Vascular risk factors, large-artery atheroma, and brain white matter hyperintensities

ABSTRACT

Objective: To determine the magnitude of potentially causal relationships among vascular risk factors (VRFs), large-artery atheromatous disease (LAD), and cerebral white matter hyperintensities (WMH) in 2 prospective cohorts.

Methods: We assessed VRFs (history and measured variables), LAD (in carotid, coronary, and leg arteries), and WMH (on structural MRI, visual scores and volume) in: (a) community-dwelling older subjects of the Lothian Birth Cohort 1936, and (b) patients with recent nondisabling stroke. We analyzed correlations, developed structural equation models, and performed mediation analysis to test interrelationships among VRFs, LAD, and WMH.

Results: In subjects of the Lothian Birth Cohort 1936 (n = 881, mean age 72.5 years [SD ±0.7 years], 49% with hypertension, 33% with moderate/severe WMH), VRFs explained 70% of the LAD variance but only 1.4% to 2% of WMH variance, of which hypertension explained the most. In stroke patients (n = 257, mean age 74 years [SD ±11.6 years], 61% hypertensive, 43% moderate/severe WMH), VRFs explained only 0.1% of WMH variance. There was no direct association between LAD and WMH in either sample. The results were the same for all WMH measures used.

Conclusions: The small effect of VRFs and LAD on WMH suggests that WMH have a large “nonvascular,” nonatheromatous etiology. VRF modification, although important, may be limited in preventing WMH and their stroke and dementia consequences. Investigation of, and interventions against, other suspected small-vessel disease mechanisms should be addressed.

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GLOSSARY

ABPI = ankle-brachial pressure index; BP = blood pressure; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; IMT = intima-media thickness; LAD = large-artery atheromatous disease; Lothian Birth Cohort 1936; MSS = Mild Stroke Study; RCT = randomized controlled trial; SVD = small-vessel disease; VRF = vascular risk factor; WMH = white matter hyperintensity.

White matter hyperintensities (WMH) are a major component of cerebral small-vessel disease (SVD) and substantially increase the risk of dementia, stroke,1 and physical disability.2 Despite this considerable clinical and societal impact, the causes of SVD and WMH are poorly understood.3

WMH are associated with several common vascular risk factors (VRFs) offering potentially modifiable targets: hypertension,4–9 diabetes, hypercholesterolemia, smoking, and possibly carotid stenosis.10 Hypertension was associated with WMH progression6–9; better blood pressure (BP) control delayed WMH progression in observational studies9 and in one randomized controlled trial (RCT).11 However, there are anomalies: in larger RCTs, antihypertensive treatment did not prevent WMH progression,12 intensive BP reduction did not prevent recurrent lacunar stroke,13 and the associations between BP and WMH were often weak14 or disappeared with correction for age and baseline WMH, both strong predictors of WMH progression.15–17 Statins

From the Centre for Clinical Brain Sciences (J.M.W., F.N.D., M.V.H., Z.M., M.B., M.S.D.) and Centre for Cognitive Ageing and Cognitive Epidemiology (M.A., M.V.H., A.J.G., M.B., J.M.S., I.J.D.), University of Edinburgh, UK.

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did not prevent WMH progression,\textsuperscript{18} and dual (vs mono) antiplatelet therapy increased death in patients with lacunar stroke without preventing recurrence.\textsuperscript{19,20}

These discrepancies question the strength of associations among VRFs, atheroma, and SVD, contrasting with the effectiveness of antihypertensive, antiplatelet drugs and statins in preventing atheromatous ischemic stroke. We hypothesized that if WMH mainly occur secondary to VRFs or are a “small-vessel” form of atheroma, then either of these or both should explain most WMH variance. We determined how much WMH variability was attributable to VRFs and/or large-artery atheromatous disease (LAD) in 2 cohorts.

METHODS The derivation cohort is the Lothian Birth Cohort 1936 (LBC1936),\textsuperscript{21} community-dwelling older subjects born in 1936, now being studied to determine lifetime influences on aging. The replication cohort is a prospective study of patients with recent nondisabling ischemic stroke, the Mild Stroke Study (MSS).\textsuperscript{22} The LBC1936 subjects were aged 71 to 74 years (mean 72.5, SD 0.72) at assessment. The MSS patients were aged 34 to 95 years (mean 74, SD 11.62). In both groups, we obtained medical history, physiologic measurements, blood samples, brain MRI, and carotid Doppler ultrasound imaging (full details in references 21–23).

We recorded hypertension, diabetes, hypercholesterolemia (all medically diagnosed and/or on relevant drugs), ischemic heart disease, peripheral vascular disease or other circulatory problems (all diagnosed by general practitioner or hospital doctor), and smoking (current vs stopped >1 year ago or never smoked). History of stroke was also collected in the LBC1936 cohort. All MSS participants had an index stroke (on clinical criteria and MRI with diffusion imaging\textsuperscript{22}) as a study entry criterion.

In the LBC1936 cohort, we measured systolic and diastolic BP, each 3 times sitting and standing during a 4-hour Clinical Research Facility assessment. We also measured the following: ankle-brachial pressure index (ABPI), carotid intima-media thickness (IMT) in the common carotid artery and carotid bulb on both sides (mean of 3 measures by Framingham\textsuperscript{24} and by manual caliper measurements), carotid flow velocities, maximum stenosis affecting the internal carotid artery/bulb/common carotid artery,\textsuperscript{25} hemoglobin A1c (HbA1c), plasma total cholesterol and...
[A] This model is the total association between LAD and WMH. (B) Hierarchical association with VRFs controlled. (C) Total effect of VRFs on WMH. (D) The mediation model (see the text). Standardized regression coefficients (parameter weights) are shown adjacent to each path. Each arrow is directed from a predictor variable to the outcome variable. In model B, the 0.828 indicates that approximately 70% of the variance in LAD is explained by VRFs and the 0.111 indicates that approximately 2% of the variance in WMH is explained by VRFs. The 0.292 and 0.984 adjacent to the lateral arrows in model B indicate the variance that is unexplained by VRFs on LAD and WMH, respectively. The estimates shown in the figure are for WMH measured using combined periventricular and deep Fazekas scores. The estimates for the model using other WMH measures are shown in table 2. $R^2$ is the WMH model $R^2$ value; $s^2$ is the residual variance. LAD = large-artery atheromatous disease; LBC1936 = Lothian Birth Cohort 1936; VRF = vascular risk factor; WMH = white matter hyperintensity.
| Variable                                      | LBC1936 | Descriptive | MSS | Descriptive |
|----------------------------------------------|---------|-------------|-----|-------------|
| Sample no.                                   | 861     |             | 257 |             |
| Age, mean (SD)                               | 72 (0.7)|             | 74 (12) |     |
| Sex                                          |         |             |     |             |
| Female                                       | 446 (52)|             | 88 (34) |    |
| Male                                         | 415 (48)|             | 169 (66) |   |
| Large-artery disease                         |         |             |     |             |
| Intima-media thickness, mm (common carotid artery)

|  | [0.4, 0.8] | 228 (28) |
|  | [0.7, 1.1] | 521 (64) |
|  | [1.1, 1.4] | 56 (7)   |
|  | [1.4, 1.7] | 10 (1)   |
| Stenosis (%, NASCET, left carotid)

|  | [1, 24] | 656 (81) |
|  | [25, 49] | 146 (18) |
|  | [50, 74] | 10 (1)   |
|  | [75, 100] | 3 (0.4)  |
| Stenosis (%, NASCET, right carotid)

|  | [1, 24] | 627 (77) |
|  | [25, 50] | 170 (21) |
|  | [50, 75] | 14 (2)   |
|  | [75, 100] | 4 (1)    |
| Ischemic heart disease                       |         |             |     |             |
| No                                           | 613 (71)|             | 206 (80) |   |
| Yes                                          | 248 (29)|             | 52 (20)   |  |
| Peripheral vascular disease                  |         |             |     |             |
| Pain in the leg when walking or in bed at night|       |             |     |             |
| No                                           | 496 (58)|             | 247 (96) |   |
| Yes                                          | 365 (42)|             | 11 (4)    |  |
| Ankle-brachial pressure index

|  | [0.54, 0.87] | 63 (8) |
|  | [0.87, 1.19] | 509 (68) |
|  | [1.19, 1.52] | 167 (22) |
|  | [1.52, 1.85] | 12 (7)   |
| Vascular risk factors                        |         |             |     |             |
| Hypertension                                  |         |             |     |             |
| No                                           | 439 (51)|             | 100 (39) |   |
| Yes                                          | 422 (49)|             | 158 (61) |   |
| Diabetes                                     |         |             |     |             |
| No                                           | 767 (89)|             | 221 (86) |   |
| Yes                                          | 94 (11) |             | 37 (14)   |  |
| Hypercholesterolemia                         |         |             |     |             |
| No                                           | 508 (59)|             | 166 (65) |   |
| Yes                                          | 353 (41)|             | 90 (35)    |  |
| Plasma cholesterol, mmol/L

|  | [2, 4] | 226 (27) |
|  | [4, 6] | 452 (55) |
|  | [6, 8] | 141 (17) |
|  | [8, 10] | 8 (1)    |
We performed a similar analysis in the MSS cohort by testing groupings of VRF and LAD measured variables and WMH (figure e-1).

We used Mplus version 6.131 to fit the measurement and structural models of regression relationships between the variables simultaneously. We estimated model parameters by weighted least-squares and assessed the indirect effect in the mediation model (model D) using a bias-corrected bootstrapped confidence interval derived by Monte Carlo sampling.32,33 We controlled for sex in all variables but not age (adjusting for age had negligible effect and all subjects were of very similar ages, SD 0.71 years).

We examined estimates of factor loadings (unstandardized, standardized, and squared multiple correlation coefficient) and several indices of model fit: the comparative fit index ($\chi^2$ indicates acceptable fit), the root mean square error of approximation (0.06 indicates acceptable fit), and the maximum modification index (indicates the degree of greatest local strain within the model in terms of a potential reduction in model $\chi^2$).

**RESULTS** Primary analysis. In the LBC1936, 861 subjects (415, 48% male) of mean age 72.5 years (SD 0.7, range 71–74 years) had full clinical assessment and carotid imaging; 681 subjects completed brain imaging and provided WMH scores and volumes. Of the 861, 422 (49%) had hypertension, 94 (11%) had diabetes, 248 (29%) had ischemic heart disease, the median carotid stenosis was 20%, and 33% had moderate or severe WMH scores (table 1).

Multivariate measurement models to derive the VRF and LAD latent variables (figure 1) indicate that all observed variables contributed significantly to the latent variable ($p < 0.05$) except for smoking ($p = 0.66$), which nonetheless we included in the VRF model. The models all fitted the data well (figure 1).

Structural models (figure 2) show the standardized estimates for WMH measured using Fazekas scores. Without accounting for VRFs (figure 2A), there was a small but reliable shared variance of approximately 4% and 6% between LAD and WMH, depending on which WMH score was used (all 3 WMH measures were statistically significant; table 2).

| Table 1 Continued |
|-------------------|
| Variable          | LBC1936 | Descriptive | MSS  | Descriptive |
|                   | Plasma HbA1C (n subjects) | Blood glucose, mmol/L |
|                   | [4, 6] | 440 (58) | [3, 8] | 129 (86) |
|                   | [6, 7] | 275 (36) | [8, 13] | 11 (7) |
|                   | [7, 8] | 41 (5) | [13, 17] | 8 (5) |
|                   | [8, 10] | 8 (1) | [17, 22] | 2 (1) |
| Smoker            | Ex or never smoked | 789 (92) | No | 107 (43) |
|                   | Yes | 72 (8) | Yes | 144 (57) |
| Diastolic BP, mm Hg* | [50, 66] | 92 (11) | [37, 62] | 15 (6) |
|                   | [66, 82] | 474 (55) | [62, 86] | 123 (51) |
|                   | [82, 98] | 276 (32) | [86, 111] | 97 (40) |
|                   | [98, 114] | 19 (2) | [111, 135] | 5 (2) |
| Systolic BP, mm Hg* | [82, 117] | 38 (4) | [98, 130] | 52 (22) |
|                   | [117, 151] | 446 (52) | [130, 162] | 121 (50) |
|                   | [151, 186] | 351 (41) | [162, 194] | 53 (22) |
|                   | [186, 220] | 26 (3) | [194, 226] | 14 (6) |
| White matter hyperintensities | R + L combined | Right | Left |
| Fazekas score periventricular | 0 | 23 (4) | 9 (4) | 9 (4) |
|                   | 1 | 444 (65) | 132 (52) | 133 (52) |
|                   | 2 | 171 (25) | 65 (26) | 64 (25) |
|                   | 3 | 43 (6) | 48 (19) | 48 (19) |
| Fazekas score (deep white matter overall) | 0 | 111 (16) | 40 (18) | 43 (17) |
|                   | 1 | 430 (63) | 140 (55) | 136 (54) |
|                   | 2 | 120 (18) | 36 (14) | 37 (15) |
|                   | 3 | 20 (3) | 38 (15) | 38 (15) |

**Abbreviations:** BP = blood pressure; HbA1c = hemoglobin A1c; LBC1936 = Lothian Birth Cohort 1936; MSS = Mild Stroke Study; NASCET = North American Symptomatic Carotid Endarterectomy Trial.

Data are counts (%) unless otherwise indicated; numbers in square brackets are quartile boundaries.

*The numbers reported are the counts and percentages in 4 intervals, the thresholds chosen to give 4 equal intervals of the observed range of each variable.

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However, when VRFs were accounted for (figure 2B), the total association between LAD and WMH became smaller and nonsignificant with all 3 WMH measures (table 2). Therefore, the small association between LAD and WMH seen in model A before VRFs were considered was mainly explained by VRFs acting through LAD. In addition, VRFs were a far stronger predictor of LAD than of WMH, accounting for approximately 70% of variation in LAD burden (standardized parameter weight 0.828) but less than 2% of variation in WMH (standardized parameter weight 0.111).

The mediation model (figure 2, C and D) indicates that the standardized total effect of VRFs (figure 2C, effect c in table e-1), explained no more than a small (2%) but significant variance in WMH. Exploring the effect of LAD as a mediating variable for VRFs (figure 2D, appendix e-1, and table 1) did not explain the missing variance in WMH, instead emphasizing the presence of large influences on WMH that are not captured in history or concurrent measures of VRFs or LAD.

The magnitude of individual VRF contributions to WMH (table e-2, a and b) were all small; e.g., the largest individual contributions to WMH variance were hypertension (2.4%) and smoking (0.8%).

Replication in the stroke cohort. The MSS patients (n = 257) had similar mean age although a wider range (74.2, SD ± 11.6 years, range 34–95 years) than the LBC1936, but more MSS patients were hypertensive (61%), smoked (57.4%), and had moderate to severe WMH scores (44.3% periventricular, 29.6% deep; table 1, figure e-1). A combined hierarchical factor analysis model showed that VRFs explained 35% of LAD variance (standardized parameter weight 0.594) but only 0.1% of WMH variance (standardized parameter weight −0.033), with hypertension again being the strongest individual factor.

DISCUSSION WMH are a huge health problem, doubling the risk of dementia and trebling the risk of stroke. We were surprised to find that although VRFs explained 70% of the burden of LAD and hypertension was the strongest single risk factor for WMH, all common VRFs combined failed to account for 98% of WMH. Furthermore, there was no direct association between LAD and WMH; any apparent association was through a coassociation with VRFs. We found the same results in 2 separate cohorts, one community-dwelling, the other with stroke, regardless of how WMH were assessed. The mediation model highlighted the absence of key factors to account for most of the WMH variance.

The proportion of subjects with hypertension in the LBC1936 (49%) was similar to the proportion in other similar aging studies, and the proportion MSS patients (61%) was similar to stroke patients elsewhere (55%–66%). Hypertension was the strongest risk factor for WMH in LBC1936, as in other observational studies. Consistent with our results, large increments in diastolic BP (e.g., 10 mm Hg above the mean baseline diastolic BP of 83 ± 11 mm Hg) were associated with small differences in WMH in cross-sectional studies (e.g., 1.21% larger WMH volume); large increments in systolic BP (20 mm Hg) were associated with small increases in WMH volume (2.5 mL) at follow-up. The association between WMH and hypertension applied only to diastolic or systolic BP, indicating variation in strength of association. Most studies adjusted for age, but not for baseline WMH, a strong predictor of WMH progression, although baseline adjustment should be handled cautiously because it may distort estimates of change in longitudinal studies. Others also noted a lack of independent association between WMH and BP in patients with stroke.

The modest VRF effect is supported by RCTs. Antihypertensive treatment had no effect in the large PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) MRI substudy (n = 771) after an average of 28 months: insufficient BP lowering was blamed for not preventing WMH progression, but the average systolic/diastolic BP reduction in PROFESS (3.0/1.3 mm Hg) was identical to the systolic/diastolic BP increment (3.0/2.0 mm Hg) blamed for WMH progression over only 14 months of follow-up in a 584-patient observational cohort. Intensive vs usual antihypertensive treatment did not significantly reduce recurrent lacunar stroke. In RCTs of other

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**Table 2** Results for hierarchical (structural) models A and B in figure 2

| WMH measure                          | Model A | Model B | β₁    | β₂    | R² | R² | p * |
|--------------------------------------|---------|---------|-------|-------|----|----|-----|
| Fazekas score (combined)             | 0.202 (p < 0.01) | 0.135 (p = 0.28) | 0.828 (p < 0.01) | 0.111 (p = 0.03) | 0.708 | 0.016 |
| WMH as % of intracranial volume      | 0.238 (p < 0.01) | 0.208 (p = 0.13) | 0.830 (p < 0.01) | 0.114 (p = 0.02) | 0.711 | 0.016 |
| WMH as % of brain tissue             | 0.249 (p < 0.01) | 0.220 (p = 0.11) | 0.830 (p < 0.01) | 0.118 (p = 0.02) | 0.711 | 0.016 |

Abbreviation: LAD = large-artery atheromatous disease; VRF = vascular risk factor; WMH = white matter hyperintensity.

Model A is total association. Model B is hierarchical with VRFs controlled. r is the correlation between LAD and WMH. β₁ and β₂ are standardized regression coefficients: LAD on VRFs and WMH on VRFs. R² and R² are R² values: LAD on VRFs and WMH on VRFs. Sex is controlled in all variables.
VRF modifications that reduce adverse outcomes from LAD, statins had no effect in preventing WMH progression, and dual vs mono antiplatelet therapy caused excess hemorrhage and death without reducing recurrent stroke in patients with lacunar stroke. However, data on lipids and WMH are lacking and should be addressed in further studies.

Our study strengths include the large sample (total n = 1,118), a development (n = 861) and replication (n = 257) cohort, and robust statistics. The narrow age range of the LBC1936 subjects minimized the powerful confounding effect of age on WMH, LAD, and VRFs. The results were the same in the MSS patients whose ages spanned 6 decades and had more vascular disease. The LBC1936 subjects are all white Caucasian, minimizing any influence of ethnic differences on VRFs. We have no reason to think that our subjects are unrepresentative of other Caucasian cohorts (Scotland has one of the highest vascular disease rates in the world). A third of the LBC1936 and approximately 40% of MSS patients had moderate to severe WMH. We found the same results for WMH assessed by visual rating and volume. We carefully excluded infarcts from the WMH volume: inadvertent inclusion of infarcts in “WMH volume” may have inflated associations among VRFs, LAD, and WMH previously.

The study had limitations. We lacked continuous BP monitoring but used the average of 3 systolic and diastolic BP readings obtained over 4 hours at sitting positions by trained technicians. Most other studies of WMH and BP have not used continuous BP measures. Perhaps our subjects were too old: BP decreases between middle and old age, WMH may be more closely associated with long-standing elevated BP from middle age. However, BP measured 3 years earlier at approximately age 69 was very similar; our “history of hypertension” captured prior hypertension and was the strongest risk factor. Age 72 is not particularly “old.” The stroke cohort including much younger subjects produced the same result. Future studies could test other BP parameters. Adding other imaging markers of SVD might increase the sensitivity for detecting causal relationships. Some variables were missing but without evidence of bias and we used all available data. The high prevalence of peripheral vascular disease in the LBC1936 may represent overreporting but is counterbalanced by the objective measure of peripheral vascular disease with the ABPI and by the MSS where history and examination were very detailed and the same associations were found.

Our results suggest that WMH have a large “nonvascular” component. The remaining unexplained 98% of WMH variance will hinder advances in prevention of dementia, stroke, and physical dependency in aging. Treating hypertension and diabetes, lowering cholesterol, and stopping smoking are important. Lifestyles that minimize vascular risk should be encouraged. Other modifiable risk factors (e.g., vitamins), dietary factors (e.g., salt), inflammation, and other nonvascular contributing mechanisms should be sought.

**AUTHOR CONTRIBUTIONS**

J.M. Wardlaw, M. Allerhand, I. Deary, F. Doudal: study concept and design. F. Doudal, A. Gow, I. Deary, J. Starr, M. Bastin, M. Dennis, J.M. Wardlaw: acquisition of data. M. Allerhand, M. Valdez Hernandez, Z. Morris, F. Doudal, M. Dennis, J. Deary, J. Starr, J.M. Wardlaw: analysis and interpretation. I. Deary, M. Dennis, F. Doudal, M. Allerhand, M. Valdez Hernandez, A. Gow, J.M. Wardlaw: critical revision of the manuscript for important intellectual content. J.M. Wardlaw, I. Deary: study supervision.

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**DISCLOSURE**

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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