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Brain MRI-markers Associate Differentially with Cognitive Versus Functional Decline Leading to Dementia

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BACKGROUND: Brain MRI-markers are risk factors of dementia and decline in cognition and daily functioning. It is unknown to what extent the associations of brain MRI-markers with cognition and daily functioning are part of the pathway leading to dementia. We aimed to investigate associations of brain MRI-markers with change in cognition and daily functioning during 15 years of follow-up, including their relation to dementia.

DESIGN, SETTING, AND PARTICIPANTS: Four hundred and sixty three stroke-free and non-demented participants from the population-based Rotterdam Study that underwent brain-MRI, yielding brain volumetrics, between 1995 and 1996.

MEASUREMENTS: We assessed cognition using the Mini-Mental State Examination (MMSE) and daily functioning using instrumental and basic activities of daily living (IADL and BADL) up to seven times between 1990 and 2011. Analyses were performed both including and excluding incident demented participants.

RESULTS: Smaller brain volume associated with larger decline in MMSE, IADL, and BADL. Larger white matter lesion volume associated with larger decline in MMSE. Frontal lobe volume associated strongest with decline in IADL and BADL, and temporal lobe volume with decline in MMSE. After excluding incident demented participants (n = 63), associations with IADL and BADL remained, while associations with MMSE disappeared.

CONCLUSIONS: Smaller brain volumes and larger white matter volume associate with larger decline in cognition and daily functioning, during 15 years of follow-up. Importantly, the relation of brain volume with cognition, but not daily functioning, was driven by those individuals that ultimately developed dementia. **J Am Geriatr Soc 65:1258–1266, 2017.**

Key words: activities of daily living; brain; cognition; dementia; MRI

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With aging, accumulating brain pathology can lead to deterioration in cognition and daily functioning,[1] which in turn may result in loss of independence and ultimately institutionalization.[1]

Cognition is commonly assessed using the Mini-Mental State Examination (MMSE), a screening test for global cognitive functioning.[2] Daily functioning is assessed by activities of daily living (ADL), including physical basic-ADL (BADL, e.g. eating) and cognitively more challenging instrumental-ADL (IADL, e.g. meal preparation).[3] Together, these tests capture a wide spectrum from cognition to daily functioning.

In extreme form, impairment in cognition and daily functioning may lead to dementia.[1] Brain MRI-markers are strong risk factors of dementia, they include volumes of the brain, hippocampus, and lobes, as well as white matter lesions and lacunar infarcts.[4,5] Of these, the smaller hippocampal and temporal lobe volume strongly associate with an increased risk of dementia.[4] It is important to note that even in non-demented persons, brain MRI-markers associate with change in cognition and daily functioning.[5–13] However, previous studies were unable to investigate whether these associations are part of the pathway that ultimately leads to dementia.

We aimed to investigate associations of brain MRI-markers with change in cognition and daily functioning in

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a community-dwelling population, with up to 15 years of follow-up. Importantly, we investigated whether the associations remain after excluding people with incident dementia.

METHODS

Setting

The study was embedded in the Rotterdam Study, a population-based cohort study in the Netherlands.[14] The study initiated in 1990, inviting all inhabitants of Ommoord, a suburb of Rotterdam, aged ≥55 years to participate. At each visit, participants underwent a home interview and had medical examinations at the research center. According to the Population Screening Act: Rotterdam Study, which was executed by the Ministry of Health, Welfare, and Sports of the Netherlands, the Rotterdam Study was approved by the medical ethics committee. Written informed consent was obtained from all participants.

Between 1995 and 1996, 965 participants of the Rotterdam Study were invited to undergo additional examinations, including MRI.[8,15] Participants were randomly invited, based on strata of age (5 years) and gender.[8] After excluding people with contraindications for participation (MRI-contraindications, blindness, or dementia), 832 were deemed eligible to participate. Five hundred and thirty-six people agreed to undergo an MRI (68%), however, 52 participants did not complete MRI due to claustrophobia. Additionally, we excluded 45 participants for artifacts or cortical infracts found on the MRI, or for other technical reasons. Furthermore, three participants were excluded for missing data on dementia or education.

Finally, 463 participants were included in the study. For technical reasons, mostly motion artifacts, hippocampus volumes could only be estimated in 420 participants.

In total, MMSE, IADL, and BADL were assessed at up to seven visits. A population flow chart is provided in Figure 1. Study drop out was mainly due to death.

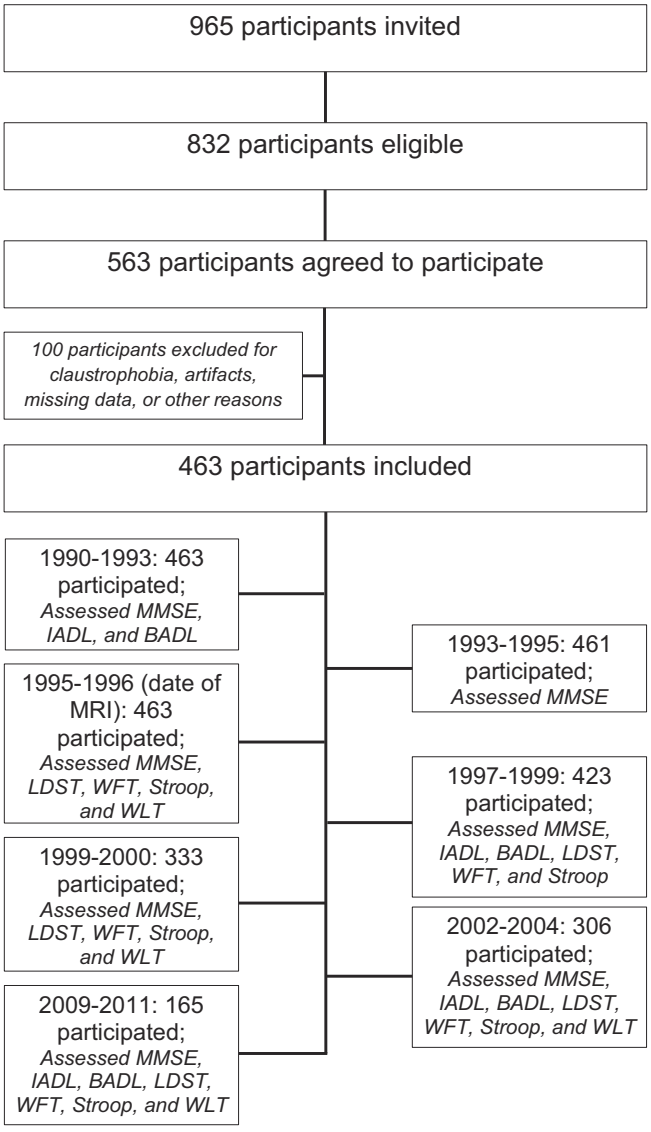

Figure 1. Flowchart of the study population.

MRI-Acquisition

Brain MRI-imaging was performed using a 1.5-tesla MRI system (VISION MR, Siemens AG), including T1-weighted, proton-density-weighted, T2-weighted, and inversion-recovery HASTE sequences.[16]

Automated brain tissue classification based on a k-nearest neighbor classifier was used to quantify supratentorial intracranial, brain, grey matter, white matter, and white matter lesion volume.[16,17] Total white matter volume was the sum of normal-appearing white matter and white matter lesion volume. Automated lobar segmentation was used to determine volumes of frontal, temporal, parietal, and occipital lobes, which were summed for both hemispheres.[4]

Hippocampal volumes were manually outlined on coronal HASTE-slices reconstructed perpendicular to the long axis of the hippocampus.[18]

Lacunar brain infarcts were rated visually as focal parenchymal hyperintensities on T2-weighted images with corresponding hypointensity on T1-weighted images (≥3 mm), without cortical involvement.[5]

Cognitive Assessment

During all visits, cognition was assessed using the MMSE.[2] Additionally, a cognitive test battery was administered: the Letter-Digit Substitution Task (LDST), Stroop reading, color naming, and interference task, word fluency test (WFT), and an immediate, delayed, and recognition 15-word verbal learning test (15-WLT).[19–22] These cognitive tests were included from the date of the MRI onwards and assessed at up to five visits.

Basic Activities of Daily Living

Basic activities of daily living (BADL) was assessed with the Dutch version of the disability index from the Stanford Health Assessment Questionnaire, consisting of 20 items constituting eight components: activities, arising, dressing and grooming, eating, grip, hygiene, reaching, and walking.[23] We combined two out of the three items for eating (ability to lift a glass of milk and ability to cut meat) into one. Each item could be scored 0–3, with higher scores

indicating worse ability: 0 = without difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to. Component scores were calculated as the highest scored item belonging to that component. Each item scored as non-applicable or missing was accounted for in the respective component. Subsequently, the BADL-score, between 0 and 24, was calculated by the total of all component scores.

Instrumental Activities of Daily Living

Instrumental activities of daily living (IADL) was assessed using the Dutch version of the Instrumental Activities of Daily Living scale.[24] The IADL scale consists of eight items: finance management, housekeeping, laundry, meal preparation, medication maintenance, phoning, shopping, and travelling on your own. Similar to the disability index, items were scored 0–3. For telephone use, participants using an adapted telephone were scored as 2 (with much difficulty).

For IADL, items scored as non-applicable were imputed by means of five imputations, based on age, sex, scores on BADL items, and scores on the other IADL items. Imputation was performed separately for each visit. Overall, <5.3% of variables were imputed for each study round. Imputation of non-applicable values has been suggested and adopted to prevent loss of data.[3,9] The IADL-score was calculated by the total of all items, obtaining a score between 0 and 24.

Diagnosis of Dementia

Participants were evaluated for incident dementia using three steps.[25] Participants were screened for dementia at each visit using the MMSE and Geriatric Mental State schedule (GMS).[26] Participants scoring ≤25 on the MMSE or >0 on the GMS underwent the Cambridge Mental Disorders of the Elderly Examination diagnostic interview.[27] Participants suspected of having dementia based on this interview underwent further extensive neuropsychological testing. In addition to the screening, the cohort was continuously monitored for diagnoses of dementia through medical records of the general practitioner's office and Regional Institute for Outpatient Mental Health Care (RIAGG). Diagnoses of dementia were made based on the internationally accepted DSM-III-R criteria. Follow-up on dementia was complete until January 1, 2011.

Covariates

During the interview and examinations on the date of MRI, educational level, height, weight, systolic and diastolic blood pressure, smoking status, glucose level, total cholesterol level, high-density lipoprotein (HDL) level, and use of blood pressure lowering and anti-diabetic medication were evaluated. Educational level was divided into seven categories: 0 = primary education or less, 1 = intermediate vocational education, 2 = intermediate general education, 3 = higher vocational education, 4 = higher general education, 5 = college, 6 = university. Body mass index (BMI) was calculated as weight divided by the squared height. Diabetes mellitus was defined as a non-fasting glucose level ≥11.1 mmol/L, or use of anti-diabetic medication or insulin.

Statistical Analysis

White matter lesion volumes were natural-log transformed to obtain a normal distribution. Subsequently, volumetric MRI-markers were Z-standardized.

We used linear mixed models to investigate associations of MRI-markers with annual change in MMSE, IADL, and BADL. Random effects for slope and intercept were included to account for between-person differences and within-person correlations across time. In all analyses, MRI-markers and their interaction with time were included in the same models. Grey matter volume and total white matter volume were included in one model to investigate independent effects. All analyses were adjusted for age, sex, education, their interactions with time, age*-time^2, time, and time^2. Analyses on volumetric MRI-markers were adjusted for intracranial volume and intracranial volume*time. The age and time used in the analyses were calculated at or from the date of MRI.

Analyses were repeated after excluding participants diagnosed with dementia during follow-up and separately after excluding those diagnosed with Alzheimer's disease. Furthermore, we tested whether effect sizes differed significantly before and after exclusion.

To visualize effects of brain volume on MMSE, IADL, and BADL over time, we created quartiles of brain volume adjusted for intracranial volume. Subsequently, linear mixed models were used to determine trajectories of decline in MMSE, IADL, and BADL per quartile of total brain volume across visits, adjusted for the covariates specified above. These analyses were repeated after excluding participants with incident dementia.

To investigate whether differences in associations for MMSE were due to the use of MMSE as a screening tool for dementia, we repeated analyses on MMSE while excluding visits after dementia diagnosis.

Furthermore, we explored associations of brain MRI-markers with annual change in separate cognitive tests: LDST, Stroop subtasks, WFT, and 15-WLTs in the overall population and the population without incident dementia. Similar to MMSE, we visualized the trajectories for cognitive tests, which related significantly with brain volume continuously, for different quartiles of brain volume adjusted for intracranial volume in the overall population and after excluding incident dementia.

We repeated all analyses on MMSE, IADL, and BADL adjusting for cardiovascular risk factors (BMI, systolic blood pressure, diastolic blood pressure, blood pressure lowering medication, current or past smoking, diabetes mellitus, total cholesterol level, and HDL level) and their interactions with time.

To investigate whether lobar specific white matter lesions influenced associations for lobar volumes, we investigated whether lobar white matter lesion volumes associated with change in MMSE, IADL, and BADL. Additionally, we investigated whether adjustment for lobar white matter lesion volumes influenced the respective associations of lobar volumes with change in MMSE, IADL, and BADL.

To investigate whether brain MRI-markers also predict incident dementia, we performed cox-regression models adjusted for age, sex, and education.

All analyses were performed using IBM SPSS version 21.0.0.1 for Windows.

RESULTS

Mean age of the study population was 68.4 years (standard deviation (SD) 7.9) at initial visit (1990–1993) and 73.1 (SD 7.8) at date of MRI (1995–1996). It should be noted that 51.8% of participants were women. At initial visit, mean MMSE-score was 28.2 (SD 1.5), IADL-score 2.0 (SD 3.0), and BADL-score 2.4 (SD 3.4). Mean total follow-up from date of MRI onwards was 7.4 years (SD 4.7, max 14.9) and from initial visit onwards 12.1 years (SD 4.8, max 20.0). Sixty-three (13.6%) participants were diagnosed with dementia during follow-up, of which 52 were diagnosed with Alzheimer's disease, six diagnosed with vascular dementia, one had Parkinson's dementia, one had spinocerebellar ataxia, and three were undetermined. Population characteristics of participants with and without incident dementia are shown in Table 1.

Smaller brain volume, driven by grey and white matter, associated with larger decrease in MMSE-score (−0.12points/SD*year [95% confidence interval: −0.18; −0.06]), and larger increase in IADL-score (0.26/SD*year [0.15; 0.37]) and BADL-score (0.19/SD*year [0.09; 0.29]), see Table 2. Smaller hippocampus volume only showed a trend of association with larger increase in IADL-score ($P < .10$).

Smaller frontal and parietal lobe volume associated with larger decrease in MMSE-score and larger increase in IADL-score and BADL-score, while temporal lobe volume only associated with MMSE-score and IADL-score (Table 2).

Larger white matter lesion volume associated with greater decline in MMSE-score, while lacunar infarcts did not associate with MMSE, IADL, or BADL (Table 2).

When excluding visits after incident dementia, associations with MMSE significantly attenuated, with only some volumes remaining associated with larger decrease in MMSE (Table S1). The associations of MRI-markers with IADL-score attenuated less strongly, with only associations of temporal and parietal lobe volume becoming non-significant. Associations of MRI-markers with BADL-score did not materially change.

When totally excluding participants with incident dementia associations with MMSE attenuated even further, with all associations of MRI-markers with change in MMSE-score becoming non-significant, except associations of temporal lobe and white matter lesion volume (Table 3). The associations of MRI-markers with IADL-score and BADL-score remained very similar to when only visits after dementia diagnosis were excluded.

Similar patterns of attenuation were found when excluding people with Alzheimer's disease instead of any dementia (Table S2).

Participants in the lowest quartile with smallest brain volumes showed larger change in MMSE, IADL, and BADL compared to participants in the highest quartile (*P*-trends < .05, Figure 2). After excluding participants with incident dementia, *P*-trends remained significant for IADL and BADL, but not for MMSE.

Table 1. Population Characteristics at Date of MRI

	Non-Demented (n = 400)	Incident Demented (n = 63)
Age, years	72.7 (7.7)	76.0 (7.7)[a]
Females, n	200 (50.0%)	40 (63.5%)[a]
Education[b]	2 (0, 3)	1 (0, 3)
MMSE, points	28.2 (1.4)	28.0 (1.5)
IADL, points	2.0 (3.0)	2.1 (3.3)
BADL, points	2.4 (3.4)	2.4 (3.3)
Brain volume, mL	876.8 (97.6)	853.1 (103.9)
Grey matter volume, mL	525.1 (55.2)	518.4 (54.6)
Total white matter volume, mL	351.7 (83.1)	334.7 (78.0)
Hippocampus volume[c], mL	6.5 (0.8)	6.4 (0.8)
Frontal lobe volume, mL	310.8 (38.0)	303.0 (38.7)
Temporal lobe volume, mL	176.1 (20.4)	169.8 (22.3)
Parietal lobe volume, mL	179.1 (21.7)	174.2 (22.9)
Occipital lobe volume, mL	101.7 (13.0)	97.9 (13.7)
White matter lesion volume, mL	13.4 (15.2)	17.8 (17.7)
Lacunar infarcts, n	95 (23.8%)	16 (25.4%)
Body mass index, kg/m^2	26.3 (3.5)	25.7 (3.4)
Systolic blood pressure, mmHg	145.6 (20.8)	145.6 (20.5)
Diastolic blood pressure, mmHg	76.5 (11.3)	77.8 (13.0)
Blood pressure lowering medication, n	152 (38.0%)	21 (33.3%)
Ever smoker, n	289 (72.3%)	36 (57.1%)
Diabetes, n	21 (5.3%)	4 (6.3%)
Total cholesterol level, mmol/L	5.9 (1.0)	6.0 (1.2)
High-density lipoprotein level, mmol/L	1.3 (0.4)	1.3 (0.4)

Values are means (SD) or numbers of participants (percentages).

[a]Age and sex differed significantly between incident demented and dementia-free remaining participants ($P < .05$), none of the other differences were significant after adjusting for age and sex.

[b]Education was categorized as follows: 0 = primary education or less, 1 = intermediate vocational education, 2 = intermediate general education, 3 = higher vocational education, 4 = higher general education, 5 = college, 6 = university. Since it is a categorical variable, we use the median (lower quartile, upper quartile).

[c]Non-demented: n = 362; Incident demented: n = 58.

Smaller brain volume, grey matter volume, white matter volume, and frontal lobe volume associated with larger decline in LDST and all Stroop subtasks (Table S3). Additionally, smaller temporal and parietal lobe volume associated with larger decline in Stroop 1 and 3, and smaller hippocampal volume with larger decline in Stroop 1.

Similar to MMSE, associations of brain volumes with change in LDST and the Stroop subtasks clearly attenuated when excluding participants with incident dementia (Table S4). However, associations of brain volume and particularly frontal lobe volume with change in LDST and all Stroop subtasks remained nominally significant ($P < .05$). No associations were found for brain MRI-markers with WFT or 15-WLT tests. Similar results were found when analyzing volumes in quartiles instead of continuously (Figure S1).

After additional adjustment for cardiovascular risk factors, longitudinal associations of MRI-markers with MMSE, IADL, and BADL slightly attenuated, but did not meaningfully impact significance levels.

Table 2. Associations of MRI-markers with Change in Cognition and Daily Functioning in the Overall Population

	Annual Change In		
	MMSE	IADL	BADL
Brain volume/SD smaller	**−0.12 (−0.18; −0.06)**	**0.26 (0.15; 0.37)**	**0.19 (0.09; 0.29)**
Grey matter volume[a]/SD smaller	**−0.08 (−0.12; −0.04)**	**0.16 (0.08; 0.24)**	**0.09 (0.02; 0.17)**
Total white matter volume[a]/SD smaller	**−0.10 (−0.15; −0.05)**	**0.22 (0.13; 0.31)**	**0.15 (0.07; 0.24)**
Hippocampus volume/SD smaller	−0.01 (−0.03; 0.01)	0.04 (0.000; 0.08)	0.01 (−0.03; 0.05)
Frontal lobe volume/SD smaller	**−0.04 (−0.09; −0.001)**	**0.18 (0.10; 0.25)**	**0.14 (0.07; 0.21)**
Temporal lobe volume/SD smaller	**−0.09 (−0.13; −0.05)**	**0.12 (0.04; 0.20)**	0.06 (−0.01; 0.13)
Parietal lobe volume/SD smaller	**−0.07 (−0.11; −0.03)**	**0.09 (0.02; 0.16)**	**0.08 (0.02; 0.14)**
Occipital lobe volume/SD smaller	−0.02 (−0.05; 0.01)	0.02 (−0.04; 0.07)	0.003 (−0.05; 0.05)
White matter lesion volume/SD larger	**−0.03 (−0.05; −0.01)**	−0.004 (−0.04; 0.03)	0.03 (−0.002; 0.07)
Lacunes, yes versus no	−0.02 (−0.06; 0.03)	0.07 (−0.01; 0.16)	0.06 (−0.02; 0.14)

MMSE, Mini-Mental State Examination; IADL, instrumental activities of daily living; BADL, basic activities of daily living.
Values represent annual changes in MMSE, IADL, or BADL-score (with 95% confidence intervals). Analyses were adjusted for age, sex, education, intracranial volume (if applicable), their interactions with time, time, time,^{2} age*time,^{2} and the respective MRI-marker. Results in bold survived thresholds of nominal significance ($P < .05$).
[a]Grey matter and total white matter volume were included in one model.

Table 3. Associations of MRI-markers with Change in Cognition and Daily Functioning, Excluding Incident Demented Participants

	Annual Change In		
	MMSE	IADL	BADL
Brain volume/SD smaller	−0.03 (−0.08; 0.02)	**0.17 (0.07; 0.28)**	**0.17 (0.06; 0.27)**
Grey matter volume[a]/SD smaller	−0.01 (−0.05; 0.03)	**0.11 (0.03; 0.19)**	**0.09 (0.01; 0.17)**
Total white matter volume[a]/SD smaller	−0.02 (−0.07; 0.02)	**0.15 (0.06; 0.24)**	**0.14 (0.05; 0.23)**
Hippocampus volume/SD smaller	0.01 (−0.01; 0.03)	0.03 (−0.01; 0.07)	0.02 (−0.02; 0.06)
Frontal lobe volume/SD smaller	0.000 (−0.04; 0.04)	**0.14 (0.07; 0.22)**	**0.13 (0.06; 0.21)**
Temporal lobe volume/SD smaller	**−0.04 (−0.08; −0.002)**	0.08 (−0.002; 0.15)	0.06 (−0.02; 0.14)
Parietal lobe volume/SD smaller	−0.03 (−0.06; 0.01)	0.03 (−0.03; 0.10)	0.06 (−0.01; 0.12)
Occipital lobe volume/SD smaller	−0.01 (−0.03; 0.02)	−0.02 (−0.07; 0.03)	−0.02 (−0.07; 0.04)
White matter lesion volume/SD larger	**−0.02 (−0.04; −0.002)**	−0.02 (−0.05; 0.02)	0.03 (−0.001; 0.07)
Lacunes, yes versus no	−0.02 (−0.06; 0.02)	0.04 (−0.05; 0.12)	0.07 (−0.01; 0.15)

MMSE, Mini-Mental State Examination; IADL, instrumental activities of daily living; BADL, basic activities of daily living.
Values represent annual changes in MMSE, IADL, or BADL-score (with 95% confidence intervals). Analyses were adjusted for age, sex, education, intracranial volume (if applicable), their interactions with time, time, time,^{2} age*time,^{2} and the respective MRI-marker. Results in bold survived thresholds of nominal significance ($P < .05$).
[a]Grey matter and total white matter volume were included in one model.

Larger frontal, parietal, and occipital white matter lesion volume was associated with a larger decline in MMSE (Table S5). These associations attenuated slightly after excluding individuals with incident dementia, with the association for occipital white matter lesion volume becoming non-significant. Larger temporal and occipital white matter lesion volume was associated with a larger decline in BADL. Exclusion of people with incident dementia did not affect these associations for BADL.

Additional adjustment for lobe specific white matter lesion volume barely affected any of the associations for lobar volumes, with only the association of frontal lobe volume with MMSE in the overall population becoming non-significant.

In cox-regression models, we found brain volume (hazard ratio [HR] 0.17 [0.07; 0.39]) and temporal lobe volume (HR 0.21 [0.11; 0.40]) to most strongly predict incident dementia (Table S6). Furthermore, smaller white matter volume, grey matter volume, hippocampus volume, parietal lobe volume, and occipital lobe volume associated with a higher risk of dementia.

DISCUSSION

In this study of community-dwelling individuals, we found brain MRI-markers to associate with a change in cognition and daily functioning during up to a 15-year follow-up. Smaller brain volume, driven by grey and white matter was associated with a larger decline in MMSE, IADL, and BADL, while white matter lesions only associated with MMSE. Smaller frontal lobe volume associated strongest with IADL and BADL, while temporal lobe volume associated with MMSE and IADL. When excluding participants with incident dementia, associations with daily functioning

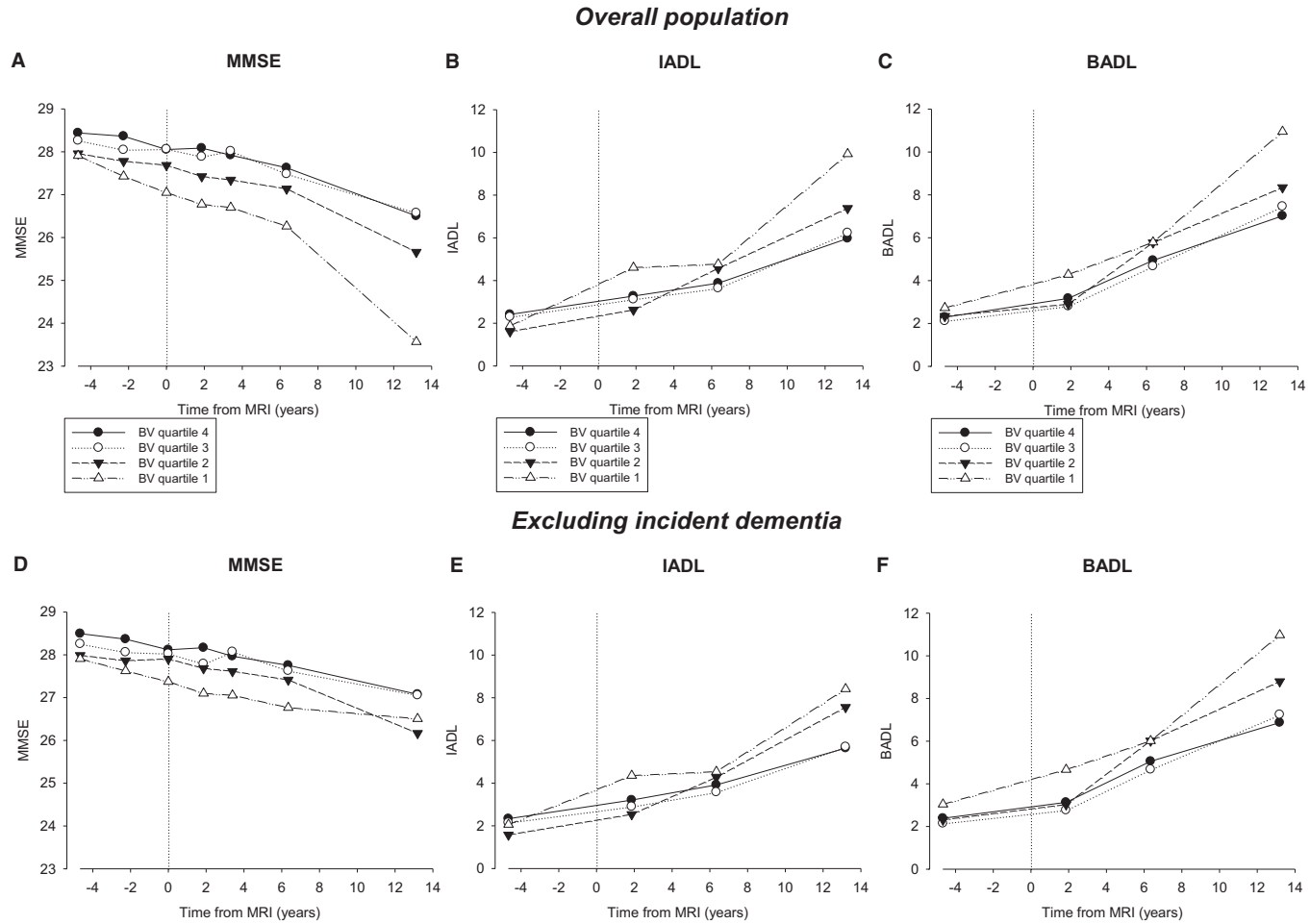

Figure 2. Trajectories of change in cognition and daily functioning across quartiles of brain volume. Symbols are estimates of cognition and daily functioning at the visits for each quartile of brain volumes (BV), calculated from linear mixed models. Lower scores on MMSE reflect worse cognition, while higher scores on IADL and BADL reflect worse daily functioning. Higher quartiles of brain volume represent participants with larger brain volumes.

only slightly attenuated, while associations of MRI-markers with cognition largely disappeared.

Strengths of our study include the population-based setting, long follow-up, assessment of MMSE, IADL, BADL, and other cognitive tests at multiple visits, and quantitative measurement of brain, grey matter, white matter, white matter lesion, and lobar volumes.

Limitations of our study include the use of MRI at only one time-point. Therefore, we could not investigate whether decline in cognition or daily functioning coincides with progression of brain MRI-markers. Additionally, MMSE was used as outcome as well as a screening tool for dementia. Therefore, attenuation after excluding people with incident dementia may partly have been driven by this link of MMSE to dementia. Nonetheless, associations remained present when excluding visits after incident dementia and further attenuated after excluding people with incident dementia altogether, suggesting a true relationship with dementia. This is further supported by the similar pattern of findings for the other cognitive tests. Another limitation is that only few people were diagnosed with types of dementia other than Alzheimer's disease, limiting our interpretation with respect to other pathologic processes such as vascular dementia or Lewy body dementia. Finally, our participants may have been relatively healthy, because they were required to come to the research center for examinations. Hence, true rates of decline in cognition and daily functioning in the underlying population may have been underestimated. Generalizability of our study may thus be restricted to a relatively healthy population.

One of our key findings is that associations of brain MRI-markers, especially brain volume, with cognitive decline attenuated after excluding persons that went on to develop dementia. This suggests that the association between brain volume and cognitive decline lies on the pathway that ultimately leads to dementia. Previous studies found similar associations between brain MRI-markers and cognitive decline, but due to a short follow-up, these studies were unable to extend this link to dementia.[5,6,12,13] In our study, exclusion of participants with incident dementia led to the disappearance of nearly all associations between brain MRI-markers and a decline in MMSE. Similarly, associations of brain volume with change in LDST and the Stroop subtasks strongly attenuated after excluding participants with incident dementia. These findings suggest that the association of brain volume with cognitive decline may be an early manifestation of

dementia-related pathology that lies on the pathway that ultimately leads to dementia. Unfortunately, we were not able to determine whether this truly was an early manifestation in individual patients. The strong association of temporal lobe volume with MMSE and the subsequent attenuation after dementia exclusion correspond to the idea that the temporal lobe is affected early in the dementia process, especially Alzheimer's disease.[28] All in all, our findings indicate an essential role of Alzheimer-related pathology, e.g., amyloid deposition and neurofibrillary tangles, in the relationship of brain MRI-markers with cognition.[29] We note however, that the associations of brain volumes with change in LDST, Stroop 1, and Stroop 3 did not completely disappear after excluding incident dementia, possibly explained by their assessment of mainly executive functioning and information processing speed. The frontal lobe is thought to be particularly important in executive functioning, while the temporal lobe and hippocampus are primarily affected by dementia-related pathology.[28,30] This may explain why largest attenuation in associations was found for the temporal lobe with change in the Stroop subtasks, while attenuation of associations for the frontal and parietal lobe was less pronounced. Nonetheless, the large attenuation in associations with Stroop 1 and 3 and disappearance with Stroop 2 does suggest that the relationship of smaller brain volumes with worse functioning in executive functioning and information processing speed also has a role in the pathway towards dementia. This corresponds to the definition of dementia, that impairment in at least another domain than memory is required for its diagnosis.

In contrast to cognitive decline, the relation between brain MRI-markers and decline in daily functioning was largely independent from incident dementia. This may be explained by the natural course of dementia. Since decline in, especially basic, daily functioning is mainly apparent at the last stage before dementia diagnosis, there is a shorter time frame for very strong decline as compared to cognition.[31] In particular, frontal lobe volume was strongly associated with change in IADL and BADL, contrasted by a weak association with MMSE. The frontal lobe is considered to be important for movement and executive functioning, which are essential in daily functioning.[30,32] Since frontal lobe volume remained weakly associated with executive functioning (i.e., LDST and Stroop) after dementia exclusion, executive functioning may partly mediate the relationship between frontal lobe and daily functioning. Yet, the exact biological origin of this relationship remains unknown. Importantly, adjustment for frontal lobe white matter lesion volume did not affect the association, suggesting that white matter lesion volume did not drive this association. Similarly, adjustment for cardiovascular risk factors only slightly attenuated the relationship, suggesting that cardiovascular disease is not primarily involved. However, as of yet, treatment of cardiovascular risk factors has been the only successful intervention to reduce progression of brain atrophy and white matter lesions.[33] Further research is needed to determine the pathology underlying the associations of brain MRI-markers with change in daily functioning. In turn, this may aid in identifying novel intervention targets for prevention of impairment in daily functioning.

Similar to previous studies, we found white matter lesions, especially in the frontal, parietal and occipital lobe, to associate with cognitive decline.[6,12,13] Since the temporal lobe is closely related to dementia, the lack of an association for temporal white matter lesion volume may explain why the association of global white matter lesion volume with MMSE did not attenuate after dementia exclusion.[28] We found temporal and occipital white matter lesion volume to associate with change in BADL, corresponding to previous studies.[7,10]

CONCLUSIONS

In a community-dwelling population, brain MRI-markers are related to change in both cognition and daily functioning. Most importantly, the relationship of brain volumes with a decline in cognition (but not daily functioning) was driven by those individuals that ultimately developed dementia. Hence, brain volume is predictive of a decline in daily functioning, however it is not universally predictive of cognitive decline, except in people that ultimately develop dementia.

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Authors Contributions: Study concept and design: Verlinden, Hofman, van der Lugt, Vernooij, Ikram. Acquisition of data: Verlinden. Analysis and interpretation of data: Verlinden, van der Geest, de Groot, Hofman, Niessen, van der Lugt, Vernooij, Ikram. Drafting the manuscript: Verlinden, Vernooij, Ikram. Critical revision of the manuscript for imporant intellectual content: Verlinden, van der Geest, de Groot, Hofman, Niessen, van der Lugt, Vernooij, Ikram. All authors gave final approval of the version of the manuscript to be published. The corresponding author affirms that he has listed everyone who contributed significantly to the work.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Associations of MRI-markers with Change in Cognition and Daily Functioning, Excluding Measurements from Visit of Dementia Diagnosis Onwards. Values represent annual changes in MMSE, IADL, or BADL-score (with 95% confidence intervals). Analyses were adjusted for age, sex, education, intracranial volume (if applicable), their interactions with time, time, time,^{2} age*time,^{2} and the respective MRI-marker. Results in bold survived thresholds of nominal significance ($P < .05$).

Table S2. Associations of Brain Volume with Change in Cognition and Daily Functioning, after Excluding Specific Subtypes of Dementia. Values represent annual changes in MMSE, IADL, or BADL-score (with 95% confidence intervals). Analyses were adjusted for age, sex, education, intracranial volume (if applicable), their interactions with time, time, time,^{2} age*time,^{2} and the respective MRI-marker. Results in bold survived thresholds of nominal significance ($P < .05$).

Table S3. Associations of MRI-Markers with Change in Cognitive Tests in the Overall Population. Values represent annual changes in the number of correct answers (LDST, WFT, WLT) or time taken (Stroop) on the cognitive tests (with 95% confidence intervals). Except for WML and lacunes, values reflect changes per SD smaller volume. Analyses were adjusted for age, sex, education, intracranial volume (if applicable), their interactions with time, time, time,^{2} age*time,^{2} and the respective MRI-marker. Results in bold survived thresholds of nominal significance ($P < .05$).

Table S4. Associations of MRI-markers with Change in Cognitive Tests, Excluding Incident Demented Participants. Values represent annual changes in the number of correct answers (LDST, WFT, WLT) or time taken (Stroop) on the cognitive tests (with 95% confidence intervals). Except for WML and lacunes, values reflect changes per SD smaller volume. Analyses were adjusted for age, sex, education, intracranial volume (if applicable), their interactions with time, time, time,^{2} age*time,^{2} and the respective MRI-marker. Results in bold survived thresholds of nominal significance ($P < .05$).

Table S5. Associations of Lobar White Matter Lesion Volume with Change in Cognition and Daily Functioning.

Values represent annual changes in MMSE, IADL, or BADL-score (with 95% confidence intervals). Analyses were adjusted for age, sex, education, intracranial volume (if applicable), their interactions with time, time, time,^{2} age*time,^{2} and the respective MRI-marker. Results in bold survived thresholds of nominal significance ($P < .05$).

Table S6. Associations of MRI-markers with Incident Dementia. Values represent hazard ratio's (with 95% confidence intervals) on incident dementia. Analyses were adjusted for age, sex, education, and intracranial volume (if applicable). Six people were dropped from the analyses because they dropped out before the first case of incident dementia occurred. Results in bold survived thresholds of nominal significance ($P < .05$).

Figure S1. Trajectories of change in cognition across quartiles of brain volume. Symbols are estimates of cognition and daily functioning at the visits for each quartile of brain volumes (BV), calculated from linear mixed models. Lower scores on LDST and longer time on the Stroop subtasks reflect worse cognition. Higher quartiles of brain volume represent participants with larger brain volumes.