Lower Susceptibility to Cerebral Small Vessel Disease in Human Familial Longevity

The Leiden Longevity Study

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Background and Purpose—On MRI, cerebral white matter lesions, lacunar infarcts, and cerebral microbleeds are common imaging correlates of cerebral small vessel damage in apparently healthy elderly individuals. We investigated whether middle-aged to elderly offspring of nonagenarian siblings, who are predisposed to become long-lived as well, have a lower prevalence of white matter lesions, lacunar infarcts, and cerebral microbleeds than control subjects.

Methods—All subjects were from the Leiden Longevity Study. In this study, middle-aged to elderly offspring of nonagenarian siblings, who are predisposed to become long-lived as well, were contrasted to their spouses. Cerebral small vessel disease was assessed using 3-T MRI.

Results—Offspring were less likely to have severe periventricular frontal caps (odds ratio [OR], 0.3; 95% confidence interval [CI], 0.1–1.1; P trend=0.01) and severe periventricular bands (OR, 0.4; 95% CI, 0.2–0.8; P trend=0.02). Moreover, offspring were less likely to have frontal (OR, 0.4; 95% CI, 0.2–0.9; P trend=0.05), parietal (OR, 0.4; 95% CI, 0.1–0.9; P trend=0.001), temporal (OR, 0.3; 95% CI, 0.1–0.8; P trend=0.004), and occipital subcortical white matter lesions (OR, 0.3; 95% CI, 0.1–0.6; P trend=0.001). Prevalence of lacunar infaracts also was lower in offspring (OR, 0.3; 95% CI, 0.1–1.1; P=0.07). Prevalence of microbleeds was not significantly different in offspring and control subjects.

Conclusions—Exceptional familial longevity is associated with a lower susceptibility to white matter lesions and lacunar infarcts, but not cerebral microbleeds.

Key Words: aging ▪ brain ▪ cerebral small vessel disease ▪ longevity ▪ magnetic resonance imaging ▪ neuroimaging

Cerebral small vessel disease is common in old age. On MRI, cerebral white matter lesions, lacunar infarcts, and cerebral microbleeds (CMBs) frequently can be detected in apparently healthy elderly individuals as imaging correlates of cerebral small vessel damage. Presence of WMLs, lacunar infarcts, and CMBs in the elderly has been shown to be associated with cerebrovascular disease, such as ischemic stroke or cerebral hemorrhage, progression of these diseases, and increased mortality risk. For WMLs, a high degree of heritability has been reported. The relative absence of WMLs, lacunar infarcts, and CMBs may reflect a decelerated process of biological aging and serve as a marker for the phenotype of human longevity. The Leiden Longevity Study was designed to investigate factors associated with human longevity. Offspring of long-lived nonagenarian siblings, who are predisposed to become long-lived as well, were contrasted to their spouses. The propensity to become long-lived in the middle-aged to elderly offspring as compared with their spouses is marked by a low incidence of morbidity, beneficial serum levels of lipid and thyroid parameters, preservation of insulin sensitivity, and a lower prevalence of myocardial infarction, hypertension, diabetes mellitus, and use of cardiovascular medication.

To study whether the phenotype of human familial longevity also is reflected by a lower susceptibility to cerebral small vessel disease, we investigated whether middle-aged to elderly individuals, who are enriched for familial factors of longevity, have a lower WML load and a lower amount of lacunar infarcts and CMBs compared with their spouses using MRI.

 Patients and Methods

Study Subjects

Subjects were included from the Leiden Longevity Study, which has been described in more detail elsewhere. In short, 421 Dutch white families were enrolled in the study between 2002 and 2006 based on the following inclusion criteria: (1) there were at least 2 living
siblings per family who fulfilled the age criteria and were willing to participate; (2) men had to be aged 289 years and women had to be aged ≥91 years; and (3) the sib pairs had to have the same parents. Additionally, offspring of these long-lived siblings were included because they have a 35% lower mortality rate compared with the general population. Their partners, who share the same socioeconomic and geographic background, were enrolled as the age-matched control group.11

For the current study, subjects were recruited from the offspring of the long-lived siblings and their spouses. In total, 502 subjects (251 couples) participated in the current study, of which 370 subjects (194 offspring and 176 control subjects) underwent an MRI scan of the brain. Some offspring (n=57) and control subjects (n=75) were excluded because of contraindications for MRI. Of 194 offspring, 93 were related to at least 1 other offspring who participated in the current study. The Medical Ethical Committee of the Leiden University Medical Center approved the study, and written informed consent was obtained from all subjects. The study was performed in accordance with institutional guidelines.

### MRI Acquisition

All imaging was performed on a whole-body magnetic resonance system operating at a field strength of 3-T (Philips Medical Systems). Three-dimensional (3-D) T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR), and T2*-weighted images were acquired with the following imaging parameters.

#### 3-D T1-Weighted Images

Repetition time was 9.7 ms, time to echo was 4.6 ms, flip angle was 8°, and field of view was 224×177×168 mm, resulting in a nominal voxel size of 1.17×1.17×1.4 mm, covering the entire brain and with no gap between slices. Acquisition time was ≈5 minutes.

#### T2-Weighted Images

Repetition time was 4200 ms, time to echo was 80 ms, flip angle was 90°, field of view was 224×180×144 mm, matrix size was 448×320, and 40 transverse slices covered the entire brain, with a slice thickness of 3.6 mm with no gap between slices.

#### FLAIR

Repetition time was 11 000 ms, time to echo was 125 ms, flip angle was 90°, field of view was 220×176×137 mm, matrix size was 320×240, and 25 transverse slices covered the entire brains, with a slice thickness of 5 mm with no gap between slices.

#### T2*-Weighted Images

Repetition time was 45 ms, time to echo was 31 ms, flip angle was 15°, and field of view was 250×175×112 mm.

Because of technical problems, T2-weighted and FLAIR images were available for 368 subjects (194 offspring and 174 control subjects) and T2*-weighted images were available for 285 subjects (149 offspring and 136 control subjects).

### MRI Analysis: Cerebral Microbleeds

MRI scans were visualized using the freely available software MIPAV. CMBs were analyzed blinded to subject identity, age, sex, and affiliation to the study group. CMBs were defined as focal areas of signal void on T2-weighted images, which increased in size on T2*-weighted images (blooming effect). In this way, CMBs were distinguished from vascular flow voids. Symmetric hypointensities in the basal ganglia, likely to represent calcifications or nonhemorrhagic iron deposits, were disregarded.20 For each subject, the number and localization (corticosubcortical junction, deep white matter, and basal ganglia) were recorded.

### Statistical Analysis

If not otherwise stated, data are presented as mean with SD (characteristics of the study population) or odds ratios (ORs) with 95% CI to assess differences among groups. Differences in sex, history of hypertension, diabetes mellitus, smoking, myocardial infarction, and stroke between offspring and control subjects were calculated using χ² tests. Differences in age, body mass index, and levels of cholesterol were tested using independent samples t tests. To assess differences in WML load, presence of lacunar infarcts, and CMBs between offspring and control subjects, a logistic regression model was applied. Study participants with no lesions were set as a reference group and ORs were calculated for all other groups relative to the reference group. The P value for trend indicates whether the OR increases with increasing degree of severity of a certain type of lesion. All analyses of differences between offspring and control subjects were adjusted for age and sex (model 1) and additionally for cardiovascular risk factors (history of hypertension, diabetes mellitus, myocardial infarction, stroke and smoking, body mass index, and cholesterol; model 2). Robust standard errors were calculated to correct for family relationships among the offspring. Significance thresholds were set at P<0.05. For statistical analysis, SPSS software for windows (version 17.0.1; SPSS) was used. Robust standard errors were calculated with Stata statistical software for windows (version 10; Stata).

### Results

Characteristics of the study population are shown in Table 1. In total, 368 subjects participated in the study (194 offspring of...
long-lived siblings and 174 control subjects). The mean age was 66 years for offspring and 65 years for control subjects, with a significantly lower female percentage of 43% among offspring compared with 61% among control subjects (P=0.001). All analyses of differences between offspring and control subjects were, therefore, adjusted for sex. Moreover, significantly more control subjects had a history of diabetes mellitus compared with the offspring. No differences were found concerning other cardiovascular risk factors. Five offspring (3%) and 4 control subjects (3%) had a history of clinical stroke.

Different degrees of severity of periventricular and subcortical WMLs are shown in Figure 2. Prevalence of periventricular WMLs in offspring and control subjects is shown in Table 2. Offspring of long-lived siblings were less likely to have severe frontal caps compared with control subjects (OR, 0.3; 95% CI, 0.1–1.1; P trend=0.01), which remained after additional adjustment for cardiovascular risk factors (P trend=0.03). Moreover, offspring of long-lived siblings were less likely to have severe periventricular bands (OR, 0.4; 95% CI, 0.2–0.8; P trend=0.02). After additional adjustment for cardiovascular risk factors, effect estimates remained similar, whereas significance attenuated (P trend=0.06). Prevalence of occipital caps was not significantly different between the 2 groups.

Prevalence of subcortical WMLs for offspring and control subjects is shown in Table 3. Offspring of long-lived siblings were less likely to have frontal (OR, 0.4; 95% CI, 0.2–0.9; P trend=0.05), parietal (OR, 0.4; 95% CI, 0.1–0.9; P trend=0.001), temporal (OR, 0.3; 95% CI, 0.1–0.8; P trend=0.004), and occipital subcortical WMLs (OR, 0.3; 95% CI, 0.1–0.6; P trend=0.001). All associations remained similar after additional adjustment for cardiovascular risk factors. Prevalence of lacunar infarcts was low, with a nonsignificant difference between offspring (2%) and control subjects (5%) (OR, 0.3; 95% CI, 0.1–1.1; Table 4).

Prevalence of CMBs was similar in offspring (14%) and control subjects (13%) (OR, 1.0; 95% CI, 0.5–2.1). Additional adjustment for cardiovascular risk factors did not alter the results.

**Discussion**

This study shows that middle-aged to elderly individuals who have a familial higher susceptibility to become long-lived have a lower periventricular as well as subcortical WML load and a lower prevalence of lacunar infarcts compared with control subjects independent of their cardiovascular risk profile. In contrast, prevalence of CMBs was similar in both groups.

Our findings suggest that exceptional familial longevity is associated with a lower susceptibility to WMLs as well as lacunar infarcts. Studies on the genetic determinants of cerebral WMLs have reported a high degree of heritability in younger study subjects with a low prevalence of cerebral WMLs, suggesting WMLs to be an excellent genetic marker of brain aging.11,12 The Notch3 gene, apolipoprotein E (APO E) gene, and the angiotensin-converting enzyme (ACE) gene are examples of genes, that have been identified to be associated with the formation of WMLs.21–23 However, it is not known, so far, whether the genetic difference in the susceptibility to the formation of WMLs is because of genetic differences in the aging process itself or because of a genetically determined different susceptibility to cardiovascular damage or both.11 In our study, additional adjustment for cardiovascular risk factors did not change the association of exceptional familial longevity with a lower prevalence of periventricular as well as subcortical WMLs, suggesting a genetically determined lower susceptibility of the offspring to the formation of cerebral WMLs in the course of aging, regardless of their cardiovascular risk profile. Several genes have been identified to be associated with the presence of lacunar infarcts.23–26 In this study, a lower prevalence of lacunar infarcts was associated with familial longevity, barely reaching statistical significance. Reported prevalence of lacunar infarcts in the

**Table 1. Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Offspring (n=194)</th>
<th>Controls (n=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>66 (6)</td>
<td>65 (7)</td>
</tr>
<tr>
<td>Women*</td>
<td>84 (43)</td>
<td>106 (61)</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>40 (23)</td>
<td>43 (28)</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>4 (2)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (3)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.65 (1.26)</td>
<td>5.71 (1.17)</td>
</tr>
<tr>
<td>Smoking</td>
<td>20 (10)</td>
<td>24 (14)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.2 (3.3)</td>
<td>25.5 (3.4)</td>
</tr>
</tbody>
</table>

Values are numbers (percentage) for dichotomous variables or means (standard deviation) for continuous variables. *P<0.05.

**Figure 2.** Different degrees of periventricular and subcortical white matter lesions (WMLs) on magnetic resonance imaging (MRI): (A) subject without WMLs, (B) subject with a severe degree of frontal and occipital caps and periventricular bands (score 2/2/2), and (C) subject with a severe degree of subcortical WMLs (score 6/6/6/6).
general elderly population ranges from 5% to ≈30%.27–29 Thus, overall prevalence in our study population (3%) was relatively low. Because the prevalence of lacunar infarcts increases with age, with a low prevalence at an age of ~60 years, our study subjects were, with a mean age of 66 years, relatively young for the detection of lacunar infarcts.30 A higher mean age of the study population could have increased the detected difference in prevalence of lacunar infarcts between both groups. Additional adjustment for cardiovascular risk factors did not alter the results, suggesting that offspring of long-lived siblings have a lower susceptibility to the formation of lacunar infarcts during the aging process compared with control subjects, regardless of their cardiovascular risk profile. However, the low prevalence of lacunar infarcts hampers a proper interpretation of the data.

In the Leiden Longevity Study, the propensity to become long-lived in the middle-aged to elderly offspring as compared with control subjects is marked by a low incidence of morbidity, beneficial serum levels of lipid and thyroid parameters, preservation of insulin sensitivity, and a lower prevalence of myocardial infarction, hypertension, diabetes mellitus, and use of cardiovascular medication.14–17 In the current substudy, offspring also showed a lower prevalence of hypertension, diabetes mellitus, and myocardial infarction, with the difference only reaching statistical significance for history of diabetes mellitus. This is most likely because of the lower number of study participants as compared with the original cohort.

Exceptional familial longevity was not associated with a lower prevalence of CMBs. The age-specific prevalence of CMBs has been reported to increase from ~7% in individuals aged 45 to 50 years to ~36% in individuals aged ≥80 years in the population-based Rotterdam Scan Study.31 The APOE ε4 gene was associated with the presence of strictly lobar CMBs.31,32 Overall, prevalence of CMBs in our study confirms the age-stratified prevalence of CMBs reported in the Rotterdam Scan Study (mean age of our study population, 66 years; age range, 46–85 years).31 Prevalence of CMBs was similar in offspring and control subjects, suggesting that the propensity of familial longevity is not associated with a lower susceptibility to CMBs.

One of the strengths of our study is the unique study design of comparing middle-aged to elderly individuals, who have a genetically determined higher susceptibility to become long-lived, with control subjects. This will allow us to gain more insight in the relevance of age-related changes of the human brain, which can be frequently detected on MRI scans in the general aging population. Second, by including the partners of the offspring of the long-lived siblings as the control group, the 2 groups were highly comparable concerning their socioeconomic and geographic background. Finally, our inclusion algorithm resulted in a large study sample, which allows us to investigate even small differences between the 2 groups.

The fact that the study subjects were relatively young concerning age-related changes of the human brain belongs to the limitations of this study. Because differences between the 2 groups are likely to be small, a higher mean age of the study groups would probably facilitate the detection of possible

| Table 2. Periventricular White Matter Lesion load of Offspring and Control Subjects |
|-------------------------------|-------------------|-------------------|-------------------|
|                               | Offspring (n=194) | Controls (n=174)  | OR (95% CI)   |
|                               | Model 1 Value     | Model 2 Value     |                 |
| Frontal caps                  |                  |                  |                 |
| 0                              | 10 (5) 1.0 (ref)  | 5 (3) 1.0 (ref)   |                 |
| 1                              | 140 (72) 0.6 (0.2–1.8) | 109 (63) 0.6 (0.2–1.8) | 0.35 0.37 |
| 2                              | 44 (23) 0.3 (0.1–1.1) | 60 (35) 0.3 (0.1–1.1) | 0.07 0.09 |
| P for trend                    | 0.01              | 0.03              |                 |
| Bands                          |                  |                  |                 |
| 0                              | 40 (21) 1.0 (ref)  | 24 (14) 1.0 (ref)  |                 |
| 1                              | 134 (69) 0.6 (0.4–1.1) | 122 (70) 0.6 (0.4–1.1) | 0.14 0.14 |
| 2                              | 20 (10) 0.4 (0.2–0.8) | 28 (16) 0.4 (0.2–0.8) | 0.02 0.06 |
| P for trend                    | 0.02              | 0.06              |                 |
| Occipital caps                 |                  |                  |                 |
| 0                              | 78 (40) 1.0 (ref)  | 59 (34) 1.0 (ref)  |                 |
| 1                              | 93 (48) 0.8 (0.5–1.3) | 86 (49) 0.8 (0.5–1.3) | 0.40 0.25 |
| 2                              | 23 (12) 0.6 (0.3–1.1) | 29 (17) 0.6 (0.3–1.1) | 0.10 0.11 |
| P for trend                    | 0.11              | 0.09              |                 |
| Total score                    |                  |                  |                 |
| 0                              | 6 (3) 1.0 (ref) 1 (1–3) | 2 (1) 1.0 (ref) 1 (1–3) | 0.22 0.21 |
| 1                              | 145 (75) 0.4 (0.1–2.0) | 113 (65) 0.4 (0.1–2.0) | 0.05 0.05 |
| 2                              | 43 (22) 0.2 (0.04–1.1) | 59 (34) 0.2 (0.04–1.1) | 0.01 0.01 |
| P for trend                    | 0.01              | 0.01              |                 |

CI indicates confidence interval; OR, odds ratio. Values are numbers (percentage) or OR (95% CI). P values are adjusted for age and sex and corrected for family relationships among the offspring (model 1), and are additionally adjusted for cardiovascular risk factors (model 2).
differences. Second, some individual categories did not reach statistical significance or did not remain significant after full adjustment for cardiovascular risk factors. The described phenomenon mostly appeared in categories with a low number of study participants, which have relatively low statistical power and were usually the most severe categories. However, a clear dose–response could be observed for almost all abnormalities in both models, which was expressed in decreasing ORs with increasing severity of the lesions. This also was indicated by the \( P \) value for trend.

**Conclusions**

To the best of our knowledge, this is the first study to compare imaging markers of cerebral small vessel disease between elderly individuals with a familial predisposition to become long-lived and their partners. Our findings indicate that at a

### Table 3. Subcortical White Matter Lesion Load of Offspring and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Offspring (n=194)</th>
<th>Controls (n=174)</th>
<th>OR (95% CI)</th>
<th>( P ) Value</th>
<th>OR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td>Frontal</td>
<td>0</td>
<td>37 (19)</td>
<td>25 (14)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (1–3)</td>
<td>132 (68)</td>
<td>111 (64)</td>
<td>0.8 (0.5–1.5)</td>
<td>0.60</td>
<td>0.9 (0.5–1.7)</td>
</tr>
<tr>
<td></td>
<td>2 (4–6)</td>
<td>25 (13)</td>
<td>38 (22)</td>
<td>0.4 (0.2–0.9)</td>
<td>0.05</td>
<td>0.5 (0.2–1.1)</td>
</tr>
<tr>
<td>( P ) for trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td>0</td>
<td>95 (49)</td>
<td>52 (30)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (1–3)</td>
<td>87 (45)</td>
<td>106 (61)</td>
<td>0.4 (0.3–0.7)</td>
<td>&lt;0.001</td>
<td>0.4 (0.3–0.7)</td>
</tr>
<tr>
<td></td>
<td>2 (4–6)</td>
<td>12 (6)</td>
<td>16 (9)</td>
<td>0.4 (0.1–0.9)</td>
<td>0.03</td>
<td>0.4 (0.2–1.1)</td>
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<tr>
<td>( P ) for trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>0</td>
<td>100 (52)</td>
<td>67 (39)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (1–3)</td>
<td>85 (44)</td>
<td>92 (53)</td>
<td>0.5 (0.4–0.9)</td>
<td>0.01</td>
<td>0.5 (0.3–0.9)</td>
</tr>
<tr>
<td></td>
<td>2 (4–6)</td>
<td>9 (5)</td>
<td>15 (9)</td>
<td>0.3 (0.1–0.8)</td>
<td>0.02</td>
<td>0.4 (0.1–1.1)</td>
</tr>
<tr>
<td>( P ) for trend</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>0</td>
<td>128 (66)</td>
<td>96 (55)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (1–3)</td>
<td>52 (27)</td>
<td>48 (26)</td>
<td>0.7 (0.4–1.1)</td>
<td>0.16</td>
<td>0.9 (0.5–1.5)</td>
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<td></td>
<td>2 (4–6)</td>
<td>14 (7)</td>
<td>30 (17)</td>
<td>0.3 (0.1–0.6)</td>
<td>0.001</td>
<td>0.3 (0.1–0.7)</td>
</tr>
<tr>
<td>( P ) for trend</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total score</td>
<td>0</td>
<td>31 (16)</td>
<td>18 (10)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (1–6)</td>
<td>109 (56)</td>
<td>83 (48)</td>
<td>0.8 (0.4–1.5)</td>
<td>0.48</td>
<td>0.9 (0.4–1.8)</td>
</tr>
<tr>
<td></td>
<td>2 (7–12)</td>
<td>35 (18)</td>
<td>41 (24)</td>
<td>0.5 (0.2–1.0)</td>
<td>0.06</td>
<td>0.5 (0.2–1.1)</td>
</tr>
<tr>
<td></td>
<td>3 (13–24)</td>
<td>19 (10)</td>
<td>32 (18)</td>
<td>0.3 (0.1–0.7)</td>
<td>0.01</td>
<td>0.4 (0.1–1.0)</td>
</tr>
<tr>
<td>( P ) for trend</td>
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</table>

CI indicates confidence interval; OR, odds ratio. \( P \) values are adjusted for age and sex and corrected for family relationships among the offspring (model 1), and are additionally adjusted for cardiovascular risk factors (model 2). Values are numbers (percentage) or OR (95% CI).

### Table 4. Lacunar Infarcts and Cerebral Microbleeds in Offspring and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Offspring (n=194)</th>
<th>Controls (n=174)</th>
<th>OR (95% CI)</th>
<th>( P )</th>
<th>OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td>Lacunar infarcts</td>
<td>Not present</td>
<td>190 (97.9)</td>
<td>166 (95.4)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>4 (2.1)</td>
<td>8 (4.6)</td>
<td>0.3 (0.1–1.1)</td>
<td>0.07</td>
<td>0.5 (0.1–1.8)</td>
</tr>
<tr>
<td>Cerebral microbleeds</td>
<td>Not present</td>
<td>128 (66)</td>
<td>118 (67)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>21 (14)</td>
<td>18 (13)</td>
<td>1.0 (0.5–2.1)</td>
<td>0.92</td>
<td>1.2 (0.5–2.6)</td>
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</tbody>
</table>

CI indicates confidence interval; OR, odds ratio. Values are numbers (percentage) or OR (95% CI) adjusted for age and sex and corrected for family relationships among the offspring (model 1), and are additionally adjusted for cardiovascular risk factors (model 2).
mean age of 66 years, exceptional familial longevity is associated with a lower susceptibility to WMLs and lacunar infarcts but not CMBs. Because this association did not change after additional adjustment for cardiovascular risk factors, it is likely that differences in the susceptibility to WMLs and lacunar infarcts between offspring of long-lived siblings and control subjects are because of genetic differences in the process of aging and are not driven by a genetically determined different susceptibility to cardiovascular damage.

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Disclosures
None.

References
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