Progression of White Matter Disease and Cortical Thinning Are Not Related in Older Community-Dwelling Subjects

David Alexander Dickie, PhD; Sherif Karama, MD, PhD; Stuart J. Ritchie, PhD; Simon R. Cox, PhD; Eleni Sakka, MSc; Natalie A. Royle, PhD; Benjamin S. Aribisala, PhD; Maria Valdés Hernández, PhD; Susana Muñoz Maniega, PhD; Alison Pattie, BSc; Janie Corley, MA; John M. Starr, MD; Mark E. Bastin, DPhil; Alan C. Evans, PhD; Ian J. Deary, PhD*; Joanna M. Wardlaw, MD*

Background and Purpose—We assessed cross-sectional and longitudinal relationships between whole brain white matter hyperintensity (WMH) volume and regional cortical thickness.

Methods—We measured WMH volume and regional cortical thickness on magnetic resonance imaging at ≈73 and ≈76 years in 351 community-dwelling subjects from the Lothian Birth Cohort 1936. We used multiple linear regression to calculate cross-sectional and longitudinal associations between regional cortical thickness and WMH volume controlling for age, sex, Mini Mental State Examination, education, intelligence quotient at age 11, and vascular risk factors.

Results—We found cross-sectional associations between WMH volume and cortical thickness within and surrounding the Sylvian fissure at 73 and 76 years (rho=−0.276, Q=0.004). However, we found no significant longitudinal associations between (1) baseline WMH volume and change in cortical thickness; (2) baseline cortical thickness and change in WMH volume; or (3) change in WMH volume and change in cortical thickness.

Conclusions—Our results show that WMH volume and cortical thinning both worsen with age and are associated cross-sectionally within and surrounding the Sylvian fissure. However, changes in WMH volume and cortical thinning from 73 to 76 years are not associated longitudinally in these relatively healthy older subjects. The underlying cause(s) of WMH growth and cortical thinning have yet to be fully determined. (Stroke. 2016;47:410-416. DOI: 10.1161/STROKEAHA.115.011229.)

Key Words: ageing ■ brain ■ cortex ■ MRI ■ white matter hyperintensities

Brain white matter hyperintensity (WMH) growth and cortical thinning are commonly seen on magnetic resonance imaging (MRI) in community-dwelling older people.1–5 The incidence of these features is highly variable between individuals but those with the largest WMH volumes and/or thinnest cortices are at increased risk of stroke, dementia, and cognitive and physical impairment.6–8 Effective interventions are dependent on understanding the mechanisms of WMH growth and cortical thinning and whether one feature may be an underlying cause of the other.

Cross-sectional studies have found associations between larger whole brain WMH volume and reduced gray matter (GM) volume, density, and thickness.3,5,9–12 Those with larger WMH volumes generally had relatively reduced cortical thickness3 and density5,11 in frontotemporal and inferior parietal regions. Others have found similar cross-sectional patterns of negative associations between whole brain WMH volume and regional GM volume in the default mode network (which includes medial temporal lobe structures, the inferior parietal lobe, and cuneus) using a region of interest analysis.10 Larger WMH volume in small vessel disease patients has also been associated with reduced structural connectivity in frontotemporal and inferior parietal regions.7

These studies were cross-sectional and so cannot ascertain a direction of causation or effect. Additionally, the regions of cortical thinning that were associated with WMH volume did...
subjects from the Lothian Birth Cohort 1936 (LBC1936) study.\textsuperscript{14,15} In the present study, we assessed longitudinal associations between change in WMH volume and change in cortical thickness to determine if the relationship between WMH and regional cortical thinning could be causal in community-dwelling subjects from ages 73 to 76.\textsuperscript{3,11} If the relationship between WMH and the regions of cortex that were thinned was potentially causal, then we hypothesized that there would be an association between (1) baseline whole WMH volume and change in cortical thickness over the next few years; (2) baseline cortical thickness and change in WMH volume; and (3) change in WMH volume and change in cortical thickness. To test these hypotheses, we measured progression of WMH volume and cortical thinning from =73 to =76 years of age in community-dwelling subjects from the Lothian Birth Cohort 1936 (LBC1936) study.

### Methods

#### Study Approval and Subject Consent

Approval for the LBC1936 study protocol was obtained from the Multicentre Research Ethics Committee for Scotland (MREC/01/0/56) and Lothian Research Ethics Committee (LREC/2003/2/29). All subjects gave written, informed consent.

#### Subjects

In the present study, we assessed 351 (N\textsubscript{male}=202) community-dwelling subjects from the LBC1936 study\textsuperscript{14,15} that had full brain MRI data sets at baseline and follow-up (Figure 1). These subjects were not deliberately selected, rather they were simply those who agreed to participate in brain scanning and had complete data sets at baseline and follow-up (Figure 1).

We recorded Mini Mental State Examination (MMSE) scores at baseline and follow-up to screen for possible dementia.\textsuperscript{14,15} We did not exclude subjects based on MMSE but included MMSE as an adjustment variable. We recorded the following vascular risk factors (VRF) during a clinical research facility visit: history of hypertension, hypercholesterolemia, diabetes mellitus, smoking, history of cardiovascular disease, and body mass index. History of cardiovascular disease includes self-reported incidences of coronary heart disease, stroke, peripheral arterial disease, and aortic disease. We also took blood samples and measured blood pressure but did not include these variables (eg, systolic blood pressure and glycated hemoglobin) in the present analysis to maximize the number of subjects with complete data sets and to be consistent with previous work.\textsuperscript{4} Further, we have previously shown that historical variables, for example, history of hypertension, have greater associations with WMH than measured variables, for example, systolic blood pressure.\textsuperscript{4}

### Brain MRI Acquisition

Brain MRI acquisition parameters were described in detail previously.\textsuperscript{16} Briefly, all subjects had brain MRI on the same 1.5 tesla GE Signa Horizon HDx clinical scanner (General Electric, Milwaukee, WI), maintained on a careful quality assurance programme, at baseline and follow-up. The scanning protocol was the same at baseline and follow-up and acquired T1-, T2-, T2*- and fluid-attenuated inversion recovery–weighted images.\textsuperscript{16}

### WMH Volume and Cortical Thickness Measurement

We measured intracranial volume and whole WMH volume in milliliters using a validated multispectral image processing method that combines T1-, T2-, T2*- and fluid-attenuated inversion recovery–weighted images\textsuperscript{16} and follow-up and acquired T1-, T2-, T2*- and fluid-attenuated inversion recovery–weighted images\textsuperscript{16} and therefore, we maintained their original scale (proportion of intracranial volume) to simplify interpretation. We assessed changes in binary variables used in adjustment, for example, history of hypertension, using $z$-tests of proportion.

### Statistical Analysis

All statistical analyses were performed in Matrix Laboratory (MATLAB) R2014a (© 1994–2014 The MathWorks, Inc). We assessed changes in overall mean cortical thickness (mean thickness of the whole cortical mantle), whole brain WMH volume, and continuous variables used in adjustment, for example, body mass index, from 73 years to 76 years using paired $t$-tests. Log-transforming the positively skewed WMH distributions had little effect on our results, and therefore, we maintained their original scale (proportion of intracranial volume) to simplify interpretation. We assessed changes in binary variables used in adjustment, for example, history of hypertension, using $z$-tests of proportion.

Cortical vertex-wise regression analyses were performed using the SurfStat MATLAB toolbox (http://www.math.mcgill.ca/keith/surfstat). We tested 5 vertex-wise regression models where (1) cortical thickness at 73 years at each vertex was the dependent variable and WMH volume at 73 years was the independent variable; (2) cortical thickness at 76 years at each vertex was the dependent variable and WMH volume at 76 years was the independent variable; (3) change in cortical thickness at each vertex...
was the dependent variable and WMH volume at 73 years was the independent variable; (4) cortical thickness at 73 years at each vertex was the dependent variable and change in WMH volume was the independent variable; and (5) change in cortical thickness at each vertex was the dependent variable and change in WMH volume was the independent variable. We defined change in WMH and cortical thickness as individual measurements at 73 years minus measurements at 73 years.

We used false discovery rate to correct for multiple comparisons and calculated Q values, that is, false discovery rate–corrected P values, for all vertex-wise regressions thresholded at 0.05. As reported by others, all models were controlled for sex, MMSE, age in days, years of education, body mass index, and VRF. Finally, we also included childhood (age 11) intelligence quotient as a controlling variable to test whether any associations between WMH and cortical thickness were because of the influence of premorbid levels of cognitive ability.

Results
Baseline Only and Follow-Up Subject Comparisons
There were no significant differences at baseline (73 years) between subjects who did return for follow-up cortical thickness measurement and subjects who did not return for follow-up (at 76 years) in overall mean cortical thickness (3.11 mm versus 3.10 mm, z=0.75; P=0.46); WMH volume (0.78% intracranial volume versus 0.84% intracranial volume, t=-0.78; P=0.43); history of cardiovascular disease (27.3% versus 26.2%, z=0.29; P=0.39); current smoking (6.5% versus 8.2%, z=-0.76; P=0.22); hypercholesterolemia (40.0% versus 43.1%, z=-0.71; P=0.24); hypertension (46.5% versus 51.8%, z=-1.2; P=0.11); diabetes mellitus (10.1% versus 11.3%, z=-0.43; P=0.33); body mass index (27.8 versus 27.8, t=-0.21; P=0.84); years of education (10.85 years versus 10.89 years, t=-0.448; P=0.65); nor age 11 intelligence quotient (101.9 versus 100.2, t=1.24; P=0.22). Subjects who did return had higher MMSE scores at baseline than those who did not return (28.9 versus 28.6, z=0.29; P=0.37). There were no significant differences at baseline (73 years) for all other independent variables (Table 2) shows that cortex thinning was generally more pronounced in older subjects (r=0.13; P=0.02). All other independent variables had limited partial effects on WMH and cortical thinning (beyond the effect of time point; Table 2).

Cross-Sectional and Longitudinal Global Correlations Between Overall Mean Cortical Thickness and WMH Volume
Cross-sectional global correlations between overall mean cortical thickness and WMH volume at 73 years (r=−0.06; P=0.27) and 76 years (r=−0.08; P=0.12) were not significant. Pairwise longitudinal global correlations between (1) WMH volume at 73 years and change in overall mean cortical thickness (r=−0.07; P=0.19); (2) overall mean cortical thickness at 73 years and change in WMH volume (r=0.01; P=0.82); and (3) change in WMH volume and change in overall mean cortical thickness (r=−0.02; P=0.67) were also not significant.

Cross-Sectional Vertex-Wise Regression Models of Regional Cortical Thickness and WMH Volume
Cross-sectional vertex-wise regression models of cortical thickness and WMH volume at 76 years are shown in Figure 2. Cross-sectional data from 73 years are not shown because the pattern of associations between cortical thickness and WMH volume was almost identical at 73 and 76 years. All models are corrected for VRF, MMSE, education level, and baseline age.}

### Table 1. Baseline, Follow-Up, and Changes in Cognitive, VRF, Cortical Thickness, and WMH Measurements

| N=351 | 11 Years | 73 Years | 76 Years | 3 Year Change |
|-------|----------|----------|----------|---------------|
| Childhood IQ | 102.21±15.75 | ... | ... | ... |
| Sex (%male) | ... | 57.39 | 57.39 | ... |
| Education, y | ... | 10.86±1.18 | 10.86±1.18 | ... |
| Hypertension (% +ve) | ... | 46.31% | 52.56% | 6.25% (z=1.66, P=0.049)* |
| Hypercholesterolemia (% +ve) | ... | 39.20% | 46.02% | 6.82% (z=1.83, P=0.034)* |
| History of CVD (% +ve) | ... | 26.14% | 32.67% | 6.53% (z=1.90, P=0.029)* |
| Smoking (% current) | ... | 6.53% | 5.97% | −0.85% (z=−0.31, P=0.378) |
| Diabetes (% +ve) | ... | 9.09% | 12.22% | 3.13% (z=1.34, P=0.090) |
| BMI | ... | 27.57±4.25 | 27.65±4.46 | −0.02±1.49 (z=−0.24, P=0.812) |
| MMSE | ... | 28.97±1.26 | 28.72±1.46 | −0.25±1.48 (z=−3.01, P=0.003)* |
| Mean overall cortical thickness, mm | ... | 3.17±0.15 | 3.12±0.15 | −0.05±0.11 (z=−8.18, P=0.001)* |
| WMH volume (% of ICV) | ... | 0.76±0.71 | 1.02±0.91 | 0.26±0.28 (z=17.50, P<0.001)* |

BMI indicates body mass index; CVD, cardiovascular disease; ICV, intracranial volume; IQ, intelligence quotient; MMSE, Mini Mental State Examination; and WMH, white matter hyperintensity.

*P<0.05.
sex. Inclusion of age 11 intelligence quotient as a controlling variable made little difference to the cortical t-maps (data not shown).

Warm colors in Figure 2 show regions where greater WMH volume was associated with reduced cortical thickness. The significance of cross-sectional associations is shown on the left panel of Figure 3. There were consistent patterns of negative cross-sectional associations at 73 and 76 years within and surrounding the Sylvian fissure extending superiorly to the parietal lobe, posteriorly to the occipital lobe, and anteriorly to the frontal lobe. Therefore, having greater WMH volume was cross-sectionally associated with reduced cortical thickness in specific regions only, that is, within and surrounding the Sylvian fissure. Associations between greater WMH volume and greater cortical thickness in superior regions (cold colors in Figure 2) were all nonsignificant.

A scatter plot of the peak cross-sectional association in the Sylvian fissure and surrounding area at 76 years (ρ=−0.276; Q=0.004) is shown in Figure 3.

**Longitudinal Vertex-Wise Regression Models of Regional Cortical Thickness and WMH Volume**

Longitudinal vertex-wise associations between (1) baseline WMH volume and change in cortical thickness (gC-wB in Figure 2); (2) baseline cortical thickness and change in WMH volume; and (3) change in WMH volume and change in cortical thickness (C-C in Figure 2) were all nonsignificant across the cortex (Q>0.05; Figure 3). Therefore, having a larger WMH volume at 73 years (or larger change in WMH volume between 73 and 76 years) did not predict greater cortical thinning between 73 and 76 years at any part of the cortex. Neither did a thinner cortex at 73 years predict greater WMH growth between 73 and 76 years.

The longitudinal association between WMH change and overall mean cortical thickness change was descriptively much stronger in subjects with MMSE≤26 (r=−0.220; P=0.41 versus r=−0.003; P=0.96) but this was not statistically significant potentially because of the small number of subjects with MMSE≤26 (N=16).

**Discussion**

We have replicated cross-sectional associations between greater WMH volume and regional cortical thinning around the Sylvian fissure15,9–12; however, we found no longitudinal associations between (1) baseline WMH volume and change in cortical thickness; (2) baseline cortical thickness and change in WMH volume; or (3) change in WMH volume and change in cortical thickness at any part of the cortex in community-dwelling subjects from 73 to 76 years. The cross-sectional associations found here between greater WMH volume and

---

**Table 2. Spearman Correlation Matrix of Overall Mean Cortical Thickness and WMH Changes and Independent Variables**

| Variable | Cort chng | WMH chg | BMI | Sex | CVD | DIAB | HCHL | HBP | SMOK | EDU | IQ11 | MMSE | Age |
|----------|-----------|---------|-----|-----|-----|------|------|-----|------|-----|-----|------|-----|
| **rho (P Value)** | | | | | | | | | | | | | |
| Cort chng | | | | | | | | | | | | | |
| WMH chg | 0.029 | (0.595) | | | | | | | | | | | |
| BMI | −0.056 | −0.043 | | | | | | | | | | | |
| (0.306) | (0.441) | | | | | | | | | | | |
| Sex | 0.058 | 0.038 | −0.002 | | | | | | | | | | |
| (0.292) | (0.486) | (0.964) | | | | | | | | | | |
| CVD | 0.017 | −0.050 | 0.088 | −0.148 | | | | | | | | | |
| (0.753) | (0.370) | (0.109) | (0.007)* | | | | | | | | | |
| DIAB | 0.058 | 0.025 | 0.149 | −0.078 | 0.098 | | | | | | | |
| (0.295) | (0.652) | (0.007)* | (0.159) | (0.076) | | | | | | | | |
| HCHL | 0.050 | 0.055 | 0.106 | 0.003 | 0.179 | 0.220 | | | | | | |
| (0.361) | (0.317) | (0.054) | (0.956) | (0.001)* | | | | | | | | |
| HBP | 0.052 | −0.010 | 0.195 | −0.018 | 0.216 | 0.150 | 0.283 | | | | | |
| (0.350) | (0.855) | (<0.001)* | (0.747) | (<0.001)* | (<0.001)* | (<0.001)* | | | | | |
| SMOK | 0.025 | 0.003 | 0.045 | −0.084 | 0.115 | 0.068 | 0.068 | 0.024 | | | | |
| (0.648) | (0.962) | (0.417) | (0.126) | (0.038)* | (0.218) | (0.218) | (0.658) | | | | |
| EDU | −0.051 | 0.074 | −0.171 | 0.039 | −0.019 | −0.084 | 0.011 | −0.020 | −0.086 | | | |
| (0.355) | (0.183) | (0.002)* | (0.462) | (0.728) | (0.126) | (0.846) | (0.717) | (0.119) | | | |
| IQ11 | 0.060 | −0.029 | −0.142 | 0.073 | −0.006 | −0.072 | 0.019 | −0.017 | −0.121 | 0.528 | | |
| (0.273) | (0.604) | (0.010)* | (0.185) | (0.913) | (0.191) | (0.738) | (0.756) | (0.028)* | (<0.001)* | | |
| MMSE | 0.035 | 0.012 | −0.064 | 0.104 | −0.043 | −0.061 | −0.035 | −0.048 | −0.107 | 0.234 | 0.378 | |
| (0.529) | (0.835) | (0.250) | (0.059) | (0.432) | (0.271) | (0.521) | (0.386) | (0.052) | (<0.001)* | (<0.001)* | |
| Age | −0.128 | 0.039 | −0.004 | 0.086 | −0.015 | 0.022 | 0.011 | −0.003 | −0.048 | −0.009 | −0.014 | −0.077 | |
| (0.020)* | (0.483) | (0.941) | (0.119) | (0.783) | (0.692) | (0.849) | (0.951) | (0.387) | (0.864) | (0.802) | (0.164) | |

BMI indicates body mass index; Cort chng, change in overall mean cortical thickness from 73 to 76 years; CVD, cardiovascular disease; DIAB, diabetes mellitus; EDU, education; HCHL, high cholesterol; HBP, high blood pressure; IQ11, intelligence quotient at age 11 years; MMSE, Mini Mental State Examination; SMOK, smoking; and WMH, white matter hyperintensity.

*P<0.05.
reduced cortical thickness in the region of the Sylvian fissure are consistent with previous GM volume, voxel-based morphometry, and cortical thickness studies. As with previous studies, the regions of cortical thinning–WMH associations that we found are not consistent with the most frequent WMH locations and areas of expansion, for example, centrifugally around the ventricles and superiorly towards the cranial vertex.

Our results suggest that WMH volume and cortical atrophy both worsen with age and that their individual differences share some causes—thus the cross-sectional associations. However, their changes from 73 to 76 years do not appear to be associated, and such correlated change would have been one indicator of a possible causal association. This conclusion is consistent with a longitudinal study in CADASIL patients that, although finding strong associations between lacunar lesions and cortical morphological changes, found a limited association between cortical morphological changes and WMH volume.

Strengths of our study include the ability to test longitudinal and cross-sectional associations between WMH volume and regional cortical thickness in a large sample of community-dwelling subjects. Other strengths include the age-homogeneous subjects with childhood intelligence quotient assessments and who are now in the eighth decade of life where the risk of dementia increases substantially. As well as the narrow age range, other novel features of the LBC1936 study (eg, all subjects are white Caucasian) may have minimized any potentially strong confounding effects that factors such as age, mixed ethnicity, and geography might have had in a less homogeneous sample. We measured WMH volume and cortical thickness using well-validated quantitative techniques that we manually checked and quality controlled post-pipeline for each subject at both time points. The raw brain MRI from which we measured WMH volume and cortical thickness were obtained using the same protocol on the same carefully maintained scanner at both time points.

Despite these strengths and our replication of previous cross-sectional findings, our study has limitations. The follow-up time of 3 years is a major limitation because it may not have been long enough to detect correlated changes between WMH and cortical thinning. We chose 3-year follow-up (rather than a longer time) to maximize subject retention and to be consistent with previous studies, for example, Austrian Stroke Prevention Study. Further, we have previously detected cross-sectional differences in WMH because of age within the narrow age band (<3 years) in the LBC1936 study. We are studying these subjects again at 6 years follow-up, and this may provide better evidence for any potentially causal relationships not identified here. We will attempt to ascertain the reasons for subjects lost to follow-up and will use full information maximum likelihood analyses, checked against analyses of completers, to minimize the effect of loss to follow-up. We defined change as individual measurements at 76 years minus measurements.

**Figure 2.** Cross-sectional (76y panel) and longitudinal (C-C, gC-wB, and wC-gB panels) t-maps of vertex-wise associations between cortical thickness and whole white matter hyperintensity (WMH) volume. Warm colors show where greater WMH volume is associated with reduced cortical thickness. The significance of these associations is shown in Figure 3. C-C indicates cortical thickness change and WMH volume change from 73 to 76 years; gC-wB, cortical thickness change and WMH volume at 73 years; wC-gB, WMH volume change and cortical thickness at 73 years.
at 73 years. We are aware that there are other ways of assessing change, for example, those often applied to cognitive variable change. However, the approach we used here is often applied to measure changes in brain morphology. Although the homogeneous nature of the LBC1936 cohort may provide increased power from having less need to control for confounding variables, for example, age and ethnicity, it limits the generalizability of our results. The longitudinal subjects we assessed here generally had higher MMSE than subjects who did not return for follow-up, and this may also limit the generalizability of our results, for example, longitudinal associations between WMH, and cortical thinning may be stronger in subjects with lower cognitive scores. We could not adequately test this here because of the small number of subjects with MMSE ≤ 26 (N=16), and future work is required to determine whether associations are stronger in cognitively impaired subjects. Although the locations of cross-sectional associations that we (and others) found between WMH and cortical thinning do not directly reflect common areas for WMH expansion, areas of associations were proximate to the tapetum of the corpus callosum fiber tracts which extend inferiorly and anteriorly into the temporal lobes. Further work is required to determine whether the locations of cross-sectional WMH and cortical thinning associations are because of an indirect connection through the perisylvian cortex and tapetum of the corpus callosum. Finally, it is difficult to prove or disprove a causal relationship between WMH and cortical thinning in observational studies. However, we adjusted for a number of variables known to influence WMH and cortical thinning, and although correlation is not necessarily causation, correlation is fundamental to causation. Therefore, the lack of longitudinal associations implies the lack of a causal relationship from 73 to 76 years. Notwithstanding these limitations, we have shown that although they both worsen with age, WMH volume progression and regional cortical thinning do not seem to have a relative/causal longitudinal relationship from 73 to 76 years. Further longitudinal studies with longer follow-up times and with more time points at different ages are required to determine whether causal relationships become apparent over longer periods of time and/or at different stages of life. The underlying cause(s) of WMH growth and cortical thinning have yet to be fully determined.

Acknowledgments
We thank the funders, participants, research centers, clinical, and administrative staff who contributed to the LBC1936 study (detailed fully at http://www.lothianbirthcohort.ed.ac.uk/).

Sources of Funding
This work was funded by a Scottish Funding Council Early Career Researcher grant to the Scottish Imaging Network—A Platform for Scientific Excellence (http://www.sinapse.ac.uk; DAD); Research into Ageing program grant (Drs Deary and Starr) and the Age UK-funded Disconnected Mind project (Drs Deary, Starr, and Wardlaw), with additional funding from the UK Medical Research Council (Drs Deary, Starr, and Wardlaw, and M.E. Bastin); and Scottish Funding Council through the Scottish Imaging Network—A Platform for Scientific Excellence (Dr Wardlaw).
Disclosures

Dr Wardlaw reports money (grants) paid to The University of Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council for her efforts on the LBC1936 study and various imaging projects. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Dr Wardlaw reports money (grants) paid to The University of Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council for her efforts on the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Dr Wardlaw reports money (grants) paid to The University of Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council for her efforts on the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.

Study. Dr Deary reports money paid to him for board membership of the LBC1936 study and various imaging projects. Dr Deary reports the following research support: Charitable Trust, and Scottish Funding Council for his efforts on the Edinburgh from Medical Research Council, Age UK, Row Fogo Charitable Trust, and Scottish Funding Council.
Progression of White Matter Disease and Cortical Thinning Are Not Related in Older Community-Dwelling Subjects

David Alexander Dickie, Sherif Karama, Stuart J. Ritchie, Simon R. Cox, Eleni Sakka, Natalie A. Royle, Benjamin S. Aribisala, Maria Valdés Hernández, Susana Muñoz Maniega, Alison Pattie, Janie Corley, John M. Starr, Mark E. Bastin, Alan C. Evans, Ian J. Deary and Joanna M. Wardlaw

*Stroke.* 2016;47:410-416; originally published online December 22, 2015;
doi: 10.1161/STROKEAHA.115.011229

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/47/2/410
Free via Open Access

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/12/20/STROKEAHA.115.011229.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/
地域在住の高齢者において白質病変の進行と皮質の非薄化は関連しない

Progression of White Matter Disease and Cortical Thinning Are Not Related in Older Community-Dwelling Subjects

David Alexander Dickie, PhD1,2,6; Sherif Karama, MD, PhD7; Stuart J. Ritchie, PhD1,4; Simon R. Cox, PhD1,2,4; Elein Sarkka, MSc1,2,5; Natalie A. Royle, PhD1,2,4; Benjamin S. Aribisala, PhD1,2,6; Maria Valdés Hernández, PhD1,2,6; Susana Muñoz Maneiga, PhD1,2,6; Alison Pattie, BSc1; Janie Corley, MA1; John M. Starr, MD3,5; Mark E. Bastin, DPhil1,2,6; Alan C. Evans, PhD7; Ian J. Deary, PhD1,4; Joanna M. Wardlaw, MD1,2,4,6

1 Brain Research Imaging Centre, 2Neuromaging Sciences, Centre for Clinical Brain Sciences, 3Department of Psychology, 4Centre for Cognitive Ageing and Cognitive Epidemiology, 5Alzheimer Scotland Dementia Research Centre, 6The University of Edinburgh, Edinburgh, UK; Scottish Imaging Network, a Platform for Scientific Excellence (SINAPSE) Collaboration; 7Department of Neurology and Neurosurgery, McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal, QC, Canada; and 8Department of Psychiatry, Douglas Mental Health University Institute, McGill University, Verdun, QC, Canada

地域在住の高齢者では、MRI により、脳白質高信号病変（WMH）の拡大と皮質の非薄化を認めることが多い。このような所見の発現には顕著な個人差があるが、WMH 容積の増加や皮質厚の減少が非常に高度にみられる人には、脳卒中、認知症、認知機能障害および身体機能障害のリスクが高くなる。こうした状況に効果的に介入するためには、WMH の拡大と皮質の非薄化に関する因子と、両者がお互いの原因となっているかを理解することが非常に重要である。

全脳の WMH 容積の拡大と、灰白質（GM）の容積、密度、厚さの減少との間に関連があることは、横断的研究で明らかにされている。WMH 容積が大きい人は、一般的に、前頭側頭葉および頭頂葉下部領域における皮質の厚さおよび密度が比較的減少している。他の関心領域解析による研究でも、デフォルトモードネットワークにおいて全脳 WMH 容積と局所 GM 容積（内側側頭葉構造、頭頂葉下部、楔部を含む）の間に、同様の横断的な負の関連パターンが認められている。また、小血管病の患者では、WMH 容積の増加が前頭側頭葉および頭頂葉下部領域の構造的な連絡性的低下に関連する。

ただし、これらの研究は横断的であり、原因または結果の方向性を確認することはできない。また、WMH 容積との関連が認められた皮質の非薄化領域は、WMH が最も多く発生する領域（例えば、脳室から遠心性に広がる領域、頭頂皮質）と、向かう上方向の領域など）と重なっていたわけではない。ベースラインで大きな WMH 容積および WMH 容積の顕著な拡大が、その後の局所的な皮質の非薄化に関連するか否かを明らかにするには、縦断的研究が必要である。以前には、皮質下梗塞および白質脳症を伴う常染色体優性遺伝性脳動脈硬化症（CADASIL）患者を対象に、皮質の形態と WMH 容積の増加との関連性を検討
する繰り返し研究が実施された。その結果、CADASILにおいても、ラクナ病変は皮質内の微血管障害によるものと推定される。WMH容積と皮質内の微血管障害との関係は、これまでの研究においても一部確認されている。

本研究では、WMHと局所皮質の菲薄化との関係を明らかにするため、地域住民を対象に、WMH容積の変化と皮質厚の変化との関連を73歳から76歳において継続的に評価した。WMHと菲薄化した皮質領域との関係を明らかにするとすれば、（1）ベースラインの全脳WMH容積と数年前の皮質厚の変化、（2）ベースラインの皮質厚とWMH容積の変化、（3）WMH容積の変化と皮質厚の変化との関連が検出できるという仮説を立てた。上記の仮説を検証するため、Lothian Birth Cohort 1936 (LBC1936)研究の地域住民の被験者において、約73歳から約76歳の時点においてWMH容積と皮質の菲薄化の経過を評価した。

研究の承認および被験者の同意

LBC1936研究のプロトコルは、Multicentre Research Ethics Committee for Scotland (MREC/01/0/56)およびLothian Research Ethics Committee (LREC/2003/2/29)の承認を受けた。すべての被験者から書面でインフォームド・コンセントを得た。

被験者

LBC1936研究の被験者は351例（男性のN=202）を評価した。この研究では、全脳MRI検査、臨床評価、認知機能評価がベースラインの画像検査の時点（平均年齢72.71 ± 0.72歳）および追跡調査の時点（平均年齢76.40 ± 0.64歳）で実施された。これらの被験者は意図的に行われており、単純に、脳画像の撮像に同意し、ベースラインおよび追跡調査時点における完全なデータセットが揃っていた被験者である（図1）。

認知症の可能性をスクリーニングするため、ベースラインと追跡調査の時においてミネンマルステート検査（MMSE）のスコアを記録した。MMSEに基づく被験者の除外は行われず、MMSEは補正のための変数として取り入れた。臨床研究施設への来院時、血管病変の既往、高血圧の既往、髄コレステロール血症、糖尿病、喫煙状態、心血管疾患の既往、肥満指数（BMI）を記録した。血管疾患の既往には、自己申告による冠動脈疾患、脳卒中、末梢動脈疾患、大動脈疾患を含め、血液検査の採取と血圧測定も実施したが、完全なデータセットが揃った被験者数をできるだけ増やし、かつ過去の研究との一貫性を保つため、これらの変数（収縮期血圧、糖化ヘモグロビンなど）は解析に含めなかった。血压などの既往歴の変数が、収縮期血圧などの測定値の変数よりもWMHと強く関連することは既報の通りである。

脳MRI画像

脳MRIの撮像パラメーターについては以前に詳しく報告した。簡単に述べると、厳密な品質保証プログラムで管理されている1.5ティスタの同一のGE Signa Horizon HDX臨床画像診断装置（General Electric, Milwaukee, WI）を用い、ベースラインと追跡調査の時点においてすべての被験者で脳MRI検査を実施した。ベースラインと追跡調査の撮像プロトコルは同じであり、T1, T2, T2*強調画像およびFLAIR画像を得た。

WMH容積と皮質厚の測定

MRIのT1, T2, T2*強調画像およびFLAIR画像を結合してセグメント化する、検証済みのマルチスペクトル画像処理方法により、頭面内容積および全脳WMH容積をmL単位で測定した。皮質の厚さは、Montreal Neurological Instituteで開発された完全自動Civet画像処理パイプラインにより測定した。Civetは、皮質全体で81,924ヵ所の頂点（GMとWMの表面の垂直距離）において、その厚みを測定する。我々は明確性を期して、この頂点を頭頂（cranial vertex）ではなく、GMとWM表面の垂直距離と呼んでいる。

過去に報告された方法に従い、手作業によりWMH
容積マスクと皮質厚マップを検証した17-19,22,23。具体的には、STRIVE（Standards for Reporting Vascular Changes on Neuroimaging）ガイドラインに従い、WMHをセグメント化し、WMHマスクから皮質および皮質下梗塞を手作業で除去した19。さらに、皮質厚20-22およびWMH17-23の測定値の信頼性を検証したが、その結果については以前に報告している。

統計解析
統計解析はすべてMatrix Laboratory（MATLAB）R2014a（©1994-2014 The MathWorks, Inc）で実施した。73歳から76歳の全身体脂厚（全皮質外周の平均厚）、全脳WMH容積、補正に用いた連続変数（BMIなど）の変化は、対応のあるr検定で評価した。正の相関がみられたWMH分布の対数変換により、結果への影響はほとんどみられなかったため、解析を簡略化するために最初の尺度（頭蓋内容積の比率）のまま検討した。高血圧の既往ならびに、補正に用いた連続変数の変化、比率のz検定を評価した。

皮質を頂点とする回帰分析はSurfStat MATLABツールボックスで実施した（http://www.math.mcgill.ca/keith/surfstat）。皮質を頂点とする回帰モデルとして次の5つを検証した。すなわち、(1)各頂点における73歳時の皮質の厚さ＝従属変数、73歳時のWMH容積＝独立変数、(2)各頂点における76歳時の皮質の厚さ＝従属変数、76歳時のWMH容積＝独立変数、(3)各頂点における皮質の厚さの変化＝従属変数、73歳時のWMH容積＝独立変数、(4)各頂点における73歳時の皮質の厚さ＝従属変数、WMH容積の変化＝独立変数、(5)各頂点における皮質の厚さの変化＝従属変数、WMH容積の変化＝独立変数，とするモデルである。「76歳時の各測定値」－「73歳時の各測定値」を、WMHおよび皮質厚の変化量と定義した。

多重比較の補正是偽の発見率を用い、Q値、すなわち偽の発見率で補正したP値を算出し、すべての頂点に関する回帰分析で閾値を0.05とした23。他の研究者らの報告に従い23、すべてのモデルにおいて性別、MMSE、日齢、学歴（教育年数）、BMI、VRFで調整した。さらに、小児期11歳時)の知能指数を調整変数として加え、WMHと皮質厚との関連が、発症前の認知機能レベルの影響によるものか否かを検証した。

| 結 果 |

ベースラインのみ来院した被験者群と追跡調査にも来院した被験者群との比較

皮質厚測定の追跡調査（76歳時）のために再来院した被験者と再来院しなかった被験者とを比較したところ、ベースラインの時点（73歳）において、全体の平均皮質厚（3.11 mm vs. 3.10 mm，t = 0.75，P = 0.46）、WMH容積（頭蓋内容積の0.78% vs. 0.84%，t = -0.78，P = 0.43）、血管腔病の既往（27.3% vs. 26.2%，z = 0.29，P = 0.40）、現在の喫煙（6.5% vs. 8.2%，z = 0.76，P = 0.22）、高血圧（44.0% vs. 43.1%，z = -0.71，P = 0.24）、高血圧（46.5% vs. 51.8%，z = 1.2，P = 0.11）、糖尿病（10.1% vs. 11.3%，z = -0.43，P = 0.33）、BMI（27.8 vs. 27.8，t = -0.21，P = 0.84）、学歴（教育年数）10.85年 vs. 10.89年、

| 表1 ベースラインおよび追跡調査における認知機能、VRF、皮質厚、WMHのデータとその変化 |
|-----------------|--------|--------|--------|--------|
| N = 351 | 11歳 | 73歳 | 76歳 | 3年間の変化 |
| 小児期IQ | 102.21 ± 15.75 | ... | ... | ... |
| 性別(％、男性) | ... | 57.39 | 57.39 | ... |
| 学歴、教育年数 | ... | 10.86 ± 1.18 | 10.86 ± 1.18 | ... |
| 高血圧(％、陽性者) | ... | 46.31% | 52.56% | 6.25%(z = 1.66，P = 0.049)* |
| 高コレステロール血症(％、陽性者) | ... | 39.20% | 46.02% | 6.82%(z = 1.83，P = 0.034)* |
| CVDの既往(％、陽性者) | ... | 26.14% | 32.67% | 6.53%(z = 1.90，P = 0.029)* |
| 喫煙(％、現喫煙者) | ... | 6.53% | 5.97% | 0.85%(z = -0.31，P = 0.378) |
| 糖尿病(％、陽性者) | ... | 9.09% | 12.22% | 3.13%(z = 1.34，P = 0.090) |
| BMI | ... | 27.57 ± 4.25 | 27.56 ± 4.46 | -0.02 ± 1.49(t = -0.24，P = 0.812) |
| MMSE | ... | 28.97 ± 1.26 | 28.72 ± 1.46 | -0.25 ± 1.48(t = -3.01，P = 0.003)* |
| 全体の平均皮質厚、mm | ... | 3.17 ± 0.15 | 3.12 ± 0.15 | -0.05 ± 0.11(t = -3.18，P < 0.001)* |
| WMH容積(IVCに対する％) | ... | 0.76 ± 0.71 | 10.2 ± 0.91 | 0.26 ± 0.28(t = 17.50，P < 0.001)* |

BMI：基準指数、CVD：心血管病変、IVC：頭蓋内容積、IQ：知能指数、MMSE：ミニメンタルステート検査、WMH：自覚高信号病変。

*P < 0.05。
ベーサラインおよび追跡調査における認知機能、VRF、皮質厚、WMH のデータとその変数
ベーサラインおよび追跡調査における認知機能、VRF、皮質厚、WMH のデータおよびその変化を表 1 に示す。高血圧、高コレステロール血症、心血管疾患のある被験者の比率是有意に増加し、MMSE についてもベーサライン（73 歳時）から追跡調査（76 歳時）までに有意な低下がみられた。全体において、平圧平均厚は一般に加齢とともに減少し（変化に関する Cohen の d = 0.45）、WMH 容積は一般に加齢とともに増加した（変化に関する Cohen の d = 0.93）（表 1）。全脳の変化と独
立変数との関係を示す Spearman 相関マトリックス（表 2）から、一般に高齢の被験者ほど、皮質の薄化がより顕著であることが明らかになった（ρ = 0.13, P = 0.02）。その他の独立変数ではいずれにおいても、WMH および皮質薄化に対する効果（時点の効果を超える）は限定的で部分的であった（表 2）。

全体の平均皮質厚と WMH 容積との横断的および縦断的な総合相関性（global correlation）
全体の平均皮質厚と WMH 容積の横断的な総合相関性（global correlation）は、73 歳治（r = 0.06, P = 0.27）および76 歳治（r = 0.08, P = 0.12）ともに有意ではなかった。統計検定において、73 歳時 WMH 容積と全体の平均皮質厚の変化（r = 0.07, P = 0.19）、（2）73 歳時の全体の平均皮質厚と WMH 容積の変化（r = 0.01, P = 0.82）、（3）WMH 容積の変化と全体の平均皮質厚の変化（r = 0.02, P = 0.67）の対による縦断的な総合相関性に関しても、有意ではなかった。

| 表 2 全体の平均皮質厚の変化、WMH の変化、独立変数に関する Spearman 相関マトリックス | モデュレーション | Cort chg WMH chng BMI 別性 CVD DIAB HCHL HBP SMOG EDU IQ11 MMSE 年齢 |
|-------------------------------|---------|----------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| モデュレーション | | | | | | | | | | | | | | |
| P | | | | | | | | | | | | | | |
| BMI | | -0.056 -0.043 | | | | | | | | | | | | |
| 別性 | | 0.058 0.038 -0.002 | | | | | | | | | | | | |
| CVD | | 0.017 -0.050 0.088 -0.148 | | | | | | | | | | | | |
| DIAB | | 0.058 0.025 0.149 -0.078 0.098 | | | | | | | | | | | | |
| HCHL | | 0.050 0.055 0.106 0.003 0.179 0.220 | | | | | | | | | | | | |
| HBP | | 0.052 -0.010 0.195 -0.018 0.216 0.150 0.283 | | | | | | | | | | | | |
| SMOG | | 0.025 0.003 0.045 -0.084 0.115 0.068 0.068 0.024 | | | | | | | | | | | | |
| EDU | | -0.051 0.074 -0.171 0.039 -0.019 -0.084 0.011 -0.020 -0.066 | | | | | | | | | | | | |
| IQ11 | | 0.060 -0.029 -0.142 0.073 -0.006 -0.072 0.019 -0.017 -0.121 0.528 | | | | | | | | | | | | |
| MMSE | | 0.035 0.012 -0.064 0.104 -0.043 -0.061 -0.035 -0.048 -0.107 0.234 0.378 | | | | | | | | | | | | |
| 年齢 | | -0.128 0.039 -0.004 0.086 -0.015 0.022 0.011 -0.003 -0.048 -0.009 -0.014 -0.077 | | | | | | | | | | | | |

BMI：肥満指数。Cort chng：73 歳から 76 歳における全体の平均皮質厚の変化。CVD：心血管疾患。DIAB：糖尿病。EDU：学歴。HCHL：高コレステロール。HBP：高血圧。IQ11：11 歳時の知能指数。MMSE：ミンニルスレート検査。SMOG：喫煙。WMH chng：73 歳から 76 歳における白質高信号病変の変化。

*P < 0.05。
皮質厚と全体の白質高信号病変（WMH）容積との皮質頂点による関連性を示す横断的（76歳）および縦断的（C-C, gC-wB, wC-gB）tマップ。慢性化、WMH容積の増加が皮質厚の減少に関連する領域を示す。これらの関連の有意性は図3に示す。C-C：73歳から76歳における皮質厚の変化とWMH容積の変化。gC-wB：皮質厚の変化と73歳時のWMH容積、wC-gB：WMH容積の変化と73歳時の皮質厚。

局所の皮質厚およびWMH容積の横断的皮質を頂点とする回帰モデル

76歳時の皮質厚とWMH容積に関する横断的皮質頂点回帰モデルを図2に示す。皮質厚とWMH容積との関連性のパターンは73歳時と76歳時ではほぼ同じであったため、73歳時の横断データは示していない。すべてのモデルにおいてVRF, MMSE, 学歴、性格による補正を行った。11歳時の知能指数を調整変数に追加したことによる皮質のtマップの差は、ほとんどみられなかった（データ非表示）。

図2の暖色表示は、WMH容積の増加に関連して皮質厚の減少が認められた領域を示す。横断的関連の有意性を図3の左側に示す。73歳および76歳の時点において、シルビウス裂の内部および周辺部、外頭葉、外頭葉にまた、頭部方向へと広がる負の横断的関連性の一定パターンが認められた。したがって、WMH容積の増加が特定領域、すなわちシルビウス裂の内部および周辺部の皮質厚減少と横断的関連していた。上方領域（図2の冷色）では、WMH容積の増加と皮質厚の増加との関連はすべて有意ではなかった。

局所の皮質厚およびWMH容積の縦断的皮質を頂点とする回帰モデル

（1）ベースラインのWMH容積と皮質厚の変化（図2のgC-wB）、（2）ベースラインの皮質厚とWMH容積の変化（図2のwC-gB）、（3）WMH容積の変化と皮質厚の変化（図2のC-C）について、皮質頂点の縦断的関連性はすべて有意ではなかった（図3, Q > 0.10）。したがって、73歳時のWMH容積（または73歳から76歳時のWMH容積の変化量）が大きいことにより、73歳から76歳におけるいずれかの皮質領域の非薄化が顕著であることは予測されなかった。また、73歳時の皮質がより薄いことにより、73歳から76歳までにおけるWMHの拡大は予測されなかった。

WMHの変化と全体の平均皮質厚の変化との間の縦断的関連は、記述上、MMSE 26以下者の検査者で大幅に顕著であったが（r = -0.220, P = 0.10 vs. r = -0.003）。
皮質厚と白質高信号病変（WMH）容積との皮質頂点による横断的（X-S）および縦断的（L）関連の有意性。73歳（データ非表示）と76歳の時点において、シルピウス裂内部および周辺部で頭頂葉、前頭葉、前頭頂方向へと広がる負の横断的関連の一定パターンが認められた（左）。無着色のグレーのQマップ（右）は、皮質厚とWMH容積との間に有意な縦断的関連がみられないことを示す。

考察

本研究では、73～76歳の地域在住の被験者において、WMH容積の増加とシルピウス裂周辺領域の皮質還流化との間に横断的関連が認められた。しかし、皮質のどの部分においても、1）ベースラインのWMH容積と皮質厚の変化、2）ベースラインの皮質厚とWMH容積の変化、3）WMH容積の変化と皮質厚の変化について、縦断的関連は認められなかった。本研究で認められたWMH容積の増加とシルピウス裂領域の皮質厚の減少との横断的関連は、以前に行われたGM容積10、ボクセルベースの形態計測5,11、皮質厚3に関する研究の結果を一致する。過去の研究と同様に、本研究で皮質の萎縮化とWMHとの関連が確認された領域は、WMHの多発部とその拡大範囲4（脳室から遠心状に広がる領域や頭頂方向など）とは異なる。

本研究の結果から、WMH容積と皮質萎縮はいずれも加齢とともに悪化し、これらの個人差には一部の共通する原因が関与しており、それが横断的関連をもたらしていることが示唆される。一方、73歳から76歳に生じるこれらの変化には関連がないとみられ、もし、こうした相関的な変化があるとすれば、因果関係を示す1つの指標として認められたはずである。この結論はCADASIL患者の縦断的研究と一致し、これ以前の研究では、ラクナ病変と皮質の形態の変化に強い関連を認めながらも、皮質の形態の変化とWMH容積との間にはわずかな関連しか認められなかった13,15。

本研究の強みは、地域在住の大規模な被験者集団において、WMH容積と局所皮質厚との縦断的および横断的関連を検証できたことである。もう1つの強みは、小児期に知能指数検査を受けており、本研究時点で認知症リスクが大きく高まる70代に入った同年代の被験者を対象としたことである26。年齢範囲が狭いこと以外に、LBC1936研究の他の目新しい特徴（全被験者が白人など）も、潜在的な強い交絡因子を最小限に抑えたと考えられる（均質性の低い被験者集団では、年齢、民族の混合、地理といった因子が影響を及ぼした可能性がある）。WMH容積と皮質厚の測定には十分に検証された定量方法を使用し、手作業で確認の上、バイブレイン処理後に両時点および各被験者で品質管理を行った17,20,22。WMH

\[ P = 0.96\]。MMSE 26以下の被験者が少なかったことが潜在的理由となり（N = 16）、統計学的な有意差は認められなかった。
容積と皮質厚の測定に用いた脳MRIの元画像は、両点で同じプロトコルに従い、厳密に管理されている同じ画像診断装置で撮像した7。以上の強みに加え、これまでの横断的研究結果を再現したとはいえ3,5,11,本研究にも限界がある。3年間の追跡調査期間はWMHと皮質の非薄化との相関的な変化を検出するのに十分であった可能性があり、これが大きな限界の1つである。被験者をできるだけ維持し、Austrian Stroke Prevention Studyなどの過去の研究1,2との一致性もできるだけ高めるため、本研究では追跡調査期間（より長期ではなく）3年間とした。また、我々は以前に、WMH LBC1936研究の狭い年齢範囲により（3歳未満）22でWMHに横断的な差を検出している。現在、これらの被験者を対象に約6年後時点の追跡調査を実施中であるが、これによって、本研究で特定されなかった潜在的な因果関係の良好なエビデンスが明らかになる可能性がある。今後は、追跡不能例の理由を確認の上、完全な情報による最大尤度の解析法を使用し、試験完了例の解析と照らし合わせることで、追跡不能例の影響を最小限に抑える予定である。本研究では、「76歳時の各測定値」を「73歳時の各測定値」を「変化」と定義した。我々は、これ以外にも変化の評価方法は、認知機能の変数の変化に大きく使用されるもの22を含め、複数あることを認識している。しかし、本研究で使用したアプローチ、脳の形態変化の測定にしばしば使用されている20。LBC1936研究のコホートは均質性が高く、年齢や家族などの交絡変数を調整する必要性が低いため、検出力が高いが、本研究結果の一般化できる可能性は制限されている。本研究で縦断的に評価した被験者は全般に、追跡調査のため再連院しなかった被験者に比べ、MMSEが高かった。例えば、認知機能スコアが低い被験者では、WMHと皮質の非薄化との間により強い縦断的関連を認める可能性があり、これも本研究結果を一般化できる可能性を低下させていることが考えられる。本研究では、MMSE 26以下の被験者数（N = 16）が少なかったため、この点を十分に検証することはできなかった。今後の研究では、認知機能が低下した被験者が関連がより強くかかるか否かを確認する必要がある。本研究において他の研究3,5,8,11でWMHと皮質の非薄化との間に横断的関連が認められた位置は、WMHの拡大がよくみられる領域を直接反映していないが、関連が示された位置は、側頭葉へと下方および前方に延びる脳神経束の帯板（tapetum）に最も近かった21。今後の研究により、WMHと皮質の非薄化との間に横断的関連が認められた位置について、その理由がシルピウス裂周囲の皮質および脳幹の間接的な連絡によるものか否かを評価する必要がある。最後に、WMHと皮質の非薄化との因果関係の有無を観察研究で証明するのは困難である。しかし、本研究では、WMHと皮質の非薄化に影響することができ知られている多くの変数について補正した。また、相関は必ずしも因果関係を意味しないが、因果関係の基礎である22,33。したがって、73歳から76歳において縦断的関連が認められなかったことは、因果関係が存在しないことを示唆している。以上の限界はあるものの、両者について加齢による悪化がみられ、一方、73歳から76歳においてWMH容積の進行と局所皮質の非薄化に関し、相関性/因果関係を示す縦断的関連はない考えられた。さらに長い期間や異なるライフステージでの因果関係の有無を明らかにするためには、追跡調査期間を延長し、評価時点の年齢をより多く設定した縦断的研究が必要である。WMHの拡大と皮質の非薄化の根本原因はまだ完全には解明されていない。

謝辞
LBC1936研究（詳細：http://www.lothianbirthcohort.ed.ac.uk）をご協力いただいた資金提供者、被験者、研究施設、臨床スタッフおよび運営スタッフに感謝する。

研究費の財源
本研究はScottish Imaging Network—A Platform for Scientific Excellence（http://www.sinapse.ac.uk, DAD）への助成金, Research into Ageingプロジェクト助成金（Dr DearyおよびDr Starr）, Age UKの支援するDisconnected Mindプロジェクト（Dr Deary, Dr Starr, Dr Wardlaw）による支援を受けた。また, UK Medical Research Council（Dr Deary, Dr Starr, Dr Wardlaw, Dr M.E. Bastin）, Scottish Funding CouncilからScottish Imaging Network—A Platform for Scientific Excellenceへの助成金（Dr Wardlaw）による支援を受けた。

情報開示
Dr Wardlawは, LBC1936研究およびさまざまな画像研究プロジェクトへの協力に対し, Medical Research Council, Age UK, Row Fogo Charitable Trust, Scottish Funding Councilからエジンバラ大学への金銭（助成金）の支払いがあったことを報告している。Dr Dearyは, LBC1936研究への協力に対し, Medical Research CouncilおよびAge UKからエジンバラ大学への金銭（助成金）の支払いがあったことを報告している。Dr Dearyは, Medical Research Councilの委員としての
