Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam Study

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Article abstract—Cerebral white matter lesions are a common finding on MRI in elderly persons. We studied the prevalence of white matter lesions and their relation with classic cardiovascular risk factors, thrombogenic factors, and cognitive function in an age- and gender-stratified random sample from the general population that consisted of 111 subjects 65 to 84 years of age. Overall, 27% of subjects had white matter lesions. The prevalence and severity of lesions increased with age. A history of stroke or myocardial infarction, factor VIIc activity, and fibrinogen level were each significantly and independently associated with the presence of white matter lesions. Significant relations with blood pressure level, hypertension, and plasma cholesterol were present only for subjects aged 65 to 74 years. White matter lesions tended to be associated with lower scores on tests of cognitive function and were significantly associated with subjective mental decline. This study suggests that classic cardiovascular risk factors, as well as thrombogenic factors, are associated with white matter lesions in subjects over 65 years of age in the general population, and that these lesions may be related to cognitive function.

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Brain MRI in elderly persons frequently shows lesions of the cerebral white matter. The frequency of these lesions reportedly increases with age[1-7] and with the presence of cardiovascular risk factors.[1,2,6-10] Pathologic correlates of white matter lesions support the hypothesis that arteriolosclerosis plays an important role in their pathogenesis.[11-13] Although some have suggested that these lesions represent the anatomic substrate of vascular dementia,[14,15] the clinical significance of these lesions remains controversial. Some studies found a relation between white matter lesions and cognitive function,[10,16,17] but others did not.[3,4,18,19] Another issue is the type of white matter lesions on MRI; several studies[16,18,20] reported that periventricular hyperintensities were more frequent in demented patients than in age-matched controls.

Most studies on white matter lesions were based on retrospectively selected hospital series or small samples of volunteers. We studied the prevalence of white matter lesions in a population-based sample and assessed whether white matter lesions were related to cardiovascular risk factors and whether they were associated with impairment in cognitive function. We investigated coagulation factors along with classic vascular risk factors, since thrombogenesis is an important determinant of cardiovascular disease.[21]

Methods. *Subjects.* Subjects—65 to 84 years of age and stratified by gender and 5-year age groups—were randomly selected from the list of participants of the Rotterdam Study. The Rotterdam Study is a single-center prospective follow-up study of the total population aged 55 years and older in the suburb of Ommoord in Rotterdam, The Netherlands. The study has been approved by the Medical Ethics Committee of Erasmus University. Writ-

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ten informed consent is obtained from all participants. The rationale and design of the Rotterdam Study have been described elsewhere.[22] In short, the objective of the study is to investigate determinants of chronic and disabling cardiovascular, neurogeriatric, locomotor, and ophthalmologic diseases. All participants are extensively interviewed at home and subsequently undergo physical examination during two visits at a research center. The total eligible population comprises 11,854 persons, with 6,494 persons aged 65 to 84 years. Enrollment in the study started in 1990 and was based on random selection procedures. By December 31, 1991, 3,352 residents of Ommoord had participated, including 1,994 subjects aged 65 to 84 years. The refusal rate in those aged 65 to 84 years was 18%, and was similar for men and women. Subjects were invited to participate in the additional MRI study directly after they had finished the standard study protocol. Of 134 individuals initially selected at random, three were excluded because they had a pacemaker or metal prostheses or clips, one because he was suffering from a major psychiatric disorder, and two because they were wheelchair-bound. Individuals residing in homes for the elderly were included. Of the 128 subjects who were actually invited to take part in the additional MRI study, 111 (87%) agreed to participate.

Measurements. Information on current health status, medical history, drug prescriptions and actual use, smoking behavior, and level of education was obtained by means of a computerized questionnaire. Prevalence of coronary heart disease was assessed by means of a Dutch version of the cardiovascular questionnaire of Rose et al.[23] The history of cerebrovascular events or myocardial infarction was assessed primarily by direct questioning, after which confirmation was obtained from medical records. For diagnosis of a cerebrovascular event to have been made, symptoms should have been present for at least 24 hours and affirmation of the diagnosis by neuroimaging or by a neurologist was required. For a diagnosis of myocardial infarction, confirmation by ECG or enzyme readings at the time of the infarction was required. With respect to smoking behavior, subjects were categorized as current smokers, former smokers, and those who had never smoked. During the two visits at the research center, several cardiovascular risk factors were measured. Diabetes mellitus was considered to be present if the subject was taking oral antidiabetics or insulin or if the random serum glucose level was higher than 11.1 mmol/l.[24] Blood pressure was measured in the sitting position at the right upper arm with a random-zero sphygmomanometer. The average of two measurements, separated by a count of the pulse rate, was used in the analysis.[25] A subject was considered to have hypertension if the systolic blood pressure was 160 mmHg or higher or the diastolic blood pressure was 95 mmHg or higher, or if the subject used antihypertensive drugs.[25] Isolated systolic hypertension was defined as a systolic blood pressure of at least 160 mmHg with a diastolic blood pressure below 95 mmHg, with the exclusion of subjects on antihypertensive medication.[26]

Venipuncture was performed, with minimal stasis, through a 21-gauge butterfly needle with tube (Surflo winged infusion set, Terumo, Leuven, Belgium). Blood samples were collected in siliconized Vacutainer tubes (Becton & Dickinson, Meylan, France) containing clotting activator and separator for serum, or 0.129 M sodium citrate for plasma. Serum was separated by one-stage centrifugation for 10 minutes at 1,600 *g*. From the citrate tubes platelet-poor plasma was prepared by two-stage centrifugation, first for 10 minutes at 1,600 *g* at 4 °C and then for 10 minutes at 10,000 *g* at 4 °C. All samples were quickly frozen in liquid nitrogen and then stored at −80 °C before assay. Serum total cholesterol was determined with an automated enzymatic procedure.[27] The high-density lipoprotein (HDL) cholesterol level was measured similarly, after precipitation of the non-HDL fraction with phosphotungstate magnesium. The plasma fibrinogen level was assessed according to the Clauss method (Diamed AG, Morat, Switzerland).[28] Factor VIIc and factor VIIIc were assayed by means of Automatic Coagulation Laboratory (Instrumentation Laboratory, IJsselstein, The Netherlands) with the aid of factor VII- and factor VII-deficient plasma (Ortho Diagnostic Systems, Beerse, Belgium) with Thromborel S (Behringwerke, Marburg/Lahn, Germany) and Thrombosil I (Ortho Diagnostic Systems), respectively, as reagents. Plasma obtained from 40 healthy men was pooled and served as a reference for the measurements of factor VIIc and factor VIIIc. The factor VIIc and factor VIIIc levels of the donors were all within normal range, and no differences could be detected between the factor VIIc and factor VIIIc levels of consecutive donor pools.

Subjective impairment of memory was assessed as part of the home interview; participants were considered to have subjective impairment of memory if they reported memory problems that interfered with daily life and that had developed during adulthood. The CAMCOG, the neuropsychological test from the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX), was administered as an objective measure of cognitive function to all subjects who participated in the MRI study.[29,30] The CAMCOG is a composite cognitive test that consists of 60 items, has a maximum score of 107, and allows the calculation of 11 subscores (orientation, language comprehension, language expression, recent memory, remote memory, learning memory, attention, praxis, calculation, abstract thinking, and perception). A cutoff of 79/80 has been recommended for distinguishing possibly demented from nondemented subjects.[29]

Brain MRIs were obtained with a 1.5-T Philips Gyroscan. Multiple-slice spin-echo sequences were performed with a repetition time of 2,000 msec and echo times of 50 and 100 msec, producing a T_2-weighted image. Images were obtained in the axial plane with slice thickness of 7 mm and slice increments of 1.4 mm. The MRIs were analyzed by two independent assessors who were blinded to all clinical information. To date, no universally accepted scale exists for rating white matter lesions on MRI. We previously used a rating system that distinguished only between the absence of lesions, punctate lesions, and confluent lesions; the reliability of this method was satisfactory.[31] For the present study, the presence of punctate lesions was dichotomized at fewer than five and five or more lesions.[18] Infarcts on MRI were recorded, but they were not included in the rating of the white matter lesions. In addition, we distinguished between white matter lesions directly adjacent to the ventricles (periventricular lesions) and punctate or confluent lesions at some distance from the ventricles (focal lesions), in accordance with several other authors.[2,18,20,32,33] Small caps on the horns of the lateral ventricles and pencil-thin lining around the ventricles were considered normal.[9,18,19,34] On the basis of these criteria, the overall severity of white matter lesions was graded as follows (method developed by Drs. L.R. Caplan and J.C. van Swieten). Grade 0 scans showed no or slight periventricular hyperintensity (small caps or pencil-thin lining), fewer

than five focal lesions, and no confluent lesions. Grade 1 scans showed moderate periventricular hyperintensity (caps on both anterior and posterior horns of the lateral ventricles, corpus only partly involved, not irregularly extending into the deep white matter) or five or more focal lesions, or both, but no confluent lesions. Scans with severe periventricular hyperintensity (irregularly extending into the deep white matter or marked areas of hyperintensity completely surrounding the lateral ventricles) or confluent lesions were classified as grade 2, regardless of the presence of focal lesions. Agreement between the two assessors was complete with respect to absence (grade 0) or presence (grades 1 or 2) of white matter lesions, and nearly complete (there was initial disagreement in three instances, but consensus was reached by joint review and discussion) with respect to the distinction between grade 1 and 2 severity of lesions.

Analysis. The prevalence of white matter lesions was calculated by 5-year age category for men and women separately. Because age was significantly associated with the prevalence of white matter lesions, and because gender tended to be associated, the relations between all other variables and white matter lesions were evaluated with adjustment for both age and gender. Odds ratios (ORs) and 95% CIs were calculated, by means of multiple logistic regression analysis, as a measure of the strength of the association between the putative determinants in subjects with white matter lesions (grade 1 or 2) compared with that in subjects without white matter lesions (grade 0). For the analyses of factor VIIc activity, subjects taking anticoagulant drugs at the time were excluded. Subjects taking antihypertensive medication were excluded from the analyses of isolated systolic hypertension. Continuous variables were evaluated continuously and were also classified in quartiles of their distribution. When the two analyses yielded the same information, only the results from the first analysis are reported.

The relation between the presence of white matter lesions and subjective memory impairment also was assessed by means of logistic regression, with the presence of complaints about memory as the dependent variable. Mean scores and 95% CIs were calculated for the CAMCOG for each of the three levels of severity of white matter lesions. The relation between severity of white matter lesions and performance on the CAMCOG was evaluated after logarithmic transformation with multiple linear regression. To examine the relation between white matter lesions and cognitive function as restrictively as possible, we performed a separate analysis excluding five subjects with a diagnosis of probable Alzheimer's disease (AD) based on the NINCDS-ADRDA criteria,[35] since the Alzheimer dementia probably accounted for most of the cognitive impairment in those individuals.

Results. The distribution of the vascular risk factors in the 111 subjects in whom MRI was performed was very similar to that in all 65- to 84-year-old subjects examined in the Rotterdam Study. White matter lesions were seen in 27% of subjects, with severe lesions in 10%. The prevalence of white matter lesions increased with age, rising from 11% among 65- to 69-year-old subjects to 54% among 80- to 84-year-old subjects (table 1). The severity of the lesions also increased with age; whereas severe lesions constituted 25% of all lesions in 65- to 69-year-old subjects, the corresponding figure was 50% for subjects 80 to 84 years of age. In each age category, the observed prevalence and severity of white matter lesions was higher among women than among men, but this difference just failed to reach significance (OR = 2.1; 95% CI = 0.9 to 4.9). The female predominance was independent of a history of stroke or myocardial infarction.

Table 1. Prevalence of white matter lesions by age and gender

	Age	No. of subjects	White matter lesions (% in age group)		
			No/Slight*	Moderate†	Severe‡
Men	65-69	17	94	6	0
	70-74	12	83	17	0
	75-79	11	73	27	0
	80-84	11	64	27	9
	Total	51	80	18	2
Women	65-69	19	84	11	5
	70-74	11	73	18	9
	75-79	15	74	13	13
	80-84	15	33	27	40
	Total	60	67	17	17
Total	65-69	36	89	8	3
	70-74	23	78	17	4
	75-79	26	73	19	8
	80-84	26	46	27	27
	Total	111	73	17	10

* Fewer than five focal lesions, no/slight periventricular hyperintensities, and no confluent lesions.
† Fewer than five focal lesions, moderate periventricular hyperintensities, and no confluent lesions; or ≥5 focal lesions and no/slight/ moderate periventricular hyperintensities, but no confluent lesions.
‡ Confluent lesions and/or severe periventricular hyperintensities.

A history of a major cardiovascular event was present more often among subjects with white matter lesions, with an OR of 4.4 and a 95% CI of 1.4 to 13.7 (table 2). We found no evidence for a relation between diabetes mellitus and white matter lesions (table 2). With increasing blood pressure there was only a slight and nonsignificant increase in risk of white matter lesions for all subjects combined (table 2). However, systolic blood pressure and diastolic blood pressure were significantly associated with white matter lesions in subjects 65 to 74 years of age, but not in those 75 to 84 years of age. These relations did not change when subjects on antihypertensive medication were excluded (table 2). In the younger group, the OR for systolic blood pressure was 1.6 per 10 mmHg (95% CI = 1.1 to 2.5) and the OR for diastolic blood pressure 5.7 per 10 mmHg (95% CI = 1.6 to 20.1). The different association with blood pressure across age groups was found for both levels of lesion severity, but it was more distinct for grade 2 lesions: among subjects 65 to 74 years of age the OR was 1.5 (95% CI = 1.0 to 2.4) for grade 1 and 6.8 (95% CI = 1.0 to 44.0) for grade 2 per 10-mmHg increase in systolic blood pressure; among subjects 75 to 84 years of age the ORs were 1.0 (95% CI = 0.7 to 1.4) for grade 1 and

Table 2. Positive history of cardiovascular events, diabetes mellitus, and blood pressure in relation to presence of white matter lesions, adjusted for age and gender

Variable	No. of subjects included in analysis (events)	Age 65-74 years OR	95% CI	Age 75-84 years OR	95% CI	All ages OR	95% CI
Stroke	110* (10)	2.0	0.1-28.6	5.8	0.8-41.7	3.4	0.8-14.8
Myocardial infarction	110* (14)	5.2	0.5-50.3	3.6	0.7-17.8	3.9	1.1-14.1
Stroke or myocardial infarction	110* (20)	3.0	0.4-23.1	6.5	1.4-30.8	4.4	1.4-13.7
Diabetes mellitus	111 (9)	0.0	0-∞	2.2	0.4-12.2	1.5	0.3-6.8
SBP (continuous, per 10 mmHg)	111	1.6	1.1-2.5	0.9	0.6-1.2	1.2	0.9-1.5
Excl subjects on antihypertensive drugs	85	2.9	1.2-7.0	0.8	0.6-1.2	1.1	0.8-1.5
DBP (continuous, per 10 mmHg)	111	5.7	1.6-20.1	0.6	0.3-1.3	1.3	0.8-2.1
Hypertension†	111	8.2	1.4-49.5	0.7	0.2-2.6	1.8	0.7-4.9
Isolated systolic hypertension‡	85	45.5	2.5-825.1	0.8	0.1-6.5	4.0	0.8-19.3

SBP Systolic blood pressure.
DBP Diastolic blood pressure.
* Interview information was missing for one subject, due to accidental deletion from the database.
† Defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg, or use of antihypertensive medication (n = 35 with hypertension).
‡ Defined as systolic blood pressure ≥160 mmHg and diastolic blood pressure <95 mmHg. Subjects currently on antihypertensive medication excluded (n = 9 with isolated systolic hypertension).

Table 3. Levels of plasma lipids and thrombogenic factors in relation to presence of white matter lesions, adjusted for age and gender

Variable	No. of subjects included in analysis	Age 65-74 years OR	95% CI	Age 75-84 years OR	95% CI	All ages OR	95% CI
Cholesterol (per mmol/l)	109	1.8	0.9-3.6	0.7	0.4-1.2	1.1	0.7-1.5
Adjusted for BMI	107	2.2	1.0-4.7	0.8	0.5-1.4	1.2	0.8-1.7
HDL (per 10^{-1} mmol/l)	108	0.1	0.0-2.8	0.6	0.1-3.7	0.4	0.1-1.9
Adjusted for BMI	106	0.2	0.0-4.0	0.4	0.1-2.7	0.3	0.1-1.7
Factor VIIc activity (per 10^{-1} U/ml)*	94	1.3	0.9-1.9	1.2	0.8-1.7	1.2	0.9-1.6
Above vs below 75th percentile	94	5.1	0.9-29.7	5.3	0.8-33.7	4.7	1.4-15.8
Factor VIIIc activity (per 10^{-1} U/ml)	100	1.1	0.9-1.2	1.0	0.9-1.2	1.1	1.0-1.1
Fibrinogen (per g/l)†	82	2.7	0.3-25.3	2.4	0.9-6.8	2.7	1.1-6.8

BMI Body mass index (weight [kg]/height $[m]^2$).
HDL High-density lipoprotein cholesterol.
* Subjects currently taking anticoagulant drugs excluded.
† Current smokers excluded.

0.7 (95% CI = 0.5 to 1.1) for grade 2. The same pattern was observed for the dichotomized definition of hypertension or isolated systolic hypertension (table 2). The observed relations persisted after adjustment for a previous stroke or myocardial infarction.

Total cholesterol and HDL cholesterol levels were not significantly associated with the presence of white matter lesions among all subjects combined. However, for subjects 65 to 74 years of age, higher levels of total cholesterol tended to be associated with white matter lesions (table 3). Body mass index (weight in kilograms divided by height squared in meters) was not related to the presence of white matter lesions. We nevertheless evaluated the relation between lipoprotein levels and white matter lesions, adjusting for body mass index, since the latter is a known risk factor for vascular disease and usually strongly related to lipoprotein levels. However, this only marginally influenced the results (table 3).

Of the hemostatic factors, factor VIIIc activity was not associated with white matter lesions (table 3). When analyzed continuously, factor VIIc activity showed a slight positive relation with white matter lesions, but this was not significant. More detailed analysis revealed a threshold effect, in that subjects with a high factor VIIc activity (above the 75th percentile of the distribution) had white matter lesions significantly more often than did subjects with lower factor VIIc activity (below the 75th percentile) (OR = 4.7, 95% CI = 1.4 to 15.8). The OR of plasma fibrinogen with the presence of lesions was 1.6 (95% CI = 0.8 to 3.3). Because smoking increases fibrinogen levels, we subsequently excluded current smokers from the analyses. This increased the strength of the relation (OR = 2.7, 95% CI = 1.1 to 6.8) (table 3). No threshold

Table 4. Subjective memory impairment and performance on the CAMCOG test of cognitive function according to severity of white matter lesions

	White matter lesions			Test for linear trend (p)
	Grade 0	Grade 1	Grade 2	
All subjects				
Total number of subjects	81	19	10	
Subjects with memory complaints	11	5	4	
OR for memory complaints* (95% CI)	1	2.1 (0.6; 7.7)	4.1 (0.8; 21.1)	0.02
CAMCOG score, mean (95% CI)	90.9 (88.3; 93.5)	88.1 (83.2; 93.0)	84.6 (96.6; 99.5)	0.23†
Excluding Alzheimer patients				
Total number of subjects	77	17	10	
Subjects with memory complaints	9	3	4	
OR for memory complaints* (95% CI)	1	1.6 (0.3; 7.1)	5.1 (0.9; 28.8)	0.16
CAMCOG score, mean (95% CI)	92.8 (91.0; 94.6)	89.5 (85.4; 93.7)	84.6 (69.6; 99.5)	0.08†

* Adjusted for age, gender, and previous stroke.
† Adjusted for age and gender.

effects were discerned. With regard to smoking itself, no relation was observed between white matter lesions and current or former smoking. When we adjusted for previous stroke or myocardial infarction, our findings did not substantially change.

A multiple logistic regression analysis in which all vascular factors mentioned above were simultaneously included in the model, together with age and gender, yielded comparable estimates—previous cardiovascular event: OR = 3.7 (95% CI = 1.0 to 13.2); systolic blood pressure: OR = 1.2 (95% CI = 0.9 to 1.5); cholesterol: OR = 0.9 (95% CI = 0.6 to 1.4); factor VIIc activity (dichotomized at the 75th percentile): OR = 3.5 (95% CI = 1.0 to 12.7); fibrinogen: OR = 1.5 (95% CI = 0.6 to 3.6) (when current smokers were excluded, OR = 2.9 [95% CI = 1.0 to 8.7]). When adjusted for all other vascular risk factors, the OR for subjects 65 to 74 years of age was 1.7 (95% CI = 1.0 to 2.9) for systolic blood pressure and 2.2 (95% CI = 0.9 to 5.4) for cholesterol.

Subjective memory impairment was reported by 18% of all subjects, and significantly more often by subjects with white matter lesions. There was a significant trend for more memory complaints to occur with increasing level of severity of lesions. This relation did not change after we controlled for age, gender, and history of stroke. When we excluded AD patients, the estimated strength of the associations, as reflected in the ORs, remained similar (table 4).

The average score on the CAMCOG increased from 84.6 for individuals with severe white matter lesions to 90.9 for subjects without lesions; when AD patients were excluded, the corresponding figures were 84.6 and 92.8. These differences were, however, partly confounded by age. After we controlled for age, lower scores still tended to be associated with increasing severity of lesions, but this was not significant at the 5% level. Analysis of performance on the subtests of the CAMCOG did not reveal performance to be more severely affected on any particular subtests. Level of education on its own was highly correlated with cognitive test scores. However, when age was controlled for, additional adjustment for the period of formal education (in three categories—6 years or less, 7 to 13 years, and 14 years or more) did not affect the results.

Discussion. We studied the prevalence, risk factors, and relation with cognitive function of cerebral white matter lesions in a sample from the general population of those 65 years of age or older. Both the prevalence and the severity of lesions increased with age. These observations suggest that history of stroke or myocardial infarction, factor VIIc activity, and fibrinogen level are independent risk factors for all subjects 65 years of age or older; for subjects between 65 and 74 years of age, blood pressure and plasma cholesterol levels are additional independent risk factors. This study also suggests an association between white matter lesions and cognitive function, particularly subjective impairment of memory.

Most previous studies on the presence of white matter lesions were based on hospital series and are therefore not representative of the prevalence of white matter lesions in the general population. A few studies addressed the presence of white matter lesions in smaller samples of healthy elderly volunteers and reported frequency estimates of moderate to severe lesions that were similar to[3,4] or somewhat higher than[18] those we found. Our study presents population-based estimates of the prevalence of white matter lesions. However, because the response rate in our study was lower than 100%, there was the possibility of selection bias. Although we have no actual information on those who refused to participate, in some instances refusal seemed to be related to physical or mental impairment and therefore our results possibly slightly underestimate the true prevalence.

The increase of white matter lesions with age seems to have shifted by 5 years toward earlier

ages among women compared with men, resulting in a female predominance for the prevalence of these lesions. This finding is in contrast with the usual reports of age-specific predominance of men in cardiovascular disease. Other studies did not report gender differences in frequency of MRI lesions. In a study of patients with AD, Diaz et al[36] found white matter lesions on CT to be disproportionately common in female patients. On the basis of our data, we cannot conclude whether the higher prevalence that we found among women is merely the result of unequal survival of women and men once they developed the lesions, the result of a higher incidence of white matter lesions among women, or a chance finding.

In accordance with other studies, we found previous cardiovascular events to be related to white matter lesions. Several explanations are possible for the age-dependent results regarding blood pressure and total cholesterol, which were associated with the presence of white matter lesions only in the 65- to 74-year age group. First, they could be the result of selection bias. However, subjects were randomly sampled and we have no indication that cerebral disorders or multiple vascular morbidity were directly related to refusal to undergo MRI. Furthermore, the relatively high response rates in both the overall study (82%) and the MRI study (87%) make it unlikely that this can fully explain the difference between older and younger subjects. Second, the findings could be the result of selective survival. Most studies of cardiovascular risk factors in the elderly report a decrease in relative importance of total cholesterol with age.[37] Analogously, in the very old, the importance of elevated blood pressure for the risk of vascular disease seems to diminish or even reverse.[38] Our findings in 75- to 84-year-old subjects fit these observations. Since cardiovascular risk factors are all associated with increased mortality, very old persons with these risk factors may form a special group by natural selection. A third explanation is that the relative importance of various atherogenic factors could actually change with age.

Thrombogenic and hemostatic factors are important risk factors for the initiation and progression of cardiovascular disease,[21,39-43] and elevated fibrinogen levels have been reported in patients with subcortical arteriosclerotic encephalopathy (Binswanger's disease), as well as in patients with lacunar infarcts.[44] The increased prevalence of white matter lesions with both increased fibrinogen and increased factor VIIc levels suggests that the coagulation system may be involved in the pathogenesis of white matter lesions of the brain.

In our study, moderate or severe lesions of the white matter were significantly associated with lower scores on tests of cognitive function when demented patients were excluded, and tended to be so after controlling for age and education. Leukoencephalopathy was significantly associated with subjective impairment of memory. It is unknown whether such subjective impressions are indicative of actual cognitive decline, but the lower scores on the CAMCOG suggest that this might be so. A few other studies reported a relation between white matter lesions on MRI in nondemented elderly persons and cognitive impairment,[10,17] although small lesions did not seem to have an effect on intellectual function.[3,4] However, because all these reports come from cross-sectional surveys, inferences regarding a causal relationship between white matter lesions and cognitive function remain tentative.

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