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White Matter Lesions and the Risk of Incident Hip Fracture in Older Persons:

Results From the Progetto Veneto Anziani Study

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Abstract

Background—White matter lesions (WMLs) are associated with hypertension, an increased risk of falling, and impaired physical and cognitive performance that may affect the mechanical effect of falls.

Methods—We hypothesized that WMLs are a risk factor for hip fracture (HF). We studied a sample of 820 community-dwelling Italian persons 65 years and older from the cohort of the Progetto Veneto Anziani Study who underwent brain magnetic resonance imaging at baseline. Subjects were classified as having no lesions, focal lesions, or diffuse WMLs.

Results—Compared with those with no lesions, participants with diffuse WMLs were older, reported more falls, and had worse physical and cognitive performance, all factors implicated in the causal pathway to HF. During 9 years of follow-up, 51 HFs occurred. Hip fracture risk associated with diffuse WMLs markedly differed between participants younger than 80 years vs those 80 years and older. After adjustment among participants younger than 80 years, diffuse WMLs compared with no lesions were associated with a 2.7-fold (95% confidence interval, 1.1-7.1) increase in the risk of HF. Focal lesions were not statistically significantly associated with an increased risk of HF in the same age group (hazard ratio, 2.0; 95% confidence interval, 0.6-7.6). No associations between diffuse

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WMLs, focal lesions, and HF were evident among participants 80 years and older, possibly because of the limited sample size.

Conclusions—White matter lesions represent an independent risk factor for HF in persons younger than 80 years. Older persons with diffuse WMLs should be considered candidates for multifactorial interventions aimed at reducing the risk of falling and fractures.

White Matter Lesions (WMLs), frequently found on magnetic resonance (MR) imaging of the aging brain,[1] are attributed to cerebral microangiopathic changes.[2,3] They are particularly frequent in patients with cardiovascular risk factors such as hypertension[4-6] and diabetes mellitus.[7] Although the clinical significance of WMLs in older populations is uncertain,[8] studies have demonstrated that WMLs are associated with gait and balance impairment,[9-11] frequent falling,[12] depressive symptoms,[13] incident stroke,[14] cognitive impairment,[15] and urinary incontinence.[16]

Hip fracture (HF) is a catastrophic event in the life of older persons and is an important concern for public health.[17] Hip fractures are associated with a 15% to 30% 1-year mortality.[18,19] A large proportion of HF survivors experience a permanent loss of physical function[20] and have a high rate of nursing home admission.[21,22]

Hip fracture has a multifactorial origin,[23] and its occurrence is the consequence of an increased tendency to fall, loss of protective reflexes, and reduced bone strength.[24] Studies have shown that multiple impairments, individual behaviors, and hazardous environments can affect the risk of falling and fracturing[25,26] and that older persons have neurological, musculoskeletal, and sensory impairments that decrease their ability to use compensatory strategies for minimizing the probability of fracture during a fall.[27,28] The objective of this study was to explore whether WMLs, detected on brain MR imaging, are associated with an increased risk of HF in a cohort of older Italian men and women. We postulated that WMLs damage key areas of interhemispheric neural integration and may impair the ability to prevent lateral falls, which most likely result in HF.[29] To our knowledge, while preliminary results from a clinical series of patients with stroke suggest this association,[30] no previous studies have explored this association in a general population.

Methods

Study Population

The study population consisted of a subsample of an age- and sex-stratified random sample of 1599 persons from the Camposampiero site of the Progetto Veneto Anziani Study. This is an observational cohort study of the Italian population living in 2 separate geographical areas (Camposampiero and Rovigo) near the city of Padova designed to assess the effects of cardiovascular and osteoarticular disease on disability.[31] The baseline assessment started in 1995, finished in 1997, and was followed by 2 in-person follow-up visits (at 5 and 7 years), with ongoing morbidity and mortality surveillance. All participants provided informed written consent to study participation and to morbidity surveillance. The study design and protocol were approved by institutional review boards of the Veneto region health agencies (Azienda Unità Locale Socio Sanitaria 15 for Camposampiero and 18 for Rovigo). Participants were interviewed at their homes and were subsequently examined by physicians and nurses at the 2 study clinics using an extensive battery of clinical, instrumental, biochemical, and physical performance tests. The physician who performed the physical examination (G. Barbato and S.Z.) determined the disease status, integrating information from the interview, examination, use of medications, and medical records review. In Camposampiero, brain MR imaging was offered to participants who were willing to be referred to a nearby hospital (Cittadella) 1 week

later. Among these 1599 persons, 822 accepted the MR imaging examination. None of them were living in a nursing home.

Variables Measurement and Classification

Information on falls history, smoking status, physical activity, use of medications, urinary incontinence, physical activity level, demographic variables, Mini-Mental State Examination (MMSE) score, and activities of daily living (ADL) disability were collected during an in-person or a proxy interview. The MMSE was administered and proxy interviews were performed for participants who scored less than 5 on the first 10 questions of the MMSE. Only 15 of the MR imaging study participants (1.8%) received a proxy interview. Disability in ADLs was defined as the need for help from a person or as an inability to perform 1 or more of the following activities: bathing, dressing, eating, using the toilet, walking across a room, or transferring from bed to chair. Physical activity level was computed using 3 questions on the frequency of gardening, walking 500 m, and riding a bike farther than 1 km. Those who reported never doing these 3 activities were coded as sedentary, those who reported engaging in at least 2 of these activities every day or more than once a day were coded as active, and those in between were coded as intermediately active.

Instrumental and Physical Performance Tests

Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure (BP), measured using the Hypertension Detection Follow-up Program protocol,[32] was the mean of 3 readings while the subject was supine. Orthostatic hypotension was defined as present if at least a 20% or 20–mm Hg drop in systolic BP was recorded after at least 5 minutes of the subject's being in a supine position immediately and 2 minutes after standing. Instrumental determination of the bone mass was performed using quantitative ultrasonography of the heel (Achilles Plus; Lunar, Madison, Wisconsin). The instrument provides an index for bone stiffness and the *t* statistic and the *z* score (ie, the number of SDs compared with the mean distribution of the index for bone stiffness in young adults and in an age- and sex-matched population, respectively). In the present study, osteoporosis was defined as a *t* statistic less than −2.5 SD. For those who had unmeasurable values in both heels (1.5%), the physician adjudicated the presence of osteoporosis using previous medical records. Lower extremity function was assessed at the participant's home by measures of standing balance, walking speed, and ability to rise from a chair using the short physical performance battery administered by trained interviewers.[33] Participants were then classified using a summary performance score by adding categorical scores from the tests of standing balance, walking, and repeatedly rising from a chair.[34]

Disease and HF Adjudication

Disease presence at baseline and at follow-ups was determined by study physicians (G. Barbato and S.Z.) using all the information collected on each participant, including interview, surveillance, blood assays, hospital records, x-ray film readings, and physical examination. For participants who died before a follow-up, a proxy interview and a review of medical and hospital discharge records were performed at the expected follow-up time by nurses and physicians (G. Barbato and S.Z.) to adjudicate major incident conditions, including HF, occurring before death. Hip fracture was adjudicated as definite by study physicians only when self-reported or proxy-reported or if physical examination data suggesting HF were confirmed by hospital discharge records or x-ray films. No participants were completely lost to follow-up, including those who refused to return to the first (2%) or second (4%) follow-up; these participants were passively surveyed for morbidity and mortality through the Veneto region health care system.

MR Imaging

In all participants, axial T1-weighted, T2-weighted, and proton density–weighted cerebral MR imaging was acquired using a 1.0-T MR scanner. Magnetic resonance images were read by a single radiologist who was blinded to individual risk factors for brain lesions. Two participants had unreadable scans and were not considered in this analysis. Lesions were classified as focal lesions (1-2 lesions in any site, including cortical areas) or as diffuse WMLs (≥3 subcortical or periventricular lesions) that were hyperintense on T2-weighted transverse images and not hypointense on T1-weighted images. One participant with focal (truncal) lesions and diffuse WMLs was classified as having diffuse WMLs, and 1 participant with focal cortical lesions and diffuse WMLs was classified as having focal lesions.

Statistical Analysis

Unadjusted means and crude prevalence rates were compared using *t* and χ^2 tests. Age- and sex-adjusted means were computed from generalized linear regression models, while adjusted prevalence rates were computed using logistic or polychotomous regression models. Follow-up time was calculated as the time from baseline to the HF or as the time from baseline to death or censoring for those who did not experience an HF. Crude event rates were obtained by dividing the number of events by the accumulated number of person-years. Bivariate analyses were performed for the potential explanatory variables to assess their association with the risk of HF. Variables were classified according to their role as potential mediators in the hypothetical relationship between WMLs and HF. Then, confounders and potential mediators were included sequentially in the final Cox proportional hazards regression model and were retained if they were independently associated with the HF risk at $P<.10$. Summary estimates of the hazard ratio (HR) for HF, adjusted for potential confounders and mediators, were computed from Cox proportional hazards regression models by using the SAS PHREG procedure[35] (SAS Institute, Cary, North Carolina).

Results

The 822 subjects who agreed to participate in the MR imaging study were younger, less disabled, more educated, and more physically active, and had a lower prevalence of chronic diseases (48% vs 60% for osteoporosis and 8% vs 12% for diabetes mellitus) than the 777 subjects who refused. They were also more likely to have better performance on tests of physical (8.8 vs 5.9 on the short physical performance battery) and cognitive performance (25 vs 20 on the MMSE). No differences were noted for levels of systolic or diastolic BP or for the presence of orthostatic hypotension, while the use of high BP medications was less frequent among those who participated (30%) compared with those who did not participate (33%) in the MR imaging study.

Table 1 gives the characteristics of the study population according to incident HF, the main study outcome. The demographic and health-related characteristics of the study population according to the presence of brain lesions are given in Table 2. Compared with those with no lesions, those with diffuse WMLs were older and had lower body mass index and higher systolic BP and were more frequently affected by osteoporosis and ADL disability. They reported a lower level of physical activity and more falls and had lower scores on tests of physical and cognitive performance. Compared with those with no lesions, subjects with focal lesions were older and, as expected, had a more frequent history of stroke and lower MMSE scores and were more likely to be incontinent and disabled in ADLs.

During 9 years of follow-up, 51 subjects sustained an HF, with an incidence rate of 10.6 cases per 1000 person-years, compared with the group who refused MR imaging, which experienced a rate of 11.6 cases per 1000 person-years (Table 3). When crude HF rates were computed

according to age groups and sex, important differences were noted. As expected, women had consistently higher rates of HF than men, especially in the group with diffuse WMLs (19.5 vs 8.6 cases per 1000 person-years), but the age-adjusted relative risk of HF associated with diffuse WMLs was consistent, although not statistically significant, across men and women (relative risk, 1.7 for men and women). Rates differed markedly across the age groups. The relationship between HF and brain lesions was strong and was consistent in the group younger than 80 years old, while it was inconsistent in the group 80 years and older, in which a high rate of HF (24.5 per 1000 person-years) in the reference group was observed. A formal test for an age × diffuse WML interaction was not statistically significant ($P = .09$) when the group with diffuse WMLs was compared with the group with no lesions. Therefore, analyses were stratified by age, and data were presented separately.

White matter lesions and focal lesions were present in 73% and 14% of subjects 80 years and older, respectively, compared with 43% and 18% among those younger than 80 years. Compared with those younger than 80 years, subjects 80 years and older were more likely to be women (60% vs 51%), be more sedentary (33% vs 11%), have reported fewer falls (61% vs 73%), use a higher number of medications (3.7 vs 2.7), and have higher prevalences of osteoporosis (62% vs 45%) and stroke (6% vs 3%). They also had lower scores on physical (6.3 vs 9.1 on the short physical performance battery) and cognitive (20 vs 25 on the MMSE) performance.

The results of the Cox proportional hazards regression models predicting HF and adjusted for confounders and mediators are given in Table 4. Variables were sequentially included in multivariate models to show the effect of the inclusion on the HR estimates. Among participants younger than 80 years, diffuse WML presence was associated with a risk of HF almost 3 times higher than that among participants with no lesions after adjusting for potential confounders that were not in the causal pathway (HR, 2.7; 95% confidence interval [CI], 1.1-7.1). As expected, the inclusion of variables postulated to be in the causal pathway reduced the strength of the association (HR, 2.4; 95% CI, 0.9-7.1), which was no longer statistically significant. Focal lesions were associated with an increased risk of HF among those younger than 80 years, although this did not reach statistical significance (HR, 2.0; 95% CI, 0.6-7.6). No clear association was shown between focal lesions or WMLs and HF among those 80 years and older.

Comment

In this sample of community-living older persons, those with diffuse WMLs were older, experienced more falls and HFs, and had worse physical and cognitive performance and higher systolic BP than those with no lesions. The association between WMLs and HF was present among participants younger than 80 years and was not detected in the older group. In particular, after adjusting for possible confounding variables, persons younger than 80 years with diffuse WMLs were almost 3-fold (HR, 2.7; 95% CI, 1.1-7.1) more likely to have an HF compared with those with no lesions (Table 4).

The association of WMLs with the risk of incident HF has a strong biological plausibility. Consistent with previous literature,[9,16,36,37] subjects with diffuse WMLs in our study were more sedentary, reported more ADL disability and falls, and had worse performance on physical and cognitive tests. Postulating a temporal sequence along the causal pathway (diffuse WMLs leading to physical and cognitive dysfunction, leading to falls, leading to impaired compensatory abilities, and leading to HF), we translated this progression into an analytic approach that performs sequential analyses with and without variables in the causal pathway from the risk factors to the HF (Table 4).

Multivariate modeling of these data identified the key association. The association between diffuse WMLs and HF was strong and statistically significant (HR, 2.7; 95% CI, 1.1-7.1) in persons younger than 80 years as long as variables postulated to be mediators in the causal pathway were not included in the analyses. Including these variables decreased the statistical significance of the association (*P*=.07) but did not substantially affect the magnitude of the association (HR, 2.4; 95% CI, 0.9-7.1). Focal lesions were associated with an increased risk of HF (HR, 2.0; 95% CI, 0.6-7.6), a finding that (although not statistically significant) is consistent with previous findings that infarctlike brain lesions and stroke are important risk factors for HF.[23,30,38-40]

Two reasons could explain the differential association between diffuse WMLs and HF according to age. First, the small sample size of persons 80 years and older (161 subjects and 20 HFs) may explain the instability of risk estimates, especially for HF in persons with focal lesions (HR, 0.15; 95% CI, 0.01-1.60), who experienced only 1 HF (Table 4). As expected, this older population experienced higher absolute rates of HF compared with younger subjects (Table 3). However, these subjects were characterized by a high prevalence of nonneurological risk factors for HF such as female sex, osteoporosis, physical inactivity, and lower educational level, and among those 80 years and older, osteoporosis was one of the strongest risk factors for HF (data not shown). Second, a possible survival effect of those with less severe lesions into older age could also explain the findings, with the accumulation over time of other age-related HF risk factors such as inactivity and osteoporosis, conditions less prevalent among younger subjects. In fact, in separate multivariate analyses, focal lesions and diffuse WMLs in those 80 years or younger were associated with higher mortality risks compared with those with no lesions (data not shown), while this increased risk was not present in those 80 years and older, a finding consistent with previous results.[30]

This study has 2 limitations. First, the study population is a self-selected subgroup of a sample that is representative of a general population 65 years and older. The sample of healthier, less disabled, and less cognitively impaired individuals who agreed to undergo MR imaging could have introduced biases into the analyses. A second limitation is that diffuse WMLs were not scored based on a graded severity measure and were not contrasted by brain location. However, the possible biases this might have introduced are likely to be conservative biases diluting the association toward the null.

This study has several strengths. To our knowledge, this is the first longitudinal study demonstrating an association between the presence of WMLs and the incidence of HF in a population-based sample of older persons. To date, only clinic-based investigations of stroke patients have looked at the association of WMLs with HF,[30] and our study supports greater generalizability of the findings to the older population given the high prevalence of diffuse WMLs among apparently healthy older individuals. The Progetto Veneto Anziani Study was able to control for several possible confounders, having collected extensive baseline data on lifestyle, physical and cognitive function, and other predictors of HF.[23,41] Although we did not collect information on the circumstances leading to the HF, we were probably able to better address issues related to HF risk in the younger (more active and less disabled) group, in which the interactions between fall initiation, balance recovery, fracture determinants, and high-impact vs low-impact trauma might differ from factors in the older (less active and more disabled) group.[25,42]

The findings of this study need to be replicated in other populations using measures of diffuse WML severity and adequate sample size for the population 80 years and older. However, these results have important clinical implications for HF preventive strategies. Magnetic resonance imaging and computed tomographic scans of older patients hospitalized or referred for falls, syncope, or other nonspecific neurological symptoms often disclose patterns of WMLs with

various degrees of severity, recently described as being associated with functional decline.[43] Clinically, WMLs are considered an age-related finding, but in light of the results of this study and those of a previous study,[43] they should no longer be overlooked, especially among less disabled older persons. The presence of WMLs should be considered an important risk factor for HF and should trigger, where indicated,[27] the initiation of a multifactorial intervention to reduce the risk of falling and fractures.

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Table 1

Demographic and Health-Related Characteristics of the Progetto Veneto Anziani Study Population Stratified by Incident Hip Fracture (HF)[a]

Characteristic	Overall (N = 822)[b]	Incident HF		*P* Value[c]
		No (n = 769)	Yes (n = 51)	
Age, y	73.4±6.7	72.7±6.7	77.0±6.2	<.001
Brain MR imaging pattern				
No lesions	33	34	24	<.001
Focal lesions	17	18	10	
Diffuse WMLs	49	48	66	
Male sex	42	43	22	<.02
Education, y	4.5±2.2	4.5±2.2	4.4±2.9	.68
Body mass index[d]	27.4±4.3	27.5±4.2	26.0±4.4	.03
Smoking status				
Never	67	59	73	.17
Former	24	31	22	
Current	10	10	6	
Physical activity				
Sedentary	15	15	25	<.001
Intermediate	59	59	61	
Active	26	27	14	
Blood pressure, mm Hg				
Systolic	147.9±19.7	147.6 ±19.1	152.3±26.7	.09
Diastolic	79.2 ±11.7	79.4 ± 11.7	76.6 ± 12.2	.10
Orthostatic hypotension	21	18	24	.33
Ever fell during past year	30	29	39	.12
No. of falls during past year	0.6±1.4	0.6± 1.4	0.8 ±1.4	.42
No. of medications	3.1 ±2.5	3.1 ±2.5	3.4±2.3	.45
Taking high blood pressure medication	31	30	35	.44

Characteristic	Overall (N = 822)[b]	Incident HF		*P* Value[c]
		No (n = 769)	Yes (n = 51)	
Disease status				
Previous HF	2.7	2.2	9.8	.001
Other fractures after age 50 y	29	28	35	.33
Stroke	3.6	3.5	3.9	.87
Osteoporosis	48	46	80	<.001
Diabetes mellitus	8.4	8.0	14	.15
Any urinary incontinence	23	22	26	.63
Physical and cognitive function				
Activities of daily living disability	16	15	27	.02
Mini-Mental State Examination score	24.7±4.2	24.8±4.1	22.8±5.9	.01
Short physical performance battery score	8.8±2.5	8.9±2.6	7.2 ±2.7	<.001

Abbreviations: MR, magnetic resonance; WMLs, white matter lesions.

[a] Data are given as mean±SD or as percentages unless otherwise indicated. Percentages may not total 100% owing to rounding.

[b] Two participants had unreadable MR images and were excluded from further analyses.

[c] Comparing prevalence from χ^2 test and means from *t* test among those who did and did not experience an HF during follow-up.

[d] Calculated as weight in kilograms divided by height in meters squared.

Table 2

Age- and Sex-Adjusted Distribution of Demographic and Health-Related Characteristics by Brain MR Imaging Pattern[a]

Characteristic	No Lesions	Focal Lesions	Diffuse WMLs
Follow-up time to HF or censoring, y	274±6.5	140±6.3	406±6.4
Age, y	70.7±5.5	72.6±6.5[b]	75.5±6.9[c,d]
Age <80 y	92	84	71[c,d]
Male sex	45	46	38[c,d]
Education, y	4.6 ±2.1	4.6±2.5	4.3± 2.1[c]
Body mass index[e]	27.9±4.1	27.4±4.3	26.9±4.3
Smoking status			
Never	62	55	60[d]
Former	31	35	29
Current	7	10	11
Physical activity			
Sedentary	8	11	15[c]
Intermediate	61	67	61
Active	31	23	25
Blood pressure, mm Hg			
Systolic	144.7 ± 18.6	146.9 ± 19.9	150.5 ± 19.9[c]
Diastolic	78.8 ± 11.2	78.7 ± 11.9	79.2 ± 11.8
Orthostatic hypotension	18	15	18
Ever fell during past year	28	24	30
No. of falls during past year	0.5±1.0	0.44±0.95[d]	0.7±1.7[c,d]
Disease status			
Previous HF	2.5	2.8	2.7
Other fractures after age 50 y	29	33	28
Stroke	1	6[b]	4[c]
Osteoporosis	46	45	50[c]
Diabetes mellitus	9	7	8
Any urinary incontinence	17	25	24[c]
Physical and cognitive function			
Activities of daily living disability	6	12	18[c,d]
Short physical performance battery score	9.4±2.3	9.0±2.6[d]	8.1±2.8[c,d]
Mini-Mental State Examination score	25.8±3.3	24.8±3.9[b]	23.6±4.6[c]
No. of medications	2.8±2.3	3.1±2.6	3.5±2.5[c,d]
Taking high blood pressure medication	29	39[b]	28[d]

Abbreviations: HF, hip fracture; MR, magnetic resonance; WMLs, white matter lesions.

[a] Data are given as mean±SD or as percentages unless otherwise indicated. Percentages may not total 100% owing to rounding.

[b] $P<.05$ comparing focal lesions with no lesions.

[c] $P<.05$ comparing diffuse WMLs with no lesions.

[d] $P<.05$ comparing diffuse WMLs with focal lesions. From linear regression models for continuous variables, from logistic regression models for dichotomous variables, and from polynomial logistic regression models for multilevel variables.

[e] Calculated as weight in kilograms divided by height in meters squared.

Table 3

Hip Fracture (HF) Incidence Rates per 1000 Person-Years and Age-Adjusted Relative Risks (RRs) of HF by Brain Magnetic Resonance (MR) Imaging Pattern, Age Group, and Sex[a]

Variable	Overall		Age <80 y		Age ≥80 y		Men		Women	
	Rate per 1000 Person-Years	Age-Adjusted RR (95% CI)	Rate per 1000 Person-Years	Age-Adjusted RR (95% CI)	Rate per 1000 Person-Years	Age-Adjusted RR (95% CI)	Rate per 1000 Person-Year	Age-Adjusted RR (95% CI)	Rate per 1000 Person-Years	Age-Adjusted RR (95% CI)
With MR Imaging										
	(n=820; 51 HF)		(n=659; 31 HF)[b]		(n=161; 20 HF)[c]		(n=343; 11 HF)		(n=477; 40 HF)	
Brain MR Imaging pattern										
Diffuse WMLs	14.8	1.8 (0.9-3.8)	10.3	2.7 (1.1-7.0)	28.7	1.1 (0.3-3.5)	8.6	1.7 (0.3-8.5)	19.5	1.7 (0.7-4.1)
Focal lesions	6.1	1.1 (0.3-3.1)	5.6	1.9 (0.5-6.9)	8.8	0.3 (.03-3.0)	5.7	2.1 (0.3-15.3)	2.1	0.5 (0.1-2.7)
No lesions	7.1	1.0 [Reference]	5.7	1.0 [Reference]	24.5	1.0 [Reference]	2.9	1.0 [Reference]	10.0	1.0 [Reference]
Total rate	10.6	…	7.7	…	25.0	…	5.9	…	13.5	…
Refused MR Imaging										
	(n=77 7; 46 HF)		(n=39 0; 18 HF)		(n=388; 28 HF)		(n=2 75; 10 HF)		(n=503 ; 36 HF)	
Total rate	11.6	…	7.9	…	16.5	…	7.7	…	13.5	…

Abbreviations: CI, confidence interval; WMLs, white matter lesions; ellipses, not applicable.

[a] Age-adjusted RRs were calculated from Cox proportional hazards regression models, adjusted for age as a continuous variable.

[b] Of these 31 HFs, 9, 2, and 20 HFs were recorded among those with diffuse WMLs, focal lesions, and no lesions, respectively.

[c] Of these 20 HFs, 3, 1, and 16 HFs were recorded among those with diffuse WMLs, focal lesions, and no lesions, respectively.

Table 4

Hazard Ratios (HRs) and 95% Confidence Intervals for Hip Fracture (HF) Stratified by Age Groups From Cox Proportional Hazards Regression Models[a]

	Age<80 y (n = 659)					Age ≥80 y (n = 161)				
Brain MR Imaging Pattern	**Crude**	**Plus Age and Sex**	**Plus Osteoporosis**	**Plus Other Risk Factors[b]**	**Plus Variables in the Causal Pathway[c]**	**Crude**	**Plus Age and Sex**	**Plus Osteoporosis**	**Plus Other Risk Factors[b]**	**Plus Variables in the Causal Pathway[c]**
Diffuse WMLs	3.1 (1.2-7.9) *P*=.002	2.7 (1.0-6.9) *P*=.01	2.7 (1.0-6.9) *P*=.03	2.7 (1.1-7.1) *P*=.04	2.4 (0.9-7.1) *P*=.07	1.1 (0.3-3.7)	0.9 (0.2-3.0)	0.6 (0.1-2.2)	0.5 (0.1-2.9)	0.5 (0.1-3.3)
Focal lesions	1.9 (0.5-6.7)	2.1 (0.6-7.8)	2.3 (0.6-8.6)	2.0 (0.6-7.6)	2.1 (0.5-8.2)	0.34 (0.04-3.30)	0.20 (0.02-2.30)	0.20 (0.02-1.70)	0.15 (0.01-1.60)	0.2 (0.1-2.4)
No lesions	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: MR, magnetic resonance; WMLs, white matter lesions.

[a] Data are given as HR (95% confidence interval) unless otherwise indicated. Variables were considered for these models if *P*<.10 in bivariate analyses.

[b] Education, smoking, and number of medications.

[c] Previous HF, previous falls, physical activity, systolic blood pressure, Mini-Mental State Examination score, short physical performance battery score, and taking high blood pressure medication.