

# Small Vessel Disease and General Cognitive Function in Nondisabled Elderly

## The LADIS Study

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**Background and Purpose**—On cerebral magnetic resonance imaging (MRI), white matter hyperintensities (WMH) and lacunes are generally viewed as evidence of small vessel disease. The clinical significance of small vessel disease in terms of global cognitive function has as yet not been completely clarified. We investigated the independent contribution of WMH and lacunes to general cognitive function in a group of independently living elderly with varying degrees of small vessel disease.

**Methods**—Data were drawn from the multicenter, multinational Leukokraurosis and Disability (LADIS) study. There were 633 independently living participants. General cognitive function was assessed using the Mini Mental State Examination (MMSE) and the modified Alzheimer Disease Assessment Scale (ADAS). On MRI, WMH was rated as mild, moderate, or severe. Lacunes were rated as none, few (1 to 3), or many (4 or more).

**Results**—In the basic analysis, increasing severity of both WMH and lacunes was related to deteriorating score on the MMSE and ADAS. When WMH and lacunes were entered simultaneously, both MRI measures remained significantly associated with MMSE score. Increasing severity of WMH remained associated with ADAS score, whereas the association with lacunes became less prominent. These associations were independent of other risk factors for dementia, like education, depression, vascular risk factors, or stroke.

**Conclusion**—We found WMH and lacunes to be independently associated with general cognitive function in a sample of independently living elderly. These results highlight the fact that WMH and lacunes should both be evaluated when assessing small vessel disease in relation to cognitive function. (*Stroke*. 2005;36:2116-2120.)

**Key Words:** cognition ■ elderly ■ lacunes ■ small vessel disease ■ white matter hyperintensities

Cerebrovascular disease encompasses both (large vessel) cortical ischemic and hemorrhagic infarcts and subcortical small vessel disease. Although it is generally accepted that cortical stroke may cause cognitive impairment, the clinical significance of small vessel disease in terms of global cognitive function has as yet not been completely clarified. On cerebral magnetic resonance imaging (MRI), white matter hyperintensities (WMH) and lacunes, both of which are frequently observed in the elderly, are generally viewed as evidence of small vessel disease.<sup>1-4</sup> Associations with vascular risk factors have been shown for both WMH and lacunes,

providing circumstantial support for the view that these MRI abnormalities reflect small vessel disease.<sup>5-10</sup>

There is increasing attention for the importance of small vessel disease as a predictor of cognitive decline and dementia. Small vessel disease is implicated in vascular dementia.<sup>11,12</sup> Moreover, it seems to amplify the effects of pathologic changes of Alzheimer disease.<sup>13-15</sup> Subtle associations between WMH and cognitive impairment have been reported in nondemented elderly.<sup>5,16,17</sup> The cognitive correlates of lacunes have received less attention. Results are conflicting, because some authors report associations with cognitive impairment, whereas others

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do not.<sup>9,18,19</sup> In addition, the relative impact of WMH and lacunes on cognitive impairment is not known.

In the present study, we investigated the independent contribution of WMH and lacunes to general cognitive function in a group of independently living elderly with varying degrees of small vessel disease.

## Materials and Methods

Data were drawn from the multicenter, multinational Leukoaraiosis and Disability (LADIS) study. The LADIS project prospectively studies the role of WMH as an independent predictor of the transition to disability in nondisabled elderly.<sup>20</sup> In short, 639 elderly subjects, who had no or only mild disability in their instrumental activities of daily living (IADLs), and were stratified for grade of WMH severity, were enrolled. Subjects presented for evaluation in the following settings: stroke units or stroke departments, cerebrovascular disease clinics, memory or dementia clinics, neurologic or geriatric wards/clinics, population studies on aging, and controls in other studies. Among the reasons for presentation were mild memory loss, minor motor disturbances, minor focal cerebrovascular events, or nonspecific reasons for undergoing a cranial neuroimaging study (WMH as incidental finding). To be included, subjects had to have: (1) age between 65 and 84 years; (2) WMH on MRI of any degree, according to the categorization into the 3 severity classes of the Fazekas scale,<sup>21</sup> (3) no or only mild disability as determined by the IADL scale<sup>22</sup>; (4) presence of a regularly contactable informant; and (5) agreement to sign an informed consent. Exclusion criteria were: (1) likely dropout because of the presence of severe illnesses (cardiac, hepatic, or renal failure, cancer or other relevant systemic diseases), (2) severe unrelated neurologic diseases, (3) leukoencephalopathy of nonvascular origin (immunologic–demyelinating, metabolic, toxic, infectious, other), (4) severe psychiatric disorders, (5) inability to give informed consent, and (6) inability or refusal to undergo cerebral MRI. Subjects are currently followed up for 3 years with repeated clinical and MRI studies. The present article is based on the baseline data of the LADIS project.

All subjects were assessed using clinical and functional tests, including global functioning, cognitive, motor, psychiatric, and quality-of-life measures. For the present study, general cognitive function was measured using the Mini Mental State Examination (MMSE)<sup>23</sup> and a modified version of the Alzheimer Disease Assessment Scale (ADAS).<sup>24</sup> The ADAS was slightly modified to include the item “delayed word recall.” A higher MMSE score indicates better performance, whereas a higher ADAS score corresponds to worse performance. ADAS score was missing in 6 subjects, so 633 subjects had available data for the present study. The following variables were evaluated as confounders: age, sex, education (years), depressive symptoms,<sup>25</sup> motor function,<sup>26,27</sup> hypertension, diabetes, smoking, and history of stroke.

All subjects were studied by MRI following a standard protocol on the same day as the clinical investigation. Scans were made on a 0.5-T (one center) or 1.5-T scanner (10 centers) and were collected centrally at the Image Analysis Centre (IAC) of the Vrije Universiteit Medical Center, Amsterdam. Imaging guidelines were distributed among all centers, specifying naming convention and scan positioning. To check and maintain quality, dummy runs were requested before the beginning of the study and in case of upgrades. Data transfer was electronic through FTP. The MR protocol included the following sequences: T1-weighted 3D MPRAGE (magnetization prepared rapid-acquisition gradient-echo, scan parameters: coronal or sagittal plane, field of view [FOV] 250 mm, matrix 256×256 or 512×512, slice thickness: 1 mm [isotropic voxels], TE: 2 to 7 ms, TR: 9 to 26 ms, FA 10% to 30%), T2-weighted FSE (fast spin echo, scan parameters: axial plane, FOV 250 mm, matrix 256×256 or 512×512, slice thickness: 5 mm, interslice gap 0.5 mm, TE: 100 to 130 ms, TR: 4000 to 8000 ms), and FLAIR (fluid-attenuated inversion recovery, scan parameters: axial plane, FOV 250 mm, matrix 256×256 or 512×512, slice thickness: 5 mm, interslice gap 0.5 mm, TE: 100 to 160 ms, TR: 6000 to 10000 ms, TI: 2000 to

**TABLE 1. Baseline Characteristics of Subjects in the LADIS Study (n=633)**

Age (y)	74 (5)
Women	350 (55%)
Education (y)	10 (4)
Mini Mental State Examination	27 (2)
Alzheimer Disease Assessment Scale (ADAS)*	17 (7)
White matter hyperintensities	
Mild	282 (44%)
Moderate	195 (31%)
Severe	156 (25%)
Lacunes	
None (0)	332 (52%)
Few (1 to 3)	218 (35%)
Many (≥4)	83 (13%)

Values are means (standard deviation) or numbers (percentages).

\*The ADAS was slightly modified to include the item “delayed word recall.”

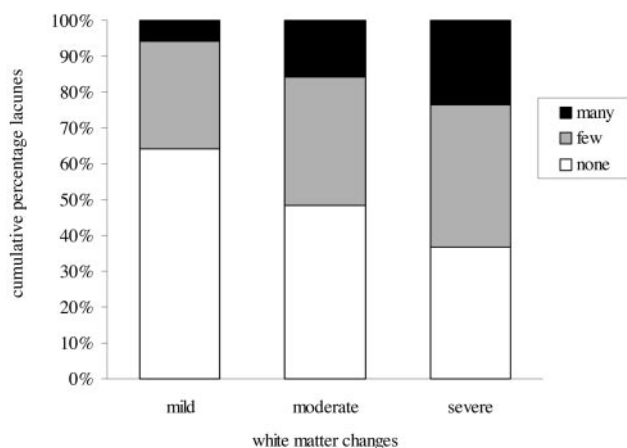
2400). Visual ratings of WMH and counts of lacunes were performed centrally by a single rater (ECWvS) who was blind to clinical details. The degree of WMH severity was rated visually on axial FLAIR images using the Fazekas scale as grade 1 (punctate), grade 2 (early confluent), or grade 3 (confluent).<sup>21</sup> Lacunes were defined as hypointense foci of ≥3 mm on MPRAGE that were surrounded by white matter or subcortical gray matter and not located in areas with a high prevalence of widened perivascular spaces (eg, anterior commissure, vertex).<sup>28</sup> The number of lacunes was recoded into none, few (1 to 3 lacunes), and many (4 lacunes or more). The intrarater reliability of rating of WMH was determined on 18 randomly selected scans that were scored twice (weighted Cohen  $\kappa=0.84$ ). Interrater reliabilities and intrarater reliability of lacunes were not determined.

Statistical analysis was performed using SPSS for windows (release 11.5). Spearman’s correlation was used to assess the association between WMH and lacunes. The strength of the associations between small vessel disease and cognitive measures was assessed using partial correlations, correcting for age and sex. Associations between small vessel disease and general cognitive function were assessed using general linear models for MMSE and ADAS separately. WMH and lacunes were entered as continuous variables. Age and sex were entered as covariates in all models. First, basic associations between general cognitive function and WMH and between general cognitive function and lacunes were assessed. Subsequently, WMH and lacunes were entered simultaneously to assess their independent contribution to cognitive function. The interaction between WMH and lacunes was tested. Because 11 different centers participate in the LADIS project, it is conceivable that center of origin acts as a confounder in the association between small vessel disease and cognition. Therefore, center of origin was entered as a factor in the GLM. Additional corrections were made for education, depressive symptoms, motor function, hypertension, diabetes, smoking, and a history of stroke.

## Results

Characteristics of the participants are presented in Table 1. The number of lacunes increased with the severity of WMH (Spearman  $r=0.25$ ,  $P<0.001$ ; Figure 1).

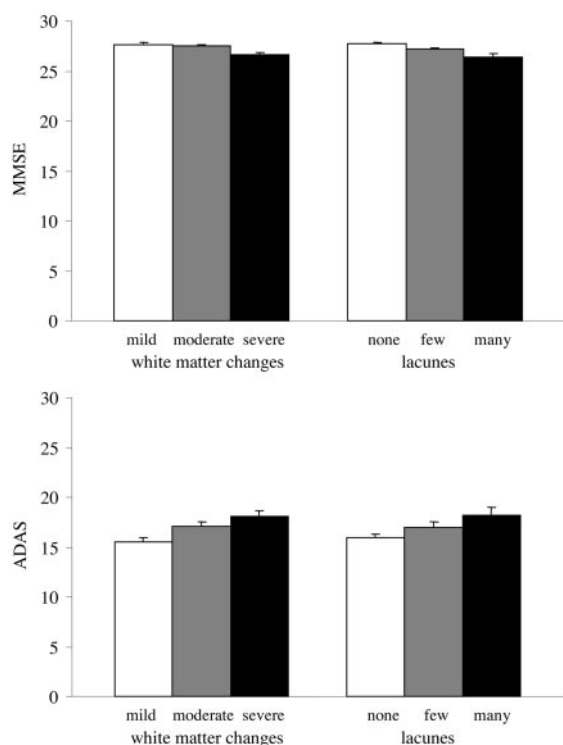
General linear models were performed for WMH and lacunes separately, correcting for age and sex and with the MMSE and the ADAS as dependent variable. In these basic models, WMH and lacunes each were associated with score on the MMSE and ADAS (MMSE-WMH:  $\beta[\text{se}]=-0.48$  [0.12],  $P<0.001$ ; MMSE-lacunes:  $\beta[\text{se}]=-0.62$  [0.14],



**Figure 1.** The number of lacunes increases with the extent of white matter hyperintensities (Spearman  $r=0.25$ ,  $P<0.001$ ).

$P<0.001$ , ADAS-WMH:  $\beta$ [se]=1.31 [0.35],  $P<0.001$ ; ADAS-lacunes:  $\beta$ [se]=1.12 [0.41],  $P=0.007$ , Figure 2). Partial correlations corrected for age and sex were  $-0.16$  and  $-0.18$  (both  $P<0.001$ ) for MMSE with WMH and lacunes, respectively, and  $0.15$  ( $P<0.001$ ) and  $0.11$  ( $P=0.007$ ) for ADAS with WMH and lacunes.

To assess the independent effect of WMH and lacunes on general cognitive function, both variables were entered simultaneously into general linear models (Table 2). Increasing WMH and lacunes were independently associated with a lower score on the MMSE. With increasing severity of



**Figure 2.** Bars represent estimated means (corrected for age and sex) with estimated standard errors. After correction for age and sex, general linear models revealed significant associations between white matter hyperintensities (WMH) and Mini Mental State Examination (MMSE) and modified Alzheimer Disease Assessment Scale (ADAS), and between lacunes and MMSE and ADAS.

WMH, the performance on the ADAS deteriorated. In the multivariate model, increasing severity of lacunes tended to be associated with worse performance on the ADAS, but this association was less prominent. There was no interaction between lacunes and WMH. The interaction term was therefore left out of subsequent analyses. Correction for possible confounders left results largely unaltered. Results did not change after exclusion of subjects with an infarct other than a lacune on MRI.

## Discussion

The main finding of the current study is that WMH and lacunes are independently associated with general cognitive function in a large sample of nondisabled elderly subjects.

Small vessel disease is prevalent among the elderly.<sup>29,30</sup> Several population-based studies have shown before that, small vessel disease may cause subtle cognitive deficits in nondemented subjects.<sup>5,9,16,17</sup> In the present study, we demonstrated that both WMH and lacunes independently influence cognitive function. We found only a moderate correlation between WMH and lacunes, supporting the view that they are 2 distinct expressions of small vessel disease. Lacunar infarcts are produced when the ischemic damage is focal and of sufficient severity to result in a small area of necrosis.<sup>12</sup> They are largely confined to the cerebral white matter and subcortical structures, including the basal ganglia, thalamus, and brain stem. In contrast, diffuse WMH, considered to be a form of rarefaction or incomplete infarction, are usually widespread.

In the present study, we defined small vessel disease as WMH and lacunes on MRI. Although these MRI abnormalities are generally considered as measures of small vessel disease, they have in fact variable pathologic correlates.<sup>1-3,31</sup> Arteriolosclerosis has been reported to be the primary factor in the pathogenesis of WMH in the elderly. Alternatively, WMH may have as diverse pathologic correlates as loss of myelin, axons, and oligodendroglial cells, dilatation of perivascular spaces, and mild reactive astrocytic gliosis.

There have been a few studies evaluating the simultaneous effect of WMH and lacunes in a sample of subjects with a broad range of cognitive impairment.<sup>19,32,33</sup> In these studies, WMH were found to be related to cognitive impairment, but there were no independent associations between lacunes and cognitive dysfunction. In addition, there has been a large population-based study assessing risk factors and functional consequence of lacunes that showed associations between lacunes and cognitive function, even after correction for WMH.<sup>9</sup> In the present study, we demonstrated both lacunes and WMH to be associated with general cognitive function as measured using the MMSE. Scores on the ADAS were related to WMH and lacunes in the basic analysis. However, the association between ADAS score and lacunes was not independent of WMH, although associations remained borderline significant. Insufficient power may be partly responsible for the disappearance of the significant association, because the variability in ADAS is larger than the variability in MMSE. Furthermore, ADAS and MMSE are both widely used tests of general cognitive function. The fact that even with these relatively crude measures, clear associations with

**TABLE 2. Multivariate Associations Between Small Vessel Disease and Cognitive Function**

Variables Adjusted for	MMSE		ADAS	
	WMH	Lacunes	WMH	Lacunes
Age, sex	-0.36 (0.12)†	-0.51 (0.14)†	1.13 (0.37)†	0.78 (0.42)§
Age, sex, center of origin*	-0.40 (0.13)†	-0.50 (0.14)†	1.17 (0.35)†	0.61 (0.40)
Age, sex, education	-0.34 (0.12)†	-0.33 (0.14)‡	1.08 (0.35)†	0.35 (0.41)
Age, sex, depressive symptoms	-0.31 (0.12)‡	-0.47 (0.14)†	1.00 (0.37)†	0.68 (0.42)
Age, sex, motor function	-0.21 (0.13)§	-0.44 (0.14)†	0.87 (0.38)‡	0.67 (0.43)
Age, sex, hypertension, diabetes, smoking	-0.30 (0.12)‡	-0.51 (0.14)†	1.09 (0.37)†	0.73 (0.42)§
Age, sex, history of stroke	-0.38 (0.13)†	-0.52 (0.14)†	1.20 (0.38)†	0.83 (0.43)§

Values are betas and their standard errors. Betas represent the increase in test score with one-level increase of WMH or lacune. Models have MMSE or ADAS as the dependent variable and both WMH and lacunes as independent variables. Therefore, the reported associations of WMH are conditional on lacunes and vice versa. In addition, other potentially confounding variables were entered into the model. The number of missing values varied but was less than 2% of the total number of participants in a particular model.

\*Because 11 different centers participate in the LADIS project, center of origin may act as a confounder. Therefore, center of origin was entered as a factor in the GLM.

† $P < 0.01$ , ‡ $P < 0.05$ , § $P < 0.10$ .

small vessel disease were observed, underlines the clinical relevance of both WMH and lacunes. However, it is conceivable that tests of cognitive functions specifically associated with small vessel disease such as mental speed and executive function may yield even stronger associations with WMH and lacunes.

Among the strengths of the present study is the large sample size. Each subject underwent MRI scanning. All scans were analyzed centrally, which guaranteed reliability of MRI measures. Patients were selected to represent a broad range of WMH, enabling us to assess the subtle associations of small vessel disease and cognitive function. Among the limitations of the study may be the subject selection. Subjects were identified mainly in a hospital or secondary/tertiary referral setting. The study sample was selected to represent the full range of severity of WMH. Although stratification by WMH may hamper the generalizability of the results to the general population, the reasons for referral were those commonly leading to discover WMH in elderly persons, so that the LADIS sample likely reflects the assorted patient population with WMH encountered in everyday clinical practice. Because subjects were selected to be nondisabled, we were not able to evaluate the full spectrum of cognitive impairment. Subjects were allowed to have minor problems such as mild memory loss or minor motor disturbances. However, because subjects were required to be nondisabled, subjects with fullfledged dementia were not eligible. Consequently, we may even have underestimated the strength of the associations between small vessel disease and cognitive function. Another limitation is the fact that we did not include a measure of cerebral gray matter volume. Therefore, it is conceivable that the reported associations are the result of global or regional atrophy rather than ischemic changes. The cross-sectional setting of the present study prevents inferences on the causality of the reported associations. Further research is currently being performed to determine the contribution of small vessel disease to cognitive decline over time.

In conclusion, we found WMH and lacunes to be independently associated with cognitive function in a sample of independently living elderly. These results provide further evidence for the importance of small vessel disease in cognitive impairment at old age, and they highlight the fact that WMH and lacunes should both be evaluated when assessing small vessel disease in relation to cognitive function.

## Appendix

### List of Participating Centers and Personnel

Helsinki, Finland (Memory Research Unit, Department of Clinical Neurosciences, Helsinki University): Timo Erkinjuntti, MD, PhD, Tarja Pohjasvaara, MD, PhD, Pia Pihanen, MD, Raija Ylikoski, PhD, Hanna Jokinen, LPsych, Meija-Marjut Somerkoski, Mpsych, Riitta Mäntylä, MD, PhD; Graz, Austria (Department of Neurology and MRI Institute, Medical University): Franz Fazekas, MD, Reinhold Schmidt, MD, Stefan Ropele, PhD, Alexandra Seewann, MD, Katja Petrovic, MagPsychol, Ulrike Garmehi; Lisboa, Portugal (Serviço de Neurologia, Centro de Estudos Egas Moniz, Hospital de Santa Maria): José M. Ferro, MD, PhD, Ana Verdelho, MD, Sofia Madureira, PsyD; Amsterdam, The Netherlands (Department of Neurology, VU Medical Center): Philip Scheltens, MD, PhD, Ilse van Straaten, MD, Wiesje van der Flier, PhD, Alida Gouw, MD, Frederik Barkhof, MD, PhD; Goteborg, Sweden (Institute of Clinical Neuroscience, Goteborg University): Anders Wallin, MD, PhD, Michael Jonsson, MD, Karin Lind, MD, Arto Nordlund, PsyD, Sindre Rolstad, PsyD, Kerstin Gustavsson, RN; Huddinge, Sweden (Neurotec Department, Section of Clinical Geriatrics, Karolinska Universitetssjukhuset): Lars-Olof Wahlund, MD, PhD, Militta Crisby, MD, PhD, Anna Pettersson, physiotherapist, Kaarina Amberla, PsyD; Paris, France (Department of Neurology, Hopital Lariboisiere): Hugues Chabriat, MD, PhD, Ludovic Benoit, MD, Karen Hernandez, Solene Pointeau, Annie Kurtz, Daniel Reizine, MD; Mannheim, Germany (Department of Neurology, University of Heidelberg, Klinikum Mannheim): Michael Hennerici, MD, Christian Blahak, MD, Hansjorg Baezner, MD, Martin Wiarda, PsyD, Susanne Seip, RN; Copenhagen, Denmark (Copenhagen University Hospital: Memory Disorders Research Unit, Department of Neurology, Rigshospitalet, and the Danish Magnetic Resonance Research Center, Hvidovre Hospital): Gunhild Waldemar, MD, DMSc, Egill Rostrup, MD, MSc, Charlotte Ryberg, Tim Dyrby; Newcastle-upon-Tyne, U.K. (Institute for Ageing and Health, University of Newcastle): John O'Brien, DM, Sanjeet Pakrasi, MRCPsych, Thais

Minnet, PhD, Michael Firbank, PhD, Jenny Dean, PhD, Pascale Harrison, BSc, Philip English, DCR. The coordinating center is in Florence, Italy (Department of Neurological and Psychiatric Sciences, University of Florence): Domenico Inzitari, MD (Study Coordinator); Leonardo Pantoni, MD, PhD, Anna Maria Basile, MD, Michela Simoni, MD, Giovanni Pracucci, MD, Monica Martini, MD, Luciano Bartolini, PhD, Emilia Salvadori, PhD, Marco Moretti, MD, Mario Mascalchi, MD, PhD.

The LADIS Steering Committee is formed by Domenico Inzitari, MD (study coordinator), Timo Erkinjuntti, MD, PhD, Philip Scheltens, MD, PhD, Marieke Visser, MD, PhD, and Kjell Asplund, MD, PhD.

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