Supplementary appendix

Supplement to: Moll van Charante E*, Richard E*, Eurelings L et al. Prevention of Dementia by Intensive Vascular Care (preDIVA) – a 6-year cluster-randomised controlled trial

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Supplementary appendix

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Section 1. Trial enrollment procedure

Health care system: Dutch primary health care

In the Netherlands, nearly all non-institutionalised inhabitants are registered with a General Practitioner (GP). Dutch GPs fulfil the role as 'gatekeeper': when patients seek medical care from a medical specialist, they have to be referred by their GP and, after consultation, the medical specialist reports back to the patient's GP. GPs have contact with all patient groups in a large range of disease stages, without selection regarding age, gender, socio-economic status, or ethnicity. Their electronic health records (EHR) are therefore regarded as a valid source of information on morbidity in the Dutch population. Furthermore, the completeness of this registry makes a precise determination of the epidemiological denominator possible.[1]

Recruitment of family practices

Between June 2006 and March 2009, 125 GP practices within 29 healthcare centres were invited to participate in the preDIVA study. Nine primary care practices within three healthcare centres (7·2%) decided not to take part due to internal organisational problems.

Recruitment of participants

All community-dwelling persons aged 70-78 years who were registered with one of the participating general practices were selected from the EHR by their GP. Persons were excluded if, according to their GP, they suffered from (probable) dementia, were terminally ill, did not understand Dutch, or had other conditions that could hinder successful long-term follow-up, like serious chronic diseases, cancer or alcoholism.

Eligible persons received a letter with study information, signed by their GP and the investigators, along with a written informed consent form, and a pre-paid envelope. A postal reminder was sent after two to three weeks if no response had been received. After four to six weeks, the practice nurse made a telephone call to those who had failed to respond.

In total, 7772 persons from the 116 GP practices were aged 70-78 years. Of these, 13·2% (1010/7772) were excluded by the GP (see Flowchart main article). Of the remaining 6762 persons, 46·8% (3162/6762) declined to participate or failed to respond. Informed consent was received from 3600 eligible persons, but another 74 (2·1%) were excluded before baseline. Therefore, overall 52·1% (3526/6762) of the eligible population between 70 and 78 underwent a baseline assessment, between June 7, 2006 and March 12, 2009. At the moment of signing informed consent, 44 subjects were 69 years old, 17 had turned 79, and one subject was 80 years. Since these participants were already included through their GP, i.e. because their partner participated in the study, they were allowed to stay in the study.

Health care centres had different numbers of GP practices (median 4, IQR 3-6), and practices had different numbers of participants who completed baseline measurements (median 24, IQR 16-39; full range 2-113). In addition, the randomisation procedure required that in each HCC at least one GP practice had to be randomised to the intervention condition. Randomisation of GP practices took place within each HCC after all baseline visits had been performed in that HCC. Since it took a relatively long time to recruit new HCCs and to complete all baseline measurements in these centres, we chose to randomise practices within each separate HCC rather than waiting for a number of HCCs simultaneously, to avoid long delays between the baseline visits and start of the intervention, potentially resulting in drop-outs prior to the start of the intervention.

Non-respondents

In seven healthcare centres, data on age and sex were analysed in 687 non-respondents. When compared to the 900 respondents in these centres, non-respondents were older (mean 74·6 versus 74·2, p=0·021) and there were slightly more women (58·8% versus 54·4%, p=0·092)

References

1. van den Dungen C, Hoeymans N, van den Akker M et al. Do practice characteristics explain differences in morbidity estimates between electronic health record based general practice registration networks? BMC Fam Pract 2014;15:176.

Section 2. Study questionnaires and tests

The following questionnaires and tests were administered at every 2-year follow-up visit:

-The *Mini-Mental State Examination (MMSE)* was used to assess overall cognitive function.[1] Possible scores range between 0 and 30 with higher scores indicating better functioning.

-The *Visual Association Test (VAT)* was used to screen for anterograde amnesia.[2] It is a brief learning task based on imagery mnemonics and is sensitive for early stages of Alzheimer's disease.

-The *Academic Medical Center Linear Disability Score (ALDS)* was used to measure level of physical disability.[3] It is a generic disability measure based on the Item Response Theory which quantifies functional status by assessing the ability to perform activities of daily life.

-The *15-item Geriatric Depression Scale (GDS-15)* was administered to screen for depressive symptoms.[4] Possible scores range between 0 and 15 with higher scores indicating more depressive symptoms.

-The *LASA Physical Activity Questionnaire (LAPAQ)* was used to assess level of physical activity.[5] It measures the frequency and duration of walking outside, bicycling, gardening, light and heavy household activities, and sport activities during the previous two weeks. It has been validated against 7-day physical activity diaries and 7-day pedometer counts in a sample of Dutch community-dwelling older individuals.

1. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-198.
2. Lindeboom J, Schmand B, Tulner L, Walstra G, Jonker C. Visual association test to detect early dementia of the Alzheimer type. J Neurol Neurosurg Psychiatry 2002;73(2):126-133.
3. Holman R, Lindeboom R, Vermeulen M, de Haan RJ. The AMC Linear Disability Score project in a population requiring residential care: psychometric properties. Health Qual Life Outcomes 2004;2:42.
4. Yesavage JA, Brink TL, Rose TL et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17(1):37-49.
5. Stel VS, Smit JH, Pluijm SM, Visser M, Deeg DJ, Lips P. Comparison of the LASA Physical Activity Questionnaire with a 7-day diary and pedometer. J Clin Epidemiol 2004;57(3):252-258.

Note: further details on study procedures are described in the original Dutch study procedures and can be obtained from the authors.

Section 3. Outcome adjudication

Sources of information to identify incident cases of dementia

The following three main sources were used to identify potential incident cases of dementia during the study (Figure S1, Section 4, p7):

End-of-study form

At every 2-yearly follow-up visit, consultation of the family physician (GP) was indicated for the practice nurse in case of: (a) specific complaints about cognition of participants and/or caregivers, (b) a decline of ≥3 points from the baseline Mini-Mental State Examination (MMSE) score or (c) ≥2 points from the preceding visit or (d) an MMSE score of ≤24. In case of a decline of ≥3 points from the baseline MMSE or ≥2 points from the preceding visit, the GP was advised by the study protocol to perform further evaluation to rule out other potential reasons for the decline in MMSE (e.g. depression, medication side effect). If no other reason was likely, the protocol prescribed to repeat the MMSE within two weeks. If the decline of ≥3 points from baseline or ≥2 points from the preceding visit was confirmed, the GP was advised to refer the participant for further diagnostic work-up. In case of a MMSE score of ≤24 at a 2-yearly visit, the GP was also advised to refer the participant. During the course of the study, GPs could also establish a diagnosis of dementia based on all available clinical information. If needed, the preDIVA research group was available for consultation at all times. After a diagnosis of dementia had been established in a participant, the research group was notified by the practice nurse through an end-of-study form. Upon this notification, all available clinical information was collected (e.g. reports on neuropsychological assessment, neuroimaging, hospital admissions, outpatient diagnostic evaluations by geriatricians, neurologists, psychiatrists,) to enable blinded outcome adjudication.

Retrieved drop-out form

For all individuals who did not attend the final follow-up assessment and no end-of study form indicating a diagnosis of dementia was received, information on dementia status was collected by a research nurse through contact with GPs, practice nurses, nursing home physicians, dementia case managers, and occasionally with relatives. If a participant had developed dementia, clinical information on dementia diagnosis was collected from medical records for blinded outcome adjudication, as described above.

MMSE score at final follow-up visit

Indications for the preDIVA research group to contact the GP to inquire about the cognitive status of the participant were: (a) a decline of ≥3 points from the baseline MMSE or (b) ≥2 points from the preceding visit or (c) an MMSE score of ≤24 at the final follow-up visit. In case the GP indicated that no dementia was present, this judgment was used in the analysis. In other cases, further evaluation was performed. In case the GP indicated that a diagnosis of dementia was already established, clinical information on the diagnosis was shared with a dementia expert panel consisting of two senior neurologists and a GP who were blinded to the treatment allocation. In case dementia was suspected and a participant provided consent for further cognitive evaluation, the participant was referred by the GP and the outcome of this evaluation was shared with the dementia expert panel and used in the analysis. In case of suspected dementia and the participant declined further cognitive evaluation, all available information was evaluated and sometimes the GP and practice nurse were interviewed by one of the members of the masked dementia expert panel in order to reach a conclusion.

Outcome adjudication

During the study, an independent outcome adjudication committee, consisting of neurologists, old age psychiatrists, geriatricians, family physicians, and cardiologists, evaluated all clinical outcomes (e.g. dementia, mortality, cause of death) blinded to treatment allocation. This committee evaluated the dementia diagnoses as derived from the end-of-study form and the retrieved drop-out form using a standard format if sufficient clinical information was available (e.g. reports on hospital admissions, outpatient diagnostic evaluations by geriatricians, neurologists, psychiatrists, neuroimaging, neuropsychological examinations). A final judgment on dementia diagnosis and type was established by consensus between two adjudicators. In case of disagreement between two adjudicators a third independent adjudicator was consulted and a final judgment was made if two of the three adjudicators reached consensus. If still no consensus was reached the judgment was based upon the

opinion of a dementia expert panel. If only inadequate clinical information was available a judgment on dementia diagnosis and type was established by the dementia expert panel as well.
Possible outcomes of the adjudication process were dementia, possible dementia, and no dementia. Possible outcomes regarding types of dementia were probable and possible Alzheimer's dementia, probable and possible vascular dementia, probable and possible dementia with Lewy bodies, Parkinson dementia, frontotemporal dementia, primary progressive aphasia, and 'other' (See Table 2 in main text, or Section 9, page 15). Dementia diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV.[1] Diagnosis of Alzheimer's disease, vascular dementia, dementia with Lewy bodies and frontotemporal dementia was made according to widely accepted guidelines.[2-5]

Quality check of dementia diagnoses

As a quality check, dementia diagnoses (dementia and possible dementia) were re-evaluated after one year by asking family physicians, practice nurses, nursing home physicians and/or dementia case managers whether dementia was still the most likely diagnosis. In case of doubt concerning a previous diagnosis of dementia or possible dementia one year later, a final judgment was established, by the dementia expert panel, based upon the most recent available clinical information, while blinding for treatment allocation was preserved. In case the initial judgment was possible dementia and after one year dementia was most likely, the diagnosis dementia was used in the analysis. In case the initial judgment was dementia and no one year follow-up could be obtained, the initial diagnosis dementia was used (see Figure S1). In case the initial judgment was possible dementia and no one year follow-up could be retrieved, a final judgment was established by the dementia expert panel masked for the treatment group.

References

1. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition ed. Washington D.C. American Psychiatric Association:1994.
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3. Roman GC, Tatemichi TK, Erkinjuntti T et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43(2):250-260.
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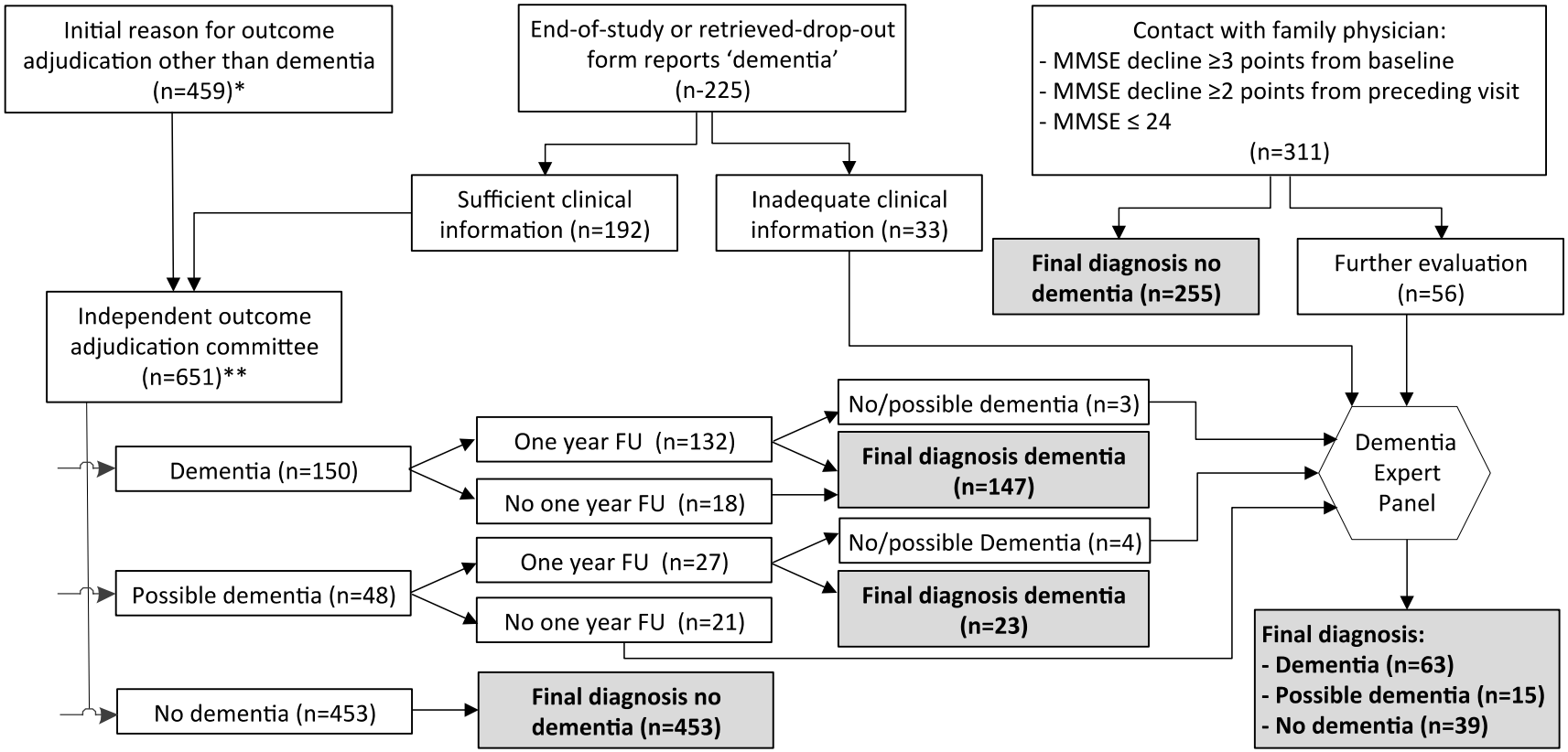
5. Neary D, Snowden JS, Gustafson L et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51(6):1546-1554.1-3

Section 4. Figure S1. Diagnosis of dementia during the study



MMSE, Mini-Mental State Examination; FU, follow-up.

* This indicates the number of individuals with an initial reason for outcome adjudication other than dementia (e.g. mortality, serious illness). For these individuals the dementia status was also assessed by the independent outcome adjudication committee.

**If no consensus was reached after three independent adjudicators the final diagnosis was based upon the opinion of the dementia expert panel blinded for treatment allocation

Section 5. Statistical analyses

Models used for analysis

For time to event analyses a random effect cox proportional hazard model was used with random intercepts per health care centre (HCC) and general practitioner (GP) practice nested within each HCC, to account for clustering in HCCs and in GP practices within HCCs. A multiple measurements linear mixed model was used to assess the overall effect on continuous outcomes measured during the study after baseline, corrected for the value measured at baseline and a time-by-treatment interaction. The model incorporated a random intercept and random slope for the time to the measurement and the value measured at baseline. Random effects were fitted per HCC, per nested GP practice, and per participant nested within each GP practice, to account for clustering at the HCC and GP practice levels and for repeated observations within participants respectively. Note that results represent the differences between treatment groups for the means of all measurements obtained during the study after baseline, not only those obtained at the final assessment. They therefore reflect the overall mean difference during the study, not at the end of the study. Due to inclusion of a time-by-treatment interaction, estimated adjusted mean differences are time dependent. In order to represent the adjusted mean difference for all measurements included in the analysis,
the reported adjusted mean differences were calculated for the mean time of all included measurements (circa 4·3 years). For time-to-event analyses we used the R-package "coxme"[1] and for the linear mixed models "LME4"[2]. The R code used can generally be written as below.

Time to event (R-package coxme):
coxme(surv(event_censoring_time, event) ~ randomisation + (1|HCC/GP practice)

Continuous measurements (R-package LME4):
lmer(value_during_study ~ 1 + randomisation * time to measurement + value_at_baseline + (1|HCC/GP practice/participant) + (0 + time to measurement + value_at_baseline| participant)

Rationale behind random intercepts and exploration of random slope

Randomisation in the study was performed at GP practice level in blocks per HCC with the condition that each HCC should at least have one GP practice receiving the intervention. Since participant population clustering may be present both within HCCs as in GP practices within HCCs, a random intercept was fitted for both levels, with the intercept for the GP practice nested within the HCC. Since the practice nurses performing the intervention were positioned at the HCC level, the effect of the intervention may have varied across HCCs. The utility of fitting a random slope for the intervention at the HCC level to account for this variation was explored. However, inclusion of a random slope for the intervention resulted in a worse model fit (based on Akaike Information Criterion (AIC)) and the random slope was therefore left out of the final model. Similarly, since GPs may have responded differently to baseline measures (e.g. elevated blood pressure) collectively within HCCs and/or GP practices we explored the utility of including a random slope for baseline values on these levels, in addition to the random slope at the participant level to account for repeated observations within one participant. Again, this resulted in a worse model fit (based on AIC) and the random slopes at the HCC and GP practice level were therefore left out of the final models. In addition, for the continuous measures model, random slopes for time to measurement and the value measured at baseline significantly improved the model fit and were therefore included.

References

1. Terry M. coxme: Mixed Effects Cox Models. R package version 2.2-5 2015. http://CRAN.R-project.org/package=coxme
2. Bates D, Maechler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. Journal of Statistical Software 2015;67(1):1-48. http://www.jstatsoft.org/v67/i01.

Section 6. Sensitivity analyses, including missing data

Several sensitivity analyses were performed as listed below. Each was adjusted for the predefined potential confounders of age, sex and education in model 2, plus systolic blood pressure and antihypertensive use at baseline in model 3, plus serum low-density lipoprotein, body mass index, diabetes mellitus, current smoking and physical activity in model 4.

Intention to treat analysis: hazard ratio of developing dementia in the intervention versus control group as in the main analysis, adjusted for potential confounders in models 2 through 4.

Per protocol analysis: exclusion of intervention group participants who on average had received <2 intervention visits per year upon reaching a study endpoint (dementia/death/end of trial), and control group participants who had received >2 undue intervention visits per year. In the control group, 125 participants unduly received the intervention with an average of >2 visits per year, and were left out of the per protocol analysis. In the intervention group, 544 participants received less than two visits per year before reaching an endpoint or end of study, and were therefore left out of the per protocol analysis.

Analysis including possible dementia cases: cases of possible dementia (15 cases (0.43% of all participants), 8 in the control, 7 in the intervention group) -which were regarded as "no dementia" in the main analysis- were included as having developed dementia.

Best case scenario: participants with an unknown/possible dementia status censored as not having developed dementia at time of death or end of the trial.

Worst case scenario: participants with an unknown/possible dementia status censored as having developed dementia one day after the last study contact.

Age as timescale: repetition of the main analysis with age at the time of censoring as the time to event (rather than time since randomisation), to account for the strong relation between age and incident dementia. In these analyses, age was left out as a potential confounder in models 2 through 4.

Excluding the first two years of follow-up: exclusion of participants who developed dementia within the first two years after randomisation, to account for the possibility that the effect of the intervention would only become apparent after a certain lag time.

Sensitivity analysis on missing data

Study outcome data were not imputed. The repeated measurements model used for the main analysis assumes missing data to be missing at random. Since death during follow-up will generate a pattern of missingness which cannot be considered at random, and some measurement values (e.g. unfavorable disability scores) may be associated with study drop- out, results of the repeated measurements analyses may have been influenced by violation of the missing at random assumption. To assess the effect of missing values on the differences between treatment groups in the repeated measurements analyses, joint model analyses were performed.[1] In these analyses, the repeated measurements and drop-out process are modelled separately, and subsequently combined into a single joint model, accounting for associations between study drop-out and measurement values. If results are similar to those in the main analyses, they are unlikely to be related to the faulty assumption of missingness at random in the main analysis model. Joint model analyses were performed using the "JM" package in R.[1]

The drop-out process was modeled in a Cox proportional hazard analysis with study drop-out as event and time to the last available measurement + 1 day as time to event. Complete cases were censored as 'no event' at the time of the final measurement.

The repeated measurements analysis was modeled similar to the main analysis but with the random structure of the mixed models restricted to individual intercept and slope with respect to time. Effects at the health care centre (HCC) and general practitioner (GP) practice levels were left out since the joint model does not allow nested random effects. Adjusted mean differences and 95% confidence intervals for the joint model are time dependent and were recalculated to the same time as the main mixed model analyses (i.e. mean time to measurement, circa 4.3 years).

Handling of cases of possible dementia

In the study, possible outcomes of the adjudication process were "no dementia", "possible dementia" or "dementia". Cases considered possible dementia (15 cases (0.43% of all participants), 8 in the control, 7 in the intervention group) were regarded as "no dementia" in the main analyses. They were later added in a sensitivity analysis (see Appendix section S6b). Cases of dementia were also rated for the dementia type, with the option to differentiate "probable" and "possible" types (e.g. possible or probable Alzheimer's disease). It is important to note that only the cases in which the diagnosis of

dementia (not type of dementia) was considered possible were regarded as “no dementia” in the main analyses.

Competing risk analysis

The risk of developing dementia increases exponentially with age. Although the treatment groups in the preDIVA study were well-balanced regarding age, a difference in mortality rate between treatment groups could have introduced age imbalances, substantially increasing the risk of dementia in the group with longer survival. To investigate whether differences in mortality rates between treatment groups could have influenced the hazard ratio of dementia, we performed a competing risk analysis according to the cause-specific hazard method.[2]

In this method, time to event analyses of the event of interest are repeated but with cases additionally censored at the time of occurrence of the competing risk. Also, a time to event analysis of the competing risk is performed, censored at the time of occurrence of an event of interest. Since time to event analyses of dementia are inevitably censored at the occurrence of the competing risk of death, we only performed the analyses for the occurrence of mortality. The risk of death did not differ between treatment groups, neither in the full-case analysis (HR: 0.98, 95%-CI 0.80-1.18) nor in the analysis in which participants with dementia were censored as not deceased at the time of dementia (HR: 0.99, 95%-CI 0.80-1.21). We therefore concluded there was no risk of delayed mortality increasing the number of incident dementia cases in either group.

References

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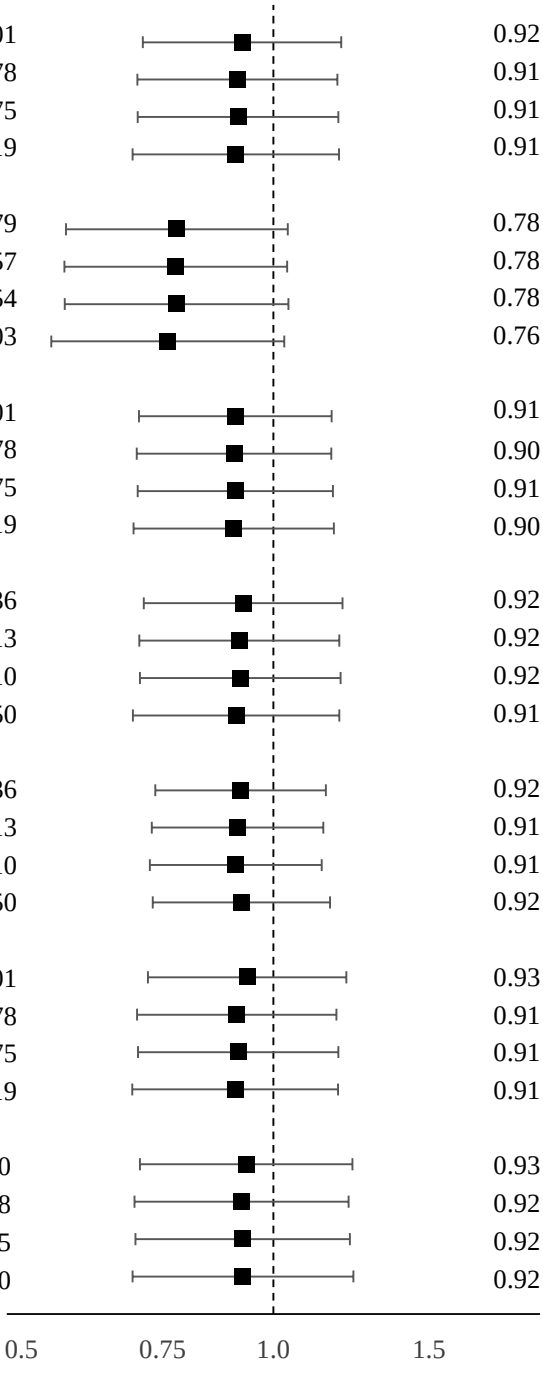
2. Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant 2013;28(11):2670-2677.

Section 6. Table S1a: sensitivity analyses

	Intervention events/n	Control events/n	HR (95% CI)
Intention to treat analysis			
- model 1	121/1853	112/1601	0.92 (0.71 to 1.19, p=0·54)
- model 2	119/1842	110/1578	0.91 (0.70 to 1.18, p=0·48)
- model 3	118/1838	110/1575	0.91 (0.70 to 1.18, p=0·49)
- model 4	112/1754	106/1519	0.91 (0.69 to 1.19, p=0·48)
Per protocol analysis			
- model 1	85/1403	107/1479	0.78 (0.58 to 1.04, p=0·09)
- model 2	84/1397	105/1457	0.78 (0.58 to 1.04, p=0·09)
- model 3	83/1395	105/1454	0.78 (0.58 to 1.04, p=0·09)
- model 4	77/1331	101/1403	0.76 (0.56 to 1.03, p=0·08)
Including possible dementia			
- model 1	128/1853	120/1601	0.91 (0.71 to 1.16, p=0·44)
- model 2	126/1842	117/1578	0.90 (0.70 to 1.16, p=0·43)
- model 3	125/1838	117/1575	0.91 (0.70 to 1.17, p=0·44)
- model 4	119/1754	113/1519	0.90 (0.70 to 1.17, p=0·44)
Best case scenario			
- model 1	121/1890	112/1636	0.92 (0.71 to 1.20, p=0·55)
- model 2	119/1878	110/1613	0.92 (0.71 to 1.19, p=0·51)
- model 3	118/1874	110/1610	0.92 (0.71 to 1.19, p=0·52)
- model 4	112/1788	106/1550	0.91 (0.69 to 1.19, p=0·48)
Worst case scenario			
- model 1	165/1890	155/1636	0.92 (0.74 to 1.15, p=0·45)
- model 2	162/1878	152/1613	0.91 (0.73 to 1.14, p=0·41)
- model 3	161/1874	152/1610	0.91 (0.73 to 1.13, p=0·39)
- model 4	153/1788	144/1550	0.92 (0.73 to 1.16, p=0·48)
Age as time scale			
- model 1	121/1853	112/1601	0.93 (0.72 to 1.21, p=0·60)
- model 2	119/1842	110/1578	0.91 (0.70 to 1.18, p=0·47)
- model 3	118/1838	110/1575	0.91 (0.70 to 1.18, p=0·49)
- model 4	112/1754	106/1519	0.91 (0.69 to 1.18, p=0·47)
Excluding the first 2 years of follow-up			
- model 1	106/1785	97/1540	0.93 (0.71 to 1.23, p=0·62)
- model 2	104/1775	95/1518	0.92 (0.70 to 1.22, p=0·56)
- model 3	104/1772	95/1515	0.92 (0.70 to 1.22, p=0·57)
- model 4	99/1691	91/1460	0.92 (0.69 to 1.23, p=0·59)



Appendix Table S1a. Sensitivity analyses

Model 1: crude

Model 2: adjusted for age, sex and education

Model 3: additionally adjusted for baseline systolic blood pressure and antihypertensive use

Model 4: additionally adjusted for serum low-density lipoprotein, body mass index, diabetes mellitus, current smoking and physical activity

Section 6. Table S1b: joint model sensitivity analysis

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)	-0·07 (-0·43 to 0·29)	0·70	0·00 (0·00 to 0·00)
Systolic blood pressure (mmHg)	148·0±19·4 (1494)	149·6±20·7 (1334)	-2·49 (-3·55 to -1·43)	<0·001	0·66 (0·27 to 1·05)
- *WHO normotension*	136·9±17·9 (344)	135·9±18·2 (307)	0·89 (-1·19 to 2·97)	0·40	0·80 (0·06 to 1·54)
- *WHO hypertension*	151·3±18·6 (1150)	153·7±19·7 (1027)	-3·29 (-4·5 to -2·07)	<0·001	0·63 (0·17 to 1·09)
Diastolic blood pressure (mmHg)	77·4±10·5 (1495)	78·8±10·9 (1334)	-1·41 (-1·97 to -0·85)	<0·001	0·53 (0·33 to 0·73)
- *WHO normotension*	74·7±10·0 (344)	75·0±10·3 (307)	-0·09 (-1·24 to 1·06)	0·88	0·59 (0·20 to 0·98)
- *WHO hypertension*	78·2±10·5 (1151)	79·9±10·9 (1027)	-1·78 (-2·42 to -1·14)	<0·001	0·51 (0·28 to 0·75)
Waist circumference female (cm)	96·7±12·4 (818)	96·7±12·3 (716)	0·01 (-0·76 to 0·78)	0·98	0·08 (-0·13 to 0·28)
Waist circumference male (cm)	102·2±10·2 (665)	101·8±10·1 (604)	-0·10 (-0·67 to 0·47)	0·74	0·20 (0·02 to 0·38)
Body Mass Index (kg/m^2)	27·4±4·8 (1492)	27·1±4·7 (1334)	0·10 (-0·05 to 0·25)	0·21	-0·02 (-0·09 to 0·04)
Total Cholesterol (mmol/L)	5·0±1·1 (1310)	5·1±1·1 (1172)	-0·03 (-0·10 to 0·03)	0·28	0·02 (0·00 to 0·04)
LDL (mmol/L)	2·8±1·0 (1309)	3·0±1·0 (1167)	-0·04 (-0·10 to 0·02)	0·19	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)	0·62	0·00 (-0·03 to 0·04)
VAT A	5·3±1·1 (1484)	5·3±1·1 (1325)	-0·01 (-0·07 to 0·05)	0·75	0·01 (-0·02 to 0·03)
MMSE score	28·2±2·1 (1494)	28·3±2·0 (1330)	-0·01 (-0·13 to 0·10)	0·80	0·01 (-0·03 to 0·05)
GDS score	1·8±2·2 (1490)	1·7±2·2 (1333)	0·04 (-0·08 to 0·15)	0·52	0·00 (-0·04 to 0·04)

Appendix Table S1b. Joint model sensitivity analysis. Means and standard deviations of repeated measurement analyses with mean difference for the intervention. 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 individuals, taking all measurements at all time points into account.

Section 7. Table S2 subgroup analyses for dementia

	Intention to treat				Per protocol analysis			
	Intervention events/n	**Control events/n**	**HR (95% CI)**	**P-value**	**Intervention events/n**	**Control events/n**	**HR (95% CI)**	**P-value**
Sex								
Male	49/827 (5.9%)	51/742 (6.9%)	0.83 (0.56 - 1.25)	0.38	35/631 (5.5%)	49/703 (7.0%)	0.72 (0.46 to 1.11)	0.14
Female	72/1026 (7.0%)	61/859 (7.1%)	0.99 (0.71 - 1.4)	0.97	50/772 (6.5%)	58/776 (7.5%)	0.83 (0.56 to 1.24)	0.36
Age								
< 74.3 years	42/926 (4.5%)	42/799 (5.3%)	0.85 (0.56 - 1.31)	0.46	32/717 (4.5%)	41/738 (5.6%)	0.77 (0.47 to 1.26)	0.29
≥ 74.3 years	79/927 (8.5%)	70/802 (8.7%)	0.97 (0.7 - 1.34)	0.83	53/686 (7.7%)	66/741 (8.9%)	0.80 (0.55 to 1.15)	0.22
Primary vs. secondary prevention								
no CVD history	71/1196 (5.9%)	71/1023 (6.9%)	0.86 (0.62 - 1.19)	0.35	45/911 (4.9%)	69/934 (7.4%)	0.64 (0.44 to 0.94)	0.02
CVD history	47/635 (7.4%)	40/558 (7.2%)	0.98 (0.63 - 1.51)	0.92	38/476 (8.0%)	37/526 (7.0%)	1.03 (0.65 to 1.63)	0.90
APOE4 genotype								
APOE4 negative	46/1132 (4.1%)	34/976 (3.5%)	1.17 (0.74 - 1.84)	0.51	32/850 (3.8%)	32/904 (3.5%)	0.99 (0.59 to 1.68)	0.98
APOE4 positive	52/439 (11.8%)	48/360 (13.3%)	0.87 (0.58 - 1.29)	0.48	35/328 (10.7%)	47/336 (14.0%)	0.70 (0.45 to 1.09)	0.11
WHO hypertension at baseline								
Grade I-III	92/1438 (6.4%)	82/1235 (6.6%)	0.95 (0.7 - 1.28)	0.74	65/1102 (5.9%)	78/1137 (6.9%)	0.79 (0.56 to 1.1)	0.16
- *With AHD treatment*	60/790 (7.6%)	46/711 (6.5%)	1.13 (0.77 - 1.67)	0.54	42/589 (7.1%)	43/664 (6.5%)	0.97 (0.63 to 1.5)	0.88
- *No AHD treatment*	31/646 (4.8%)	36/522 (6.9%)	0.69 (0.43 - 1.11)	0.13	22/512 (4.3%)	35/471 (7.4%)	0.54 (0.32 to 0.92)	0.02
No hypertension	29/415 (7.0%)	30/364 (8.2%)	0.82 (0.49 - 1.38)	0.46	20/301 (6.6%)	29/340 (8.5%)	0.74 (0.42 to 1.32)	0.31
Indication for CLD treatment								
Hypercholesterolemia	54/771 (7.0%)	49/679 (7.2%)	0.97 (0.64 - 1.47)	0.89	40/562 (7.1%)	46/640 (7.2%)	0.93 (0.59 to 1.47)	0.76
- *With CLD treatment*	28/413 (6.8%)	27/349 (7.7%)	0.87 (0.48 - 1.58)	0.65	22/316 (7%)	25/330 (7.6%)	0.88 (0.47 to 1.67)	0.70
- *No CLD treatment*	25/356 (7.0%)	22/330 (6.7%)	1.03 (0.58 - 1.82)	0.93	17/245 (6.9%)	21/310 (6.8%)	0.95 (0.5 to 1.81)	0.87
No indication at baseline	67/1053 (6.4%)	62/908 (6.8%)	0.94 (0.66 - 1.34)	0.74	45/822 (5.5%)	60/827 (7.3%)	0.72 (0.48 to 1.09)	0.12

Appendix Table S2a. Subgroup analyses for dementia

Age: dichotomised at the median; primary prevention: no history of cardiovascular disease at baseline; secondary prevention: history of cardiovascular disease at baseline; APOE4 genotype, dichotomised at the median; WHO hypertension: World Health Organisation definition of hypertension grade I-III; AHD treatment: treatment with antihypertensive drugs at baseline ; CLD: cholesterol lowering drugs ; CLD indication: history of CVD or HDL/total cholesterol ratio >6.5 mmol/L.

Section 8. Table S3. Additional information on treatment and self-reported outcomes

	Intervention events/n	Control events/n	OR (95% CI)	P Value
Treatment				
Started antihypertensive treatment	329/568 (57·9%)	231/479 (48·2%)	1·48 (1·16 to 1·89)	0·002
Started cholesterol lowering drug treatment	259/767 (33·8%)	211/675 (31·3%)	1·12 (0·90 to 1·40)	0·31
Started anticoagulant treatment	295/803 (36·7%)	251/700 (35·9%)	1·04 (0·82 to 1·31)	0·74
Self-reported lifestyle factors				
Started to conform to WHO physical activity guidelines	110/146 (75·3%)	100/134 (74·6%)	1·04 (0·60 to 1·79)	0·89
Started to consume fruit daily	191/279 (68·5%)	175/273 (64·1%)	1·24 (0·82 to 1·87)	0·31
Started to consume fish at least once a week	351/819 (42·9%)	261/705 (37·0%)	1·27 (0·99 to 1·63)	0·06
Changed alcohol consumption to moderate levels*	324/747 (43·4%)	259/621 (41·7%)	1·07 (0·86 to 1·33)	0·53
Quit smoking	78/152 (51·3%)	57/139 (41·0%)	1·53 (0·95 to 2·46)	0·08

Appendix Tabel S3. Additional information on treatment and self-reported outcomes
N and % unless denoted otherwise. Participants who at baseline were already on medication or whose life style were already conform guidelines were left out of the denominator. *Moderate levels of alcohol consumption defined as up to 1glass per day for women and up to 2 glasses per day for men.

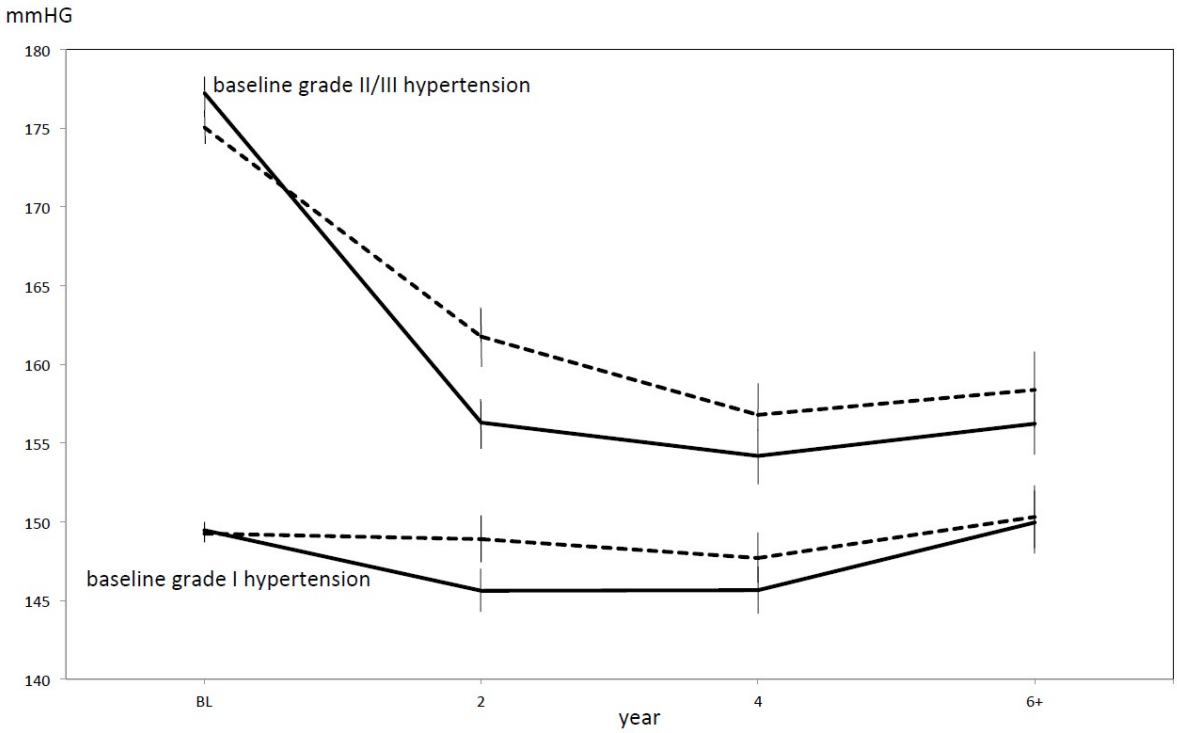
Section 9. Table S4. Dementia subtype

Dementia Type	Intervention	Control	HR (95%-CI)	P-Value
Alzheimer's disease	99/1831 (5·4%)	81/1570 (5·2%)	1·05 (0·78 to 1·41)	0·74
Total non-Alzheimer's disease	11/1743 (0·6%)	23/1512 (1·5%)	0·37 (0·18 to 0·76)	0·007
- Vascular dementia	7/1739 (0·4%)	12/1501 (0·8%)	0·43 (0·17 to 1·12)	0·09
- Lewy Body Dementia	2/1734 (0·1%)	6/1495 (0·4%)	0·29 (0·06 to 1·43)	0·13
- Other*	2/1734 (0·1%)	5/1494 (0·3%)	0·29 (0·05 to 1·67)	0·17
Unclassified	11/1743 (0·6%)	8/1497 (0·5%)	1·24 (0·46 to 3·41)	0·67

Appendix Tabel S4. Dementia subtype

*Other dementia (n intervention/control): Parkinson dementia: 2/2, frontotemporal dementia: 0/1, primary progressive aphasia: 0/1, other: 0/1.

Section 10. Figure S2. Blood pressure



Number of subjects				
Grade I hypertension:				
control	645	514	420	358
intervention	685	535	448	374
Grade II/III				
control	618	488	380	327
intervention	782	591	483	424

Figure S2. Blood pressure. Mean values and 95%CI of systolic blood pressure measurements in intervention (solid line) and control (dashed line) groups over the study course. BL: baseline, hypertension grades according to WHO classification.

Systolic blood pressure reduction in all participants with baseline hypertension was greater in the intervention than the control group (-2·93 mmHg, 95%CI -4·29;-1·57) but attenuated in the course of the study (0·65 mmHg/year, 95%CI 0·19-1·10).

Section 11. Table S5. Adverse events.

	Intensive (n=1890)	Standard (n=1636)	Adjusted mean difference (p-value)
Median number of hospital admissions per 1000 participants per year	117	108	-3 (0·78)

	No. of patients (%)	No. of patients (%)	Hazard ratio (p-value)
Serious Adverse Events[1] (hospital admissions)	784 (41·6)	696 (42·6)	0·96 (0·56)
Conditions of interest:	106 (7·1)	103 (7·7)	0·91 (0·52)
- Hypotension/syncope/bradycardia	25 (1·7)	26 (1·9)	0·9 (0·72)
- Electrolyte abnormality	11 (0·7)	4 (0·3)	2·43 (0·13)
- Injurious fall[2]	75 (5·0)	78 (5·8)	0·84 (0·28)
- Acute Kidney Injury or Acute Renal failure	3 (0·2)	4 (0·3)	0·66 (0·59)

Table S5. Serious Adverse Events leading to ER-visit and subsequent hospital admission.

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.

[1]Defined as an event that was fatal or life threatening, resulting in significant or persistent disability, requiring a hospitalisation.

[2]An injurious fall was defined as a fall that resulted in evaluation in an emergency department and a subsequent hospitalisation.

Section 12. Interim analysis

The interim analysis recommendations were given by the Data Safety Monitoring Committee (DSMC) based on the 4-year follow-up data report (below), on 23 January 2014.

Data Safety Monitoring Committee
J. Stam, MD, PhD, Neurologist, Academic Medical Center, Amsterdam
A.J.M. de Craen†, PhD, Epidemiologist, Leiden University Medical Center, Leiden
N. de Wit, MD, PhD, Family physician, University Medical Center Utrecht, Utrecht

Goal of the interim analysis:

- To identify a possible preliminary unequivocal and statistically significant effect on the primary outcomes (dementia and disability), rendering continuation of the trial unethical.
- To identify a possible preliminary unequivocal and statistically significant effect on the secondary outcome mortality as safety parameter.

Recommendations that the DMC could give to the Study Group:

- No action needed, trial continues as planned.
- Early stopping due to unequivocal benefit or harm of the intervention, or external evidence.

Outcome assessments

If a participant is suspected to suffer from dementia by the general practitioner (GP), the preDIVA study group is notified through an end-of-study form. Subsequently, further information is collected on the results of ancillary investigations, including neuropsychological assessment, laboratory tests and imaging. This information is presented to an independent outcome adjudication committee that is blinded for the treatment allocation.
This committee determines whether the cognitive decline is likely to be caused by dementia, and if so, classifies the type of dementia. For further details on this procedure we refer to Section 3, page 5 onwards.
The preDIVA study group is notified through an end-of-study form when a participant has died. Subsequently, information on cause of death is collected from the electronic health records of the GP. This information is presented to the independent outcome adjudication committee that classifies the causes of death into cardiovascular, carcinoma, other non- vascular, or into uncertain cause. For the present interim analysis, only all-cause mortality has been assessed.

Interim-analysis (IA)

1. Percentages of participants with dementia (primary outcome) and of participants who died (secondary outcome) and hazard ratios for dementia and mortality within the interim-analysis period (Table IA-1 and IA-2). The interim-analysis period is the time between baseline and the 4-year follow-up assessment or, if not present, the median date of the 4-year follow-up visit of the respective health care centre;
2. Mean change in Academic Medical Center Linear Disability Score (ALDS) between baseline and 4-year follow-up assessment (primary outcome) (Table IA-3). ALDS is not available for participants without a 4-year follow-up assessment.

1. Outcomes

Dementia (primary outcome)
Due to the ongoing nature of the trial, not all participants with cognitive decline within four years of follow-up have already been assessed by the independent outcome adjudication committee. Therefore, percentages of participants with (suspected) incident dementia within the interim-analysis period have been calculated separately for all cases, irrespective of assessment, and for those participants who have been assessed as having dementia by the independent outcome adjudication committee (Table IA-1). A time-to-event analysis has been performed for all cases, irrespective of whether an adjudication committee assessment was available (Table IA-2).

Mortality (secondary outcome)
Percentages of participants who died within the interim-analysis period are reported in Table IA-1 and results from the time-to-event analysis are reported in Table IA-2.

Table IA-1. Incident dementia and all-cause mortality within the interim-analysis period

Characteristic	**All** **n=3274[a] (100%)**	**Intervention** **n=1792 (54·7 %)**	**Control** **n=1482 (45·3%)**	***P*[b]**
Primary outcome				
Dementia (all cases), *n* (%)	54 (1·6%)	25 (1·4%)	29 (2·0%)	0·217
SensA: only adjudicated dementia cases, n (%)	32 (1·0%)	16 (0·9%)	16 (1·1%)	0·598
Secondary outcome				
All-cause mortality, *n* (%)	199 (6·1%)	98 (5·5%)	101 (6·8%)	0·123

SensA, sensitivity analysis. [a] for n=259 cases no current status is available. [b]P value by Fisher's exact test comparison between intervention and control group.

Table IA-2. Hazard ratios for dementia and all-cause mortality within the interim-analysis period

Characteristic	Hazard Ratio [a]	95 % CI	*P*
Primary outcome			
Dementia (all cases, n=54/3274)	0·79	0·46 – 1·35	0·383
Secondary outcome			
All-cause mortality (n=199/3274)	0·86	0·65 – 1·13	0·272

CI confidence interval, SensA sensitivity analysis. [a] Hazard Ratios by Cox regression.

Comments on time-to-event analyses for dementia and all-cause mortality

All participants with a 4-year follow-up assessment were censored at the date of the assessment. The median period between baseline and 4-year follow-up visit was 50 months. If dementia was diagnosed before the 4-year follow-up visit, these participants were included as demented in the time-to-event analysis with a follow-up time until the date of diagnosis (=failure). If no 4-year follow-up assessment was available and dementia or mortality had occurred before the median date of the 4-year follow-up visit of their health care centre, these participants were included as demented or deceased in the respective time-to-event analyses with a follow-up time until the event (date of dementia diagnosis or death). If participants had terminated study participation before the median date of the 4 year follow-up visit of their health care centre, they were censored at the date of study participation termination. If participants received a diagnosis of dementia, died, or terminated study participation after the median date of the 4-year follow-up visit of their health care centre, they were censored at the median date of the 4-year follow-up visit of their health care centre.

For 226 participants without a 4-year follow-up assessment, an end-of-study form is missing at this moment, leading to missing information on dementia/death status. For an additional 33 participants who terminated study participation on own request or (mostly) due to relocation, the date of study termination is unknown. For these reasons, a total of 259 participants could not be included in the time-to-event analyses. For the final analysis after six years of follow- up, efforts are currently being made to obtain a minimal final assessment on mortality, dementia status, and living situation (nursing home or not) for all participants without completed follow-up. This information is not yet complete for the interim analysis. However, the preliminary results are promising: in the first five health care centres with a relatively large dropout-rate, 83% of dropouts have already been retrieved and a minimal functional assessment could be made. The importance of this effort is illustrated by the following 'best and worst case' sensitivity analyses, for both dementia and all-cause mortality. In the best case scenario, all 259 participants with a currently unknown status were assumed to be alive and non-demented. They were thus censored at the median date of the 4-year follow-up assessment of their health care centre. Hazard ratios (HRs) and confidence intervals (CIs) for dementia and mortality did not change importantly in this best case scenario: HR for dementia 0·83 (95% CI 0·48 – 1·42), HR for mortality 0·90 (95% CI 0·68– 1·19). In the worst case scenario, these 259 participants were all considered to be demented or deceased at the median date of the 4-year measurement of their health care centre, showing the following results: HR for dementia 0·75 (0·60 – 0·94), HR for mortality 0·80 (0·66 – 0·96). The latter significant differences emphasizes the importance of obtaining the status of as many dropouts as possible. Notably, participants in the control group are more likely to have missing data due to less frequent visits (every 2 year as opposed to every 4 months), which may partly explain the apparently favorable effect of the intervention in the worst case scenarios.

2. Mean change ALDS

Disability (primary outcome)

All various forms of morbidity other than dementia (including cardiovascular events) are likely to ultimately translate into increasing disability that will affect scores on the other primary outcome, the ALDS. The ALDS is a generic linear handicap scale with a range from 0-100 where higher scores reflect better functioning. For the interim analysis, the mean change in ALDS between baseline and 4-year follow-up assessment has been reported (Table IA-3).

Table IA-3. Mean change in ALDS between baseline and 4-year follow-up assessment (n=2190)[a]

Characteristic	All n=2190 (100%)	Intervention n=1189 (54·3 %)	Control n=1001 (45·7%)	*P*[b]
Primary outcome				
ALDS, mean change (SE)		-1·56 (0·14)	-1·50 (0·16)	0·863

[a] missing ALDS for 26 participants with a 4-year follow-up assessment. [b]P value by Mann-Whitney U test, comparison between intervention and control group. ALDS, AMC Linear Disability Score, SE standard error.

Recommendations DSMC

On 23 January 2014, the DSMC discussed the interim report and judged that, since there were no significant differences on dementia, disability or mortality between study arms, the study should continue according to protocol.