.

The mobile application will be connected to a coach portal, allowing for remote lifestyle support by a health coach. The PRODEMOS platform also comprises a separate assessor- and researcher portal for data collection and outcome assessment, and a static mobile application with written healthcare advice only and without interactive features, for those randomized to the control condition of the trial. The assessor- and researcher portals and control application have been designed within the research context of the PRODEMOS project, of which the protocol is described in more detail elsewhere[12]. Figure 1 shows the components of the PRODEMOS platform and their interrelationships. All key functionalities of the PRODEMOS platform will be similar in the UK and China. Besides differences in language, certain cultural adaptations will be made to ensure adequate fit of the intervention with the target population. The PRODEMOS mobile application will be built to support participants with limited digital literacy, operationalized as at least being able to send a message using a smartphone.

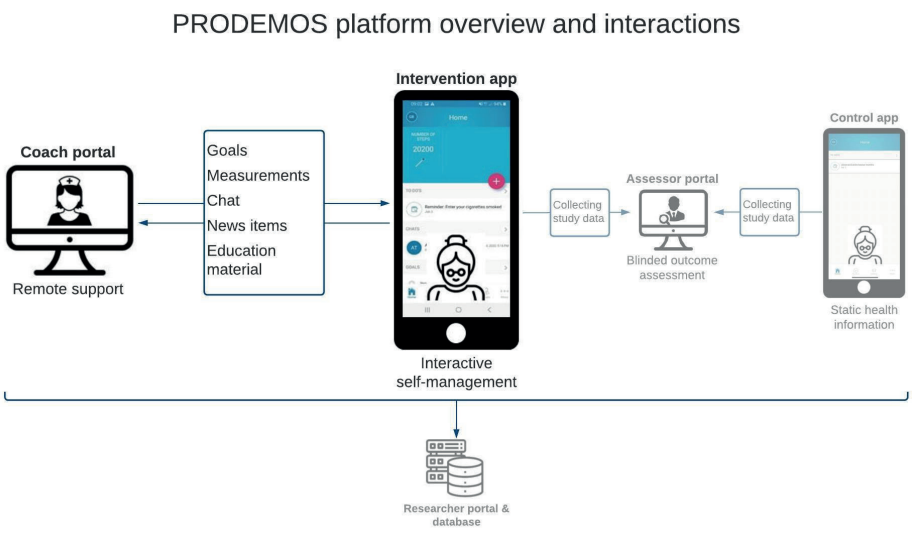

Figure 1. Overview of the PRODEMOS platform and its interactions

Phases of Development

The development of the PRODEMOS platform is visualized in Figure 2. Although technical interventions are typically developed in an iterative cycle of overlapping phases, several distinct phases can be distinguished in the development of the PRODEMOS platform.

1. Conceptualization

First, we performed a thorough evaluation of the HATICE platform, focusing on the perceived value and usability of the eHealth intervention, as well as on the overall implementation. Through thematic analysis of semi-structured interviews with HATICE participants, we learned which factors affected initial and sustained engagement with the eHealth platform[20]. In subsequent focus groups, we asked HATICE participants and coaches to share their experiences, views and recommendations for future use of the platform and coach support. Following this, we assessed the specific needs and wishes of the PRODEMOS target population regarding an mHealth intervention to change their lifestyle behavior. We performed semi-structured interviews with 19 low SES Dutch older adults and 26 Chinese older adults and thematically analyzed them[21]. To gather further data on the needs of the target population for successful use of the platform and remote coaching, focus group sessions with older adults of low SES were held in both the UK and the Netherlands. In separate sessions, other stakeholders, including Clinical

Research Network nurses and experienced health coaches, were interviewed about their perspectives regarding coach-support for vulnerable populations.

2. Initial technical development

Based on the HATICE eHealth platform and the additional lessons learned, the study group drafted an outline capturing all necessary functionalities for the new portal and mobile application. Initial technical development was undertaken by Philips Vital Health (PVH; for the UK) and Fuzhou Comvee Network & Technology (Comvee; for China) in 2-weekly "sprint" sessions over 4–6 months, according to the agile principle[22]. In iterative cycles, researchers from the coordinating research team at Amsterdam UMC provided detailed descriptions of all desired functionalities and gave feedback on functionalities that were newly developed.

3. Evaluation and adaptation

Following initial technical development, the functionality of the portal and mobile application were meticulously evaluated. Software experts from PVH and Comvee and researchers from the coordinating research team, UK, and China internally tested the software. During "thinking aloud" sessions, we asked potential participants to navigate through the mobile application and directly share their thoughts with the developers. The developers also tested user experience (i.e., how the participants interact with the mobile application) and the user interface (i.e., the look and feel, presentation, and interactivity of the mobile application) with potential participants using predefined scripts and success criteria for participants to navigate through the most important functionalities of the application. The functionality of the portal and mobile application was subsequently trialed in sixweek pilot studies in the UK and China. We used qualitative data, gathered through focus groups with pilot participants and participating coaches, and data on user statistics to evaluate usability. User statistics included details on goals, measurements, and chat history and were gathered manually from the platform, as the automated export functionality for user statistics had not been finalized by that stage. Findings from the internal test sessions, thinking aloud session, and pilot evaluation informed the final adaptation phase, in which the portal and mobile application was prepared for use in the full trial.

Unless stated otherwise, all qualitative sessions were led by at least one member of the research team and one member of the technical team, following a topic guide. We audiotaped all sessions and shared written summaries with the coordinating research team. Through plenary discussions between the researchers and technical developers, we translated the evaluation results into concrete development steps when deemed appropriate and feasible. More detail on demographics, methodology and recruitment of the evaluation processes is provided in Supplement 1.

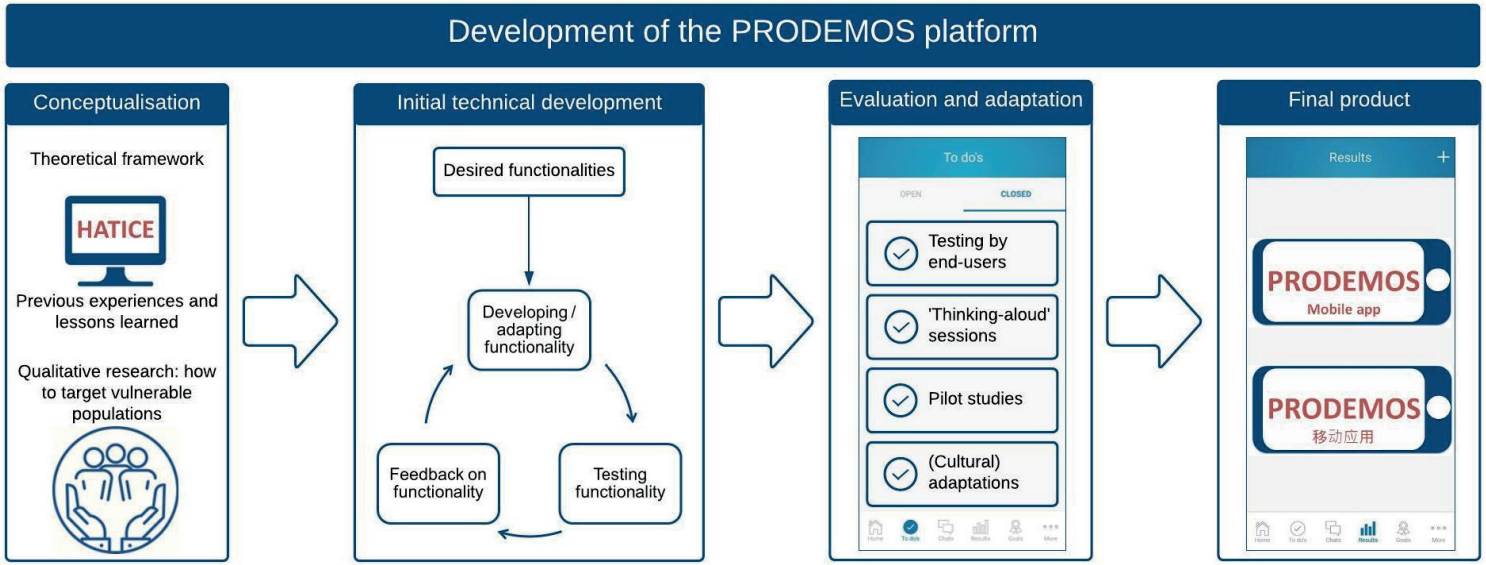

Figure 2. Phases of development of the PRODEMOS platform

Results

Conceptualization phase

Lessons Learned From the HATICE Study

Prior to the start of the development of the PRODEMOS mHealth portal and mobile application construction, a qualitative evaluation among participants and coaches of the HATICE intervention took place. This demonstrated that most participants had appreciated the HATICE platform and coach support, and felt that it had helped them to pursue their lifestyle goals. Participants had used the platform mostly in a reactive way, by responding to notifications about chat messages and questionnaires[20]. To capitalize on this finding, more (automatic) reminders to enter measurements were built in to the PRODEMOS mobile application, the frequency and content of which can be adjusted to the participant's needs. The qualitative evaluation of HATICE also revealed that participants had a wish for more tailored and frequently updated education material to stimulate sustained engagement over time. Furthermore, they expressed a need for more options to tailor the intervention to (changes in) their personal situation. As a response, we developed several additional features to facilitate personalization of the intervention, as displayed in Supplement 2. Some HATICE participants noted that they had rarely used several functionalities of the intervention and thought that additional guidance, e.g., by adding a tutorial video on the home page, could help participants to make more use of all features of the platform. We therefore built an explanatory animation video accessible through the library of the mobile application, covering the main functionalities of the PRODEMOS application.

From the HATICE trial, we learned that coach support was very important to stimulate both initial and sustained platform use. Participants expressed a need for active encouragement from the coach when a goal was reached or when their commitment weakened. Similarly, as HATICE coaches would have liked to keep better track of their participants' progress, we redesigned certain functionalities of the coach portal to facilitate better support of participants, as shown in Supplement 2.

Lessons Learned From Potential PRODEMOS End-Users

Input from focus group sessions and individual interviews with older adults at increased cardiovascular risk in China and of additional low SES in the Netherlands and the UK, and focus groups with healthcare professionals in the UK and China was used to tailor the intervention to the PRODEMOS end-users. For the current section, we distinguish aspects of user-friendliness and personalization of the PRODEMOS mobile application.

User-Friendliness: As previously mentioned by the HATICE participants, members of the target population expressed the desire for a simple and intuitive-to-use mobile application, for example as suggested by a 77 year old male interview participant: "If you're going to introduce this [app], you'd really have to educate a group of people, like how do you use something like that?." Both potential coaches and participants favored pre-set options for lifestyle goals, to ensure easy-to-achieve and feasible goals. We developed the goalsetting flow in such a way that participants are able to build their lifestyle goals in several consecutive steps with wide choice from pre-set options, using the SMART principle (e.g., losing weight by increasing physical activity levels by walking twice a week for 30 mins). Participants also indicated the need for positive framing (e.g., 'improving blood pressure' as opposed to 'working on high blood pressure') and easy (non-medical) language, for example a 63 year old female interview participant: "[The app has to be] understandable! Don't go tossing around big words and medical terms and all that." For this, we have adapted the wording throughout the mobile application. Another important aspect of a user-friendly intervention was trustworthy and easy-to-understand material. Lastly, we have simplified login procedures, to facilitate easy access (Supplement 2). Based on wishes from the Chinese target population, we made the Chinese mobile application available as a WeChat subapplication or "mini-program." WeChat is a widely used Chinese multi-purpose messaging, social media, and mobile payment application with a wide range of such mini-programs.

Personalization: In addition to user-friendliness, personalization of and flexibility during the intervention were regarded important aspects of (digital) lifestyle support. We learned from interviews with members of the target population that their lifestyle goals are often very specific, person-related, and result-driven on the short term (e.g., losing weight to fit in their favorite jeans rather than to prevent future chronic disease; 63 year old male interview participant *"[. . .]I can hardly tie my shoelaces. And look, that annoys the hell out of me. But now I've been wearing slippers for 3 months [. . .]so now I'm not annoyed. And soon I'm gonna have to wear my shoes again, and maybe that will cause to flip a switch."*). Also,

members from the target group mentioned that lifestyle advice should be tailored to their personal situation. As we learned that Chinese elderly often perform tai chi or square dancing (i.e., low-key dancing groups on public squares) in order to stay active, we included corresponding options to the Chinese mobile application. A comprehensive overview of adaptations made to the mobile application based on input from the PRODEMOS target population can be found in Supplement 2.

Technical development

Following the lessons learned, technical development of the UK platform commenced in April 2019. In accordance with the project planning, development in China started in July 2020. Due to differences in hosting requirements between the countries, both platforms were developed and hosted in separate environments in the UK and China. As mentioned previously, both platforms were developed based on the same concepts and requirements, with certain cultural adaptations wherever deemed necessary.

The development of the platforms followed an iterative process, allowing for timely redirection and adaptations. Development was evaluated every other week with the European and Chinese software developers. To bridge the gap between (medical) researchers and technical developers, we used storyboards, containing user-stories, and functional flow block diagrams, mapping all connections between the coach portal and the mobile application. The platform and mobile application were ready for preliminary internal testing by the developers and coordinating research team 5 months after the initial start of development. An overview of the basic functionalities of the PRODEMOS application can be found in Supplement 3.

Evaluation and adaptation phase

Internal Testing

After internal testing by the technical developers, the software was meticulously tested by the coordinating research team to detect potential technical issues, e.g., software bugs. One or more software developers were present during these test sessions to immediately investigate encountered issues and to deliver technical support where needed. After several test cycles, researchers and health coaches from the British and Chinese teams gained access to the mobile application and coach portal to interactively test the system over a longer period of time. The majority of findings concerned software bugs that had to do with the interaction between the mobile application and coach portal. Findings were recorded in a living document. After prioritization on relevance, urgency, and feasibility in collaborative sessions, findings were resolved by the software developers.

User Test and Pilot

After internal testing, the platforms were evaluated through thinking aloud sessions and pilot studies. The thinking aloud session provided good insight into the (intuitive) handling of the mobile application by our target population. Findings yielded mostly suggestions to further improve its usability and userfriendliness. Subsequently, the mobile application and portal were tested in a six-week pilot study in both the UK (n = 21) and China (n = 56). This way, we gained information about frequently used and potentially neglected functionalities and options in the app (e.g., goals were often set by sending chat messages to the coach rather than by using the goal-setting engine; the library was often overlooked).

In the UK, participants indicated the need for more intuitive operationalization of the mobile application with a consistent user interface. Text density and font size needed to be adjusted to better suit the target population. Moreover, log-in procedures were often found to be too complex. In China, as there is already a lot of information available on WeChat, participants stressed the need for more in-depth education material.

Coaches in the UK expressed the need to further improve the graphical overview of the progress of participants. Moreover, coaches felt like they would be able to support participants better if they were able to help participants with their goal setting by adjusting certain aspects, such as the evaluation date or the goal target, to make the goals more achievable or relevant. Additionally, coaches in China indicated the need for more extensive instructional information explaining the mobile application and coach portal. A more detailed description of adaptations made to the mobile application and platform based on the evaluation findings is displayed in Supplement 2.

Discussion

In this paper, we describe the design, development, and piloting of an mHealth portal and mobile application for the prevention of dementia in the context of the PRODEMOS trial, building upon the existing evidence and experience from the HATICE eHealth platform. Based on extensive input from all stakeholders involved, we developed a platform for behavior change for older adults, with adaptations for specific needs from the low SES population in the UK and the general population in China.

For the thorough development of an mHealth platform, many stakeholders from several backgrounds need to be involved, including researchers, healthcare professionals, software developers, and the target population. We believe clear communication is crucial to understand each other's idioms and ways of thinking during development and evaluation. We identified several learning points for open and clear communication between the involved parties. Structural (weekly) meetings stimulated transmission of knowledge and updates on progression. We believe this kept the whole team informed on advancement and allowed timely redirection if necessary. During these meetings, we kept structural documentation on wishes, adaptations and platform errors.

Involving potential end-users in the development process is thought to result in a more appropriate platform design[23–26]. To optimally benefit from the feedback of (potential) end-users, we think the timing of these evaluation sessions is of great importance. Early involvement of end-users may be ideal, giving the developers sufficient time to optimally translate feedback into platform development. However, we learned that obtaining specific feedback on platform functionalities in the early stages can be very challenging for potential endusers, given its theoretical and conceptual rather than practical setting. Demonstrating a prototype of the platform, by using clickable designs and wireframes, can make these concepts more tangible, probably increasing the yield of end-user involvement in platform development. User testing of the preliminary functionalities through thinking aloud sessions greatly improved our insights in potential pitfalls of the platform and allowed for early adaptations. Our experience was that the direct presence of software developers during these sessions can benefit the usercentered design process, resulting in more mutual understanding and, ultimately, greater efficiency and quality.

Limitations

While the evidence-based development of the PRODEMOS portal and mobile application provides exciting opportunities to test the efficacy and implementation of an mHealth intervention in vulnerable populations, we faced several limitations. During focus groups, potential end-users expressed a wish for peer contact and activities to initiate and sustain behavior change. We have investigated the possibilities of incorporating this in our platform, however, concluded that this would yield too many complications regarding organization and privacy regulation. A similar limitation was the integration of external health monitoring devices and other health applications with the PRODEMOS application. Due to the variety and rapidly advancing technologies of smartphones and wearable sensors, we could

not ensure continued compatibility of these monitoring tools and decided not to integrate them in our mobile application.

The PRODEMOS mobile application was specifically designed for older, vulnerable populations, integrating a simple, intuitive interface, with written and digital instruction manuals and in-person familiarization with the mobile application, guided by the health coach. However, it is conceivable that part of the target population may not be able to overcome some of the technological challenges involved in using the mobile application. Additionally, to use the application, participants need to have regular and affordable access to the internet. Increasing smartphone possession and usage among older adults suggests that this may be a decreasing barrier[27]. Until this barrier is completely omitted, mHealth should be complimentary to alternative methods to facilitate behavior change in older adults. Finally, mHealth is a rapidly advancing field, therefore it is important to appraise the reported findings within the context of this changing landscape of innovation, for example by taking new software features and design trends into account[28].

Implications for Future Practice and Research

mHealth may recently have become an even more attractive and desirable way to deliver interventions for risk factor management and disease prevention, as the COVID-19 pandemic has highlighted the need for preventive care that can be accessed remotely. Despite the increasing availability of mHealth applications for the prevention of dementia and cardiovascular disease, studies on the development, implementation, and effectiveness of these platforms are scarce. In order to demonstrate the added value of such technologies, there is an urgent need for evidence-based mHealth interventions and high-quality evaluation studies[29]. We believe that when developing such digital interventions, early involvement of end-users and other stakeholders will likely aid success and implementation. Moreover, development of a platform that is sustainably used could benefit from consistency of team members and documentation of all steps and decisions taken during each phase of development.

The actual use and usability of the PRODEMOS intervention will be assessed over the coming years in the PRODEMOS trial, with a dual focus on effectiveness and implementation outcomes. If effective, it likely increases the yield of preventive programs in resource-poor settings. If implementable, it will contribute to an improved understanding how such interventions may be successfully provided in the real-world setting.

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Supplementary material

Supplement 1. Evaluation processes during the conceptualization, development and evaluation and adaptation phase

Target group	N	Date	Method	Demographics	Recruitment
HATICE Evaluation					
Former participants of the HATICE study	6	Mar 2018	Structured focus group guided by predefined topic lists, covering: *experiences with HATICE platform, role of the health coach, goal setting and monitoring functionalities, suggested improvements.* Focus groups were transcribed verbatim; summaries were shared with the research group	50% male, mean age 69 years, 2-3 dementia risk factors.	Recruited via health care centre that participated in the HATICE study
Former coaches of HATICE study	3	Sep 2018	Structured focus group guided by predefined topic lists, covering: *logistics during trial, coaching of participants, use of platform, suggested improvements.* Focus groups were transcribed verbatim; summaries were shared with the research group	100% female, mean age 57 years	Invited by email, sent to all former HATICE coaches
	3	May 2019		100% female, mean age 58 years	
Potential PRODEMOS end-users †					
Interviews with Dutch participants	19	2018-2019	Semi-structured interviews, guided by a predefined interview guide that was iteratively adapted when necessary. Topics covered included: *experiences and attitudes regarding lifestyle behaviour change and needs for and views on the potential role for mHealth.* Participants were purposively sampled on age, sex, and history of CVD and diabetes. Interviews were transcribed verbatim, coded by two researchers independently, and thematically analysed. Findings were shared with the research group and will be published.	58% male, median age 67 years, 63% history of CVD	Participants were recruited through six general practices in the Netherlands.
Interviews with Chinese participants [21]	26	Feb-Dec 2019	Semi-structured interviews, guided by a predefined interview guide that was iteratively adapted when necessary. Topics covered included: *experiences and attitudes regarding lifestyle behaviour change, needs for coaching, and the use of mHealth.* Participants were purposively sampled on age, sex, living area, and history of CVD and diabetes. Interviews were transcribed verbatim, coded by two researchers independently, and thematically analysed. Findings were shared with the research group and will be published.	50% male, mean age 70 years, 35% history of CVD	Participants were recruited through seven Chinese hospitals participating in the PRODEMOS study.

Target group	N	Date	Method	Demographics	Recruitment
Dutch potential end-users with cardiovascular disease	10	Feb 2019	Structured focus group guided by predefined topic lists, covering: *Coaching for lifestyle change, interface of lifestyle application (guided by example screenshots), goal setting, education material.* Focus groups were transcribed verbatim; summaries were shared with the research group	60% male, mean age 71 years. All participants had a history of CVD. Two participants did not possess a smartphone.	Recruited via cardiac rehabilitation group
British potential end-users	2	April 2019	Structured interview guided by predefined interview guide, covering: *working with a remote coach, working with predefined goals, education material, interface and functionalities of lifestyle application (guided by example screenshots).* Interviews were transcribed verbatim; summaries were shared with the research group	100% female, mean age 56 years.	Recruited via UK based general practitioner
British potential end-users	3	June 2019	Structured interview guided by predefined interview guide, covering: *use of health applications, goal setting, sustained engagement, monitoring of progress.* Interviews were transcribed verbatim; summaries were shared with the research group	100% female, aged 40-66 years	Recruited via UK based general practitioner and word-to-mouth
British potential end-users	5	Jan 2020	User test structured by predefined user testing scripts. These scripts covered several scenarios (*contact with coach, setting a new goal, entering a measurement)* that participants had to follow through on the prototype of the app. Usage of the app was observed and evaluated by one researcher and one developer. User tests were followed up by individual interviews that were guided by the topics covered during user testing. Findings were summarized and shared with the research group	40% female, aged 55-75 years	Recruited via participating general practice surgery
British PRODEMOS pilot study participants	5	Feb 2020	Structured focus group guided by predefined topic lists, covering: *Contact with the coach, goal setting, measurement entering, health information, general app usage.* Focus groups were transcribed verbatim; summaries were shared with the research group	40% female, aged 55-75 years	Participants of the PRODEMOS pilot study were invited to participate in a dedicated focus group during the final visit.
Chinese PRODEMOS pilot study participants	15	Apr 2021	Structured interview guided by predefined topic lists covering: *Contact with the health coach, goal setting, measurement entering, health information, general app usage, working on lifestyle improvements using the app* Interviews were transcribed verbatim; summaries were shared with the research group	33% male, mean age 64 years	Participants of the PRODEMOS pilot study were invited to participate in a dedicated interview during the final visit.

Supplement 1. Continued

Target group	N	Date	Method	Demographics	Recruitment
Health coaches and professionals					
Experienced community health coaches from Brighton, UK	4	Feb 2019	Structured focus group guided by predefined topic lists, covering: *working with deprived populations, training of coaches, available health sources, coaching with mHealth.* Focus groups were transcribed verbatim; summaries were shared with the research group	100% female, multiple years' experience as health coach in deprived areas.	Recruited via University of Sussex, word-to-mouth
Experienced UK Clinical Research Network health coaches	2	June 2019	Structured focus group guided by predefined topic lists, covering: *Coaching experiences, use of health applications, goal setting.* Focus groups were transcribed verbatim; summaries were shared with the research group	100% female, multiple years' experience as health coach in deprived areas.	Recruited via NHS clinical research network
Health care professionals (UK general practitioner and practice nurse)	2	June 2019	Structured interview guided by predefined interview guide, covering: *working with the target population, education of (deprived) patients, monitoring of progress, sustained engagement.* Interviews were transcribed verbatim; summaries were shared with the research group	50% male, Both multipole years' experience working in deprived areas.	Recruited via University of Sussex, word-to-mouth
British coaches after PRODEMOS pilot	2	Feb 2020	Structured focus group guided by predefined topic lists, covering: *study logistics, contact with participants, patient management, goal evaluation.* Focus groups were transcribed verbatim; summaries were shared with the research group	100% female	Participating coaches in the PRODEMOS pilot study were invited to participate in a dedicated focus group
Chinese coaches after PRODEMOS pilot	13	Apr 2021	Structured focus group guided by predefined topic lists, covering: *Contact with the coach, goal setting, measurement entering, health information, general app usage.* Focus groups were transcribed verbatim; summaries were shared with the research group	23% male, mean age 33 Differing levels of experience: nurses, health management specialist, under- and postgraduate students majored in clinical medicine with experience	Coaches of the PRODEMOS pilot study were invited to participate in a dedicated focus group during the final visit.

† Participants were included based on the PRODEMOS study inclusion criteria; aged 55-57 years, living in an area ranked as equal to or less than the lowest third decile of index of multiple deprivation (UK only), possession of smartphone, two or more dementia risk factors, and smartphone literate (being able to send a message). CVD = cardiovascular disease; UK = United Kingdom.

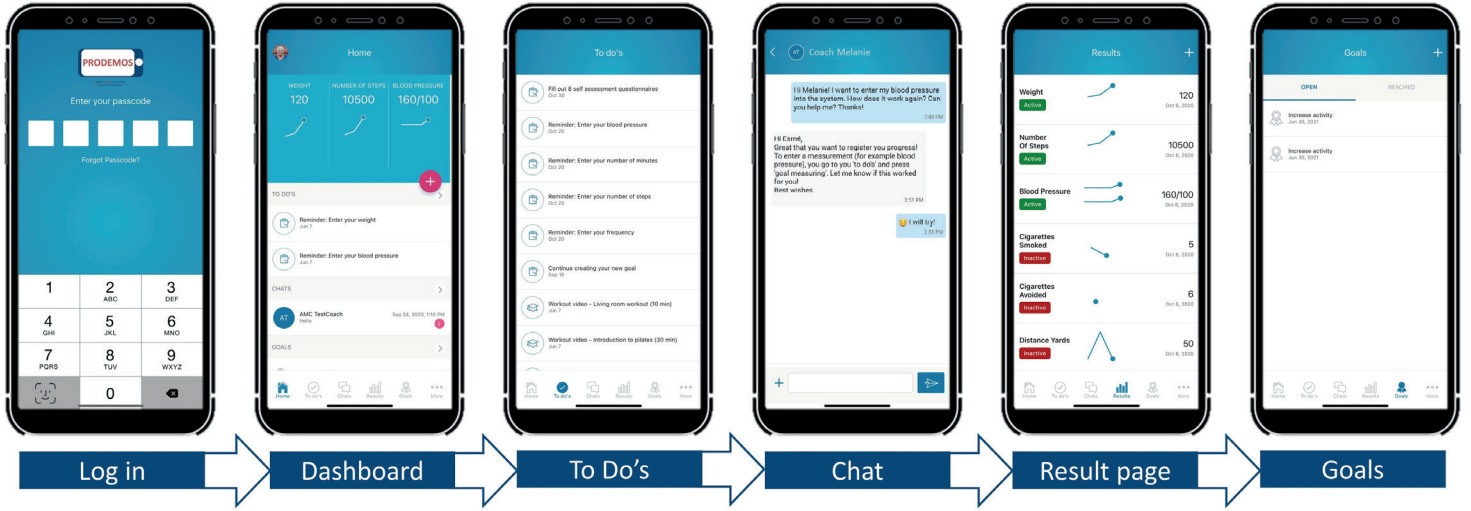
Supplement 2. Overview of main evaluation findings and adaptations to the PRODEMOS platform

	Evaluation finding	Adaptation
Lessons learned from HATICE[a]		
Participants	Reactive platform use in HATICE	Automatic reminders for engagement with intervention (for example to enter measurements or received chat message)
	Tailored and frequently updated education material	Goal-specific education material flows; new education items (based on the goals set by the participant) are sent to the participant's library weekly
	Need for more options to tailor the intervention	Intermediate adjustments to goals, for example editing the evaluation date and the goal target
		Possibility to tailor the notification frequency per goal (daily, bi-weekly, weekly)
		Pause-functionality, which temporarily stops all notifications for a predefined period of time (e.g. in case of illness)
	Need for more support to use platform	Explanatory video describing the basic platform functionalities (accessible in library)
Coaches	Need for better coaching functionalities to create a better overview of participants	Feature to add notes about individual participants
		Graphic overviews of participant's progress
		Tailored notifications to alert coaches, for example about newly set goals and achieved milestones.
		Interactive goal overview page to help adjust goals from participants
Lessons learned from interviews and focus groups with the PRODEMOS target population		
Participants	User-friendliness	Wide range of pre-defined goals, including country specific options
		Positive wording throughout the application
		Carefully selected education items from governmental health institutions, including (peer) videos
		Simplified login procedure with 5 (UK[b])- or 4 (CH[b])-digit code
		Integration with WeChat, using phone number (CH[b])
	Personalisation	Can add personal notes when setting a goal
		Measurement options tailored to be relevant for participants
		Tailored education material can be manually sent by coaches
		Goal specific education material

Supplement 2. Continued

Evaluation finding		Adaptation
Technical development		
Evaluation and adaptation based on internal testing, user tests and the pilot study		
Participants	Accessibility	Decreased text density by using visual substitutes
		Increased font size
		Changing order on navigation bar to most frequently used
		Visualisation of measurement methods
		Email address instead of separate username (UK[b])
		Help menu, appraising Frequently Asked Questions (CH[b])
	More intuitive operationalisation	Button on home screen to directly enter measurements
		Equalisation of buttons throughout the application
	More-in-depth material	Adaptation of education material (CH[b])
Coaches	Better patient management	Graphical overview of measurements
		Adjustment of goal specifics (date and target of goal)

[a] Development of the PRODEMOS platform built on the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) eHealth platform, which was proven effective for lowering cardiovascular risk of European older adults in a randomized controlled trial (RCT).[13] The coach-supported HATICE platform enabled self-management of cardiovascular risk factors, integrating European guideline recommendations on prevention of cardiovascular disease (CVD) and principles of Bandura's social-cognitive theory of self-management and behavioural change. [b] If an adaptation is country specific this is indicated with (UK) for the United Kingdom and (CH) for China.



Supplement 3. Overview of basic functionalities of the PRODEMOS app

Displayed are screenshots from the application used in the United Kingdom. The application used in China comprises some functionalities with several cultural adaptations.

PART II

Dementia risk factors and treatment of hypertension in older adults

7

Low values for blood pressure, BMI and non-HDL cholesterol and the risk of late-life dementia

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Abstract

Background and objectives

Low values of blood pressure, Body Mass Index (BMI) and non-high density lipoproteine (non-HDL) cholesterol have all been associated with increased dementia risk in late life, but whether these risk factors have an additive effect is unknown. This study assessed whether a combination of late-life low values for systolic blood pressure (SBP), BMI and non-HDL cholesterol are associated with higher dementia risk than individual low values of these risk factors.

Methods

This is a post-hoc analysis based on an observational extended follow-up of the Prevention of Dementia by Intensive Vascular Care (preDIVA) trial, including community-dwelling individuals, aged 70-78 years and free from dementia at baseline. We assessed the association of baseline low values of SBP, BMI and non-HDL cholesterol with incident dementia using Cox regression analyses. First, we assessed the respective associations between quintiles of each risk factor and dementia. Second, we explored whether combinations of low values for cardiovascular risk factors increased dementia risk, adjusted for interaction and potential confounders.

Results

During a median follow-up of 10.3 years (IQR 7.0-10.9), 308 of 2789 participants (11.0%) developed dementia and 793 (28.4%) died. For all risk factors, the lowest quintile was associated with the highest adjusted risk for dementia. Individuals with one, two, and three low values had adjusted HRs of 1.18 (95%CI 0.93-1.51), 1.28 (95%CI 0.85-1.93), and 4.02 (95%CI 2.04-7.93) respectively, compared to those without any low values. This effect was not driven by any specific combination of two risk factors and could not be explained by competing risk of death.

Discussion

Older individuals with low values for SBP, BMI or non-HDL cholesterol have a higher dementia risk compared to individuals without any low values. Dementia risk was substantially higher in individuals with low values for all three risk factors than expected based on a dose-response relationship. This suggests the presence of an overarching phenomenon that involves multiple risk factors simultaneously, rather than resulting from independent effects of each individual risk factor.

Trial registration Information

ISRCTN registry preDIVA: ISRCTN29711771. Date of study submission to ISRCTN registry: 14/02/2006. Recruitment start date: 01/01/2006. https://doi.org/10.1186/ISRCTN29711771

Introduction

Cardiovascular risk factors including high blood pressure, obesity and high cholesterol in midlife, commonly defined as 45-64 years, are important risk factors for dementia in latelife (65 years and above)[1, 2]. However, in late life, low values for these risk factors have also been associated with increased dementia risk[3-8].

The relationship between late-life systolic blood pressure (SBP) and incident dementia may be inverse or follow a U-shaped curve, with both high and low blood pressure values indicating an increased dementia risk.[9, 10] U-shaped associations with dementia have been described for non-High Density Lipoprotein (non-HDL) cholesterol levels6, and inverse relations for late-life total cholesterol (TC) levels[4, 5] and BMI[7, 8].

Contrasting relationships have been described for a variety of (cardiovascular) risk factors and outcomes in older people, a term generally used to describe individuals aged > 65[11]. Still, the exact nature of inverse or U-shaped associations and how they develop in late life remain unclear. For each of the risk factors above, different pathophysiological mechanisms have been proposed[6, 12, 13]. However, as these relationships develop similarly with ageing for several cardiovascular risk factors and have been observed for other adverse outcomes including cardiovascular disease (CVD) and all-cause mortality, these may reflect an overarching phenomenon involving all of these risk factors. Several overarching hypotheses have been proposed to explain these inverse or U-shaped relationships. Firstly, survival bias might play a role, wherein the selection of individuals who survive to old age with high values of cardiovascular risk factors might be less susceptible to their potential harmful effects[4]. Second, contrasting associations in late life might reflect a state of impaired homeostasis across a range of physiological processes and organ systems, possibly contributing to the development of dementia or indicating increased dementia risk by being a marker of physical ageing beyond calendar years. Alternatively, the relationship may be retro-causal, with low values for risk factors being early signs of neurodegeneration. Previous research suggests that declining risk factor values over time may precede dementia diagnosis. If measured at one time-point, it may therefore appear that individuals

with low levels have the highest risk[11, 14-17]. Lastly, competing risk of death might play a role in these associations in older people, as similar contrasting relationships with cardiovascular risk factors have been observed for mortality[11].

Better identification of older individuals at increased risk of dementia is especially important in clinical practice where prevention guidelines are based on risk factors in midlife. Furthermore, if older individuals with low values for a combination of risk factors might explain the inconsistent associations reported in the literature, while positive linear associations are observed in younger groups, trials might (re)evaluate the efficacy of intensive treatment of risk factors in this subgroup.

In this study, we investigated the associations of low SBP, low BMI and low non-HDL cholesterol with the risk of dementia, and whether the combination of these factors signal increased risk beyond the sum of their individual associations. Furthermore, we assessed how these relationships are influenced by the competing risk of death.

Methods

Study design and participants

We used data from the preDIVA trial and the preDIVA observational extension (POE) study[18, 19]. The preDIVA cluster-randomized trial compared the effect of intensive vascular care, i.e. 4-monthly visits to a practice nurse, comprising assessment of cardiovascular risk factors and tailored lifestyle advice, with care-as-usual on incident dementia after a median intervention and follow-up period of 6.7 years in 3526 community-dwelling older adults (70-78 years). After an additional 3.6 years of observational extension in the POE study, information on dementia status and mortality was obtained of those participants who had not reached the primary endpoint or had not deceased during the preDIVA trial, resulting in information about dementia status in a total of 3491 participants (99%). Study protocols and outcomes have been published in detail elsewhere[18-20]. Since there was no effect of the intervention, we considered the population as one cohort for the current study. This study is presented following the STROBE guidelines for observational cohort studies[21].

Independent outcome variables

Data on demographics and other independent variables were collected at baseline. All variables were assessed using standardized devices and operating procedures. SBP was calculated using the mean of two measurements on the same

arm, measured at least 5 minutes apart, performed with the electronic OMRON M6 device. Cholesterol levels were determined in local laboratories affiliated with the GP practices. We computed non-HDL cholesterol levels for each participant by subtracting HDL cholesterol from TC values. Self-reported data on medical history and medication use were crosschecked with GPs' electronic health records. ApoE genotype was determined at a central laboratory in the Amsterdam University Medical Center, location AMC. Data on education and smoking were self-reported and defined in line with the WHO criteria[18].

Dementia diagnosis

The adjudication process for the outcome dementia has previously been described in detail.[18] In short, a clinical dementia diagnosis was evaluated by an independent outcome adjudication committee, according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)[22]. Participants underwent regular assessments every two years and at the final assessment, during the 6-8 years trial phase of preDIVA. Individuals with cognitive complaints, an MMSE score of ≤24, a decline of ≥3 points from baseline MMSE or ≥2 points since the preceding two-yearly visit were referred to their general practitioner for clinical evaluation and adjudication by the outcome committee. All diagnoses were re-evaluated after one year. In case of drop-out, dementia status was retrieved from the general practitioner or the electronic health records and evaluated by the adjudication committee.

For the observational extension, the Telephone Interview for Cognitive Status (TICS) was administered to all participants who were still alive and willing to participate, 3-4 years after the conclusion of the preDIVA trial[23]. Participants with a TICS score >30 and no formal dementia diagnosis were classified as not having dementia. In all other cases, the general practitioners' electronic health records were searched to verify whether a diagnosis of dementia had been made. All data pertaining to incident dementia diagnoses were subsequently evaluated for confirmation by the adjudication committee.

Statistical analysis

We included all participants with available baseline data on SBP, BMI and non-HDL cholesterol, covariates and outcome data of dementia. Descriptive variables were stratified by dementia diagnosis and presented using mean and standard deviation when normally distributed. Not normally distributed continuous variables were presented as median and interquartile range, and categorical variables as frequencies and percentages.

All analyses were performed using Cox proportional hazards regression analysis. First, we assessed the association between each risk factor at baseline (SBP, BMI and non-HDL cholesterol) divided in quintiles and dementia during follow-up. We used quintiles as independent variable because there is no consensus on the optimal values for cardiovascular risk factors in late life, since current guidelines are based on risk prediction in midlife. Use of quintiles balances the advantage of sufficient data granularity with the loss of power due to small groups. Second, to assess the association between a combination of low values of these risk factors and incident dementia, we dichotomized the independent variables into low versus any higher values based on quintiles (lowest quintile vs. all other quintiles). According to this dichotomization, each individual was assigned to one of four groups: 1) no low values, 2) one low value, 3) two low values, and 4) three low values. We included the number of low values as a categorical variable in our model, with "no low values" as the reference category. The p-value for trend and overall hazard ratio (HR) was calculated by including the number of low values as numeric variable in the model. Third, interactions between low values of the risk factors on dementia incidence were assessed using interaction terms (low values of: SBP * non-HDL, non-HDL * BMI, and BMI * SBP). We used three models for each analysis. In model 1, age was used as timescale and age at baseline as time of study entry, without further adjustments. Model 2 was additionally adjusted for sex and educational level. Model 3 was additionally adjusted for smoking status, history of diabetes, stroke or CVD (angina pectoris, myocardial infarction and/or peripheral artery disease), and ApoE4 genotype. We assessed the proportional hazards assumption by visual inspection of Schoenfeld residuals.

Predefined subgroup analyses were performed for 1) sex, 2) ApoE4 genotype, 3) history of CVD, 4) antihypertensive medication (AHM) use vs. no AHM use, and 5) cholesterol-lowering drug (CLD) use vs. no CLD use, as the associations might differ when risk factor values are low due to medication effects. We used the maximally adjusted model (model 3) for the subgroup analyses.

We performed several sensitivity analyses. First, we repeated the main analysis with low values based on clinical cut-off values instead of quintiles (i.e. SBP 140 mmHg, BMI 25 kg/m2, and non-HDL cholesterol 3.4 mmol/L), to compare our results with regard to current clinical practice. Second, we explored whether effects observed in our main analysis were driven by specific combinations of cardiovascular risk factors. Third, we performed analyses according to median time to dementia diagnosis to evaluate the influence of time between risk factor exposure and dementia onset. Low values for SBP, BMI and non-HDL cholesterol might be prodromal factors developing with incipient dementia, in which case their

association with increased dementia risk would be particularly strong in the short term[14, 15]. Fourth, analyses according to randomization group were performed to investigate if there were differential effects between the intervention and control group of the original preDIVA trial, even though the trial results were neutral. Fifth, because mortality is an important competing risk for dementia, especially in cohorts of older people with relatively long follow-up which have substantial mortality rates, we performed sensitivity analyses to assess the competing risk of death in a cause-specific hazard approach, with mortality and the combined outcome dementia and mortality[24]. Sixth, we repeated the main analysis with data divided in tertiles rather than quintiles, increasing the number of cases in each group. Lastly, to assess the effect of our specific choices for measures of cholesterol and blood pressure, we repeated the main analyses using different commonly used measures, including total cholesterol, LDL cholesterol and HDL cholesterol (highest quintile) instead of non-HDL cholesterol, and diastolic instead of systolic blood pressure. Analyses were conducted in Rstudio (version 4.0.3).

Results

A total of 2789 individuals with a median age of 74 years (IQR 72-76) were included in this analysis (Figure 1). Over a median follow-up of 10.3 years (IQR 7.0-10.9), 308 participants (11.0%) developed dementia and 793 (28.4%) deceased. Individuals who were diagnosed with dementia were older (median age 75.2 vs. 74.1 years) and were more often male (62.3% vs. 54.2%). Mean baseline SBP, BMI and non-HDL cholesterol did not differ significantly between both groups (Table 1).

The individual relationships for SBP, BMI and non-HDL cholesterol with incident dementia are presented in Figure 2. For all these variables, the lowest quintile was associated with the highest adjusted HR for dementia compared to all other quintiles. As compared to the reference group (no risk factors with low value), fully adjusted HRs on dementia for individuals with one, two, and three low values were 1.18 (95%CI 0.93-1.51), 1.28 (95%CI 0.85-1.93) and 4.02 (95%CI 2.04-7.93) respectively (Table 2). Significant two-way interactions were observed between low BMI and low non-HDL cholesterol levels (Table 3), suggesting that individuals with low BMI and low non-HDL had a 125% increased risk compared to those with higher values for these two factors (HR 2.25, 95%CI 1.41-3.60, p-interaction 0.01), which was substantially greater than for those with exclusively low BMI (HR 1.13, 95%CI 0.83-1.54) or low non-HDL (HR 0.89, 95%CI 0.61-1.30). Other two-way interactions were not significant (p-interaction>0.5).

Table 1. Baseline characteristics for full cohort and individuals with and without dementia diagnosis

	Overall (n =2789)	No dementia (n = 2481)	Dementia (n=308)	p-value
Age, y, median [IQR]	74.3 [72.1, 76.3]	74.1 [72.0, 76.2]	75.2 [72.7, 77.1]	<0.001
Male sex, n (%)	1536 (55.1)	1344 (54.2)	192 (62.3)	0.008
Systolic blood pressure, mmHg, mean (SD)	155.4 (21.3)	155.6 (21.2)	153.7 (21.9)	0.13
Diastolic blood pressure, mmHg, mean (SD)	81.5 (10.9)	81.6 (10.9)	80.6 (10.9)	0.12
Antihypertensive medication use, n (%)	1538 (55.2)	1366 (55.1)	172 (56.0)	0.81
History of stroke, n (%)	289 (10.4)	250 (10.1)	39 (12.7)	0.19
History of cardiovascular disease, n (%)	823 (29.5)	743 (29.9)	80 (26.0)	0.17
History of diabetes mellitus type II, n (%)	497 (17.8)	435 (17.5)	62 (20.1)	0.30
Smoking status, n (%)				0.05
Current smoker	363 (13.0)	335 (13.5)	28 (9.1)	
Never	935 (33.5)	819 (33.0)	116 (37.7)	
Quit	1491 (53.5)	1327 (53.5)	164 (53.2)	
Body Mass Index, kg/m^2, mean (SD)	27.5 (4.20)	27.5 (4.2)	27.3 (4.4)	0.46
High density lipoprotein, mmol/L, mean (SD)	1.5 (0.4)	1.5 (0.4)	1.6 (0.4)	0.02
Non-high density lipoprotein, mmol/L, mean (SD)	3.7 (1.0)	3.7 (1.0)	3.8 (1.1)	0.79
Cholesterol lowering drug use, n (%)	958 (34.4)	846 (34.2)	112 (36.5)	0.46
MMSE score median [IQR]	28 [27, 29]	29 [27, 29]	28 [26, 29]	<0.001
Education				0.09
< 7 years	666 (23.9)	577 (23.3)	89 (28.9)	
7-12 years	1572 (56.4)	1411 (56.9)	161 (52.3)	
> 12 years	551 (19.8)	493 (19.9)	58 (18.8)	
ApoE4 positive, n (%)	772 (27.7)	615 (24.8)	157 (51.0)	<0.001

APOE = Apolipoprotein E; IQR = interquartile range; MMSE = Mini Mental-State Examination; SD = Standard Deviation.

In subgroup analyses, significant interactions with number of low values for risk factors were observed for individuals with ApoE4 genotype, a history of CVD and those who used CLD at baseline (Supplement 1). After Bonferroni correction for the number of subgroup analyses (n=5, corrected p<0.01), only the interaction with history of CVD was significant (p-interaction=0.009), suggesting that individuals with a history of CVD had a particularly higher risk (three low values: HR 19.8, 95%CI 7.61-51.6) compared to those without (three low values: HR 1.76, 95%CI 0.56-5.55).

Table 2. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia.

		Model 1 N=2789	Model 2 N=2789	Model 3 N=2789
Number of risk factors with low value	**N total/ dementia**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
No low	1511/155	1	1	1
One low	992/116	1.19 (0.94 - 1.52)	1.19 (0.94 1.52)	1.18 (0.93 - 1.51)
Two low	249/28	1.26 (0.84 - 1.88)	1.27 (0.85 - 1.91)	1.28 (0.85 - 1.93)
Three low	37/9	3.19 (1.63 - 6.26)	3.33 (1.69 - 6.53)	4.02 (2.04 - 7.93)
P for trend		0.008	0.006	0.005

Cut-offs were: systolic blood pressure ≤138mmHg, Body Mass Index ≤24.2 kg/m2, non-HDL-cholesterol ≤2.8 mmol/L. Model 1: adjusted for age at baseline; model 2: model 1 + sex, and education; model 3: model 2 + history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. All models used age as timescale. HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

The results for associations between number of low values for SBP, BMI and non-HDL cholesterol and dementia risk remained largely unchanged in sensitivity analyses using clinical cut-off points to define low values (Supplement 2). No specific combination of two individual risk factors with low values could explain the high risk observed in the group with three low values, and individuals with low values for all risk factors combined had a disproportionally higher HR for dementia compared to individuals in groups with one or two risk factors with low values (HR 3.19, 95%CI 1.63-6.26, Supplement 3). In analyses according to median time to dementia diagnosis, similar results were observed with somewhat stronger effects in the group of individuals with a follow-up time below the median (<6.75 years three vs. no low values: HR 4.55, 95%CI 1.96-10.56) compared to a longer (>6.75 years) follow-up time (three vs. no low values: HR 3.00 95%CI 0.94-9.65, Supplement 4). No differential effects were observed between randomization groups (Supplement 5). Analyses with mortality as outcome showed increased HRs for individuals with one, two and three low values as compared to the reference group (no risk factors with low value) (HR 1.07, 95%CI 0.92-1.25; HR 1.10, 95%CI 0.86-1.40; HR 1.37, 95%CI 0.79-2.39 respectively; p for trend 0.19, Supplement 6). When dementia incidence and mortality were combined as outcome, HRs for participants with one, two or three low values were HR 1.11, 95%CI 0.97-1.27; HR 1.13, 95%CI 0.92-1.41; HR 1.48, 95%CI 0.90-2.44 respectively; p for trend 0.04 (Supplement 7). Results of sensitivity analyses using data divided in tertiles were highly similar, although point estimates in those with three low risk factors strongly attenuated compared to the original analysis, suggesting that our results were particularly driven by more extreme low values (Supplement 8). Sensitivity

analyses using different measures for cholesterol and blood pressure yielded similar findings, although the associations for low diastolic blood pressure and high HDL cholesterol were less strong than those for systolic blood pressure and non-HDL cholesterol respectively (Supplement 9-12).

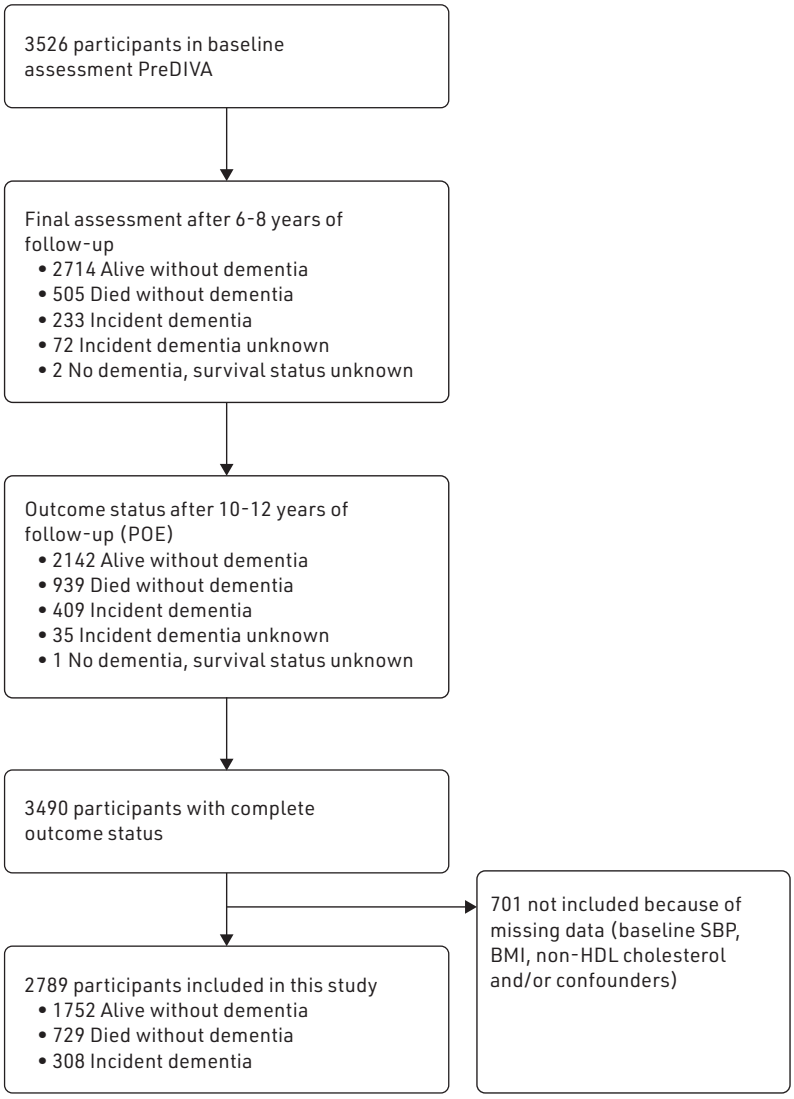

Figure 1. Flowchart

POE = preDIVA Observational Extension; SBP = systolic blood pressure; BMI = Body Mass Index; non-HDL = non-High Density Lipoprotein

Table 3. Interactions between low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol - based on lowest quintile - on incident dementia.

	Model 1 N=2789	**Model 2 N=2789**	**Model 3 N=2789**
Interaction	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
No low SBP or BMI	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI < 24.2 (no low SBP)	1.38* (1.01 - 1.87)	1.36 (0.999 - 1.84)	1.32 (0.97 - 1.80)
SBP < 138 (no low BMI)	1.35 (0.99 - 1.84)	1.34 (0.98 - 1.83)	1.33 (0.98 - 1.82)
Low SBP and low BMI	1.58 (0.99 - 2.50)	1.59 (1.00 - 2.53)	1.70 (1.07 - 2.71)
p for interaction	0.6	0.7	0.9
No low SBP or non-HDL	1.00 (ref)	1.00 (ref)	1.00 (ref)
SBP < 138 (no low non-HDL)	1.26 (0.94 - 1.70)	1.26 (0.94 - 1.70)	1.29 (0.95 - 1.73)
non-HDL < 2.8 (no low SBP)	1.00 (0.71 - 1.41)	1.03 (0.73 - 1.45)	1.07 (0.75 - 1.54)
Low SBP and low non-HDL cholesterol	1.60 (0.95 - 2.71)	1.65 (0.97 - 2.79)	1.73 (1.01 - 2.97)
p for interaction	0.5	0.5	0.5
No low BMI or non-HDL	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI < 24.2 (no low non-HDL)	1.15 (0.85 - 1.56)	1.14 (0.84 - 1.54)	1.13 (0.83 - 1.53)
non-HDL < 2.8 (no low BMI)	0.86 (0.60 - 1.23)	0.88 (0.61 - 1.26)	0.89 (0.61 - 1.30)
Low BMI and low non-HDL cholesterol	2.10 (1.32 - 3.32)	2.16 (1.36 - 3.43)	2.25 (1.41 - 3.60)
p for interaction	0.02	0.02	0.01

A significant interaction between variables indicates that the effect of one variable depends on the level of the other variable in the interaction. Interpretation example: Model 3, Low BMI*non-HDL cholesterol: Individuals with low BMI, without low non-HDL had a 13% higher (HR=1.13) dementia risk. Individuals with low non-HDL, without low BMI had an 11% lower (HR=0.89) dementia risk. The HR for low values for both variables was 2.25, indicating that individuals with low values for both variables have a 125% higher risk of dementia compared to individuals without low values for both variables. Model 1: adjusted for age at baseline; model 2: model 1 + sex, and education; model 3: model 2 + history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. All models used age as timescale. BMI = Body Mass Index; HDL = High-density lipoprotein; HR = hazard ratio; SBP = systolic blood pressure; 95%CI = 95% confidence interval.

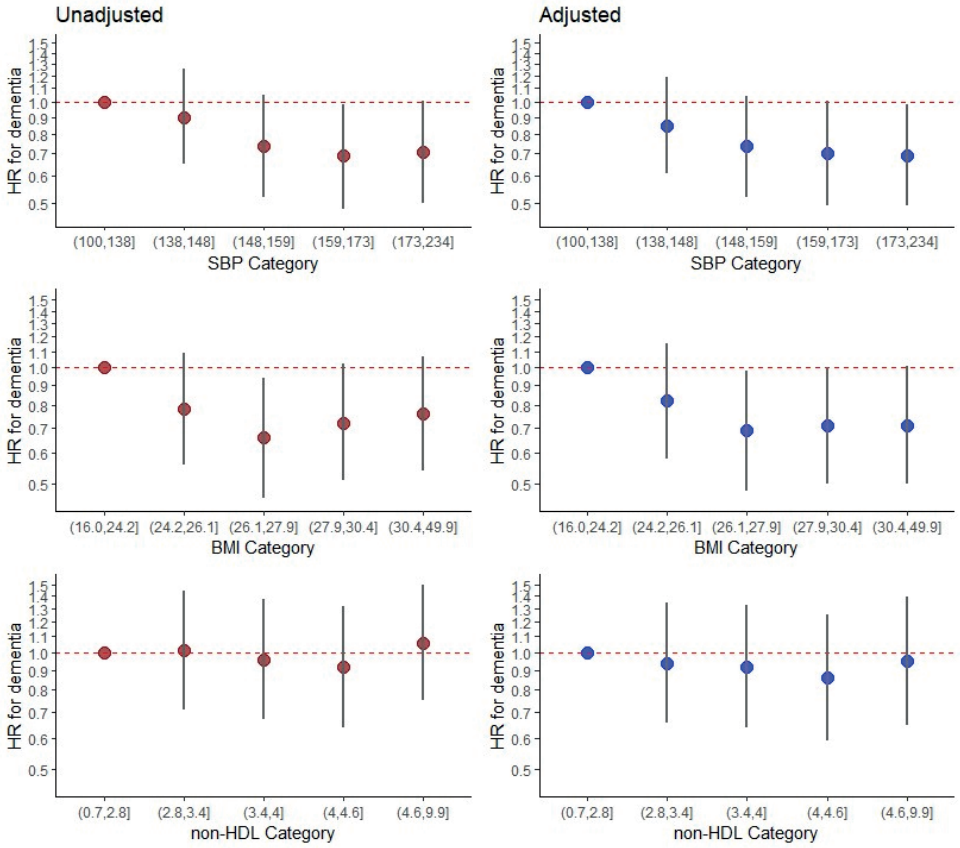

Figure 2. Association for quintiles of cardiovascular risk factors with dementia incidence.

These figures display the relative association compared to the lowest quintile (reference) with dementia incidence for systolic blood pressure, BMI and non-HDL cholesterol. Figures at the right: Adjusted for age at baseline, sex, education, history of stroke, cardiovascular disease or diabetes mellitus, smoking status and APOE 4 genotype.

Discussion

This study including longitudinal data from community-dwelling older individuals aged 70-78 years at baseline showed that low values of SBP, BMI and non-HDL cholesterol were associated with an increased risk of incident dementia over a median follow-up of 10.3 years. Dementia risk was substantially higher in individuals with low values for all three risk factors than expected based on a dose-response relationship (302% versus 18% and 28% for one or two low values respectively, compared to individuals without any low values). We did not observe any specific combination of two risk factors that could explain these results. The only observed interaction was between low BMI and low non-HDL cholesterol, which was associated with a 125% increase in dementia risk, and therefore could not fully explain the 302% higher risk for individuals with low values for all three cardiovascular risk factors. Furthermore, low SBP was not associated with higher dementia risks in combination with low values for BMI or non-HDL cholesterol, but it strongly increased dementia risk in combination with low values for both risk factors. These results increase the plausibility that an overarching phenomenon, signalled by low values for multiple risk factors, may precede a clinical diagnosis of dementia. Competing risk of mortality could not explain our results

These findings are in line with prior observational studies reporting contrasting associations for late life SBP, BMI and non-HDL cholesterol when assessed individually[4, 5, 7, 9, 25, 26]. A pooled analysis of two population based studies reported an inverse association between SBP and dementia risk, but only in AHM users[26]. A 2015 review on BMI and Alzheimer's Disease and dementia risk reported inverse associations in multiple studies.7 Also, prior studies reported U-shaped associations for non-HDL cholesterol6 and inverse associations for TC[4, 5]. For LDL-cholesterol, U-shaped associations were described in the general population on outcome mortality, not on incident dementia[27]. We used non-HDL cholesterol in our analyses because of its strong associations with cardiovascular events[28-30]. While previous studies focused on individual risk factors, the present study shows that these inverse relationships with dementia risk occur for multiple risk factors simultaneously, suggesting that particularly individuals with concurrent low values for the three risk factors studied here are at increased dementia risk, more than individuals with single, isolated low risk factor values.

Subgroup analyses suggested that the association between the number of risk factors with low values and dementia may be particularly strong in individuals with a history of CVD. This may be due to low values in this group signaling increased dementia risk in relatively vulnerable individuals. Also, in this group,

low risk factor values may be more out of the ordinary. History of CVD is generally associated with relatively high values of cardiovascular risk factors, and therefore low values in CVD patients may be a more distinctive feature, and more often related to disease, than in those without CVD in whom low risk factor values are more common. Finally, if the low risk factor values are markers of an underlying state of (cardiovascular) ageing beyond calendar years, such a state is likely to be present more often in individuals with a CVD history, which could also explain why low risk factor values more often indicate increased dementia risk.

Strengths and limitations

A strength of this study is the integrated approach assessing the concurrent associations for multiple risk factor values and their interactions, whereas previous studies have mainly focused on studying individual risk factors independently. Thereby, this study is able to give an indication of the potential validity of the hypothesis that an overarching phenomenon, involving multiple risk factors, is associated with incipient disease, rather than individual risk factors. Other strengths of this study are the long follow-up duration (>10 years), and the complete follow-up for all-cause dementia (99.0%) and mortality (99.9%). Dementia diagnosis was established by an independent panel, and all diagnoses in preDIVA were re-evaluated after one year to reduce the risk of a false positive diagnosis[18].

Our study has several limitations. First, our results may have been impacted by selection bias, since those who survived up to the age of inclusion and participated in the study are relatively healthy older individuals with less cardiovascular morbidity and mortality and better cognitive functioning. Selection of relatively healthy older individuals, or individuals that are less susceptible for the negative effects of high values for cardiovascular risk factors, could have contributed to an inverse relation with dementia incidence. However, the stronger associations in the CVD subgroup seemingly speak against this. Individuals with a history of CVD are likely relatively vulnerable to risk factor exposure, having developed disease previously. Therefore, the effects should be stronger in the non-CVD group if such survival bias would play a major role in our findings. Moreover, previous analyses have shown that participants of the preDIVA study are largely comparable, in terms of demographics and cardiovascular risk factors, with the overall Dutch population and with a large Dutch cohort study[31]. Second, the effect of medical treatment on the associations between low values for cardiovascular risk factors and dementia incidence is unknown. To address this issue, we performed subgroup analyses for baseline AHM and CLD use and observed no relevant or significant interactions, suggesting that this low risk factor phenomenon is independent

of medication use, and that it occurs both in patients with and without a chronic history of hypertension and/or dyslipidemia. Third, low values may in fact indicate declines of these risk factors over the preceding period, which have previously been associated with increased dementia risk. In our study we were unable to assess the association between dementia risk and changes in risk factors over time, since the data collected after baseline may have been affected by the preDIVA intervention. Fourth, the number of individuals and dementia cases with low values for all three risk factors was small, resulting in wide confidence intervals. In a post-hoc sensitivity analysis defining low blood pressure, low BMI and low non-HDL cholesterol based on the lowest tertile rather than lowest quintile, our results remained largely unchanged, although HRs for dementia in the group with three low risk factors strongly attenuated compared to the original analysis (HR 2.45 vs. HR 4.02). Furthermore, we had insufficient data and power to analyze specific subtypes of all-cause dementia.

Interpretation and mechanism

We showed that particularly individuals with a combination of low values for SBP, BMI and non-HDL cholesterol are at increased risk of dementia. Previous studies assessed the associations between individual risk factors and dementia risk. A case-control study of 962 participants reported weight loss in the years preceding dementia diagnosis, which the authors attributed to pre-dementia apathy, loss of initiative, and reduced olfactory function[32]. The steep increase in risk for individuals with low values for all three cardiovascular risk factors combined in our study indicates that an overarching phenomenon, involving multiple risk factors, might precede a clinical dementia diagnosis, rather than risk factor-specific phenomena. This phenomenon might either be a multisystem state of decline that contributes to dementia (causal relation), an early sign of neurodegeneration as part of the disease (reverse causality), or a marker of physical ageing beyond calendar age, which has been associated with increased dementia risk[33]. Our results are derived from observational data, and therefore no statements about causality of the observed association can be made. Dementia has a long prodromal period and studies have shown that cardiovascular risk factor values start to decline long before clinical symptoms of dementia occur[15-17]. However, in analyses according to time before dementia diagnosis we observed stronger effects in short-term compared to long-term dementia cases. This finding is in line with a previous longitudinal cohort study, where no association with SBP measured 13 years before diagnosis was observed, but analyses with SBP measured 4 years before diagnosis showed an inverse association[25]. This might suggest that low values for risk factors are a marker of imminent dementia, rather than a cause.

In analyses with mortality as outcome, a combination of low values for SBP, BMI and non-HDL cholesterol was associated with an increased risk of mortality. This suggests that the relationship between low values and dementia risk is not affected by competing risk of death.

Clinical relevance

In midlife, high values for cardiovascular risk factors are widely acknowledged to increase dementia risk. However, this study shows that, in late life, low values of three important cardiovascular risk factors are associated with increased dementia risk in community-dwelling individuals. The risk of dementia was substantially higher for individuals with concomitant low values for SBP, BMI and non-HDL cholesterol than for the sum of these individual associations, increasing the plausibility that an overarching phenomenon, involving multiple risk factors, is associated with increased dementia risk. If these results could be corroborated in other cohorts, we might be able to better identify older individuals at increased risk for cognitive decline and dementia. It may also invite new risk prediction models for dementia specifically for older people, and this may contribute to future guidelines with respect to risk factor targets in older persons. Future studies will need to address the causality of this association or whether observations reflect merely prodromal signs of incipient dementia.

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Supplementary material

Supplement 1. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia in pre-defined subgroups

		Number of risk factors with low value, HR (95%CI)				
	N	**No low**	**One low**	**Two low**	**Three Low**	**P for interaction**
Sex						*0.3*
Female	1253	1.0	1.19 (0.79-1.80)	1.38 (0.73-2.61)	8.91 (3.64-21.83)	
Male	1536	1.0	1.16 (0.86-1.57)	1.26 (0.74-2.17)	1.82 (0.57-5.80)	
ApoE4 genotype						*0.02*
Positive	772	1.0	1.59 (1.14-2.22)	1.02 (0.54-1.96)	4.54 (1.38-14.96)	
Negative	2017	1.0	0.81 (0.56-1.18)	1.58 (0.93-2.69)	3.72 (1.60-8.62)	
History of CVD						*0.009*
Yes	823	1.0	1.35 (0.82-2.21)	1.60 (0.78-3.30)	19.81 (7.61-51.58)	
No	1966	1.0	1.16 (0.87-1.53)	1.26 (0.77-2.08)	1.76 (0.56-5.55)	
Antihypertensive medication use						*0.3*
Yes	1538	1.0	1.22 (0.88-1.69)	1.11 (0.60-2.06)	5.95 (2.68-13.18)	
No	1247	1.0	1.15 (0.79-1.69)	1.34 (0.75-2.40)	2.23 (0.51-9.72)	
Cholesterol lowering drug use						*0.05#*
Yes	958	1.0	1.13 (0.74-1.71)	0.99 (0.49-1.97)	5.63 (2.69-11.78)	
No	1826	1.0	1.23 (0.91-1.67)	1.45 (0.87-2.44)	-*	

Cut-offs were: systolic blood pressure ≤138mmHg, Body Mass Index ≤24.2 kg/m2, nonHDL-cholesterol ≤2.8 mmol/L. Fully adjusted model (model 3): adjusted for sex, education, history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. Age was used as timescale. AHM = antihypertensive medication; ApoE = Apolipoprotein; CVD = cardiovascular disease; HDL = High-density lipoprotein; HR = hazard ratio; ref. = reference; 95%CI = 95% confidence interval. * Calculation of HR not possible because there were no dementia cases in the group of individuals that did not use cholesterol-lowering drugs. #P=0.049.

Supplement 2. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on clinical cut-off points, and incident dementia

		Model 1 N=2789	**Model 2 N=2789**	**Model 3 N=2789**
Number of risk factors with low value	**N total/dementia**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
No low	996/109	1	1	1
One low	1202/116	0.92 (0.71 - 1.20)	0.94 (0.72 - 1.22)	0.94 (0.72 - 1.22)
Two low	499/63	1.27 (0.93 - 1.73)	1.29 (0.94 - 1.76)	1.28 (0.93 - 1.75)
Three low	92/20	2.43 (1.51 - 3.92)	2.47 (1.53 - 3.98)	2.78 (1.72 - 4.50)
P for trend		0.005	0.004	0.002

Cut-offs were: systolic blood pressure ≤140mmHg, Body Mass Index ≤25 kg/m2, nonHDL-cholesterol ≤3.4 mmol/L. Model 1: adjusted for age at baseline; model 2: model 1 + sex, and education; model 3: model 2 + history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. All models used age as timescale. HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

Supplement 3. Sensitivity analyses for specific combinations of low values for systolic blood pressure, Body Mass Index and non-HDL cholesterol based on lowest quintile and incident dementia risk

	No dementia cases	**Dementia cases**	**HR (95%CI)**
no low	1356	155	1 (ref)
Low non-HDL cholesterol	285	29	0.91 (0.61 - 1.35)
Low BMI	296	42	1.27 (0.90 - 1.79)
Low SBP	295	45	1.39 (1.0* - 1.94)
Low SBP & low non-HDL cholesterol	66	6	0.98 (0.43 - 2.22)
Low SBP & low BMI	100	11	1.09 (0.59 - 2.01)
Low non-HDL cholesterol & low BMI	55	11	1.80 (0.98 - 3.32)
Low SBP, low BMI & low non-HDL cholesterol	28	9	3.19 (1.63 - 6.26)

This analysis shows the association with dementia risk for low values for systolic blood pressure, Body Mass Index and non-HDL cholesterol individually, and in combination compared to no low values for any of these risk factors. Fully adjusted model (model 3): adjusted for sex, education, history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. Age was used as timescale. Abbreviations: SBP = systolic blood pressure; HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval. *Lower 95%CI=0.999.

Supplement 4. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, according to median time to dementia diagnosis based on lowest quintile, and incident dementia.

	time to dementia <6.75 years		**time to dementia ≥6.75 years**	
Number of risk factors with low value	**N total/dementia**	**HR (95%CI)**	**N total/dementia**	**HR (95%CI)**
No low	1511/72	1	1147/80	1
One low	992/60	1.31 (0.93 - 1.85)	785/55	1.00 (0.71 - 1.42)
Two low	249/16	1.48 (0.86 - 2.57)	194/16	1.35 (0.78 - 2.34)
Three low	37/6	4.55 (1.96 - 10.56)	26/3	3.00 (0.93 - 9.65)
P for trend		0.005		0.2

Cut-offs for lowest quintiles differed slightly in the respective groups (<median/>median): systolic blood pressure ≤138/138.5mmHg, Body Mass Index ≤24.2/24.2 kg/m2, nonHDL-cholesterol ≤2.8/2.9 mmol/L. Fully adjusted model (model 3): adjusted for sex, education, history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. Age was used as timescale. HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

Supplement 5. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia in sensitivity analyses according to randomization group

	Study arm	
	Intervention	**Control**
Number of individuals	1510	1279
No low, HR (95%CI)	1.0	1.0
One low, HR (95%CI)	1.29 (0.93-1.79)	1.05 (0.72-1.52)
Two low, HR (95%CI)	1.55 (0.94-2.57)	0.97 (0.48-1.98)
Three low, HR (95%CI)	1.79 (0.44-7.35)	6.99 (3.07-15.92)
P for interaction	0.2	

Abbreviations: HR = hazard ratio; 95%CI = 95% confidence interval.

Supplement 6. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and mortality

		Model 1 N=2788	Model 2 N=2788	Model 3 N=2788
Number of risk factors with low value	**N total/event (mortality)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
No low	1511/403	1	1	1
One low	991/297	1.16 (1.00 - 1.35)	1.17 (1.00 - 1.35)	1.07 (0.92 - 1.25)
Two low	249/80	1.35 (1.06 - 1.71)	1.32 (1.04 - 1.68)	1.10 (0.86 - 1.40)
Three low	37/13	1.67 (0.96 - 2.90)	1.61 (0.93 - 2.80)	1.37 (0.79 - 2.39)
P for trend		0.002	0.003	0.2

Cut-offs were: systolic blood pressure ≤138mmHg, Body Mass Index ≤24.2 kg/m2, nonHDL-cholesterol ≤2.8 mmol/L Model 1: adjusted for age at baseline; model 2: model 1 + sex, and education; model 3: model 2 + history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. All models used age as timescale. HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

Supplement 7. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia and mortality combined

		Model 1 N=2789	Model 2 N=2789	Model 3 N=2789
Number of risk factors with low value	**N total/event (dementia+mortality)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
No low	1511/528	1	1	1
One low	992/391	1.18 (1.03 - 1.34)	1.17 (1.03 - 1.34)	1.11 (0.97 - 1.27)
Two low	249/102	1.32 (1.07 - 1.63)	1.30 (1.06 - 1.61)	1.13 (0.92 - 1.41)
Three low	37/16	1.58 (0.96 - 2.60)	1.56 (0.95 - 2.57)	1.48 (0.90 - 2.44)
P for trend		0.0006	0.0008	0.04

Cut-offs were: systolic blood pressure ≤138mmHg, Body Mass Index ≤24.2 kg/m2, nonHDL-cholesterol ≤2.8 mmol/L Model 1: adjusted for age at baseline; model 2: model 1 + sex, and education; model 3: model 2 + history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. All models used age as timescale. HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

Supplement 8. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest tertile instead of lowest quintile, and incident dementia

		Model 1 N=2789	Model 2 N=2789	Model 3 N=2789
Number of risk factors with low value	**N total/dementia**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
No low	897/87	1	1	1
One low	1191/122	1.12 (0.85 - 1.47)	1.13 (0.86 - 1.49)	1.11 (0.84 - 1.46)
Two low	578/79	1.53 (1.13 - 2.08)	1.55 (1.14 - 2.10)	1.51 (1.11 - 2.05)
Three low	123/20	2.12 (1.30 - 3.45)	2.18 (1.34 - 3.55)	2.45 (1.50 - 4.01)
P for trend		<0.001	<0.001	<0.001

Cut-offs were: systolic blood pressure ≤145mmHg, Body Mass Index ≤25.5 kg/m2, non-HDL cholesterol ≤3.2 mmol/L. Model 1: adjusted for age at baseline; model 2: model 1 + sex, and education; model 3: model 2 + history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. All models used age as timescale. HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

Supplement 9. Associations between number of low values of systolic blood pressure, Body Mass Index, and total cholesterol instead of non-HDL cholesterol, based on lowest quintile, and incident dementia

		Model 1 N=2789	Model 2 N=2789	Model 3 N=2789
Number of risk factors with low value	**N total/dementia**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
No low	1461/155	1	1	1
One low	1044/121	1.17 (0.92 - 1.48)	1.18 (0.93 - 1.50)	1.16 (0.92 - 1.48)
Two low	251/24	1.05 (0.69 - 1.62)	1.08 (0.70 - 1.66)	1.08 (0.70 - 1.68)
Three low	33/8	3.36 (1.65 - 6.84)	3.64 (1.78 - 7.46)	5.30 (2.57 - 10.95)
P for trend		0.05	0.03	0.03

Cut-offs were: systolic blood pressure ≤138mmHg, Body Mass Index ≤24.2 kg/m2, total cholesterol ≤4.3 mmol/L. Model 1: adjusted for age at baseline; model 2: model 1 + sex, and education; model 3: model 2 + history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. All models used age as timescale. HR = hazard ratio; 95%CI = 95% confidence interval.

Supplement 10. Associations between number of low values of systolic blood pressure, Body Mass Index, and LDL cholesterol instead of non-HDL cholesterol, based on lowest quintile, and incident dementia

		Model 1 N=2787	Model 2 N=2787	Model 3 N=2787
Number of risk factors with low value	**N total/dementia**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
No low	1449/149	1	1	1
One low	1044/118	1.16 (0.91 - 1.47)	1.16 (0.91 - 1.48)	1.14 (0.89 - 1.46)
Two low	260/31	1.33 (0.90 - 1.96)	1.35 (0.92 - 1.99)	1.34 (0.90 - 1.98)
Three low	34/9	3.52 (1.79 - 6.90)	3.69 (1.88 - 7.24)	4.67 (2.36 - 9.23)
P for trend		0.005	0.004	0.005

Cut-offs were: systolic blood pressure ≤138mmHg, Body Mass Index ≤24.2 kg/m2, LDL cholesterol ≤2.3 mmol/L. Model 1: adjusted for age at baseline; model 2: model 1 + sex, and education; model 3: model 2 + history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. All models used age as timescale. LDL = Low-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

Supplement 11. Associations between number of low values of systolic blood pressure (lowest quintile), Body Mass Index (lowest quintile), and high values of HDL cholesterol (highest quintile) instead of non-HDL cholesterol and incident dementia

		Model 1 N=2789	Model 2 N=2789	Model 3 N=2789
Number of risk factors with low value	**N total/dementia**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
No low	1542/149	1	1	1
One low	923/113	1.27 (1.00 - 1.63)	1.25 (0.98 - 1.60)	1.26 (0.98 - 1.62)
Two low	269/36	1.40 (0.98 - 2.02)	1.39 (0.97 - 2.01)	1.50 (1.03 - 2.18)
Three low	55/10	2.41 (1.27 - 4.57)	2.38 (1.25 - 4.54)	2.35 (1.23 - 4.50)
P for trend		0.002	0.003	0.002

Cut-offs were: systolic blood pressure ≤138mmHg, Body Mass Index ≤24.2 kg/m2, HDL cholesterol ≥ 1.8 mmol/L. Model 1: adjusted for age at baseline; model 2: model 1 + sex, and education; model 3: model 2 + history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. All models used age as timescale. HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

Supplement 12. Associations between number of low values of diastolic blood pressure instead of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia

		Model 1 N=2787	**Model 2 N=2787**	**Model 3 N=2787**
Number of risk factors with low value	**N total/dementia**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
No low	1480/151	1	1	1
One low	986/111	1.14 (0.89 - 1.46)	1.14 (0.89 1.46)	1.13 (0.88 - 1.45)
Two low	291/38	1.36 (0.95 - 1.94)	1.36 (0.95 - 1.94)	1.36 (0.94 - 1.96)
Three low	30/7	2.45 (1.15 - 5.23)	2.66 (1.24 - 5.70)	2.38 (1.10 - 5.15)
P for trend		0.02	0.01	0.03

Cut-offs were: diastolic blood pressure ≤72.5 mmHg, Body Mass Index ≤24.2 kg/m2, non-HDL-cholesterol ≤2.8 mmol/L. Model 1: adjusted for age at baseline; model 2: model 1 + sex, and education; model 3: model 2 + history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. All models used age as timescale. HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

8

Antihypertensive medication classes and the risk of dementia – findings from the preDIVA observational extension study

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Abstract

Introduction

Use of angiotensin II (ATII)-stimulating antihypertensive medication (AHM), including angiotensin receptor blockers (ARBs) and dihydropyridine calcium channel blockers (CCBs), has been associated with lower dementia risk. Previous studies had relatively short follow-up periods. The aim of this study is to investigate if these effects are sustained over longer periods.

Methods

This post-hoc observational analysis was based on data from a dementia prevention trial (preDIVA and its observational extension), among Dutch community-dwelling older adults without prior diagnosis of dementia. Differential associations between AHM classes and incident dementia were studied after 7.0 and 10.4 years, based on the median follow-up durations of dementia cases and all participants.

Results

After seven years, use of ATII-stimulating antihypertensives (HR=0.68, 95%CI=0.47- 1.00), ARBs (HR=0.54, 95%CI=0.31-0.94) and dihydropyridine CCBs (HR=0.52, 95%CI=0.30-0.91) was associated with lower dementia risk. After 10.4 years, associations for ATII-stimulating antihypertensives, ARBs and dihydropyridine CCBs attenuated (HR=0.80, 95%CI=0.61-1.04; HR=0.75, 95%CI=0.53-1.07; HR=0.73, 95%CI=0.51-1.04 respectively), but still suggested lower dementia risk when compared to use of other AHM classes. Results could not be explained by competing risk of mortality.

Conclusion

Our results suggest that use of ARBs, dihydropyridine CCBs and ATII-stimulating antihypertensives is associated with lower dementia risk over a decade, although associations attenuate over time. Apart from methodological aspects, differential effects of antihypertensive medication classes on incident dementia may in part be temporary, or decrease with ageing.

Introduction

Dementia is a major global health problem, which is expected to increase over the coming years, due to global aging[1]. Results from several prospective studies suggest that hypertension is a risk factor for late-life dementia, in particular vascular dementia and Alzheimer's disease[2-5], with a population attributable fraction of approximately 5%[6]. Targeting hypertension may be a promising strategy to delay or prevent dementia, given its high prevalence and the wide availability of antihypertensive medication (AHM) worldwide[7]. Class-specific mechanisms of AHM may contribute to a differential effect on dementia risk[8-10], potentially explaining some of the inconsistent results of previous hypertension trials and meta-analyses[11-13]. A network meta-analysis of studies comparing dementia risks between users of different AHM classes suggests that users of angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) had a 12-17% lower risk of dementia compared to individuals using angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, but less so versus diuretics[14].

A potential mechanism underlying these findings is the 'angiotensin hypothesis', which suggests that antihypertensive agents that stimulate the angiotensin II type 2 (AT2) and 4 (AT4) receptors, including ARBs, dihydropyridine CCBs and thiazide diuretics, may reduce dementia risk by inhibiting neuronal damage and preserving memory function[15, 16]. We observed that specifically these angiotensin II (ATII)-stimulating antihypertensive users had a 45% lower dementia risk compared to users of other AHM types in the Prevention of Dementia by Intensive Vascular care (preDIVA) population[15]. This finding was recently replicated in the SPRINT-MIND trial population, wherein ATII-stimulating AHM users had a 24% lower dementia risk when compared to other AHM users[16]. Moreover, we previously observed that individuals who used ARBs and CCBs at baseline had an approximately 40% lower dementia risk compared to individuals using other AHM types over 6.7 years of follow-up[17].

It is unclear how these associations are affected by follow-up time, and whether they are sustained over long periods. A network meta-analysis suggests that protective effects are particularly observed in studies with longer follow-up[14]. Crucially however, these findings were nearly exclusively based on studies with a maximum follow-up of approximately seven years. Duration of follow-up may be especially important in dementia, as it can develop insidiously over many years, implying that any protective effects of AHM classes may only become apparent in the long-term. Alternatively, protective associations may wear off over time, and/or attenuate due to changes in blood pressure and AHM regimen.

The preDIVA observational extension (POE) study yields longitudinal data on AHM use and dementia status of 3526 older adults up to twelve (median 10.4) years of follow-up. The aim of this study is to assess whether the associations between ARBs and CCBs, as well as dihydropyridine CCBs and ATII-stimulating AHM as a group and dementia persist, attenuate or increase over up to twelve years of follow-up, using the POE data.

Methods

For the current study, we have used data from the preDIVA study and its observational extension. The initial preDIVA cluster-randomized controlled trial assessed the effect of intensive vascular care versus standard care on the incidence of all-cause dementia after a median intervention period of 6.7 years in 3526 Dutch community-dwelling, older adults (70-78 years) without dementia.[18] In the subsequent POE study, we included former preDIVA participants who had not deceased or developed dementia during that period. After adding another four years of observational follow-up, leading to a median follow-up of 10.4 years since baseline, information on dementia status or death could be obtained in 3491 (99.0%) and 3521 (99.9%) participants respectively. The study protocols and outcomes of the preDIVA and POE studies have been reported in more detail elsewhere[18-20]. The preDIVA trial was registered at the ISRCTN-registry (no.29711771). Both preDIVA and POE were approved by the medical ethics committee of the Academic Medical Centre, Amsterdam, the Netherlands. Participants gave written informed consent at the respective preDIVA and POE baselines. Since the preDIVA trial results for dementia and mortality were similar between the intervention and control groups, for the current analysis we considered the trial population as a single cohort, using additional adjustment for randomization group.

Independent variables

Demographics and data on other independent variables were collected at baseline and two, four, and six to eight years thereafter. Data on medication use and medical (cardiovascular) history gathered during these visits were crosschecked with participants' electronic health records (EHR). Blood pressure (BP) was assessed by taking the mean of two baseline BP measurements, performed at the same arm in sitting position with an automated BP monitor (M6,OMRON Healthcare Co., Ltd.,Kyoto,Japan)[21]. Body mass index (BMI) and low-density lipoprotein (LDL) cholesterol were measured using standardized devices and procedures. Selfreported data on education, smoking, and physical activity were defined according to WHO criteria.

We identified five main classes of AHM: ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics. We further distinguished between use of dihydropyridine and non dihydropyridine CCBs, and between ATII-stimulating and inhibiting AHM, as this was differentially associated with dementia risk in previous studies[15, 16, 22]. ARBs, dihydropyridine CCBs or thiazide diuretics increase Angiotensin II levels and were thus included in the ATII-stimulating group[15, 23-25]. AHM were (sub)-categorized into classes according to WHO Anatomical Therapeutic Chemical (ATC) codes (supplement 1)[26].

Outcome assessment

Diagnosis of dementia was defined according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). An independent outcome adjudication committee, blinded for study allocation, evaluated the diagnosis of dementia, and re-evaluated the diagnosis after 1 year, to minimize the risk of false-positive diagnoses. In the POE study, the municipal death registry was consulted first. Of those participants who had deceased since the final visit of preDIVA, information on the development of dementia since the end of preDIVA was obtained from the general practitioner (GP). Those still alive were asked to participate in the telephone interview of cognitive status (TICS), which is an 11-item, validated screening tool (maximum score=41)[27]. For participants with a TICS score >30 and no known diagnosis of dementia, we assumed no dementia had occurred. For those with a TICS score ≤30 or missing score, the EHR of the GP was checked for a diagnosis of dementia[28].

Statistical analysis

We included all participants who used AHM at preDIVA baseline, with available baseline data on AHM use, covariates and outcome of dementia and mortality. Individuals who did not use AHM at baseline were excluded to limit the potential influence of selective dropout. In order to focus on the differential effects between AHM classes, we compared use of specific AHM classes with use of any other AHM classes. Participants who used multiple classes simultaneously (for instance those using fixed combination therapy) were represented in multiple classes or subgroups at once. The association between AHM class and dementia incidence was analysed using Cox proportional hazards regression models, using number of years from baseline to diagnosis of dementia, time of death, or date of outcome assessment as timescale. Model 1 was unadjusted. In model 2, we adjusted for age, sex, history of cardiovascular disease (CVD) (i.e. myocardial infarction, stroke and/or transient ischemic attack), and type 2 diabetes. In model 3, we additionally adjusted for randomization group and number of used AHM classes, as indicator for the intensity of treatment. Sensitivity- and subgroup analyses were adjusted

according to model 2. In order to compare potential differences between short- and long-term results, we repeated the main analysis with a shorter follow-up period. Short-term was defined using the median follow-up of participants who developed dementia, ensuring even distribution of cases on either side of the cut-off value.

Several sensitivity analyses were performed to assess the robustness of the main analyses. First, we included all AHM classes in one model, to adjust for concurrent use of multiple AHM classes. Second, to assess the potential influence of AHM class changes during follow-up, we performed a sensitivity analysis for stable users, defined as use of the same AHM class at baseline and during at least one follow-up visit of preDIVA. Third, to assess the influence of the competing risk of death, we used the cause-specific hazard approach, repeating all analyses with mortality and dementia/mortality combined as outcomes. In a post-hoc sensitivity analysis, we compared use of ARBs and/or CCBs with use of any other AHM. As both classes have a presumed negative association with dementia risk, we used this approach to limit potential concealment of the effect between use of ARBs and dementia risk by use of CCBs in the reference group, and vice versa. Finally, we included dihydropyridine CCBs and ATIIstimulating AHM in (pre-specified) sensitivity- and subgroup analyses.

Subgroup analyses were performed for age (cut-off 75 years at baseline, based on the mean age at baseline in preDIVA), for participants with(out) CVD, type 2 diabetes, (un)controlled hypertension (systolic blood pressure cut-off at 150mmHg, based on the prevailing primary care guideline on hypertension at the start of the preDIVA study[29]) at baseline, and on monotherapy vs. combination therapy, as these may be proxies for different cardiovascular risk profiles, with different dementia risks. Finally, a subgroup analysis for sex was performed, as previous studies have suggested that the relation between the RAS system and development of dementia may be different between males and females[23].

No imputations were deemed necessary, due to the low number of missing values in both the preDIVA trial and observational follow-up (supplement 2). All analyses were performed in RStudio(v1.3) based on R(v4.0.2).

Results

In total, 1907 (54.1%) AHM users out of 3526 participants were included in the analyses. Mean age of participants at baseline was 74.5 (±2.5) years, 1027

(53.9%) were female. Mean systolic blood pressure was 156.2 (±21.5) mmHg. Including combination therapy, 620 (32.5%) participants used ACE inhibitors, 390 (20.5%) ARBs, 958 (50.2%) beta-blockers, 512 (26.8%) CCBs, (51.1%) 974 (51.1%) diuretics. More specifically, within the CCB group 399 (77.9%) used dihydropyridines and 115 (22.5%) nondihydropyridines. Within the diuretic group 752 (77.4%) used thiazides. Table 1 gives an overview of baseline data for participants in each AHM class.

Among all participants, after a median 10.4 years (range 0.2-12.8, IQR 6.8-11.0) of follow-up, 225 (11.8%) participants had developed dementia (figure 1). Risk of dementia was not significantly different for any of the AHM classes of interest as compared with use of any other AHM class in the crude and adjusted model (table 2). Point estimates for use of ARBs (HR=0.75, 95%CI=0.53-1.07), dihydropyridine CCBs (HR=0.73, 95%CI=0.51-1.04), and ATII-stimulating AHM (HR=0.80, 95%CI=0.61-1.04) suggested a negative association with incident dementia (table 2, figure 2, and supplement 4).

Short-term use, with follow-up cut-off at 7 years (median follow-up of dementia cases), of ARBs (HR=0.54, 95%CI=0.31-0.94), CCBs (HR=0.60, 95%CI=0.37-0.97), dihydropyridine CCBs (HR=0.52, 95%CI=0.30-0.91) and ATII-stimulating AHM (HR=0.68, 95%CI=0.47-1.00) was associated with reduced dementia risk (supplement 5). Results from the main analyses remained largely unchanged after additional adjustment for number of AHM and randomisation group (supplement 6) and when mutually adjusting for all main AHM classes in one model (supplement 7). When restricting analyses to participants in the stable-use group (supplement 8), use of ATII-stimulating AHM was associated with lower dementia incidence (HR=0.73, 95%CI=0.52-0.99). Use of ARBs, dihydropyridine CCBs, and ATII-stimulating AHM were not associated with increased mortality rates (HR=0.94, 95%CI=0.77-1.14; HR=0.99, 95%CI=0.82-1.20; HR=0.94, 95%CI=0.81-1.11 respectively), suggesting no evident influence of competing risk of death (supplement 9). Finally, use of ARBs and CCBs combined was associated with a lower dementia incidence (HR=0.69, 95%CI=0.52-0.92, supplement 10).

Associations between AHM classes and dementia were largely similar across the predefined subgroups (supplement 11), although in ARB users, the association with dementia was stronger in participants aged 75 and over (HR=0.60, 95%CI=0.36-0.99) when compared to those under 75 years of age at baseline (HR=0.95, 95%CI=0.57-1.58). In participants using ATII-stimulating AHM, the association was stronger in those with a history of diabetes (HR=0.58, 95%CI=0.36-0.94) when compared to individuals without history of diabetes (HR=0.90, 95%CI=0.65-1.25).

Table 1. Baseline characteristics of participants with different classes of antihypertensive medication.

		Total N=1907	ACEi N=620	ARB N=390	Beta-blocker N=958	CCB N=512	Diuretic N=974	Dihydropyridine CCB N=399	ATII-stimulating AHM N=1180
Sociodemographic									
Age (years)	Mean ± SD [Range]	74.5 ± 2.5 [69-80]	74.5 ± 2.5 [69-80]	74.3 ± 2.5 [69-79]	74.4 ± 2.5 [69-80]	74.5 ± 2.5 [69-80]	74.5 ± 2.5 [69-80]	74.4 ± 2.5 [69-80]	74.4 ± 2.5 [69-80]
Sex (female)	N (%)	1027 (53.9)	280 (45.2)	219 (56.2)	492 (51.4)	273 (53.3)	591 (60.7)	215 (53.9)	682 (57.8)
MMSE	Median [IQR]	28 [27-29]	28 [27-29]	29 [27-29]	28 [27-29]	29 [27-29]	29 [27-29]	29 [27-29]	29 [27-29]
Cardiovascular risk factors and medication use									
CVD history (yes)	N (%)	947 (49.7)	315 (50.8)	184 (47.2)	589 (61.5)	289 (56.4)	438 (45.0)	204 (51.1)	517 (43.8)
DM history (yes)	N (%)	501 (26.3)	233 (37.6)	110 (28.2)	240 (25.1)	154 (30.1)	301 (30.9)	126 (31.6)	332 (28.1)
Systolic BP (mmHg)	Mean±SD [Range]	156.2±21.5 [100-232.5]	156.6±21.9 [100-233]	156.5±23.1 [103-222]	156.6±22.5 [100-233]	155.8±20.4 [109-218]	155.9±21.5 [100-233]	157.5±20.3 [109-218]	157.7±21.0 [101-233]
Diastolic BP (mmHg)	Mean±SD [Range]	81.4±11.2 [50-131]	81.4±11.9 [52-131]	81.5±11.2 [55-118]	80.9±11.4 [50-131]	79.4±10.4 [52-125]	81.3±10.8 [52-119]	79.7±10.4 [52-125]	81.6±10.9 [52-125]
BMI (kg/m^2)	Mean±SD	28.4±4.3	28.2±4.1	29.1±4.6	28.3±4.0	28.5±4.2	28.9±4.5	28.6±4.1	28.7±4.4
LDL (mg/dL)	Mean±SD	112.0±38.6	108.1±34.8	112.0±38.6	108.1±34.8	108.1±34.8	112.0±38.6	108.1±34.8	112.0±38.6
Current smoking (yes)	N (%)	232 (12.2)	79 (12.7)	40 (10.3)	121 (12.6)	66 (12.9)	117 (12.0)	52 (13.0)	141 (11.9)
Physically active (yes)	N (%)	1565 (82.1)	493 (79.5)	321 (82.3)	797 (83.2)	414 (80.9)	778 (79.9)	325 (81.5)	974 (82.5)
Number of AHM	Median [IQR]	2 [2-3]	2 [2-3]	2 [2-3]	2 [1-3]	2 [2-3]	2 [2-3]	2 [2-3]	2 [2-3]

Individual participants are represented in different classes of antihypertensive medication when they use combination therapy. Data are presented as numbers (percentage), mean ± SD, median (IQR) or ranges. Physical activity was self-reported and defined according to WHO criteria. ACEi = angiotensin-converting enzyme inhibitor; AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CVD = cardiovascular disease; DM = diabetes mellitus; LDL = low-density lipoprotein; MMSE = Mini-Mental State Examination

Table 2. Association between use of a specific antihypertensive medication class and incident dementia, compared with use of any other antihypertensive medication.

	Dementia cases (%) in AHM class of interest	Dementia cases (%) in other AHM users	Crude model HR (95% CI)	Model 2 HR (95% CI)
ACEi	72/620 (11.6)	153/1287 (11.9)	1.09 (0.82-1.44)	1.07 (0.81-1.43)
ARB	37/390 (9.5)	188/1517 (12.4)	0.75 (0.53-1.07)	0.75 (0.53-1.07)
Beta-blocker	113/958 (11.8)	112/949 (11.8)	1.01 (0.78-1.31)	0.99 (0.76-1.30)
CCB	58/512 (11.3)	167/1395 (12.0)	0.96 (0.71-1.29)	0.92 (0.68-1.25)
Diuretic	117/974 (12.0)	108/933 (11.6)	1.07 (0.82-1.39)	1.03 (0.79-1.34)
Dihydropyridine CCB	37/399 (9.3)	188/1508 (12.5)	0.74 (0.52-1.05)	0.73 (0.51-1.04)
ATII-stimulating AHM	129/1180 (10.9)	96/727 (13.2)	0.81 (0.62-1.05)	0.80 (0.61-1.04)

Median follow-up: 10.4 years. Model 2: adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. The dementia cases (percentages) represent the number of participants with incident dementia from the participants using the AHM class of interest. ATII-stimulating AHM include ARB's, dihydropyridine CCB's and thiazide diuretics. ACEi = angiotensin converting enzyme inhibitor; AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; ATII = angiotensin II; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

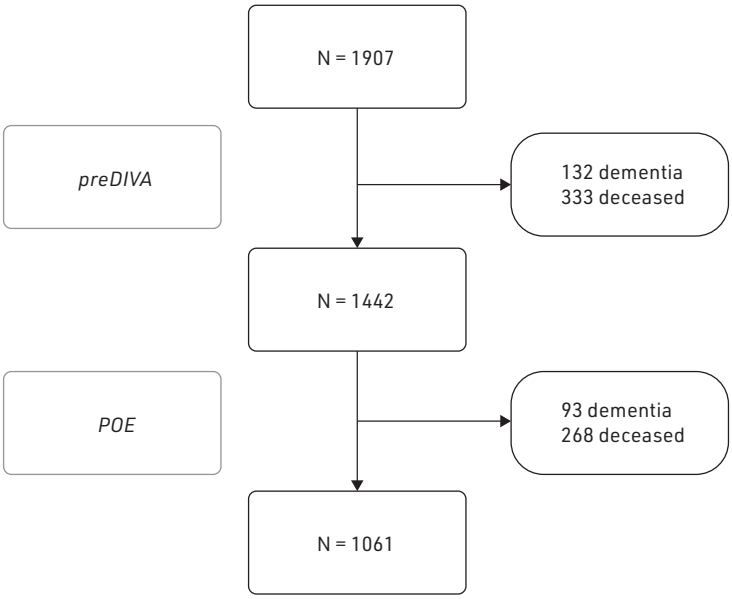

Figure 1. Overview of outcome assessment

Participants who had dementia and subsequently deceased, were included in the number of people with dementia only.
AHM = antihypertensive medication; preDIVA = prevention of dementia by intensive vascular care; POE = preDIVA observational extension; RCT = randomised controlled trial.

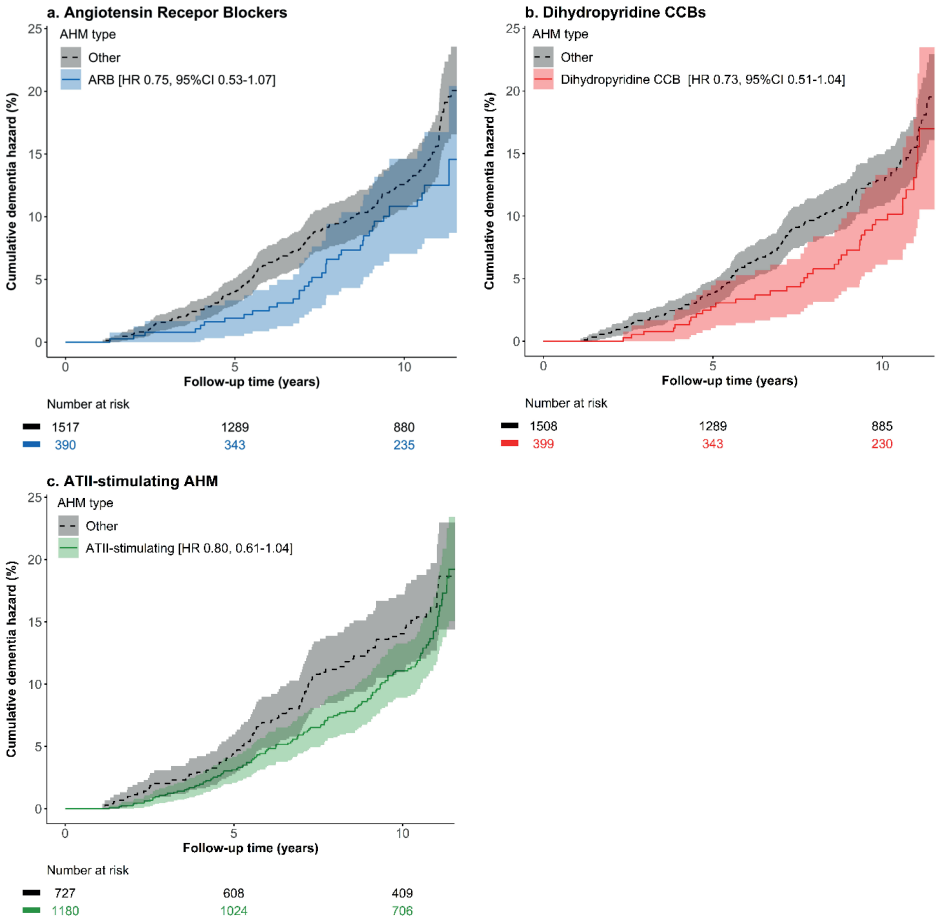

Figure 2. Cumulative hazard of dementia for ARBs, dihydropyridine CCBs and ATII-stimulating antihypertensive medication

a. ARBs (blue), b. Dihydropyridine CCBs (red) and c. ATII-stimulating AHM (green) versus any other AHM classes (grey). ARB = angiotensin receptor blocker; CCB = calcium channel blocker; ATII = angiotensin II. AHM = antihypertensive medication; HR = hazard ratio, CI = confidence interval.

Discussion

Main findings

In our population of 1907 AHM-using Dutch older adults, use of ARBs, dihydropyridine CCBs,

and ATII-stimulating AHM was non-significantly associated with 20-27% lower risk of incident dementia over a median follow-up duration of 10.4 years, and significantly with 32-48% lower risk of dementia after seven years follow-up, when compared to use of any other AHM class.

Interpretation of findings

The non-significant 20-27% lower dementia risks after median 10.4 years had decreased compared to the 30-45% lower risks over seven years. This suggests that the associations of ARBs, (dihydropyridine) CCBs or ATII-stimulating AHM with decreased dementia risk might attenuate over time. Possibly, as many of the known risk factors for dementia are age dependent[8, 30, 31], differential effects of AHM classes partly decrease with aging. Analyses stratified by age however do not support this hypothesis. Another explanation may be that, with increasing follow-up time, baseline data on medication use have become less reliable indicators of actual medication use. Nevertheless, sensitivity analyses in participants who used the same AHM class at baseline and during at least one follow-up visit did not substantially alter our results. Thirdly, differential effects of AHM classes on dementia risk could have a temporary nature, regardless of age. Finally, regression to the mean could in part explain the difference between associations on the short and longer term.

Baseline blood pressure levels and number of prescribed AHM were comparable between the different AHM class users. Any differential effects between AHM classes and incident dementia we observed are therefore likely caused by class-specific mechanisms rather than their effect on blood pressure. Several hypotheses exist around the potential neuroprotective effect of CCBs and ARBs, ranging from their abilities to improve cerebral blood flow and reduce cerebral oxidative stress markers, to protection against neuronal death[32]. In addition, dihydropyridine CCBs and ARBs stimulate AT2 and AT4 receptors through the ATII pathway, which potentially protects against ischemia and preserve memory respectively[15,16,33-36].

An important potential challenge in studies with dementia as outcome is the competing risk of mortality before the development of dementia. In our study,

we observed associations between use of ACE inhibitors and mortality (HR1.19, 95%CI=1.01-1.40) and dementia/mortality combined (HR1.18, 95%CI=1.02-1.36). This may be related to the high number of individuals with diabetes in this group. As no association between use of any other AHM class and mortality were observed, with HRs around 1.0, our results appear unaffected by the competing risk of death.

Strengths and limitations

Main strengths are the judicious assessment of the most clinically relevant outcome of incident dementia, the long follow-up period of up to twelve years, and completeness of follow-up on all-cause dementia (99.0%) and mortality (99.9%). Furthermore, our study population consists of a broadly representative sample of community-dwelling Dutch older adults[18]. A limitation is potential confounding by indication, as former Dutch guidelines recommended a stepped approach for AHM prescriptions in which ARBs and CCBs represented second or later steps in treatment. In our study, baseline blood pressure values were comparable across classes, but beta-blockers, ACE inhibitors, and ARBs were more often prescribed among specific groups, including those with a history of CVD or diabetes. To address this issue, we adjusted for CVD and diabetes history in the main model, which did not change the results of the crude analyses. Additional adjustment for number of AHM classes did not change the results. Also, results were highly comparable in subgroup analyses for participants with and without diabetes, a history of CVD and uncontrolled hypertension.

A second limitation is the lack of complete data on medication history prior to baseline assessment, medication adherence, and dosage. In the main analysis, we only used data on AHM use collected at baseline, ignoring intermediate changes in AHM use. We repeated the main analysis in a sample of participants who used the same AHM class at baseline and at least one follow-up visit and observed similar results. The available data did not allow for a more thorough analysis on the effects of post-baseline AHM class switching and medication exposure over time.

Comparison with previous studies

The HRs for incident dementia ranging between 0.73 and 0.80 we found, are in line with findings from previous studies on class-specific effects of AHM. Two individual participant data (IPD) studies with dementia as secondary outcome compared use of various AHM classes with use of any other AHM class. Both studies reported negative, albeit non-significant associations with incident dementia. One study found that use of ARBs was associated with a 12-24% lower dementia risk and the other reported 7-24% lower ORs for ARBs and CCBs[37, 38].

A recent network meta-analysis compared use of various AHM classes to each other and demonstrated that use of CCBs and ARBs was associated with a 12-17% reduced dementia risk compared to ACE inhibitors and beta blockers, but less so versus diuretics (7-11%)[14]. However, all but one included studies had a follow-up period of less than approximately seven years and most applied non-use of AHM classes, including individuals who did not use any AHM at all, as reference groups, hindering accurate comparison with our results[22, 39, 40]. One study with a follow-up of over 10 years compared use of CCBs with use of other AHM classes and found a significant 19% reduction of dementia risk in those using CCBs[41]. Our study is the first to assess the sustainability of class-specific associations between various AHM classes and incident dementia over a prolonged period of time.

Conclusion

In our study population of Dutch community-dwelling older persons, we did not observe statistically significant associations between use of any specific AHM class and dementia risk over a median 10.4 years of follow-up, although point estimates for ARBs, dihydropyridine CCBs and ATII-stimulating AHM suggest a lower risk of dementia when compared to use of any other AHM class. Possibly, significant associations observed in the short-term represented effects that were to some extent temporary, or could not be replicated over the complete followup period because baseline AHM data were not fully representative of actual medication use over time. However, even temporary effects, resulting in delayed manifestation of dementia, could be meaningful to both individuals and society. Further studies assessing the sustainability of class-specific associations in older adults should comprise detailed registration of AHM use over time, to account for intermediate class-changes and to assess potential dose-effect relationships.

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Supplementary material

Supplement 1. AHM classes and corresponding ATC codes

AHM class	ATC codes
ACEi	C09A; C09B
ARB	C09C; C09D
Beta-blocker	C07A; C07B; C07C; C07D; C07E; C07F; C09BX02, C09BX04; C09DX06
CCB	C08C, C08D, C08E, C08G; C07FB; C09XA53; C09XA54; C09DX01; C09DX03; C09DX07; C09DB; C09BX04; C09BX01; C09BX03; C09BB
Diuretic	C03A, C03B, C03C, C03D, C03E, C03X; C02L; C07B; C07C; C07D; C08G; C09BA; C09BX01; C09BX03; C09DA; C09DX01; C09DX03; C09DX07; C09XA52; C09XA54
Other	C02A, C02B, C02C, C02D, C02K, C02L, C02N, C09X
Dihydropyridine CCB	C08G; C07FB; C09XA53; C09XA54; C09DX01; C09DX03; C09DX06; C09DX07; C09DB; C09BX01; C09BX03; C09BX04; C09BB02; C09BB03; C09BB04; C09BB06; C09BB07; C09BB12
Angiotensin II-stimulating AHM	C02L; C03A; C03EA01; C03EA02; C03EA03; C03EA04; C03EA05;C03EA07; C03EA013; C03EA014; C07B; C07D; C07FB; C08CA; C08G; C09BA; C09BB02; C09BB03; C09BB04; C09BB05; C09BB06; C09BB07; 09BB12; C09BX01; C09BX03; C09BX03; C09BX04; C09CA; C09DA; C09DB; C09DX; C09XA52; C09XA53; C09XA54

Angiotensin II-stimulating AHM include ARBs, dihydropyridine CCBs and thiazide diuretics. AHM = antihypertensive medication; ATC = Anatomical Therapeutic Chemical; ACEi = angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; CCB = calcium channel blocker.

Supplement 2. Number of participants with missing data for each variable of interest

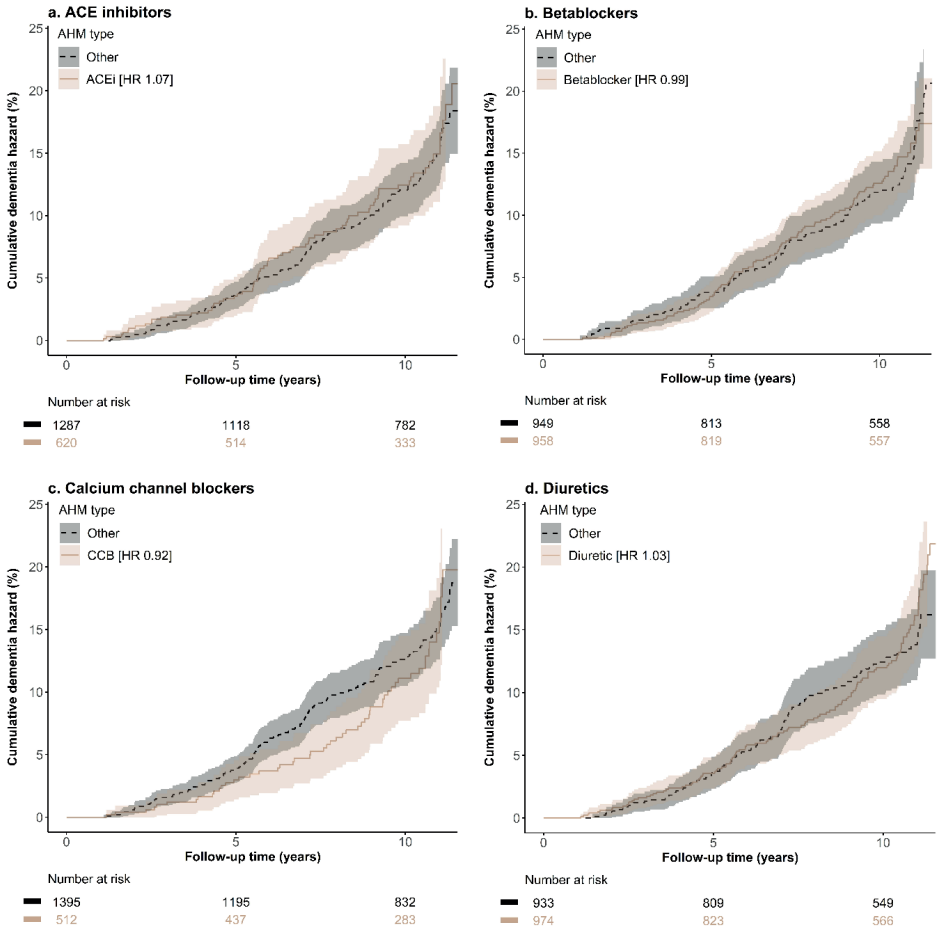
Variables	Participants with missing data (%)
Age	0 (0)
Dementia	21 (1.1)
History of CVD	24 (1.2)
Diabetes mellitus	0 (0)
Systolic blood pressure	0
Diastolic blood pressure	0
Smoking	3 (0.2)
Physical activity	41 (2.1)
LDL	53 (2.7)
BMI	1 (0.1)
MMSE	3 (0.2)

Data presented for all participants who used who used antihypertensive medication at baseline (n=1953). CVD = cardiovascular disease; LDL = low-density lipoprotein; BMI = Body-Mass index; MMSE = Mini-Mental State Examination.

Supplement 3. Number of antihypertensive medication (AHM) classes and combinations of AHM at baseline.

	ACEi (N=620)	ARB (N=390)	Beta-blocker (N=958)	CCB (N=512)	Diuretic (N=974)
Number of AHM classes, N (%)					
1	137 (22.1)	90 (23.1)	282 (29.4)	104 (20.3)	182 (18.7)
2	247 (39.8)	164 (42.1)	364 (38.0)	172 (33.6)	457 (46.9)
3	181 (29.2)	101 (25.9)	233 (24.3)	157 (30.7)	255 (26.2)
≥4	55 (8.9)	35 (9.0)	79 (8.2)	79 (15.4)	80 (8.2)
AHM classes					
ACEi	620 (100.0)	13 (3.3)	258 (26.9)	161 (31.4)	342 (35.1)
ARB	13 (2.1)	390 (100.0)	150 (15.7)	107 (20.9)	201 (20.6)
Beta-blocker	258 (41.6)	150 (38.5)	958 (100.0)	225 (43.9)	434 (44.6)
CCB	161 (26.0)	107 (27.4)	225 (23.5)	512 (100.0)	230 (23.6)
Diuretic	342 (55.2)	201 (51.6)	434 (45.3)	230 (44.9)	974 (100.0)
Cholesterol lowering medication	346 (55.8)	183 (46.9)	528 (55.1)	266 (52.0)	448 (46.0)

Median follow-up: 10.4 years. Individual participants are represented in different classes of antihypertensive medication when they use combination therapy. ACEi = angiotensin-converting enzyme inhibitor; AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker.



Supplement 4. Cumulative hazard of dementia for ACE inhibitors, beta-blockers, calcium channel blockers and diuretics

a. ACEi, b. beta-blockers, c. CCBs, d. diuretics (brown) versus any other AHM classes (grey). ACEi = angiotensin-converting enzyme inhibitor, AHM = antihypertensive medication, HR = hazard ratio; CCB = calcium channel blocker, AHM = antihypertensive medication, HR = hazard ratio

Supplement 5. Short-term associations between use of a specific antihypertensive medication class and incident dementia, compared with use of any other antihypertensive medication classes

	Dementia cases (%)	HR (95% CI)
ACEi	39/620 (6.3)	1.12 (0.75-1.66)
ARB	14/390 (3.6)	0.54 (0.31-0.94)
Beta-blocker	58/958 (6.4)	1.05 (0.72-1.54)
CCB	21/512 (4.1)	0.60(0.37-0.97)
Diuretic	57/974 (5.9)	0.96 (0.66-1.40)
Dihydropyridine CCB	18/399 (3.5)	0.52 (0.30-0.91)
AT II-stimulating AHM	36/1180 (3.1)	0.68 (0.47-1.00)

Follow-up cut off at 7 years. Model 2: adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. The dementia cases (percentages) represent the number of participants with incident dementia from the participants using the AHM class of interest. ATII-stimulating AHM include ARB's, dihydropyridine CCB's and thiazide diuretics. ACEi = angiotensin converting enzyme inhibitor; AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; AT II = angiotensin II; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

Supplement 6. Associations between use of antihypertensive medication (AHM) classes and incident dementia, compared with use of any other AHM class – maximally adjusted model

	Dementia cases (%) in AHM class of interest	Dementia cases (%) in other AHM users	Model 3 HR (95% CI)
ACEi	72/620 (11.6)	153/1287 (11.9)	1.13 (0.83-1.52)
ARB	37/390 (9.5)	188/1517 (12.4)	0.76 (0.53-1.09)
Beta-blocker	113/958 (11.8)	112/949 (11.8)	1.05 (0.78-1.37)
CCB	58/512 (11.3)	167/1395 (12.0)	0.96 (0.69-1.32)
Diuretic	117/974 (12.0)	108/933 (11.6)	1.10 (0.81-1.50)
Dihydropyridine CCB	37/399 (9.3)	188/1508 (12.5)	0.73 (0.50-1.07)
ATII-stimulating AHM	129/1180 (10.9)	96/727 (13.2)	0.79 (0.58-1.08)

Median follow-up: 10.4 years. Model 3: adjusted for age, sex, history of cardiovascular disease, history of diabetes mellitus, number of antihypertensive drugs, and randomization group. ATII-stimulating antihypertensives include ARBs, dihydropyridine CCBs, and thiazide diuretics. ACEi = angiotensin converting enzyme inhibitor; AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; ATII = angiotensin II; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

Supplement 7. Associations between use of antihypertensive medication class and dementia, mutually adjusted for use of multiple classes

	HR (95% CI)
ACEi	0.98 (0.72-1.34)
ARB	0.74 (0.51-1.08)
Beta-blocker	0.96 (0.73-1.27)
CCB	0.92 (0.68-1.24)
Diuretic	1.01 (0.77-1.33)

Cox proportional hazard model adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus.
ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

Supplement 8. Associations between use of antihypertensive medication classes and dementia within stable users

	Stable- /total users (%)	Dementia cases (%)	HR (95% CI)
ACEi	418/620 (67.4)	50/418 (12.0)	1.12 (0.80-1.57)
ARB	302/390 (77.4)	29/302 (9.6)	0.78 (0.52-1.16)
Beta-blocker	713/958 (74.4)	87/713 (12.2)	1.01 (0.74-1.38)
CCB	372/512 (72.7)	40/372 (10.7)	0.87 (0.61-1.24)
Diuretic	685/974 (70.3)	73/685 (10.6)	0.79 (0.58-1.08)
Dihydropyridine CCB[a]	286/399 (71.7)	27/286 (9.4)	0.77 (0.51-1.17)
ATII-stimulating AHM[a]	883/1180 (74.8)	91/883 (10.3)	0.73 (0.52-0.99)

Median follow-up: 10.4 years. Cox proportional hazard model adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. Stable users as defined as using the same antihypertensive medication group at baseline and at one or more preDIVA follow-up visits. ATII-stimulating AHM include ARBs, dihydropyridine CCBs and thiazide diuretics. ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio. aPost hoc analysis.

Supplement 9. Associations between use of antihypertensive medication classes and mortality, and dementia and mortality combined

	Death cases (%)	HR death (95% CI)	Dementia or death cases (%)	HR dementia or death (95% CI)
ACEi	237/620 (38.2)	1.19 (1.01-1.40)	294/620 (47.4)	1.18 (1.02-1.36)
ARB	122/390 (31.3)	0.94 (0.77-1.14)	154/390 (39.5)	0.91 (0.77-1.09)
Beta-blocker	323/958 (33.7)	0.89 (0.76-1.04)	410/958 (42.8)	0.92 (0.80-1.05)
CCB	194/512 (37.9)	1.13 (0.95-1.34)	237/512 (46.3)	1.06 (0.91-1.24)
Diuretic	333/974 (34.2)	1.15 (0.98-1.34)	424/974 (43.5)	1.13 (0.98-1.30)
Dihydropyridine CCB[a]	135/399 (33.8)	0.99 (0.82-1.20)	165/399 (41.4)	0.93 (0.79-1.11)
ATII-stimulating AHM[a]	382/1180 (32.4)	0.94 (0.81-1.11)	486/1180 (41.2)	0.93 (0.81-1.07)

Median follow-up: 10.4 years. Cox proportional hazard model adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. ATII-stimulating AHM include ARBs, dihydropyridine CCBs and thiazide diuretics. ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio. aPost hoc analysis.

Supplement 10. Association between use of ARBs or dihydropyridine CCBs and incident dementia

	Dementia cases (%) in AHM class of interest	Dementia cases (%) in other AHM users	Crude model HR (95% CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)
ARB or dihydropyridine CCB	692/1907 (36.3)	65/692 (9.8)	0.69 (0.52-0.92)	0.69 (0.52-0.92)	0.67 (0.49-0.92)

Model 2: adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. Model 3: adjusted for age, sex, history of cardiovascular disease, history of diabetes, number of used AHM-classes, and randomization group. AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

Supplement 11. Subgroup analyses for the association between use of different antihypertensive medication classes and incident dementia

	Sex		CVD history		DM history	
	Female	**Male**	**Yes**	**No**	**Yes**	**No**
ACEi						
Dementia cases (%)	33/340 (9.7)	39/280 (13.9)	34/315 (10.8)	38/305 (12.5)	33/233 (14.2)	39/387 (10.1)
HR	1.14	1.04	0.95	1.25	1.26	0.99
(95% CI)	(0.72-1.79)	(0.72-1.51)	(0.63-1.42)	(0.83-1.87)	(0.77-2.04)	(0.69-1.42)
P for interaction	0.85		0.36		0.49	
ARB						
Dementia cases (%)	10/171 (5.8)	27/219 (12.3)	18/184 (9.8)	19/206 (9.2)	12/110 (10.9)	25/280 (8.9)
HR	0.58	0.83	0.77	0.71	0.71	0.77
(95% CI)	(0.30-1.13)	(0.55-1.26)	(0.46-1.27)	(0.43-1.16)	(0.38-1.34)	(0.50-1.18)
P for interaction	0.42		0.70		0.86	
Beta-blocker						
Dementia cases (%)	45/466 (9.7)	68/492 (13.8)	71/589 (12.1)	42/369 (11.4)	33/240 (13.8)	80/718 (11.1)
HR	1.08	0.96	1.09	0.91	0.90	1.03
(95% CI)	(0.69-1.70)	(0.68-1.34)	(0.74-1.60)	(0.62-1.34)	(0.56-1.47)	(0.75-1.43)
P for interaction	0.91		0.54		0.80	
CCB						
Dementia cases (%)	22/239 (9.2)	36/273 (13.2)	34/289 (11.8)	24/223 (10.8)	22/154 (14.3)	36/358 (10.1)
HR	0.98	0.89	1.00	0.84	1.09	0.88
(95% CI)	(0.60-1.59)	(0.61-1.30)	(0.66-1.49)	(0.53-1.32)	(0.61-1.97)	(0.59-1.31)
P for interaction	0.89		0.58		0.50	
Diuretic						
Dementia cases (%)	39/383 (10.2)	78/591 (13.2)	50/438 (11.4)	67/536 (12.5)	40/301 (13.3)	77/673 (11.4)
HR	1.25	0.92	0.90	1.15	0.86	1.10
(95% CI)	(0.80-1.94)	(0.66-1.29)	(0.61-1.31)	(0.79-1.69)	(0.53-1.39)	(0.80-1.53)
P for interaction	0.28		0.62		0.42	
Dihydropyridine CCB[a]						
Dementia cases (%)	15/184 (8.2)	22/215 (10.2)	19/204 (9.3)	18/195 (9.2)	15/126 (11.9)	22/273 (8.1)
HR	0.83	0.69	0.78	0.67	0.80	0.67
(95% CI)	(0.47-1.45)	(0.44-1.08)	(0.47-1.28)	(0.41-1.12)	(0.45-1.43)	(0.43-1.05)
P for interaction	0.64		0.66		0.57	
ATII-stimulating AHM[a]						
Dementia cases (%)						
HR	43/498 (8.6)	86/682 (12.6)	52/517 (10.1)	77/663 (11.6)	39/332 (11.7)	90/848 (10.6)
(95% CI)	0.80	0.81	0.69	0.90	0.58	0.90
	(0.51-1.23)	(0.57-1.14)	(0.48-1.01)	(0.60-1.34)	(0.36-0.94)	(0.65-1.25)
P for interaction	0.89		0.49		0.13	

Adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. ATII-stimulating AHM include ARBs, dihydropyridine CCBs and thiazide diuretics. ACEi = angiotensin converting enzyme inhibitor; AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; ATII = angiotensin II; CCB = calcium channel blocker; CI =confidence interval; CVD = cardiovascular disease; DM = diabetes mellitus; HR = hazard ratio. aPost hoc analysis. bCut-off for controlled hypertension is 150 mmHg.

Hypertension[b]		Mono vs. multi-therapy		Age	
Uncontrolled	**Controlled**	**Mono**	**Multi**	**< 75**	**≥ 75**
40/385 (10.4) 0.99 (0.67-1.45)	32/235 (13.6) 1.25 (0.81-1.91)	19/137 (13.9) 1.29 (0.77-2.16)	53/483 (11.0) 1.01 (0.71-1.45)	32/309 (10.4) 1.25 (0.81-1.94)	40/311 (12.9) 0.95 (0.65-1.39)
	0.29		0.37		0.38
17/226 (7.5) 0.62 (0.37-1.04)	20/164 (12.2) 0.93 (0.57-1.53)	7/90 (7.8) 0.60 (0.28-1.30)	30/300 (10.0) 0.81 (0.54-1.22)	19/201 (9.5) 0.95 (0.57-1.58)	18/189 (9.5) 0.60 (0.36-0.99*)
	0.27		0.52		0.82
66/576 (11.5) 1.11 (0.78-1.57)	47/382 (12.3) 0.85 (0.56-1.30)	33/282 (11.7) 0.97 (0.63-1.51)	80/676 (11.8) 1.06 (0.73-1.53)	49/493 (9.9) 1.04 (0.68-1.59)	64/465 (13.8) 0.97 (0.68-1.37)
	0.56		0.66		0.58
28/294 (9.5) 0.80 (0.52-1.22)	30/218 (13.8) 1.07 (0.70-1.66)	15/104 (14.4) 1.22 (0.70-2.12)	43/408 (10.5) 0.84 (0.58-1.22)	20/250 (8.0) 0.79 (0.48-1.29)	38/262 (14.5) 1.01 (0.69-1.48)
	0.24		0.30		0.51
72/583 (12.3) 1.25 (0.87-1.78)	45/391 (11.5) 0.80 (0.53-1.21)	23/182 (12.6) 0.96 (0.59-1.56)	94/792 (11.9) 1.18 (0.79-1.78)	45/471 (9.6) 0.95 (0.62-1.45)	72/503 (14.3) 1.07 (0.75-1.51)
	0.15		0.66		0.36
19/240 (7.9) 0.66 (0.41-1.08)	18/159 (11.3) 0.81 (0.48-1.35)	9/6 (13.6) 1.10 (0.55-2.20)	28/333 (8.4) 0.64 (0.42-0.98)	14/203 (6.9) 0.67 (0.38-1.18)	23/196 (11.7) 0.78 (0.49-1.22)
	0.51		0.19		0.36
77/739 (10.4) 0.79 (0.55-1.13)	52/441 (11.8) 0.83 (0.55-1.27)	36/300 (12.0) 0.91 (0.59-1.39)	93/880 (10.6) 0.67 (0.44-1.01)	52/591 (8.8) 0.78 (0.51-1.19)	77/598 (13.1) 0.79 (0.55-1.12)
	0.91		0.27		0.32

9

General discussion

The focus of this thesis is on the prevention of dementia in middle-aged and older adults by targeting lifestyle-related risk factors for dementia. **Part I** of this thesis addresses the self-management of these risk factors and the potential supportive role for digital health. **Part II** focusses on risk factors for dementia in old age, and on the relationship between use of specific antihypertensive medication classes and dementia in older adults.

Part I: Lifestyle behaviour change to prevent dementia using mHealth

There is an abundance of smartphone applications to help individuals adopt a healthier lifestyle. Digital lifestyle support may be a promising strategy to improve healthy behaviours on a large scale, as these interventions are generally easy and inexpensive to implement across different health care systems. However, only very few of these applications have been developed based on an evidence-based rationale, or have been proven effective to prevent disease in randomised controlled trials (RCTs)[1]. For dementia specifically, there are insufficient high-quality studies to draw conclusions on the effectiveness of smartphone-based interventions on cognition and dementia outcomes[2]. Part I of this thesis addresses the development of the PRODEMOS trial, which aims to test the efficacy and implementation of a coach-supported mobile health (mHealth) intervention to improve the risk of dementia in high-risk individuals in the UK and China.

One of the main challenges of the PRODEMOS project is to develop a smartphone application that is suitable for use by older adults from both populations. From the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) study we learned that human support, regular reminders and options to tailor the intervention to personal preferences are facilitators for sustained use of a self-management internet platform for older people[3]. We used the HATICE platform and the lessons learned from its evaluation as the basis for development of our app.

As involvement of end-users during development has been associated with more appropriate app design[4], we interviewed low socioeconomic status (SES) older adults in the Netherlands (***chapter 4***) and Chinese older adults living in the Greater Beijing area (***chapter 5***) on their needs and views regarding lifestyle behaviour change in the context of dementia and cardiovascular disease (CVD) prevention, and the potential role for mHealth. In general, results from both studies were remarkably similar, despite the large cultural differences between both study populations. Most participants had attempted to adopt healthier lifestyle behaviours before, but had failed to sustain these new behaviours, reducing their faith in renewed attempts. In line with previous studies, such attempts were often

provoked by (symptoms of) disease or by suggestions from family members[5, 6] and were most easily started and maintained when undertaken together with peers[7, 8]. Moreover, participants from both populations highlighted that, especially with ageing, current quality of life was more meaningful than potential future gains associated with a healthy lifestyle. In addition to these similarities, we also found some culture-specific themes, such as the burden experienced by Chinese older adults to take care of their (grand)children or parents, impeding regular exercise, and the view that traditional Chinese hospitality standards, such as offering alcohol and cigarettes, do not always match with own efforts to pursue more healthy behaviours. From the Dutch participants we learned that they consider lifestyle behaviour a very personal and private matter, and do not easily accept support from any healthcare professional.

In the process of integration and translation of all qualitative findings into the app development (***chapter 6***), we faced several challenges. According to the user centred design methodology, we involved end-users throughout the design process[9]. In the early phase of app development, we successfully gained information regarding the basic needs of the end-users. However, during sessions aimed at gathering more specific information on app requirements later in the process, we lacked viable prototypes and clickable wireframes of the app to sufficiently feed these sessions. Moreover, our team lacked a member specifically experienced in user centred design. Input from mHealth specialists in the field of user research could have improved the yield of end-user consultation and the translation of our findings into app requirements. A final challenge is related to the analysis of the Chinese interviews. Although we performed the analysis in concertation with our Chinese research colleagues and in the presence of a professional translator, we cannot completely rule out the possibility that our interpretation may have been influenced by our specific European view. Although interpretation is at the heart of qualitative research and does not limit its validity[10], it may be that subconscious assumptions, for example about the Chinese population and its relation with digital devices, has affected the translation into technical requirements.

Recommendations for development of mHealth interventions for vulnerable older adults

Process

In user centred design, end-users are typically involved during the entire development process, in iterative cycles of prototyping and user testing[9]. We largely followed this approach in PRODEMOS, but had difficulty gaining specific feedback from our target population regarding app requirements. Perhaps, when designing interventions for - likely less tech-savvy - older adults from underserved

populations, it becomes even more important to show prototypes and wireframes (two-dimensional illustrations of app pages) during feedback sessions, and to perform systematic user testing in addition to the interviews.

Considering our target population, it was especially important to develop an app that is easy to use. This is important as sustained engagement with interventions has been recognized as a major challenge related to mHealth development[11,12] and is essential for intervention effectiveness. However, sustained engagement requires more than user friendliness alone. There is an increasing body of evidence on improving user engagement of digital interventions, including recommendations on interface aesthetics, options for personalisation, and reinforcement through rewards and reminders[13]. Developers of future mHealth interventions for lifestyle behaviour change should ideally look beyond the question whether participants can use the app, and focus more explicitly on the prerequisites to ensure people will use the app. Existing guidelines to improve engagement with digital interventions can be consulted in addition to, or probably even prior to, involving the specific target population.

App functionality and content

Based on results from our interviews and supported by previous research, mHealth interventions for dementia prevention in older adults may be most attractive and effective when combined with human support[14,15], and when embedded in existing healthcare structures[16]. Given the need for peer support[7,8], such blended interventions should facilitate group activities or enable contact with people from the same age with comparable lifestyle goals. Moreover, efficiency and minimum user input, such as fewer required tasks, have been associated with app engagement[13]. As many smartphones (can) collect data on health parameters, future mHealth interventions can perhaps make use of these (sometimes automatically collected) data to facilitate self-monitoring. Finally, as needs and wishes regarding content and functionalities may differ between participants and can change within the same participant over time, future mHealth interventions should have sufficient options to tailor the intervention to personal preferences. Examples of such tailoring are modifiable options for intensity of coach support and educational material that is adjustable in terms of subject and complexity.

Recommendations for trials testing lifestyle interventions for dementia prevention

Methodological challenges associated with dementia prevention trials have been discussed extensively in ***chapter 2*** of this thesis. In short, one of the main challenges is the time lag between the optimal timing of the intervention,

initiated not later than midlife or early late-life[17, 18], and the onset of dementia decades later in life. This requires long follow-up periods and/or large sample sizes to reach sufficient statistical power to test for differences in dementia incidence rates or clinically relevant cognitive decline[19, 20]. Cluster randomization could fuel valuable opportunities to deliver the intervention in the community, allowing for group activities and peer support at low risk of contamination, but would require even larger numbers of participants as a result of design-related loss of power[21].

Alternative, propitious outcome measures for use in lower age ranges, including biomarkers and dementia risk scores, can be used to reduce the power problem associated with dementia prevention trials. However, biomarkers have not been validated as a surrogate outcome measure[22], and for existing dementia risk scores it is also uncertain how intervention effects might translate into effects on long-term dementia incidence rates[23]. In order to study the actual effect of (digital) lifestyle interventions on dementia incidence, there is an urgent need to design large-scale trials with sufficient numbers of participants and sustained follow-up over 5-10 years, to establish solid knowledge on potential effectiveness.

The ideal RCT to test a (digital) lifestyle intervention for dementia prevention would have incident dementia, perhaps combined with a (pragmatically operationalised) measure for clinically relevant cognitive decline, as primary outcome. Secondary outcomes should include changes in individual dementia risk factors to provide insight into the mechanisms of the potential effect. Moreover, the intervention and follow-up period should be sufficient to assess engagement with and effectiveness of the intervention over a prolonged period. Given their relatively poor access to preventive healthcare and the high prevalence of (risk factors for) dementia in these populations, individuals in low- and middle-income countries and minority populations in high-income countries have the largest potential window of opportunity. Finally, cluster randomisation at the level of 'natural' clusters in the population, such as community centres or neighbourhoods, may be considered to optimise overall program effectiveness and implementation and at the same time minimise contamination.

A potential difficulty associated with long intervention periods is that, given the constantly evolving app market, mHealth interventions may become outdated during or shortly after the study period. Traditionally, researchers try to standardise external factors to avoid introducing bias, whereas software developers usually keep updating and refining a product to keep up with the competition. With extensive documentation and a focus on successful app principles rather than on

fixed apps, allowing certain adaptations to the mHealth intervention during the study may result in more up to date interventions that suit the ever changing needs of their users.

Recommendations for clinical practice

The interviews with older adults that we performed to inform development of our mHealth intervention provided important insights in their needs and views regarding lifestyle change in general and the potential role for professional support. I will try to translate these insights into implications for clinical practice; however, given my limited knowledge of the Chinese healthcare system, I will restrict myself to the Dutch situation.

In the interviews with Dutch low SES older adults, the general practitioner (GP) and GP nurse were the most recognised healthcare professionals that provided lifestyle support. We learned from the interviewees that lifestyle behaviour was generally viewed as a personal and private matter, which was not easily discussed with healthcare professionals. Patients sometimes perceived it as interference when their GP (nurse) raised the subject of behaviour change or gave unsolicited advice, evoking feelings of resistance. As a healthcare professional, it may therefore be important to very cautiously approach subjects in this context, and to make sure that the patient retains a sense of autonomy. Second, we learned that, in line with previous research[24], following healthy behaviours was often associated with feelings of suffering and discomfort (i.e. sweating, feeling hungry and eating distasteful food). The interviewees often deemed these sacrifices disproportionate, given the little faith they had in the advantages of healthy behaviours on the long term. As especially older adults prefer current quality of life to possible future health gains6, short-term and patient-centred outcomes, such as functional independence, can perhaps serve as an alternative starting point for healthcare professionals to discuss lifestyle behaviour change. Finally, given the importance of social support in low SES individuals[7, 8], healthcare professionals may actively support changing behaviour together with the spouse, a family member, or peer groups.

Concluding remarks and future perspective for lifestyle interventions to prevent dementia

At the time of writing this thesis, the PRODEMOS trial is still ongoing. Results from this trial are expected to inform the development of future (digital) lifestyle interventions for dementia prevention and will add to the body of literature on the effect of modifiable risk factors on dementia risk. To assess to what extent the PRODEMOS app is attractive and easy to use, we will assess certain implementation

outcomes, including the intervention's appropriateness, feasibility, acceptability, adoption and sustainability.

Although an RCT is the ideal design to assess whether lifestyle changes can lead to a lower risk of dementia, dementia prevention trials are costly, and are at the risk of Type II errors if methodological challenges are not adequately addressed[25]. Multiple high-quality population-based cohort studies[18, 26], multi-domain intervention studies with small effects in (subgroups of) high-risk populations[27, 28], and the possible decline in age-dependent dementia incidence over time in high-income countries[29, 30] all suggest a (partly) causal relationship between lifestyle-related dementia risk factors and reduced dementia risk. As risk factor modification has proven beneficial on CVD outcomes, and dementia and CVD share multiple risk factors, implementation of (existing) lifestyle interventions for CVD prevention may result in additional beneficial effects on dementia risk.

A final consideration is the extent to which healthy behaviours are a matter of individual choice. After all, also external factors such as somebody's social- and living environment affect health behaviours[31, 32]. From our interviews with low SES older adults we learned that behaviour change is not easily sustained over time, especially when the benefits are not tangible on the short term. Thus, in the case of dementia prevention, where healthy behaviours should be established at a relatively young age and need to be sustained over a long time, individual lifestyle interventions should be supplemented by interventions in the social and public domain.

Part II: Dementia risk factors and treatment of hypertension in older adults

In part II of this thesis, we focussed on risk factors and treatment of hypertension in older adults. First, we aimed to assess the associations between blood pressure, BMI and cholesterol and dementia in older adults. Second, we aimed to assess whether certain antihypertensive medication classes are associated with lower dementia risk. For these analyses, we used data from the Prevention of Dementia by Intensive Vascular care (preDIVA) observational extension (POE) study, including 3526 older adults aged 70-78 at baseline without dementia, with a median follow-up of 10.3 years.

Blood pressure, BMI and cholesterol as risk factors for dementia in middle- and old age

High values for blood pressure, BMI and cholesterol in midlife have all been associated with increased dementia risk later in life. The relationship between these risk factors and dementia can in part be explained by the coincidence of common disorders[33], but there are also several hypotheses around the (in) direct contribution of vascular risk factors to the onset of cognitive impairment and dementia. In short, risk factors such as high blood pressure, obesity and dyslipidaemia often coexist[34], and are thought to cause structural and functional changes in the cerebral blood vessels, leading to altered brain perfusion and cognitive impairment[35, 36]. Moreover, cardiovascular risk factors increase the risk of stroke, which increases the risk of dementia[37].

The relationships between vascular risk factors, including blood pressure, cholesterol and BMI and dementia appear to reverse with ageing[38-43]. In line with these studies, we observed in the POE study that for systolic blood pressure, BMI and non-HDL cholesterol, low values (i.e. below 138 mmHg, 24.2 kg/m2 and 2.8 mmol/L respectively) were associated with the highest risk to develop dementia. Furthermore, we observed that individuals with low values for all three risk factors together had a substantially higher risk of dementia than those with only one or two low values (***chapter 7***). As these findings could not be explained by any combination of two risk factors or by competing risk of death, our results suggest that a diagnosis of dementia may be most distinctly preceded by a phenomenon that involves all three risk factors.

Our results are derived from observational data, so no inferences about causality can be drawn. A causal relationship would imply that target values for hypertension and cholesterol treatment should perhaps be higher for older adults. In contrast, however, the recent SPRINT-MIND trial has suggested that intensive blood pressure control (<120 mmHg) in older adults with hypertension may reduce the risk for dementia as compared to standard treatment (<140 mmHg), although dementia was a secondary outcome[44]. Alternatively, reverse causality may be at play. As dementia is known to have a long prodromal period of up to decades, low values of risk factors may be early symptoms of neurodegeneration. However, theories on a (direct) effect of neurodegeneration on, for example, changes in cholesterol levels, are still lacking. Finally, the combination of low values may be a marker of another condition, such as a catabolic state, which is associated with increased dementia risk[45]. If the latter would be the case, this subset of individuals can perhaps explain (the majority of) the inverse relationships between dementia risk and late-life blood pressure, cholesterol and BMI values.

Antihypertensive medication classes and dementia risk in old age

Besides their effects on blood pressure, certain antihypertensive medication classes may have class-specific effects on dementia risk. Angiotensin receptor blockers (ARBs), dihydropyridine calcium channel blockers (CCBs) and angiotensin (AT) II-stimulating AHM as a group have all been associated with decreased dementia risk in recent studies with follow-up periods up to seven years[46-48]. For dementia, it may take at least several years for AHM to exert their potential protective effects. This is illustrated by the finding that associations between certain AHM and dementia risk are stronger with longer follow-up[48]. In ***chapter 8***, we assessed whether the presumed protective effect of certain AHM classes on dementia risk in older individuals holds over time. After a median of 10.3 years of follow-up, use of ARBs, CCBs and AT II-stimulating AHM was associated with decreased dementia risk, but associations had attenuated compared to associations assessed after seven years of follow-up in the same cohort, and were no longer statistically significant.

Our study population consists of relatively old individuals (i.e. 70-78 at study baseline). Possibly, the potential protective effects of ARBs, dihydropyridine CCBs and AT II-stimulating AHM on dementia risk decrease with age. Such an age-dependent effect is conceivable, as dementia prevention interventions appear most effective in midlife or early late life. Another explanation may be that effects are temporary, regardless of age. However, despite the decrease in effect sizes, use of ARBs, dihydropyridine CCBs and AT II-stimulating AHM was still associated with a decreased dementia risk of approximately 20% after up to twelve years of follow-up as compared to use of other AHM. As these substances are widely available and inexpensive, prescription of ARBs and CCBs in older people with hypertension may be a promising strategy to decrease dementia risk on a large scale, if confirmed by randomised controlled studies.

Our analyses should be interpreted in the light of some methodological limitations. Since there was no effect of the preDIVA intervention, and loss to follow-up for the primary outcome was negligible, we considered the population as one cohort. In general, trial participants differ from the general population[49]. In preDIVA specifically, participants were aged 70-78 at baseline. This may have led to a selection of older adults who had reached this age in a relatively healthy condition, limiting external validity of our results. However, PreDIVA was a pragmatic trial, including community-dwelling older adults who appeared to be comparable to the Dutch general population in terms of demographics and cardiovascular risk factors[50]. Another limitation related to use of RCT data is the potential effect of the intervention on all data collected after study baseline. For our study on dementia

risk factors in old age specifically, the lack of usable data on risk factor values after baseline impeded assessment of the association between dementia risk and changes in risk factors over time. Low values may in fact signal declines of these risk factors over the preceding period, which have previously been associated with increased dementia risk[51-53]. With regard to our study on AHM use and dementia risk, the lack of intermediate data on AHM use has likely led to reduced association between AHM use at baseline and actual use at the time of outcome assessment. As former Dutch guidelines recommended use of ARBs and CCBs as second or later steps in hypertension treatment, it may be that significant numbers of participants who were classified as using other AHM, actually switched to ARBs and/or CCBs after baseline, potentially leading to underestimation of the effect size. Another potential limitation related to previous hypertension guidelines is confounding by indication, as ARBs and CCBs may have been prescribed more often to individuals with therapy-resistant forms of hypertension. Subgroup analyses for CVD history, hypertension and diabetes suggest that these factors do not explain our results, however, confounding by indication cannot be ruled out completely, as also other factors may play a role in the choice for a specific AHM.

Suggestions for future research

As the combination of low values of vascular risk factors is associated with increased dementia risk beyond their individual associations, this subset of individuals may perhaps explain the inverse or J-shaped relations between vascular risk factors and incident dementia as observed in older adults. It would be interesting to (re-) assess the effect of interventions targeting these risk factors on dementia risk for this particular subgroup. In our observational study, the direction of the associations between low values and dementia risk remained largely unclear. An RCT is the gold standard to assess causality, however, comparing long-term treatment of blood pressure, BMI and cholesterol vs. care as usual would perhaps not be the most feasible (or ethical) option. Large cohort studies, possibly increasing internal validity by using propensity scores, may serve as a good alternative, although resulting in a different level of evidence. Such studies should have a considerable follow-up period and should include data on change of vascular risk factors over time, in order to evaluate trajectories of these risk factors preceding dementia diagnosis. When linked with parameters of imaging and neuropathology, mechanisms behind the association can be further unravelled.

Regarding the associations between certain AHM classes and dementia risk, an RCT would be the ideal design to assess potential protective effects in older adults. As according to the Dutch GP guidelines ARBs, CCBs, diuretics, beta-blockers and ACE

inhibitors are equivalent agents for treatment of de novo essential hypertension in most patients, those patients could be randomised between treatment with AT II-stimulating and AT II-inhibiting AHM. Through semi-structured interviews, it is currently being studied whether, and under what conditions, GPs and potential participants are prepared to participate in such a trial.

Implications for clinical practice

Based on a vast body of evidence in middle age, most clinicians will automatically link high values for vascular risk factors to a patient's future risk for CVD and, perhaps, dementia. In older adults however, (a combination of) low values for these risk factors should also trigger a clinician to think about a potentially increased dementia risk. Current risk prediction models for dementia are based on risk factors in midlife. As we cannot make statements on causality, future studies should assess whether current target values for vascular risk factors from younger populations still apply to the elderly. Therefore, specific risk prediction tools for older individuals should be developed[54].

Guidelines on blood pressure management leave ample room for physicians' own preferences. Clinicians can take the presumed protective effect of ARBs and dihydropyridine CCBs on dementia risk into consideration, when initiating treatment in patients with de novo hypertension. However, evidence from at least one high-quality RCT is needed before recommendations on medication preferences is justified.

Overall conclusions

In the first part of this thesis, we described the development of the PRODEMOS smartphone-based dementia prevention intervention and the RCT to test its effectiveness and implementation. In the second part, we studied dementia risk factors and treatment of hypertension in older adults. We found that older adults with a low BMI, low blood pressure and low non-HDL cholesterol had a much higher dementia risk than those with two or less low values for these risk factors. Moreover, we discovered that, even after ten years of follow-up, use of ARBs, CCBs and AT II-stimulating AHM was associated with decreased, albeit non-significanty lower, dementia risk. To build further knowledge on whether dementia can actually be prevented or delayed by improvements in lifestyle-related risk factors or use of specific antihypertensives, large-scale, long-term randomised controlled trials will be needed, aimed at the reduction of cumulative, all-cause dementia incidence.

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Summary

The number of people with dementia is increasing worldwide, due to global ageing. In absence of curative treatment options, prevention of dementia may be a promising strategy to slow this increase. This thesis addresses the prevention of dementia by targeting modifiable risk factors.

In **part I** of this thesis we focus on lifestyle behaviour change for the prevention of dementia, and on the potential role for remote mobile health (mHealth) support. Observational studies have suggested that healthy lifestyle behaviours, including a healthy diet and physical exercise, are associated with decreased dementia risk. However, results from RCTs so far have not confirmed a causal relationship between these risk factors and dementia incidence. In ***Chapter 2***, we elaborate on the current evidence for dementia prevention, reflect on the evidence gap between observational and experimental research, and provide an outline for further research and future prevention strategies.

As the expected increase in dementia prevalence will mostly occur in low- and middle-income countries, dementia prevention interventions should be easily accessible and inexpensive. The Prevention Of Dementia using Mobile Phone Applications (PRODEMOS) trial assesses the effectiveness and implementation of a coach-supported mHealth intervention for self-management of dementia risk factors over 18 months. The main effectiveness outcome is change in the Cardiovascular risk factors, Aging and Incidence of Dementia (CAIDE) risk score. Implementation outcomes include acceptability, adoption, appropriateness, and feasibility of the intervention. The target population consists of older adults in Beijing and low socioeconomic status (SES) older adults in the United Kingdom (UK), all with at least 2 dementia risk factors. ***Chapter 3*** describes the protocol for the PRODEMOS trial.

In order to design an intervention that fits the needs and wishes of the target population, we performed interviews with low SES older adults in the Netherlands (***chapter 4***) and with Chinese older adults living in Beijing (***chapter 5***). The aim of the interviews was to assess the needs and views of the target population regarding lifestyle behaviour change in order to prevent cardiovascular disease (CVD) and dementia, and their views on the potential role for an mHealth intervention with remote coaching. Results from both studies were largely similar. Most participants had attempted to adopt healthier lifestyle behaviours, but had failed to sustain them, reducing their faith in renewed attempts. Such attempts were often provoked by (symptoms of) disease or by suggestions from family members, and were perceived to be most successful when undertaken with peers. More specifically for the Chinese context, we learned that Chinese older

adults experienced a great burden of care for family members, impeding regular exercise. Specific for the Dutch setting, we learned that the target population with low SES considers lifestyle behaviour a very private matter, which is not easily discussed with any healthcare professional.

The development of the PRODEMOS mHealth platform built on the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) internet platform, which has been proven effective in improving cardiovascular risk factors in European older adults. Main features of the HATICE platform include functionalities for goal setting, entering measurements, and a chat functionality for coach support. In addition to the transition from an eHealth (web-based) to mHealth (smartphone-based) intervention, adjustments were made to the platform in repeated cycles of interaction with end users, in order to tailor the PRODEMOS intervention to their needs. In an iterative process, input from focus groups and test sessions served as a guideline for further development (***chapter 6***). Examples of adjustments are an intuitive design, frequent reminders to enter measurements, trustworthy and easy-to-understand education material, and options to personalise the app functionalities. To assess to what extent our efforts have led to an attractive and easy-to-use app that fits well into daily routines, in the ongoing PRODEMOS trial, data are collected on implementation outcomes through questionnaires, interviews and user statistics.

Part II of this thesis focuses on risk factors for dementia in older adults. Dementia risk has been associated with high values for cardiovascular risk factors in midlife, such as high blood pressure, high cholesterol and high BMI. However, in late life, these relationships may follow an inverse or U-shaped curve, with both high and low values imposing increased dementia risk. The nature of these inverse relationships is however still unclear. As inverse relationships are observed for several risk factors and outcomes, including CVD and mortality, it may be that low risk factor values reflect an overarching phenomenon that precedes a clinical diagnosis of dementia. In ***chapter 7***, we observed that dementia risk in older adults with low blood pressure, low cholesterol and low BMI was substantially higher than in those with one or two low values. This suggests that the inverse relationships between low values for risk factors in old age and dementia risk can be explained by an underlying mechanism, involving these risk factors simultaneously, rather than by risk factor-specific aspects.

In ***chapter 8***, we focus on treatment of hypertension in older adults. Beside their effects on blood pressure, certain antihypertensive medication (AHM) classes may have independent, class-specific effects on dementia risk. Angiotensin receptor blockers (ARBs), dihydropyridine calcium channel blockers (CCBs) and angiotensin (AT) II-stimulating AHM as a group have previously all been associated with decreased dementia risk. As these studies had follow-up periods of up to 7 years, it is unclear whether these associations sustain over a longer period of time. Using data of 1907 community-dwelling older adults, we assessed whether use of ARBs, CCBs and AT II-stimulating AHM is still associated with decreased dementia risk after more than 10 years of follow-up. We observed that associations were not statistically significant with longer follow-up, although dementia risk estimates were still up to 25% lower compared to use of other classes.

Nederlandse samenvatting

Wereldwijd groeit het aantal mensen met dementie, met name door toenemende vergrijzing. Omdat een curatieve behandeling ontbreekt, is preventie mogelijk een veelbelovende strategie om de groei van het aantal mensen met dementie te vertragen. Dit proefschrift gaat over de preventie van dementie door aan te grijpen op modificeerbare risicofactoren.

In **deel I** van dit proefschrift zoomen we in op preventie van dementie door middel van leefstijlverandering, en op de mogelijke rol voor ondersteuning op afstand via mobile health (mHealth).

Observationeel onderzoek suggereert dat een gezonde leefstijl, zoals bijvoorbeeld een gezond dieet en bewegen, geassocieerd is met een verlaagd dementie risico. Resultaten van RCT's hebben echter tot dusver geen causale relatie aangetoond tussen deze risicofactoren en dementie. In ***hoofdstuk 2*** beschrijven we de bestaande literatuur over dementie preventie, reflecteren we op de verschillen tussen resultaten van observationele en experimentele onderzoeken en doen we suggesties voor toekomstige onderzoeken en preventiestrategieën.

Aangezien verwacht wordt dat de prevalentie van dementie vooral zal stijgen in lage- en middeninkomenslanden, moeten interventies om dementie te voorkomen gemakkelijk toegankelijk en betaalbaar zijn. De Prevention Of Dementia using Mobile Phone Applications (PRODEMOS) trial onderzoekt de effectiviteit en implementatie van een mHealth interventie voor zelfmanagement van dementie risicofactoren met begeleiding van een coach op afstand gedurende achttien maanden. De primaire uitkomstmaat voor effectiviteit is verandering in de Cardiovascular risk factors, Aging and Incidence of Dementia (CAIDE) dementie risicoscore. De implementatie-uitkomsten omvatten o.a. aanvaardbaarheid, adoptie, geschiktheid en haalbaarheid van de interventie. De doelgroep bestaat uit ouderen in Beijing en ouderen met een laag sociaaleconomische status (SES) in het Verenigd Koninkrijk, beiden met minimaal twee dementie risicofactoren. ***Hoofdstuk 3*** bespreekt het protocol voor de PRODEMOS trial.

Om een interventie te ontwerpen die past bij de wensen en behoeftes van de doelgroep hebben we interviews gehouden met lage SES ouderen in Nederland (***hoofdstuk 4***), en met Chinese ouderen in Beijing (***hoofdstuk 5***). Het doel van de interviews was om te onderzoeken wat de behoeftes en visies van de doelgroep zijn t.a.v. leefstijlverandering voor de preventie van hart- en vaatziekten (HVZ) en dementie, en om uit te zoeken wat de mogelijke rol is voor (coaching via) mHealth.

De resultaten van beide onderzoeken waren grotendeels vergelijkbaar. De meeste deelnemers hadden al pogingen gedaan om gezonder te gaan leven, maar was het vaak niet gelukt om dit nieuwe gedrag vol te houden. Minder succesvolle ervaringen verlaagden het vertrouwen in volgende pogingen om gezonder te gaan leven. De pogingen om te veranderen waren vaak aangewakkerd door (symptomen van) ziekte of door aansporingen vanuit de familie, en waren vaak het meest succesvol wanneer ondernomen samen met anderen. Specifiek voor de Chinese situatie leerden we dat Chinese ouderen intensieve zorgtaken hadden voor familieleden, wat bewegen op regelmatige basis lastig maakte. Specifiek voor de Nederlandse situatie leerden we dat Nederlandse ouderen met een lage SES de leefstijl beschouwden als iets in het privédomein, wat niet zomaar wordt besproken met iedere zorgprofessional.

De ontwikkeling van het PRODEMOS mHealth platform bouwt voort op het Healthy Ageing Through Internet Counselling in the Elderly (HATICE) internet platform, dat effectief is gebleken in het verbeteren van cardiovasculaire risicofactoren bij Europese ouderen. De belangrijkste kenmerken van het HATICE platform zijn functies voor het stellen van doelen, het invoeren van metingen, en een chatfunctie voor contact met de coach. Behalve de transitie van eHealth (internet) naar mHealth (smartphone app), werd het platform in een iteratief proces aangepast op basis van input uit focusgroepen en test sessies (***hoofdstuk 6***). Voorbeelden van aanpassingen zijn een intuïtief design, regelmatige herinneringen om metingen in te voeren, betrouwbaar en makkelijk te begrijpen educatiemateriaal en opties om de functies van de app te personaliseren. Om te beoordelen in hoeverre deze inspanningen inderdaad hebben geleid tot een aantrekkelijke en makkelijk bruikbare app die goed past in de dagelijkse routines van de gebruikers, verzamelen we in de PRODEMOS trial middels vragenlijsten, interviews en gebruiksstatistieken data over implementatie van de interventie.

Deel II van dit proefschrift gaat over risicofactoren voor dementie, specifiek bij ouderen.

Op middelbare leeftijd wordt dementie geassocieerd met hoge waardes voor cardiovasculaire risicofactoren, zoals een hoge bloeddruk, hoog cholesterol en een hoog BMI. Echter, op latere leeftijd lijken deze verbanden om te draaien, of krijgen ze een U-vorm, waarbij zowel hoge als lage waardes geassocieerd zijn met verhoogd dementie risico. De aard van de omgekeerde relaties is tot dusver onbekend. Aangezien de omgekeerde verbanden zijn beschreven voor meerdere risicofactoren en uitkomstmaten, zoals HVZ en mortaliteit, zou het kunnen zijn dat de lage waardes voor risicofactoren duiden op een overkoepelend mechanisme

dat voorafgaat aan een dementiediagnose. In ***hoofdstuk 7*** hebben we beschreven dat het dementierisico bij ouderen met een lage bloeddruk, laag cholesterol en laag BMI substantieel hoger was dan bij mensen met één of twee lage waardes. Dit suggereert dat de omgekeerde relaties tussen lage waardes voor risicofactoren op latere leeftijd en het dementierisico kunnen worden verklaard door een overkoepelend fenomeen, dat betrekking heeft tot deze drie risicofactoren gezamenlijk, in plaats van door risico factor-specifieke invloeden.

In ***hoofdstuk 8*** zoomen we in op de behandeling van hypertensie bij ouderen. Er wordt gedacht dat bepaalde klassen van antihypertensiva naast hun effect op bloeddruk ook een onafhankelijk klasse-specifiek effect hebben op het dementie risico. Angiotensine receptor blokkers (ARB's), dihydropyridine calcium kanaal blokkers (CCB's) en angiotensine II-stimulerende antihypertensiva als groep zijn eerder geassocieerd met verlaagd dementie risico. Aangezien de follow-up van die onderzoeken maximaal 7 jaar was, is niet bekend of deze associaties ook na langere tijd blijven bestaan. Aan de hand van data van 1907 thuiswonende ouderen hebben we uitgezocht of het gebruik van ARB's, dihydropyridine CCB's en angiotensine II-stimulerende antihypertensiva ook na meer dan 10 jaar follow-up geassocieerd is met verlaagd dementierisico. We vonden dat de associaties niet langer significant waren, hoewel het dementierisico nog steeds 25% lager was dan bij degenen die andere antihypertensivaklassen gebruikten.

A

Appendices

PhD portfolio

Phd period: March 2018 – June 2022
Total amount of ECT: 53

1.General courses

Year	Course	ECTS
2018-2022	Weekly PhD education	6
2018-2022	Monthy journal club in General Practice	1.3
2018	BMJ course motivational interviewing	0.1
2019	AMC Graduate School – Practical Biostatistics	1.1
2019	AMC Graduate School – English writing	1.5
2019	AMC Graduate School – Randomized Controlled Trials	0.6
2019	BABEL - Mandarin courses HSK 1	3.5
2020	BABEL – Mandarin courses HSK 2	3.5
2021	Chinese College Nederland – Mandarin course HSK 3	3.5

2. Seminars, workshops and master classes

Year	Seminar, workshop or master class	ECTS
2018-2019	PRODEMOS kick-off events Amsterdam and Beijing	0.8

3. (Inter)national conferences visited

Year	Conference	ECTS
2018	NHG Wetenschapsdag	0.2
2018	Alzheimer's Association Academy by Alzheimer Europe – Brussels	0.2
2019	WONCA Europe – Bratislava	1.0
2020	AAIC - online	0.8
2020	GACD - online	0.2
2021	WONCA Europe – online	0.2
2021	Alzheimer Europe conference	0.2

4. Poster presentations

Year	Poster presentation	ECTS
2020	AAIC conference – 'The PRODEMOS trial'	0.5
2021	WONCA Europe –'Prevention of dementia using mobile phone applications (PRODEMOS): a multinational randomized controlled trial in progress'	0.5
2021	WONCA Europe – 'Antihypertensive drug classes and incident dementia: findings from the preDIVA observational extension (POE) study'	0.5

5. Oral presentations at international conferences

Year	Oral presentation	ECTS
2018	Alzheimer's Association Academy by Alzheimer Europe – 'Prevention of dementia through mobile Health'	0.5
2019	WONCA Europe – 'Motives and needs of low SES older adults with increased dementia risk to improve their lifestyle'	0.5
2020	GACD – 'The prevention of dementia using mobile phone applications (PRODEMOS) ongoing trial'	0.5
2021	WONCA Europe – 'Needs and views on healthy lifestyles for the prevention of dementia through mobile health interventions in China: a qualitative study'	0.5
2021	Alzheimer Europe conference – 'Attitudes and views on healthy lifestyles for the prevention of dementia and cardiovascular disease among older adults with low socioeconomic status: a qualitative study'	0.5
2022	ESOC – 'Low values for blood pressure, BMI, and non-HDL cholesterol signal higher late-life dementia risk'	0.5

6. Oral presentations on PRODEMOS consortium meetings

Year	Oral presentation	ECTS
2018	PRODEMOS Gerenal Assembly Toulouse – Work package 'Qualitative research'	0.5
2019	PRODEMOS General Assembly Brighton – Work package 'Qualitative research'	0.5
2019	PRODEMOS meeting in Beijing – presentations on the trial logistics, coaching and training	1.0
2019	PRODEMOS General Assembly Cambridge – 'The PRODEMOS mHealth platform'	0.5
2020	PRODEMOS General Assembly online – 'The PRODEMOS mHealth platform'	0.5
2020	PRODEMOS General Assembly online – 'Interviews with the Chinese target population'	0.5

7. Teaching - lecturing

Year	Lecture	ECTS
2019	Bachelor geneeskunde jaar 2 AMC, practicum 'Klinisch redeneren – dyspneu en hoesten'	0.5
2019	Bachelor geneeskunde jaar 1 AMC, symposium 'statistische benadering van ziekte'	0.5
2020	PRODEMOS trial – training for health nurses in the UK	0.5
2020	PRODEMOS trial – training for health nurses in Beijing	1.0

8. Teaching - mentoring

Year	Project	ECTS
2019	Supervising Joachim van Willigen with 'The needs and barriers of low socioeconomic adults for use of electronic- or mobile-health to improve cardiovascular risk factors'	1.3

9. Coordination tasks

Year	Task	ECTS
2019-2020	Chair of the journal club in General Practice	1.0
2019	Chair of the monthly junior researchers lunch	0.5
2019-2022	Board member of the Ondernemingsraad AMR BV	15

10. Publications

den Brok, M. G.*, Eggink, E.*, Hoevenaar-Blom, M. P., van Gool, W. A., van Charante, E. P. M., Richard, E., & van Dalen, J. W. (2022). Low Values for Blood Pressure, BMI, and Non-HDL Cholesterol and the Risk of Late-Life Dementia. *Neurology*, *99*(15), e1630-e1639.

Eggink, E., Hafdi, M., Hoevenaar-Blom, M. P., Richard, E., & van Charante, E. P. M. (2022). Attitudes and views on healthy lifestyle interventions for the prevention of dementia and cardiovascular disease among older people with low socioeconomic status: a qualitative study in the Netherlands. *BMJ open*, *12*(2), e055984.

Hafdi, M.*, Eggink, E*., Hoevenaar-Blom, M. P., Witvliet, M. P., Andrieu, S., Barnes, L., ... & Richard, E. (2021). Design and Development of a Mobile Health (mHealth) Platform for Dementia Prevention in the Prevention of Dementia by Mobile Phone Applications (PRODEMOS) Project. *Frontiers in neurology*, *12*, 733878.

Eggink, E., Hafdi, M., Hoevenaar-Blom, M. P., Song, M., Andrieu, S., Barnes, L. E., ... & Richard, E. (2021). Prevention of dementia using mobile phone applications (PRODEMOS): protocol for an international randomised controlled trial. *BMJ open*, *11*(6), e049762.

Eggink, E., Moll van Charante, E. P., van Gool, W. A., & Richard, E. (2019). A population perspective on prevention of dementia. *Journal of clinical medicine*, *8*(6), 834.

Eggink, E.*, de Waal, M. M.*, & Goudriaan, A. E. (2019). Criminal offending and associated factors in dual diagnosis patients. *Psychiatry research*, *273*, 355-362.

Schroevers, J. L.*, Eggink, E.*, Hoevenaar-Blom, M. P., Van Dalen, J. W., Van Middelaar, T., Van Gool, W. A., ... & Van Charante, E. P. M. (2022). Antihypertensive medication classes and the risk of dementia over a decade of follow-up. *Journal of Hypertension*, 10-1097.

Zhang, J.*, Eggink, E.*, Zhang, X., Li, X., Jiang, B., Liu, H., ... & Song, M. (2022). Needs and views on healthy lifestyles for the prevention of dementia and the potential role for mobile health (mHealth) interventions in China: a qualitative study. *BMJ open*, 12(11), e061111.

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Chapter 2. A population perspective on prevention of dementia

Authors: **E. Eggink**, E.P. Moll van Charante, W.A. van Gool, E. Richard

Contributions: EE, EMC and ER designed the outlines of the paper, EE wrote the paper. EMC, WG and ER improved and corrected the style of the article.

Chapter 3. Prevention of Dementia using Mobile Phone Applications (PRODEMOS): protocol for an international randomised controlled trial

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Chapter 4. Attitudes and views on healthy lifestyle interventions for the prevention of dementia and cardiovascular disease among older people with low socioeconomic status: a qualitative study

Authors: **E. Eggink**, M. Hafdi, M.P. Hoevenaar-Blom, E. Richard, E.P. Moll van Charante on behalf of the PRODEMOS-consortium

Contributions: EE was responsible for the drafting of the manuscript. EE, MH and MHB conducted the interviews. EE, MH, MHB and EMC were responsible for coding of the interviews. ER was involved in interpretation of the results, and critically revised the manuscript. All authors approved the final version of the manuscript.

Chapter 5. Needs and views on healthy lifestyles for the prevention of dementia through mobile health (mHealth) interventions in China: a qualitative study

Authors: J. Zhang*, **E. Eggink***, X Zhang, X Li, B. Jiang, H. Liu, S. Ge, W. Zhang, J. Lyu, Y. Niu, Y. Yu, H. Hou, X. Xu, X. Ye, W. Wang, R. Terlou, E. Richard, W. Wang, Y. Wang, E.P. Moll van Charante, M. Song on behalf of the PRODEMOS consortium. * *contributed equally as first author.*

Contributions: EE and JZ were responsible for the drafting of the manuscript. ER, WW, YW, EMC, and MS were responsible for the study design. JZ, XL, BJ, HL, WZ, JL, YN, YY, and XX were responsible for performing the interviews. JZ, EE, XZ, MS, RT and EMC were responsible for the analysis of the data. SG, HH, XY and WW were responsible for the study logistics, and critically revised the manuscript. All authors approved the final version of the manuscript.

Chapter 6. Design and development of a mobile health (mHealth) platform for dementia prevention

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Contributions: EE and MH were responsible for the drafting of the manuscript. MH, EE, and MW were responsible for designing included figures. ER, EMC, MHB, CB, and WeiW were responsible for the study conception. ER, EMC, MHB, MS, SA, CB, NC, JG, HM, WenzhiW, YW, AW, and WeiW were responsible for the design of the trial. MH, EE, MHB, MW, LB, RB, AG, MM, LS, MS, XY, EMC, and ER were involved in platform design and development. All authors were responsible for critically revising the manuscript. All authors approved the final version of the manuscript.

Chapter 7. Low values for blood pressure, BMI and non-HDL cholesterol and the risk of late-life dementia

Authors: M.G.H.E. den Brok*, **E. Eggink***, M. P. Hoevenaar-Blom, W.A. van Gool, E.P. Moll van Charante, E. Richard, J.W. van Dalen. * Contributed equally as first author.

Contributions: EE, MB, MHB and JD were responsible for analysis and interpretation of data. EE and MB were responsible for drafting the manuscript. WG, EMC and ER had a major role in the acquisition of data. MHB, WG, EMC, ER and JD critically revised the manuscript. All authors approved the final version of the manuscript.

Chapter 8. Antihypertensive medication classes and the risk of dementia – findings from the preDIVA observational extension study

Authors: J. L. Schroevers*, **E. Eggink***, M.P. Hoevenaar-Blom, J.W. van Dalen, T. van Middelaar, W.A. van Gool, E. Richard, E.P. Moll van Charante. * *Contributed equally as first author.*

Contributions: EE, JS, MHB and JD were responsible for analysis of the data. EE and JS provided the manuscript. MHB, JD, TM, WG, ER and EMC revised the manuscript. All authors approved the final version of the manuscript.

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