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Vascular brain lesions, brain atrophy, and cognitive decline. The Second Manifestations of ARTerial disease—Magnetic Resonance (SMART-MR) study

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ABSTRACT

We examined the association between brain atrophy and vascular brain lesions (i.e., white matter lesions [WMLs] or brain infarcts), alone or in combination, with decline in memory and executive functioning over 4 years of follow-up in 448 patients (57 ± 9.5 years) with symptomatic atherosclerotic disease from the Second Manifestations of ARTerial disease—Magnetic Resonance SMART-MR study. Automated brain segmentation was used to quantify volumes of total brain, ventricles, cortical gray matter, and WMLs on 1.5-T magnetic resonance imaging (MRI). Brain infarcts were rated visually. WML volume was associated with significant decline in *z* score of executive functioning. No independent associations between MRI measures and memory decline were found. Significant declines in *z* scores of memory performance and of executive functioning were observed in patients with a combination of severe atrophy (upper quartile) and most vascular brain lesions (upper quartile) compared with those with minimal atrophy (lowest quartile) and fewest vascular brain lesions (lowest quartile). Our findings suggest that in patients with symptomatic atherosclerotic disease, the combination of brain atrophy and WMLs or brain infarcts accelerates cognitive decline over 4 years.

1. Introduction

Vascular disease and vascular risk factors have been associated with brain magnetic resonance imaging (MRI) abnormalities (e.g., brain atrophy, white matter lesions [WMLs], and brain infarcts) (Geerlings et al., 2010; Ikram et al., 2008). Vascular brain lesions, in particular WMLs and infarcts, and brain atrophy often coexist (Appelman et al., 2010). Also, these brain abnormalities have been associated with cognitive impairment (e.g., memory performance, executive functioning, and information processing speed) not only in patients with clinical manifestations of vascular disease (Akisaki et al., 2006; Geerlings et al., 2009; Manschot et al., 2007) but also in healthy middle-aged and older populations (Au et al., 2006; Kramer et al., 2007; Longstreth et al., 2005; Prins et al., 2005).

Previous cross-sectional studies have suggested that the combination of vascular brain lesions and brain atrophy is particularly detrimental to cognitive performance, more than the sum of their separate effects (Muller et al., 2011; van der Flier et al., 2005). Also, in a prospective population-based study in older adults, it was found that WMLs and brain atrophy interact to produce cognitive decline (Godin et al., 2010). This was confirmed in a recently conducted clinical-based study of patients with WMLs (Jokinen et al., 2012). Most of these previous studies were conducted in older populations. Yet, it is still unknown if the combination of vascular brain lesions and brain atrophy is associated with cognitive decline in late middle-aged patients and whether the association is different for multiple cognitive domains depending on the location of brain atrophy (cortical or subcortical).

The aim of the present study was to assess the association between brain atrophy and vascular lesions, in particular WMLs and brain infarcts, alone or in combination, with cognitive decline over 4 years of follow-up in a large cohort of middle-aged patients with symptomatic atherosclerotic disease.

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2. Methods

2.1. SMART-MR study

Data were used from the Second Manifestations of ARTerial disease—Magnetic Resonance (SMART-MR) study, a prospective cohort study aimed to investigate brain changes on MRI in 1309 independently living patients with symptomatic atherosclerotic disease. Details of the design and participants have been described elsewhere (Geerlings et al., 2010). In brief, between May 2001 and December 2005, all patients newly referred to the University Medical Center Utrecht with manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease, or an abdominal aortic aneurysm and without MR contraindications were invited to participate. During a 1-day visit to our medical center, an MRI of the brain was performed, in addition to a physical examination, ultrasonography of the carotid arteries, and blood and urine sampling. Risk factors, medical history, and functioning were assessed with questionnaires. Neuropsychological assessment was introduced in the SMART-MR study in January 2003 and was performed on the same day as the MRI and other investigations. Neuropsychological testing was performed in 831 patients. Between January 2006 and May 2009, all participants still alive were invited for follow-up measurements, including MRI of the brain and neuropsychological assessment. The SMART-MR study was approved by the ethics committee of our institution, and written informed consent was obtained from all participants.

2.2. MRI protocol

MRI investigations were performed on a 1.5-T whole-body system (Gyroscan ACS-NT; Philips Medical Systems, Best, The Netherlands). The protocol consisted of transversal T1-weighted gradient-echo (repetition time [TR]/echo time [TE] 235/2 ms), transversal T2-weighted turbo spin-echo (TR/TE 2200/11 and 2200/100 ms, turbo factor 12), fluid-attenuated inversion recovery (FLAIR) (TR/TE/inversion time 6000/100/2000 ms), and transversal IR (TR/TE/inversion time 2900/22/410 ms) sequences (field of view 230 × 230 mm, matrix size 180 × 256, slice thickness 4 mm, no slice gap 38 slices).

2.3. Brain segmentation

We used the T1-weighted gradient-echo, IR, and FLAIR sequences for brain segmentation. The segmentation was done with *k*-nearest neighbor classification, which is a probabilistic segmentation technique that has been described elsewhere (Anbeek et al., 2004, 2005). The segmentation program distinguishes cortical gray matter, white matter, sulcal and ventricular cerebrospinal fluid, and WMLs. The automatic segmentation was visually checked, and a further distinction was made between WML and infarct volumes by manually assigning the lesion volumes to 1 of these 2 categories. Total brain volume was calculated by summing the volumes of gray and white matter and, if present, the volumes of WMLs and infarcts. All volumes cranial to the foramen magnum were included. As a result, the total brain volume includes the cerebrum, brain stem, and cerebellum. Total intracranial volume (ICV) was calculated by summing the total brain volume and the volumes of sulcal and ventricular cerebrospinal fluid.

2.4. Brain infarcts and WMLs

At baseline and follow-up, infarcts were rated visually by an investigator and a neuroradiologist, blinded to clinical characteristics, and were reevaluated in a consensus meeting. Infarcts were defined as focal hyperintensities on T2-weighted images of >3 mm in diameter. Hyperintensities that were classified as infarcts and were located in the white matter had to be hypointense on T1-weighted and FLAIR images to distinguish them from WMLs. Infarcts were classified as present or absent. WML volumes were normalized for ICV and natural log transformed.

2.5. Brain volumes

Total brain, cortical gray matter, and ventricular volumes were expressed relative to ICV. Total brain volume, cortical gray matter volume, ventricular volume were used as indicators of global brain atrophy, cortical brain atrophy, and subcortical brain atrophy, respectively.

2.6. Neuropsychological assessment

At baseline and follow-up, memory and executive functioning was assessed with neuropsychological tests, sensitive to mild impairments as described earlier (Muller et al., 2011). Composite *z* scores for the domains memory and executive functioning were calculated. The composite score for memory included immediate and delayed recall and the retention score of the 15-word learning test (a modification of the Rey Auditory Verbal Learning test) (Brand and Jolles, 1985) and the delayed recall of the Rey-Osterrieth Complex Figure test (Osterrieth, 1944). The composite score for executive function included the Visual Elevator test (Robertson et al., 1996), the Brixton Spatial Anticipation test (Burgess and Shallice, 1996), and the Verbal Fluency test (letter N for baseline and letter A for follow-up, 1-minute time frame) (Wilkins et al., 1987). Composite *z* scores were computed by converting raw scores to standardized *z* scores and averaging them across all subtests per domain. Before calculating *z* scores, the scores of the Visual Elevator test and the Brixton Spatial Anticipation test were multiplied by −1 so that lower scores represented poorer performance. The composite *z* scores at follow-up were calculated by using the means and standard deviations of the baseline test scores.

2.7. Covariates

Premorbid intellectual functioning was assessed using the Dutch version of the National Adult Reading test (DART) (Schmand et al., 1998). Educational level was divided into 7 categories: graded from primary school (more or less 6 years of education) to academic degree (more or less 16 years of education), according to the Dutch educational system. An overnight fasting venous blood sample was taken to determine lipid and glucose levels. Height and weight were measured without shoes and heavy clothing, and body mass index was calculated (kilogram per square meter). Systolic and diastolic blood pressure (millimeters of mercury) were measured twice in supine position with sphygmomanometer and averaged. Diabetes mellitus was defined as the use of glucose-lowering agents, a known history of diabetes mellitus, or a fasting plasma glucose level ≥7.0 mmol/L. Use of antidepressants or benzodiazepines, smoking habits, and alcohol intake was assessed with questionnaires. Pack-years of smoking was calculated, and alcohol intake was categorized into never, former, and current. Ultrasonography was performed to measure the intima-media thickness (millimeter) in the left and right common carotid arteries as a measure of severity of subclinical atherosclerosis, represented by the mean value of 6 measurements (Kanters et al., 1998; Simons et al., 1999).

2.8. Study sample

Of the 831 patients in whom neuropsychological assessment was performed at baseline, MR segmentation data were not available in

51 patients (MR data irretrievable [$n = 11$], missing FLAIR sequence [$n = 8$], and motion or other artefacts [$n = 32$]). Of the remaining 780 patients, 31 died during follow-up and 460 (61% of survivors) participated in the follow-up examination ($n = 282$ refused and $n = 7$ were lost to follow-up). Neuropsychological assessment at follow-up was missing in 12 patients. As a result, the analytical sample consisted of 448 patients. Compared with the 448 participants, the 332 patients not included in the present analyses were at study entry on average older (mean age [standard deviation {SD}] 59 [10] vs. 57 [10] years, $p = 0.004$), more often female (27% vs. 20%, $p = 0.02$), had higher systolic and diastolic blood pressure levels (148 [24] vs. 141 [20] mmHg, $p < 0.001$, and 85 [12] vs. 83 [11] mmHg, $p = 0.01$, respectively), and more often had diabetes (26% vs. 15%).

2.9. Data analysis

Missing data rarely occur completely at random, and a complete case analyses (deletion of all participants with ≥1 missing values) leads to loss of statistical power and to biased results (Donders et al., 2006; Rubin and Schenker, 1991). We therefore used multiple imputation (10 datasets) to address missing values in the study sample of 448 patients, using the statistical program R (aregImpute).

First, baseline characteristics were calculated for the analytical sample. Second, linear regression analyses were used to investigate independent associations of measures of brain atrophy (total brain, cortical gray matter, and ventricular volumes), WML volume, and presence of brain infarcts at baseline with decline in memory and executive functioning. z scores of memory and executive functioning at follow-up were entered as the respective dependent variables, and z scores of memory and executive functioning at baseline were entered as respective covariates. Analyses were also adjusted for age, sex, educational level, DART score, and follow-up time in years (model 1). Further adjustments were made for other baseline MRI measures (total brain volume, total WML volume, brain infarcts) (model 2).

To assess the combined associations, we first explored whether the combination of brain atrophy and WML volume or presence of brain infarcts accelerated cognitive decline, beyond the sum of their separate effects. Therefore, we added interaction terms between measures of brain atrophy (total brain, gray matter, and ventricular volumes) and WML volume or presence of brain infarcts to the regression model (model 1). Because the effects of brain atrophy and vascular brain lesions on cognitive decline are expected to lead to an effect in a similar direction, we did not want to miss any indications for a combined association and therefore chose a liberal cut-off p value for interaction of $p < 0.10$. If the regression analyses indicated a combined association, we performed further analyses by creating joint exposure categories of measures of vascular lesions (highest quartile of WML volume vs. 3 lower quartiles, presence vs. absence of infarcts) and categories of measures of brain atrophy (lowest quartile of total brain volume and gray matter volume vs. 3 highest quartiles and highest quartile of ventricular volume vs. 3 lowest quartiles). The reference category consisted of patients with fewest vascular lesions and fewest brain atrophy. The patients with the most pronounced brain abnormalities were the category of patients in the upper quartile of WML volume or presence of infarcts and patients in the quartile with most pronounced brain atrophy (lower quartile of total brain volume and gray matter volume and upper quartile of ventricular volume). Analysis of covariance was used to calculate mean change in cognitive performance among the groups. Additional adjustments were made for the presence of brain infarcts or WML volume at baseline (model 2). The previously mentioned associations were additionally adjusted for brain infarcts at follow-up and also for cardiovascular risk factors (smoking, alcohol use, body mass index, blood pressure, diabetes, hyperlipidemia) and carotid atherosclerosis. Finally, the associations with memory decline as dependent variable were additionally adjusted for executive functioning (Parks et al., 2011).

Data were analyzed using SPSS version 17.0 (Chicago, IL, USA), by pooling the 10 imputed datasets.

3. Results

Mean (SD) age of the study population was 57 (10) years, and the majority were men (80%). Mean baseline ICV was 1463 (126) mL, and mean total brain volume was 1162 (104) mL. Median (10th–90th percentile) total WML volume was 1.3 (0.3–5.8) mL (Table 1).

After a mean (range) of 3.7 (3.0–4.6) years of follow-up, larger baseline WML volume was associated with a significant decline in executive functioning over time (Table 2). These findings were independent of age, sex, education, DART score, and follow-up time. Further adjustments for total brain volume and brain infarcts at baseline did not change the effect estimate ($B = -0.09$; 95% CI: −0.15, −0.02). Presence of brain infarcts at baseline was associated with decline in memory performance over time but not with decline in executive functioning. However, this association was not independent of WML volume and cardiovascular risk factors (Table 2). No significant associations were found between measures of brain atrophy and cognitive decline on either domain (Table 2).

We found indications for combined associations of brain atrophy and vascular lesions with memory decline, in particular between

Table 1
Baseline patient characteristics (mean ± SD, unless stated otherwise) of the total study sample ($n = 448$)

Characteristics	Total study sample ($n = 448$)
Age (y)	57 ± 9.5
Gender (% male)	80
Level of education (range 1–7)[a]	4 (2–6)
DART score[a]	82 (59–97)
Vascular disease categories	
Coronary artery disease (%)	63
Cerebrovascular disease (%)	21
Peripheral arterial disease (%)	18
Abdominal aortic aneurysm (%)	5
Vascular risk factors	
BMI (kg/m^2)	27 ± 3
Systolic blood pressure (mmHg)	141 ± 20
Diastolic blood pressure (mmHg)	82 ± 10
Pack-years smoking[a]	20 (0–48)
Alcohol intake (% current)	78
Carotid intima-media thickness (mm)	0.91 ± 0.26
Hyperlipidemia (%)	75
Diabetes mellitus (%)	15
Medication	
Antidepressant use (%)	5.4
Benzodiazepine use (%)	4.0
MRI measurements	
ICV (mL)	1463 ± 126
Total brain volume (mL) (%ICV ± SD)	1162 ± 104 (79 ± 3)
Cortical gray matter volume (mL) (%ICV ± SD)	531 ± 57 (36 ± 3)
Ventricular volume (mL) (%ICV ± SD)	29 ± 13 (2.0 ± 0.8)
Total WML volume (mL)[a], (%ICV)[a]	1.3 (0.3–5.8), 0.09 (0.02–0.39)
Total infarcts (yes/no, % yes)	160/342, 24

Percentage of missing values before imputation: level of education (2.5%), DART score (0.9%), BMI (0.2%), smoking (0.2%), alcohol intake (0.2%), carotid intima media thickness (1.8%), hyperlipidemia (0.9%), diabetes mellitus (1.1%), cortical gray matter volume (24.8%), and all other variables (0.0%).
Key: BMI, body mass index; DART, Dutch version of the National Adult Reading test; ICV, intracranial volume; MRI, magnetic resonance imaging; SD, standard deviation; WML, white matter lesion.
[a] Median (10th–90th percentile).

Table 2
Association of baseline brain volumes and vascular brain lesions with decline in memory performance and executive functioning

	Model	Memory decline (*z* score)		Executive functioning decline (*z* score)	
		B	95% CI	*B*	95% CI
Measures of brain atrophy (% ICV)					
Total brain volume, per SD decrease	1	−0.06	−0.14, 0.01	−0.05	−0.13, 0.02
	2	−0.05	−0.12, 0.02	−0.05	−0.12, 0.03
Cortical gray matter volume, per SD decrease	1	0.02	−0.05, 0.09	−0.01	−0.08, 0.06
	2	0.03	−0.04, 0.10	0.01	−0.07, 0.08
Ventricular volume, per SD increase	1	−0.05	−0.12, 0.01	−0.04	−0.10, 0.03
	2	−0.04	−0.10, 0.03	−0.03	−0.09, 0.04
Measures of vascular brain lesions					
WML volume[a] (% ICV), per SD increase	1	−0.05	−0.11, 0.02	−0.09[b]	−0.15, −0.03
	2	−0.03	−0.10, 0.03	−0.09[b]	−0.15, −0.03
Infarcts, yes/no	1	−0.14[b]	−0.28, −0.00	−0.00	−0.15, 0.14
	2	−0.11	−0.25, 0.03	0.05	−0.10, 0.19

B (95% CI) represents the change in *z* score for cognitive functioning at follow-up per SD decrease of total brain volume (SD = 2.52%), decrease in gray matter volume (SD = 3.32%), increase in ventricular volume (SD = 0.82%), and increase in WML volume (SD = 1.10%) and the change for presence (yes/no) infarcts. Model 1 is adjusted for sex, age, educational level, DART score, baseline cognition *z* score, and follow-up time in years, and model 2 is additionally adjusted for baseline measures of either WML volume (not if WML volume was independent variable) or total brain volume (not if total brain, gray matter, or ventricular volume was independent variable) and for the presence of brain infarcts at baseline (not if infarcts were independent variable).
Key: BMI, body mass index; CI, confidence interval; DART, Dutch version of the National Adult Reading test; ICV, intracranial volume; SD, standard deviation; WML, white matter lesion.
[a] Log-transformed WML.
[b] $p < 0.05$.

WML volume and total brain volume (p interaction = 0.01), WML volume and gray matter volume (p interaction = 0.07), and presence of infarcts and total brain volume (p interaction = 0.06). Trends for combined associations were observed for the interaction between WML volume and ventricular volume (p interaction = 0.10) and presence of infarcts and gray matter volume ($p = 0.11$). Patients with most pronounced brain abnormalities (lower quartile of total brain or gray matter volume or upper quartile of ventricular volume in combination with upper quartile of WML volume or presence of brain infarcts) showed a significant decline in memory performance compared with the reference category. Those with either small total brain or gray matter volume, large ventricular volume, or large WML volume or presence of brain infarcts did not show a decline in memory performance (Fig. 1). Compared with the reference category, the mean difference (95% CI) in *z* score of memory decline was −0.38 (−0.59, −0.17) for patients with large WML volume and small total brain volume; −0.23 (−0.43, −0.02) for patients with large WML volume and small gray matter volume; −0.18 (−0.38, 0.02) for patients with large WML volume and large ventricular volume; −0.29 (−0.50, −0.07) for patients with brain infarcts and small total brain volume; and −0.29 (−0.53, −0.06) for patients with brain infarcts and small gray matter volume.

We found indications for combined associations of brain volume and WML volume or presence of brain infarcts with decline in executive functioning, in particular between WML volume and total brain volume (p interaction = 0.09) and between WML volume and ventricular volume (p interaction = 0.08). There were no indications for combined associations of gray matter volume and WML volume or presence of infarcts or indications for combined associations of total brain or ventricular volume and presence of infarcts ($p > 0.10$). Patients with small total brain volume or large ventricular volume in combination with large WML volume showed a significant decline in executive functioning compared with the reference category, whereas those with small total brain volume, large ventricular volume, or large WML volume did not show such a decline (Fig. 2). Compared with the reference category, the mean difference (95% CI) in *z* score of executive functioning was −0.27 (−0.48, −0.06) for patients with large WML volume and small total brain volume and −0.26 (−0.49, −0.06) for patients with large WML volume and large ventricular volume.

Additional adjustment for other MRI measures at baseline, cardiovascular risk factors, use of antidepressants or benzodiazepines, brain infarcts at follow-up, and executive functioning (in the associations with memory decline) only slightly attenuated the effect estimates (data not shown). Finally, after the use of multiple imputation to accommodate the missing values, the results remained essentially the same.

4. Discussion

In this prospective cohort study of late middle-aged patients with symptomatic atherosclerotic disease, we observed that the combination of brain atrophy and vascular brain lesions increased the likelihood of cognitive decline beyond the sum of their separate effects. For memory decline, cortical brain atrophy interacted with WML volume or presence of brain infarcts, whereas for executive functioning decline, this was primarily driven by the combination of subcortical atrophy and WML volume.

Considering the independent associations between brain imaging measures and cognitive decline, WML volume was associated with a decline in executive functioning, but not with memory decline, which is in line with the literature (Kramer et al., 2007; Prins et al., 2005). However, whereas associations between measures of brain atrophy and memory decline have previously been reported (Kramer et al., 2007), these were not observed in our present study or in other previous studies (Prins et al., 2005). The observed associations between measures of brain atrophy and memory decline that have been reported in previous studies were mainly found for hippocampal atrophy (Kramer et al., 2007) and medial temporal lobe atrophy (Rusinek et al., 2003). Because we had no data of hippocampal or medial temporal lobe atrophy at baseline, we were not able to examine this. Furthermore, whereas we did not find a significant association between measures of brain atrophy and decline in executive functioning, others did (Kramer et al., 2007; Prins et al., 2005). A possible reason for this discrepancy in finding could be that our study included late middle-aged participants with relatively intact cognition and relatively few brain abnormalities.

The combination of brain atrophy and vascular lesions was related to accelerated decline in memory and executive functioning. Few previous studies addressed this interaction of brain

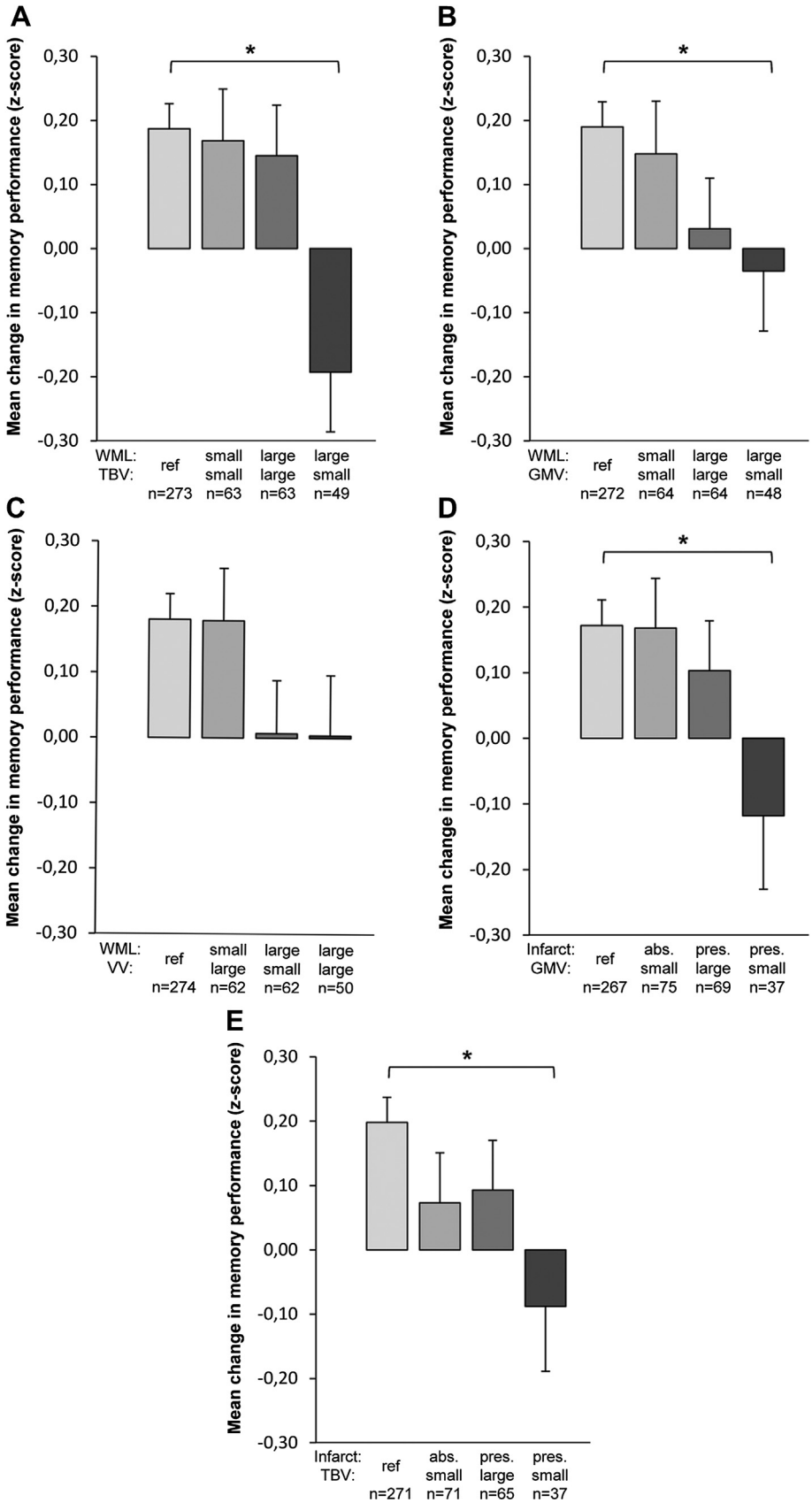

Fig. 1. Mean changes in memory performance during 4 years of follow-up according to the combination of WML volume and TBV (A), WML volume and GMV (B), WML volume and VV (C), presence of infarcts and TBV (D), or presence of infarcts and GMV (E). Analyses are adjusted for age, sex, educational level, Dutch version of the National Adult Reading test score, *z* score baseline memory performance, and follow-up time. All brain volumes are expressed relative to intracranial volume. Abbreviations: abs., absent; GMV, gray matter volume; pres., present; TBV, total brain volume; VV, ventricular volume; WML, white matter lesion; *, significantly different from reference category ($p < 0.05$).

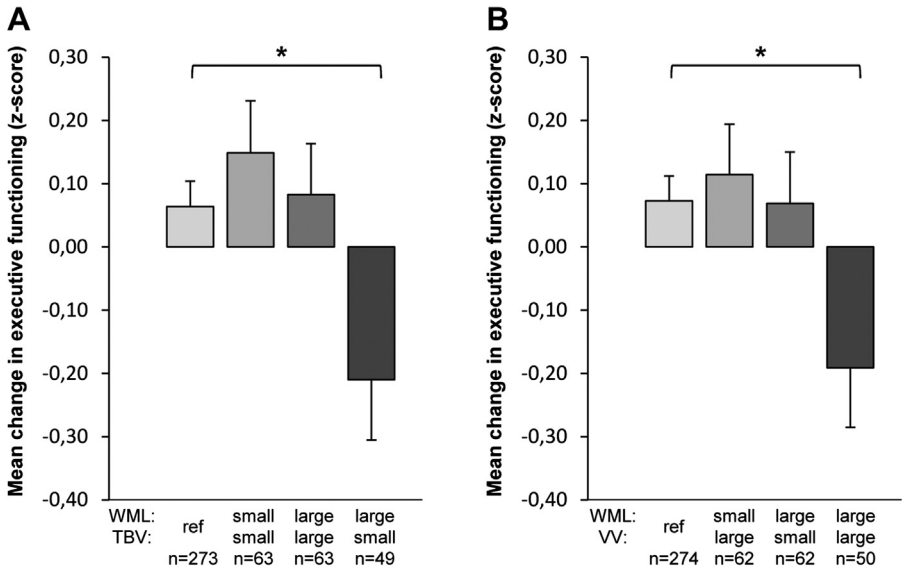

Fig. 2. Mean changes in executive functioning during 4 years of follow-up according to the combination of WML volume and TBV (A), or WML volume and VV (B). Analyses are adjusted for age, sex, educational level, Dutch version of the National Adult Reading test score, *z* score baseline executive functioning, and follow-up time. All brain volumes are expressed relative to intracranial volume. Abbreviations: TBV, total brain volume; VV, ventricular volume; WML, white matter lesion; *, significantly different from reference category ($p < 0.05$).

atrophy and vascular lesions on cognitive functioning. Some of these focused on patients with Alzheimer's disease (AD) (Brickman et al., 2008; van der Flier et al., 2004) and suggested that brain atrophy and vascular brain lesions interact in the clinical syndrome of AD. Patients with large WML volume and large medial temporal lobe atrophy were found to have the highest risk for AD (van der Flier et al., 2004). Also, AD patients with a combination of large brain atrophy and large WML volume showed the steepest rate of cognitive decline (Brickman et al., 2008). A neuropathological study has suggested that vascular brain lesions reduce the threshold for AD pathology (Snowdon et al., 1997). Furthermore, in a hospital-based prospective cohort study of patients with different degrees of WMLs, significant interactions were observed between WMLs and brain atrophy on cognitive functioning at baseline and follow-up (Jokinen et al., 2012). This effect was observed for global cognition and executive functioning but not for memory performance. Over time, the interaction of global brain atrophy and WMLs was only present for global cognition. Finally, interactions between WMLs and hippocampal atrophy with general cognitive functioning were found in a population-based cohort study of noninstitutionalized older individuals (Godin et al., 2010). In the present study, we extend previous observations by providing an evaluation of the domains memory and executive functioning in a younger study population of patients with symptomatic atherosclerotic disease. In this patient group where the majority had normal cognitive functioning, the observed single and combined associations of brain atrophy and vascular brain lesions on cognitive decline were subtle. Nevertheless, we show that single brain abnormalities (i.e., measures of brain atrophy or vascular lesions) have limited effect on cognitive decline over 4 years, whereas the combination of brain atrophy measures and WMLs or infarcts has significant, although perhaps, modest effect on cognitive decline. Subcortical brain atrophy in combination with vascular lesions was related to decline in executive functioning, whereas cortical brain atrophy in combination with vascular lesions was related to decline in memory performance.

Strengths of this study are the prospective design and the large number of patients investigated. The volumetric assessment of brain atrophy and WMLs made it possible to investigate the associations on a continuous scale, without loss of information because of categorization of data. This enabled us to more accurately measure WMLs and total brain volume estimates that were less influenced by observer bias than visual rating methods. As in many other follow-up studies of aging, loss to follow-up was a limitation of the study. However, because patients with better clinical perspectives will stay in the study, the possible selective loss to follow-up will have caused an underestimation of the effects. Furthermore, we did not have longitudinal measures of information processing speed or global cognitive performance, although decline on these domains has previously been associated with brain atrophy and vascular lesions (Jokinen et al., 2012; Prins et al., 2005). The majority of patients in this study were men. A possible explanation is that the far majority of patients with manifest arterial disease are men, at least when the study started (i.e., 10 years ago). Men have a higher risk to develop vascular disease compared with women (Barrett-Conner, 1997).

In summary, we observed that in late middle-aged patients with symptomatic atherosclerotic disease, the combination of brain atrophy and WMLs or presence of infarcts accelerates cognitive decline over 4 years, in a relative cognitive domain-specific manner. These findings provide further evidence for a combined involvement of brain atrophy and vascular lesions in the etiology of cognitive decline, already in relatively young patients with symptomatic atherosclerotic disease.

Disclosure statement

All authors confirm that they have no actual or potential conflicts of interest to disclose.

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