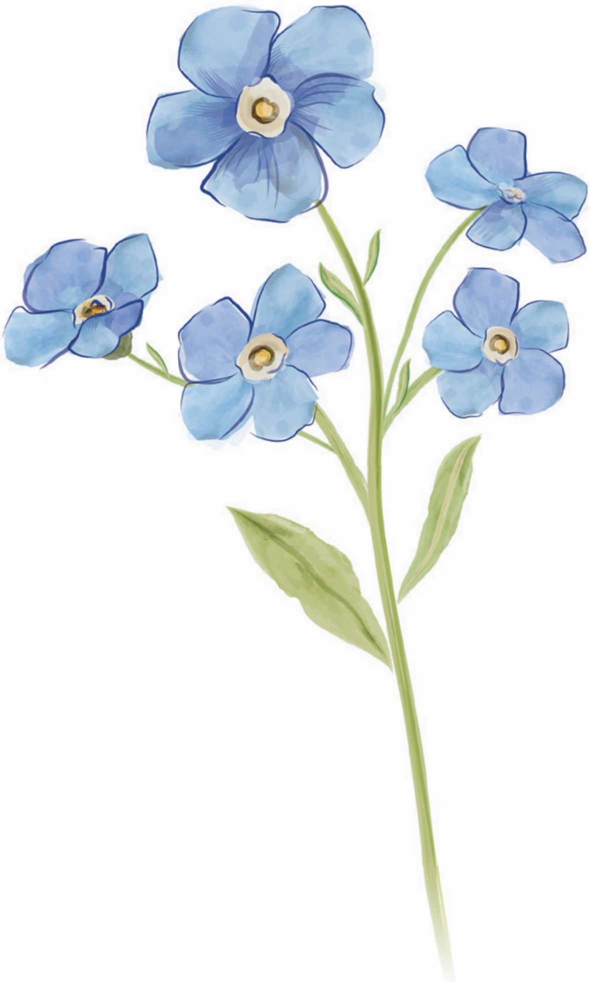

Evaluating Methods for the Prevention of Cognitive Decline and Dementia

Melina den Brok

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Evaluating Methods for the Prevention of Cognitive Decline and Dementia

Melina den Brok

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Melina den Brok

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Introduction

1

General introduction

Dementia

Dementia is one of the leading causes of disability and death worldwide.[1] Due to the growth and ageing of the population, especially in low- and middle income countries, the number of people living with dementia is expected to increase from 55 million in 2019 to 153 million by 2050.[2] Dementia is characterized by cognitive decline in two or more cognitive domains that interferes with independence in everyday activities.[3] On average, survival time from the moment of diagnosis is 5.8 years or less depending on dementia subtype,[4] and quality of life is greatly impacted, both for patients and their caregivers. With an estimated annual cost of over 1.3 trillion US dollar in 2019 the economic impact of dementia is tremendous, and these costs are expected to rise to 2.8 trillion US dollar by 2030.[5] The search for prevention strategies and disease modifying treatments in the last decades has yielded important insights in several aspects of the disease, but whether it benefits (future) dementia patients is far from clear. This thesis focusses on modifiable risk factors of old age dementia and aims to contribute to the prevention and treatment of cognitive decline and dementia.

The most prevalent subtype of dementia in older people is Alzheimer's disease (~60-70%)[6-8] which is pathologically defined by accumulation and extracellular deposition of amyloid beta (neuritic plaques) and intracellular accumulation of hyperphosphorylated tau protein (neurofibrillary tangles) in the brain. The second most common etiology is vascular dementia (~15-25%),[6-8] which is primarily caused by cerebrovascular disease or impaired cerebral blood flow. However, autopsy studies suggest that most people with dementia in old age have accumulation of both cerebrovascular, and Alzheimer related pathologies. Moreover, both of these types of cerebral damage are frequently found post mortem in cognitively healthy older individuals,[9] and there seems to be a dose-response relationship between accumulation of either or both types and increased old-age dementia risk.[10] This suggests that in old age dementia, Alzheimer's and vascular dementia are not strictly separate entities, but rather extreme ends of a spectrum of dementias following accumulation of cerebrovascular and Alzheimer related damage.

Dementia prevention strategies

Dementia is generally diagnosed in older people, therefore, the most important factor associated with dementia is ageing. However, risk factors for dementia have been identified in all stages of life, starting in early life, where low educational level is associated with increased dementia risk. Important risk factors in midlife (age 45-65 years) are traumatic brain injury, hypertension, excessive alcohol use, hearing loss and obesity. In late life (age ≥65 years), smoking, depression, social isolation, physical inactivity, diabetes and air pollution are associated with higher dementia risk. All these risk factors combined account for 40% of global dementia cases, and most of these risk factors are modifiable and potential targets for interventions.[11] However, conclusive evidence that interventions aimed at these risk factors actually decrease dementia incidence is lacking.

Randomized controlled trials investigating the effect of interventions targeting single risk factors reported inconsistent results.[12] This might partly be explained by age dependent associations observed for several risk factors, with positive associations in midlife[11,13] and diminishing or even contrasting associations (U-shaped/ inverse) in late life.[14-19] These contrasting associations have been observed for systolic blood pressure,[20-22] non-HDL[15] and total[16,18] cholesterol levels, and BMI.[14,19] The exact nature of these associations and how they develop in late life remains unclear. However, since similar relations are observed for several cardiovascular risk factors and for other adverse outcomes such as cardiovascular disease and mortality, these associations might not be independent effects of each individual risk factor but potentially be part of an overarching phenomenon that involves multiple risk factors simultaneously. **Chapter 2** of this thesis investigates the associations of low SBP, low BMI, and low non-high density lipoprotein (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, in community-dwelling older people. [23,24] Better identification of older individuals at an increased risk of dementia may be relevant in clinical practice where prevention guidelines are based on risk factors in midlife. Furthermore, trials might (re)evaluate the efficacy of intensive treatment of risk factors in older populations.

Alternative explanations for inconsistent results in trials include that the associations found in observational studies do not reflect a causal relationship or that targeting single risk factors may not be sufficient to prevent the occurrence of dementia. In 2016, the preDIVA trial was the first study examining the effect of interventions simultaneously targeting multiple risk factors to prevent dementia. These multidomain interventions have been subject of several large dementia prevention trials conducted in the previous years (e.g. MAPT, FINGER).[25,26] However, evidence in favor of a multidomain intervention with clinically relevant effects on cognitive decline or dementia outcomes has so far not been reported.[27] This may be caused by methodological issues. First, individuals included in the multidomain intervention trials may have been too old to benefit from the interventions since harmful effects may have been effectuated by the time these interventions started. Second, high quality of standard care in the country of the included population reduces the contrast observed between the intervention and control group. Third, individual multidomain trials may have suffered from lack of power, due to the improvement of lifestyle and risk factors in those in the control condition.

Promising results from multidomain interventions have been observed in individuals with untreated hypertension at baseline who were adherent to the intervention and in participants without a history of cardiovascular disease.[24] In **chapter 3** we pooled individual participant data from two randomized controlled trials investigating the effect of multidomain interventions targeting cardiovascular and lifestyle related risk factors on cognition, symptoms of depression and apathy. This approach increased power to detect an overall effect and in specific subgroups that could potentially benefit more from multidomain interventions and might lead to a more personalized approach in dementia prevention trials.

Blood pressure and antihypertensive medication treatment

The relation between blood pressure and dementia is complex and age dependent. Hypertension in midlife has consistently been associated with increased dementia risk, [11,13,28] but in late life this association seems to disappear or even reverse.[22] Blood pressure lowering with antihypertensive medication may delay cognitive impairment and dementia onset.[29]

Hypertension is a promising target for dementia prevention strategies because of its high prevalence (20-62% in people aged 40-69 and ≥70% in people aged ≥70)[30] and widely available effective medical treatments. In addition to blood pressure lowering, class specific effects have been attributed to the different antihypertensive medication (AHM) treatments. We systematically investigated differential effects of antihypertensive medication classes on dementia risk in **chapter 4** using network meta-analysis. Especially in low- and middle-income countries where the greatest rise in dementia prevalence is expected, an inexpensive and scalable strategy like a change in first choice prescription drug for hypertension might cause an important reduction in dementia incidence.

Blood pressure level is highly variable over time. This fluctuation in blood pressure level, known as blood pressure variability (BPV), might also be associated with incident dementia risk. Positive associations with BPV are described for stroke, coronary heart disease and mortality,[31-33] but results of studies assessing the association for dementia are inconsistent.[34-37] Variation in BPV definition and study design may partly explain these inconsistent results. A meta-analysis suggested that BPV had a relatively stronger contribution to the risk of cognitive impairment and dementia than mean blood pressure level.[38] The age dependent effects observed for blood pressure level may play a role in these findings, and it is unknown whether these effects also occur in the association between BPV and dementia. **Chapter 5** assessed the association between blood pressure variability in different age categories and lifetime risk of dementia in a cohort with blood pressure measurements from the age of 50 until the moment of dementia diagnosis or death.[39]

Treatment of Alzheimer's disease

To date, there is no curative treatment for Alzheimer's disease and the exact pathogenesis remains unclear. For the past twenty years, research into treatment of Alzheimer's disease has been dominated by the 'amyloid cascade hypothesis' stating that accumulation and deposition of amyloid beta peptides in the brain are crucial in the causal pathway leading to Alzheimer's disease. Intensive efforts have been made to decrease the level of amyloid beta by intervening in the balance between amyloid beta production and clearance in the brain. For almost a decade, large phase 3 trials have focused on therapeutic strategies to clear amyloid beta depositions from the brain using monoclonal antibodies against amyloid beta.[40] Most of these trials failed to show a significant difference between the intervention and control group. These neutral effects have been explained by 'bad luck' due to sampling variability or shortcomings in the design of the trial (sample size too small, target population not sufficiently well-defined, follow-up too short, etc.). Using Bayesian statistics, we assessed whether there is 'absence of evidence', or 'evidence of absence' of a therapeutic effect of anti-amyloid beta immunotherapy in people with dementia (**chapter 6**).

Aim and outline of this thesis

This thesis evaluates possibilities for prevention and treatment of cognitive decline and dementia focusing both on cardiovascular and lifestyle related risk factors. This might contribute to tailored interventions to prevent cognitive decline and dementia.

In **Part I** of this thesis we evaluated methods to improve strategies to prevent old age cognitive decline and dementia by focusing on subgroups with more potential to benefit from (tailored) interventions. **Part II** focusses on blood pressure and antihypertensive treatment in relation to incident dementia. **Part III** presents a short overview of trials assessing anti-amyloid beta for the treatment of Alzheimer's disease. In **part IV** I summarize and discuss the most important findings and implications of our research.

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Part I

Dementia prevention strategies

2

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.

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 late life (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 levels[6], 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.

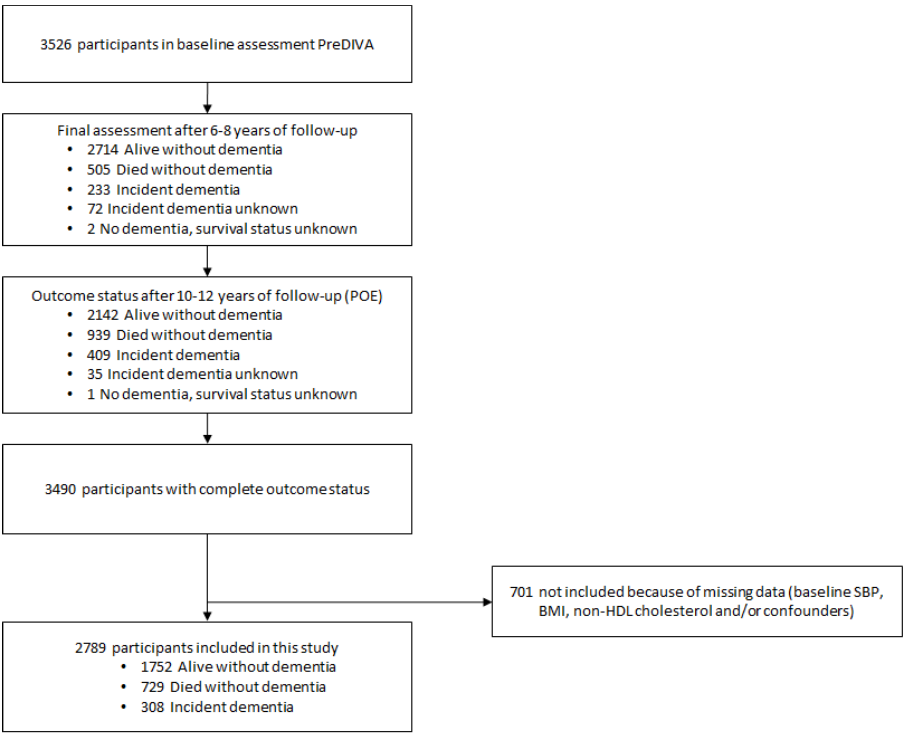
Predefined subgroup analyses were performed for 1) sex, 2) ApoE4 genotype, 3) history of CVD, 4) antihypertensive medication (AHM) use vs. no AHM use, and 5) cholesterol-lowering drug (CLD) use vs. no CLD use, as the associations might differ when risk factor values are low due to medication effects.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

Figure 1. Flowchart



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

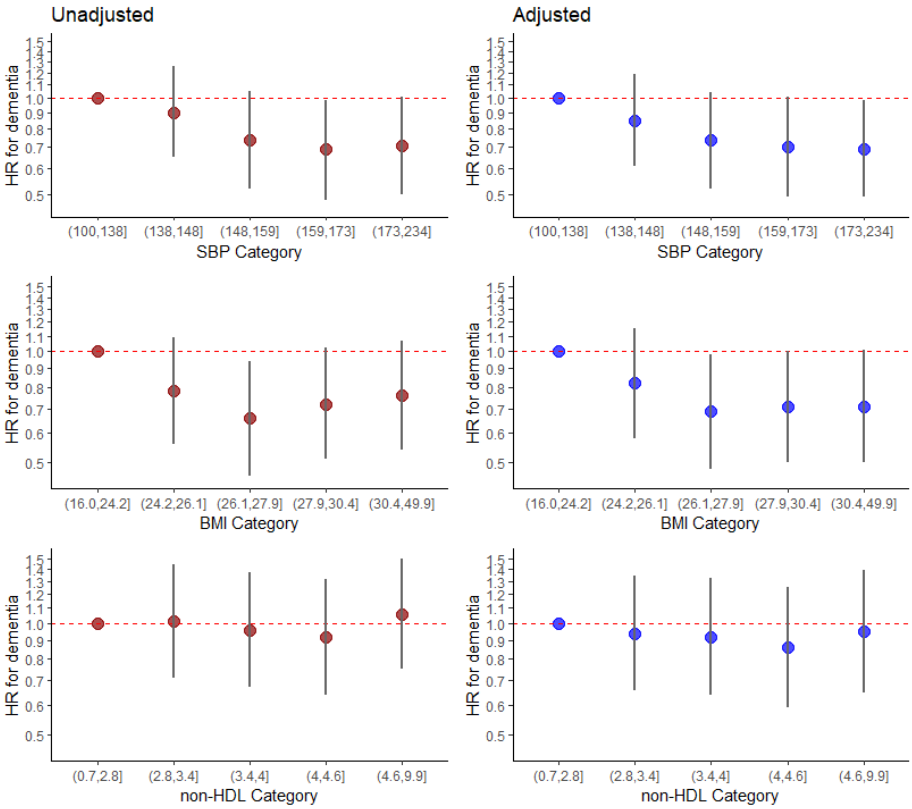
Table 1. Baseline characteristics for full cohort and individuals with and without dementia diagnosis

	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
Total 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.

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).

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. BMI = body mass index; HDL = high-density lipoprotein; HR = hazard ratio; SBP = systolic blood pressure

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.

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.

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 (Table S1). 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).

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 (Table S2). 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, Table S3). 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, Table S4). No differential effects were observed between randomization groups (Table S5). 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, Table S6). 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 (Table S7). 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 (Table S8). 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 (Tables S9-12).

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 cholesterol[6] 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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Supplemental material

Table S1. 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.

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Table S1. 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						
Female	1253	1.0	1.19 (0.79-1.80)	1.38 (0.73-2.61)	8.91 (3.64-21.83)	*0.3*
Male	1536	1.0	1.16 (0.86-1.57)	1.26 (0.74-2.17)	1.82 (0.57-5.80)	
ApoE4 genotype						
Positive	772	1.0	1.59 (1.14-2.22)	1.02 (0.54-1.96)	4.54 (1.38-14.96)	*0.02*
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						
Yes	823	1.0	1.35 (0.82-2.21)	1.60 (0.78-3.30)	19.81 (7.61-51.58)	*0.009*
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						
Yes	1538	1.0	1.22 (0.88-1.69)	1.11 (0.60-2.06)	5.95 (2.68-13.18)	*0.3*
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						
Yes	958	1.0	1.13 (0.74-1.71)	0.99 (0.49-1.97)	5.63 (2.69-11.78)	*0.05#*
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.

Table S2. 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.

Table S3. 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. Model 1: adjusted for age at baseline. 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.

Table S4: 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.

Table S5. 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	0.15	

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. Abbreviations: SBP = systolic blood pressure; HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

Table S6. 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.

Table S7. 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.

Table S8. 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.

Table S9. 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		*0.050*	*0.034*	*0.033*

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.

Table S10. 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.

Table S11. 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.

Table S12. 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		*0.016*	*0.014*	*0.026*

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.

3

The effect of multidomain interventions on global cognition, symptoms of depression and apathy – a pooled analysis of two randomized controlled trials

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Abstract

Background: Cardiovascular risk factors and lifestyle factors are associated with an increased risk of cognitive decline and dementia in observational studies, and have been targeted by multidomain interventions.

Objectives: We pooled individual participant data from two multi-domain intervention trials on cognitive function and symptoms of depression to increase power and facilitate subgroup analyses.

Design: Pooled analysis of individual participant data.

Setting: Prevention of Dementia by Intensive Vascular Care trial (preDIVA) and Multidomain Alzheimer Preventive Trial (MAPT).

Participants: Community-dwelling individuals, free from dementia at baseline.

Intervention: Multidomain interventions focused on cardiovascular and lifestyle related risk factors.

Measurements: Data on cognitive functioning, depressive symptoms and apathy were collected at baseline, 2 years and 3-4 years of follow-up as available per study. We analyzed crude scores with linear mixed models for overall cognitive function (Mini Mental State Examination [MMSE]), and symptoms of depression and apathy (15-item Geriatric Depression Scale). Prespecified subgroup analyses were performed for sex, educational level, baseline MMSE <26, history of hypertension, and history of stroke, myocardial infarction and/or diabetes mellitus.

Results: We included 4162 individuals (median age 74 years, IQR 72, 76) with a median follow-up duration of 3.7 years (IQR 3.0 to 4.1 years). No differences between intervention and control groups were observed on change in cognitive functioning scores and symptoms of depression and apathy scores in the pooled study population. The MMSE declined less in the intervention groups in those with MMSE <26 at baseline (N=250; MD: 0.84; 95%CI: 0.15 to 1.54; p<0.001).

Conclusions: We found no conclusive evidence that multidomain interventions reduce the risk of global cognitive decline, symptoms of depression or apathy in a mixed older population. Our results suggest that these interventions may be more effective in those with lower baseline cognitive functioning. Extended follow-up for dementia occurrence is important to inform on the potential long-term effects of multidomain interventions.

Introduction

The global prevalence of dementia is expected to triple in the coming decades. Over 50 million individuals were living with dementia in 2019, and this number might rise to 152 million by 2050.[1] Around 30-40% of dementia cases might be attributable to potentially modifiable risk factors such as midlife hypertension, depression and physical inactivity.[2-4] However, evidence from randomized controlled trials targeting these risk factors is inconsistent.[5-6]

Several large multidomain intervention studies using cognitive functioning or dementia as primary outcome have been performed in older persons from the general population free from dementia at baseline.[7-9] Two major trials, the prevention of dementia by intensive vascular care trial (preDIVA) and Multidomain Alzheimer Preventive Trial (MAPT) reported no significant effect on their respective primary outcomes dementia and cognitive decline.[10,11] The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability trial (FINGER) is the only study so far which reported a modest excess improvement of cognitive functioning in the intervention group compared to an improvement in the control group.[12]

There is a bidirectional association between depression and cardiovascular risk factors and events,[13-17] and depression is a potentially modifiable risk factor for dementia.[3] Apathy is associated with cardiovascular risk factors and increased risk of dementia.[18,19] A multidomain intervention targeting the same risk factors as those for dementia, could potentially reduce depressive symptoms and apathy. However, none of the trials reported significant effects of the interventions on symptoms of depression, and apathy was not reported.

Individual multidomain trials may have suffered from lack of power, due to the improvement in those in the control condition. In the preDIVA study, subgroup analyses suggested a potential beneficial effect in those with untreated hypertension and those with no history of cardiovascular disease at baseline, and in males.[10] A more personalized approach, with interventions tailored to specific subgroups, could potentially lead to better intervention effects than a one-size-fits-all approach.

We pooled individual participant data from two large multidomain intervention trials targeting cardiovascular and lifestyle related risk factors to increase power and allow for subgroup analyses to detect possible intervention effects on cognition, symptoms of depression and apathy.

Methods

Study design and participants

We combined individual participant data from two large multidomain intervention trials targeting vascular and lifestyle-related risk factors in older people.[10,11] Both studies were European multicenter randomized controlled trials and included 3526 (preDIVA) and 1679 (MAPT) community dwelling individuals free from dementia at baseline, recruited from either general practices (preDIVA) and memory centers (MAPT). Individuals were aged 70 years or older and participants in MAPT were at increased risk for cognitive decline, operationalized as at least one of the three following criteria: spontaneous memory complaint expressed, limitation in one instrumental activity of daily living, or slow gait speed. The multidomain interventions consisted of individual or group sessions providing lifestyle advice concerning diet, physical activity and vascular risk factors. The MAPT study included cognitive training in the intervention. If needed, participants were advised to contact their general practitioner for optimization or initiation of drug treatment for cardiovascular risk factors. Control groups received usual care.[10,11] Main characteristics of the trials are specified in table 1. Study protocols have been published previously.[20,21] The MAPT study had a factorial design, with omega-3 supplementation in an additional arm (but there was no effect of this intervention on the trial's primary or secondary outcomes). In this analysis we only evaluate the multidomain intervention. The ethics committees in the respective medical centers approved both trials and all individuals gave written informed consent. Both trials were registered, respectively in the ISRCTN registry (preDIVA: ISRCTN29711771) and on ClinicalTrials.gov (MAPT: NCT00672685).

Outcomes

Global cognitive function was assessed with the Mini-Mental State Examination (MMSE). MMSE items were divided into memory, evaluated with the delayed recall item (item 5, max 3 points) or 'other cognitive functions' (all other items). Both studies used different neuropsychological tests for memory (Visual Association Test[22] in preDIVA and Free and Cued Selective Reminding[23] in MAPT), precluding the possibility to use these more extensive memory tests in our analyses. As measure of subjective memory loss we used question 10 of the 15-item Geriatric Depression Scale (GDS-15): 'Do you feel you have more problems with memory than most?'. Depressive symptoms were quantified using the crude scores of the 15-item Geriatric Depression Scale (GDS-15) and using a dichotomized cut-off (GDS-15 >5: indicative of depression; ≤5: not indicative of depression). We additionally assessed the effect on apathy, operationalized as the three apathy items from the GDS-15 (GDS-3A), as has previously been shown to be an appropriate screening instrument for symptoms of apathy.[24]

Table 1. Main characteristics of pooled trials

	preDIVA	MAPT
Country	the Netherlands	France
Duration	2006-2015	2008-2014
Sample size	3526	1679
Study design	open-label, cluster randomized controlled trial	placebo-controlled randomized superiority trial with four parallel groups
Inclusion site	116 general practices in 26 health-care center buildings	13 memory centers
Population	- age 70-78 - community-dwelling	- age 70+ - community-dwelling - spontaneous memory complaint, and/or limitation in activity of daily living, and/or slow gait speed
Intervention	Nurse-led multidomain cardiovascular care (lifestyle advice supported by motivational interviewing techniques and drug treatment for hypertension, dyslipidaemia, and type 2 diabetes mellitus or antithrombotic drugs)	Factorial design with two interventions: • Multidomain intervention (cognitive training, physical activity, nutrition counseling, and three preventive consultations) • Omega 3 supplement
Control	usual care	• Usual care (vs. multidomain) • Placebo (vs. omega-3)
Primary outcome	cumulative incidence of dementia	change in composite Z score combining four cognitive tests
Main secondary outcomes	cardiovascular events, mortality, change in cognitive function and depressive symptoms	cardiovascular events, functional assessment, depressive symptoms
Follow-up	6-8 years	3 years

Statistical Analysis

We included participants with at least one follow-up visit to analyze the effect of the intervention on cognitive decline, symptoms of depression and apathy. Mean differences in change between the intervention and control group were calculated using linear mixed regression models. Crude continuous and binary scores were used as outcome, adjusted for baseline scores of the specific tests using analysis of covariance (ANCOVA). We used follow-up measures of the outcome of interest as outcome and treatment allocation as predictor, including random intercepts for participant and health center level. Model fit was estimated using Akaike Information Criterion values, and more complex models (i.e. with additional random slope for randomization allocation or the time difference between randomization and the follow-up visit) did not result in a better fit. Analyses were adjusted for the baseline measure of the outcome of interest, study, age, sex, time in study and also for LDL cholesterol and systolic blood pressure because of significant differences in baseline values between randomization groups. Furthermore, linear interaction for time in study was assessed by means of an interaction term. Predefined subgroup analyses were performed for 1) sex, since multidomain interventions may have differential effects in men and women, 2) baseline hypertension status defined as history of hypertension and/or systolic blood pressure of >140 mmHg, 3) history of myocardial infarction, stroke and/or diabetes at baseline, since there is a high probability that individuals with a history of cardiovascular disease already receive a form of intervention and therefore, there might be more room for improvement in participants without a history of cardiovascular disease, 4) baseline MMSE <26, since individuals with lower baseline cognitive functioning might benefit more from a multidomain intervention, 5) educational level (low and high) because this is an important risk factor for dementia and is also associated with low socioeconomic status.[3] Additional analyses were performed by study, to assess heterogeneity between the different studies. A p-value for interaction <0.05 was considered to reflect a significant interaction. Post-hoc analyses included exploration of differential dropout by comparing baseline characteristics of individuals included in the current study to individuals without any follow-up visits, and subgroup analyses for different cutoff values of baseline MMSE. Analyses were conducted in Rstudio (version 3.6.1, package "lme4").[25]

Results

Of a total of 5205 individuals in the two studies, 4162 (80%) individuals had at least one follow-up visit and were included in the present analysis (median follow-up duration: 3.7 years; IQR 3.0 to 4.14 years). The median age at baseline was 74 years (IQR 72, 76 years) and slightly more women were included (57.7%). No significant between-group differences in baseline characteristics were found in the pooled population, except for mean systolic blood pressure (control 149.3, SD 20.9; intervention 151.2, SD 22.1; p=0.006) and mean LDL cholesterol (control 3.19, SD 0.97; intervention 3.10, SD 0.95; p=0.003) (Table 2). Table S1 shows baseline characteristics of included individuals per study. Participants who did not have a follow-up visit were slightly older, had a lower educational level, a slightly lower MMSE score, and a higher mean systolic blood pressure (Table S2).

Table 2. Baseline characteristics of the pooled sample

	All individuals N=4162 (100%)	Control N=1996 (48.0%)	Intervention N=2166 (52.0%)	P-value
Study				
• preDIVA	2818 (67.7)	1329 (66.6)	1489 (68.7)	
• MAPT	1344 (32.3)	667 (33.4)	677 (31.3)	
Demographics				
Age y, median (IQR)	74 (72-76)	74 (72-77)	74 (72, 76)	0.8
Female sex, n (%)	2403 (57.7)	1159 (58.1)	1244 (57.4)	0.7
Educational level, n (%)				
• Low	922 (22.4)	451 (23.0)	471 (21.9)	0.7
• Intermediate	2070 (50.3)	976 (49.7)	1094 (50.8)	
• High	1125 (27.3)	536 (27.3)	589 (27.3)	
Biological risk factors				
Systolic blood pressure (mmHg), mean (SD)	150.3 (21.6)	149.3 (20.9)	151.2 (22.1)	0.006
LDL cholesterol (mmol/L), mean (SD)	3.1 (1.0)	3.2 (1.0)	3.1 (1.0)	0.003
BMI (kg/m2), mean (SD)	27.0 (4.2)	27.0 (4.1)	27.1 (4.2)	0.3

All individuals with at least one follow-up visit, and comparison of the intervention and control group. Differences between randomization groups in spite of the large numbers, may partly be due to cluster randomization in preDIVA. P-value for comparison between control and intervention. Abbreviations: BMI: Body Mass Index; IQR: interquartile range; LDL cholesterol: low-density lipoprotein cholesterol; SD: standard deviation

There were no differences in change from baseline to 3-4 year follow-up in MMSE and GDS scores between the control and intervention groups: Total MMSE score deteriorated by 0.09 points in the control group versus 0.05 points in the intervention group (mean difference in change [MDc] between intervention and control group: 0.03; 95% confidence interval [95%CI] -0.06 to 0.13). Total GDS score deteriorated by 0.21 points in the intervention group versus 0.22 points in the control group (MDc between intervention and control group: -0.04, 95%CI -0.16 to 0.07). The GDS-apathy score deteriorated by 0.12 points in both randomization groups (MDc between intervention and control group: -0.007 (-0.05 to 0.04). There was no time by treatment interaction for any of the outcome variables (Table 3).

Table 3. Mean difference in effect of multidomain interventions on cognition, symptoms of depression and apathy after 3-4 years of follow-up

	Number of observations in analysis	Number of individuals in analysis	Baseline mean		Mean difference baseline and follow-up		Mean difference between intervention and control group
	N	N	Control	Intervention	Control	Intervention	MDc (95%CI)
Cognitive functioning							
MMSE (range 0-30)*	6677	3704	28.26	28.25	-0.09	-0.05	0.03 (-0.06 to 0.13)
Memory (MMSE item 5) (range 0-3)*	6774	3704	2.31	2.29	0.03	0.05	0.004 (-0.04 to 0.05)
Other (range 0-27)*	6677	3704	25.95	25.96	-0.12	-0.10	0.03 (-0.05 to 0.10)
Subjective memory loss (GDS15-Q10, % yes)†	6388	3503	18.15	19.53	0.03	-0.79	-0.51 (-2.52 to 1.50)
Depressive symptoms							
GDS (range 0-15)†	6279	3506	2.05	1.96	0.22	0.21	-0.04 (-0.16 to 0.07)
Depressive symptoms (% GDS >5)†	6279	3506	8.93	8.04	2.59	2.54	-0.68 (-2.32 to 0.97)
Apathy (range 0-3)†	6325	3503	0.70	0.69	0.12	0.12	-0.007 (-0.05 to 0.04)

* high score indicates better results; † low score indicates better results. Abbreviations: GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: 'Do you feel you have more problems with memory than most?'; MDc: mean difference in change between the intervention and control group; MMSE: Mini-Mental State Examination; 95%CI: 95% confidence interval

Subgroup analysis

In individuals with a baseline MMSE score <26, total MMSE score improved over time in both randomization groups, but more in the intervention group (MDc 0.84 points, 95%CI 0.15 to 1.54). Similar effects were seen for anterograde episodic memory (MDc 0.21, 95%CI -0.01 to 0.43) and other MMSE items (MDc 0.74, 95%CI 0.26 to 1.21). In those with a baseline MMSE score ≥26, some deterioration or no change in MMSE scores (total, memory or other items) was seen with similar effects in both randomization groups (Table 4, Table S3). No significant differences between randomization groups in change in test scores for cognitive functioning, depressive symptoms or apathy were found for sex, educational level, baseline hypertension status and history of cardiovascular disease or diabetes at baseline (Table 4, Table 5). In MAPT, stronger deterioration on other MMSE items was seen in the control group compared to the intervention group, but there was no effect in preDIVA. None of the other outcomes were significantly different between both studies (Table S4).

To assess the consistency of the effects favoring the intervention in individuals with a low baseline MMSE, we performed post-hoc subgroup analyses stratified for various baseline MMSE cutoff scores (Table S5). The highest MDc were found with a baseline MMSE cut-off score <26, and with increasing baseline MMSE scores, MDc between the intervention and control group gradually decreased. Individuals with MMSE score <26 at baseline were significantly lower educated and had a higher Body Mass Index at baseline (Table S6). Additional adjustment for these covariates did not significantly change the MDc between the intervention and control group in total MMSE score (baseline MMSE ≤26: MMSE MDc 0.77, 95%CI 0.07 to 1.47; p<0.001). There was no differential dropout between both randomization groups in individuals with a baseline MMSE score <26 and >26 points.

Table 4. Mean difference in effect of multidomain interventions on cognition, symptoms of depression and apathy in subgroups (baseline cognition and educational level) after 3-4 years of follow-up

	Baseline MMSE			Educational level		
	<26 (n=296) MDc (95%CI)	**≥26 (n=3866) MDc (95%CI)**	**P for interaction**	**Low (n=922) MDc (95%CI)**	**High (n=3240) MDc (95%CI)**	**P for interaction**
Cognitive functioning						
MMSE (range 0-30)*	0.84 (0.15 to 1.54)	-0.03 (-0.12 to 0.06)	<0.001	0.13 (-0.11 to 0.37)	-0.002 (-0.10 to 0.10)	0.23
Memory (MMSE item 5) (range 0-3)*	0.21 (-0.01 to 0.43)	-0.01 (-0.05 to 0.03)	0.008	0.02 (-0.08 to 0.11)	0.0008 (-0.05 to 0.05)	0.68
MMSE other (range 0-27)*	0.74 (0.26 to 1.21)	-0.02 (-0.09 to 0.05)	<0.001	0.07 (-0.13 to 0.27)	-0.002 (-0.08 to 0.08)	0.32
Subjective memory loss (GDS15-Q10, % yes)†	-1.83 (-10.86 to 7.21)	-0.37 (-2.42 to 1.67)	0.81	-2.32 (-7.00 to 2.37)	0.13 (-2.07 to 2.34)	0.41
Depressive symptoms						
GDS (range 0-15)†	-0.17 (-0.66 to 0.32)	-0.04 (-0.16 to 0.08)	0.74	0.05 (-0.22 to 0.32)	-0.06 (-0.19 to 0.06)	0.43
Depressive symptoms (% GDS >5)†	-0.06 (-0.14 to 0.02)	-0.003 (-0.02 to 0.01)	0.099	0.01 (-0.03 to 0.05)	-0.009 (-0.03 to 0.008)	0.39
Apathy (range 0-3)†	0.03 (-0.16 to 0.21)	-0.01 (-0.06 to 0.04)	0.58	0.003 (-0.10 to 0.11)	-0.005 (-0.06 to 0.05)	0.86

* high score indicates better results; † low score indicates better results. Abbreviations: GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: 'Do you feel you have more problems with memory than most?'; MDc: mean difference in change between the intervention and control group; MMSE: Mini-Mental State Examination; 95%CI: 95% confidence interval

Table 5. Mean difference in effect of multidomain interventions on cognition, symptoms of depression and apathy in subgroups (biological and clinical factors) after 3-4 years of follow-up

	Sex			Stroke, myocardial infarction or diabetes mellitus history			Hypertension		
	Male (n=1759) MDc (95%CI)	**Female (n=2403) MDc (95%CI)**	**P for interaction**	**No (n=2739) MDc (95%CI)**	**Yes (n=1390) MDc (95%CI)**	**P for interaction**	**No (n=946) MDc (95%CI)**	**Yes (n=3216) MDc (95%CI)**	**P for interaction**
Cognitive functioning									
MMSE (range 0-30)*	-0.02 (-0.17 to 0.12)	0.08 (-0.05 to 0.21)	0.30	0.08 (-0.04 to 0.20)	-0.04 (-0.22 to 0.13)	0.26	0.11 (-0.10 to 0.31)	-0.006 (-0.12 to 0.11)	0.28
Memory (MMSE item 5) (range 0-3)*	-0.04 (-0.11 to 0.02)	0.04 (-0.01 to 0.09)	0.05	0.02 (-0.03 to 0.08)	-0.04 (-0.11 to 0.04)	0.21	0.02 (-0.07 to 0.12)	-0.007 (-0.05 to 0.04)	0.49
Other (range 0-27)*	-0.006 (-0.12 to 0.11)	0.05 (-0.05 to 0.15)	0.46	0.05 (-0.04 to 0.15)	-0.009 (-0.15 to 0.13)	0.43	0.06 (-0.10 to 0.22)	0.003 (-0.09 to 0.09)	0.52
Subjective memory loss (GDS15-Q10, % yes)†	1.31 (-1.89 to 4.51)	-1.59 (-4.14 to 0.97)	0.15	-0.49 (-2.84 to 1.86)	-1.01 (-5.06 to 3.03)	0.91	-1.27 (-5.34 to 2.79)	-0.66 (-3.00 to 1.68)	0.71
Depressive symptoms									
GDS (range 0-15)†	-0.11 (-0.28 to 0.07)	-0.0004 (-0.15 to 0.15)	0.35	-0.06 (-0.20 to 0.08)	-0.06 (-0.27 to 0.15)	0.89	-0.04 (-0.31 to 0.24)	-0.07 (-0.20 to 0.05)	0.62
Depressive symptoms (% GDS >5)†	-0.01 (-0.03 to 0.01)	-0.002 (-0.02 to 0.02)	0.52	-0.008 (-0.03 to 0.01)	-0.009 (-0.04 to 0.02)	0.87	0.008 (-0.03 to 0.05)	-0.01 (-0.03 to 0.005)	0.22
Apathy (range 0-3)†	-0.04 (-0.11 to 0.03)	0.02 (-0.04 to 0.08)	0.22	-0.01 (-0.07 to 0.04)	0.01 (-0.08 to 0.10)	0.96	-0.05 (-0.16 to 0.05)	0.002 (-0.05 to 0.06)	0.44

* high score indicates better results; † low score indicates better results. Abbreviations: GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: 'Do you feel you have more problems with memory than most?'; MDc: mean difference in change between the intervention and control group; MMSE: Mini-Mental State Examination; 95%CI: 95% confidence interval

3

Discussion

This pooled analysis of two large randomized controlled trials in community-dwelling individuals over 60 years old did not show an overall effect of multidomain interventions on cognitive function or symptoms of depression or apathy after 3-4 years follow-up. Subgroup analyses suggests that multidomain interventions may improve cognition in those with lower cognitive scores at baseline. We observed no interaction of the effect of the interventions with sex, history of stroke, diabetes mellitus and/or myocardial infarction, hypertension and educational level.

Strengths and limitations

The major strength of this study is that we pooled data on individual participant level from two large randomized controlled trials, providing more power to detect possible intervention effects on cognition, symptoms of depression and apathy, and to better allow for subgroup analyses to explore whether interventions may be more effective in specific subgroups. Furthermore, variation in inclusion criteria and multidomain interventions between the different trials improved the external validity of our overall results.

Several limitations should be noted. First of all, the use of the MMSE as outcome measure for cognitive studies has limitations. This time-honored test was designed as a cognitive screening test and does not measure cognitive function as comprehensively or sensitively, or with such detailed quantification, as a full neuropsychological evaluation does. Assessments using cognitive screening instruments such as the MMSE are known to show substantial variation over time, depending on conditions such as e.g. illness, stress or sleep deprivation, particularly in people without cognitive impairments,[26] although the same holds for full neuropsychological evaluation. A possible random error caused by these fluctuations may have resulted in bias towards the null. Another disadvantage of the MMSE in populations such as under study here, is its ceiling effect. It lacks the ability to differentiate well between healthy individuals and early signs of dementia in individuals with MMSE scores in the range of 24-30. However, despite its limitations, as with any other screening test, the MMSE is characterized by an unprecedented dissemination and appreciation among the scientific epidemiological and dementia community. Moreover, these interventions were not designed to boost cognition, but to prevent cognitive decline. Less decline in MMSE was a more likely hypothesis than more increment in MMSE due to the intervention – nuancing the potential ceiling effect. Secondly, attrition bias could have influenced our results, since those who dropped out were significantly older, had a lower educational level, higher mean systolic blood pressure, and lower MMSE scores; i.e. they were at higher risk of cognitive decline. This could have biased our results to the null, since those with lower cognitive function appear to potentially benefit most from intervention. Lastly, while both studies were designed to test the efficacy of multidomain interventions in elderly, there were important differences in study design and populations between both trials which could have impacted the results of this study. The recruitment strategy of individuals in preDIVA was population-based through general practices, whereas MAPT recruited individuals at risk for cognitive decline through memory centers. Cognitive training was not part of the intervention in preDIVA, but the intervention in MAPT strongly focused on cognitive training in the intervention group, which was given in supervised sessions, in contrast to the physical activity and nutrition components which were simply based on advice. Moreover, cardiovascular risk factors in the intervention group in preDIVA were assessed every four months by a practice nurse, and if necessary, medical interventions such as drug treatment were advised according to a detailed protocol. The MAPT intervention assessed cardiovascular risk factors annually, and there was less focus on drug treatment. These differences might improve the external validity of our results, but they are likely to also cause heterogeneity. However, there were no structural differences in intervention effects between the MAPT and preDIVA intervention.

Although overall this study did not show beneficial effects of multidomain interventions on depression, apathy and cognitive function, several methodological challenges associated with dementia prevention trials complicate the interpretation of these results. First, the development of cognitive impairment and dementia is a slow and insidious process, and risk factors in midlife have a stronger association with incident dementia than risk factors in later life.[27-30] However, since inclusion of participants in midlife requires an unrealistically long follow-up,[31] these trials included participants in later life, far beyond the stage of life in which interventions are expected to have their optimal effect. Second, follow-up durations for the current analyses were too short to detect an effect on incident dementia, as most clear clinically relevant outcome. Long-term interventions starting at a younger age might be needed to achieve clinically relevant effects.

Although observational studies have shown consistent evidence supporting the association of cardiovascular risk factors and lifestyle related factors with cognitive decline and dementia, and some interventions targeting these factors have shown to improve cognitive function,[3,4,32] trials evaluating multidomain interventions report inconsistent results.[10-12,33] Variation in intensity, components of the multidomain intervention, and characteristics of the control condition in the individual trials may partly explain these inconsistent results. Alternative explanations include that the associations found in observational studies do not reflect a causal relationship or that the harmful effects have been effectuated by the time these interventions started.

Subgroup analyses for individuals with low baseline MMSE score yielded consistent results with beneficial effects of the multidomain intervention on cognitive function: total MMSE score, including anterograde episodic memory and other MMSE items increased more in the intervention group. Similar effects on memory were seen in a multidomain intervention trial in black individuals with MCI.[34] The size of these groups (MMSE <26) was small within the overall studies (n=250). However, the gradual decrease in MDc with increasing baseline MMSE score appeared to be consistent (Table S5), and the results did not change with additional adjustment for differences in baseline characteristics. Furthermore, results were still statistically significant after multiple-comparison correction (p <0.01 after Bonferroni correction). These findings should be confirmed in the multidomain intervention trials that are currently underway.[35-37]

The underlying etiology of dementia is heterogeneous, and a multidomain intervention tailored to specific subgroups could potentially lead to better intervention effects than a one-size-fits-all approach. The results of this study, showing that, in later life, this type of intervention may be more effective in those with lower baseline cognitive scores, should be considered in the design of future dementia prevention trials.

Conclusion

This study with pooled data at the individual participant level from two large, randomized controlled trials did not show conclusive evidence that multidomain interventions can reduce the risk of cognitive decline or symptoms of depression and apathy in a mixed older population. These interventions may be more effective in those with lower baseline cognitive function. Extended follow-up for dementia outcomes is important to evaluate whether multidomain interventions can indeed have beneficial effects crossing the threshold of minimal clinically important difference. These extended follow-ups are planned and ongoing in both trials.

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Supplemental material

Table S1. Baseline characteristics of the pooled sample per study

Table S2. Baseline characteristics of individuals with at least a baseline and follow-up visit and individuals without any follow-up visits

Table S3. Mean difference in effect of multidomain interventions on cognition, symptoms of depression and apathy in subgroups by baseline cognition, after 3-4 years of follow-up

Table S4. Mean difference in effect of multidomain interventions on cognition, symptoms of depression and apathy by study, after 3-4 years of follow-up

Table S5. Mean difference in effect of multidomain interventions on cognition for different baseline MMSE cutoff scores, after 3-4 years of follow-up

Table S6. Baseline characteristics according to baseline cognitive scores

Table S1. Baseline characteristics of the pooled sample per study

	preDIVA N=2818	MAPT N=1344	P-value
Demographics			
Age y, median (IQR)	74 (72-76)	74 (72-78)	<0.001
Female sex, n (%)	1533 (54.4)	870 (64.7)	<0.001
Educational level, n (%)			<0.001
- Low	630 (22.6)	292 (22.1)	
- Intermediate	1617 (57.9)	453 (34.2)	
- High	546 (19.5)	579 (43.7)	
Biological risk factors			
Systolic blood pressure (mmHg), mean (SD)	154.8 (21.0)	140.8 (19.6)	<0.001
LDL cholesterol (mmol/L), mean (SD)	3.1 (1.0)	3.2 (0.9)	<0.001
BMI (kg/m^2), mean (SD)	27.5 (4.1)	26.1 (4.0)	<0.001
Test scores			
MMSE, mean (SD) (range 0-30)	28.2 (1.7)	28.2 (1.6)	0.4
Memory (MMSE item 5), mean (SD) (range 0-3)	2.2 (0.8)	2.4 (0.8)	<0.001
MMSE other, mean (SD) (range 0-27)	26.0 (1.4)	26.0 (1.2)	<0.001
GDS, mean (SD) (range 0-15)	1.5 (2.1)	3.1 (2.5)	<0.001
Subjective memory loss (GDS15-Q10, n, % yes)	473 (16.9)	306 (22.8)	<0.001
Apathy, mean (SD) (range 0-3)	0.7 (0.9)	0.7 (0.9)	0.2
Depressive symptoms (n, % GDS >5)	144 (5.4)	211 (15.8)	<0.001

Individuals with at least one follow-up visit with a test score for Mini-Mental State Examination or Geriatric Depression Scale. Abbreviations: BMI: Body Mass Index; GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: 'Do you feel you have more problems with memory than most?'; IQR: interquartile range; LDL cholesterol: low-density lipoprotein cholesterol; SD: standard deviation; MMSE: Mini-Mental State Examination

Table S2. Baseline characteristics of individuals with at least a baseline and follow-up visit and individuals without any follow-up visits

	Included individuals* (n=4162)	Individuals without follow-up (n=1043)	P-value
Study, n (%)			
- preDIVA	2818 (67.7)	708 (67.9)	
- MAPT	1344 (32.3)	335 (32.1)	
Randomization, n (%)			0.3
Intervention	2166 (52.0)	561 (53.8)	
Control	1996 (48.0)	482 (46.2)	
Demographics			
Age y, median (IQR)	74 (72, 76)	75 (73, 77)	<0.001
Female sex, n (%)	2403 (57.7)	603 (57.8)	1.0
Educational level, n (%)			0.001
- Low (max primary school)	922 (22.4)	285 (28.0)	
- Intermediate	2070 (50.3)	461 (45.3)	
- High (min high school)	1125 (27.3)	271 (26.6)	
MMSE score, mean (SD) (range 0-30)	28.19 (1.7)	27.76 (1.9)	<0.001
Biological risk factors			
Systolic blood pressure (mmHg), mean (SD)	150.29 (21.6)	152.53 (23.1)	0.003
LDL cholesterol, mean (SD)	3.14 (1.0)	3.09 (1.0)	0.1
BMI (kg/m^2), mean (SD)	27.0 (4.2)	27.0 (4.3)	1.0

*These individuals had at least one follow-up visit with a test score for Mini-Mental State Examination or Geriatric Depression Scale. Abbreviations: BMI: Body Mass Index; GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: 'Do you feel you have more problems with memory than most?'; IQR: interquartile range; LDL cholesterol: low-density lipoprotein cholesterol; SD: standard deviation; MMSE: Mini-Mental State Examination

Table S3. Mean difference in effect of multidomain interventions on cognition, symptoms of depression and apathy in subgroups by baseline cognition, after 3-4 years of follow-up

	Baseline MMSE <26					Baseline MMSE ≥26				
	Baseline mean		Mean difference baseline and follow-up		Mean difference between intervention and control group	Baseline mean		Mean difference baseline and follow-up		Mean difference between intervention and control group
	Control	Intervention	Control	Intervention	MDc (95%CI)	Control	Intervention	Control	Intervention	MDc (95%CI)
Cognitive functioning										
MMSE (range 0-30)*	24.20	24.08	0.65	1.58	0.84 (0.15 to 1.54)	28.53	28.54	-0.14	-0.16	-0.03 (-0.12 to 0.06)
Memory (MMSE item 5) (range 0-3)*	1.42	1.24	0.22	0.59	0.21 (-0.01 to 0.43)	2.37	2.36	0.01	0.009	-0.01 (-0.05 to 0.03)
Other (range 0-27)*	22.77	22.81	0.38	0.99	0.74 (0.26 to 1.21)	26.16	26.17	-0.16	-0.18	-0.02 (-0.09 to 0.05)
Subjective memory loss (GDS15-Q10, % yes)†	0.34	0.33	1.48	1.86	-1.83 (-10.86 to 7.21)	0.17	0.19	-0.07	-0.97	-0.37 (-2.42 to 1.67)
Depressive symptoms										
GDS (range 0-15)†	3.06	2.48	0.42	0.41	-0.17 (-0.66 to 0.32)	1.98	1.93	0.21	0.20	-0.04 (-0.16 to 0.08)
Depressive symptoms (% GDS >5)†	0.14	0.13	11.34	4.85	-0.06 (-0.14 to 0.02)	0.09	0.08	2.00	2.38	-0.003 (-0.02 to 0.01)
Apathy (range 0-3)†	0.88	0.77	0.14	0.22	0.03 (-0.16 to 0.21)	0.69	0.68	0.12	0.11	-0.01 (-0.06 to 0.04)

* high score indicates better results; † low score indicates better results. Abbreviations: GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: 'Do you feel you have more problems with memory than most?'; MDc: mean difference in change between the intervention and control group; MMSE: Mini-Mental State Examination; 95%CI: 95% confidence interval

Table S4. Mean difference in effect of multidomain interventions on cognition, symptoms of depression and apathy by study, after 3-4 years of follow-up

	Study		
	preDIVA MDc (95%CI)	**MAPT MDc (95%CI)**	**P for interaction**
Cognitive functioning			
MMSE (range 0-30)*	-0.03 (-0.14 to 0.09)	0.16 (-0.02 to 0.33)	0.07
Memory (MMSE item 5) (range 0-3)*	-0.007 (-0.06 to 0.04)	0.03 (-0.05 to 0.11)	0.43
Other (range 0-27)*	-0.03 (-0.12 to 0.06)	0.13 (-0.006 to 0.27)	0.0498
Subjective memory loss (GDS15-Q10, % yes)†	-0.76 (-3.22 to 1.69)	-0.14 (-3.65 to 3.37)	0.90
Depressive symptoms			
GDS (range 0-15)†	0.02 (-0.11 to 0.15)	-0.15 (-0.38 to 0.08)	0.21
Depressive symptoms (% GDS >5)†	-0.0001 (-0.02 to 0.02)	-0.02 (-0.05 to 0.02)	0.36
Apathy (range 0-3)†	0.02 (-0.03 to 0.08)	-0.06 (-0.14 to 0.03)	0.14

* high score indicates better results; † low score indicates better results. Abbreviations: GDS: Geriatric Depression Scale; GDS15-Q10: question 10 of the Geriatric Depression Scale: 'Do you feel you have more problems with memory than most?'; MDc: mean difference in change between the intervention and control group; MMSE: Mini-Mental State Examination; 95%CI: 95% confidence interval

Table S5. Mean difference in effect of multidomain interventions on cognition for different baseline MMSE cutoff scores, after 3-4 years of follow-up

Baseline MMSE cutoff score	N individuals	N observations	MMSE MDc (95%CI)	P for interaction
<26	250	422	0.84 (0.15 to 1.54)	<0.001
<27	492	840	0.29 (-0.15 to 0.72)	0.11
<28	963	1682	0.22 (-0.05 to 0.49)	0.03
<29	1798	3192	0.10 (-0.07 to 0.27)	0.24
<30	2864	5130	0.02 (-0.10 to 0.14)	0.73

Abbreviations: MDc: mean difference in change between the intervention and control group; MMSE: Mini-Mental State Examination (range 0-30) ; 95%CI: 95% confidence interval

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Table S6. Baseline characteristics according to baseline cognitive scores

	MMSE < 26 (n=250)	MMSE ≥ 26 (n=3454)	P-value
Study, n (%)			0.1
preDIVA	160 (64.0)	2379 (68.9)	
MAPT	90 (36.0)	1075 (31.1)	
Demographics			
Age, y, mean (SD)	74.82 (3.6)	74.42 (3.2)	0.07
Female sex (%)	149 (59.6)	1991 (57.6)	0.6
Educational level , n (%)			<0.001
- Low (max primary school)	116 (47.0)	708 (20.7)	
- Intermediate	92 (37.2)	1739 (50.9)	
- High (min high school)	39 (15.8)	967 (28.3)	
Biological risk factors			
Systolic blood pressure (mmHg) (mean (SD)	150.11 (22.4)	150.32 (21.6)	0.9
LDL cholesterol, mean (SD)	3.1 (1.0)	3.2 (1.0)	0.3
BMI (kg/m^2), mean (SD)	27.8 (4.2)	26.9 (4.1)	0.002

Abbreviations: BMI: Body Mass Index; LDL cholesterol: low-density lipoprotein cholesterol; MMSE: Mini-Mental State Examination (range 0-30)

Part II

Blood pressure, antihypertensive treatment and dementia

4

Antihypertensive medication classes and the risk of dementia: a systematic review and network meta-analysis

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Abstract

Objectives: To systematically review and synthesize the evidence on differential associations between antihypertensive medication (AHM) classes and the risk of incident dementia.

Design: Systematic review and random effects frequentist network meta-analysis. Embase, MEDLINE and the Cochrane library were searched from origin to December 2019.

Setting and participants: Randomized controlled trials (RCTs) and prospective cohort studies that compared associations of different AHM classes with incident all-cause dementia and/or Alzheimer's disease over at least one year of follow-up.

Measures: All cause dementia and/or Alzheimer's disease.

Results: Fifteen observational studies and seven RCTs were included. Data on AHM classes were available for 649,790 participants and dementia occurred in 19,600 (3.02%). Network meta-analysis showed that in observational studies, treatment with either calcium channel blockers (CCBs) or angiotensin II receptor blockers (ARBs) was associated with lower dementia risks than treatment with other antihypertensives: CCBs versus angiotensin converting enzyme inhibitors (ACE inhibitors) (HR=0.84, 95% CI 0.74–0.95), beta blockers (HR=0.83, 95% CI 0.73–0.95) and diuretics (HR=0.89, 95% CI 0.78–1.01) and ARBs versus ACE inhibitors (HR=0.88, 95% CI 0.81–0.97), beta blockers (HR=0.87, 95% CI 0.77–0.99) and diuretics (HR=0.93, 95% CI 0.83–1.05). There were insufficient RCTs to create a robust network based on randomized data alone.

Conclusions and implications: Recommending CCBs or ARBs as preferred first-line antihypertensive treatment may significantly reduce the risk of dementia. If corroborated in a randomized setting these findings reflect a low-cost and scalable opportunity to reduce dementia incidence worldwide.

Introduction

Dementia prevalence world-wide is expected to increase from 50 million in 2019 to 152 million in 2050.[1] No curative treatments are available, but several modifiable risk factors have been identified, treatment of which may delay dementia onset.[2] One of the most important is midlife hypertension. Its high prevalence (20-62% in people aged 40-69) and widely available effective medical treatments,[3] make optimizing antihypertensive treatment a potentially promising, inexpensive and scalable strategy to reduce dementia incidence worldwide.

Blood pressure lowering treatment may lower dementia risk,[4-6] but certain antihypertensive medication (AHM) classes may reduce dementia more than others, through mechanisms beyond blood pressure lowering alone.[7,8] Individual reports on such class specific effects are inconsistent and difficult to interpret. RCTs have not compared AHM classes directly, used widely different control conditions, only evaluated dementia as a secondary outcome and were generally underpowered for this purpose. Observational studies often used individuals without AHM as comparator groups, potentially masking class differences, since normotensive individuals have a lower dementia risk. Furthermore, sensitivity to bias, especially confounding by indication, complicates interpretation of individual observational studies. Two recent individual participant data (IPD) collaborative studies found between -24% and +16% difference in dementia risk associated with individual AHM classes compared to all other classes combined.[5,9] These differences were not significant, with wide confidence intervals possibly resulting from heterogeneity between participating cohorts and lack of direct comparison between AHM classes. With the large number of studies reporting on differential effects of AHM classes on dementia risk, an extensive overview, appraisal and quantitative synthesis of the evidence is warranted.

With this systematic review and network meta-analysis, we aimed to comprehensively collate and synthesize current evidence from RCTs and observational studies, generating effect sizes for each individual treatment comparison, and extensively addressing potential sources of bias and confounding. Network meta-analysis allows combining all available data, comparing AHM classes directly, evaluating potential sources of heterogeneity, and corroborating results by analyzing consistency between direct and indirect evidence.

Methods

Search strategy

We searched MEDLINE, Embase and Cochrane databases (last updated: 06 December 2019), for terms for dementia and cognitive impairment, cross-referenced with terms for antihypertensive treatment and individual AHM classes (Table S1). Terms were exploded if possible. Reference lists of retrieved relevant reviews were examined for additional studies.

Two reviewers (MB, HA) screened titles and abstracts independently. Inclusion criteria were: 1) RCT or population based prospective cohort study, 2) clearly defined all-cause dementia or Alzheimer's dementia (AD) as outcome, 3) AHM treatment as exposure. Exclusion criteria were study populations with: 1) diagnosis of dementia at baseline, 2) <50 participants, 3) Institutionalized individuals, 4) <1 year follow-up. A review protocol was published on PROSPERO in February 2019 (CRD42019124820).

Data extraction

One reviewer (MB) conducted data extraction, a second (JD) verified the collected data. A piloted data extraction form was used including general study and population characteristics, analysis details, exposure and outcome definitions, and potentially important confounders (Table S2). Disagreements between reviewers were resolved through discussion and consulting a third reviewer (ER) if necessary. Authors were approached for additional data if needed to calculate effect sizes.

Data analysis

Random effects frequentist network meta-analyses were conducted in Rstudio (3.6.1, package: "netmeta").[10] Analyses used data on all-cause dementia; if only AD data were available, these were used. We analyzed the five most commonly used AHM classes (angiotensin II receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACE inhibitors), diuretics, calcium channel blockers (CCBs) and beta blockers) and if sufficient data were available, subcategories were assessed (e.g. dihydropyridine CCBs). We assessed heterogeneity using I^2 indices. We assessed the contribution of within study treatment comparisons to the pooled effect and the inconsistency between direct and indirect evidence for each treatment comparison using net heat plots and node splitting. We followed the network meta-analysis PRISMA-guideline[11] and MOOSE statement.[12]

We performed prespecified sensitivity analyses based on outcome definition (all-cause versus AD), and three post-hoc sensitivity analyses on: outcome adjudication (diagnostic codes [eg insurance databases] versus expert adjudication), follow-up duration (split by median) and adjustment (unadjusted versus adjusted estimates in studies reporting both). To evaluate additional evidence from two recent two-stage IPD meta-analyses, we included those in two additional sensitivity analyses,[5,9] using individual effect sizes from each contributing study separately if available,[9] or else the overall estimates.[5] Influence of individual studies on overall results were evaluated using leave-one-out-analyses. For the main analyses, non-AHM-specific comparator groups included "None" (no AHM use), "Other" (any other AHM), and "None_Other" (combination of the previous two). Since we were only interested in heterogeneity from comparisons between individual AHM classes, we conducted a sensitivity analysis only including estimates for these comparisons.

Subgroup analyses were conducted according to patient characteristics (age, gender, ethnicity) and comorbidity (diabetes, stroke, myocardial infarction, heart failure). If effect sizes were not reported, we calculated them from the numbers of participants and dementia events in the different AHM groups. If studies provided multiple (adjusted) hazard ratios (HR), maximally adjusted HRs were used. If studies only reported effects or summary measures for subgroups, we calculated combined estimates (R-packages: 'metafor', 'fishmethods').[13,14]

Quality Assessment

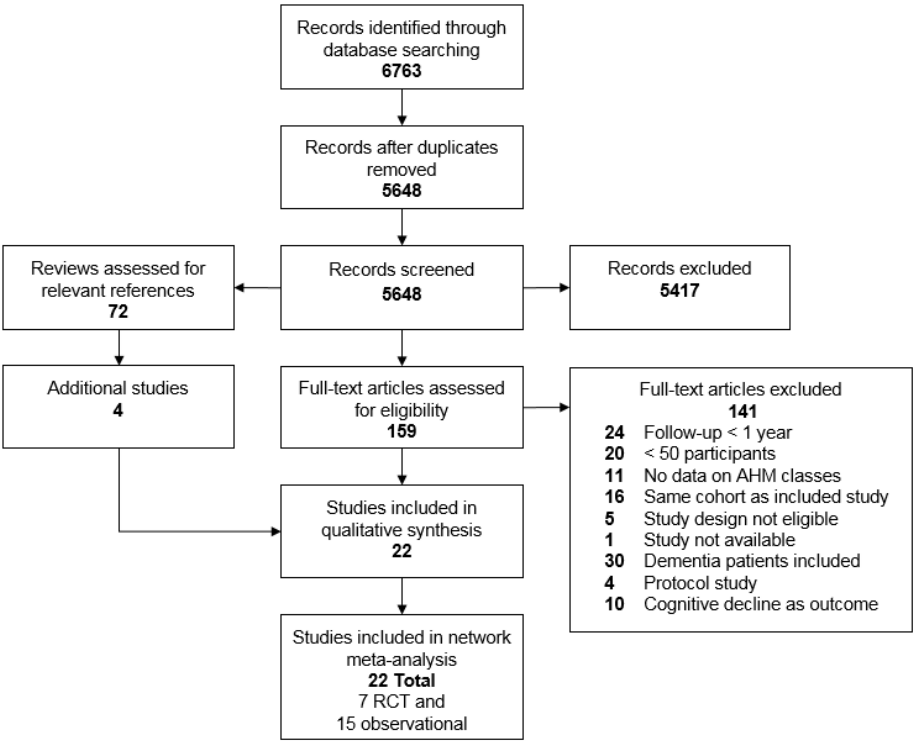
For RCTs, bias was assessed using the Cochrane bias tool.[15] For observational studies, the Newcastle Ottawa Scale, tailored to the research question, rating population selection (representativeness, exposure ascertainment, baseline exclusion of outcome), comparability of AHM groups based on study design/analysis, and outcome ascertainment (assessment, follow-up duration/adequacy).[16] Sensitivity analyses were performed based on study quality scores. Publication bias was assessed using comparison-adjusted funnel plots.

Results

Screening 5648 abstracts, yielded 159 potentially eligible studies (Fig. 1). After full-text evaluation, 22 were included: seven RCTs[17-23] and fifteen observational studies.[24-38] Table 1 provides an overview of the included studies. Patients were included from a population level (n=11),[24,26-29,32,34-38] clinical setting (n=7),[17-23] healthcare databases (n=2),[25,33] or insurance databases (n=2).[30,31] Sample sizes ranged 634[34]-799,069[33] participants (median=3,377). Baseline age ranged 64[23]-84.1[37] years (median=74.4). The percentage of women included ranged from 1.8%[33]

to 75.1%[38] (median=57.7%) Observational studies based AHM use on a prescription database or electronic health record verified with medication lists or containers brought by participants (n=3),[26,37,38] prescription database/electronic healthcare record only (n=6),[25,27,30,31,33,35] or medication containers brought by participants only (n=6).[24,28,29,32,34,36] Seven studies defined dementia using DSM-IV criteria,[21-23,26,27,29,36] six DSM-III-R,[19,24,28,32,35,38] four ICD codes,[20,30,33,35] one American Psychiatric Association criteria,[17] and one "clinical impression" after MMSE screening.[18] Seven studies diagnosed AD using NINCDS-ADRDA criteria.[24,26,28,29,32,34,36] Seventeen studies analysed all-cause dementia,[17-23,25-27,31-33,35-38] five AD only.[24,28-30,34] Follow-up ranged 2.2[22,32]-11[28] years (median=4.3). Overall, dementia occurred in 19,600 of 649,790 participants (3.02%)(Table 2).

Figure 1. PRISMA flow diagram



Abbreviations: AHM: antihypertensive medication; RCT: randomized controlled trial

Table 1. Characteristics of the studies included

Study	Year	Cohort Nationality	Design	Inclusion setting	Medical treatment	Selection criteria	Total number (% women)	Age, mean (SD), y*	AHM use, N (%)†
Applegate[17] (SHEP)	1991	United States	RCT	Clinical	**Intervention**: Diuretic (Chlorthalidone) (add-on BB (Atenolol) or Reserpine) **Control:** Placebo	**in:** age ≥60, SBP 160-219, DBP <90 **ex:** dementia, arrhythmia, stroke, CABG/MI <6 months, CKD, insulin, AntiCoag, AHM, CHF, cancer, malignant HTN	4736 (56.8)	71.6 (6.7)	2365 (49.9)
Forette[19] (Syst-Eur)	1998	Europe	RCT	Clinical	**Intervention:** CCB (Nitrendipine) (add-on ACEi (Enalapril) and/or Diuretic (Hydrochlorothiazide) **Control:** Placebo	**in:** age ≥60, SBP 160-219, DBP <95 **ex:** dementia, SecHTN, severe HTN complications, ICH/SAH, MI <1 year, HDF, cancer	2418 (65.7)	69.9 (6.4)	1238 (51.2)
Tzourio[23] (PROGRESS)	2003	Inter-continental	RCT	Clinical	**Intervention:** ACEI (Perindopril) and Diuretic (Indapamide) **Control:** Placebo	**in:** stroke/TIA in past 5 years **ex:** compelling (contra) indication for ACEi, SAH	6105 (30.3)	64 (10)	3064 (50.2)
Lithell[20] (SCOPE)	2004	Inter-continental	RCT	Clinical	**Intervention:** ARB (Candesartan) (add-on Diuretic (Hydrochlorothiazide)) **Control:** Diuretic only	**in:** age 70–89, SBP 160–179, DBP 90-99, MMSE ≥24 **ex:** dementia, AHM other than HCTZ, SecHTN, stroke/MI <6 months, HDF, CKD	2098 (66.3)	76.4 (4.5)	1253 (59.7)

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Table 1. Continued

Study	Year	Cohort Nationality	Design	Inclusion setting	Medical treatment	Selection criteria	Total number (% women)	Age, mean (SD), y[*]	AHM use, N (%)[†]
Patel[21] (ADVANCE)	2007	Inter-continental	RCT	Clinical	**Intervention:** ACEi (Perindopril) and Duiretic (Indapamide) **Control:** Placebo	**in:** age ≥55, DM2, increased CV risk **ex:** HbA1c ≤6.5%, long-term insulin	11140 (42.5)	66.0 (6.5)	5569 (50)
Diener[18] (PRoFESS)	2008	Inter-continental	RCT	Clinical	**Intervention:** ARB (Telmisartan) **Control:** Placebo	**in:** age ≥55 and stroke <90 days; age 50-54 or stroke <90–120 days if ≥2 CVRF **ex:** ICH/SAH, brain tumor, dementia, mRS >4, SBP ≥180, DBP ≥110, CKD, HDF, CAD	20332 (36)	66.1 (8.6)	10146 (49.9)
Peters[22] (HYVET-COG)	2008	Inter-continental	RCT	Clinical	**Intervention:** Diuretic (Indapamide) (add-on ACEi (Perindopril)) **Control:** Placebo	**in:** age ≥80, SBP 160-199 and DBP 90-109 **ex:** dementia, HDF, CKD, ICH/SAH<6 months, terminal illness, SecHTN, gout	3336 (60)	83.5 (3.1)	1687 (50.6)
Guo[38] (Kungsholmen)	1999	Sweden	Prospective cohort	Population	Diuretic, None	**in:** age ≥75 **ex:** dementia	1201 (75.1)	82.1 (5.2)	584 (44.9)
In 't Veld[32] (Rotterdam)	2001	the Netherlands	Prospective cohort	Population	CCB, Diuretic, None	**in:** age ≥55 **ex:** dementia	6416 (58.7)	68.7	2015 (31.4)
Morris[34] (EPESE)	2001	United States	Prospective cohort	Population	BB, Diuretic, None+other	**in:** age ≥65 **ex:** dementia	634 (63.4)	72.2	214 (33.8)
Yasar[28] (BLSA)	2005	United States	Prospective cohort	Population	CCB, None+other	**in:** age >60 at last FU **ex:** dementia	1092 (37.3)	Last FU: 78.1 (r: 61-104)	NA

Table 1. Continued

Study	Year	Cohort Nationality	Design	Inclusion setting	Medical treatment	Selection criteria	Total number (% women)	Age, mean (SD), y*	AHM use, N (%)†
Sink[36] (CHS)	2009	United States	Prospective cohort	Population	ACEi, Other	**in:** age >65, AHM and self-reported HTN **ex:** dementia, HDF	1054 (63.8)	74.8 (4.9)	1054 (100)
Li[33] (US Veteran Affairs)	2010	United States	Prospective cohort	Healthcare database	ACEi, ARB	**in:** age ≥65 **ex:** dementia	799069 (1.8)	74 (5.5)	799069 (100)
Yasar[29] (GEMS)	2013	United States	Prospective cohort‡	Population	ACEi, ARB, BB, CCB, Diuretic, None	**in:** age >75 **ex:** dementia, AntiCoag, AntiPsyc, TCA, donepezil, vit E, PD, cancer, HDF	2248 (47)	78.7	1605 (71.4)
Hsu[30]	2013	Taiwan	Prospective cohort§	Insurance database	ARB, other	**in:** newly diagnosed HTN **ex:** dementia	32911 (49.9)	NA	32911 (100)
Chuang[24] (Cache County)	2014	United States	Prospective cohort	Population	ACEi, BB, CCB, Diuretic, Other	**in:** age ≥65 **ex:** dementia	3417 (58.2)	74.6 (6.6)	1992 (58.3)
Goh[25]	2014	United Kingdom	Prospective cohort	Healthcare database	ACEi, ARB	**in:** age ≥18 **ex:** dementia <first 12 months FU, cognitive impairment	469366 (48)	Med: 64.5 IQR: 54-74	469366 (100)
Hwang[31]	2016	Korea	Prospective cohort study	Insurance database	ACEi, ARB, BB, CCB, Diuretic	**in:** age ≥60, HTN **ex:** dementia, CVD, cancer	18423 (57.2)	67.25	18423 (100)
Tully[26] (3C study)	2016	France	Prospective cohort	Population	ACEi, ARB, BB, CCB, Diuretic, None	**in:** age ≥65 **ex:** dementia	6537 (62)	77.2 (5.8)	3962 (60.6)
van Middelaar[27] (PreDIVA)	2017	the Netherlands	Prospective cohort‡	Population	ACEi, ARB, BB, CCB, Diuretic, Other	**in:** age 70-78 **ex:** dementia	1951 (53.8)	74.4 (2.5)	1951 (100)

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Table 1. Continued

Study	Year	Cohort Nationality	Design	Inclusion setting	Medical treatment	Selection criteria	Total number (% women)	Age, mean (SD), y*	AHM use, N (%)†
Murray[35] (IIDP)	2018	United States	Prospective cohort	Population	ACEi, ARB, BB, CCB, Diuretic	**in:** age ≥65, HTN **ex:** dementia	1236 (73.3)	74.9 (6.5)	816 (66)
Tan[37] (SNAC-K)	2018	Sweden	Prospective cohort	Population	ACEi, ARB, BB, CCB, Diuretic, None	**in:** age ≥78 **ex:** dementia	1208 (70.2)	84.1 (5.6)	681 (56.4)

*mean age of intervention group in RCT or antihypertensive medication (AHM) users in observational study; † AHM use at baseline for observational studies and directly after inclusion for RCT studies; ‡ post-hoc analysis of RCT study; § Propensity score matched analysis. Reference categories: 1) None: no antihypertensive medication use, 2) Other: use of antihypertensive medicine, other than the class of interest, 3) None+other: combination of individuals not using antihypertensive medication and individuals using antihypertensive medicine, other than the class of interest. Abbreviations: ACEi: ACE inhibitor; ARB: Angiotensin II receptor blocker; BB: Beta blocker; CCB: calcium channel blocker; in: inclusion criteria; ex: exclusion criteria; AHM: antihypertensive medication use; AntiCoag: anticoagulant medicine use; AntiPsyc: antipsychotic medication use; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CHF: chronic heart failure; CKD: chronic kidney disease; CV: cardiovascular; CVD: cerebrovascular disease; DBP: diastolic blood pressure; DM2: type 2 diabetes mellitus; HCTZ: Hydrochlorothiazide; HDF: hepatic dysfunction/chronic hepatic failure; HTN: hypertension; ICH: intracerebral hemorrhage; FU: follow-up; MI: myocardial infarction; MMSE: Mini-Mental State Examination; mRS: Modified Rankin Scale; PD: Parkinson's disease; SAH: subarachnoid hemorrhage; SBP: systolic blood pressure; SecHTN: secondary hypertension; TCA: tricyclic antidepressants use; TIA: transient ischemic attack.

Table 2. Main outcomes as reported in the studies included

Author (Study)	Year	Design	Dementia type	Dementia definition	Events, n/N (%)	Events/medical treatment, n/N (%)*	Follow-up	Study findings, RR/OR/HR, 95%CI
Applegate[17] (SHEP)	1991	RCT	All-cause	American Psychiatric Association criteria	81/4736 (1.7)	**Intervention**: Diuretic (add-on BB or Reserpine) 37/2365 (1.6) **Control:** Placebo 44/2371 (1.9)	Average 4.5 years	RR 0.84 (0.54-1.31)†
Forette[19] (Syst-Eur)	1998	RCT	All-cause	DSM-III-R	22/2418 (0.9)	**Intervention:** CCB (add-on ACEi and/or Diuretic) 7/1238 (0.6) **Control:** Placebo 15/1180 (1.3)	median 3.9 years (IQR 2.8-5.6 years)	RR 0.44 (0.18-1.09)†
Tzourio[23] (PROGRESS)	2003	RCT	All-cause	DSM-IV	410/6105 (6.7)	**Intervention:** ACEi and Diuretic 193/3051 (6.3) **Control:** Placebo 217/3054 (7.1)	mean 3.9 years	RR 0.89 (0.73-1.09)†
Lithell[20] (SCOPE)	2004	RCT	All-cause	Modified ICD-10	49/2098 (2.3)	**Intervention:** ARB (add-on Diuretic) 31/1253 (2.5) **Control:** Diuretic 18/845 (2.1)	intervention: 3.7 years (mean) comparison: 3.5 years (mean)	RR 1.16 (0.65-2.09)†
Patel[21] (ADVANCE)	2007	RCT	All-cause	DSM-IV	109/11140 (1.0)	**Intervention:** ACEi and Diuretic 53/5569 (1.0) **Control:** Placebo 56/5571 (1.0)	mean 4.3 years (range <1 month-to 5.6 years)	RR 0.95 (0.65-1.38)†

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Table 2. Continued

Author (Study)	Year	Design	Dementia type	Dementia definition	Events, n/N (%)	Events/medical treatment, n/N (%)*	Follow-up	Study findings, RR/OR/HR, 95%CI
Diener[18] (PRoFESS)	2008	RCT	All-cause	MMSE ≤24 or ≥3 points decline and clinical impression	817/17270 (4.7)	**Intervention:** ARB 408/8624 (4.7) **Control:** Placebo 409/8646 (4.7)	2.44 years (median)	RR 1 (0.87-1.15)†
Peters[22] (HYVET-COG)	2008	RCT	All-cause	DSM-IV	263/3336 (7.9)	**Intervention:** Diuretic (add-on ACEi) 126/1687 (7.5) **Control:** Placebo 137/1649 (8.3)	mean 2.2 years	RR 0.90 (0.70-1.16)†
Guo[38] (Kungsholmen)	1999	Prospective cohort	All-cause	DSM-III-R, CDRS	207/1201 (17.2)	Diuretic 73/484 (15.1) None 134/717 (18.7)	mean 36.7 months (max. 63.1 months)	**HR unadjusted (ref. none)** Diuretic 0.7 (0.5-1)
In 't Veld[32] (Rotterdam)	2001	Prospective cohort	All-cause	DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	118/2015 (5.9)	AHM users 48/2015 (2.4) None 70/4401 (1.6)	mean 2.2 years	**HR unadjusted (ref. none)** CCB 0.7 (0.32-1.52) Diuretic 0.83 (0.33-1.3)
Morris[34] (EPESE)	2001	Prospective cohort	Alzheimer's disease	NINCDS-ADRDA	99/634 (15.6)	NA	4 years‖	**OR (ref. none+other)** BB 0.91 (0.26-3.17) Diuretic 1.03 (0.64-1.66)‡
Yasar[28] (BLSA)	2005	Prospective cohort	Alzheimer's disease	DSM-III-R, NINCDS-ADRDA	115/1092 (10.5)	CCB 18/220 (8.2) None+other 97/872 (11.1)	mean 11.0 years (range 0.3-19.6)	HR adjusted (ref. none+other) CCB 0.42 (0.13-1.38)
Sink[36] (CHS)	2009	Prospective cohort	All-cause	DSM-IV, NINCDS-ADRDA, ADDTC, NINDS-AIREN	158/1054 (15.0)	ACEi 47/414 (11.4) Other 111/640 (17.3)	median 6 years	**HR adjusted (ref. other)** ACEi 1.01 (0.87-1.18)

Table 2. Continued

Author (Study)	Year	Design	Dementia type	Dementia definition	Events, n/N (%)	Events/medical treatment, n/N (%)*	Follow-up	Study findings, RR/OR/HR, 95%CI
Li[33] (US Veteran Affairs)	2010	Prospective cohort	All-cause	ICD-9	4163/102671 (4.1)	ACEi 3768/91164 (4.1) ARB 395/11507 (3.4)	mean 31 months	**HR adjusted (ref. ACEi)** ARB 0.81 (0.73-0.9)
Yasar[29] (GEMS)	2013	Prospective cohort	Alzheimer's disease	DSM-IV, NINCDS-ADRDA	290/2248 (12.9)	ACEi n/276 ARB n/124 BB n/403 CCB n/281 Diuretic n/311 None NA	median 6.1 years	**HR adjusted (ref. none)** ACEi 0.74 (0.48-1.14) ARB 0.31 (0.14-0.68) BB 0.77 (0.51-1.15) CCB 0.91 (0.58-1.42) Diuretic 0.74 (0.49-1.11)
Hsu[30]	2013	Prospective cohort	Alzheimer's disease	ICD (version not specified)	1031/32911 (3.1)	ARB 488/16426 (3.0) Other 543/16485 (3.3)	Mean 5.24±2.01 years	**HR adjusted (ref. other)** ARB 1 (0.88-1.13)
Chuang[24] (Cache County)	2014	Prospective cohort	Alzheimer's disease	DSM-III-R, NINCDS-ADRDA	325/3417 (9.5)	ACEi 59/4430 (1.3)[§] BB 56/4125 (1.4)[§] CCB 51/4115 (1.2)[§] Diuretic 95/7289 (1.3)[§] Other NA	Mean 7.1 years	**HR adjusted (ref. other)** ACEi 1.06 (0.76-1.5) BB 1.02 (0.73-1.43) CCB 0.85 (0.6-1.2) Diuretic 0.77 (0.56-1.06)
Goh[25]	2014	Prospective cohort	All-cause	Specific read codes in UK Clinical Practice Research Datalink	6517/426089 (1.5)	ACEi 5853/380548 (1.5) ARB 664/45541 (1.5)	Median 4.25 years (IQR 2.51-6.65)	**HR unadjusted (ref. ACEi)** ARB 0.89 (0.82-0.97)
Hwang[31]	2016	Prospective cohort	All-cause	At least 1 dementia record as an admission or 3 records as an outpatient	4005/18423 (21.7)	ACEi 1554/5594 (27.8) ARB 6160/21431 (28.7) BB 3736/13388 (27.9) CCB 7105/25926 (27.4) Diuretic 5691/19506 (29.2)	Mean 9.4 years	**HR adjusted (ref. BB)** ARB 0.9 (0.87-0.93) ACEi 1 (0.95-1.06) CCB 0.88 (0.85-0.9) Diuretic 1 (0.97-1.03)

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Table 2. Continued

Author (Study)	Year	Design	Dementia type	Dementia definition	Events, n/N (%)	Events/medical treatment, n/N (%)*	Follow-up	Study findings, RR/OR/HR, 95%CI
Tully[26] (3C study)	2016	Prospective cohort	All-cause	DSM-IV, NINCDS-ADRDA and NINDS-AIREN	446/6537 (6.8)	NA	median 8.4 years (IQR 6.7-9.0)	**HR adjusted (ref. none)** ACEi 0.87 (0.63-1.19) ARB 0.82 (0.54-1.25) BB 1.12 (0.83-1.5) CCB 0.64 (0.43-0.93)‡ Diuretic 0.71 (0.51-0.98)‡
van Middelaar[27] (PreDIVA)	2017	Prospective cohort	All-cause	DSM-IV	136/1951 (7.0)	ACEi 43/600 (7.2) ARB 20/389 (5.1) BB 69/963 (7.2) CCB 26/512 (5.1) Diuretic 54/784 (6.9) Other NA	median 6.7 years (IQR 6.0-7.3)	**HR adjusted (ref. other)** ACEi 1.05 (0.72-1.51) ARB 0.63 (0.39-1.02) BB 0.9 (0.63-1.29) CCB 0.56 (0.36-0.86) Diuretic 0.82 (0.57-1.18)
Murray[35] (IIDP)	2018	Prospective cohort	All-cause	DSM-III-R and ICD-10	114/1236 (9.2)	NA	NA	**HR adjusted (ref. none)** ACEi 0.62 (0.38-0.99) ARB 0.34 (0.15-0.77) BB 0.43 (0.26-0.74) CCB 0.59 (0.37-0.95) Diuretic 0.54 (0.34-0.84)
Tan[37] (SNAC-K)	2018	Prospective cohort	All-cause	DSM-IV	125/1208 (10.3)	ACEi 9/135 (6.7) ARB 1/47 (2.1) BB 35/301 (11.6) CCB 12/159 (7.5) Diuretic 46/439 (10.5) None NA	median 5.15 years	**HR adjusted (ref. none)** ACEi 0.49 (0.25-0.96) ARB 0.57 (0.21-1.51) BB 0.92 (0.59-1.43) CCB 0.49 (0.24-0.99) Diuretic 0.68 (0.45-1.01)

[*] In some studies, patients were scored for each individual class of AHM if they took multiple AHM; [†] calculated from incidence numbers in article; [‡] AHM classes were merged (eg loop- and thiazide diuretics); [§] AD/person-years; [||] 4-year risk of incident AD. Reference categories: 1) None: no antihypertensive medication use, 2) Other: use of antihypertensive medicine, other than the class of interest, 3) None+other: combination of individuals not using antihypertensive medication and individuals using antihypertensive medicine, other than the class of interest. Abbreviations: RCT: randomized controlled trial; ADDTC: state of California Alzheimer's Disease Diagnostic and Treatment Centers; CDRS: Clinical Dementia Rating Scale; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, third edition, revision; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; ICD-10: International Classification of Diseases and Related Health Problems, tenth edition; MMSE: Mini-Mental State Examination; NINCDS-ADRDA: the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; ACEi: ACE inhibitor; ARB: Angiotensin II receptor blocker; BB: Beta blocker; CCB: calcium channel blocker; AHM: antihypertensive medication; HR: hazard ratio; OR: odds ratio; RR: risk ratio; ref.: reference group.

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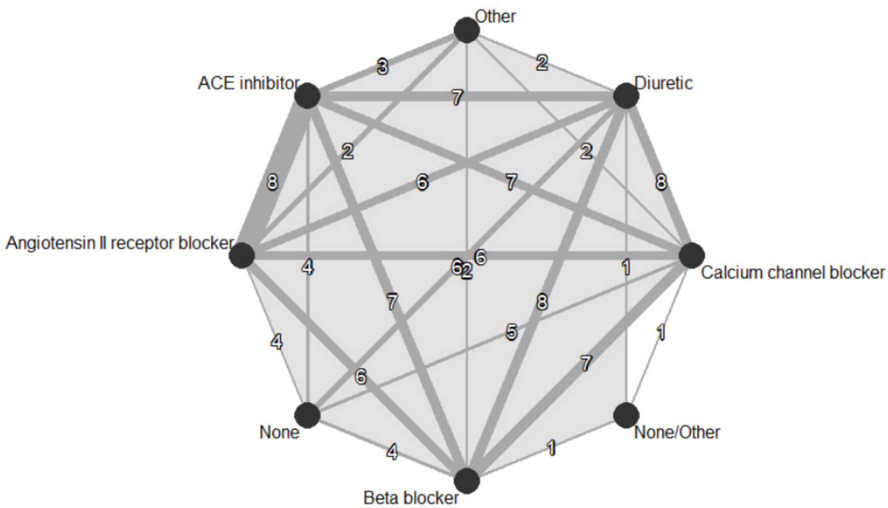
Quality assessment

Risk of bias in RCTs (Table S3) was generally low. In observational studies (Table S4), bias risk was mainly seen in exposure ascertainment, due to most studies basing AHM use on either medication lists/containers (n=6) or medical records (n=6), and follow-up adequacy, with four studies having >20% loss-to-follow-up, and four not describing loss-to-follow-up. Four studies scored above the median risk of bias.[31-33,35]

Primary analysis

Observational analyses included 15 studies with 11 different designs and 107 pairwise comparisons.[24-38] CCBs were associated with 16% lower dementia risk compared to ACE inhibitors (HR=0.84, 95%CI=0.74–0.95, I2=27.4%), 17% lower risk versus beta blockers (HR=0.83, 95%CI=0.73–0.95) and 11% versus diuretics (HR=0.89, 95%CI=0.78–1.01). ARBs were associated with 12% lower dementia risk compared to ACE inhibitors (HR=0.88, 95%CI=0.81–0.97), 13% versus beta blockers (HR=0.87, 95%CI=0.77–0.99) and 7% versus diuretics (HR=0.93, 95%CI=0.83–1.05) (Fig. 2, Table 3).

Figure 2. Network graph: antihypertensive medication classes and dementia risk



The thickness of the lines represents the weight of the comparisons and the numbers represent the number of studies in which information about that comparison was available. Heterogeneity: $I^2 = 27.4\%$, within designs p-value = 0.02, between designs p-value = 0.42. Number of studies included: 15, pairwise comparisons: 107, designs: 11. Reference categories used by included studies: 1) None: no antihypertensive medication use, largely comprising individuals without hypertension, 2) Other: use of antihypertensive medicine, other than the class of interest, 3) None/Other: combination of individuals not using antihypertensive medication and individuals using antihypertensive medicine, other than the class of interest.

Table 3. Results of network meta-analysis of observational studies: antihypertensive medication classes and dementia risk

	vs ACE inhibitor	vs angiotensin II receptor blocker	vs beta blocker	vs calcium channel blocker	vs diuretic
ACE inhibitor	-	**1.13 (1.04-1.24)**	0.99 (0.88-1.12)	**1.19 (1.05-1.34)**	1.06 (0.94-1.19)
angiotensin II receptor blocker	**0.88 (0.81-0.97)**	-	**0.87 (0.77-0.99)**	1.05 (0.93-1.19)	0.93 (0.83-1.05)
beta blocker	1.01 (0.90-1.14)	**1.15 (1.01-1.29)**	-	**1.20 (1.06-1.37)**	1.07 (0.94-1.21)
calcium channel blocker	**0.84 (0.74-0.95)**	0.95 (0.84-1.08)	**0.83 (0.73-0.95)**	-	0.89 (0.78-1.01)
diuretic	0.95 (0.84-1.07)	1.07 (0.95-1.21)	0.94 (0.82-1.06)	1.12 (0.99-1.28)	-

Estimated treatment effects (hazard ratio's) and 95% confidence intervals from the network meta-analysis. A number below 1 shows a beneficial effect of the AHM class that is listed in the row compared to the AHM class listed in the corresponding column. Treatment effects in bold: significant $p < 0.05$.

The net heat plot and node splitting showed no major sources of inconsistency (Fig. A1, Table S5). The comparison-adjusted funnel plot did not indicate publication bias for any specific AHM class, although comparison results for beta blockers versus no AHM in one study did appear as an outlier (Fig. A2).[35] Excluding this study did not influence the results, nor did excluding the only study reporting odds ratios instead of HRs as effect size (Table S8a).[34]

Separate meta-analysis of RCTs was little informative, since only seven RCTs with seven pairwise comparisons were available, providing insufficient data for a robust network (Fig. A3). Adding RCTs to observational study results yielded similar heterogeneity and treatment estimates, with slightly narrower confidence intervals for all AHM classes (Table S7). Analyses for AHM subcategories (e.g. dihydropyridine CCBs) were not possible because of insufficient available evidence.

Sensitivity analysis

Since only seven RCTs were available, sensitivity and subgroup analyses were performed in observational studies only. Leaving out HRs for non-informative comparator groups (ie "None", "Other", "None_Other"), gave unchanged estimates for AHM class comparisons but resolved heterogeneity completely (Table S8a). In leave-one-out analyses (Table S9a), compared to ACE inhibitors, effect estimates for CCBs ranged 0.78-0.86 (95%CI=0.62–0.97; 0.77–0.97), for ARBs 0.86-0.91

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(95%CI=0.79–0.94; 0.82–1.00); for beta blockers 0.99-1.06 (95%CI=0.92–1.06; 0.86–1.31); and for diuretics 0.88-0.98 (95%CI=0.72–1.07; 0.91–1.06)). The lowest heterogeneity was 6.15%, the highest 33.43% (Table S9b).

Sensitivity analyses based on outcome (all-cause dementia[25-27,31-33,35-38] vs AD[24,28-30,34]), inclusion method (clinical[24,26-29,32,34,36-38] vs code-based diagnosis[25,30,31,33,35]), duration of follow-up (dichotomized at the median), adjustment for potential confounders (yes[24,25,27,29,30,36] vs no[24,25,27,29,30,36]) and Newcastle-Ottawa scale score (dichotomized at the median) gave similar findings (Table S8b-c, 10a-b). Dementia risk remained consistently lower for CCBs and ARBs compared to other AHM classes in most sensitivity analyses, with some exceptions: Firstly, compared all-cause dementia, studies using AD as outcome showed higher HRs for ARBs and lower HRs for diuretics. Secondly, dementia risk reduction was stronger in studies with longer follow-up, for all AHM classes compared to ACE inhibitors (Table S8b). Sensitivity analysis adding overall estimates from a recent IPD meta-analysis to our main analysis (individual cohort estimates were not available upon request), yielded significant 10-13% lower dementia risks for CCBs or ARBs compared to ACE inhibitors, beta blockers and diuretics (Table 11a).[5] Adding separate individual cohort estimates from another recent IPD yielded significant 13-18% lower dementia risks for CCBs or ARBs compared to ACE inhibitors and beta blockers (Table 11b).[9]

Subgroup analyses

Regarding the most important confounders, most studies adjusted for age, sex, diabetes and cardiovascular disease (Table S12), but did not report on interactions between comorbidities and AHM classes in relation to dementia risk. To explore potential moderators, we dichotomized studies based on baseline characteristics (Table S13). Effect sizes were generally consistent across subgroups, but most analyses included few studies and confidence intervals were wide, rendering most comparisons inconclusive. Most relevantly, in the subgroup with low diabetes prevalence (<17.1%, n=7), risks were relatively low for both ARBs and ACE inhibitors, but ARBs still had a lower HR compared to ACE inhibitors (HR=0.93, 95%CI=0.68-1.00). Furthermore, beta blockers had relatively high HRs in studies with more women (>58.2%, n=7, HR=1.20, 95%CI=0.83-1.74) and higher mean age (>74.7 years, n=7, HR=1.20, 95%CI=0.84-1.72). Insufficient data precluded prespecified subgroup analyses according to ethnicity.

Discussion

In this network meta-analysis, use of either CCBs or ARBs was associated with a 12 to 17% lower dementia risk compared to ACE inhibitors and beta blockers. Compared to diuretics this reduction was 7 to 11%, but not significant.

Although we initially planned to analyse RCTs and observational studies together, we chose to analyse them separately because of large differences in setting, the irregularity and lack of detail in RCT control conditions, and observational studies potentially being subject to confounding by indication. Due to the limited number of RCTs, our results were mainly based on observational studies. To minimize bias due to confounding by indication, we used maximally adjusted data in our main analyses (Table S12). Combining RCT and observational data gave comparable results with smaller confidence intervals, corroborating observational evidence. We extensively explored potential sources of bias and confounding. Net heat plots and node splitting showed good distribution and low heterogeneity and inconsistency in the network, indicating that both direct and indirect evidence from studies is consistent. Therefore, it seems unlikely that bias plays a major role in our results. The high consistency also decreases the likelihood that our results are mainly driven by confounding by indication, because studies originate from different settings and time periods, with different AHM classes serving as first-choice medication. Sensitivity analyses were consistent and leave-one-out analyses did not identify any individual studies substantially influencing effect sizes or heterogeneity. Some large registration cohorts could have dominated our main results. However, sensitivity analysis leaving out these studies resulted in even lower dementia risks for CCB and ARB users, suggesting that effect sizes in these studies may be an underestimation, possibly due to non-differential misclassification which often occurs in these types of studies. Adding results from two recent two-stage IPD meta-analyses gave similar results, with possibly slightly lower HRs for CCBs and ARBs compared to diuretics.[5,9]

Most subgroup and sensitivity analyses consistently associated CCB and/or ARB treatment with lower dementia risk compared to other AHM classes. The lower risks compared to ACE inhibitors were stronger with longer follow-up for all AHM classes, consistent with the expectation that AHM need more time to exert their protective effects on a condition that increases with age. ACE inhibitors performed worse in studies with high diabetes prevalence, possibly because ACE inhibitors are the first-choice AHM in diabetes, which also increases dementia risk. However, ARBs have the same indication and consistently showed lower dementia risks compared to ACE inhibitors, also in diabetes subgroups. This strengthens our findings associating ARBs with lower dementia risk. Cardiovascular co-indications could have reduced dementia risk for other AHM classes, particularly beta blockers, due to increased competing risk of cardiovascular mortality. We found no clear indication for differential effects of beta blockers depending on comorbidity. However, few studies reported on cardiovascular comorbidities and subgroup analyses' estimates had wide confidence intervals.

Strengths and limitations

The key strength of this network meta-analysis is that it integrates all available evidence for differential effects of AHM classes on dementia risk, even if AHM classes were not directly compared within individual studies. Integrating 114 comparisons, among 649,790 participants with 19,600 events in 22 studies, provides substantially more power than traditional meta-analysis. Second, the population-based observational studies take place in regular care, following guidelines that account for patient characteristics and comorbidities, increasing generalizability to hypertensive patients in real-world clinical practice. Third, our sensitivity and subgroup analyses yielded consistent results, suggesting relatively low risk of confounding by indication. The symmetrical comparison-adjusted funnel plot suggests low risk of publication bias. The only outlier compared beta blockers to untreated hypertension in an Afro-American population.[35] This may relate to Afro-American ethnicity predisposing to an attenuated response to beta blockers. Excluding this study gave unchanged results. Analyses including only AHM class reference categories completely resolved heterogeneity, while retaining similar treatment effects. This suggests that heterogeneity in our analyses is largely attributable to the irregular constitution of the "none" and "other" comparator groups; "none" including varying proportions of individuals with elevated blood pressure, and "other" varying proportions of AHM class use.

Several limitations exist. First, paucity of information complicated subgroup analyses evaluating potential moderators, leading to considerable uncertainty and large studies potentially dominating results in small subgroups, warranting cautious interpretation. However, effect sizes were consistent in leave-one-out analyses, suggesting single studies did not unduly influence overall results. Second, the RCT analysis only included seven studies, only two comparing the same AHM, with greatly varying placebo conditions often including non-detailed other AHM use, complicating interpretation. Third, insufficient evidence was available to analyze subcategories of AHM classes (e.g. dihydropyridine CCBs might convey lower dementia risk than non-dihydropyridine).[39] Fourth, few studies reported on the competing risk of mortality, which needs more comprehensive evaluation in future studies, together with potential modifiers including coronary artery disease and stroke. Fifth, dementia diagnostics and antihypertensive treatment regimen changed over the last decades, and secular trends could have influenced our results. However, the data did not allow for quantification of such a secular trend, due to changes in study design over time, most notably the tendency to compare multiple AHM classes against each other in more recent studies, and only two AHM classes in older studies, in combination with an important imbalance in weights of AHM comparisons in earlier studies.

Comparison with other studies

Several other studies support our findings. A 2017 narrative review of 20 longitudinal studies, 10 RCTs and 9 meta-analyses, identified CCBs and renin-angiotensin-system blockers as most promising to reduce dementia risk.[8] Our results confirm this, although specifically for ARBs and not for ACE inhibitors. A 2013 network meta-analysis including 17 RCTs with 13,734 individuals associated ARB use with less decline on cognitive function scores in individuals without dementia, compared to placebo, beta blockers, diuretics and ACE inhibitors.[7] Two recent important IPD studies evaluated AHM class differences. One (3-6 cohorts, 630-1,100 cases) found 12-24% lower HRs for ARBs and 4-9% higher HRs for CCBs compared to any other AHM class in individuals with high blood pressure.[5] The second (6-9 cohorts, ~318-366 cases) 7-24% lower ORs for ARBs and CCBs respectively versus any other AHM class.[9] In both, these results were non-significant with wide confidence intervals.[5,9] Incorporating findings by including overall and/or individual study estimates in our analyses corroborated our results. Although the studies did not report clear significant AHM class differences, wide confidence intervals, and reference groups combining all other classes (averaging beneficial and detrimental class effects) might play a role in their neutral findings. Our study is the first using network meta-analysis to compare AHM classes to each other individually, using the most clinically relevant outcome of incident dementia, and evaluating all available evidence from RCTs and observational studies.

Several pathophysiological mechanisms might explain how CCBs and ARBs reduce dementia risk.[8,40-42] ARBs block angiotensin-II AT1-receptors and cause upregulation of AT2-receptors, which may promote cerebral perfusion and neurite growth, decrease inflammation and axonal degeneration, and reduce amyloid beta.[40,41] CCBs decrease intracellular calcium, which is elevated in the aging brain and may contribute to neurodegeneration, amyloid beta production and Tau hyperphosphorylation, pathological hallmarks of AD.[8,40]

Our study further supports the notion that AHM treatment may aid preventing dementia. Recently, a systematic review and an IPD meta-analysis indicated that blood pressure treatment may lower dementia risk.[5,6] On the primary outcome effect of the SPRINT MIND trial, probable dementia, there was no statistically significant difference between treatment groups, but results of a secondary analysis suggested that intensive blood pressure control to a target of 120 mmHg instead of 140 mmHg may reduce the combined incidence of mild cognitive impairment plus probable dementia. Although these results should be interpreted with caution, especially because mild cognitive impairment is an unstable construct, they are promising.[4] Preferring CCBs or ARBs might provide an additional viable strategy to optimize dementia prevention in future clinical practice. These medication types are long-established and widely available. Current antihypertensive treatment guidelines do not recommend any antihypertensive drug as being superior in reducing dementia but the American College of Cardiology guidelines currently recommend ARBs, CCBs, thiazide diuretics, and ACE inhibitors as equivalent first-line treatments for primary hypertension without comorbidity indicating a specific AHM class, which includes most patients.[43] Treating hypertension in older persons could offer the typical benefit of blood pressure lowering and a secondary, repurposed benefit of lowering dementia risk. Hypertension prevalence is high (>70%) and dementia risk becomes increasingly important in persons over 65, providing a large window of opportunity for population-level prevention. This is particularly relevant, because expected rises in dementia incidence mostly involve low- and middle-income countries, where cheap and widely available interventions are the only way forward.

Conclusions and implications

Treating hypertensive patients with CCBs or ARBs may significantly reduce dementia risk. This could have important implications for hypertension management guidelines. If corroborated in a randomized setting, adapting AHM regimen may be a low cost and scalable prevention strategy to reduce the risk of dementia globally.

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Supplemental material

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Table S1. Full search strategy

Table S1a. Search strategy and number of records identified in Medline and Embase databases through OVID platform. Last update: 06-12-2019.

No.	Search items	Hits Total	Hits/ database
1	**dementia.mp. or exp DEMENTIA/ or exp dementia/ or dementia.mp.**	**581637**	
	MEDLINE		200064
	Embase		381573
2	**exp cognition/ or cognit*.mp. or exp COGNITION DISORDERS/ or exp COGNITION/**	**3247516**	
	MEDLINE		490137
	Embase		2757379
3	**mild cognitive impairment.mp. or exp cognitive defect/ or exp mild cognitive impairment/ or exp Cognitive Dysfunction/**	**505903**	
	MEDLINE		24114
	Embase		481789
4	**diuretic.mp. or exp diuretic agent/ or exp Diuretics/ or diuretics.mp.**	**489243**	
	MEDLINE		98584
	Embase		390659
5	**thiazide-like.mp.**	**565**	
	MEDLINE		226
	Embase		339
6	**calcium channel blocker.mp. or exp calcium channel blocking agent/ or exp Calcium Channel Blockers/ or calcium channel blockers.mp. or calcium antagonist. mp. or exp calcium antagonist/**	**360735**	
	MEDLINE		92947
	Embase		267788
7	**(angiotensin converting enzyme inhibitor or angiotensin-converting enzyme inhibitors).mp. or exp Angiotensin-Converting Enzyme Inhibitors/ or ACE inhibitors.mp.**	**229538**	
	MEDLINE		54553
	Embase		174985
8	**angiotensin receptor blocker.mp. or exp angiotensin receptor antagonist/ or angiotensin receptor.mp.**	**122408**	
	MEDLINE		27571
	Embase		94837
9	**beta blocker.mp. or exp beta adrenergic receptor blocking agent/**	**312833**	
	MEDLINE		12603
	Embase		300230
10	**adrenergic beta-antagonists.mp. or exp Adrenergic beta-Antagonists/**	**382143**	

Table S1a. Continued

No.	Search items	Hits Total	Hits/ database
	MEDLINE Embase		83550 298593
11	**antihypertensives.mp. or exp antihypertensive agent/ or antihypertensive.mp.**	**1039687**	
	MEDLINE Embase		275182 764505
12	**exp Prospective Studies/ or prospective cohort.mp. or exp prospective study/**	**1148453**	
	MEDLINE Embase		541496 606957
13	**exp controlled clinical trial/ or RCT.mp. or randomized controlled trial.mp. or randomized controlled trial.mp. or exp Randomized Controlled Trial/**	**1591828**	
	MEDLINE Embase		623155 968673
14	**1 or 2 or 3**	**3387281**	
	MEDLINE Embase		618311 2768970
15	**4 or 5 or 6 or 7 or 8 or 9 or 10 or 11**	**1611390**	
	MEDLINE Embase		448258 1163132
16	**12 or 13**	**2553105**	
	MEDLINE Embase		1073398 1479707
17	**14 and 15 and 16**	**6660**	
	MEDLINE Embase		766 5894
18	**limit 19 to human**	**6554**	
	MEDLINE Embase		754 5800
19	**remove duplicates from 18**	**5439**	
	MEDLINE Embase		727 4712

Table S1b. Search strategy and number of records identified in Cochrane library. Last update 10-12-2019.

	Search items		Hits total
1.	**Dementia**	All text	209
2.	**Antihyperten***	All text	

Table S2. Data extraction form

Item	Additional information
Characteristics	
Author (studyname)	-
Publication year	-
Cohort nationality	-
Study design	-
Setting	-
Population	-
Inclusion criteria	-
Exclusion criteria	-
Intervention	-
Comparison	-
Primary endpoint study	-
Secondary endpoint study	-
Participants	Baseline: total, intervention, comparison group
Mean age, SD	Baseline: total, intervention, comparison group
Female N, %	Baseline: total, intervention, comparison group
Antihypertensive treatment N, %	Baseline: total, intervention, comparison group
Blood pressure (SBP/DBP) mean, SD	Baseline: total, intervention, comparison group
History of coronary artery disease	Baseline: total, intervention, comparison group
History of heart failure	Baseline: total, intervention, comparison group
History of stroke	Baseline: total, intervention, comparison group
History of diabetes	Baseline: total, intervention, comparison group
Ethnicity	Baseline: total, intervention, comparison group
Cognition	-
Cognition test	-
Outcomes	
Dementia type	All cause or Alzheimer's disease
Diagnosis of dementia	How was diagnosis established?
Dementia criteria	-
Follow-up mean, SD or median	-
Dementia incidence	total, intervention, comparison group
Decline in cognitive function	intervention, comparison
Study conclusion	-

Table S3. Bias assessment randomized-controlled trials based on Cochrane Collaboration's tool for assessing risk of bias in randomized trials

		Selection bias		Performance bias
Author (study)	**Year of publication**	**Random sequence generation**	**Allocation concealment**	**Blinding of participants and personnel**
Applegate (SHEP)[1]	**1991**	+	+	+
Diener (PRoFESS)[2]	**2008**	+	+	+
Forette (Syst-Eur)[3]	**1998**	+	+	+
Patel (ADVANCE)[4]	**2007**	+	+	+
Peters (HYVET-COG)[5]	**2008**	+	+	+
Lithell (SCOPE)[6]	**2004**	+	+	+
Tzourio (PROGRESS)[7]	**2003**	+	+	+

+ Bias, if present, is unlikely to alter the results seriously, - Bias may alter the results seriously, ? A risk of bias that raises some doubt about the results. In the PRoFESS trial, involvement of the sponsor in study design, collection, analysis and data interpretation created risk of bias. The risk of detection bias was unknown for the PRoFESS and ADVANCE trials, since the authors did not describe assessment of dementia diagnosis. The authors of the PRoFESS trial did not explain the high amount of missing patients in the dementia analyses, which raises questions about attrition bias. Some reporting bias was expected in the SCOPE and Syst-Eur trials, due to missing or incomplete protocol studies. The authors of the SHEP trial did not give a declaration of conflicts of interest which raises questions about influence of sponsors on the results of the study. Authors from the ADVANCE and preDIVA trial supplied additional data.

Detection bias	Attrition bias	Reporting bias	Other bias
Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Anything else, ideally pre-specified
+	+	+	?
?	?	+	-
+	+	?	+
?	+	+	+
+	+	+	+
+	+	?	+
+	+	+	+

Table S4. Bias assessment based on Newcastle-Ottawa quality assessment scale for observational studies

		Selection			
Author (Study)	**Publication year**	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**
Guo[8] (Kungs-holmen)	1999	A) population based cohort	A) same community	A) Prescription database/ electronic health record, verified with medication list or container brought by patient	A) nondemented, examination at baseline
in 't Veld[9] (Rotterdam)	2000	A) population based cohort	A) same community	C) Medication containers brought by patient	A) nondemented, examination at baseline
Morris[10] (EPESE)	2001	A) population based cohort	A) same community	C) Medication containers brought by patient	A) nondemented, examination at baseline
Yasar[11] (BLSA)	2005	A) population based cohort	A) same community	C) Medication containers brought by patient	A) nondemented, examination at baseline
Sink[12] (CHS)	2009	A) population based cohort	A) same community	C) Medication containers brought by patient	A) nondemented, examination at baseline
Li[13] (US Veteran Affairs)	2010	C) selected group (veterans)	A) same community	B) Electronic health record alone	B) nondemented, exclusion based on medical health record or database code

Table S4. Continued

	Comparability	Outcome			
	Comparability of cohorts on the basis of the design or analysis	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow-up of cohorts**	**Score**
	A) controls for age, sex, education, systolic BP, heart disease and stroke	A) Panel of expert clinicians using DSM-III-R, severity using CDRS	B) 2-5 years of FU	B) 9.6% lost to follow up	2
	D) no description or not adjusted	A) Panel of expert clinicians using DMS-III-R, NINCDS-ADRDA and NINDS	B) 2-5 years of FU	B) 21% lost to follow up	7
	A) controls for age, sex and level of education, interval to disease diagnosis and stratified sampling	A) Panel of expert clinicians using NINCDS-ADRDA	D) not reported	B) 32.8% lost to follow up	6
	A) controls for age, gender, education, smoking, blood pressure, and history of heart problems	A) Panel of expert clinicians using DSM-III-R and NINCDS-ADRDA	A) ≥ 5 years of FU	C) not described	4
	A) controls for age, sex, race, education level, income, smoking status, alcohol use, diabetes, coronary artery disease, serum creatinine level, serum low density lipoprotein level, 3MSE score, time-dependent depression score, time-dependent systolic BP and incident stroke and other HTN medications.	A) Panel of expert clinicians using DSM-IV, NINCDS-ADRDA and NINDS	A) ≥ 5 years of FU	B) no significant difference between different groups	3
	B) controls for age, stroke, cardiovascular disease, and diabetes.	C) Diagnosis in electronic health database	B) 2-5 years of FU	B) no significant differences between different groups	9

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Table S4. Continued

		Selection			
Author (Study)	**Publication year**	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**
Hsu[14]	2013	A) population based cohort	A) same community	B) Prescription database alone	B) nondemented, exclusion based on medical health record or database code
Yasar[15] (GEMS)	2013	A) population based cohort	A) same community	C) Medication containers brought by patient	A) nondemented, examination at baseline
Chuang[16] (Cache County)	2014	A) population based cohort	A) same community	C) Medication containers brought by patient	A) nondemented, examination at baseline
Goh[17]	2014	B) somewhat selected population based cohort (new users of ARBs or ACEi)	A) same community	B) Prescription database alone	B) nondemented, exclusion based on medical health record or database code
Hwang[18]	2016	C) selected group (from insurer system)	A) same community	B) Electronic health record alone	B) nondemented, exclusion based on medical health record or database code

	Comparability	Outcome			
	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Score
	A) controls for age, sex, history of hypertension, diabetes mellitus, CAD, hyperlipidemia, and arrhythmia.	C) Diagnosis in electronic health database	A) ≥ 5 years of FU	C) not described	6
	A) controls for age, sex, education, income, no. of vascular diseases, BMI, SBP, DBP	A) Panel of expert clinicians using DSM-IV and NINCDS-ADRDA	A) ≥ 5 years of FU	B) 26.8% lost to follow up	3
	B) controls for age, sex, education, number of APOE ε4 alleles, and smoking and drinking habits at baseline plus history of high cholesterol, diabetes, stroke, CABG, and MI	A) Panel of expert clinicians using DSM-III-R and NINCDS-ADRDA criteria	A) ≥ 5 years of FU	B) 25.7% lost to follow up	4
	A) controls for age at first prescription, sex, body mass index, smoking, alcohol use, diabetes, hypertension, heart failure, statin use, socioeconomic status, calendar year, number of consultations in last 6 months and attained age	C) Diagnosis in electronic health database	B) 2-5 years of FU	A) complete FU	6
	A) controls for age, sex, blood pressure, body mass index, income, urbanization, smoking, alcohol, coronary artery disease, hypercholesterolemia, diabetes, number of hypertensive drugs	C) Diagnosis in electronic health database	A) ≥ 5 years of FU	C) not described	8

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Table S4. Continued

		Selection			
Author (Study)	**Publication year**	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**
Tully[19] (3C study)	2016	A) population based cohort	A) same community	A) Prescription database/ electronic health record, verified with medication list or container brought by patient	A) nondemented, examination at baseline
van Middelaar[20] (PreDIVA)	2017	A) population based cohort	A) same community	B) Electronic health record alone	C) nondemented, no description
Murray[21] (IIDP)	2018	A) population based cohort	A) same community	B) Prescription database alone	B) nondemented, exclusion based on medical health record or database code
Tan[22] (SNAC-K)	2018	A) population based cohort	A) same community	A) Prescription database/ electronic health record, verified with medication list or container brought by patient	A) nondemented, examination at baseline

An adapted version of the Newcastle Ottawa Scale tailored to the research question was used to assess the quality of observational studies. Selection: Representativeness of the exposed cohort: A) population based cohort, B) somewhat selected population based cohort, C) selected group (e.g. volunteers), D) no description of the derivation of the cohort; Selection of the non-exposed cohort: A) drawn from the same community as the exposed cohort, B) drawn from a different source, C) no description of the non-exposed cohort; Ascertainment of exposure: A) prescription database/electronic health record, verified with patient (medication list / container), B) prescription database alone / electronic health record

Comparability	Outcome			
Comparability of cohorts on the basis of the design or analysis	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow-up of cohorts**	**Score**
A) controls for sex, center, education, body mass index, cardiovascular disease including stroke, hypercholesterolemia, diabetes, Center for Epidemiological Studies–Depression Scale, chronic kidney disease, APOE4, mean systolic blood pressure quartiles, mean diastolic BP quartiles, SBP and DBP variability quartiles	A) Panel of expert clinicians using DMS-IV and NINCDS-ADRDA and NINDS	A) ≥ 5 years of FU	B) 4.1% lost to follow up	1
C) controls for history of cardiovascular disease and diabetes mellitus	A) Panel of expert clinicians using DSM-IV	A) ≥ 5 years of FU	B) 2.1% lost to follow up	6
A) controls for age, gender, years of education, and relevant comorbidities and blood pressure control	A) Panel of expert clinicians using DSM-III-R and ICD-10	D) not reported	C) not described	7
A) controls for age, sex, education, history of cardiovascular disease, diabetes, hypertension, dyslipidemia, MMSE at baseline, and APOE ε4 status	A) Panel of expert clinicians using DSM-IV	A) ≥ 5 years of FU	B) 4.7% lost to follow up	1

alone, C) patient brought medication containers, D) self-report; Demonstration that outcome of interest was not present at start of study: A) nondemented, examination at baseline; B) nondemented, exclusion based on medical health record or database code; C) nondemented, no description. Comparability: Comparability of cohorts on the basis of the design or analysis: A) controls for age and blood pressure, B) controls for age or blood pressure, C) controls for other variables, D) no description or not adjusted; Outcome: Assessment of outcome: A) expert panel, B) scale used, no expert panel, C) Diagnosis in electronic health database; Was follow-up long enough for outcomes to occur: A) ≥ 5 years of FU, B) 2-5 years of FU, C) <2 years of FU, D) not reported; Adequacy of follow-up of cohorts: A) complete FU, B) percentage lost to FU, or no significant difference between different groups, C) not described.

Table S5. Inconsistency in network meta-analysis: node spitting approach

AHM treatment comparison	Number of studies providing direct evidence	Estimated treatment effect (HR) in network meta-analysis	Estimated treatment effect (HR) derived from direct evidence	Estimated treatment effect (HR) derived from indirect evidence	p-value for disagreement (direct versus indirect)
ACEi – ARB	8	1.13	1.15	0.99	0.28
ACEi – BB	7	0.99	0.98	1.04	0.67
ACEi – CCB	7	1.19	1.17	1.26	0.64
ACEi – Diuretic	7	1.06	1.05	1.07	0.89
ACEi – None-other	0	0.96	-	0.96	-
ACEi – None	4	0.71	0.67	0.73	0.60
ACEi – Other	3	0.99	1.02	0.96	0.61
ARB – BB	6	0.87	0.85	0.93	0.50
ARB – CCB	6	1.05	1.01	1.17	0.31
ARB – Diuretic	6	0.93	0.89	1.05	0.21
ARB – None-other	0	0.85	-	0.85	-
ARB – None	4	0.63	0.57	0.64	0.57
ARB - Other	2	0.87	0.94	0.82	0.28
BB – CCB	7	1.20	1.19	1.85	0.34
BB – Diuretic	8	1.07	1.08	0.92	0.63
BB – None-other	1	0.97	0.91	0.98	0.92
BB – None	4	0.72	0.82	0.66	0.14
BB – Other	2	1.00	0.97	1.01	0.82
CCB – Diuretic	8	0.89	0.89	0.77	0.65
CCB – None-other	1	0.81	0.42	0.90	0.25
CCB – None	5	0.60	0.61	0.59	0.86
CCB – Other	2	0.83	0.72	0.87	0.26
Diuretic – None-other	1	0.91	1.03	0.61	0.31
Diuretic – None	6	0.67	0.66	0.69	0.78
Diuretic – Other	2	0.93	0.79	1.00	0.14
None-other – None	0	0.74	-	0.74	-
None-other – Other	0	1.03	-	1.03	-
None - Other	0	1.39	-	1.39	-

No significant disagreement was found for direct versus indirect evidence for any of the AHM treatment comparisons. Abbreviations: AHM: antihypertensive medication; ACEi: ACE inhibitor; ARB: angiotensin II receptor blocker; BB: beta blockers; CCB: calcium channel blockers; HR: hazard ratio.

Table S6. Results of network meta-analysis of randomized controlled trials: antihypertensive medication classes and dementia risk

	vs ACE inhibitor	vs angiotensin II receptor blocker	vs calcium channel blocker	vs diuretic
ACE inhibitor	-	0.90 (0.72-1.12)	2.02 (0.81-5.07)	1.02 (0.78-1.34)
angiotensin II receptor blocker	1.11 (0.89-1.39)	-	2.25 (0.90-5.60)	1.14 (0.90-1.44)
calcium channel blocker	0.49 (0.20-1.24)	0.44 (0.18-1.11)	-	0.51 (0.20-1.28)
diuretic	0.98 (0.75-1.28)	0.88 (0.69-1.11)	1.98 (0.78-4.99)	-

Estimated treatment effects (risk ratio's [RR]) and 95% confidence intervals from the network meta-analysis. A number below 1 shows a beneficial effect of the AHM class that is listed in the row compared to the AHM class listed in the corresponding column. Treatment effects in bold: significant $p < 0.05$ (none in this table). The results of this network meta-analysis should be interpreted cautiously, because only seven studies were included, with only two comparing the same AHM classes. Interpretation is further complicated by the large heterogeneity in placebo control conditions, with varying data on how many control participants used alternative antihypertensive treatment and which class.

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Table S7. Sensitivity analysis with data from observational studies and randomized controlled trials combined

	vs ACE inhibitor	vs angiotensin II receptor blocker	vs beta blocker	vs calcium channel blocker	vs diuretic
ACE inhibitor	-	**1.13 (1.04-1.23)**	1.01 (0.91-1.13)	**1.21 (1.08-1.36)**	1.08 (0.97-1.21)
angiotensin II receptor blocker	**0.88 (0.82-0.96)**	-	0.90 (0.80-1.00)	1.07 (0.96-1.20)	0.96 (0.86-1.07)
beta blocker	0.99 (0.88-1.10)	1.12 (1.00-1.25)	-	**1.20 (1.06-1.35)**	1.07 (0.95-1.20)
calcium channel blocker	**0.82 (0.74-0.92)**	0.93 (0.83-1.05)	**0.84 (0.74-0.94)**	-	0.89 (0.79-1.01)
diuretic	0.92 (0.83-1.03)	1.04 (0.94-1.16)	0.93 (0.83-1.05)	1.12 (0.99-1.26)	-

Treatment effects, lower and upper 95% confidence intervals from direct and indirect treatment comparisons. A number below 1 shows a beneficial effect of the AHM class that is listed in the row compared to the AHM class listed in the corresponding column. Treatment effects in bold: significant $p < 0.05$. Heterogeneity: $I^2 = 24.1\%$, within designs p-value = 0.05, between designs p-value = 0.33. Number of studies included: 22, pairwise comparisons: 114, designs: 16.

Table S8. Sensitivity analyses in observational studies

Table S8a.

AHM	**Without Morris[10] (OR), TE, 95%CI**		**Without Murray[21] (outlier), TE, 95%CI**		**AHM reference categories only*, TE, 95%CI**		**All reference categories, TE, 95%CI**	
CCB	0.84	0.74 – 0.96	0.84	0.75 – 0.94	0.87	0.83 – 0.91	0.86	0.76 – 0.97
ARB	0.88	0.80 – 0.97	0.89	0.81 – 0.96	0.88	0.84 – 0.92	0.87	0.79 – 0.95
BB	1.01	0.90 – 1.15	1.01	0.90 – 1.14	0.99	0.94 – 1.04	1.02	0.91 – 1.15
Diuretic	0.94	0.83 – 1.06	0.95	0.84 – 1.06	0.98	0.93 – 1.04	0.96	0.85 – 1.08
ACEi	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-
Heterogeneity								
I^2 (%)	29.5		25.6		0		21.7	
Between designs (p-value)	0.38		0.35		0.90		0.75	
Within designs (p-value)	0.02		0.047		0.50		0.02	
Characteristics								
Number of studies	14		14		11		11	
Number of pairwise comparisons	104		92		70		103	
Number of designs	10		11		5		7	

Estimates of treatment effects in hazard ratios with 95% confidence intervals. Sensitivity analyses conducted: Morris (OR): leaving out Morris e.a.[10] because treatment effect was calculated as an odds ratio instead of hazard ratio, Murray[21] (outlier): left out because this study was a clear outlier in the comparison of beta blockers versus diuretics, only AHM reference categories: only AHM class reference categories were included in analysis, all reference categories: analysis with the same studies included in "only AHM reference categories", but now all reference categories are included. * When including only AHM class reference categories in analysis, heterogeneity completely disappeared. Repeated analyses with again all reference categories included, caused heterogeneity to rise up to 22.7%, with similar treatment effects. Therefore, it was highly plausible that heterogeneity could be attributed to the large variety in the constitution of the "none" and "other" comparator groups. Abbreviations: CCB: Calcium channel blocker; ARB: Angiotensin II receptor blocker; BB: Beta blocker; ACEi: ACE-inhibitor; TE: treatment effect; 95%CI: 95% confidence interval; RCT: randomized controlled trial; obs.: observational studies.

Table S8b.

AHM	Outcome Alzheimer's disease†, TE, 95%CI		Outcome All-cause‡, TE, 95%CI		Inclusion method Clinical§, TE, 95%CI		Inclusion method Codes¶, TE, 95%CI		Follow-up <5.62 yr#, TE, 95%CI		Follow-up >5.62 yr**, TE, 95%CI	
CCB	0.87	0.57 – 1.31	0.84	0.75 – 0.94	0.74	0.59 – 0.92	0.87	0.82 – 0.93	1.07	0.50 – 2.29	0.82	0.69 – 0.98
ARB	0.98	0.71 – 1.35	0.87	0.79 – 0.94	0.72	0.53 – 0.99	0.88	0.84 – 0.93	0.88	0.82 – 0.93	0.83	0.69 – 1.01
BB	1.01	0.68 – 1.50	1.00	0.89 – 1.13	1.07	0.87 – 1.31	0.99	0.93 – 1.05	1.66	0.82 – 3.33	1.01	0.85 – 1.20
Diuretic	0.85	0.58 – 1.24	0.96	0.85 – 1.07	0.84	0.69 – 1.02	0.99	0.92 – 1.06	1.35	0.75 – 2.46	0.90	0.76 – 1.07
ACEi	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-
Heterogeneity												
I^2 (%)	0		24.9		0.3		8.2		0		32.7	
Between designs (p-value)	0.47		0.59		0.88		0.76		0.93		0.48	
Within designs (p-value)	-		0.04		0.10		0.047		0.047		0.01	
Characteristics												
Number of studies	5		10		10		5		7		7	
Number of pairwise comparisons	30		77		79		28		25		67	
Number of designs	5		7		8		4		6		6	

Estimates of treatment effects in hazard ratios with 95% confidence intervals. Sensitivity analyses conducted: Outcome: Alzheimer's disease or all-cause dementia reported as outcome, Inclusion method: patients included based on clinical evaluation or database codes and duration of follow-up: dichotomized based on duration of follow-up. † Studies included; Chuang, Hsu, Morris, Yasar 2005&2013; ‡ studies included: Goh, Guo, Hwang, Veld, Li, Murray, Sink, Tan, Tully, van Middelaar; § Studies included: Chuang, Guo, Veld, Morris, Sink, Tan, Tully, van Middelaar, Yasar 2005&2013; ¶ Studies included: Goh, Hsu, Hwang, Li, Murray; # Studies included: Veld, Li, Guo, Morris, Goh, Tan, Hsu; ** Studies included: Sink, Yasar 2005&2013, van Middelaar, Chuang, Tully, Hwang Abbreviations: CCB: Calcium channel blocker; ARB: Angiotensin II receptor blocker; BB: Beta blocker; ACEi: ACE-inhibitor; TE: treatment effect; 95%CI: 95% confidence interval.

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Table S8c.

AHM	Adjustment Yes††, TE, 95%CI		Adjustment No‡‡, TE, 95%CI	
CCB	0.76	0.58 – 0.99	0.81	0.61 – 1.08
ARB	0.93	0.86 – 1.00	0.91	0.77 – 1.08
BB	0.96	0.76 – 1.22	0.95	0.72 – 1.24
Diuretic	0.79	0.62 – 1.00	0.84	0.64 – 1.10
ACEi	1 (ref.)		1 (ref.)	
Heterogeneity				
I^2 (%)	0		34.4	
Between designs (p-value)	0.47		0.12	
Within designs (p-value)	-		-	
Characteristics				
Number of studies	6		6	
Number of pairwise comparisons	43		43	
Number of designs	6		6	

Sensitivity analyses in observational studies: Estimates of treatment effects in hazard ratios with 95% confidence intervals. Sensitivity analyses conducted: adjustment: separate analyses of unadjusted and adjusted data from studies that presented results of both analyses. †† Studies included: Chuang, Goh, Hsu, Sink, van Middelaar, Yasar 2013; ‡‡ Studies included: Chuang, Goh, Hsu, Sink, van Middelaar, Yasar 2013. Abbreviations: CCB: Calcium channel blocker; ARB: Angiotensin II receptor blocker; BB: Beta blocker; ACEi: ACE-inhibitor; TE: treatment effect; 95%CI: 95% confidence interval.

Table S9. Leave-one-out analyses observational studies

Table S9a.

Antihypertensive treatment	Reference category	Minimum treatment effect, 95%CI; I^2	Leaving out	Maximum treatment effect,95%CI; I^2	Leaving out
Calcium channel blocker	ACE inhibitor	0.78 (0.62 – 0.97); I^2: 26.46%	Hwang[18]	0.86 (0.77 – 0.97); I^2: 24.01%	van Middelaar[20]
Angiotensin II receptor blocker	ACE inhibitor	0.86 (0.79 – 0.94); I^2: 19.95%	Hsu[14]	0.91 (0.82 – 1.00); I^2: 23.12%	Li[13]
Beta blocker	ACE inhibitor	0.99 (0.92 – 1.06); I^2: 6.15%	Tully[19]	1.06 (0.86 – 1.31); I^2: 26.46%	Hwang[18]
Diuretic	ACE inhibitor	0.88 (0.72 – 1.07); I^2: 26.46%	Hwang[18]	0.98 (0.91 – 1.06) I^2: 6.15%	Tully[19]

Summary of analyses in which alternately one study is excluded. This table shows the minimum and maximum treatment effect and the study left out in these analyses. We used ACE inhibitor as reference category in leave-one-out analyses since this antihypertensive medication class was associated with the highest dementia risk in most analyses.

Table S9b.

Heterogeneity	Leaving out
Minimum I^2: 6.15%	Tully[19]
Maximum I^2: 33.43%	Tan[22]

Minimum and maximum heterogeneity, and the study left out in analyses.

Table S10. Sensitivity analyses in observational studies: Quality assessment

Table S10a.

AHM	**Quality assessment Selection**				**Quality assessment Comparability**				**Quality assessment Outcome**			
	Good[*]		**Poor[†]**		**Good[‡]**		**Poor[§]**		**Good[¶]**		**Poor[#]**	
CCB	0.74	0.54 – 1.02	0.86	0.81 – 0.90	0.89	0.78 – 1.02	0.74	0.52 – 1.05	0.75	0.59 – 0.97	0.87	0.83 – 0.92
ARB	0.92	0.74 – 1.13	0.86	0.82 – 0.91	0.92	0.83 – 1.02	0.80	0.73 – 0.88	0.74	0.53 – 1.03	0.88	0.84 – 0.93
BB	1.12	0.84 – 1.50	0.98	0.92 – 1.03	1.05	0.92 – 1.20	1.01	0.72 – 1.40	1.09	0.87 – 1.37	0.99	0.94 – 1.04
Diuretic	0.89	0.68 – 1.17	0.97	0.91 – 1.04	1.00	0.88 – 1.14	0.82	0.59 – 1.13	0.82	0.65 – 1.02	0.99	0.94 – 1.05
ACEi	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-
Heterogeneity												
I^2 (%)	30.3		0		24.7		0		11		0	
Between designs (p-value)	0.37		0.54		0.66		0.70		0.80		0.79	
Within designs (p-value)	0.08		-		0.049		-		0.10		0.47	
Characteristics												
Number of studies	7		8		11		4		6		7	
Number of pairwise comparisons	63		44		78		29		71		32	
Number of designs	5		8		8		4		4		6	

Estimates of treatment effects in hazard ratios with 95% confidence intervals. Sensitivity analyses conducted: quality assessment: dichotomized for selection, comparability and outcome. Studies included: [*] Goh, Guo, Hsu, van Middelaar, Murray, Tan, Tully; [†] Studies included: Chuang, Hwang, Li, Morris, Sink, Veld, Yasar 2005 & 2013; [‡] Studies included: Goh, Guo, Hsu, Hwang, Morris, Murray, Sink, Tan, Tully, Yasar 2005 & 2013; [§] Studies included: Chuang, Li, van Middelaar, Veld; [¶] Studies included: Chuang, Sink, Tan, Tully, van Middelaar, Yasar 2013; [#] Studies included: Goh, Guo, Hsu, Hwang, Li, Morris, Murray.

Table S10b.

AHM	Quality assessment Overall Good**, TE, 95%CI		Quality assessment Overall Poor††, TE, 95%CI	
CCB	0.83	0.62 – 1.11	0.85	0.75 – 0.97
ARB	0.84	0.55 – 1.27	0.88	0.81 – 0.97
BB	1.17	0.90 – 1.52	0.97	0.85 – 1.10
Diuretic	0.86	0.67 – 1.11	0.98	0.86 – 1.11
ACEi	1 (ref.)	-	1 (ref.)	-
Heterogeneity				
I^2 (%)	15.8		33	
Between designs (p-value)	0.87		0.20	
Within designs (p-value)	0.10		0.047	
Characteristics				
Number of studies	7		8	
Number of pairwise comparisons	58		49	
Number of designs	5		7	

Estimates of treatment effects in hazard ratios with 95% confidence intervals. Sensitivity analyses conducted: quality assessment: dichotomized for overall quality assessment. Studies included: ** Studies included (score): Tan (1), Tully (1), Guo (2), Sink (3), Yasar (3), Chuang (4), Yasar (4); †† Studies included (score): Goh (6), Hsu (6), Morris (6), van Middelaar (6), Murray (7), Veld (7), Hwang (8), Li (9)

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Table S11. Sensitivity analysis including two-stage individual participant data meta-analysis

Table S11a.

	vs ACE inhibitor	vs angiotensin II receptor blocker	vs beta blocker	vs calcium channel blocker	vs diuretic
ACE inhibitor	-	**1.13 (1.07-1.20)**	1.01 (0.94-1.08)	**1.15 (1.07-1.23)**	1.02 (0.94-1.10)
angiotensin II receptor blocker	**0.88 (0.83-0.93)**	-	**0.89 (0.83-0.95)**	1.01 (0.95-1.08)	**0.90 (0.84-0.97)**
beta blocker	0.99 (0.92-1.06)	**1.12 (1.05-1.20)**	-	**1.14 (1.07-1.22)**	1.01 (0.94-1.09)
calcium channel blocker	**0.87 (0.81-0.94)**	0.99 (0.92-1.06)	**0.88 (0.82-0.94)**	-	**0.89 (0.83-0.95)**
diuretic	0.98 (0.91-1.06)	**1.11 (1.03-1.20)**	0.99 (0.92-1.06)	**1.13 (1.05-1.21)**	-

Sensitivity analysis including recently published individual participant data meta-analysis: Ding et al. Lancet Neurology (2019).[23] Combined effect sizes were used for AHM classes versus 'other AHM class-users' since individual estimates were unavailable. Two studies included in our main analysis were excluded from this analysis because they were included in the individual participant data meta-analysis.[9,19] Treatment effects, lower and upper 95% confidence intervals from direct and indirect treatment comparisons. A number below 1 shows a beneficial effect of the AHM class that is listed in the row compared to the AHM class listed in the corresponding column. Treatment effects in bold: significant $p < 0.05$. Heterogeneity: $I^2 = 7.2\%$, within designs p-value = 0.16, between designs p-value = 0.65. Number of studies included: 14, pairwise comparisons: 104, designs: 10.

Table S11b.

	vs ACE inhibitor	vs angiotensin II receptor blocker	vs beta blocker	vs calcium channel blocker	vs diuretic
ACE inhibitor	-	**1.15 (1.01-1.31)**	0.98 (0.83-1.14)	**1.19 (1.01-1.41)**	1.05 (0.90-1.23)
angiotensin II receptor blocker	**0.87 (0.76-0.99)**	-	0.85 (0.72-1.00)	1.03 (0.87-1.23)	0.91 (0.77-1.07)
beta blocker	1.02 (0.87-1.20)	1.18 (1.00-1.40)	-	**1.22 (1.03-1.45)**	1.08 (0.91-1.27)
calcium channel blocker	**0.84 (0.71-0.99)**	0.97 (0.81-1.15)	**0.82 (0.69-0.97)**	-	0.88 (0.74-1.04)
diuretic	0.95 (0.82-1.11)	1.10 (0.93-1.29)	0.93 (0.79-1.09)	1.14 (0.96-1.34)	-

Sensitivity analysis including previously unpublished observational cohorts from a recently published individual participant data meta-analysis: Peters et al. Neurology (2020).[24] We used effect sizes for AHM classes versus 'non-users' for each contributing study separately. Treatment effects, lower and upper 95% confidence intervals from direct and indirect treatment comparisons. A number below 1 shows a beneficial effect of the AHM class that is listed in the row compared to the AHM class listed in the corresponding column. Treatment effects in bold: significant $p < 0.05$. Heterogeneity: $I^2 = 38\%$, within designs p-value = 0.06, between designs p-value = 0.002. Number of studies included: 22, pairwise comparisons: 189, designs: 13.

Table S12. Adjustments in included observational studies

Study (year)	Effect size	Analyses adjusted for covariates:
Chuang (2014)[16]	HR	age, sex, education, number of APOE E4 alleles, smoking and drinking habits at baseline, history of high cholesterol, diabetes, stroke, Coronary Artery Bypass Grafting and myocardial infarction
Goh (2014)[17]	HR	age at first prescription for ARB or ACEi, sex, body mass index, smoking status, alcohol use, diabetes, hypertension, heart failure, statin use, socioeconomic status, calendar year, number of consultations in last 6 months and attained age (time-updated variable)
Guo (1999)[8]	HR	age, sex, education, systolic blood pressure, heart disease and stroke
Hsu (2012)[14]	HR	age, sex, history of hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, and arrhythmia.
Hwang (2016)[18]	HR	age, sex, blood pressure, body mass index, income, urbanization, smoking, alcohol, coronary artery disease, hypercholesterolemia, diabetes, number of hypertensive drugs
Li (2010)[13]	HR	age, stroke, cardiovascular disease, and diabetes
Morris (2001)[10]	OR	age, sex and level of education, interval to disease diagnosis and stratified sampling
Murray (2018)[21]	HR	age, gender, years of education, and relevant comorbidities
Sink (2009)[12]	HR	age, sex, race, education level, income, smoking status, alcohol use, diabetes, coronary artery disease, serum creatinine level, serum low density lipoprotein level, Modified Mini-Mental State Examination score, time-dependent depression score, time-dependent systolic blood pressure, incident stroke and other antihypertensive medications
Tan (2018)[22]	HR	age, sex, education, history of cardiovascular disease, diabetes, hypertension, dyslipidemia, Mini-Mental State Examination score at baseline, and APOE E4 status, number and dose of antihypertensive medication
Tully (2016)[19]	HR	sex, center, education, body mass index, cardiovascular disease including stroke, hypercholesterolemia, diabetes, Center for Epidemiological Studies–Depression Scale, chronic kidney disease, APOE E4, mean systolic blood pressure quartiles, and mean diastolic blood pressure quartiles
van Middelaar (2017)[20]	HR	history of cardiovascular disease and diabetes mellitus
Yasar (2005)[11]	HR	gender, education, smoking, diastolic blood pressure, systolic blood pressure and history of heart problems
Yasar (2013)[15]	HR	age, sex, education, income, no. of vascular diseases, body mass index, diastolic blood pressure and systolic blood pressure

To minimize bias due to confounding by indication, maximally adjusted data were used in our main analyses. Abbreviations: ACEi: ACE inhibitor; ARB: angiotensin II receptor blocker; APOE E4: apolipoprotein E E4 allele.

Table S13. Subgroup analyses in observational studies

Table S13a.

AHM	Age <74.7 yr*, TE, 95%CI		Age >74.7 yr†, TE, 95%CI		Sex (% women) <58.2%‡, TE, 95%CI		Sex (% women) >58.2%§, TE, 95%CI		Coronary artery disease <19%¶, TE, 95%CI		Coronary artery disease >19%#, TE, 95%CI	
CCB	0.87	0.83 – 0.91	0.91	0.62 – 1.33	0.85	0.77 – 0.95	0.85	0.57 – 1.25	0.89	0.83 – 0.94	0.85	0.57 – 1.27
ARB	0.88	0.84 – 0.92	0.83	0.53 – 1.29	0.88	0.82 – 0.96	0.89	0.56 – 1.41	0.91	0.85 – 0.97	0.54	0.22 – 1.31
BB	0.99	0.94 – 1.04	1.20	0.84 – 1.72	0.98	0.88 – 1.09	1.20	0.83 – 1.74	1.01	0.95 – 1.07	0.87	0.59 – 1.30
Diuretic	0.98	0.93 – 1.05	0.97	0.69 – 1.36	0.96	0.86 – 1.07	0.96	0.69 – 1.35	1.01	0.94 – 1.08	0.78	0.53 – 1.14
ACEi	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-
Heterogeneity												
I^2 (%)	0		36.9		26.7		22.7		0		0	
Between designs (p-value)	0.81		0.59		0.28		0.86		0.67		0.78	
Within designs (p-value)	0.47		0.049		0.047		0.08		-		-	
Characteristics												
Number of studies	7		7		8		7		4		3	
Number of pairwise comparisons	43		63		54		53		27		28	
Number of designs	6		4		7		5		4		3	

Subgroup analyses of potential moderators, stratified according to dichotomization at the median. * Studies included: Goh, Hwang, Veld, Morris, Li, van Middelaar, Chuang; † Studies included: Sink, Murray, Tully, Yasar 2005&2013, Guo, Tan; ‡ Studies included: Li, Yasar 2005&2013, Goh, Hsu, van Middelaar, Hwang, Chuang; § Studies included: Veld, Tully, Morris, Sink, Tan, Murray, Guo; ¶ Studies included: Hsu, Yasar 2013, Sink, Hwang; # Studies included: Chuang, Morris, Murray. Abbreviations: AHM: antihypertensive medication; ACEi: ACE inhibitor; ARB: angiotensin II receptor blocker; BB: beta blockers; CCB: calcium channel blockers

Table S13. Subgroup analyses in observational studies

Table S13a.

AHM	Age <74.7 yr[*], TE, 95%CI		Age >74.7 yr[†], TE, 95%CI		Sex (% women) <58.2%[‡], TE, 95%CI		Sex (% women) >58.2%[§], TE, 95%CI		Coronary artery disease <19%[¶], TE, 95%CI		Coronary artery disease >19%[#], TE, 95%CI	
CCB	0.87	0.83 – 0.91	0.91	0.62 – 1.33	0.85	0.77 – 0.95	0.85	0.57 – 1.25	0.89	0.83 – 0.94	0.85	0.57 – 1.27
ARB	0.88	0.84 – 0.92	0.83	0.53 – 1.29	0.88	0.82 – 0.96	0.89	0.56 – 1.41	0.91	0.85 – 0.97	0.54	0.22 – 1.31
BB	0.99	0.94 – 1.04	1.20	0.84 – 1.72	0.98	0.88 – 1.09	1.20	0.83 – 1.74	1.01	0.95 – 1.07	0.87	0.59 – 1.30
Diuretic	0.98	0.93 – 1.05	0.97	0.69 – 1.36	0.96	0.86 – 1.07	0.96	0.69 – 1.35	1.01	0.94 – 1.08	0.78	0.53 – 1.14
ACEi	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-
Heterogeneity												
I^2 (%)	0		36.9		26.7		22.7		0		0	
Between designs (p-value)	0.81		0.59		0.28		0.86		0.67		0.78	
Within designs (p-value)	0.47		0.049		0.047		0.08		-		-	
Characteristics												
Number of studies	7		7		8		7		4		3	
Number of pairwise comparisons	43		63		54		53		27		28	
Number of designs	6		4		7		5		4		3	

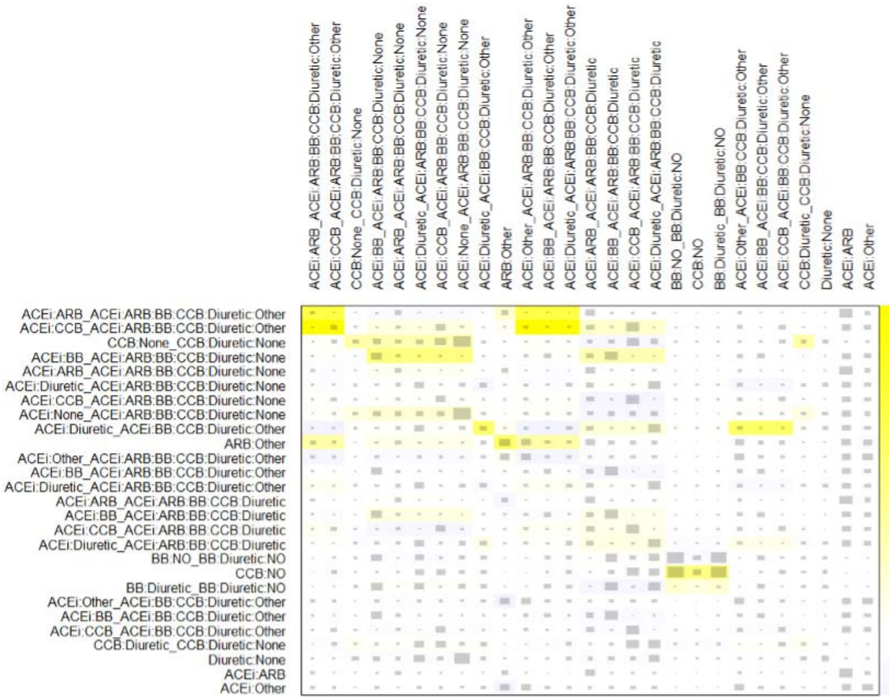
Subgroup analyses of potential moderators, stratified according to dichotomization at the median. [*] Studies included: Goh, Hwang, Veld, Morris, Li, van Middelaar, Chuang; [†] Studies included: Sink, Murray, Tully, Yasar 2005&2013, Guo, Tan; [‡] Studies included: Li, Yasar 2005&2013, Goh, Hsu, van Middelaar, Hwang, Chuang; [§] Studies included: Veld, Tully, Morris, Sink, Tan, Murray, Guo; [¶] Studies included: Hsu, Yasar 2013, Sink, Hwang; [#] Studies included: Chuang, Morris, Murray. Abbreviations: AHM: antihypertensive medication; ACEi: ACE inhibitor; ARB: angiotensin II receptor blocker; BB: beta blockers; CCB: calcium channel blockers

Table S13b.

AHM	Heart failure <7.5%[**], TE, 95%CI		Heart failure >7.5%[††], TE, 95%CI		Stroke <6.18%[‡‡], TE, 95%CI		Stroke >6.18%[§§], TE, 95%CI		Diabetes mellitus <17.1%[¶¶], TE, 95%CI		Diabetes mellitus >17.1%[##], TE, 95%CI	
CCB	1.39	0.68 – 2.83	0.82	0.45 – 1.49	1.10	0.68 – 1.77	0.77	0.55 – 1.07	1.25	0.75 – 2.10	0.82	0.71 – 0.96
ARB	0.92	0.85 – 1.00	0.80	0.42 – 1.55	0.58	0.30 – 1.12	0.88	0.82 – 0.93	0.93	0.86 – 1.00	0.83	0.73 – 0.95
BB	1.31	0.69 – 2.47	1.03	0.57 – 1.86	0.92	0.56 – 1.49	1.12	0.83 – 1.52	1.54	0.97 – 2.45	1.00	0.86 – 1.16
Diuretic	1.15	0.61 – 2.17	0.84	0.47 – 1.50	1.09	0.71 – 1.68	0.77	0.58 – 1.01	1.41	0.93 – 2.15	0.91	0.79 – 1.07
ACEi	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-
Heterogeneity												
I^2 (%)	0		65.9		0		0		0		33.2	
Between designs (p-value)	0.40		-		0.44		0.92		0.82		0.50	
Within designs (p-value)	-		-		0.96		0.047		0.57		0.01	
Characteristics												
Number of studies	3		2		5		5		7		6	
Number of pairwise comparisons	17		30		37		28		39		66	
Number of designs	3		1		4		4		6		5	

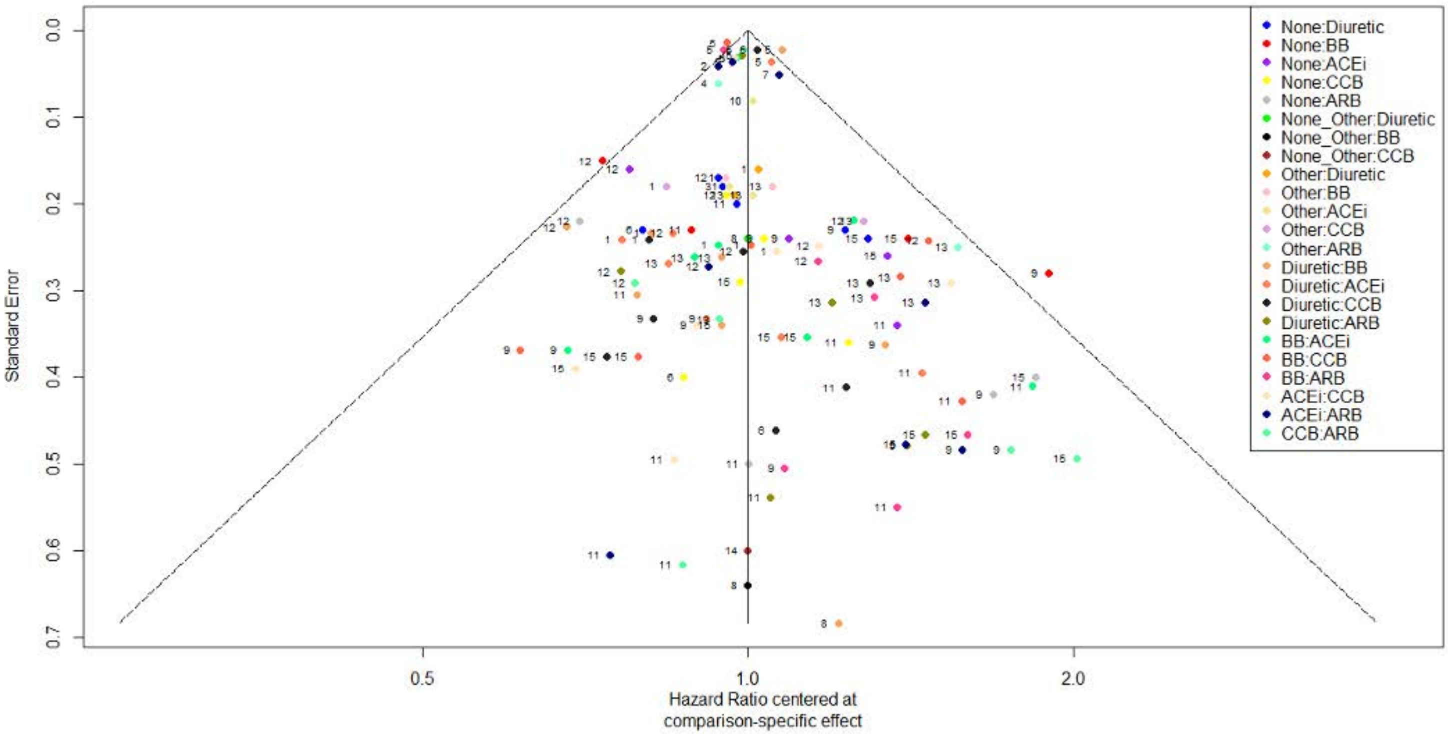
Subgroup analyses of potential moderators, stratified according to dichotomization at the median. [**] Studies included: Yasar 2013, Hsu, Goh; [††] Studies included: Tully, Murray; [‡‡] Studies included: Yasar 2013, Veld, Morris, Sink, Murray; [§§] Studies included: Tully, Goh, Guo, Li, Chuang; [¶¶] Studies included: Goh, Yasar 2013, Tan, Veld, Morris, Hsu, Sink; [##] Studies included: Tully, Hwang, Chuang, van Middelaar, Murray, Li. Abbreviations: AHM: antihypertensive medication; ACEi: ACE inhibitor; ARB: angiotensin II receptor blocker; BB: beta blockers; CCB: calcium channel blocker

Figure S1. Net heat plot of main analysis observational studies



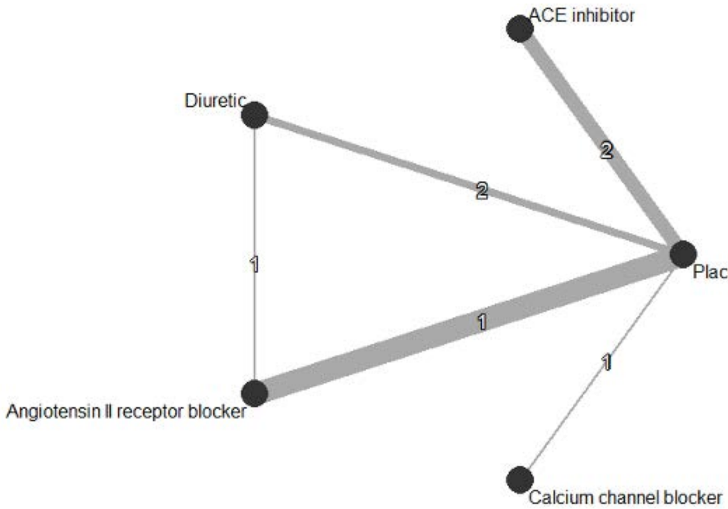
The rows and columns indicate the treatments compared within included studies (e.g. ARB: Other = ARB versus other AHM). Treatment comparisons in multi-arm studies are indicated by "_" followed by all treatments in the multi-arm study. The size of the grey squares represents the contribution from the treatment comparison in the column to the treatment comparison in the row. Grey squares on the diagonal line from the left upper corner to the right lower corner represent direct evidence. The other grey squares indicate sources of additional indirect evidence. Yellow, orange and red colors on the diagonal line indicate sources of heterogeneity between treatment comparisons (in order of severity, orange and red colored squares not visible in this plot). The other yellow colored squares indicate that evidence for the treatment comparison in the row, from the comparison in the column has some inconsistency with other evidence. As shown on the right side of the table: the darker the color, the more inconsistency.[25] Direct treatment comparisons were one of the largest sources of information for most treatment comparisons, and heterogeneity and inconsistency in the network could not be attributed to one specific treatment comparison.

Figure S2. Comparison-adjusted funnel plot for main analysis of observational studies



The figures represent a comparison of two antihypertensive classes. We ordered the antihypertensive medication classes from 'old' to 'new' based on year of introduction. Study number legend: 1. Chuang (2014)[16]; 2. Goh (2014)[17]; 3. Guo (1999)[8]; 4. Hsu (2012)[14]; 5. Hwang (2016)[18]; 6. Veld (2001)[9]; 7. Li (2010)[13]; 8. Morris (2001)[10]; 9. Murray (2018)[21]; 10. Sink (2009)[12]; 11. Tan (2018)[22]; 12. Tully (2016)[19]; 13. van Middelaar (2017)[20]; 14. Yasar (2005)[11]; 15. Yasar (2013)[15].

Figure S3. Network graph: antihypertensive medication classes and dementia risk in randomized controlled trials



[1-7] Heterogeneity: I2 = 0%, within designs p-value = 0.92, between designs p-value = 0.94. within designs p-value = 0.92, between designs p-value = 0.94. Number of studies included: 7, pairwise comparisons: 7, designs: 5. In some trials, a part of the participants in both the intervention and placebo groups used additional antihypertensive classes.

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5

Year-by-year blood pressure variability from midlife to death and lifetime dementia risk

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Abstract

Importance: High visit-to-visit systolic blood pressure variability (BPV) in late-life may reflect increased dementia risk better than mean systolic blood pressure (SBP). Evidence from midlife to late-life could be crucial to understanding this relationship.

Objective: Determine whether BPV at different ages during life is differentially associated with lifetime dementia risk.

Design: Prospective cohort supplemented with detailed medical archive data from age 50 upwards.

Setting: Population-based

Participants: Adult Changes in Thought (ACT) autopsy sub-study participants, without dementia and aged ≥65 at enrollment, with midlife to late-life BP data from Kaiser Permanente Washington medical archives, collected as part of the post-mortem brain donation program. In ACT, participants underwent biennial medical assessments, including cognitive screening. Data were collected from 1994 (ACT enrollment) through November 2019 (dataset freeze). BP data spanned back to 1953.

Exposures: Year-by-year BPV at ages 60, 70, 80 and 90 years, calculated using the coefficient of variation of year-by-year SBP measurements over the preceding 10 years.

Main outcomes: All-cause dementia adjudicated by a multidisciplinary outcome adjudication committee.

Results: We studied 820 participants (42% men), over a mean of 31.5 years (SD=9.0), with 28.35 (SD=8.4) yearly SBP measurements per person (26,435 person years). 365 (45%) developed dementia. Numbers of participants alive without dementia available for analysis ranged from 280 (age 90) to 702 (age 70). Higher BPV was not associated with higher lifetime dementia risk at age 60 (HR=0.97, 95%CI=0.85-1.11), 70 (HR=0.91 95%CI=0.80-1.02) or 80 (HR=1.02, 95%CI=0.89-1.16). At age 90, BPV was associated with higher dementia risk (HR=1.35 per SD, 95%CI=1.02-1.79). Meta-regression of HRs calculated separately for each age from 60-90, indicated that associations of high BPV with higher dementia risk were only present at higher ages, while the association for SBP with dementia gradually shifted direction linearly from positive to negative with higher ages.

Conclusions and relevance: In this cohort study of community-dwelling older people, high BPV indicated increased life-time dementia risk in very advanced old-age, but not in midlife. Results suggest that high BPV may indicate increased dementia risk in very old age but might be less viable as a midlife dementia prevention target.

Introduction

Midlife hypertension is associated with higher dementia risk.[1-3] Blood pressure (BP) lowering may decrease dementia risk.[4-5] However, the relationship between BP and dementia remains ill-understood. With older age, the relationship seems to dissipate or even reverse, with hypertensive individuals having lower dementia risk.[6] Investigating BP fluctuation may help understanding this relationship.[7]

High visit-to-visit BP variability (BPV), with months to years between consecutive measurements, is associated with increased risk of cardiovascular disease and mortality.[8-10] Studies assessing the association between BPV and dementia are heterogeneous, and mostly consider late-life BPV.[11-14] Studies investigating mid- to late-life BPV had inconsistent results.[15-17] Whether associations are age-dependent, like for mean BP, is unknown.[18] A recent meta-analysis predominantly including older populations suggested that high BPV may contribute more to dementia risk than high BP itself.[19] Since the relation between hypertension and dementia risk apparently diminishes with age, this finding may be age-dependent, BPV becoming particularly important in later life.

Several other factors require consideration to understand the inconsistent and possibly age-dependent results. First, younger populations require protracted follow-up to investigate dementia risk, because dementia mainly occurs in old-age. Second, competing risk of death may be crucial, because individuals with high BPV may not survive until age ranges wherein dementia commonly manifests. Third, the underlying mechanism is unknown, and might reflect reverse causality. For example, higher BPV may reflect extensive vascular damage, or neurodegeneration interfering with autonomic control. If so, BPV will mostly predict short-term dementia risk especially in late-life.

We studied whether visit-to-visit BPV at different ages from 50 to 90 years old is differentially associated with lifetime incident dementia risk, in community-dwelling individuals, followed from midlife to death. Moreover, we compared these associations to those for mean BP at the same ages, and examined the potential influence of competing risk of death and follow-up duration.

Methods

Population

The Adult Changes in Thought (ACT) study is a population-based prospective cohort study focusing on brain aging and incident dementia. Community-dwelling individuals without dementia aged ≥65 years were randomly sampled from Kaiser Permanente Washington (KPW, formerly Group Health Cooperative), an integrated healthcare system (Seattle area, USA). Individuals were included in three stages: n=2,581 enrolled from 1994-1996, n=811 from 2000-2002, and continuous enrolment (n~2000) compensating for attrition since 2004. Participants underwent medical assessment at baseline and subsequent two-yearly visits.[20] Race and ethnic group were self-reported.

We included ACT participants who underwent brain autopsy after death, having provided consent during the study. Of these participants specifically, detailed data on BP and medical history from midlife onwards were retrospectively collected from KPW medical archives, complementing ACT's prospective data. To ensure high data-quality, this was done manually, by extensively trained research staff, following a strict protocol, with regular supervision meetings (Methods S1).

The University of Washington and KPW institutional review boards approved this study. All participants provided written informed consent. The ACT cohort is described in detail at https://actagingresearch.org/resources/act-cohort. This study followed the STROBE reporting guidelines for observational cohort studies.[21]

Blood pressure variability

We included one SBP measurement per participant per year from age 50 upwards, based on KPW records. Age was based on birthyear, not birthdate. SBP measurements were examinations during consultations following standard clinical practice. At KPW, BP is routinely measured and recorded at medical visits, typically at least annually, making year-by-year BP data readily available. Per participant, up to 3 measurements could be available per calendar year, one per block from January-April, May-August, and September-December. Having many measurements per year might indicate frequent clinical visits, and thereby possibly more frequent/severe disease. To ensure homogeneous exposure definition, if multiple measurements were recorded within a calendar year, we only used one (the earliest), approximating year-by-year BP measurements.

Visit-to-visit BPV was calculated using the SBP's coefficient of variation: (SD/mean)*100. This measure accounts for variability increasing with higher SBP, and is most commonly used, optimizing comparability to previous studies.[22] Visit-to-visit BPV was calculated per age-decade (e.g. age 50-59) for each participant. Individuals with <3 SBP measurements available within an age-decade were excluded from analyses concerning that decade.

Dementia

At each ACT visit, the Cognitive Abilities Screening Instrument (CASI) was administered.[23] Participants scoring <86 points underwent full dementia evaluation, including physical and neurological examination, neuropsychological testing, and review of medical records, available laboratory testing and imaging results. An outcome adjudication committee including physicians, a neuropsychologist and a research nurse reviewed results. Dementia was diagnosed using DSM-IV.[24] Participants with dementia were followed-up one year after initial diagnosis to verify diagnoses. Details are described elsewhere.[25]

Covariates

For stroke, myocardial infarction (MI), and diabetes, the age at first diagnosis was derived from KPW records, and secondarily by the self-reported age of first occurrence according to the ACT dataset. Education, *APOE*-genotype, smoking status, and age of smoking cessation were collected at ACT baseline.

Statistical analysis

We performed Cox regression with standardized visit-to-visit BPV over 10-year age-decades (age 50-59, 60-69, 70-79 and 80-89) as predictor in separate models. Censoring-age was used as timescale, with ACT baseline age as time-of-entry, because participants were without dementia at baseline. Here, the association between BPV and age at dementia diagnosis is the primary interest, and the instantaneous failure rate does not depend on enrollment date, hence patients enter the risk-set at the study inclusion age. For each analysis, we only included individuals who survived without dementia throughout the BPV period. Thereby, for example, the association for BPV from 60-69 reflects the estimated hazard ratio (HR) for dementia-free individuals aged 70, during their remaining lifetime, according to their BPV over the preceding decade (Figure S1).

Model one adjusted for sex and mean SBP. Model two additionally adjusted for education (years), smoking, *APOE*-genotype (0 vs. ≥1 ε4 allele), stroke, MI, and diabetes, as risk-factors for dementia and/or elevated BPV.[1,26] Stroke, MI, diabetes, and smoking were coded categorically per BPV period as: absent (reference), new (first occurrence during BPV period), or prevalent (first occurrence before

BPV period). Individuals with missing values were left out per analysis (i.e. if they had missing values in variables relevant for that analysis). Proportional hazard assumptions were checked using Schoenfeld residuals.

Competing risk of death was evaluated using a cause-specific hazard approach, repeating analyses for the outcomes mortality, and dementia/mortality combined. This is appropriate, because we aimed to study the etiological relation between BPV and dementia risk, not to predict cumulative dementia incidence (which would justify a sub-distribution hazard approach like Fine-Gray's).[27]

To compare associations for BPV to those for mean SBP, analyses were repeated with mean SBP per age-decade as predictor, adjusted for BPV. Subgroup analyses were performed for antihypertensive medication (AHM) use (ever vs never during life) because AHM may influence BPV,[28] and for SBP (above/below median) because low SBP may precede dementia and influence BPV.[29,30]

We conducted several sensitivity analyses. First, to investigate potential survivor effects from individuals only available at older ages, we repeated the main analyses excluding participants without BPV available in the 50-59 period. Second, to examine reverse causality, which is more likely if associations are especially short-term, we repeated analyses stratified according to follow-up time (both <5 versus ≥5 years, and split-up by median time to dementia). Third, to investigate whether cardiovascular events influenced associations between BPV and dementia, we repeated analyses excluding individuals with stroke or MI ever during their lifetime Fourth, to evaluate whether selection of autopsy participants influenced results, we repeated analyses accounting for differences between the analytic sample and the full ACT cohort using inverse probability weighting (Methods S2).[31] Fifth, to investigate whether delay between the index age and ACT baseline influenced results, which it should not because we used the ACT baseline age as time-of-entry, we repeated analyses only including individuals who had attended ACT baseline at/before the index age. Sixth, we repeated analyses with 10-year BPV calculated using all available BP measurements per individual per calendar year (i.e. up to 3), adjusted for the number of measurements used to calculate that 10-year BPV. All subgroup and sensitivity analyses used the fully adjusted model.

To further examine the potential age-dependency of the associations of BPV and SBP with incident dementia, we calculated HRs for BPV and mean SBP over the preceding decade at each age from 60 to 90 separately, identically as for ages 60, 70, 80 and 90 in the main analyses. We then performed meta-regression of HRs on age, using an empirical Bayesian mixed effects model,[32] inversely weighing HRs by their standard error. The meta-regression fitted a linear relationship or non-linear relationship using natural splines with 2 degrees of freedom (one knot, at the 50th percentile), whichever fitted best according to the Akaike Information Criterion (AIC). We chose 2 degrees of freedom because we wanted to investigate non-linear relationships, but think it unlikely that the change in relationship with age would be tortuous.

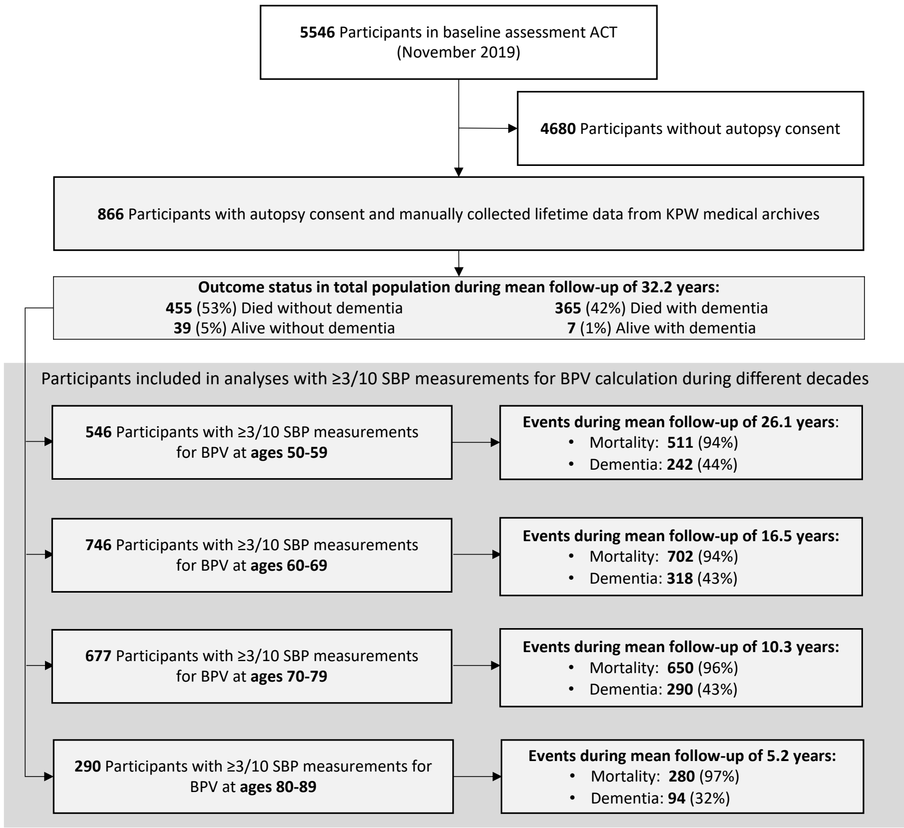
We used R 4.0.5 packages survival and meta.[33,34]

Results

We included 820 individuals (Figure 1), 344 (48%) of whom men, with a mean of 28.35 (SD=8.4) yearly SBP measurements available over 31.5 (SD=9.0) years. All-cause dementia was diagnosed in 372 (45.4%).

Numbers of individuals included per BPV period (Table 1) ranged from 280 (80-89 years) to 702 (60-69 years). The majority were white (range: 93%-96%) and women (range: 58%-65%). Mean SBP increased with age, from 131 mmHg (50-59 years), to 141 mmHg (80-89 years), and BPV from 9.3 (50-59 years) to 11.2 (80-89 years). Future lifetime dementia incidence (Table 2) ranged from 32.1% (80-89 years) to 46.2% (50-59 years).

Figure 1. Flow-chart



Abbreviations: ACT Adult Changes in Thought study, KWP: Kaiser Permanente Washington, BPV: blood pressure variability

Table 1. Characteristics of individuals per age category

Characteristics	Analysis index age (BPV period)			
	Age 60 [A] **(n total=511) N (%)**	**Age 70** [A] **(n total=702) N (%)**	**Age 80** [A] **(n total=650) N (%)**	**Age 90** [A] **(n total=280) N (%)**
Female sex	301 (58.9)	409 (58.3)	383 (58.9)	182 (65.0)
Ethnicity				
Asian	7 (1.4)	9 (1.3)	7 (1.1)	1 (0.4)
Black	8 (1.6)	10 (1.4)	8 (1.2)	4 (1.4)
White	475 (93.0)	662 (94.3)	614 (94.5)	268 (95.7)
Other, including Mixed	21 (4.1)	21 (3.0)	21 (3.2)	7 (2.5)
Education, y mean (SD)	14.8 (3.1)	14.6 (3.0)	14.5 (3.1)	14.6 (3.1)
APOE genotype with ≥ 1 ε4 allele	144 (29.4)	184 (27.4)	158 (25.2)	55 (20.2)
Systolic blood pressure, mean (SD) / 10 years	131 (13.5)	136 (13.7)	140 (13.3)	141 (13.3)
Blood pressure variability, CoV mean (SD) / 10 years	9.31 (3.93)	9.67 (3.16)	10.25 (3.20)	11.22 (3.25)
Ever antihypertensive medication use				
No	446 (87.3)	522 (74.4)	377 (58.0)	109 (38.9)
Yes	65 (12.7)	180 (25.6)	273 (42.0)	171 (61.1)
Smoking				
No	449 (90.0)	628 (91.4)	601 (93.8)	270 (97.8)
Quit during BPV period	7 (1.4)	12 (1.7)	11 (1.7)	0 (0%)
Current smoker	43 (8.6)	47 (6.8)	29 (4.5)	6 (2.2)
Myocardial infarction				
No	491 (96.1)	637 (90.7)	523 (80.5)	188 (67.1)
New event during BPV period	15 (2.9)	39 (5.6)	73 (11.2)	46 (16.4)
Yes, preceding BPV period	5 (1.0)	26 (3.7)	54 (8.3)	46 (16.4)
Diabetes mellitus				
No	483 (94.5)	633 (90.2)	567 (87.2)	243 (86.8)
Diagnosed during BPV period	20 (3.9)	36 (5.1)	30 (4.6)	21 (7.5)
Yes, preceding BPV period	8 (1.6)	33 (4.7)	53 (8.2)	16 (5.7)
Stroke				
No	502 (98.2)	651 (92.7)	533 (82.0)	189 (67.5)
New event during BPV period	6 (1.2)	37 (5.3)	79 (12.2)	51 (18.2)
Yes, preceding BPV period	3 (0.6)	14 (2.0)	38 (5.8)	40 (14.3)

[A] Individuals included in dementia analyses per age category. Individuals can be included in multiple columns since they were followed for several decades, from the moment of inclusion in the ACT study until death or dementia diagnosis. From the 820 participants included in the study, only the characteristics of individuals with available BPV measurements are depicted. Number of individuals with missing values for displayed characteristics at ages 60/70/80/90: *APOE* genotype: 21/30/23/12; Smoking: 12/15/12/10; Other variables: 0/0/0/0.

Main analyses

Results below reflect the fully adjusted model 2 (Table 2). Higher BPV was not associated with higher dementia risk at ages 60 (HR=0.97, 95%CI=0.85-1.11), 70 (HR=0.91 95%CI=0.80-1.02) or 80 (HR=1.02, 95%CI=0.89-1.16). At age 90, one SD increment in BPV was associated with a 35% higher dementia risk (HR=1.35, 95%CI=1.02-1.79). For mortality, associations were neutral at ages 60 (HR=1.04, 95%CI=0.95-1.14) and 70 (HR=1.01, 95%CI=0.93-1.09). At ages 80 (HR=1.14, 95%CI=1.05-1.24) and 90 (HR=1.16, 95%CI=1.02-1.32), one SD increment in BPV indicated a 14%-16% higher mortality risk. Associations with dementia/mortality combined were neutral at ages 60 (HR=1.02, 95%CI=0.93-1.12) and 70 (HR=0.96, 95%CI=0.88-1.03). At ages 80 (HR=1.09, 95%CI=1.00-1.19) and 90 (HR=1.19; 95%CI=1.01-1.41), one SD increment in BPV indicated a 9% and 19% higher risk respectively.

Table 2. Hazard ratios for incident dementia and mortality for participants at ages 60, 70, 80 and 90, per one SD increment in BPV

Model 1[A]		**N/n (%)**		**HR (95%CI)**		
Age	**BPV period**	**Total / dementia events**	**Total / mortality events**	**Dementia**	**Mortality**	**Dementia/ mortality**
60	**50-59**	511 / 236 (46.2)	511 / 511 (100)	0.99 (0.87-1.13)	1.03 (0.94-1.13)	1.02 (0.94-1.12)
70	**60-69**	702 / 311 (44.3)	703 / 703 (100)	0.91 (0.81-1.02)	1.02 (0.95-1.1)	0.97 (0.90-1.05)
80	**70-79**	650 / 285 (43.8)	693 / 693 (100)	1.01 (0.90-1.15)	1.17 (1.08-1.27)	1.12 (1.03-1.21)
90	**80-89**	280 / 90 (32.1)	394 / 394 (100)	1.27 (0.98-1.65)	1.22 (1.08-1.38)	1.23 (1.06-1.44)
Model 2[B]						
Age	**BPV period**	**Total / dementia events**	**Total / mortality events**	**Dementia**	**Mortality**	**Dementia/ mortality**
60	**50-59**	478 / 221 (46.2)	478 / 478 (100)	0.97 (0.85-1.11)	1.04 (0.95-1.14)	1.02 (0.93-1.12)
70	**60-69**	657 / 290 (44.1)	658 / 658 (100)	0.91 (0.80-1.02)	1.01 (0.93-1.09)	0.96 (0.88-1.03)
80	**70-79**	619 / 271 (43.8)	659 / 659 (100)	1.02 (0.89-1.16)	1.14 (1.05-1.24)	1.09 (1-1.19)
90	**80-89**	268 / 85 (31.7)	373 / 373 (100)	1.35 (1.02-1.79)	1.16 (1.02-1.32)	1.19 (1.01-1.41)

Cox proportional hazards for individuals at ages 60, 70, 80 and 90 years, alive without dementia, according to blood pressure variability (BPV) calculated of over the preceding 10 years (BPV period). [A] Model 1: Adjusted for sex and mean systolic blood pressure. [B] Model 2: Adjusted for sex and mean systolic blood pressure, years of education, smoking status, ApoE genotype and history of stroke, myocardial infarction and diabetes mellitus. [C] Hazard ratios calculated for lifetime risks.

Analyses for mean SBP showed no significant associations (Table 3). However, a gradual shift in direction of associations was apparent with higher age: from 7% higher dementia risk per SD at age 60 (HR=1.07, 95%CI=0.93–1.23), to a neutral (HR=0.99, 95%CI=0.87-1.11), 10% lower (HR=0.90, 95%CI=0.79-1.01) and 18% lower (HR=0.82, 95%CI=0.65-1.03) risk at ages 70, 80 and 90 respectively. Results were similar unadjusted for BPV. SBP was not associated with mortality (Table 3).

Table 3. Hazard ratios for incident dementia and mortality for participants at ages 60, 70, 80 and 90, per one SD increment in mean SBP

Model 1[A]		**N/n (%)**		**HR (95%CI)[C]**		
Age	**SBP period**	**Total / dementia events**	**Total / mortality events**	**Dementia**	**Mortality**	**Dementia/ mortality**
60	**50-59**	478 / 221 (46.2)	478 / 478 (100)	1.10 (0.96-1.26)	1.02 (0.92-1.12)	1.02 (0.93-1.12)
70	**60-69**	657 / 290 (44.1)	657 / 657 (100)	1.01 (0.9-1.14)	1.01 (0.93-1.09)	1.01 (0.94-1.09)
80	**70-79**	619 / 271 (43.8)	619 / 619 (100)	0.94 (0.83-1.05)	0.97 (0.89-1.05)	0.95 (0.88-1.03)
90	**80-89**	268 / 85 (31.7)	268 / 268 (100)	0.86 (0.69-1.08)	0.92 (0.81-1.05)	0.90 (0.79-1.02)
Model 2[B]						
Age	**SBP period**	**Total / dementia events**	**Total / mortality events**	**Dementia**	**Mortality**	**Dementia/ mortality**
60	**50-59**	478 / 221 (46.2)	478 / 478 (100)	1.07 (0.93-1.23)	1.01 (0.91-1.11)	1.00 (0.91-1.11)
70	**60-69**	657 / 290 (44.1)	657 / 657 (100)	0.99 (0.87-1.11)	0.99 (0.91-1.07)	0.99 (0.92-1.08)
80	**70-79**	619 / 271 (43.8)	619 / 619 (100)	0.90 (0.79-1.01)	0.96 (0.88-1.04)	0.93 (0.86-1.01)
90	**80-89**	268 / 85 (31.7)	268 / 268 (100)	0.82 (0.65-1.03)	0.96 (0.84-1.10)	0.91 (0.79-1.03)

Cox proportional hazards for individuals at ages 60, 70, 80 and 90 years, alive without dementia, according to mean systolic blood pressure (SBP) calculated of over the preceding 10 years (SBP period). [A] Model 1: Adjusted for sex and mean systolic blood pressure. [B] Model 2: Adjusted for sex and mean systolic blood pressure, years of education, smoking status, ApoE genotype and history of stroke, myocardial infarction and diabetes mellitus. [C] Hazard ratios calculated for lifetime risks.

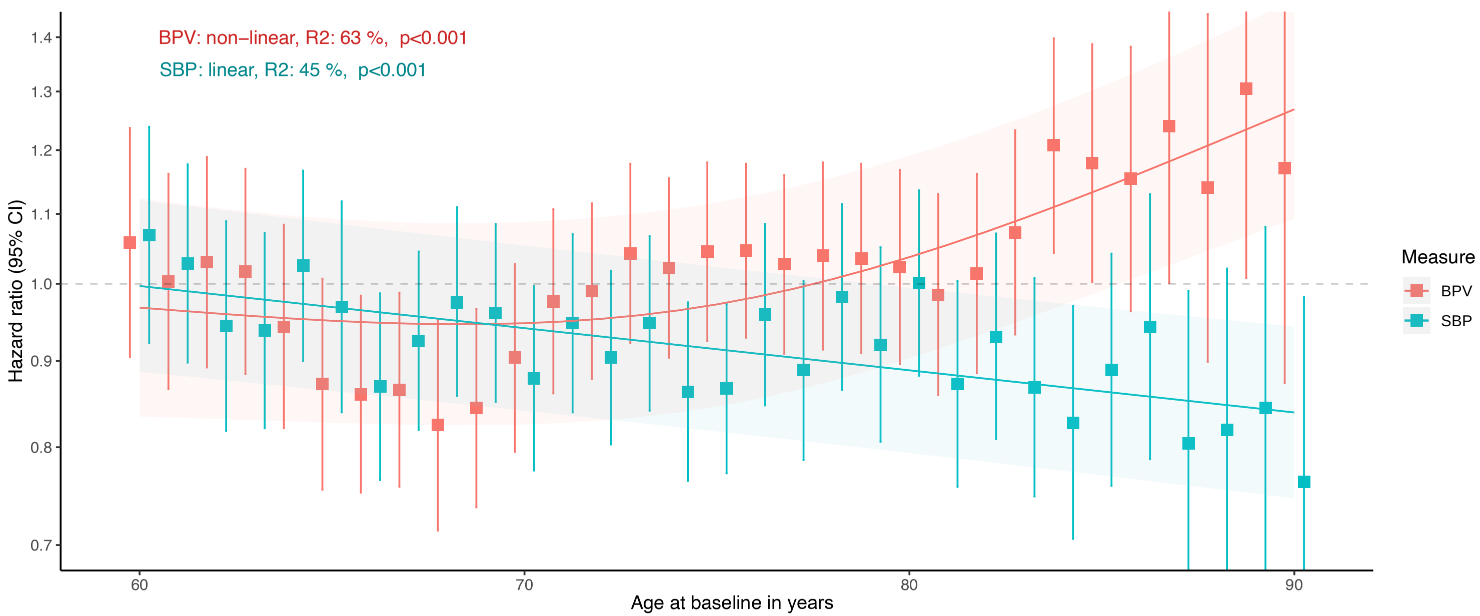
Subgroup and sensitivity analyses

Results between subgroups according to AHM-use (Table S1) were not significantly different (p-interaction all ≥0.26). Analyses stratified according to median SBP (Table S2) showed no significant differences (p-interaction all ≥0.26).

Sensitivity analyses excluding individuals without BPV available at age 60 from all analyses yielded similar results (Table S3). Analyses according to follow-up time showed no clear differences between <5 versus ≥5 years of follow-up (Table S4). Split-up according to median time to dementia (Table S5), dementia HRs for BPV at age 90 were higher in the long-term (>3.5 years: HR=1.52, 95%CI=1.07-2.16) than the short-term (HR=1.15, 95%CI=0.79-1.68). Analyses excluding individuals with ever stroke (Table S6) and ever MI (Table S7), accounting for autopsy cohort selection (Table S8), and only including individuals with ACT baseline at/before the index age (Table S9) showed results similar to the main analyses. Analyses using all available SBP measurements per individual to calculate 10-year BPV (Table S10) showed slightly attenuated results.

Figure 2 presents HRs of dementia for BPV and mean SBP at each age from 60 to 90. Meta-regression suggested that the association of BPV with elevated dementia risk only developed with higher age, non-linearly. The meta-regression line explained 63% of heterogeneity between HRs ($p<0.001$). The difference in relationship between SBP and dementia risk with higher age was negatively linear, meta-regression explaining 45% of heterogeneity between HRs ($p<0.001$).

Figure 2. HRs for the relationship of BPV and SBP with dementia at different ages from 60 to 90 years old.



Plotted are HRs from Cox regression analyses according to model 2 with blood pressure variability over the preceding decade (BPV, in red), or systolic blood pressure (SBP, in blue) as predictors, adjusted for sex, years of education, smoking status, *APOE* genotype and history of stroke, myocardial infarction and diabetes mellitus. The model for BPV was additionally adjusted for SBP and vice versa. The lines depict results of empirical Bayes mixed-effect meta-regression of the log HRs on age using linear, and non-linear natural splines (2 degrees of freedom). Depicted are the best fitting regression lines, non-linear for BPV and linear for SBP, with the shaded area representing the credible intervals. The R^2 values represent the % of heterogeneity between the HRs at different ages explained by each regression line. The change in relationship between BPV and dementia risk with higher age best fitted a non-linear model (AIC non-linear versus linear: -72.9 versus -64.3). The change in relationship between SBP and dementia risk with higher age best fitted a linear model (AIC non-linear versus linear: -85.9 versus -84.2).

Discussion

In this cohort study of 866 community-dwelling individuals followed for a mean of 32.2 years (27,885 person years) from midlife to death, only higher BPV in old-age was associated with higher dementia risk. This could not be explained by opposite relations for mortality as competing risk. At age 90, associations seemed stronger with longer time to dementia. Results did not significantly differ between subgroups according to SBP or AHM-use, and were similar excluding individuals with lifetime stroke or MI. Meta-regression corroborated that the association of high BPV with higher dementia risk only developed at higher age, while the direction of associations for SBP with dementia risk shifted from positive to negative with higher age.

No previous studies have studied BPV spanning over ≥30 years from midlife to death within the same individuals, making the current study uniquely suited to examine how age affects the relation between BPV and dementia. Higher BPV mainly indicated higher dementia risk at higher ages. A recent meta-analysis reported 27% higher odds (OR=1.27, 95%CI=1.17-1.38) for elevated systolic visit-to-visit BPV on incident dementia/cognitive impairment.[22] Nearly all (9/10) studies in this meta-analysis examined older populations (mean age >65). Associations with cognitive impairment might emerge earlier, because it may precede dementia by several years.[35] The only study of individuals in midlife (mean age 54) found that individuals with high BPV had lower cognition, but no association with subsequent cognitive decline over 15 years.[17] Studies with subgroup analyses according to age had heterogeneous findings.[14,16,36] Two observed the highest dementia risk with elevated BPV in younger participants (aged <65 and <70),[16,36] one in older participants (aged ≥70).[14] None investigated age-specific associations for BPV with lifetime dementia risk within the same individuals. Therefore, generation effects and old-age related inclusion bias may have influenced these results. Moreover, median follow-up ranged 6-15 years, so outcomes may have been missed in younger people, since dementia mostly occurs above the age of 80.[37]

The change in relationship between SBP and dementia risk from positive to negative with higher age matches the literature, wherein midlife hypertension indicates higher dementia risk,[1] while late-life hypertension indicates lower risk.[18,38,39] Our results support a meta-analysis' suggestions that BPV might predict dementia risk better than SBP,[22] but importantly add that this seems specific for old-age BPV.

The mechanism linking BPV to dementia is unknown.[40] Our finding that midlife BPV did not affect lifetime dementia risk makes a causal cumulative dose-response relationship less likely. Causality might be reversed, high BPV reflecting the effect of neurodegeneration on the autonomic nervous system[41] or extensive vascular damage. The association of BPV at 90 with dementia was particularly notable in the longer term (>3.5 years), contesting that high BPV prodromally precedes dementia. Combined with findings that high BPV predicts cerebral small vessel disease,[42] and vascular outcomes including chronic kidney disease,[43] MI and stroke,[44-46] a relationship with cerebrovascular disease seems plausible. Alternatively, the body's ability to maintain homeostasis may decrease with ageing, making old-age elevated BPV a marker of advanced biological age and thereby related to dementia. Interestingly, variability in other cardiovascular, metabolic, and renal parameters in older people, has also been associated with increased risk of cardiovascular events and dementia.[47-49] Excluding individuals with lifetime stroke and subgroup analyses for AHM-use gave largely unaltered results, suggesting that the relation between BPV and dementia is not solely dependent on post-stroke dementia or AHM-use.

Limitations

Strengths of this study are the year-by-year BP data, from the same community-dwelling individuals, spanning over 30 years from midlife to death, with systematic biennial cognitive assessment, and dementia outcome confirmation by adjudication committee. Originating from the same individuals, data at different ages more closely represent ageing effects, rather than potential age-related/generational selection biases. The follow-up length allowed for analyzing lifetime dementia risk, even for BPV at younger ages wherein limited follow-up duration usually necessitates analyzing cognitive change scores as outcomes. Using dementia diagnoses as outcome is key, because cognitive decline may often not result in dementia.[35]

Our study has limitations. First, we only included autopsy consenting ACT participants. The high dementia rate in our sample (45%) may partly reflect brain disease patients' increased willingness to consent to autopsy, next to the expected lifetime dementia risk for individuals aged ≥65 being 30-40%,[50] and the biennial cognitive screening identifying extra cases. These factors may restrict the generalizability of our findings. However, our sensitivity analyses accounting for differences between the autopsy sample and the full ACT population yielded similar results, suggesting our results are generalizable to the ACT population. However, our population mostly includes white Americans with access to relatively high-quality health care, possibly limiting the generalizability of our findings to more diverse samples and/or regions with less access to health care. Second, ACT's enrollment of individuals aged ≥65 might have selected survivors relatively impervious to high

BPV. Third, variance in methods of SBP assessors may have resulted in higher BPV estimates. However, this divergence is unlikely to systematically differ between individuals with and without incident dementia. Although 1-3 measurements per year were available per participant, we only included 1 to homogenize exposure operationalization across individuals. Sensitivity analyses including all available SBP measurements showed slightly attenuated associations. This may reflect the differences in exposure definition per participant, and the number of measurements possibly depending on health status, distorting associations. Alternatively, association for year-by-year BPV may differ from BPV within shorter time-periods.[51] Fourth, we only performed subgroup analyses comparing ever versus never AHM-users, but analyzing AHM classes, and (cumulative) dosages may be interesting, since this might impact BPV.

Conclusion

In this cohort study of 866 community-dwelling individuals, high BPV in very advanced old-age, but not in midlife, was associated with higher lifetime dementia risk. This was not due to excess mortality. Results suggest that high BPV may indicate increased dementia risk in very old age but might be less viable as a midlife dementia prevention target. Our study is unique in assessing relations between BPV at multiple ages from midlife onward with lifetime dementia risk, underlining the necessity of more long-term studies examining these relationships, in more diverse samples, to confirm the age-dependency of this association, identify underlying mechanisms, and corroborate our conclusions.

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Supplemental material

Methods S1.	ACT chart review process
Methods S2.	Weighted sensitivity analysis evaluating potential cohort selection effects
Table S1.	Hazard ratios per one standard deviation increment in systolic BPV at ages 60, 70, 80, and 90 for incident dementia in antihypertensive medication users and non-users
Table S2.	Hazard ratios per one standard deviation increment in systolic BPV at ages 60, 70, 80, and 90 for incident dementia subgroups stratified according to median systolic blood pressure
Table S3.	Hazard ratios per one standard deviation increment in systolic BPV at ages 60, 70, 80, and 90 for incident dementia excluding individuals without BPV measurement available at age 60
Table S4.	Hazard ratios per one standard deviation increment in systolic BPV at ages 60, 70, 80, and 90 for incident dementia according to moment of censoring (<5 or ≥5 years of follow-up).
Table S5.	Hazard ratios per one standard deviation increment in systolic BPV at ages 60, 70, 80, and 90 for incident dementia according median to time to dementia diagnosis
Table S6.	Hazard ratios per one standard deviation increment in systolic BPV at ages 60, 70, 80, and 90 for incident dementia, excluding individuals with stroke at any age during life
Table S7.	Association for one SD increase in mean systolic blood pressure variability over previous 10-years and lifetime dementia or mortality risk, excluding individuals with myocardial infarction at any age during life
Table S8.	Association for one SD increase in mean systolic blood pressure variability over previous 10-years and lifetime dementia or mortality risk, using inverse probability weighting to account for potential selection into the autopsy cohort from the larger ACT study population
Table S9.	Association for one SD increase in mean systolic blood pressure variability over previous 10-years and lifetime dementia or mortality risk, only including individuals who had attended ACT baseline at or before the index age
Table S10.	Association for one SD increase in mean systolic blood pressure variability over previous 10-years and lifetime dementia or mortality risk, using 10-year BPV calculated with all available SBP measurements per individual per year (maximum 3) adjusted for the number of SBP measurements
Figure S1.	Depiction of BPV periods in relation to analysis index age.

Methods S1. ACT chart review process

For the adult changes in thought (ACT) study chart review project, the prospective data recorded during the Adult Changes in Thought study, was supplemented with high-quality detailed medical data from the Kaiser Permanente Washington medical archives. Study participants provided informed consent and all study activities were approved by the Kaiser Permanente Washington Institutional Review Board. These methods describe the set-up of the chart review project, the measures taken to ensure data quality, and the collected variables.

Development and quality assurance

The initial medical record abstraction team included a physician and three medical record review professionals. The team met on a recurrent basis to discuss and outline the project. We reviewed local experience with medical record abstractions and requested materials from a research group that had published numerous case-control studies using medical records from the same healthcare delivery system.

The overall goal was to collect longitudinal medical record data across the participant's entire enrolment in the healthcare delivery system. Because of the magnitude of the task, we developed a computerized medical record abstraction tool, facilitating direct data entry into a database rather than initial abstraction onto paper forms requiring subsequent data entry.

We carefully considered data elements to abstract. We were guided by the parent study's specific aims, which at the time included specific attention to pharmacoepidemiology and in the subsequent grant cycle focused on vascular risk factors. We also considered the wide variety of data collected by the ACT study at study visits and considered whether there was likely to be additional value from abstracting related data from participant medical records. We consulted clinical researchers to review sections of the medical record abstraction in their specific area of expertise.

Documentation was a crucial component of the medical record abstraction project, and study staff prepared an extensive draft Manual of Operations to detail specific instructions about each data field. Study staff also prepared a question log in which they recorded the rationale for decisions of what to collect and what not to collect.

Due to early concerns regarding the amount of time necessary for abstracting data, the team reviewed each variable to consider its utility. The team was guided by considerations of validity and efficiency. As much as possible, we tried to facilitate instructions that would allow medical record abstractors to "abstract what you see," that is, to record what they observed in the medical records rather than trying to guess what was occurring in the mind of the provider or the body of the study participant.

Medical record abstractors abstracted data from an initial group of 40 medical records using the medical record abstraction tool. As part of quality assurance, 15 of these medical records were abstracted by more than one abstractor. The team discussed difficulties and discrepancies with each other and with frequent meetings with the lead investigator. Based on these discussions, we further modified the tool and the Manual of Operations. The team established a workflow with rapid cycles of updating the medical record abstraction tool.

Training and ongoing quality control

During the initial training period for new abstractors, all medical records abstracted by medical record abstractors were also abstracted by the lead abstractor. We required three consecutive medical records with greater than 93% agreement on selected fields with the lead abstractor to certify abstractors for this project. Fields considered for this threshold included presence/absence of medical conditions and procedures, demographics, social history, dates and numeric values for laboratory values, weights, and blood pressures. New medical record abstractors were permitted to abstract data on medical records only after completing the certification.

We have established extensive ongoing quality control efforts, including an inter-rater reliability protocol with a random 5% re-abstraction, with careful attention to discrepancies, and computer-generated error prevention and detection techniques.

The team continues to meet on a routine basis with the lead investigator. Routinely scheduled meetings include team meetings without the lead investigator, meetings with the computer programmer, and meetings to discuss re-abstraction findings.

As an estimate of the time spent per patient on data extraction, including training periods and continuous quality improvement efforts, abstracting data for the first 380 medical records took 2,352 person-hours, an average of 6.2 hours per participant.

Data elements

The medical record abstraction project includes abstraction of medication data in specific categories including antidepressants, antihypertensives, antipsychotics, diabetes medications, hormones, thyroid medications, and sedatives from years before 1977, the year electronic pharmacy record became available at Kaiser Permanente Washington (formerly Group Health). Because of difficulties abstracting accurate data, the team only abstracts drug names, with no attempt to gather dosing information. Medication data prior to 1977 are coded using a pre-populated drug library. From 1977 onwards, the ceased medications drug library is generated with a participant-specific list of medications from computerized pharmacy data.

The team records blood pressures up to three times per year, divided into 4-month bins from January through April, May through August, and September through December. If there are multiple blood pressures within a four-month bin, a hierarchical scheme preferentially chooses seated, repeat blood pressure readings performed by physicians in an outpatient setting using the following scheme. The first blood pressure (BP) taken in each period per year is recorded. Priority is given to an outpatient blood pressure, even if an inpatient BP occurs earlier in the time period. If there are multiple blood pressures listed during a single visit or time period, only one is recorded according to the following criteria:

- Clinic visit BP has priority over ER/urgent care/hospital visit BP
- Right arm BP has priority over Left arm BP
- Seated BP has priority over Lying BP over Standing BP
- MD taken BP has priority over nursing staff BP
- Repeat BP has priority over initial BP during a single visit

The team abstracts tobacco use on an annual basis across all years. The team abstracts several cardiovascular conditions, including stroke and myocardial infarction. The team also abstracts a variety of non-cardiovascular medical conditions, including diabetes.

The team enters abstracted data directly into a database application that uses Microsoft Access as its front-end interface (i.e., data entry forms) and Microsoft SQL Server as the underlying database engine. Programmers employed a wide variety of data form controls to minimize errors, including options groups, checkboxes, and drop-down lists. Programmers added alerts, range, and logic checks to date and numeric fields to prevent entry of out-of-range values. There are also program scripts that selectively enable or disable data fields depending on value(s) entered in other fields. We also implemented a tool that locks down a subject's data set once it is deemed 'complete' to eliminate the chance of accidentally altering a cleaned and verified medical record abstraction.

Abstracted data are stored in a secure SQL Server database. Access is restricted to members of the medical record review team who have been specifically granted permission.

Methods S2. Weighted sensitivity analysis evaluating potential cohort selection effects

Selection bias may occur if demographic and clinical factors are associated with inclusion in the autopsy cohort (including consent to autopsy, study withdrawal, and death). To evaluate whether this had any effects on our main analyses, we performed a sensitivity analysis using inverse probability weighting to account for differences that might exist between the analytic sample and the broader ACT cohort, similar as described previously.[1] Weights were derived as the inverse of inclusion probability estimated from a logistic regression model on selection using all ACT participants. Predictors in the selection model included age at ACT study entry, ACT cohort (i.e., original first wave, second expansion wave, or the subsequently established continuous replacement cohort), sex, education, dementia, systolic blood pressure, antihypertensive use, history of stroke, and history of coronary artery disease. To account for the uncertainty in the estimated weights, we used bootstrap analyses to calculate 1,000 weights for each participant. We subsequently repeated the main analyses calculating the effect sizes and 95%CI using 10,000 bootstraps, each time using inverse probability weighting according to a random iteration of the 1,000 probability weights. Effect sizes with 95% confidence intervals were defined as the median with the 2.5th and 97.5th percentile results of those 10,000 bootstraps.

Table S1. Hazard ratios per one standard deviation increment in systolic BPV at ages 60, 70, 80, and 90 for incident dementia in antihypertensive medication users and non-users

		Antihypertensive medication users		**Antihypertensive medication non-users**		
Age	**BPV period**	**Total / dementia (%)**	**HR (95%CI)**	**Total number of individuals**	**HR (95%CI)**	**p-value interaction**
60	**50-59**	63 / 27 (42.9)	1.07 (0.72 - 1.58)	415 / 194 (46.7)	0.94 (0.81 - 1.09)	0.31
70	**60-69**	166 / 67 (40.4)	1.07 (0.80 - 1.43)	491 / 223 (45.4)	0.88 (0.77 - 1.01)	0.26
80	**70-79**	260 / 103 (39.6)	1.00 (0.78 - 1.28)	359 / 168 (46.8)	1.02 (0.86 - 1.21)	0.75
90	**80-89**	165 / 48 (29.1)	1.43 (0.99 - 2.06)	103 / 37 (35.9)	1.32 (0.77 - 2.26)	0.57

Cox proportional hazards for individuals at ages 60, 70, 80 and 90 years, alive without dementia, according to blood pressure variability (BPV) calculated of over the preceding 10 years (BPV period). Hazard ratios indicate lifetime risks. Adjusted for sex, mean systolic blood pressure, years of education, smoking status, ApoE genotype and history of stroke, myocardial infarction and diabetes mellitus. Abbreviations: HR= hazard ratio, CI=confidence interval, BPV=blood pressure variability, SBP: systolic blood pressure

Table S2. Hazard ratios per one standard deviation increment in systolic BPV at ages 60, 70, 80, and 90 for incident dementia subgroups stratified according to median systolic blood pressure

		< median SBP		**> median SBP**		
Age	**BPV period**	**Total / dementia events (%)**	**HR dementia (95%CI)**	**Total / dementia events (%)**	**HR dementia (95%CI)**	**p-value interaction**
60	**50-59**	238 / 106 (44.5)	1.09 (0.90 - 1.33)	240 / 115 (47.9)	0.90 (0.74 - 1.09)	0.26
70	**60-69**	324 / 139 (42.9)	0.95 (0.80 - 1.13)	333 / 151 (45.3)	0.85 (0.72 - 1.01)	0.26
80	**70-79**	304 / 135 (44.4)	1.01 (0.83 - 1.24)	315 / 136 (43.2)	1.02 (0.86 - 1.22)	0.72
90	**80-89**	132 / 43 (32.6)	1.37 (0.86 - 2.18)	136 / 42 (30.9)	1.49 (0.94 - 2.36)	0.66

Cox proportional hazards for individuals at ages 60, 70, 80 and 90 years, alive without dementia, according to blood pressure variability (BPV) calculated of over the preceding 10 years (BPV period). Hazard ratios indicate lifetime risks. Adjusted for sex, mean systolic blood pressure, years of education, smoking status, ApoE genotype and history of stroke, myocardial infarction and diabetes mellitus. Abbreviations: HR= hazard ratio, CI=confidence interval, BPV=blood pressure variability, SBP: systolic blood pressure

Table S3. Hazard ratios per one standard deviation increment in systolic BPV at ages 60, 70, 80, and 90 for incident dementia excluding individuals without BPV measurement available at age 60

Age	BPV period	Total / dementia events (%)	Total / mortality events (%)	HR dementia (95%CI)	HR mortality (95%CI)	HR dementia/ mortality (95%CI)
60	**50-59**	508 / 226 (44.5)	478 / 478 (100)	0.95 (0.83 - 1.09)	1.04 (0.95 - 1.14)	1.01 (0.92 - 1.11)
70	**60-69**	495 / 221 (44.6)	467 / 467 (100)	0.84 (0.73 - 0.97)	1.01 (0.92 - 1.11)	0.93 (0.84 - 1.02)
80	**70-79**	396 / 176 (44.4)	409 / 409 (100)	0.95 (0.8 - 1.11)	1.16 (1.05 - 1.29)	1.11 (0.99 - 1.23)
90	**80-89**	154 / 51 (33.1)	208 / 208 (100)	1.32 (0.91 - 1.91)	1.07 (0.91 - 1.25)	1.11 (0.89 - 1.37)

Cox proportional hazards for individuals at ages 60, 70, 80 and 90 years, alive without dementia, according to blood pressure variability (BPV) calculated of over the preceding 10 years (BPV period). Hazard ratios indicate lifetime risks and hazard ratios for mortality are independent of dementia because dementia is not a competing risk for mortality. Adjusted for sex, mean systolic blood pressure, years of education, smoking status, ApoE genotype and history of stroke, myocardial infarction and diabetes mellitus. Abbreviations: HR= hazard ratio, CI=confidence interval, BPV=blood pressure variability, SBP: systolic blood pressure

Table S4. Hazard ratios per one standard deviation increment in systolic BPV at ages 60, 70, 80, and 90 for incident dementia according to moment of censoring (<5 or ≥5 years of follow-up)

		< 5 years of follow-up		**≥ 5 years of follow-up**	
Age	**BPV period**	**Total / dementia events (%)**	**HR dementia (95%CI)**	**Total / dementia events (%)**	**HR dementia (95%CI)**
60	**50-59**	478 / 0 (0.00)	NA (NA - NA)	478 / 221 (46.2)	0.97 (0.85 - 1.11)
70	**60-69**	657 / 11 (1.7)	1.18 (0.50 - 2.78)	645 / 283 (43.9)	0.91 (0.81 - 1.03)
80	**70-79**	619 / 88 (14.2)	1.05 (0.83 - 1.32)	515 / 205 (39.8)	1.00 (0.87 - 1.16)
90	**80-89**	268 / 64 (23.9)	1.33 (0.96 - 1.85)	119 / 31 (26.1)	1.44 (0.91 - 2.25)

Cox proportional hazards for individuals at ages 60, 70, 80 and 90 years, alive without dementia, according to blood pressure variability (BPV) calculated of over the preceding 10 years (BPV period). Hazard ratios indicate lifetime risks. Adjusted for sex, mean systolic blood pressure, years of education, smoking status, ApoE genotype and history of stroke, myocardial infarction and diabetes mellitus. Note that HR for dementia<5 years was missing at age 60, because none of the participants developed dementia <5 years at that age. Abbreviations: HR= hazard ratio, CI=confidence interval, BPV=blood pressure variability, SBP: systolic blood pressure

Table S5. Hazard ratios per one standard deviation increment in systolic BPV at ages 60, 70, 80, and 90 for incident dementia according median to time to dementia diagnosis

			< median time to dementia		> median time to dementia	
Age	**BPV period**	**Median time to dementia, y**	**Total / dementia events (%)**	**HR dementia (95%CI)**	**Total / dementia events (%)**	**HR dementia (95%CI)**
60	**50-59**	26.0	478 / 108 (22.6)	1.06 (0.89 - 1.28)	281 / 113 (40.2)	0.90 (0.74 - 1.10)
70	**60-69**	16.5	657 / 151 (23.0)	0.91 (0.76 - 1.09)	371 / 139 (37.5)	0.89 (0.75 - 1.07)
80	**70-79**	8.5	619 / 154 (24.9)	1.03 (0.86 - 1.24)	351 / 117 (33.3)	0.99 (0.83 - 1.19)
90	**80-89**	3.5	268 / 44 (16.4)	1.15 (0.79 - 1.68)	156 / 41 (26.3)	1.48 (1.03 - 2.11)

Cox proportional hazards for individuals at ages 60, 70, 80 and 90 years, alive without dementia, according to blood pressure variability (BPV) calculated of over the preceding 10 years (BPV period). Hazard ratios indicate lifetime risks. Adjusted for sex, mean systolic blood pressure, years of education, smoking status, ApoE genotype and history of stroke, myocardial infarction and diabetes mellitus. Abbreviations: HR= hazard ratio, CI=confidence interval, BPV=blood pressure variability, SBP: systolic blood pressure

Table S6. Hazard ratios per one standard deviation increment in systolic BPV at ages 60, 70, 80, and 90 for incident dementia, excluding individuals with stroke at any age during life

Age	**BPV period**	**Total / dementia events (%)**	**Total / mortality events (%)**	**HR dementia (95%CI)**	**HR mortality (95%CI)**	**HR dementia/ mortality (95%CI)**
60	**50-59**	221 / 90 (40.7)	221 / 221 (100)	1.19 (0.93 - 1.53)	1.02 (0.87 - 1.19)	1.07 (0.91 - 1.25)
70	**60-69**	318 / 121 (38.1)	318 / 318 (100)	0.93 (0.76 - 1.13)	0.97 (0.87 - 1.10)	0.94 (0.84 - 1.06)
80	**70-79**	300 / 119 (39.7)	320 / 320 (100)	1.01 (0.83 - 1.23)	1.13 (1.00 - 1.28)	1.09 (0.96 - 1.23)
90	**80-89**	132 / 43 (32.6)	172 / 172 (100)	1.71 (1.10 - 2.64)	1.26 (1.02 - 1.57)	1.46 (1.12 - 1.90)

Cox proportional hazards for individuals at ages 60, 70, 80 and 90 years, alive without dementia, according to blood pressure variability (BPV) calculated of over the preceding 10 years (BPV period). Hazard ratios indicate lifetime risks and hazard ratios for mortality are independent of dementia because dementia is not a competing risk for mortality. Adjusted for sex, mean systolic blood pressure, years of education, smoking status, ApoE genotype and history of stroke, myocardial infarction and diabetes mellitus. Abbreviations: HR= hazard ratio, CI=confidence interval, BPV=blood pressure variability, SBP: systolic blood pressure

Table S7. Association for one SD increase in mean systolic blood pressure variability over previous 10-years and lifetime dementia or mortality risk, excluding individuals with myocardial infarction at any age during life

Age	BPV period	Total / dementia events (%)	Total / mortality events (%)	HR dementia (95%CI)	HR mortality (95%CI)	HR dementia/ mortality (95%CI)
60	**50-59**	261 / 119 (45.6)	261 / 261 (100)	1.01 (0.84 - 1.22)	1.06 (0.94 - 1.20)	1.03 (0.91 - 1.17)
70	**60-69**	353 / 158 (44.8)	353 / 353 (100)	1.00 (0.85 - 1.18)	1.01 (0.91 - 1.12)	0.98 (0.88 - 1.09)
80	**70-79**	323 / 142 (44.0)	344 / 344 (100)	1.08 (0.90 - 1.3)	1.13 (1.00 - 1.29)	1.15 (1.02 - 1.29)
90	**80-89**	132 / 42 (31.8)	189 / 189 (100)	1.48 (1.01 - 2.17)	1.19 (1.00- 1.41)	1.24 (0.98 - 1.55)

Cox proportional hazards for individuals at ages 60, 70, 80 and 90 years, alive without dementia, according to blood pressure variability (BPV) calculated of over the preceding 10 years (BPV period). Hazard ratios indicate lifetime risks and hazard ratios for mortality are independent of dementia because dementia is not a competing risk for mortality. Adjusted for sex, mean systolic blood pressure, years of education, smoking status, *APOE* genotype and history of stroke, myocardial infarction and diabetes mellitus. Abbreviations: HR= hazard ratio, CI=confidence interval, BPV=blood pressure variability, SBP: systolic blood pressure

Table S8. Association for one SD increase in mean systolic blood pressure variability over previous 10-years and lifetime dementia or mortality risk, using inverse probability weighting to account for potential selection into the autopsy cohort from the larger ACT study population

Age	BPV period	Total / dementia events (%)	Total / mortality events (%)	HR dementia (95%CI)	HR mortality (95%CI)	HR dementia/ mortality (95%CI)
60	**50-59**	484 / 220 (45.5)	484 / 484 (100)	1.00 (0.88 - 1.15)	1.04 (0.94 - 1.14)	1.03 (0.94 - 1.13)
70	**60-69**	657 / 290 (44.1)	658 / 658 (100)	0.90 (0.8 - 1.02)	0.99 (0.92 - 1.07)	0.95 (0.88 - 1.03)
80	**70-79**	617 / 273 (44.2)	659 / 659 (100)	0.98 (0.86 - 1.12)	**1.12 (1.03 - 1.22)**	1.08 (0.99 - 1.17)
90	**80-89**	265 / 84 (31.7)	374 / 374 (100)	1.29 (0.96 - 1.73)	**1.14 (1.00 - 1.29)**	**1.19 (1.00 - 1.42)**

Cox proportional hazards for individuals at ages 60, 70, 80 and 90 years, alive without dementia, according to blood pressure variability (BPV) calculated of over the preceding 10 years (BPV period). Hazard ratios indicate lifetime risks. Adjusted for sex, mean systolic blood pressure, years of education, smoking status, ApoE genotype and history of stroke, myocardial infarction and diabetes mellitus. Estimates and 95% confidence intervals were calculated using 10,000 bootstraps. See Methods S2 for full description of the inverse probability weighting procedure and analyses. Abbreviations: HR= hazard ratio, CI=confidence interval, BPV=blood pressure variability, SBP: systolic blood pressure

Table S9. Association for one SD increase in mean systolic blood pressure variability over previous 10-years and lifetime dementia or mortality risk, only including individuals who had attended ACT baseline at or before the index age

Age	BPV period	Total / dementia events (%)	Total / mortality events (%)	HR dementia (95%CI)	HR mortality (95%CI)	HR dementia/ mortality (95%CI)
60	**50-59**	-	-	-	-	-
70	**60-69**	118 / 43 (36.4)	134 / 134 (100)	0.75 (0.51 - 1.10)	0.95 (0.79 - 1.14)	0.95 (0.79 - 1.14)
80	**70-79**	133 / 46 (34.6)	440 / 440 (100)	0.95 (0.8 - 1.13)	1.13 (1.01 - 1.26)	1.06 (0.95 - 1.19)
90	**80-89**	400 / 176 (44.0)	351 / 351 (100)	1.34 (1.00 - 1.81)	1.14 (1.00 - 1.29)	1.15 (0.97 - 1.37)

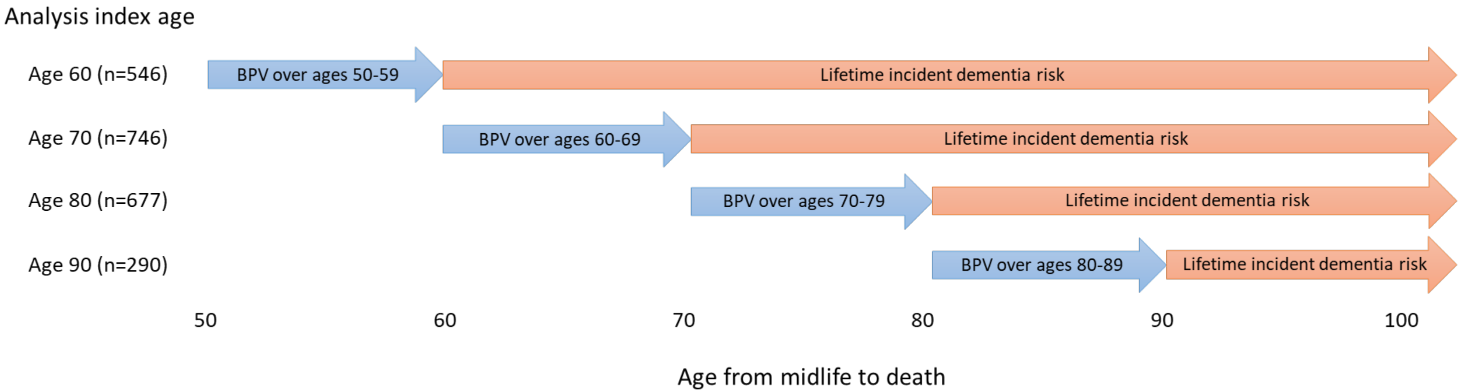
Cox proportional hazards for individuals at ages 60, 70, 80 and 90 years, alive without dementia, according to blood pressure variability (BPV) calculated of over the preceding 10 years (BPV period). Hazard ratios indicate lifetime risks. Adjusted for sex, mean systolic blood pressure, years of education, smoking status, ApoE genotype and history of stroke, myocardial infarction and diabetes mellitus. In these analyses, only individuals who were at risk from the index age (i.e. had had their ACT baseline measurement) were included in the analyses. Analyses for age 60 could not be performed because individuals were only included in the ACT from age 65 and older. Abbreviations: HR= hazard ratio, CI=confidence interval, BPV=blood pressure variability, SBP: systolic blood pressure

Table S10. Association for one SD increase in mean systolic blood pressure variability over previous 10-years and lifetime dementia or mortality risk, using 10-year BPV calculated with all available SBP measurements per individual per year (maximum 3) adjusted for the number of SBP measurements

Age	BPV period	Total / dementia events (%)	Total / mortality events (%)	HR dementia (95%CI)	HR mortality (95%CI)	HR dementia/ mortality (95%CI)
60	**50-59**	492 / 223 (45.3)	492 / 492 (100)	1.00 (0.88 - 1.14)	1.03 (0.94 - 1.13)	1.03 (0.94 - 1.13)
70	**60-69**	668 / 294 (44)	669 / 669 (100)	0.90 (0.8 - 1.02)	0.99 (0.91 - 1.07)	0.95 (0.88 - 1.03)
80	**70-79**	628 / 277 (44.1)	671 / 671 (100)	0.99 (0.87 - 1.13)	1.12 (1.03 - 1.22)	1.08 (0.99 - 1.17)
90	**80-89**	272 / 86 (31.6)	381 / 381 (100)	1.28 (0.96 - 1.72)	1.14 (1.00 - 1.3)	1.19 (1.01 - 1.42)

Cox proportional hazards for individuals at ages 60, 70, 80 and 90 years, alive without dementia, according to blood pressure variability (BPV) calculated of over the preceding 10 years (BPV period). Hazard ratios indicate lifetime risks. Adjusted for sex, mean systolic blood pressure, years of education, smoking status, ApoE genotype and history of stroke, myocardial infarction and diabetes mellitus. Abbreviations: HR= hazard ratio, CI=confidence interval, BPV=blood pressure variability, SBP: systolic blood pressure

Figure S1. Depiction of BPV periods in relation to analysis index age.



In blue the periods over which blood pressure variability (BPV) was measured and in pink the remaining lifetime over which dementia risk was analyzed. The number of individuals available per age stratum varies, because not all persons had data available from as early as age 50, and attrition due to death or dementia occurred before reaching the higher age strata.

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Part III

Treatment of Alzheimer's disease

6

Bayes analysis supports null hypothesis of anti-amyloid beta therapy in Alzheimer’s disease

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Abstract

Numerous clinical trials of anti-amyloid beta immunotherapy in Alzheimer's disease have been performed. None of these have provided convincing evidence for beneficial effects. Using traditional frequentist meta-analysis, the conclusion is that there is absence of evidence for a therapeutic effect, with a point estimate effect size of 0.05 (95% confidence interval −0.00 to 0.10, P = 0.055). In addition, this non-significant effect equates to 0.4 points per year on the cognitive subscale of the Alzheimer's Disease Assessment Scale. This is well below the minimally clinically important difference. Bayesian meta-analysis of these trial data provides strong evidence of absence of a therapeutic effect, with a Bayes factor of 11.27 in favor of the null hypothesis, opposed to a Bayes factor of 0.09 in favor of a treatment effect. Bayesian analysis is particularly valuable in this context of repeatedly reported small, non-significant effect sizes in individual trials. Mechanisms other than removal of amyloid-beta from the brain may be probed to slow progression of Alzheimer's disease.

Introduction

Since the turn of the century numerous therapeutic studies in Alzheimer's disease (AD) have targeted the cerebral amyloid beta deposits, one of the defining characteristics of this condition. Thousands of patients have participated in randomized controlled trials (RCTs) of anti-amyloid beta (AAB) immunotherapy, costing billions of dollars. So far, results have been disappointing, with none of these trials reporting statistically significant beneficial effects. Despite being sufficiently powered, well performed, and published in high-ranking journals, these studies have been characterized as "negative," "failures," or "unsatisfactory." This may be unjustified and can be understood best by the characteristics of classical frequentist statistical null hypothesis testing for significance used in all RCTs. As recently reviewed in depth by Keysers et al.,[1] non-significant study results of well-designed RCTs are open to several explanations according to this approach: (1) trialists may simply have had "bad luck" due to sampling variability; (2) the sample size may have been too small, the target population not sufficiently well-defined, the follow-up too short, or the outcome parameters too insensitive to detect subtle effects; or (3) the true effect of a therapeutic approach is indeed absent. Both the derogatory qualifications of recent AAB immunotherapy and the ever-continuing research into this approach, suggest that the first two interpretations, "bad luck" and "too small, short, or insensitive," dominate the AD field, whereas the third option, "absence of a true effect" appears not to be considered seriously. This may have a simple explanation that is related to the traditional frequentist analyses that were used. A Bayesian analysis may offer a constructive perspective on these recent AAB trial results and allow for quantifying the null hypothesis that AAB immunotherapy does not slow down cognitive decline in AD.

6

Frequentist versus Bayesian analysis of trial results

To evaluate the full body of evidence of AAB immunotherapy in AD, meta-analysis of published results of RCTs can be applied. Traditional frequentist meta-analyses of published randomized controlled trial results aim to provide an estimate of the true treatment effect, by calculating the average effect across studies. In most cases, a random effects model is indicated, which takes differences between studies into account, and will provide a weighted mean effect size, with a 95% confidence interval. This is particularly useful in case of conflicting trial results. The increased number of participants exposed to the intervention or control condition generally leads to an increase in statistical power to signal a statistically significant effect. Interpretation of statistically significant trial results ($P \leq 0.05$) is straightforward according to the conventional frequentist approach, i.e. rejection of the null hypothesis and adoption of the alternative hypothesis implying a true therapeutic effect. But the opposite finding of non-significant P values (P>0.05) does not provide a precise, quantitative, reliable metric favoring the null hypothesis, supporting the *absence* of a therapeutic effect.[1] That is because relations between sample sizes, trial power, P values and credibility of null hypotheses are complex: 'absence of evidence is not evidence of absence'.[2] A frequentist approach assumes all trials to be equally meaningful (apart from the weighing based on trial characteristics), and tends to ignore the overall picture upon publication of a single, extreme finding. It lacks a strong framework allowing to specify how trial results affect the overall odds of a specific treatment effect being plausible.

An alternative approach is using Bayesian methodology, which offers the opportunity to factor all previous RCT results in upon weighing the precise implications of new findings. This approach is based on an eighteenth-century theorem that offers a formal framework for how to update an initial belief following new observations. Following Keysers et al. we provide here a short explanation of a Bayesian approach in the context of the interpretation of new experimental findings. In the evaluation of a new therapy e.g., absence or presence of a beneficial effect, classically reflecting the null (H_0) or alternative (H_1) hypothesis respectively, may be equally believable initially. After obtaining the results from a first randomized clinical trial (RCT), e.g. in the form of an effect-size, beliefs on the (in)efficacy of a new therapy can be updated, according to the degree in which the RCT result supports either hypothesis. A description for such rival accounts in a Bayesian approach can be provided in the form of odds[1]:

$$\frac{p(H_0|data)}{p(H_1|data)} = \frac{p(H_0)}{p(H_1)} \times \frac{p(data|H_0)}{p(data|H_1)}$$

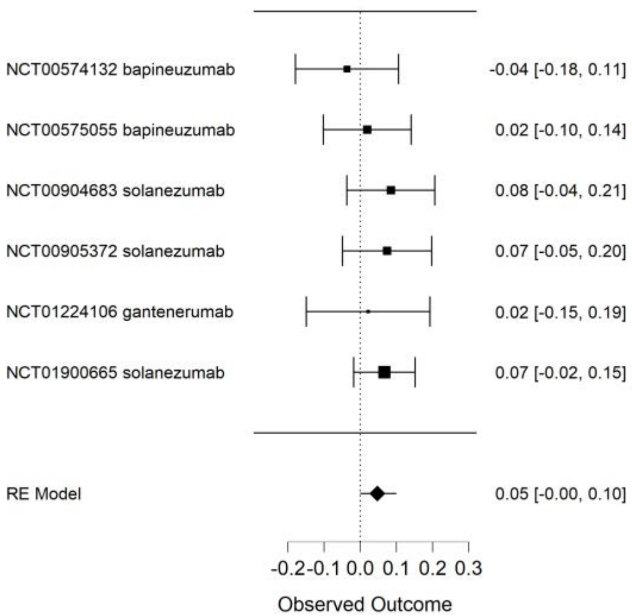
The posterior odds in the case of a meta-analysis can be calculated after including new data from each subsequent RCT. This is done by taking the product of the (prior) odds, based on all previously available RCT findings, and an updating factor based on the latest RCT data that have become newly available. The latter metric, the 'Bayes factor', reflects the relative performance of H_0 and H_1 in accounting for the findings in a given RCT. Calculation of this Bayes factor is based on different probability distributions of effects sizes under H_0 and H_1, respectively. Although rival hypotheses may have been equally plausible initially (i.e.: $p(H_0) = p(H_1) = 0.5$), thus with a prior hypothesis odds of 1, the results from a first RCT may indicate that these findings are 10 times more likely under H_1 than under H_0, rendering the posterior odds also 10, favoring H_1 in this example. In this case the RCT result has increased the probability of H_1 from 0.5 to $10/11 \approx 0.91$, as the posterior H_1

probability. A major advantage of Bayesian analysis as opposed to a frequentist approach, is its potential to quantify the strength of evidence in both directions, not only against H_0 but also in favor of H_0; i.e. the strength of evidence for absence of a therapeutic effect. See Keysers et al, for an in-depth review and more examples.[1]

Meta-analysis of AAB immunotherapy trials

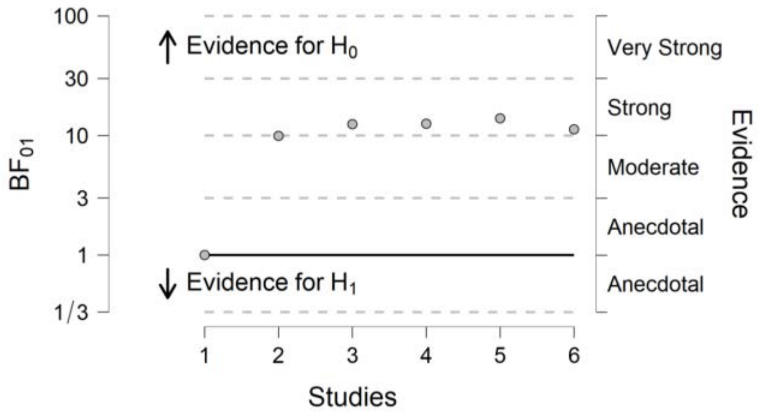
To compare a frequentist and Bayesian approach in the meta-analysis of AAB immunotherapy in AD, we performed a systematic literature search selecting publications on phase 3 AAB immunotherapy RCTs all using the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) as clinical outcome, to allow for comparison. As minimum quality criterion, studies had to include at least 50 AD patients in the main analysis who received active treatment in the highest dose, for at least 12 months. We chose this anti-conservative approach, i.e. only analyzing the groups receiving the highest dosage, to maximally benefit the intervention groups. This resulted in four papers on six RCTs including a total of 6597 participants studying the effects of solanezumab, gantenerumab, or bapineuzumab, all monoclonal antibodies against amyloid β, for 78-104 weeks.[3-6]

Figure 1. Hypothesis testing using a frequentists approach: Anti-amyloid beta immunotherapy in Alzheimer's disease



This forest plot displays six RCTs testing monoclonal antibodies and their Cohen's *d* effect sizes with confidence intervals based on a classical random-effects frequentists meta-analytical approach. The NCT numbers refer to the unique identification code given to clinical studies registered on ClinicalTrials.gov. The overall treatment effect was 0.048 (95% confidence interval: -0.001-0.096)

Figure 2. Hypothesis testing using a Bayesian approach: Anti-amyloid beta immunotherapy in Alzheimer's disease



This plot shows strong evidence for H_0. A Bayes Factor (BF) between 1/3 and 3 indicates insufficient evidence for either the null or alternative hypothesis, and a BF above 3 indicates evidence for the null hypothesis. The plot shows strong evidence supporting H_0 (no treatment effect, BF_{01}=11.27) and insufficient evidence for H_1 (beneficial treatment effect, BF_{10}=0.09).[1]

We first performed a traditional frequentist random-effects meta-analysis based on the published results of the primary analysis in all trials, using *Cohen's d* effect sizes for individual studies. This resulted in an overall treatment effect of 0.05 (95% confidence interval: -0.00 to 0.10, p=0.055), thus not rejecting the null-hypothesis (Figure 1). Subsequently, we used a Bayesian approach to investigate the plausibility of the null hypothesis being true (i.e. no treatment effect). We used the JASP software package to calculate sequential Bayes factors after adding each subsequent trial result. JASP stands for Jeffrey's Amazing Statistics Program in recognition of the pioneer of Bayesian inference Sir Harold Jeffreys. This is a free multi-platform open-source statistics package (https://jasp-stats.org), developed and continually updated by a group of researchers at the University of Amsterdam. Because also under a Bayesian framework certain assumptions have to be made, including that the probabilities stem from the same distribution, we used a random effects model. We used a Cauchy prior with scale 1/. This meta-analysis, based on the very same six RCTs as used for the frequentist analysis, yielded a final Bayes factor of 11.27 in favor of the null hypothesis, as opposed to a Bayes factor in favor of the alternative hypothesis of a beneficial treatment effect of 0.09 (Figure 2). The Bayes factor in favor of the null hypothesis should be interpreted as 'strong' support, thus going beyond the notion of 'not rejecting the null hypothesis' according to the frequentists approach.[1] Although the essence of a Bayesian approach is to interpret new information in the light of existing information, one may wonder whether results would have been different if RCT results would have appeared in a different order. Therefore, we have rerun the analyses adding the trials in a different order (i.e., arbitrarily, reverse order and by population size). This slightly changed the steps towards the final Bayes factor after including all six trials, but did not change the overall resulting Bayes factor, as expected.

Addition of a theoretical new RCT

Under the traditional frequentist statistical approach, addition of a new trial result that would have roughly a similar outcome as the previous six RCTs would further reduce the value of the p estimate, most probably reaching a value below 0.05, albeit without substantially affecting the estimate for the effect size. Under a Bayesian approach, we found that such a hypothetical, seventh study would require an unrealistic treatment effect with a Cohen's *d* effect size of at least 10 (standard error 0.02). Based on a typical ADAS-Cog standard deviation, such a scenario would require a study including at least 100.000 participants randomized 1:1 to active or placebo treatment and a difference between treatment groups of about 14-15 ADAS-Cog points at endpoint. As AD patients who receive placebo deteriorate about 4-5 ADAS-Cog points per year, this would require a study period of at least 3 years, assuming a complete halt of cognitive decline in the active treatment group. Under such an unlikely scenario an update of the current Bayesian meta-analysis would result only in equipoise between the AAB immunotherapy null hypothesis and its alternative, thus without favoring H_1 over H_0.

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Discussion

Based on these analyses of previously published clinical trial results, we conclude that there is strong *evidence of absence* of a therapeutic effect of AAB immunotherapy in Alzheimer's disease and that further pursuit of this approach in AD is likely futile, even if additional studies would replicate the findings available to date, and thus decrease the p value in a traditional frequentist meta-analysis by increasing the total number of subjects in such an analysis. The overall effect size based on the frequentist meta-analysis of these six RCTs of 0.05 is based on the difference between a yearly average deterioration of 4.5 ADAS-Cog points in 3288 placebo treated patients versus 4.1 points in 3309 patients with one of the three forms of AAB immunotherapy. This minute non-significant treatment effect of 0.4 ADAS-Cog points over a year, in the subgroups of trial participants subjected to the highest doses of AAB immunotherapy, invites the question how plausible a possible 'true' and clinically relevant treatment effect could still be. The strong support for the null hypothesis resulting from the Bayesian analysis renders a true absence of a treatment effect much more plausible.

The continued efforts of researchers and pharmaceutical companies towards persistent investment of research efforts, time and money in AAB immunotherapy may be partly driven by the relatively narrow framework of traditional frequentist statistical methods used.

Several methodological issues should be addressed. First, it could be argued that combining different specific AAB immunotherapeutic drugs in one meta-analysis may be problematic, despite the fact that all RCTs probed essentially the same hypothesis concerning AD therapy. However, a similar approach in hypertension, epilepsy or thromboembolic disease would have resulted in clear-cut conclusions concerning the efficacy of antihypertensives, antiepileptics or anticoagulants as drug-classes. Second, it could be argued that perhaps the target populations were not optimal in the studies that were used in the present analyses, and that in earlier RCTs even some patients without cerebral amyloidosis have been recruited, in whom it was on beforehand unlikely that an approach to remove amyloid-β from the brain would be effective. However, based on both in vivo amyloid-β imaging using PET and ex vivo study of cerebral amyloid-β load in trial participants who came to autopsy, there is no doubt that these AAB immunotherapies are potent drugs which can remove amyloid-β from the brain.[5,7] But even virtually complete removal of amyloid-β from the brain for more than 10 years could not protect AD patients from progression to severe dementia.[7] This renders the possibility of a type II error due to too short follow-up to detect an effect unlikely.

Third, the ADAS-Cog as outcome instrument could be questioned. However, this is a widely applied cognitive instrument which has a solid track record as outcome in AD research, including these major RCTs. In essence, the exact cognitive assessment instrument used as outcome in AD RCTs may be less relevant. Even if a minute, statistically significant treatment effect could be detected using a more sensitive, detailed outcome measure, this would most likely not meet the minimally clinically important difference if this difference could not be detected by the ADAS-Cog.

There is an important caveat to this interpretation. Current approaches in AD clinical trials implicitly assume AD to be a rather homogeneous condition, for which one specific intervention, in this case AAB immunotherapy, may be beneficial. However, the heterogeneity of underlying brain pathology has been recognized since long.[8]

In line with this recognition, more recent findings suggest that cerebrospinal fluid proteomics may define subtypes of AD that are potentially relevant from a pathophysiological perspective.[9] The same may hold for additional characteristics, resulting in both clinical as well as biological heterogeneity. If corroborated, this has major implications for selection of trial participants and development of interventions in the future. Delineation of relevant AD subgroups, for instance based on a combination of age at onset, genotype, phenotype, cerebral co-morbidity and the specific pathophysiological processes relevant in each individual patient will most likely be necessary, in order to deliver the right therapeutic intervention to the right patient. Better understanding of this heterogeneity will put neutral trial results in studies based on AD as a homogenous, generic category of disease in a new perspective and may invite new RCTs in these populations.

By contrasting the results of a traditional frequentist meta-analysis with the results from a Bayesian meta-analysis, and showing how an additional trial result would change the overall results of the latter meta-analysis, we illustrate that further pursuing AAB immunotherapy as treatment for AD as a rather homogeneous condition is likely futile. Even in the unlikely event of a new trial shifting the frequentist meta-analysis towards a significant difference, the Bayesian analysis would most likely still strongly favor the null-hypothesis over the alternative hypothesis. And the chance that a new RCT would not only shift the pooled effect size towards a significant difference, but also towards a clinically relevant effect is negligible.

Finally, there are important ethical and societal aspects that need to be addressed. All AAB immunotherapy probed has to be administered intravenously on a monthly basis, and most AAB immunotherapies have a considerable risk of adverse events, including Amyloid Related Imaging Abnormalities (ARIA), which may or may not cause serious symptoms.[10] This would be completely acceptable, if clinically important benefits could be expected, such as e.g. in chemotherapy for different forms of malignancies. Based on the currently available trial results it is highly unlikely that AAB immunotherapy will fundamentally change the course of disease in AD in a clinically meaningful way, therefore one could question whether further exposure of large numbers of older persons to this type of experimental therapy is justified. The potential target population for these drugs is very large, and the logistical challenge of intravenous administration and the accompanying costs of the infrastructure needed and the drug itself would be astronomical. Only a clinically relevant effect beyond any doubt could justify the societal burden of this expenditure on scarce healthcare resources.

Conclusion

Our message is threefold. First, based on six well-designed RCTs there is strong *evidence for absence* of an effect of AAB immunotherapy in AD. Second, the use of Bayes factor hypothesis testing allows for quantification of the plausibility of the null hypothesis, as opposed to traditional frequentist analysis, which only allows to conclude that there is absence of evidence. Third, whereas results from frequentist meta-analysis may invite the conclusion that additional studies to collect evidence may still be relevant, results from the Bayesian analysis strongly suggest the time has come to divert therapeutic efforts away from AAB immunotherapy. This leads to the potential to open up alternative lines of investigation that have more potential to bear fruit.

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Part IV

General discussion and summary

7

General discussion

Overview

The overall aim of this thesis was to evaluate possibilities for prevention and treatment of cognitive decline and dementia, focusing both on cardiovascular and lifestyle related risk factors. In the first part, we explored the relationship between cardiovascular risk factors and dementia in older individuals, and whether multidomain interventions targeting cardiovascular and lifestyle related risk factors might reduce cognitive decline. Next, we focused on blood pressure, an important risk factor for dementia, to better understand this relationship and investigate the potential of antihypertensive drug use as a cheap, accessible, and easily scalable strategy for dementia prevention. Lastly, we assessed the potential of anti-amyloid beta immunotherapy against Alzheimer's disease. In this chapter, I will expand on these results to evaluate them in a broader context regarding strategies for the prevention of cognitive decline and dementia within the framework of other relevant research, and discuss implications for clinical practice and future studies.

Part I | Dementia prevention strategies

Differential associations with ageing

There is a strong association between high risk factor values in midlife and the risk of cognitive decline and dementia.[1] Randomized controlled trials investigating multidomain interventions focusing at lowering these risk factors have not provided conclusive evidence that cognitive decline can be slowed.[2] One explanation for these results may be the inclusion of older people, since studies showed that the relationship of dementia with cardiovascular risk factors (SBP, BMI and cholesterol) is less clear and may even reverse with ageing.[3-8] In line with these studies, we observed the highest dementia risk in community dwelling older individuals with the lowest baseline values of SBP, BMI and non-HDL cholesterol (**chapter 2**). These results suggest that, in older individuals, low values may not always be better. Whereas previous studies focused on individual risk factors with low values, we showed that dementia risk was substantially higher for older adults with a combination of low values of SBP, BMI and non-HDL cholesterol than for the sum of these individual associations. These findings increase the plausibility that an overarching phenomenon, involving multiple risk factors, is associated with increased dementia risk. These observational associations do not necessarily reflect causality. The relationship could be causal, which would imply that target values of SBP, BMI and non-HDL cholesterol should be higher in older adults. Conversely, causality might be reversed, with low values of SBP, BMI and non-HDL cholesterol being early signs of neurodegeneration as part of an underlying disease eventually leading to dementia. Possibly, autonomic failure or change in behavior (due to apathy or depression) might lead to a reduction in blood pressure, cholesterol or weight. Because we used risk factor values measured at one time point, the change in risk factor value over time and its relation with dementia incidence is uncertain. However, longitudinal cohort studies assessing trajectories of cardiovascular risk factors with cognitive decline and dementia showed that cardiovascular risk factors start to decline long before a clinical dementia diagnosis.[9-12] A systematic review of trajectory studies suggested an increase in BMI and blood pressure for decades, followed by a decrease 5-10 years before dementia diagnosis.[10] This corresponds to the differential associations observed for risk factors in mid- and late life in observational studies. Future studies should further investigate causality in this relationship, however, this is challenging due to several methodological issues, as discussed later in this chapter.

Multidomain interventions

In 2006, the first large multidomain dementia prevention trial started with the aim to lower risk factor values and improve lifestyle related risk factors in an older unselected population, free from dementia at baseline.[13] In this trial, no effect of intensive vascular care was observed on incident dementia risk. In **chapter 3**, we combined individual participant data of two large multidomain intervention trials (preDIVA and MAPT) to increase power for overall and subgroup analyses, to optimize the selection of individuals for future dementia prevention trials.[13,14] We observed no effect on global cognition, symptoms of depression and apathy after 3-4 years of follow-up. Subgroup analyses showed that multidomain interventions may lead to less decline in cognitive function in those with low baseline cognitive scores. However, these results should be interpreted with caution because of the relatively low number of people included in this analysis and the post-hoc nature of the analyses.

Potential explanations for the neutral effects could, first, be the high levels of standard care in health care systems in the Netherlands (preDIVA) and France (MAPT) resulting in small differences between the control and intervention groups. Second, since most interventions were targeted at risk factors associated with dementia in midlife, the included population might have been too old for interventions to successfully reduce the risk of cognitive decline since this process might already have been initiated. In addition, as discussed previously, associations for risk factors seem to change from mid- to late life and target values may not have been optimal for the included populations. Lastly, although differences in study design and populations between both trials might improve external validity of our results, they likely also cause heterogeneity. However, no structural differences in intervention effects between both studies were observed.

The preDIVA and MAPT studies found no conclusive evidence of an effect of multidomain interventions in late life. In **chapter 2**, participants in the preDIVA trial were analyzed as an observational cohort. This study indicated that in older adults, low values of SBP, BMI and non-HDL cholesterol were associated with increased dementia risk, in particular when combined. Enhanced comprehension of these shifting associations from mid- to late life, and selection of older individuals with (combinations of) low values of risk factors in future studies may lead to better identification of individuals at higher risk for dementia. Age specific targets should be investigated in future randomized studies to assess whether low values of these risk factors are causally related to dementia. However, establishing the precise values of these targets will be challenging, and implementation is complicated by the relation of these risk factors with other cardiovascular outcomes.[15-18] Eventually, the aim is to improve prevention strategies by transitioning towards more personalized medicine.

Part II | Blood pressure, antihypertensive treatment and dementia

Blood pressure

As discussed in part I, the association between blood pressure and incident dementia may become inverse in late life. An individual participant data meta-analysis including >17,000 individuals from 7 studies, investigating the association of SBP with dementia risk in different decades reported inverse associations in older individuals, with U-shaped associations in the oldest age groups (aged >75).[8] These strong age dependent associations invite further research into age dependent blood pressure targets in relation to dementia risk, preferably in a randomized setting. Although trials have been performed using cognitive function or dementia as secondary outcome measure, none of these trials were specifically designed and powered for these outcomes.[9,19,20] A recent example is the SPRINT-MIND (Systolic Blood Pressure Intervention Trial - Memory and Cognition in Decreased Hypertension) trial, a substudy of the SPRINT trial that was powered for a reduction in cardiovascular events in older individuals with hypertension. Outcomes of the SPRINT-MIND trial suggested a 19% lower risk of mild cognitive impairment (MCI), and a 15% lower risk of MCI and probable dementia combined in the group targeting a SBP of < 120 mmHg versus <140 mmHg. The effects on probable dementia in the intervention group compared to the control group, and in subgroup analyses for older individuals (≥75 years) were similar, but not statistically significant.[20] The associations of intensive blood pressure lowering with reduced dementia risk in trials are inconsistent with the findings that older individuals with low blood pressure have the highest dementia risk reported in observational studies. This might, in part, be caused by the inclusion of individuals with hypertension in these trials, whereas observational studies assessed the effect of low blood pressure in a diverse group of people such as individuals with treated hypertension, healthy individuals, and individuals with low blood pressure possibly due to incipient neurodegenerative disease. Furthermore, frail older adults and adults with multimorbidity are often underrepresented in randomized controlled trials due to exclusion criteria.[21] Therefore, it is uncertain whether results of trials can be extrapolated to the real-life older population and should be used to inform clinical guidelines.

In addition to blood pressure level, fluctuations in blood pressure might affect the relationship between blood pressure and dementia.[22-25] To assess age dependent associations between blood pressure variability (BPV) and lifetime dementia risk we used a cohort of individuals with a follow-up duration of several decades, from midlife until dementia diagnosis or death.(**chapter 5**) No association was observed at age 60, 70, or 80 years. At age 90 years, individuals with higher BPV had an increased lifetime dementia risk. Meta-regression confirmed these associations at older ages, whereas SBP in late life was inversely associated with lifetime dementia risk. These findings align with a systematic review suggesting that, at older ages, high BPV may be a more important indicator of increased lifetime dementia risk than high blood pressure level.[26] Again, since this was an observational study the direction of causality is unknown, but a causal relationship seems less likely since no effect was observed in midlife. Reversed causality might be explained by autonomic failure due to extensive vascular damage or neurodegeneration as part of Alzheimer's disease, thereby disrupting normal regulation of blood pressure and resulting in higher variability. Antihypertensive medication (AHM) use did not affect the relationship between BPV and dementia risk in this study.

Differential effects of antihypertensive medications

Meta-analyses reported beneficial effects of blood pressure lowering using AHM treatment on cognitive impairment and dementia onset.[27,28] There is large variation in agents used to reduce blood pressure levels. Current hypertension guidelines state that ACE-inhibitors and angiotensin-II receptor blockers (ARBs) with addition of calcium channel blockers (CCBs) or diuretics are preferred first line treatments.[29]

However, results of our network meta-analysis, including all available evidence on AHM classes and dementia incidence, indicate that for dementia there may be potential differential effects. CCBs and ARBs were associated with lower incident dementia risk compared to ACE-inhibitors, diuretics and beta blockers in a combined analysis of 15 observational studies (**chapter 4**).

In contrast to our observations, two large individual participant data meta-analyses concluded that there were no differential effects between AHM classes on dementia incidence.[27,30] Both studies reported lower effect sizes for CCBs and ARBs, but results were not statistically significant and showed wide confidence intervals. In these studies, no direct comparisons between AHM classes were made, but single AHM classes were compared to all other AHM classes combined. These comparison groups include multiple AHM classes associated with both an increased and a decreased risk of dementia, resulting in an overall effect that is averaged out. Therefore, this might have contributed to the neutral effects in these studies. Adding the results of these studies to our network analysis did not substantially change our results. It is hypothesized that the differential effects might be caused by stimulation of type 2 and 4 angiotensin II receptors (angiotensin II receptor type 1 blockers, dihydropyridine calcium channel blockers, and thiazide diuretics).[31-35] However, in our network meta-analysis insufficient detailed data was available to analyze subcategories of AHM classes (e.g. (non-)dihydropyridine CCBs). To further investigate this hypothesis, a randomized controlled trial should be performed comparing AHM that stimulate vs inhibit type 2 and 4 angiotensin-II-receptors. If corroborated and reproduced in clinical trials, adaptation of preferred AHM class in clinical guidelines may contribute to the reduction of dementia incidence.

To conclude, blood pressure might be an important target for dementia prevention. It might serve as a marker for increased risk, and is an important modifiable risk factor in midlife. In addition to blood pressure lowering, adaptation of preferred first line treatment of hypertension might be a promising strategy to reduce dementia incidence.

Part III | Treatment of Alzheimer’s disease

Anti-amyloid beta immunotherapy remains a major focus of research into treatment of Alzheimer’s disease. Although anti-amyloid beta immunotherapy has shown to effectively reduce amyloid plaques in the brain, outcomes on cognition were discordant. Non-significant outcomes of frequentist anti-amyloid beta immunotherapy trials have been interpreted as inconclusive due to shortcomings in the design of the trial (e.g. sample size was too small, the follow-up too short to detect an effect, or the outcome measure was not sensitive enough), or 'bad luck' (sampling variability). The frequentist statistical approach used in these trials can lead to acceptance or rejection of the null-hypothesis, but cannot lead to rejection of the alternative hypothesis. In other words: frequentist analyses are able to show *absence of evidence*, but not *evidence of absence* of a therapeutic effect. In **chapter 6**, we used Bayesian statistics to provide an estimate of the *evidence of absence* of a therapeutic effect of anti-amyloid beta immunotherapy using the Bayes Factor. The Bayes Factor is a statistical measure used to quantify the relative plausibility of two competing hypotheses. Additionally, it quantifies the strength of evidence that the data provide for both hypotheses.[36] Our meta-analysis including large anti-amyloid beta trials showed strong *evidence of absence* of an effect of anti-amyloid beta immunotherapy on cognitive functioning. Data from aducanumab, lecanemab and donanemab trials were not included in our meta-analysis, since these were not published by the time of submission. While most of these more recent trials report significant differences between the control and intervention groups, the observed effects on cognition are modest.[37-39] Adding these studies to our meta-analysis may possibly affect the strength of the evidence, though not the direction of the effect size. The results of these latest trials were presented with pronounced optimism, but the clinical relevance of the modest effects on cognition have been called into question. Additionally, concerns regarding safety have been raised given the high incidence of adverse events, most importantly amyloid-related imaging abnormalities (ARIA), and large-scale implementation is expected to be hindered by significant practical barriers.[40] These considerations support the need to adopt a broader therapeutic strategy to delay the progression of Alzheimer's disease, beyond an exclusive focus on AAB clearance from the brain.

7

Challenges, implications, and perspectives

Methodological challenges

Dementia research is challenged by several methodological issues, some of which are already considered in previous sections. Here, some central themes will be discussed.

Dementia generally occurs in old age, and risk factors operate through a cumulative exposure-response relationship, indicating that prolonged exposure increases the risk of developing dementia. Hence, early interventions for risk factors in midlife might successfully reduce dementia risk, but to detect an effect on old age dementia incidence, unrealistically long follow-up periods of several decades are needed, leading to loss to follow up and dilution of treatment effect.[41] To overcome this issue, many clinical trials used surrogate outcomes to predict the future risk of dementia, such as change on cognitive scores. However, the correlation between these scores and dementia risk and their predictive value for future dementia is unknown. Still, all prevention trials, except preDIVA, used cognitive scores as primary outcome. For pragmatic reasons, most trials investigated the effect of interventions in older individuals, but with the neutral results observed, the question remains whether the advanced age of the participants included contributed to the absence of an effect, or if the interventions under study are truly ineffective.

Another limitation of clinical trials in general is that the individuals included are a selection of people from the general population, often with less comorbidities than the general population. Selection bias is an important limitation in the SPRINT-MIND trial, as discussed in part II of this discussion. This could have important implications for the external validity of the observed results. Although this is something to keep in mind, randomized controlled trials remain the gold standard to assess causality. Because of the challenges associated with clinical trials, a large share of dementia research is observational and demonstrating causality in these studies is difficult. In later life, survival bias might play a role, because individuals who lived up to old age may be less sensitive to the harmful effects of risk factors. Lastly, high values of cardiovascular risk factors increase the risk of cardiovascular mortality, potentially causing individuals to die before reaching the age at which dementia commonly occurs. To address this issue, we assessed the competing risk of death in our studies.

Lastly, studies comparing prevalence rates in different part of the world show that age-specific dementia incidence is declining in high income countries, where education, public health strategies and health care are generally of very high quality.[42,43] The largest increase in dementia prevalence is observed and expected in low- and middle income countries.[42] Large scale public health strategies such as improving cardiovascular health or adaptation of living environment could possibly reduce dementia incidence,[44] but it will be very difficult to reliably interpret observed changes in dementia incidence because many other factors than public health strategies alone will be at play (e.g. population ageing, population growth, increase in prevalence of risk factors despite public health strategies).

Implications for clinical practice

The studies in this thesis may enhance clinicians' awareness of (older) individuals at increased risk for dementia. Currently, there is room for clinicians' personal preference in the management of elevated blood pressure, since guidelines are not uniform when it comes to optimal blood pressure targets in older people[16,45] and recommend all five major AHM classes as initial treatment for hypertension.[29,45] If corroborated in randomized clinical trials, guidelines on first line treatment of hypertension might be modified based on associations observed for dementia risk. If future studies consistently show a higher risk of dementia in older individuals with low or declining values of SBP, BMI and/or non-HDL cholesterol, the effect of preventive medication in this group should be evaluated, and its use potentially reduced if found to be associated with an increased dementia risk. The aim is to improve dementia prevention strategies using more personalized medicine in which clinicians consider several individual specific factors such as age, life expectancy and risk factor values to estimate future dementia risk and evaluate the optimal treatment strategy.

Future perspectives

Several options for future studies have already been discussed in previous parts of this chapter. In short, observational studies should focus on change of risk factor values over time to better understand shifting associations from mid- to late life. The associations observed for (combinations of) low values of risk factors in old-aged adults should be confirmed in other studies. Both of these considerations could be combined into a single observational study including cognitively healthy older individuals followed until dementia diagnosis or death, with repeated measurements of risk factor values over time. This allows for trajectory analyses of risk factor values and their relation with dementia risk. Declining values in the years before dementia diagnosis might provide more support for a non-causal relationship opposed to a causal relationship. Naturally, the effects of factors such as the use of AHM and/or statins and lifestyle interventions should be considered.

To minimize the risk of bias and confounding in the observed observational effects for AHM classes, AHM that stimulate vs inhibit type 2 and 4 angiotensin-II-receptors should be compared in a randomized clinical trial. Ideally, this should be a simple randomized controlled trial design, including a large group of people with few exclusion criteria, to increase generalizability to the real-world situation.

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8

Summary

Introduction

Brain disease causing dementia is one of the leading causes of disability and death worldwide,[1] and the number of people living with dementia is expected to sharply rise in the coming decades.[2] The exact pathogenesis of Alzheimer's disease, as the leading cause of dementia, is unclear and currently there is no curative treatment. Several risk factors have been identified, combined accounting for 40% of global dementia cases.[3] Most of these risk factors are modifiable and potential targets for interventions, but studies assessing these interventions reported inconsistent results.[4,5] Therefore, in this thesis, we aimed to provide a better understanding of the relationship between risk factors for cognitive decline and dementia, to improve prevention strategies and treatment of dementia.

Part I | Dementia prevention strategies

Better identification of older individuals at an increased risk of dementia may contribute to improved prevention strategies. Hypertension and obesity are important risk factors for dementia in midlife.[3] In late life, low values for blood pressure, body mass index (BMI), and non-high-density lipoprotein (HDL) cholesterol have all been associated with increased dementia risk.[6-11] In **chapter 2**, we investigated the associations between these risk factors and the risk of dementia in older individuals (aged 70-78 years) after a median follow-up of 10.3 years.[12,13] This study included 2789 community-dwelling older individuals (median age 74 years) of which 308 (11%) developed dementia. Individuals with low values for SBP, BMI or non-HDL cholesterol had a higher dementia risk compared to individuals without any low values. Dementia risk was substantially higher in individuals with a combination of low values for all 3 risk factors than expected based on a dose-response relationship (302% vs 18% and 28% for 1 or 2 low values). These results could not be explained by any specific combination of 2 risk factors, increasing the plausibility that an overarching phenomenon involving multiple risk factors simultaneously might precede a clinical dementia diagnosis.

Several large trials investigated the effect of simultaneously targeting multiple cardiovascular and lifestyle related risk factors to prevent cognitive decline and dementia in older adults. No effect of multidomain interventions has been observed for incident dementia, and results for cognitive functioning are inconsistent.[14] In **chapter 3**, we pooled individual participant data from two large multidomain intervention trials targeting cardiovascular and lifestyle related risk factors to increase the power to detect an effect, both overall and in subgroups, that could potentially benefit more from multidomain interventions.[13,15] In total, 4162 nondemented individuals from the general population were included. After a median follow-up duration of 3.7 years no differences between intervention and control groups were observed on change in cognitive scores and symptoms of depression and apathy scores. In individuals with low baseline cognitive function (MMSE <26) less decline of the MMSE in the intervention group was observed. As this analysis concerned a post hoc defined subgroup, these findings require replication in a new trial of a multidomain intervention.

Part II | Blood pressure, antihypertensive treatment and dementia

Midlife hypertension is an important risk factor for dementia[3,16] and blood pressure lowering may reduce incident dementia risk.[17-19] Differential effects of AHM classes have been described, but studies reported inconsistent results.[20,21] Therefore, in **chapter 4**, we systematically investigated differential effects of antihypertensive medication classes on dementia risk using network meta-analysis. Data on AHM classes were available for 649,790 individuals from fifteen observational studies and seven randomized controlled trials and 19,600 individuals (3.02%) were diagnosed with dementia. Network meta-analysis including observational studies showed that treatment with calcium channel blockers (CCBs) or angiotensin II receptor blockers (ARBs) was associated with 7-17% lower dementia risks compared to treatment with other antihypertensive medication classes (angiotensin converting enzyme (ACE) inhibitors, beta blockers and diuretics). Similar results were observed for network meta-analysis including observational studies and RCTs combined. The number of RCTs included was too low to preform robust network-meta analysis including RCTs only. These results should be corroborated in randomized studies. Considering the high prevalence of hypertension, wide availability and low-costs of AHM treatment, implementation of CCBs or ARB as preferred first line treatment options might have major impact on global dementia incidence.

To better understand the complex relationship between blood pressure and dementia, the association between visit-to-visit blood pressure variability (BPV) and lifetime dementia risk at different ages during life was assessed in **chapter 5**. For this study, we used blood pressure data from 820 individuals aged 65 years or older, free from dementia at baseline. A mean of 28.4 yearly SBP measurements were available per individual over an average of 31.5 years and dementia was diagnosed in 372 (45%). There was no association between higher BPV and lifetime dementia risk at ages 60, 70 and 80. At age 90, dementia risk was 35% higher with one SD increment in BPV. Meta-regression confirmed these findings, while the association between SBP and lifetime dementia risk shifted direction from positive to negative with higher ages. These results lower the probability that high BPV and dementia are causally related. In addition to mean SBP, BPV may help estimate dementia risk in older individuals, but has lower potential as a target for dementia prevention.

Part III | Treatment of Alzheimer's disease

The effect of anti-amyloid beta immunotherapy as a treatment for Alzheimer's disease was systematically assessed in **chapter 6**. A systematic search yielded 6 large phase 3 trials including at least 50 Alzheimer's disease patients who received active treatment for at least 12 months. Frequentist meta-analysis showed *absence of evidence* for a therapeutic effect, with Cohen's d effect size of 0.05 (95% CI -0.00 to 0.10, P = 0.055). This corresponds to 0.4 points per year on the ADAS-cog, which is well below the minimally clinically important difference which has been suggested to be in the range of 3 points.[22,23] Bayesian meta-analysis showed strong *evidence of absence* of a therapeutic effect, with a Bayes factor of 11.27 supporting the null hypothesis (there is no effect of the intervention) and a Bayes factor of 0.09 supporting the alternative hypothesis (there is an effect of the intervention). A Bayes factor of >3 is considered moderate evidence, and a Bayes factor of >10 is considered strong evidence. This led to the conclusion that there was strong *evidence of absence* of an effect of anti-amyloid beta immunotherapy for Alzheimer's disease based on these six randomized controlled trials.

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9

Nederlandse samenvatting

Introductie

Hersenziekten die dementie veroorzaken behoren wereldwijd tot de belangrijkste oorzaken van invaliditeit en sterfte,[1] en het aantal mensen met dementie zal de komende decennia naar verwachting sterk stijgen.[2] De exacte pathogenese van de ziekte van Alzheimer, als de meest voorkomende vorm van dementie, is onduidelijk en er bestaat momenteel geen curatieve behandeling. Er zijn verschillende risicofactoren geïdentificeerd, die samen verantwoordelijk zijn voor 40% van alle gevallen van dementie wereldwijd.[3] De meeste van deze risicofactoren zijn beïnvloedbaar en daardoor potentiële aangrijpingspunten voor interventies. Studies die deze interventies evalueren rapporteren echter inconsistente resultaten.[4,5] In dit proefschrift wilden we daarom de relatie tussen risicofactoren van cognitieve achteruitgang en dementie beter leren begrijpen, om strategieën voor de preventie en behandeling van dementie te kunnen verbeteren.

Deel I | Dementie preventiestrategieën

Een betere identificatie van mensen met een verhoogd risico op dementie kan bijdragen aan betere preventiestrategieën. Hypertensie en obesitas zijn belangrijke risicofactoren voor dementie op middelbare leeftijd.[3] Op latere leeftijd zijn lage waarden voor bloeddruk, body mass index (BMI) en niet-'high-density' lipoproteïne (HDL) cholesterol in verband gebracht met een verhoogd risico op dementie.[6-11] In **hoofdstuk 2** onderzochten we de associaties tussen deze risicofactoren op latere leeftijd (70-78 jaar) en het optreden van dementie na een mediane follow-up van 10,3 jaar.[12,13] In deze studie werden 2789 thuiswonende ouderen (mediane leeftijd 74 jaar) geïncludeerd waarvan er 308 (11%) dementie ontwikkelden. Mensen met lage waarden voor systolische bloeddruk, BMI of niet-HDL-cholesterol hadden een hoger dementierisico in vergelijking met mensen zonder lage waarden. Het risico op dementie was aanzienlijk hoger bij mensen met een combinatie van lage waarden voor alle 3 de risicofactoren dan verwacht op basis van een dosis-responsrelatie (302% vs 18% en 28% voor 1 of 2 lage waarden). Deze resultaten konden niet worden verklaard door een specifieke combinatie van 2 risicofactoren, waardoor het aannemelijker wordt dat er sprake is van een overkoepelend fenomeen waarbij meerdere risicofactoren tegelijkertijd betrokken zijn, dat vooraf gaat aan de klinische diagnose van dementie.

Verschillende grote studies onderzochten het effect van het gelijktijdig adresseren van meerdere cardiovasculaire en leefstijl-gerelateerde risicofactoren om cognitieve achteruitgang en dementie bij ouderen te voorkomen. Er is echter geen effect van multidomein interventies waargenomen op de incidentie van dementie, en de resultaten voor cognitief functioneren zijn inconsistent.[14] In **hoofdstuk 3** hebben we gegevens samengevoegd van individuele deelnemers uit twee grote multidomein interventiestudies gericht op cardiovasculaire en leefstijl gerelateerde risicofactoren om de kans op het detecteren van een effect te vergroten, zowel in de gehele onderzoeksgroep als in subgroepen die mogelijk meer baat zouden kunnen hebben bij multidomein interventies.[13,15] In totaal werden 4162 personen zonder dementie uit de algemene bevolking geïncludeerd. Na een mediane follow-up duur van 3,7 jaar werden geen verschillen tussen interventie- en controlegroepen waargenomen in verandering van cognitieve scores en scores voor symptomen van depressie en apathie. Bij personen met een lage cognitieve functie (MMSE <26) bij aanvang van de studie werd minder achteruitgang van de MMSE in de interventiegroep waargenomen. Aangezien deze analyse verricht werd in een post-hoc gedefinieerde subgroep, moeten deze bevindingen worden herhaald in een nieuwe studie met een multidomein interventie.

Deel II | Bloeddruk, bloeddrukverlagende behandeling en dementie

Hypertensie op middelbare leeftijd is een belangrijke risicofactor voor dementie[3,16] en verlaging van de bloeddruk kan het risico op dementie verkleinen.[17-19] Terwijl verschillende effecten tussen groepen bloeddrukverlagende middelen werden beschreven, waren deze niet consistent over de betrokken studies.[20,21] Daarom hebben we in **hoofdstuk 4** systematisch de effecten van verschillende groepen antihypertensiva op het risico op dementie onderzocht met behulp van netwerk meta-analyse. Gegevens over groepen antihypertensiva waren beschikbaar voor 649.790 personen uit vijftien observationele onderzoeken en zeven gerandomiseerde onderzoeken met controlegroep (RCT) en bij 19.600 personen (3,02%) werd dementie vastgesteld. Netwerk meta-analyse van de observationele studies toonde aan dat behandeling met calciumkanaalblokkers (CCB's) of angiotensine II receptorblokkers (ARB's) geassocieerd was met een 7-17% lager risico op dementie in vergelijking met behandeling met andere groepen antihypertensiva (angiotensine-converterend enzym (ACE) remmers, bètablokkers en diuretica). Vergelijkbare resultaten werden waargenomen bij de netwerk meta-analyse met observationele onderzoeken en RCT's gecombineerd. Het aantal geïncludeerde RCT's was te laag om een degelijke netwerk meta-analyse met alleen RCT's uit te voeren. Deze resultaten moeten worden bevestigd in gerandomiseerde onderzoeken. Gezien de hoge prevalentie van hypertensie, brede beschikbaarheid en lage kosten van behandeling met antihypertensiva, zou implementatie van CCB's of ARB's als eerstelijnsbehandeling grote invloed kunnen hebben op de wereldwijde incidentie van dementie.

Om de complexe relatie tussen bloeddruk en dementie beter te begrijpen, werd in **hoofdstuk 5** de associatie tussen de bezoek-tot-bezoek variabiliteit in bloeddruk (BBVB) en het levenslange risico op dementie op verschillende leeftijden beoordeeld. Voor deze studie gebruikten we gegevens over de bloeddruk van 820 personen van 65 jaar of ouder, die geen dementie hadden bij aanvang van de studie. Gemiddeld waren 28,4 jaarlijkse systolische bloeddruk metingen beschikbaar per individu over een gemiddelde periode van 31,5 jaar en werd bij 372 (45%) van hen dementie gediagnosticeerd. Er was geen verband tussen een hogere BBVB en het levenslange risico op dementie op 60-, 70- en 80-jarige leeftijd. Op 90-jarige leeftijd was het risico op dementie 35% hoger met één SD stijging in BBVB. Meta-regressie bevestigde deze bevindingen, terwijl de associatie tussen bloeddruk en het levenslange risico op dementie verschoof van positief naar negatief met het stijgen van de leeftijd. Deze resultaten verlagen de waarschijnlijkheid dat hoge BBVB en dementie oorzakelijk met elkaar samenhangen. In aanvulling op de gemiddelde systolische bloeddruk, kan BBVB helpen bij het schatten van het risico op dementie bij oudere mensen, maar heeft veel minder potentieel als doel voor preventie van dementie.

Deel III | Behandeling van de ziekte van Alzheimer

Het effect van immunotherapie tegen bèta-amyloïd als behandeling voor de ziekte van Alzheimer werd systematisch beoordeeld in **hoofdstuk 6**. Een systematische zoekactie leverde 6 grote fase 3-onderzoeken op met ten minste 50 patiënten met de ziekte van Alzheimer die gedurende ten minste 12 maanden een actieve behandeling kregen. Frequentistische meta-analyse toonde *afwezigheid van bewijs* voor een therapeutisch effect, met Cohen's d effectgrootte van 0,05 (95% CI -0,00 tot 0,10, P = 0,055). Dit komt overeen met 0,4 punten per jaar op de ADAS-cog, wat ruim onder het minimaal klinisch relevant verschil ligt waarvan wordt gesuggereerd dat het in de orde van 3 punten ligt.[22,23] Bayesiaanse meta-analyse toonde sterke *aanwijzingen voor de afwezigheid* van een therapeutisch effect, met een Bayes-factor van 11,27 ter ondersteuning van de nulhypothese (er is geen effect van de interventie) en een Bayes-factor van 0,09 ter ondersteuning van de alternatieve hypothese (er is wel een effect van de interventie). Een Bayes-factor van >3 wordt beschouwd als matig bewijs, en een Bayes-factor van >10 als sterk bewijs. Dit leidde tot de conclusie dat er op basis van deze zes gerandomiseerde gecontroleerde onderzoeken sterke aanwijzingen zijn voor de afwezigheid van een effect van immunotherapie tegen bèta-amyloïd bij de ziekte van Alzheimer.

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Appendices

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Dankwoord

Dissertations of the Vascular disorders of movement research group

Donders Graduate School for Cognitive Neuroscience

Research Data Management plan

Ethics and privacy

This thesis is based on the results of research involving human participants (or existing data from published papers), which were conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct and Radboudumc policy. Recognized Medical Ethics Review Committees have given approval to conduct these studies: 'METC AMC' for PreDIVA, 'METC Amsterdam UMC' for POE, the French Ethical Committee located in Toulouse (CPP SOOM II) for MAPT, and the institutional review boards of Kaiser Permanente Washington and the University of Washington for ACT.

The privacy of the participants in the studies was warranted by the use of pseudonymization. The pseudonymization key was stored on a secured network drive that was only accessible to members of the project who needed access to it because of their role within the project. The pseudonymization key was stored separately from the research data.

Written informed consent was obtained from participants to collect and process their data by the respective research groups.

Data collection and storage

All chapters are based on data of which Radboudumc is not the owner. The data used in chapter 2 and 3 is owned by the PreDIVA research group (AmsterdamUMC). The data used in chapter 3 is owned by the MAPT study group (INSERM UMR 1027, Toulouse, France and University of Toulouse III, Toulouse, France). The data used in chapter 5 is owned by the ACT study group (Kaiser Permanente Washington Health Research Institute). Data were stored and analyzed at department of neurology of the AmsterdamUMC.

Data sharing according to the FAIR principles

All studies are published open access.

Chapters 2 and 3 are based on existing data, which was obtained by the PreDIVA research group and available for reuse upon reasonable request from the original authors (doi:10.1016/S0140-6736(16)30950-3).

Chapter 3 is based on existing data, which was obtained the MAPT research group and available for reuse upon reasonable request from the original authors (doi: 10.1016/S1474-4422(17)30040-6).

Chapter 5 is based on existing data, which was obtained from the Adult Changes in Thought research group from Kaiser Permanente Washington Health Research Institute and available for reuse upon reasonable request from the original authors (https://www.actagingresearch.org/).

About the author

Melina den Brok was born on February 14th, 1992, in Oss, the Netherlands. She graduated from high school in 2010 and was subsequently admitted to the Medicine program at the University of Amsterdam through a selective decentralized admissions process.

During medical school, she became involved in several research groups, including at the Department of Neurology at Amsterdam UMC, location AMC, where she successfully completed both her Bachelor's and Master's theses.

After obtaining her medical degree in January 2018, she began working as a non-training resident at the Department of Neurology at Noordwest Ziekenhuisgroep in Alkmaar. In 2019, her interest in research led to a position as a PhD candidate at the Department of Neurology at Radboudumc in Nijmegen and Amsterdam UMC, location AMC.

Since 2022, she has been working as a neurology resident in training at the Radboudumc, where she continues to work with great enthusiasm.

Melina lives in Nijmegen together with Marcel and their daughter Isa.

List of publications

This thesis

1. **den Brok MGHE**, Hoevenaar-Blom MP, Coley N, Andrieu S, van Dalen JW, Meiller Y, Guillemont J, Brayne C, van Gool WA, Moll van Charante EP, Richard E. The Effect of Multidomain Interventions on Global Cognition, Symptoms of Depression and Apathy – A Pooled Analysis of Two Randomized Controlled trials. The Journal of Prevention of Alzheimer's Disease 2021.

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* shared authorship

Portfolio

Presentations at international conferences

Sept 2021 European Stroke Conference, Helsinki, online
Title: The Effect of Multidomain Interventions on Global Cognition, Symptoms of Depression and Apathy – A Pooled Analysis of Two Randomized Controlled trials

Title: Very long term visit-to-visit blood pressure variability and the risk of dementia in the Adult Changes in Thought study

July 2021 Alzheimer's Association International Conference, Denver USA, online
Title: Very long term visit-to-visit blood pressure variability and the risk of dementia in the Adult Changes in Thought study

Nov 2020 European Stroke Conference, Vienna, online
Title: Antihypertensive Medication Classes and the Risk of Dementia: A Systematic Review and Network Meta-Analysis

Aug 2020 Alzheimer's Association International Conference, Amsterdam, online
Title: Antihypertensive Medication Classes and the Risk of Dementia: A Systematic Review and Network Meta-Analysis

Courses

- Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK), Nijmegen
- Scientific integrity for PhD candidates, Nijmegen
- Scientific writing for PhD candidates, Nijmegen
- Writing a review, Nijmegen
- Presentation skills, Nijmegen
- Advanced conversation, Nijmegen
- Achieving your goals, Nijmegen
- CV en motievatiebrief, Nijmegen
- Het sollicitatiegesprek, Nijmegen

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- Liselore Snaphaan. Epidemiology of post stroke behavioral consequences. Radboud University Nijmegen, 12 March 2010.
- Karlijn F. de Laat. Motor performance in individuals with cerebral small vessel disease: an MRI study. Radboud University Nijmegen, 29 November 2011.
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- Rob Gons. Vascular risk factors in cerebral small vessel disease. A diffusion tensor imaging study. Radboud University Nijmegen, 10 December 2012.
- Loes C.A. Rutten-Jacobs. Long-term prognosis after stroke in young adults. Radboud University Nijmegen, 14 April 2014.
- Noortje A.M.M. Maaijwee. Long-term neuropsychological and social consequences after stroke in young adults. Radboud University Nijmegen, 12 June 2015.
- Nathalie E. Synhaeve. Determinants of long-term functional prognosis after stroke in young adults. Radboud University Nijmegen, 28 September 2016.
- Anil M. Tuladhar. The disconnected brain: mechanisms of clinical symptoms in small vessel disease. Radboud University Nijmegen, 4 October 2016.
- Pauline Schaapsmeerders. Long-term cognitive impairment after first-ever ischemic stroke in young adults: a neuroimaging study. Radboud University Nijmegen, 24 January 2017.
- Ingeborg W.M. van Uden. Behavioral consequences of cerebral small vessel disease; an MRI approach. Radboud University Nijmegen, 14 February 2017.
- Renate M. Arntz. The long-term risk of vascular disease and epilepsy after stroke in young adults. Radboud University Nijmegen, 16 February 2017.
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- Annemieke ter Telgte. On the origin of cerebral small vessel disease. From in vivo to ex vivo to histopathology. Radboud University Nijmegen, 9 June 2020.
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- Mengfei Cai. Temporal dynamics of cerebral mall vessel disease. A motor perspective. Radboud University Nijmegen, 19 April 2022.
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- Ileana Camerino. White matter tracts associated with executive aspects of language production in small vessel disease and stroke. Radboud University Nijmegen, 27 September 2022
- Merel Sanne Ekker. Stroke in the young: from epidemiology to prognosis. Radboud University Nijmegen, 27 September 2022.
- Hanna Abdulrahman. Dementia risk factors and diagnostics. Radboud University Nijmegen, 5 juli 2023.
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- Lotte Sondag. Towards new acute treatments for spontaneous intracerebral hemorrhages - The role of surgery and perihematomal edema, Radboud University Nijmegen, 30 September 2024
- Mayra I. Bergkamp. The clinical spectrum of cerebral small vessel disease. Radboud University Nijmegen, 4 December 2024
- Gemma S. Guardia. Brain under pressure. Association between hypertension and cerebral small vessel disease. Radboud University Nijmegen, 7 Maart 2025
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- Mina A. Jacob. The course of Cerebral Small Vessel Disease. Radboud University Nijmegen, 13 Mei 2025
- Resa J. van Lith. Unmasking COVID-19 - Cerebral consequences from a neuroimaging perspective. Radboud University Nijmegen, 25 Juni 2025.

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