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Regional White Matter Hyperintensity Volume and Cognition Predict Death in a MultiEthnic, Community Cohort of Older Adults

Anne F. Wiegman[1,*], **Irene B. Meier, MS**[1,*], **Frank A. Provenzano, MS**[1], **Nicole Schupf, PhD**[1,2,3], **Jennifer J. Manly, PhD**[1,2,4], **Yaakov Stern, PhD**[1,2,4], **José A. Luchsinger, MD**[3,5], and **Adam M. Brickman, PhD**[1,2,4]

[1]Taub Institute for Research on Alzheimer's Disease and the Aging Brain. College of Physicians and Surgeons, Columbia University. New York, NY USA

[2]G.H. Sergievsky Center. College of Physicians and Surgeons, Columbia University. New York, NY USA

[3]Department of Epidemiology, Mailman School of Public Health, Columbia University. New York, NY USA

[4]Department of Neurology, College of Physicians and Surgeons, Columbia University. New York, NY USA

[5]Department of Medicine, College of Physicians and Surgeons, Columbia University. New York, NY USA

To the editor

White matter hyperintensities are distributed patches of increased lucency on T2-weighted MRI commonly present in older adults. Studies have generally supported the idea that they reflect ischemic damage due to small vessel occlusive disease, but there is emerging evidence that the underlying pathology and clinical outcomes vary based on their regional distribution. For example, WMH in anterior regions may reflect pure ischemic damage whereas posterior distributions may reflect more heterogeneous pathology, including

Corresponding author: Adam M. Brickman, PhD, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, PS Box 16, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032, Tel: 212 342 1348, Fax: 212 342 1838, amb2139@columbia.edu.
*Authors contributed equally to work.

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vascular deposition of beta-amyloid.[1] We, and others, have shown that WMH distributed in posterior regions are associated with Alzheimer's disease specifically, whereas WMH distributed in frontal regions seem to be associated with cognitive impairment in general.[1]

Given these associations, we hypothesized that frontal lobe WMH may be a marker for biological brain aging and would therefore increase the risk of mortality among older adults. Because lower cognitive functioning has also been associated with increased risk for mortality, we also examined whether the effects of WMH are independent of cognition.

Subjects were participants in the Washington Heights/Inwood Columbia Aging Project, an ongoing longitudinal community-based study of aging and dementia in northern Manhattan comprising participants 65-and-older that started in 1992.[2] Participants were evaluated every 18-24months with neuropsychological, medical, and functional assessments. Starting in 2005, 769 participants underwent high-resolution structural MRI.[3] When scheduling follow-up visits, mortality was ascertained and confirmed with family members and/or review of the National Death Index until January 10, 2011. Subjects were followed-up for 3.93(SD=2.51) years after MRI.

Subjects were scanned with a Philips Intera 1.5 T MRI scanner (Best, the Netherlands). White matter hyperintensity quantification was derived from T2-weighted FLAIR images with in-house-developed software and regional volumes in frontal, temporal, parietal, and occipital lobes were determined with a standard “lobar” atlas.[1]

The neuropsychological battery evaluated memory, language, speed/executive functions, and visuospatial abilities.[4] To derive a global measure of cognition, an average of z-scores from each domain was used.

Cox regression analysis was used to examine whether regional WMH and cognition predicted time to death over the follow-up period. The time-to-event variable was the interval from MRI acquisition to date of death or last available follow-up date. Regional WMH volumes and the cognition summary score were entered simultaneously in the model; age, years of education, sex, and race/ethnicity were additional covariates.

Of the 769 individuals that were included here, 189(26.4%) did not survive over the follow-up period. The non-surviving subjects were older(82.33±6.66 vs. 79.70±5.16, t=5.64, p<0.001), more likely to be men(45% vs. 29%, $X^2(1)=16.547$, p<0 001), less likely to be Hispanic(28% vs. 40%, $X^2(2)=9.928$, p=0.007), had poorer cognition(-0.02±0.77 vs. 0.15±0.64, t=3.140, p=0.002), had greater frontal lobe(2.64±4.06 vs. 1.78±3.25, t=2.876, p=0.004) and total WMH(4.58±6.53 vs. 3.45±5.82, t=2.168, p=0.031) volume but were similar in years of education(10.60±4.91 vs. 10.44±4.86).

Frontal lobe WMH specifically(HR=1.093, 95CI:1.033-1.156,p=0.002), cognition(HR=0.632, 95%CI:0.467-0.855, p=0.003), male sex(HR:0.569, 95%CI: 0.411-0.786, p=0.001), and age(HR:1.069, 95%CI:1.038-1.101, p<0.001) reliably predicted mortality, whereas temporal, parietal, and occipital WMH, race/ethnicity, and education did not(all p's>0.05)[Figure 1]. Cognition and regional WMH volumes did not interact significantly when the model was re-run with interaction terms.

Our findings are consistent with previous studies that demonstrated the relation of WMH and decreased cognitive functioning to an increased risk of death.[5-8] The study extends the findings to examine the regional distribution of WMH. In the context of earlier observations[1, 9] our results emphasize the importance of consideration of the regional distribution of WMH depending on the targeted clinical outcome. When distributed in the parietal lobes, WMH are associated specifically with AD whereas frontal lobe WMH are

associated with cognitive impairment in general[1, 9, 10]. Frontal lobe WMH may be a more "pure" measure of ischemic damage and a reasonable marker for biological brain aging, whereas more posterior distributionmay be more associated with mixed pathology.[1]

Strengths of our study include its community-based design, large sample size, multi-ethnicity, and evaluation of subjects with a standardized, well validated, comprehensive neuropsychological battery and quantitative neuroimaging techniques. Quantitative regional WMH analysis represents an advantage over the semi-quantitative, rating scales typically used in other studies[6, 8] because of the increased reliability, full consideration of the volume distribution, and ability to quantify regional volumes. A limitation was our inability to ascertain cause of death. Our findings underline the need for more research on etiological factors of WMH. White matter hyperintensities are also increasingly found and reported in clinical MRI scans and may provide clinicians with a marker of overall health and survival. Research addressing whether treating and preventing small vessel disease based on MRI findings can to improve survival and other important clinical outcomes is needed.

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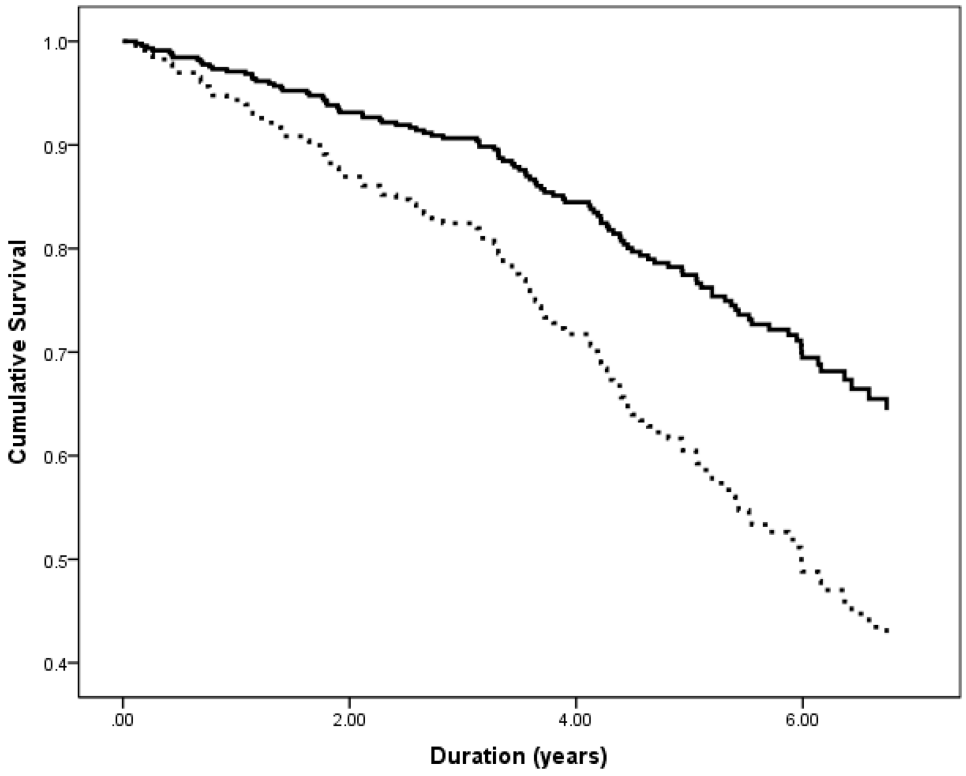

Figure 1.
Cumulative survival (y-axis) over time-to-event in years (x-axis). The solid line represents subjects with low levels of WMH in the frontal lobe (lower quartile), while the dotted line shows the survival for subjects with high levels of WMH in the frontal lobe (highest quartile).