Prevention of Dementia by Intensive Vascular Care (preDIVA) – a 6-year cluster-randomised controlled trial

Eric P. Moll van Charante MD, Edo Richard* MD, Lisa S. Eurelings MD, Jan-Willem van Dalen MSc, Suzanne A. Ligthart MD, Emma F. van Bussel MD, Marieke P. Hoevenaar-Blom PhD, Prof. Marinus Vermeulen MD, Prof. Willem A. van Gool MD*

* These authors contributed equally

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Correspondence to:

Prof. W.A. van Gool

Department of Neurology

Academic Medical Centre/ University of Amsterdam

Meibergdreef 9

1100 DD Amsterdam

w.a.vangool@amc.uva.nl

Tel. 0031-20-5663842/0031-6-21824003

Department of Neurology (Academic Medical Centre, Amsterdam)

Dr. E Richard, LS Eurelings, JW van Dalen, Dr. MP Hoevenaar-Blom, Prof. M Vermeulen, Prof. WA van Gool

Department of General Practice (Academic Medical Centre, Amsterdam)

Dr. EP Moll van Charante, Dr. SA Ligthart, EF van Bussel

Department of Neurology (Radboud University Medical Centre, Nijmegen)

Dr. E Richard

Summary

Background Cardiovascular risk factors are associated with an increased risk of dementia. We assessed whether a multidomain intervention targeting these factors can prevent dementia in a population of community-dwelling older people.

Methods In an open-label cluster randomised controlled trial with blinded outcome adjudication we recruited individuals aged 70–78 years through general practices (GPs). Computer-generated allocation was done for all GP practices within each health care centre (HCC), assigning them to a 6-year nurse-led, multidomain cardiovascular intervention or a control group (usual care). Primary outcomes were cumulative dementia incidence and disability. Main secondary outcomes were incident cardiovascular disease (CVD) and mortality. Primary analyses were by intention to treat. International Clinical Trials Registry, number ISRCTN29711771.

Findings Between June 2006 and March 2009, 116 GPs (3526 persons) within 26 HCCs were recruited and randomly assigned: 63 (n=1890) to the intervention and 53 (n=1636) to the control group.

Primary outcome data were obtained for 3454 persons (98%); median follow-up of was 6·7 years (21,341 person-years). Dementia developed in 6·5% of intervention vs. 7·0% of control participants (HR 0·92, 95%CI 0·71-1·19, p=0·54). There was no difference in disability, mortality or incident CVD. In participants with baseline hypertension, systolic blood pressure decreased more in the intervention group (adjusted mean difference -2·93 mmHg, 95%CI -4.29;-1·57).

Interpretation In the preDIVA study population, a nurse-led, multidomain intervention did not result in a reduced incidence of all-cause dementia. Treatment contrast may have been insufficient because of modest baseline cardiovascular risks and high standards of usual care. Therefore, our results do not rule out clinically meaningful effects in adherent persons with untreated hypertension.

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Research in context

Systematic review

We searched Pubmed, www.isrctn.com, ClinicalTrials.gov and WHO's International Clinical Trial Registry Platform up to Feb 19, 2016, to identify multidomain randomised controlled trials. Search terms were "prevention" and "dementia", "cognitive impairment" or "Alzheimer's disease". Further selection criteria included primary outcome dementia; lifestyle interventions in combination with drug treatment; age 60 years or older; and duration at least 2 years. We based criteria on the 2010 National Institutes of Health Evidence Report on Preventing Alzheimer's Disease and Cognitive Decline.

We identified two randomised controlled trials. The Multidomain Alzheimer Preventive Trial (MAPT; NCT00672685) has been completed but not yet published. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), which combined lifestyle interventions, drug treatment and cognitive training recently showed a small improvement on a composite score of tests for cognitive functioning after two years.

Added value of the study

To our knowledge, the Prevention of Dementia by Intensive Vascular care (preDIVA) is the first large, long-term trial in older unselected persons on the effectiveness of a multidomain cardiovascular intervention using all-cause dementia as a primary outcome. Although overall findings were neutral, subgroup analyses suggested potential beneficial effects on non-Alzheimer's disease and on all-cause dementia in adherent participants, especially those with untreated hypertension at baseline.

Interpretation

The strong association between cardiovascular risk and all-cause dementia suggests a window of opportunity for dementia prevention. The preDIVA-study was performed in a public health context, where small, sustained changes can have substantial long-term effects among unselected older persons. The window of opportunity for dementia prevention by improving cardiovascular risk factor management in health care systems with high levels of usual care in place may have been relatively small and perhaps further attenuated by a declining age-specific dementia incidence rate. Our sensitivity analyses suggest a potential benefit in adherent persons, especially those with untreated hypertension. Therefore, this type of dementia prevention strategies might have a larger impact in low- and middle income countries with generally lower levels of cardiovascular risk management and a large projected increase of dementia prevalence over the next decades.

Introduction

Dementia currently affects over 36 million individuals worldwide and the prevalence is expected to increase dramatically over the next decades.[1] The WHO and the G8 acknowledge the major societal challenge this will cause and urge for strategies aiming to prevent dementia.[2]

Observational studies have repeatedly shown an association of vascular and lifestyle related risk factors with incident dementia in people older than 65 years (over 90% of all dementia patients).[3] Furthermore, population-based autopsy studies suggest that in addition to Alzheimer's disease (AD) pathology, vascular pathologies underlie a considerable proportion of dementias.[4] It has been estimated that up to 30 percent of all AD is attributable to potentially modifiable, mostly vascular risk factors.[5] This suggests a substantial window of opportunity for dementia prevention.[6] Randomised controlled trials (RCT) targeting vascular and lifestyle related risk factors with cognitive decline or dementia as (secondary) outcome, have mostly addressed single risk factors, including hypertension, physical inactivity, unhealthy diet, and smoking.[7] Findings were mixed and meta-analyses regarding antihypertensive treatment to prevent dementia have reached divergent conclusions.[8,9] This may be explained by differences between study populations, short follow-up periods (≤2 years), insufficient sample sizes, and attrition bias.[10] Fears of side-effects from antihypertensive treatment, including counterproductive effects on cognition, further complicate treatment decisions on blood pressure lowering in older persons.[11]

In the Prevention of Dementia by Intensive Vascular care trial (preDIVA) we assessed the effects of a six-year nurse-led multi-domain intervention targeting vascular and life-style related risk factors on the prevention of dementia in 3526 older persons from a general population.

Methods

Study Design and participants

The preDIVA trial was a pragmatic, multisite, cluster-randomized, open trial carried out in 116 family practices in 26 health care centres (HCCs) in the Netherlands. The study protocol has been published previously.[12] A population-based approach was used, inviting all community-dwelling older people aged 70 to 78 years registered with a participating family practice (>98% of the Dutch population is registered). The only exclusion criteria were dementia and other conditions likely to hinder successful long-term follow-up according to their general practitioner (GP) (e.g. terminal illness, alcoholism). Recruitment was from June 7, 2006, through March 12, 2009. The detailed enrolment procedure is provided in the appendix. The study was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam. Participants gave written informed consent prior to their baseline visit.

Randomisation and masking

After completion of all baseline visits at a HCC, cluster randomisation took place with GP practice as the unit of randomisation, to minimise contamination at the level of GP practice. A centralised computer algorithm was used by the Clinical Research Unit, not involved in the study in any other way, with HCCs as blocks, and family practices as clusters, in equal proportions for both conditions, allowing a maximum difference of 250 participants between groups, to accommodate differences in cluster size and number of clusters per HCC (median 4, IQR 3-6). Within each HCC at least one GP practice was randomised to the intervention condition. All outcome assessors were blinded to treatment allocation and were not involved in intervention activities. The final clinical assessment was performed by an independent investigator blinded to treatment allocation.

Procedures

The intervention comprised of four-monthly visits to a practice nurse in the GP practice, over a period of six years (18 visits). During these visits, cardiovascular risk factors were scrutinized: smoking habits, diet, physical activity, weight, and blood pressure. Blood glucose and lipids were assessed every two years and when indicated otherwise. Based on these assessments, individually tailored lifestyle advice was given according to a detailed protocol conform prevailing Dutch GP-guidelines on cardiovascular risk management and supported by motivational interviewing techniques. If indicated, drug treatment of hypertension, dyslipidaemia, and type 2 diabetes mellitus (T2DM) was initiated or optimised and antithrombotics were started.

Medication adherence was improved where appropriate. Five educational sessions for all nurses were organised along the study-course to strengthen the consistency of the intervention. The control

participants received usual care, according to the prevailing standards for cardiovascular risk management (appendix).

Baseline data on demographic characteristics, cardiovascular and family history, medication use, and self-reported diet and smoking habits were collected and cross-checked with the participants' electronic health records (EHRs). Physical activity was assessed using the LASA Physical Activity Questionnaire (LAPAQ), disability using the Academic Medical Center Linear Disability Score (ALDS), cognitive function using the Mini-Mental State Examination (MMSE) and Visual Association Test (VAT), and depressive symptoms using the 15-item Geriatric Depression Scale (GDS-15) (appendix). Anthropometrics and blood pressure were measured using a standardised protocol and blood samples were obtained for lipid spectrum and blood glucose. Genomic DNA was stored and used for apolipoprotein-E (APOE) genotyping.

All measurements were repeated during 2-yearly follow-up assessments. To allow participants recruited early into the trial to continue follow-up until all assessments were completed, the study was extended up to 8 years for participants randomised in 2006-7.

Dementia diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV[13] and classified into Alzheimer's disease, vascular dementia, dementia with Lewy bodies and other dementia types according to current guidelines (appendix).

Outcomes

The primary outcomes were cumulative dementia incidence and disability. Disability was chosen because any effect of our intervention on either cardiovascular disease or dementia would ultimately translate into disability. Main secondary outcomes were incident cardiovascular disease (myocardial infarction, stroke and peripheral arterial disease) and cardiovascular and all-cause mortality. Other secondary outcomes were dementia subtype, cognitive decline as measured by MMSE and VAT, symptoms of depression as measured by GDS-15, blood pressure, body mass index (BMI), blood lipids and glucose.

Outcomes were collected during follow-up visits, supplemented by information from GPs' EHRs and the National Death Registry. An independent outcome adjudication committee consisting of neurologists, old age psychiatrists, geriatricians, cardiologists, and GPs, evaluated all clinical outcomes blinded to treatment allocation. As a quality check and to minimise the risk of false-positive diagnoses, dementia diagnoses were re-evaluated after one year (appendix).

Serious adverse events (SAE) were defined as events that were fatal or life threatening, or resulting in significant or persistent disability, and requiring hospitalisation. Events were included if the condition was stated as the reason for admission or if the diagnosis was listed in the hospital discharge letter to the family physician.

Statistical Analysis

We based our sample size calculation on the age-specific cumulative incidence of dementia, as available in 2004.[14] Enrolment of 3700 participants would provide 80% power to detect a 33% between-group difference in the cumulative incidence rate of dementia, with a two-sided alpha level of 0·05, and compensating for an estimated 33% drop-out rate and unknown intra-cluster coefficient.[15] The 33% between-group difference was considered realistic based on published data.[16] A planned interim-analysis by an independent committee after the 4-year follow-up assessments on dementia, disability and mortality, resulted in the recommendation to continue the trial with no change to protocol (appendix). The final analyses were completed by the study group and verified by an independent biostatistician. All analyses were intention-to-treat unless otherwise indicated. Person-years were calculated from the date of randomisation to the date of dementia diagnosis, death or the last visit. For binary time to event outcomes a random effects Cox proportional hazards model was used, accounting for clustering of participants within practices and HCCs. A similar random effects linear multiple measurements model was used for continuous measures, including disability, blood pressure, BMI, laboratory values, cognition, and depressive symptoms. Each continuous factor was adjusted for baseline imbalance and treatment by time interaction. Details of the analyses are provided in the appendix.

Sensitivity analyses for the primary outcome included a per protocol analysis (see appendix for details), best- and worst-case scenario, an analysis including all cases of possible dementia and models adjusting for additional variables including cardiovascular risk factors. The effect of values missing not at random on repeated measurements outcomes was assessed in a sensitivity analysis using a joint model. Subgroup analyses were performed for sex, age (split at the median), hypertension severity (according to WHO grades), cardiovascular history, APOE-genotype (any vs. no ε4 allele) and antihypertensive treatment at baseline (Tables S1a/b and S2, appendix).

All analyses were performed with SPSS version 22 and R version 3·2.[17] (see appendix for a more detailed description of analyses and R-codes employed) This trial is registered with the International Clinical Trials Registry, number ISRCTN29711771.

Role of the funding source

The study funders had no role in study design, data collection, analysis, interpretation, writing of the report, or the decision to submit for publication. All authors had full access to all data in the study. The report was approved for submission by all authors. The corresponding author had final responsibility for the decision to submit for publication.

Results

In 26 HCCs representing 116 family practices, 7772 people were potentially eligible (Figure 1). After 13% were deemed ineligible by their GP, 6762 were invited by letter. Of these, 3526 (52·1%) provided informed consent to participate. Mean cluster size was 30 (SD 21). The two groups were well balanced at baseline, except for a 2 mmHg difference in systolic blood pressure (Table 1). A total of 1890 participants from 63 practices were randomised to the intervention condition and 1636 participants from 53 practices to the control condition.

After a median follow-up of 2442 days (6·7 years), complete follow-up for the primary outcome was obtained for 3454 (98·0%) persons, yielding 21,341 person-years. Information on survival was available for 3519 (99·8%) participants.

Dementia developed in 121 participants (6·5%) in the intervention vs. 112 (7·0%) in the control group (HR 0·92, 95%CI 0·71-1·19, p=0·54)(Table 2). No participants diagnosed with dementia reverted to normal cognition during the 1-year follow-up after diagnosis. There was no difference in AD occurrence. Dementia other than AD occurred less frequently in the intervention group compared to the control group (0·6% vs 1·5%, HR 0·37, 95%CI 0·18-0·76, p=0·007) (Table S4, appendix). Vascular dementia occurred in 0·4% in the intervention vs 0·8% in the control group, HR 0·43, 95%CI 0·17-1·12, p=0·09). Sensitivity analyses yielded similar results (Table S1a, appendix).

In the per-protocol analysis dementia occurred in 85 of 1403 participants (6·1%) in the intervention group vs. 107 of 1479 (7·2%) in the control group (HR 0·78, 95% CI 0·58-1·04; p=0·09) (Table S1a, appendix). In participants with untreated hypertension at baseline, dementia occurred in 31/646 (4·8%) participants in the intervention group versus 36/522 (6·9%) in the control group (HR 0·69; 95%CI 0·43 - 1·11, p=0·13) (Table S2, appendix). In participants with untreated hypertension who were adherent to the intervention dementia occurred in 22/512 (4·3%) in the intervention versus 35/471 (7·4%) in the control group (HR 0·54; 95%CI 0·32-0·92; p=0·02) (Table S2, appendix).

There was no difference in disability, with ALDS scores of 85·7 in both study groups (adjusted mean difference -0·02; 95%CI -0·38 to 0·42, p=0·93). In the intervention group 309 participants (16·4%) died vs. 269 participants (16·5%) in the control group (HR 0·98, 95%CI 0·80-1·18, p=0·81) (Table 2). Cardiovascular disease (CVD) events occurred in 273 participants (18·6%) in the intervention vs. 228 (17·4%) in the control group (HR 1·06, 95%CI 0·86-1·31, p=0·57) (Table 2).

There were no differences in cognition or number of depressive symptoms between both groups (Table 3). Systolic blood pressure decreased more in the intervention group (adjusted mean difference -2·06 mmHg, 95%CI -3·21;-0·90, p=0·0005). BMI, total cholesterol and low-density lipoprotein (LDL) cholesterol decreased in both groups, but without significant differences between study arms (Table 3, Figure S2, appendix).

New antihypertensive medication was started in 329 (20·6%) participants in the intervention and 231 (16·5%) in the control group (OR 1·48, 95%CI 1·16-1·89, p=0·002). In participants who were not using antihypertensive medication at baseline, these numbers were 295/439 (67·2%) versus 203/364 (55·8%)(OR: 1·62, 95%CI: 1·22-2·17, p=0·001). Changes in other medication and lifestyle variables are provided in Table S3, appendix.

There was no excess mortality in either group. The median number of hospital admissions was 117 per 1000 participants/year in the intervention vs. 108 in the control group -3, 95%CI -24-18, p=0·78). There were no significant differences in rates of SAEs for hypotension, syncope, electrolyte abnormalities, injurious falls, or acute kidney injury or failure (Table S5, appendix).

Discussion

In this RCT we observed no effect of 6·7 years of nurse-led intensive vascular care on incident all-cause dementia. We also observed no effect on mortality, CVD or disability, despite a greater improvement in systolic blood pressure (BP) in the intervention group. Subgroup analyses suggested a reduction of non-AD dementia and the largest impact of the intervention on all-cause dementia in participants with untreated baseline hypertension and persons adherent to the intervention.

There are several possible explanations for our finding with respect to all-cause dementia. First, the contrast between study groups in cardiovascular risk reduction was relatively small. As a result of the pragmatic nature of the study, the intensity of the vascular care that was delivered may have been insufficient to induce relevant effects on lifestyle change. Moreover, in primary care settings already providing high standards of cardiovascular risk management (CVRM) it may be difficult to improve overall efficacy, especially for secondary cardiovascular prevention. This is supported by subgroup analyses showing strongest impact of the intervention in hypertensive participants not using antihypertensive medication at baseline and for participants with no history of cardiovascular disease (Table S2, appendix). In addition, a substantial Hawthorne effect may have occurred, with the 2-yearly screenings prompting interventions in high-risk cases, also in the control group. The decrease in blood pressure in the control group, in particular over the first two years, may reflect this effect (Figure S2, appendix). This may have been further enhanced by the 2011-update of the CVRM guideline, that recommended a more proactive primary prevention above the age of 70 years.Second, in view of the pragmatic, public health approach, we did not specifically select a population with increased cardiovascular risk, potentially limiting the overall impact of the intervention. Nevertheless, it appeared that the effect of our intervention was larger in persons without a cardiovascular history (Table S2, appendix), which supports the notion that it may be difficult to improve the already high standards of care in countries with well-organised CVRM programs. Third, our population was relatively old whereas most observational data show an association between midlife vascular risk factors and dementia. Although blood pressure reduction in the very old in the HYVET-trial was associated with a trend for reduced dementia incidence,[18] an inverse association of blood pressure with dementia and survival has been suggested in older age groups.[19,20] Our results mitigate fears that antihypertensive treatment in older age groups evokes cognitive decline. Moreover, they show such an intervention is safe, which is in accordance with findings from the recent SPRINT trial.[21]

Major strengths of our study are the long intervention period, the blinded adjudication of outcomes including a 1-year follow-up after the dementia diagnosis, and completeness of follow-up on all-cause dementia (98·0%) and mortality (99·8%). The pragmatic design and population-based sample

result in a high external validity of our findings, further strengthened by the fact that our population is comparable to a population from national (cohort) data.[22]

At the time of the preDIVA study-design, the available data from the syst-EUR study suggested a 55% risk reduction of dementia through modest blood pressure reduction.[16] This led to our estimated – and at that time seemingly conservative- relative risk reduction of 33% for the multi-domain intervention in our power analysis. Recently, it was estimated that up to 30% of all dementia cases may be attributable to seven modifiable risk factors, with a population attributable risk of 6·8% for hypertension only, in European populations.[5] This is in line with meta-analyses of antihypertensive treatment effects reporting all-cause dementia risk reductions of only 2 to 9%.[8,9] The HR of 0·92 in preDIVA is consistent with these findings, although our study was underpowered to detect such an effect-size. Based on the fully adjusted per protocol analysis, a 24% lower dementia hazard in adherent subjects would translate in an absolute risk reduction of 1·7% (from 7·2 to 5·5%) (Table S1a, appendix).

No other multi-domain intervention trials of similar size and follow-up duration for dementia prevention have been reported, impeding direct comparison with previous research. In the LIFE study a 2-year moderate-intensity physical activity intervention did not improve cognition or reduce dementia incidence in sedentary adults aged 70-89 years.[23] In contrast, the recent FINGER trial participants reported a small excess improvement on a composite score based on tests for cognitive functioning in 60-77 year old participants receiving a multi-domain intervention during 2 years.[24] The clinical relevance of this effect is uncertain; whether this will translate into the prevention of cognitive decline or dementia over time is to be explored after a planned extended follow-up.

The suggested effect on the subgroup of non-AD dementia, the majority of whom were vascular dementia, should be interpreted with caution, due to the small numbers. The nature of our intervention renders a preventive effect on cerebrovascular damage more plausible than an effect on the occurrence or progression of AD. It is unknown through which mechanisms vascular risk factors contribute to the development of AD. Interaction between small vessel disease and neurodegenerative changes, in particular at the neurovascular unit, may partly explain this association. Nevertheless, we did not find an effect of vascular risk management on the development of clinical symptoms of AD, as a result of insufficient contrast between study arms, or perhaps by lack of causal interaction with the neurodegenerative changes that underlie Alzheimer's disease.

Our study has several limitations. Firstly, no detailed neuropsychological testing was performed. In theory, this could have led to a type 2 error, i.e. missing a small treatment effect. However, rather than exploring effects on surrogate endpoints, we chose for a clinical diagnosis of dementia as outcome in order to draw conclusions on dementia prevention with unequivocal clinical relevance. In addition, the long follow-up further ensured reliable detection of dementia and avoidance of false-

positive diagnoses of dementia. Secondly, not all eligible persons in the participating practices consented to participation, potentially introducing recruitment bias, although differences in sex and age between participants and non-participants appeared small and such selections are inherent to preventive initiatives. Thirdly, our intervention was of modest intensity and resulted in limited contrast. Our per protocol analysis suggests better response in adherent participants and therefore we cannot exclude the possibility that a more intensive intervention would have yielded a larger effect, although such an intervention may be also associated with more side effects.

Based on our findings, future trials on multi-domain interventions may benefit from tighter controlled intervention delivery and selection of persons without appropriate hypertension treatment. Sample-size calculations for future studies will have to account for levels of usual vascular care in the target population and the recently reported declining age-adjusted risk of dementia in some Western countries.[25] Intervention at earlier ages (e.g. <60 years) will require a longer follow-up due to the low incidence of dementia in midlife, for which a classical RCT-design may fall short.[26] Multi-domain interventions to prevent dementia might have a larger impact in low and middle income countries given the projected increase in hypertension, incident cardiovascular disease and dementia and lower levels of CVRM in these settings.[27] Since the projected global increase in dementia prevalence over the next decades will also be largely attributable to an increased prevalence in low- and middle-income countries, new interventions must be low-cost, safe and easy to implement in a wide range of settings.[7]

In conclusion, our study shows that long-term nurse-led vascular care in an unselected population of community-dwelling older persons is safe but does not result in a reduction of incidence of all-cause dementia, disability or mortality. However, our results do not rule out clinically meaningful effects in adherent persons with untreated hypertension.

Contributors

MV, ER, EPMvC and WAvG conceived and designed the trial. WAvG coordinated the trial. WAvG, EPMvC and SAL designed and supervised intervention components (cardiovascular risk management, based on national guidelines for primary care). LSE, SAL and JWvD coordinated database management and outcome adjudication. JWvD and MPHB performed the data analysis. All authors interpreted the results; EPMvC, ER and WAvG drafted the report. MV, WAvG, ER and EPMvC obtained funding. All authors revised the article for important intellectual content. WAvG is the principal investigator.

Declaration of interests

We declare no competing interests.

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Table 1. Baseline characteristics*		
Characteristic†	**Intervention (n=1890)**	**Control (n=1636)**
Demographics		
Age, y, mean (SD)	74·5 (2·5)	74·5 (2·5)
Male sex, no. (%)	850 (45%)	757 (46%)
Educational level, no. (%)		
<7 years	455 (24%)	381 (24%)
7-12 years	1168 (62%)	1014 (63%)
>12 years	255 (14%)	218 (14%)
Caucasian, no. (%)	1817 (98%)	1578 (98%)
Medical history		
CVD (excl. stroke/TIA), no. (%)	568 (30%)	476 (29%)
Stroke/TIA, no. (%)	175 (9%)	172 (11%)
Cardiovascular risk factors		
SBP (mmHg), mean (SD)	156·3 (22·0)	154·2 (20·5)
DBP (mmHg), mean (SD)	81·4 (11·2)	81·5 (10·8)
Total cholesterol (mmol/L), mean (SD)	5·2 (1·1)	5·3 (1·1)
LDL cholesterol (mmol/L), mean (SD)	3·1 (1·0)	3·2 (1·0)
BMI (kg/m^2), mean (SD)	27·6 (4·2)	27·3 (4·1)
Waist circumference (cm, female), mean (SD)	102·3 (9·9)	101·6 (9·9)
Waist circumference (cm, male) , mean (SD)	97·5 (12·4)	97·4 (12·0)
Type 2 diabetes, no. (%)	357 (19%)	289 (18%)
Blood glucose (mmol/L), mean (SD)	5·8 (1·2)	5·9 (1·2)
Current smoking, no. (%)	252 (13%)	216 (13%)
Physical activity (WHO)[38], no. (%)	1594 (86%)	1398 (87%)
Genetic factors		
ApoE4, negative, no. (%)	1155 (72%)	996 (73%)
ApoE4, heterozygous, no. (%)	412 (26%)	332 (24%)
ApoE4, homozygous, no. (%)	36 (2%)	35 (3%)
Medication use		
Antihypertensive(s), no. (%)	1028 (55%)	923 (57%)
Cholesterol lowering drug(s), no. (%)	650 (34%)	550 (34%)
Antiplatelet/anticoagulant drug(s), no. (%)	616 (33%)	550 (34%)
Disability and neuropsychiatric assessment		
ALDS, median (IQ-range)	89 (86-89)	89 (86-89)
MMSE, median (IQ-range)	28 (27-29)	28 (27-29)
GDS-15, median (IQ-range)	1 (0-2)	1 (0-2)
VAT A, median (IQ-range)	6 (5-6)	6 (5-6)

* Y, years; SD, standard deviation; IQ, inter-quartile; CVD, cardiovascular disease; TIA, transient ischemic attack; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein, BMI, body mass index; ALDS, Academic Medical Center Linear Disability Score; MMSE, Mini-Mental State Examination; GDS-15, 15-item Geriatric Depression Scale, VAT A, Visual Association Test A, apoE, apolipoprotein-E, WHO, World Health Organisation.

† Number of participants with missing data: Educational level: 35, Caucasian: 59, CVD (excl. stroke/TIA): 6, Stroke/TIA: 12, SBP: 3, DBP: 2, Total cholesterol: 73, LDL cholesterol: 98, BMI: 2, Waist circumference women: 4, waist circumference men: 8, Diabetes mellitus: 0, Blood glucose: 73, Current smoking: 7, Physical activity: 71, Genetic factors: 560, Antihypertensive(s): 5, Cholesterol lowering drug(s): 6, Antiplatelet/anticoagulant drug(s): 5, ALDS: 14, MMSE: 6, GDS-15: 5, VAT A: 18.

Without APOE genotype

Table 2. Clinical outcomes

Outcome	Intervention	Control	HR (95%-CI)	P Value
All-cause dementia, n (%)	121/1853 (6·5%)	112/1601 (7·0%)	0·92 (0·71 to 1·19)	0·54
- *Alzheimer's disease**	99/1831 (5·4%)	81/1570 (5·2%)	1·05 (0·78 to 1·41)	0·74
- *non-Alzheimer's dementia*‡*	11/1743 (0·6%)	23/1512 (1·5%)	0·37 (0·18 to 0·76)	0·007
- *Unspecified types of dementia**	11/1743 (0·6%)	8/1497 (0·5%)	1·24 (0·46 to 3·41)	0·67
Cardiovascular events, n (%)†	273/1469 (18·6%)	228/1307 (17·4%)	1·06 (0·86 to 1·31)	0·57
- *Myocardial infarction*	68/1503 (4·5%)	57/1339 (4·3%)	1·03 (0·71 to 1·49)	0·87
- *Stroke including TIA*	120/1503 (8·0%)	102/1341 (7·6%)	1·05 (0·80 to 1·38)	0·74
- *Other*[#]	103/1495 (6·9%)	83/1333 (6·2%)	1·08 (0·78 to 1·50)	0·65
Death, n (%)	309/1885 (16·4%)	269/1634 (16·5%)	0·98 (0·80 to 1·18)	0·81
- *Cardiovascular death*[¶]	63/1639 (3·8%)	60/1425 (4·2%)	0·91 (0·63 to 1·32)	0·63
- *Other*[¶]	126/1702 (7·4%)	125/1490 (8·4%)	0·87 (0·68 to 1·12)	0·28

Rates of dementia, cardiovascular outcomes and death, with hazard ratio (HR) for the intervention group.
* Participants with a dementia subtype other than the one being analysed were left out the denominator.
TIA, transient ischemic attack.
†Including fatal and non-fatal myocardial infarction and stroke, and angina pectoris, TIA, and peripheral arterial disease.
Angina pectoris and peripheral arterial disease.
¶ The cause of death was unknown for 204 participants; therefore, numbers of cardiovascular and other causes of death do not add up to the grand total.
‡ Non-Alzheimer's dementia (n intervention/control): vascular dementia: 7/12, Lewy body dementia: 2/6, Parkinson dementia: 2/2, frontotemporal dementia: 0/1, primary progressive aphasia: 0/1, other: 0/1.
Further details are provided in Table S4, appendix.

Table 3. Continuous outcomes

Outcome	Intervention (n)	Control (n)	Adjusted Mean Difference (95%-CI)*	P-value	Time by treatment interaction (95%-CI)
ALDS score	85·7±6·8 (1484)	85·7±7·1 (1326)	0·02 (-0·38 to 0·42)	0·93	-0·02 (-0·17 to 0·12)
Systolic blood pressure (mmHg)	148·0±19·4 (1494)	149·6±20·7 (1334)	-2·06 (-3·21 to -0·90)	0·0005	0·69 (0·29 to 1·08)§
- *WHO normotension*	136·9±17·9 (344)	135·9±18·2 (307)	0·74 (-1·34 to 2·81)	0·49	0·80 (0·06 to 1·54)†
- *WHO hypertension*	151·3±18·6 (1150)	153·7±19·7 (1027)	-2·93 (-4·29 to -1·57)	<0·0001	0·65 (0·19 to 1·10)‡
Diastolic blood pressure (mmHg)	77·4±10·5 (1495)	78·8±10·9 (1334)	-1·15 (-1·84 to -0·46)	0·001	0·57 (0·37 to 0·78)‖
- *WHO normotension*	74·7±10·0 (344)	75·0±10·3 (307)	0·16 (-1·15 to 1·47)	0·81	0·60 (0·22 to 0·99)‡
- *WHO hypertension*	78·2±10·5 (1151)	79·9±10·9 (1027)	-1·71 (-2·41 to -1·02)	<0·0001	0·55 (0·31 to 0·78)‖
Waist circumference female (cm)	96·7±12·4 (818)	96·7±12·3 (716)	-0·20 (-1·02 to 0·62)	0·63	0·08 (-0·12 to 0·28)
Waist circumference male (cm)	102·2±10·2 (665)	101·8±10·1 (604)	-0·20 (-0·76 to 0·37)	0·50	0·18 (0·00 to 0·35)†
Body Mass Index (kg/m^2)	27·4±4·8 (1492)	27·1±4·7 (1334)	0·06 (-0·10 to 0·23)	0·45	-0·03 (-0·10 to 0·03)
Total Cholesterol (mmol/L)	5·0±1·1 (1310)	5·1±1·1 (1172)	-0·02 (-0·09 to 0·04)	0·49	0·02 (0·00 to 0·04)†
LDL (mmol/L)	2·8±1·0 (1309)	3·0±1·0 (1167)	-0·03 (-0·09 to 0·03)	0·30	0·01 (0·00 to 0·03)
Glucose (mmol/L)	6·1±1·6 (1307)	6·1±1·6 (1168)	0·02 (-0·06 to 0·10)	0·56	0·00 (-0·03 to 0·03)
VAT A	5·3±1·1 (1484)	5·3±1·1 (1325)	-0·02 (-0·09 to 0·04)	0·48	0·01 (-0·02 to 0·03)
MMSE score	28·2±2·1 (1494)	28·3±2·0 (1330)	-0·02 (-0·14 to 0·10)	0·73	0·01 (-0·03 to 0·05)
GDS score	1·8±2·2 (1490)	1·7±2·2 (1333)	0·01 (-0·09 to 0·12)	0·79	0·00 (-0·04 to 0·04)

Means and standard deviations of repeated measurements after baseline with adjusted mean difference between study groups. Time by treatment interaction in years, (n): number of participants included available for analysis, ALDS: AMC Linear Disability Score, WHO: World Health Organisation, WHO hypertension: systolic blood pressure ≥140 or diastolic blood pressure ≥90, LDL: low density lipoprotein cholesterol, VAT A: Visual Association Test A, MMSE: Mini Mental-State Examination, GDS: 15-item Geriatric Depression Scale.
* Adjusted for baseline and clustering within centers and individuals, taking all measurements at all time points into account. † p<0·05 ‡ p<0.01, § p<0.001, ‖ p<0.0001
Number of observations in analysis (intervention/control): ALDS: 4184/3701, systolic blood pressure: 4198/3633, diastolic blood pressure: 4202/3633, body mass index: 4199/3645, waist circumference female: 2262/1962, waist circumference male: 1794/1579, total cholesterol: 3079/2634, LDL: 3064/2610, glucose: 3032/2586, VATA: 4129/3586, MMSE: 4323/3724, GDS: 4177/3640

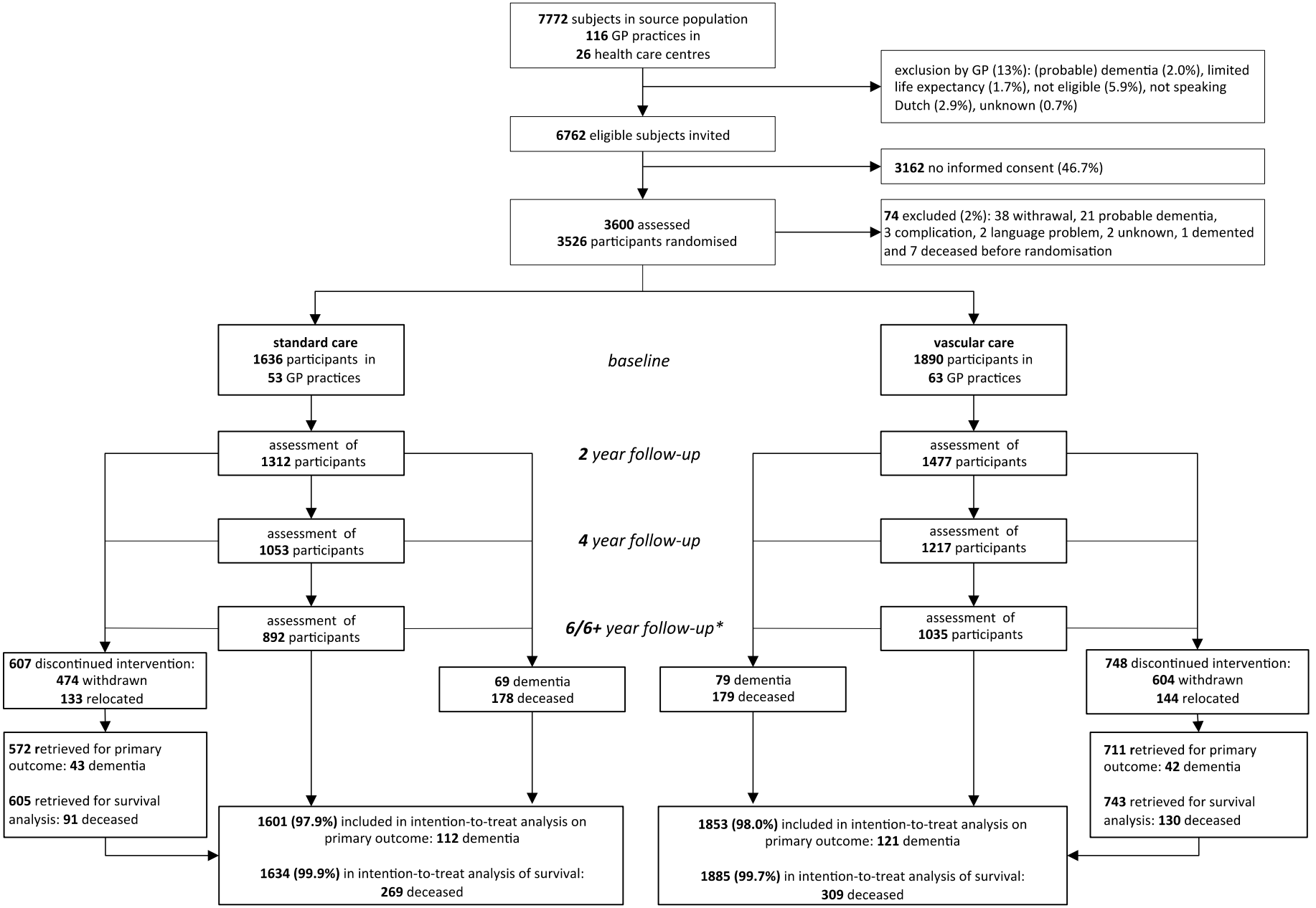
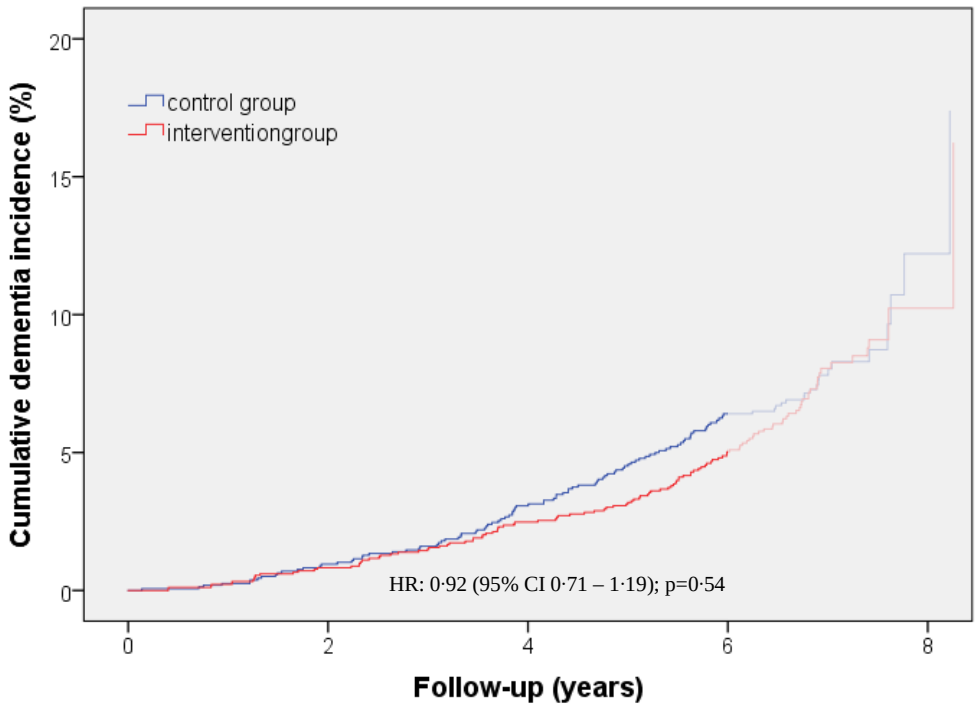


Figure 1: **Flow-chart**



Number at risk					
Control group	1601	1540	1437	1130	28
Intervention group	1853	1785	1674	1290	32

***Figure 2*: Kaplan-Meier plot**

Legend to figure 2: To allow participants recruited early into the trial to continue follow-up until the 6-year assessment of the last participant was completed, the study was extended for participants randomized early in preDIVA, in 2006-7. The hazard ratio refers to an analysis including all participants, up to 8 years of follow-up. The period beyond the planned 6-year follow-up, concerning relatively few participants, is shaded.