**Effect of Normal Aging Versus Hypertension, Abnormal Body Mass Index, and Diabetes Mellitus on White Matter Hyperintensity Volume**

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**Background and Purpose**—The natural history of white matter hyperintensity (WMH) progression resulting from normal aging versus comorbid vascular insults remains unclear. Therefore we investigated age-related differences in WMH volumes among a group with comorbid hypertension, abnormal body mass index, and diabetes mellitus to a normal aging group drawn from the same population lacking any of these comorbidities.

**Methods**—WMH volumes were acquired using 3T MRI for 2011 Dallas Heart Study participants. The slope of the WMH versus age regression was compared between normal and comorbidity groups <50 and ≥50 years of age where a change in slope was demonstrated.

**Results**—Aging was linearly associated with greater log WMH volume for both normal (P<0.0001) and comorbidity (P<0.0001) groups. Beyond 50 years of age, more rapid increases in WMH volumes for age were seen in the group with comorbidities (P<0.0001) but not in the normal group (P=0.173). The between-group difference in slope of expected WMH for age was significantly greater in the comorbidity groups ≥50 years of age (P=0.0008) but not <50 years of age (P=0.752).

**Conclusions**—After 50 years of age, but not before, comorbid hypertension, obesity, and diabetes mellitus were associated with significantly larger WMH volumes for age compared with a normal aging group lacking these conditions. These results support the assertion that age-related differences in WMH volumes are significantly increased in the presence of comorbidities, but the effect is only detectable after 50 years of age. *(Stroke. 2014;45:255-257.)*

**Key Words:** aging ■ white matter hyperintensity

**White matter hyperintensity (WMH) seen on MRI is a marker of cerebral microvascular disease and confers risk for developing cognitive impairment and Alzheimer disease.** The natural history of WMH progression attributable to normal aging itself versus the cumulative consequence of vascular insults linked to comorbidities, such as hypertension, obesity, and diabetes mellitus, remains unclear. Therefore, we investigated age-related differences in WMH volumes on 3T MRI in the multiethnic population on the basis of the Dallas Heart Study (DHS) between a normal aging group and the remaining participants aging with comorbid hypertension, obesity, or diabetes mellitus.

**Methods**

**Study Population and Participants**

The DHS is a large, multiethnic probability-based population sample of adult English- or Spanish-speaking Dallas County residents. The DHS was approved by the University of Texas Southwestern Medical Center Institutional Review Board, and each participant gave written informed consent to participate. Between September 2007 and December 2009, 3T brain MRI and clinical evaluation were obtained for 2077 participants. Twenty-nine participants were excluded for identified pathology, imaging artifact, or error precluding automated WMH analysis, and 37 were excluded for self-reported stroke, resulting in 2011 participants for this study. For more details on the study population, see Methods in the online-only Data Supplement.

**Normal and Pathological Aging Definitions**

Hypertension was defined as an average systolic blood pressure ≥140 mm Hg or an average diastolic blood pressure ≥90 mm Hg from 3 separate measurements or current treatment with antihypertensive medication. Diabetes mellitus was defined by self-report accompanied by the use of antihyperglycemic medication and elevated serum glucose (fasting, >126 mg/dL [7.0 mmol/L] or nonfasting glucose, >200 mg/dL [11.1 mmol/L]); including type 1 and 2 together. In the remaining 1725 (86%) participants with comorbidities, there were 973 (56%) with hypertension, 245 with diabetes mellitus (14%), and 1578 (91%) with abnormal body mass index (BMI).

**Procedures and Measures**

Systolic and diastolic blood pressures (mmHg) were reported as the mean of the final 3 of 5 recordings. Hypertension therapy, sex,
and ethnicity were self-reported. BMI was calculated on the basis of measured height and weight. Serum glucose was obtained from early morning venous sampling and fasting state verified.

Outcome Variable
The outcome measure for our study was WMH volume (milliliter) automatically quantified from 2D fluid attenuated inversion recovery and 3D magnetization prepared-rapid acquisition gradient echo (MP-RAGE) brain imaging acquired during Dallas Heart Study return clinic visit 2 (DHS2) on a 3T MRI system (Achieva; Philips Medical Systems), the details of which have been described previously.7

Statistical Analysis
Interaction testing was performed for the presence of comorbidities and age in predicting WMH. To explore an age-related threshold effect for WMH, an analysis using cubic splines was performed to obtain a mathematically optimal fitted curve of log WMH by age for the entire cohort. Within- and between-group difference in slope of the WMH versus age regression was compared for the normal and comorbidity groups using a linear contrast test of the $\beta$ coefficients and interaction terms before and after 50 years of age, at which a threshold was identified in spline analysis. Analyses were adjusted for sex, ethnicity, and intracranial volume as estimated by Framingham Software Library. Predicted WMH volumes were obtained from the linear regression analysis by substituting 5-year increments of age into the model. Statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Inc; Cary, NC).

Results
Characteristics for the 2011 participants are shown in Table 1. In addition to having significantly greater BMI, blood pressure, and serum glucose, the comorbidity groups also had a higher proportion of blacks, fewer whites, and fewer women ($P<0.001$ for each).

A significant interaction was seen between age and the presence of comorbidities in predicting WMH ($P=0.005$), indicating that the relationship varied with increasing age. A threshold effect was seen with greater increase in log WMH per year starting in the sixth decade, therefore the analysis was stratified at that point. For the normal aging group, each year of age was associated with 0.006 greater log of WMH volume (SD, 0.003; $P=0.029$). No significant age-related threshold of greater WMH volume after 50 years of age was seen in the normal group ($P=0.173$). For individuals with comorbidities, each year of total age was associated with 0.007 greater log WMH (SD, 0.001; $P<0.0001$) with an additional increase for each year after age 50 of 0.018 log WMH (SD, 0.002; $P<0.001$; Figure). Before 50 years of age, there was no statistically significant difference between normal and comorbidity groups in slope ($P=0.752$), but after 50 years of age, the slopes differed significantly ($P=0.008$). No significant age-related differences were seen for between-groups categorized by the presence or absence of each of the 3 individual comorbidities (for more details, see Results in the online-only Data Supplement). Estimated WMH volumes for normal and comorbidity groups and between-group differences are depicted in Table 2.

Discussion
After 50 years of age but not before, our results show comorbid hypertension, abnormal BMI, and diabetes mellitus to be associated with significantly larger WMH volumes for

| Table 1. Basic Demographics for Normal Aging and Aging With Comorbidity Groups |
|---------------------------------|-------------------------------|-----------------|
| Characteristics                  | Normal Aging (n=285) | Aging With Comorbidities (n=1726) |
| Black                            | 89 (31%)            | 802 (47%)        |
| White                            | 131 (46%)           | 555 (32%)        |
| Hispanic                         | 46 (16%)            | 287 (17%)        |
| Other/missing                    | 19 (7%)             | 82 (5%)          |
| Women                            | 173 (61%)           | 1000 (58%)       |
| Age, y                           | 46.4±10.1           | 50.6±10.5        |
| Age ≥50 years                    | 103 (36%)           | 800 (54%)        |
| BMI                              | 22.5±1.8            | 30.7±5.2         |
| Systolic BP                      | 117.5±11.2          | 132.6±18.4       |
| Diastolic BP                     | 74.4±7.2            | 81.3±8.8         |
| Blood glucose                    | 89.0±8.5            | 102.5±37.6       |

Frequency data are n (%) and continuous data are n±SD. Definition of normal and comorbidity groups based on absence or presence, respectively, of hypertension, diabetes mellitus, abnormal BMI. BMI indicates body mass index; and BP, blood pressure.

| Table 2. Expected WMH Volumes for Selected Ages |
|-----------------------------------------------|-------------------------------|
| Age, y                                       | Normal | Comorbidities | Difference |
| 30                                           | 0.62 (0.05) | 0.6 (0.03)     | 0.02 (0.06) |
| 35                                           | 0.66 (0.04) | 0.64 (0.02)    | 0.02 (0.04) |
| 40                                           | 0.71 (0.03) | 0.68 (0.02)    | 0.03 (0.04) |
| 45                                           | 0.76 (0.03) | 0.73 (0.02)    | 0.03 (0.04) |
| 50                                           | 0.81 (0.05) | 0.78 (0.02)    | 0.03 (0.05) |
| 55                                           | 0.93 (0.04) | 1.03 (0.02)    | 0.1 (0.04)  |
| 60                                           | 1.06 (0.07) | 1.36 (0.03)    | 0.3 (0.08)  |
| 65                                           | 1.21 (0.12) | 1.79 (0.06)    | 0.58 (0.13) |
| 70                                           | 1.39 (0.19) | 2.35 (0.11)    | 0.96 (0.22) |

WMH indicates white matter hyperintensity.
Small, age-related differences in WMH volume were seen before 50 years of age, with no significant difference between normal aging and aging with comorbid hypertension, abnormal BMI, diabetes mellitus. The presence of these comorbidities resulted in significantly larger age-related differences in WMH volumes after 50 years of age. No significant age-related differences were seen for each of the comorbidities when evaluated individually, highlighting the importance of considering synergism among comorbidities. Compared with normal aging, aging with these comorbidities resulted on average in 0.3±0.08 mL or 1.3× more WMH at 60 years of age, 0.58±0.13 mL or 1.5× more at 65 years of age, and 0.96±0.22 mL or 1.7× more at 70 years of age.

The age of onset for expression of WMH in the population and the expected volume for age, particularly for younger individuals, have been uncertain.8 Our study provides a set of normative values for WMH volumes both for healthy aging and aging in the presence of comorbidities in a multiethnic cohort.

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**Disclosures**
None.

**References**
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Supplemental Material

Methods: Study Population and Participants

The DHS is a large multi-ethnic probability-based population sample of adult English- or Spanish-speaking Dallas County residents, with intentional oversampling of African Americans to comprise 50% of the study cohort\(^1\). The DHS was approved by the University of Texas Southwestern Medical Center Institutional Review Board, and each participant gave written informed consent to participate. Between September 2007 and December 2009, 3072 original DHS-1 subjects were asked to participate in a continuation of the original study termed the Dallas Heart Study-2. Family members and spouses of the original participants were able to participate in DHS-2. Of 2077 participants with brain imaging in DHS-2, 29 were excluded for identified pathology, imaging artifact or error precluding automated WMH analysis and 37 were excluded for self-reported stroke. This resulted in 2,011 DHS-2 subjects with quantification of WMH volumes on 3T brain imaging for this study.

In the original DHS-1 imaging cohort ethnicity composition was Black 50.1%, White 31.2%, Hispanic 16.7% and other 2.0%. Females accounted for 55.2%. In the final DHS2 brain imaging cohort for this study the ethnic composition was Black 45.7%, White 35.1%, Hispanic 17.1% and other 2.1%. Females accounted for 58.3%. The follow up sample therefore contained a slightly lower proportion of Blacks, a higher proportion of Whites and fairly similar proportion of Hispanic participants and a slightly higher proportion of females. The original DHS-1 study design was enriched for African Americans, however, so the study sample retains a proportion higher than that of Dallas County from which it was drawn. Previous work has also shown that the DHS-2 study sample is composed of individuals from DHS-1 with slightly lower risk factor severity\(^2\), which may result in slightly underestimating the effect of comorbidities in the population and their impact on WMH.

Results

In secondary analysis, the age related differences in WMH volumes were also evaluated among groups based on presence or absence of each individual risk factor with adjustment for gender, ethnicity and intracranial volume. Among 973 with hypertension compared with 1038 without no significant age related differences in WMH were seen before \((p=0.60)\) or after \((p=0.16)\) age 50. Among 245 with diabetes compared with 1766 without no significant age related differences in WMH were seen before age 50 \((p=0.44)\) but neared significance after age 50 \((p=0.053)\). Among 1528 with abnormal BMI compared with 423 with normal BMI no significant age related differences in WMH were seen either before \((p=0.45)\) or after \((p=0.49)\) age 50.

References for Supplementary Material