A Uniform Approach to Modeling Risk Factor Relationships for Ischemic Lesion Prevalence and Extent: The Women's Health Initiative Magnetic Resonance Imaging Study

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Key Words

Statistical methods · Brain magnetic resonance imaging · Cognition · Women's health

Abstract

Background: Both the prevalence and extent of brain magnetic resonance imaging (MRI) abnormalities are related to risk factors for dementia. Typically these associations have been explored separately, but an integrated modeling approach would allow the separate relationships to be consistently described and contrasted. **Methods:** Region-specific measures of ischemic lesion volumes were obtained from standardized brain MRI from 1,403 women enrolled in the Women's Health Initiative hormone therapy trials. Mixed-effects mixed-distribution models were fitted to explore jointly the relationships that the region-specific prevalence of ischemic lesions and region-specific ischemic lesion volumes had with risk factors and scores from tests of cognitive

function. **Results:** Women with greater probabilities (prevalence) of having ischemic lesions in brain regions also tended to have larger volumes (extent) of ischemic lesions within the affected regions ($p < 0.001$). Across the 5 regions included in analyses (frontal, limbic, occipital, parietal and temporal), prevalence and extent varied ($p < 0.001$). Each was increased among women who were older, had hypertension or who had previously been classified as cognitively impaired ($p < 0.01$). Additionally, extent was significantly increased among women with a history of smoking ($p = 0.02$). Cognitive function tests were more strongly related to the extent than prevalence of ischemic lesions and relationships varied among cognitive domains ($p < 0.001$). **Conclusions:** Mixed-effects mixed-distribution models provide a coherent basis for examining relationships involving the prevalence and extent of ischemic brain lesions. Across the cohort and regions we examined, relationships with risk factors and cognitive function appeared to be stronger for extent than for prevalence.

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Introduction

Both the prevalence [1–5] and volume [3, 5–7] of abnormalities (e.g. infarcts, areas of white-matter hyperintensity) detected by brain magnetic resonance imaging (MRI) are important measures for neuroepidemiological research. While such measures are intercorrelated, the relationships that they have with risk factors may vary [8] and are often separately explored. A more integrated and potentially more informative approach is to examine these jointly within a general model. This allows investigators to distinguish individuals with numerous diffuse small ischemic lesions from those with a small number of large ischemic lesions and to explore whether there are different predictors for prevalence and extent. Such a model would need to address the intra- and intercorrelation of these measures across brain regions.

Recent progress in statistical research has developed a class of mixed-effect mixed-distribution (MEMD) models, and algorithms for fitting models, suitable for this approach [9, 10]. This paper is designed to introduce these methods to radiological research. The models we describe allow simultaneous fitting of separate risk factor prediction models to the region-specific prevalence and extent of ischemic lesion volumes in a repeated measures framework. Intraindividual correlations among regions of the brain and correlations between individuals' overall prevalence rates and ischemic lesion volumes are addressed. In this manuscript, we describe these tools and apply them to data from standardized MRI readings from a large cohort of older women to assess their relationships to dementia risk factors and cognitive function. Because our primary goal is to describe this methodology, results are provided as examples of potential applications, and extensive analyses are not reported.

Materials and Methods

The Women's Health Initiative Memory Study Magnetic Resonance Imaging (WHIMS-MRI) was an ancillary study to the Women's Health Initiative (WHI) trials of hormone therapy [11], two large, randomized, double-blind, placebo-controlled, clinical trials of postmenopausal hormone therapy: 0.625 mg/day conjugated equine estrogen alone or in combination with 2.5 mg/day of continuous medroxyprogesterone acetate. The WHIMS-MRI was undertaken to contrast neuroradiological outcomes among women who had been assigned to active versus placebo therapy during the WHI trials [12–14]. Exclusion criteria were the presence of pacemakers, defibrillators, neurostimulators, prohibited medical implants and foreign bodies (e.g. bullets, shrapnel, metal slivers) that would pose a hazard during the MRI procedure. Oth-

er exclusion criteria were shortness of breath and/or inability to lie flat, as well as conditions that can be exacerbated by stress (e.g. anxiety panic disorders, claustrophobia, uncontrolled high blood pressure or seizure disorders) severe enough to preclude an MRI. At 14 US academic centers, 1,424 women underwent a brain MRI, and 1,403 had scans containing usable data. Written informed consent was obtained from all participants. The NIH and institutional review boards approved the protocol and consent forms.

Brain Magnetic Resonance Imaging

Brain MRI scans were conducted at multiple sites and analyzed centrally using a standardized protocol [13, 14] that represents the evolution in image processing from manual human observer to automatic quantitative computerized digital image analytical techniques that are not only correlated with human observers and the semiquantitative scoring systems, but are also very reproducible and offer a greater dynamic range [15–17].

MRI scanning pulse sequences were performed in the following order:

- series 1 = 3-plane gradient echo localizer for positioning;
- series 2 = sagittal T₁-weighted imaging to demonstrate anatomical location of the AC/PC for slice angle and slice position;
- series 3 = oblique axial spin density/T₂-weighted imaging from the vertex to skull base parallel to the AC/PC plane;
- series 4 = oblique axial FLAIR T₂-weighted imaging, matching slice positions in series 3;
- series 5 = oblique axial 3-dimensional SPGR T₁-weighted imaging from the vertex to skull base parallel to the AC/PC plane.

A trained technologist reviewed all scans for technical problems, protocol compliance and participant motion. If a series needed repeating, this was done before the participant was removed from the scanner. Imaging data were then transmitted using a DICOM image transfer mechanism for central reading at the Department of Radiology, University of Pennsylvania.

Gray and white matter was classified as either normal or 'ischemic' with areas of ischemia corresponding to what is generally referred to as 'small-vessel ischemic disease' (ischemic white-matter disease and lacunar infarctions). Ischemic white-matter disease represents a nonnecrotic, ischemic effect on myelin that is secondary to the effects of aging, hypertension and other small-vessel pathological processes of the brain [18, 19]. Separate volumes (total and ischemic lesion) were provided for 92 anatomical regions of interest in the cerebrum. Examples in this paper are based on 5 regions (frontal lobe, limbic region, occipital lobe, parietal lobe and temporal lobe), which were chosen to provide ranges of size and prevalence. Total volumes for each of these regions were calculated by summing across the smaller subregions.

Risk Factors and Measures of Cognitive Function

The dementia risk factors included as examples in this report were collected by standardized procedures of the WHI at enrollment [11]. These include age and smoking history. Hypertension was based on current treatment or measured blood pressure exceeding 140/90 mm Hg. Self-reported vascular disease included myocardial infarction, stroke, angina, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting or stroke. WHI treatment assignment (hormone therapy versus placebo) was also included in analyses.

Global cognitive function had been measured annually in these women with the Modified Mini Mental State Examination [20, 21]. It consists of 15 items that sum to 0–100; higher scores reflect better cognitive functioning. Test items measure temporal and spatial orientation, immediate and delayed recall, executive function, naming, verbal fluency, abstract reasoning, praxis, writing and visuoconstructional abilities. The average (and SD) time that the most recent Modified Mini Mental State Examination test preceded the MRI was by 0.42 (0.70) years. Approximately 70% of the participants ($n = 1,079$) had also been enrolled in the WHI Study of Cognitive Aging [22], which administered an annual cognitive battery to assess a broad range of domain-specific cognitive functions. Included in the battery were the Primary Mental Abilities vocabulary test [23] to measure verbal knowledge, letter and semantic fluency tests [24, 25] to measure phonemic and category fluency, the Benton Visual Retention Test [26] to measure short-term figural memory and visuoconstruction, the California Verbal Learning Test [27] to measure verbal learning and memory, the Digit Span Test [28] to measure attention and working memory, the Card Rotation Test [29] to measure spatial rotational ability, and a finger tapping test [30] to measure fine motor speed. The average (and SD) time that the most recent battery preceded the MRI was by 0.75 (0.84) years.

Statistical Methods

Statistical Model

The underlying MEMD model, as developed by Tooze et al. [9, 10], consists of linked mixed model regression equations to parameterize relationships with ischemic lesion prevalence and extent of ischemic lesions. It is considered a 2-part model, because prevalence and extent are modeled in 2 regression equations, with covariates that are allowed to vary for each part of the model. It is called a ‘mixed model’ because it includes a mix of fixed effects (the effects of specific variables of interest) and a person-specific random effect in each of the 2 parts of the model. The separate person-specific random effect terms are included to address intrasubject correlations of prevalence among regions and ischemic lesion volumes among regions. However, even though prevalence and extent are modeled in separate regression equations, they are not independent because a shared parameter is used to express the correlation between the intraregional probability of having a lesion (i.e. prevalence) and the intraregional lesion volume (i.e. extent).

The first part of the model estimates the probability (prevalence) of having a lesion within a region using logistic regression with a person-specific random effect (mixed model). The random effect is a latent variable that captures an individual’s tendency to have lesions, after adjusting for the fixed effects of covariates. It is necessary to include this random effect in the model due to the within-person correlation that arises from modeling multiple regions simultaneously. The model for part I is:

$$\text{logit (probability of lesion)} = \text{intercept}_I + \text{slope}_I \times \text{variable} + \text{person-specific effect}_I$$

where, for probability p , $\text{logit}(p) = \log(p/1 - p)$. The subscript I indicates the association of the parameters with part I. One predictor variable is shown in the equation, but the model allows for multiple predictor variables (or no variables). These may represent region-specific characteristics (e.g. total regional volume) or person-specific characteristics (e.g. dementia risk factors, cognitive test scores), as we demonstrate.

The second part of the model predicts the ischemic lesion volume (extent) among those who have lesions. Similar to part I, part II may incorporate predictor variables of interest, which may or may not be the same variables used in part I. The model for part II is:

$$\text{log lesion volume} = \text{intercept}_{II} + \text{slope}_{II} \times \text{variable} + \text{person-specific effect}_{II} + \text{within-person variability}_{II}$$

The subscript II indicates the association of these parameters with part II. As in part I, the model is a mixed one, modeling both fixed effects of covariates, and a random person-specific effect. The random effect models the individual’s general extent of lesion volume, which is correlated across multiple brain regions within an individual. The intercept terms of parts I and II represent person-specific random effects, which are assumed to follow a bivariate normal distribution and are used to link the two underlying expressions. The joint model is fitted using the maximum likelihood method with a SAS software (version 9.1, SAS Institute, Cary, N.C., USA) macro (which may be obtained from the corresponding author). Correlation of prevalence and extent may be determined by means of a likelihood ratio test comparing the joint model to a model that fits prevalence and extent separately; this test is implemented in the macro.

Modeling of Abnormal Volume in WHIMS-MRI

The prevalence and extent of ischemic lesions were analyzed using the 2-part MEMD model described above, including markers for the 5 regions of interest in which parameters for variables were constrained to sum to zero. To demonstrate the use of region-specific predictors, total regional volumes were included in models. Two sets of subject-specific predictors were considered. The relationships that ischemic lesion prevalence and extent had with dementia risk factors (age, smoking status, hypertension, prior cardiovascular disease and assignment to hormone therapy) were examined in separate models with adjustment for region-specific volumes. The relationships with cognitive test scores were examined in a similar manner. The interregional consistency of these relationships was assessed using interaction terms. Ischemic lesion volumes were highly right-skewed; Box-Cox transformations supported the use of lognormal models for extent. The parameters of the lognormal model may be interpreted as an n -fold change in the median lesion volume.

Results

Table 1 characterizes the 1,403 women, whose age averaged 78.5 years and ranged from 72.0 to 88.6 years at the time of their MRI.

Table 2 describes the distribution of the volumes of the brain regions included in our analyses, the percentage of each region that contained ischemic lesions, and, for regions containing ischemic lesions, the mean total volume of these lesions. The frontal, temporal and parietal regions were the largest, had the greatest prevalence of ischemic lesions and, in regions in which lesions occurred,

Table 1. Distribution of risk factors for ischemic lesions

Dementia risk factor	Distribution
Age at time of MRI, years	
Mean	78.5
Range	72.0–88.6
Smoking status at WHI enrollment	
Never	806 (57.9)
Former/current	585 (42.1)
Hypertension status at WHI enrollment	
No	688 (49.0)
Yes	815 (51.0)
Prior cardiovascular disease at WHI enrollment	
No	1,313 (93.6)
History of cardiovascular disease	90 (6.4)
WHI treatment assignment	
Active CEE	257 (18.8)
Placebo CEE	263 (18.3)
Active CEE and MPA	436 (31.1)
Placebo CEE and placebo MPA	447 (31.9)

Figures in parentheses indicate percentages. Hypertension defined as blood pressure measured to exceed 140/90 mm Hg or use of current antihypertensive treatment. Cerebrovascular disease defined as myocardial infarction, stroke, angina, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting or stroke. CEE = Conjugated equine estrogen; MPA = medroxyprogesterone acetate.

had the greatest mean total volumes of lesions. Differences in the prevalence and extent of ischemic lesions among regions remain after adjustment for region-specific total volumes (both $p < 0.001$), as demonstrated in table 3. The logistic regression parameters for prevalence portray the relative ordering of regions compared to the overall mean and can be transformed to odds ratios. After adjustment for differences in volume, frontal lobes had an $e^{2.032} = 7.63$ (95% confidence interval, CI: 0.99–58.82) times higher odds of prevalent ischemic lesions than the average of other regions. The lognormal regression parameters express differences in ischemic lesion volumes: after adjustment for total regional volumes, the median volumes of ischemic lesions in the frontal lobe were 0.22 (95% CI: 0.12–0.39) times as large as the median across all regions. There was a significant within-person correlation between the prevalence and extent of ischemic lesions: the greater the number of affected regions, the larger the ischemic lesion volumes tended to be within affected regions ($p < 0.0001$). Overall, prevalence and extent of lesions tended to be greater among larger

Table 2. Mean regional volumes, prevalence of ischemic lesions and ischemic lesion volumes $\pm$ SD

Region	Total regional volume, cm ³	Prevalence of regions with ischemic lesion volumes, %	Ischemic lesion volume, cm ³
Frontal lobe	283.88 $\pm$ 28.92	98.1	3.43 $\pm$ 5.07
Limbic region	31.63 $\pm$ 4.48	17.7	0.26 $\pm$ 0.32
Occipital lobe	102.14 $\pm$ 12.72	74.5	0.68 $\pm$ 0.84
Parietal lobe	152.85 $\pm$ 15.69	85.1	2.32 $\pm$ 3.62
Temporal lobe	184.18 $\pm$ 18.72	87.4	1.85 $\pm$ 2.17

Ischemic lesion volume of regions with prevalent ischemic lesions.

regions; interaction terms could be added to the models to examine associations with region-specific volumes within regions.

Age and hypertension were each significantly related to the prevalence of ischemic lesions across regions (both $p < 0.001$), as shown in table 4. Separately, these estimates indicate that within regions, the odds of prevalent ischemic lesions increased for each year of additional age by a factor of $e^{0.090} = 1.09$ (95% CI: 1.06–1.13) and among women with hypertension by 1.50 (95% CI: 1.18–1.91). The volumes of lesions were also significantly related to age and hypertension: each year of age was associated with an increase in the median volume by a factor of $e^{0.054} = 1.06$ (95% CI: 1.04–1.07) and hypertension was associated with an increase in the median volume by a factor of 1.27 (95% CI: 1.13–1.42). Smoking was significantly associated with increased lesion volume ($p = 0.02$), but not with increased prevalence ($p = 0.21$). Prior on-study classification of cognitive impairment (either mild cognitive impairment or probable dementia) was associated with increased odds of prevalent lesions by a factor of 2.39 (95% CI: 1.24–4.61) and an increased median lesion volume by a factor of 1.49 (95% CI: 1.11–1.99), both $p < 0.01$. Neither history of cardiovascular disease nor on-trial assignment to hormone therapy were associated with the prevalence or extent of ischemic lesions (all $p > 0.10$).

Relationships that scores from tests of cognitive function had with prevalence all were in the expected direction (table 5) but reached statistical significance only for category fluency ($p = 0.05$). Overall, the relationships these test scores had with the extent of region-specific

Table 3. Relationships that prevalence and extent have with region-specific volumes: fitted regression coefficients, standard errors (in parentheses) and p values with adjustment for regional volumes and correlations between prevalence and extent

Predictor	Logistic regression parameter with prevalence		lognormal regression parameter with extent	
	β	p value	β	p value
Volume of region	0.010 (0.003)	0.005 ¹	0.006 (0.001)	<0.001 ¹
Region				
Frontal lobe	2.032 (1.042)		-1.514 (0.296)	
Limbic region	-3.106 (0.417)		-1.194 (0.110)	
Occipital lobe	0.103 (0.182)	<0.001 ²	-0.069 (0.047)	<0.001 ²
Parietal lobe	0.546 (0.088)		0.482 (0.023)	
Temporal lobe	0.504 (0.147)		0.325 (0.036)	

¹ Overall relationship with regional volume.

² Consistency of relationships with regional volumes among regions.

Table 4. Relationships that prevalence and extent have with risk factors for ischemic lesions: fitted regression coefficients, standard errors (in parentheses) and p values with adjustment for differences in volumes and correlations among regions

Risk factor	Logistic regression parameter with prevalence		lognormal regression parameter with extent	
	β	p value	β	p value
Age	0.090 (0.017)	<0.001	0.054 (0.008)	<0.001
Ever smoked	0.156 (0.124)	0.21	0.140 (0.058)	0.02
Hypertension	0.408 (0.123)	<0.001	0.236 (0.057)	<0.001
Prior cardiovascular disease	0.270 (0.252)	0.28	0.190 (0.117)	0.11
Assignment to active hormone therapy	0.132 (0.122)	0.28	0.054 (0.057)	0.35
Mild cognitive impairment or probable dementia	0.873 (0.334)	0.009	0.396 (0.149)	0.008

ischemic lesion volumes tended to be stronger than those for prevalence, with significance achieved for global cognitive function and the domains of verbal knowledge, verbal fluency, memory and spatial ability.

Table 5 portrays relationships between domain-specific cognitive function and ischemic lesions across all 5 brain regions. Interaction terms can be included in the MEMD models to examine the consistency of relationships among regions and to explore whether there may be evidence of region-specific relationships with individual domains. For example, the relationship between the extent of ischemic lesion volumes and performance on the card rotation varied significantly by region (test for interaction $p < 0.001$). Table 6 describes this interaction, list-

ing the degree (expressed as percent) by which the median volume of ischemic lesions increases for each 10 points worse score on the Card Rotation Test. The limbic region was chosen as a reference because the association between the extent of ischemic lesion volumes and performance in the Card Rotation Test appeared to be weakest for this region. The strongest associations were for the frontal, parietal and temporal lobes for which the 95% confidence intervals excluded 0. As an example of how the results can be interpreted, a score of 10 points worse on the Card Rotation Test was associated with approximately a 9% greater increase in ischemic lesion volumes in the frontal and parietal lobes than in the limbic region.

Table 5. Relationships that prevalence and extent have with cognitive test scores: fitted regression coefficients, standard errors (in parentheses) and p values with adjustment for differences in regional volumes and correlations among regions

Cognitive test score	Logistic regression parameter with prevalence		lognormal regression parameter with extent	
	β	p value	β	p value
Global cognitive function				
3MS	−0.029 (0.016)	0.08	−0.026 (0.007)	<0.001
Verbal knowledge				
PMA vocabulary	−0.010 (0.008)	0.19	−0.009 (0.004)	0.01
Verbal fluency				
Letter fluency	−0.004 (0.005)	0.47	−0.000 (0.002)	0.94
Category fluency	−0.021 (0.011)	0.05	−0.015 (0.005)	0.002
Memory				
BVRT errors ¹	0.016 (0.019)	0.40	0.026 (0.009)	0.002
CVLT total list A	−0.011 (0.010)	0.27	−0.015 (0.005)	0.001
CVLT short delay free	−0.037 (0.021)	0.08	−0.041 (0.010)	<0.001
CVLT long delay free	−0.017 (0.022)	0.42	−0.032 (0.010)	0.001
Attention and working memory				
Digits forward	0.032 (0.032)	0.32	0.024 (0.015)	0.11
Digits backward	0.022 (0.019)	0.24	0.006 (0.009)	0.51
Spatial ability				
Card Rotation Test	−0.003 (0.002)	0.18	−0.003 (0.001)	0.001
Fine motor speed				
Finger tapping dominant hand	−0.012 (0.010)	0.25	−0.004 (0.005)	0.36
Finger tapping nondominant hand	−0.020 (0.012)	0.09	−0.008 (0.006)	0.17

3MS = Modified Mini Mental State Examination; PMA = Primary Mental Abilities test; BVRT = Benton Visual Retention Test; CVLT = California Verbal Learning Test.

¹ Lower scores reflect better performance.

Table 6. Relative region-specific increases in median ischemic lesion volume associated with each 10-point lower score on the card rotation test

Region	Percent increase in median ischemic lesion volume relative to limbic region	95% CI
Frontal lobe	8.8	7.1–10.0
Occipital lobe	1.0	2.6–4.5
Parietal lobe	9.0	7.1–10.9
Temporal lobe	6.5	4.8–8.2
Limbic region (reference)	1.00	–

Discussion

The MEMD-based approach that we describe provides a uniform approach to modeling the relationships that individual’s characteristics (e.g. risk factors, measures of cognitive function) have with region-specific prevalence and extent of MRI-detected abnormalities, predominantly white-matter small-vessel ischemic lesions. This approach controls for intrasubject correlations and for any correlation between the prevalence and extent of imaging abnormalities among regions, using random effects terms. If not addressed in models, these correlations would be expected to confound results from separate analyses of relationships with prevalence and extent. MEMD models accommodate region-specific covariates (e.g. total regional brain volumes) in addition to individual-specific characteristics: this allows covariate adjustment for comparisons among regions. Interaction

terms can be included to assess the consistency of relationships among brain regions, as we have demonstrated. Documentation and software for fitting models are available from the first author.

We have included as examples analyses that reveal several features of ischemic lesion volumes that support the use of MEMD models. We found that the prevalence and extent of ischemic lesions among regions were strongly correlated. In the WHIMS-MRI cohort, the prevalence and volume of ischemic lesions varied among the 5 regions we considered, and regions that tended to be larger were more likely to have greater prevalence and volume of lesions. While within-region relationships between total volume and ischemic lesions are of interest, comparisons among regions benefit from multivariate approaches such as we describe, and from the use of region-specific covariates. The volumes of ischemic lesions were right-skewed, which warranted the use of a lognormal distribution governing differences among regions between individuals. Overall, we found that ischemic lesion extent tended to have stronger associations with dementia risk factors and measures of cognition than ischemic lesion prevalence, suggesting that, on average, volume may be a stronger measure of disease burden.

The limited analyses that we present as examples are of interest, but require further investigation. Age, hypertension and prior classification of cognitive impairment were strongly related to both the prevalence and extent of ischemic lesions, which is consistent with prior reports [2, 3, 31]. We also found that history of smoking was associated with greater extent [32]. Consistent with an earlier report, assignment to hormone therapy was not significantly associated with ischemic lesions [13]. Of the cognitive domains we examined, the strongest and most sig-

nificant relationships linked the extent of ischemic lesion volumes with measures of global cognitive function, verbal knowledge, verbal category fluency, memory and spatial ability. As we have demonstrated, these may vary by brain region. More focused analyses that examine smaller and greater numbers of regions will be important for adding clarity to these relationships. By conducting these analyses in a multivariate fashion, we are able to compare their relative strengths among regions.

Conclusion

Two-part MEMD models provide a flexible and coherent approach towards modeling data on ischemic lesions detected by MRI scanning and should be considered as a general strategy for analyzing these data.

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