1.a. Full Title:

Comparison of volumetric segmentation to visual scoring for assessment of white matter ischemic disease and brain atrophy

b. Abbreviated Title (Length 26 characters):

Volume Vs visual MRI score

2. Writing Group:

Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _DKS__ [please confirm with your initials electronically or in writing]

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3. Timeline: Preliminary analysis will begin following approval of the ARIC Publications Committee. Three months are expected to complete data analysis and manuscript preparation.
4. **Rationale:**

Cerebral white matter disease is seen to varying degrees on most brain MRI scans in the elderly and has been related to a number of risk factors including hypertension and atherosclerosis, but is of particular interest due to the increasing evidence that it is related to various forms of cognitive dysfunction.

Early studies (including the ARIC Visit 3 and CHS MRI scans) have measured severity of white matter hyperintensity (WMH) or cerebral atrophy on brain MRI scans using visual scoring systems usually matching the test case to a series to progressively abnormal standards. This technique is subject to inter- and intra-reader variability and a relatively coarse grading scale which limits accuracy and precision particularly for longitudinal analysis.

There have been a number of automated or semi-automated approaches to quantitate WMH seen on FLAIR (Fluid Attenuation Inversion Recovery) and proton density weighted images. Most involve some form of pixel-by-pixel image segmentation scheme in which the population of pixels representing abnormal white matter are segregated by their grey-scale intensity from the normal brain and cerebral spinal fluid (CSF) and the volume of disease burden calculated by summing these pixels.

The volumetric analysis carried out for the ARIC Brain MRI Study (2003 - 2006) incorporates a new approach applying a statistically-based segmentation scheme to the image intensity histogram, allowing for a robust quantification of white matter disease. The semi-quantitative methods employed in ARIC Visit 3 were also repeated in the brain follow-up study. In the current study, we propose to examine the association between these two methods (semi-quantitative and volumetric) of quantifying brain abnormalities.

As part of the ARIC Brain MRI study quality control, a set of 20 scans were re-sent to the reading centers one or more weeks after the original scan was transferred. The duplicate scans were then interpreted twice and compared to monitor the reliability of MRI measurements over time, and to identify factors that might affect reliability. In this paper, in addition to comparing the two methods of quantifying brain abnormalities (described above), we will also report on the reliability of the semi-quantitative and volumetric procedures.

References:


5. **Main Hypothesis/Study Questions:**
The purpose of this study is to describe the reliability of the methods used to quantify brain abnormalities in the ARIC Brain MRI study and to examine the association between volumetric measurements of WMH and atrophy and traditional visual semi-quantitative scoring. We anticipate a strong correlation between these two methods however, volumetric segmentation techniques may have limitations in distinguishing classical leukoaraiosis from small infarcts.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodological limitations or challenges if present).

Inclusions: Participants from the ARIC study sites in Forsyth and Jackson who underwent a brain MRI at the follow-up examination (2003-2006). These scans were recently concluded. Approximately 1000 MRI scans which have already completed both quantitative (Mayo Clinic) and semi-quantitative (Univ of Washington) analysis will be compared.

Exclusions: Patients with intracranial abnormalities unrelated to ischemic disease such as tumors (meningioma) or vascular malformations (cavernomas) will be excluded. These are noted in the “other diagnosis” field in the “radiologist interpretation” data set.

ARIC Brain MRI Data (2003-2006):

Brain MRI Semiquantitative Analysis (Univ of Washington)

1. WMH score (WMHs)
2. Ventricle score (Vs)
3. Sulcal score (Ss)
4. Infarct volume (Iv)
5. T1, T2, PD weighted images

Brain MRI Volumetric Analysis (Mayo Clinic)

1. WMH volume (WMHv)
2. Total brain volume (TBv)
3. Total intracranial volume (TIv)
4. Ventricular volume (Vv)
5. FLAIR images and segmentation maps

Analysis:

1) Intra- and inter-observer agreement of semi-quantitative variables will be evaluated with the kappa index.

2) We will estimate reliability (R) of quantitative variables from a one way analysis of variance with subject as the only factor. That is, \( R = (MS_b - MS_w)/(MS_b + MS_w) \), where using the MS_b and MS_w are the between and within-subject mean square values, respectively.

3) White matter hyperintensities – Does the visual score correlate with volumetric analysis? Correlate WMHs Vs WMHv/TIv.
4) White matter hyperintensities – separation of leukoarosis versus infarcts
   a) Were infarcts identified by visual scoring segmented as leukoarosis? Segmentation maps of subjects with visually scored infarcts will be assessed for inclusion of these regions in the WMH segmentation. Error rate will be calculated.
   b) Does the correlation of visual scoring and volumetric measurement of WMH improve if the total infarct volume is subtracted from WMHv? Correlate WMHs versus (WMHv – Iv)/Tlv - Spearman's $\rho$ (rho) rank correlation coefficient will be calculated and compared with the uncorrected correlation.

5) Cerebral Atrophy – Does visual scoring of ventricle and sulci size correlate with volumetric measures of atrophy? Vv versus Vs and (Tlv-TBv)/Tlv versus (Ss + Vs). - Spearman's $\rho$ (rho) rank correlation coefficient will be calculated

To test for potential confounding or effect modification (e.g., the influence of scan quality on the correlation between WMH score and WMH volume), partial correlation coefficients adjusted for scan or participant factors (X) will be computed and interaction tests performed. The partial correlation measures the association between response pairs having eliminated the effect of the responses being associated with variable X. A significant interaction would indicate that the correlation is significantly different as a function of the factor being considered.

7.a. Will the data be used for non-CVD analysis in this manuscript? __ Yes  _X_ No
   b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? _____ Yes  ____ No
      (This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? _____ Yes  _X___ No
   b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”? _____ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.csecc.unc.edu/ARIC/search.php
      _____X_____ Yes  _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

ARIC # 314 Mosley Neurology 2005
11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  

   X Yes   _ _ No

11.b. If yes, is the proposal  

   X A. primarily the result of an ancillary study (list number* 1999.01)  
   _ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* (_ ____________)

*ancillary studies are listed by number at http://www.cscu.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.