**SUPPLEMENTAL MATERIALS - Full Protocol eMethods**

*Recruitment*: The CDCAI follow-up visit (2017-2019), invited all surviving participants from the prior CDCAI examination (2010-2013). Field staff used phone calls, letters, or home visits to contact potential participants; explained the purpose and procedures of the study; and scheduled the MRI and office visit if interested. The order in which participants were contacted for this follow-up visit was arbitrary and largely based on study rosters, which was roughly the same order as the previous examination; the order in which participants were scheduled was based on first come, first serve. The CDCAI Coordinating Center is located at Washington State University Health Sciences, and was conducted through partnership with the University of Washington Alzheimer's Disease Research Center; the SHS Coordinating Center is located at the University of Oklahoma Health Sciences Center.

*Quality Assurance and Training*: Prior to recruitments and examinations, a week-long training event was held for field staff, including coordinators and interviewers. Based on prior success in recruitment and examination methods, and Community-Based Participatory Research standards, SHS research field staff are frequently hired from the communities that they serve. Support staff were trained in screening for eligibility; obtaining consent; collecting anthropometric and blood pressure measurements; collecting and/or processing biological samples; documenting information; and completing any post-interview responsibilities. Licensed phlebotomists collected all blood samples. Interviewers were trained on building rapport; facilitating a comfortable and cooperative environment; adhering to standardized protocols; maintaining a non-judgmental attitude; using appropriate prompts; fielding questions and comments; administering questionnaires; and administering and scoring cognitive and physical performance tests. The cognitive test trainings were covered in detail by licensed Neuropsychologists, who also attended periodic participant interviews and held additional trainings as needed to maintain consistency. Cognitive test scores were also adjudicated by a panel of measurement and neuropsychology experts, who corrected discrepancies by consensus. Weight scales, sphygmomanometers, and centrifuges were calibrated monthly to ensure consistency. Lab assays were duplicated at 5% and assessed for technical error.

*Magnetic Resonance Imaging*: A multi-stage screening process was used to ensure eligibility of participants for follow-up cranial MRI. First, all participants completed MRI in 2010-2013. Second, field staff screened for MRI eligibility during the informed consent process for this follow-up study. Third, the Radiology facility separately assessed eligibility on the day of the MRI appointment. Any of the following excluded participants from eligibility for MRI: prior surgery for cerebral aneurysm; implanted cardiac pacemaker, defibrillator, or artificial heart; contraindicating metal prostheses; cochlear implant, spinal cord stimulator, or other internal electrical device; history of employment as a metal worker; or weight of 350 pounds or more. These protocols were designed to be consistent with the previous CDCAI study, the Cardiovascular Health Study [69,70] and the Atherosclerosis Risk in Communities Study.[71,72]

The Northern Plains field center used Siemens 1.5T Symphony (Siemens Medical Solutions, Malvern, PA); the Southern Plains and Southwest used General Electric 1.5T Signa (General Electric Healthcare, Little Chalfont Buckinghamshire, UK). Six image sequences were obtained in contiguous slices: sagittal T1-weighted localizer; co-registered 5 mm axial-T1; 5 mm axial-T2 and T2* susceptibility-weighted images in the anterior commissure/posterior commissure plane; 3 mm axial fluid-attenuated inversion recovery (FLAIR); and 1.5 mm sagittal T1-weighted volumetric gradient echo.

*Incidental Findings*: MRI technologists at each Radiology facility screened participant scans for evidence of alert criteria such as acute hemorrhage, thrombosis, and/or mass effect. Additionally, neuroradiologists interpreted MRIs within two weeks scanning for abnormalities such as aneurysms, tumors, acute hemorrhage, large infarcts (>4cm), aneurysms, tumors, acute hemorrhage, and large infarcts, mass lesions, subdural hematomas, AV malformations, evidence of large cerebrovascular events, historic strokes, large growths, blood clots or other emergent findings. Any such findings prompted a standard response: reviewing physician informing the participant immediately; reviewing physician contacting the participant's primary care physician if requested; and the reviewing physician alerting the study field staff, who then provided a written letter signed by the field center PI, summarizing the abnormality. Additional support for obtaining referrals, making appointments, and providing travel arrangements for resulting appointments were provided to participants as needed.

*Neuroradiology*: As previously described in detail,[30] MRI scans were interpreted independently by two neuroradiologists blinded to participant data, with conflicting readings adjudicated until consensus. Infarcts and hemorrhages were scored for number, size, type, and location. Infarcts were defined as lesions ≥3 mm anywhere

in the brain, with characteristic shape and absence of mass effect. Lacunar infarcts were characterized as infarct lesions 3 mm-2 cm in maximum dimension, located in the caudate, lenticular nucleus, internal capsule, thalamus, brainstem, cerebellar white matter, centrum semiovale, or corona radiate. Hemorrhages, or parenchymal hematoma, were defined based on clinical criteria as lesions anywhere in the brain, any size, with hypointensity on gradient echo images. Severity of WMH lesions (leukoaraiosis), sulcal dilatation, and ventricular enlargement were graded on a semi-quantitative scale (0-9, with 9 = most severe) based on best visual fit against standard image templates.[69] Quantitative volumes were estimated using automated software processing, including Fuzzy Lesion Extractor for WMH volume;[73] FIRST in functional software library 5.0[74] and the ENIGMA1[75] protocol for hippocampus and intracranial space; and the FreeSurfer image analysis suite for total and regional brain volumes.[76-79]

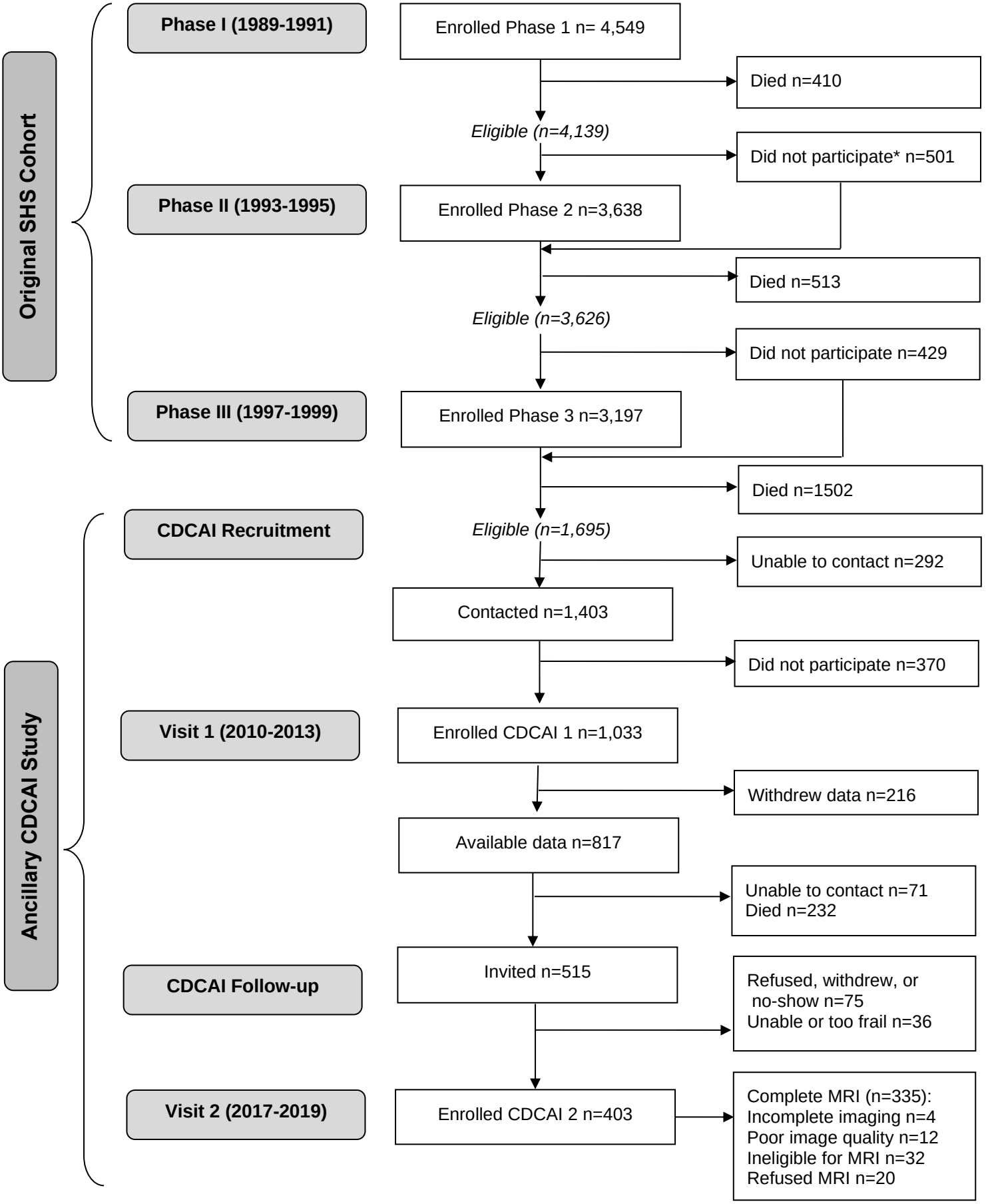
*Office Examinations*: Participants separately attended an office visit, ideally the same day as their MRI exam or within 1 month's time. At these office visits, participants underwent physical and neuropsychological examinations. These visits were designed to followed the same procedures established in the previous examination, which were specifically timed and structured to accommodate the elderly, often frail and easily fatigued condition of many participants, which is consistent with other cohort studies in older people.[80-82] First, participants, who had been asked to fast for at least 8 hours before the visit, provided blood and urine samples, which were immediately aliquoted, frozen at -80° C, and shipped to MedStar Health Research Institute (Hyattsville, MD) for standard assays, including lipids, glucose, hemoglobin A1c, creatinine, cystatin C, and urine albumin. Participants were given a small snack and/or juice and then continued with the visit procedures. Regular use of over the counter, prescription, and traditional medicines was assessed by label transcription of bottle labels for all medicines used within the past month.

*Physical Measurements*: Anthropometric measures included weight in pounds using Tanita BWB-8005 adult digital scale (Tanita Corporation, Arlington Heights, IL); standing height, and supine waist girth, erect hip circumference, and upper arm circumference all in inches, using a Novel Products Figure Finder tape measure (Novel Products, Rockton, IL). Weight and height were converted to meters and kilograms for calculation of body mass index. Seated systolic and diastolic blood pressure was measured three times, each 30 seconds apart, using an HEM-907 oscillometric blood pressure device (Omron Healthcare Inc, Lake Forest, IL), with the 2nd and 3rd measures averaged.[83] Physical performance tests included the lower-body function Short Physical Performance Battery, which includes timed stand, timed walk, and chair stand; upper body function grip strength test in kilograms, using a dynamometer (Fischer Scientific, Houston, TX); and fine motor function with Halstead finger tap test.[84]

*Administered Interviews*: Specifically trained field staff administered a neuropsychological test battery. Some of the tests were administered in the previous visit, including Modified Mini Mental Status Examination (3MSE), a global cognitive screening measure;[31] Wechsler Adult Intelligence Scale Fourth Edition Coding sub-test (WAIS), a measure of visuomotor processing speed and working memory;[32] Controlled Oral Word Association F,A,S Test (COWA), a measure of phonemic fluency and executive function;[33,34] and California Verbal Learning Test 2nd edition short form (CVLT), assessing learning and semantic memory.[35,36] New cognitive examinations included in this examination visit only were: reading subtest of the Wide Range Achievement Test 4th edition (WRAT)[37,38] a measure of reading word recognition, which can be used as a sensitive marker of achieved education; and the 10-item Functional Activities Questionnaire (FAQ) to assess instrumental Activities of Daily Living (iADL), or the capacity of an individual to perform daily tasks of independent living, the loss of which due to cognitive impairment are indicative of neurodegenerative dementia such as ADRD. [40 39 39 39] Also new to this examination visit was administration of the National Alzheimer's Coordinating Center Uniform Data Set (version 3.0, form C2) cognitive test battery,[40,41] which included Montreal Cognitive Assessment (MoCA), a common screening tool covering a broad range of cognitive subdomains, including executive function, attention, phonemic verbal fluency, abstraction, delayed verbal memory, and orientation.,[42] More detailed neurocognitive evaluation included assessment of semantic verbal fluency (animal and vegetable naming); auditory attention and working memory (DigitSpan forward and backward; visuospatial skills and visual memory (Benson Complex Figure copy and recall);[43] visual attention and set shifting (Trail Making Test A and B);[44] contextual verbal learning and memory (Craft Story immediate and delayed recall);[45] and confrontational naming (Multilingual Naming Test).[46]

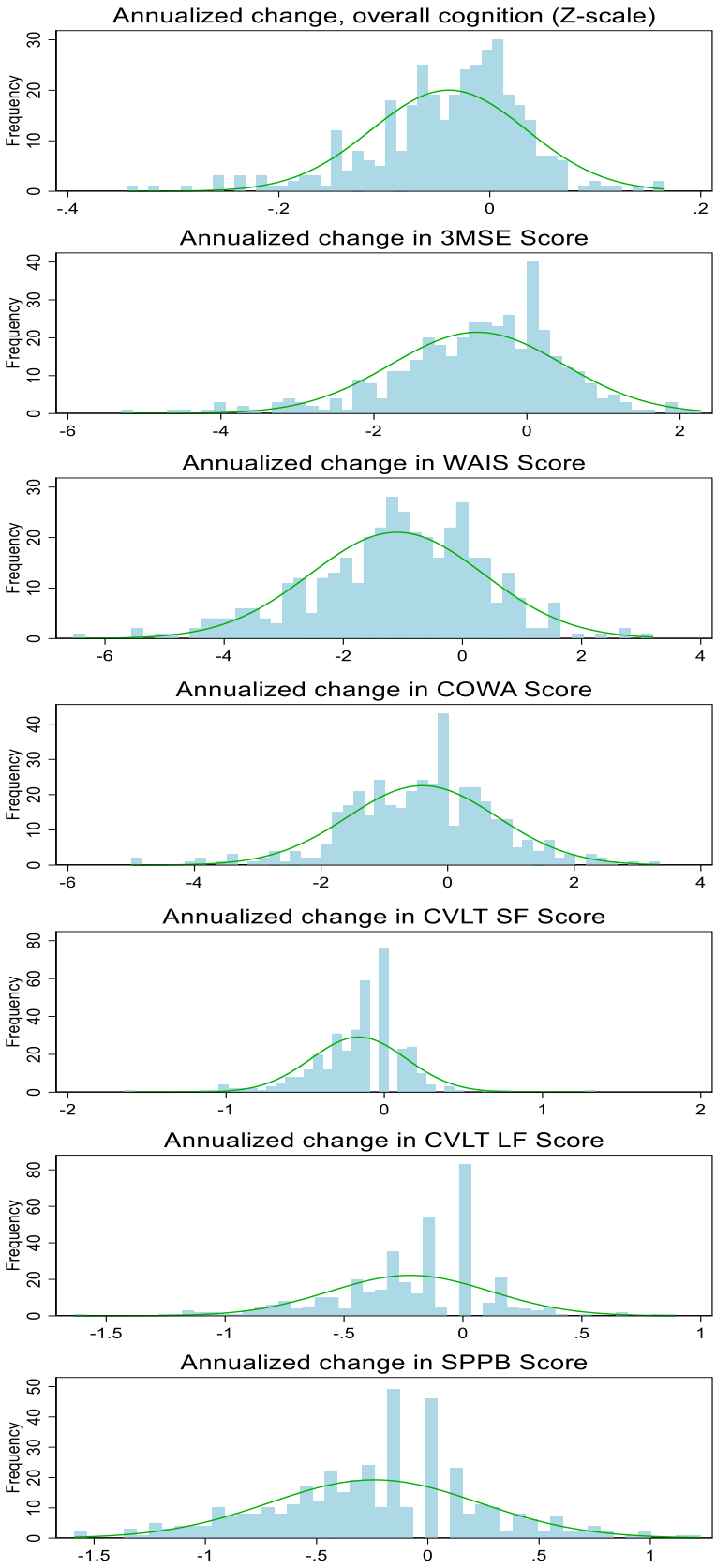
*Self-report Questionnaire*: At the office visit, consistent with the previous protocols,[27] participants also filled out questions on sociodemographics such as age, sex, years of formal education, household income, marital status, and language use; detailed neurological and family medical history, with a focus on neurological and cardiovascular conditions, events, and symptoms; health behaviors, including personal use of tobacco and

alcohol; as well as standard psychometric scales or instruments, including the Center for Epidemiologic Studies-Depression scale,[85,86] and health-related quality of life Short Form 36.[87,88] New instruments included in this examination visit only were: Brief Resilience Scale (BRS) [47]; Chow health literacy scale; and Alzheimer's Disease Knowledge Scale (ADKS).[48] Field staff were present for assistance on these questionnaires if requested, but participants were allowed to answer the questionnaires without specific guidance or interference.




**eFigure 1**: CONSORT diagram of participants recruited for original Strong Heart Study (SHS) cohort (1989-1999), and the ancillary Cerebrovascular Disease and its Consequences in American Indians (CDCAI) study Visit 1 (2010-2013) and Visit 2 (2017-2019)

**eFigure 2:** Histograms of individual annualized rate of change in cognitive test scores between Visit 1 (2010-2013) and Visit 2 (2017-2019) for American Indian adults over age 65 years. Overall cognition based on individual mean score of Z-standardized cognitive test scores for 5 domains (excluding SPPB); other test scores measured as absolute change in test performance. All measures divided by years between examinations.



**eTable 1**: P-values for associations of participant factors across all 3 categories of change in function (loss; same; gain) for each test

| | Overall cognition | 3MSE | WAIS | COWA | CVLT sf | CVLT lf | SPPB |
|---|---|---|---|---|---|---|---|
| Age (years) * | **0.0009 (0.036)** | **0.0001 (0.011)** | 0.711 | 0.323 | **0.0002 (0.011)** | 0.214 | 0.402 |
| Sex | 0.411 | 0.463 | 0.895 | 0.417 | 0.559 | 0.865 | 0.459 |
| Education (yrs) * | 0.331 | 0.999 | 0.661 | 0.039 | 0.766 | 0.604 | 0.959 |
| Smoking | 0.316 | 0.968 | 0.103 | 0.130 | 0.147 | 1.000 | 0.050 |
| Alcohol use | 0.889 | 0.173 | 0.228 | 0.542 | 0.923 | 0.443 | 0.568 |
| Hypertension | 0.925 | 0.596 | 0.561 | 0.911 | 0.407 | 0.609 | 0.019 |
| Diabetes | 1.000 | 0.108 | 0.269 | 0.560 | 1.000 | 0.557 | 0.102 |
| CKD | 0.597 | 0.960 | 0.067 | 0.439 | 0.978 | 0.094 | 0.522 |
| BMI ($kg/m^2$) * | 0.077 | 0.036 | 0.650 | 0.143 | 0.267 | 0.595 | 0.391 |
| Neuro sympt | 0.878 | 0.808 | 0.987 | 0.554 | 0.825 | 0.794 | 0.463 |
| TBI | 0.449 | 0.114 | 0.705 | 0.022 | 0.691 | 0.087 | 0.401 |
| Stroke | 0.709 | 0.253 | 0.171 | 0.811 | 0.622 | 0.303 | 0.655 |
| Infarcts | 0.625 | 0.432 | 0.930 | 0.981 | 0.162 | 0.966 | 0.913 |
| Hemorrhage | 0.095 | **0.006 (0.17)** | 0.430 | **0.008 (0.17)** | 0.062 | 0.382 | 0.650 |
| Abnormal sulci | 0.064 | 0.059 | 0.009 | 0.337 | 0.124 | 0.516 | 0.603 |
| Abnormal vent | 0.136 | 0.775 | 0.589 | 0.563 | 0.145 | 0.372 | 0.889 |
| Abnormal WMG | 0.176 | 0.055 | 0.699 | 0.099 | 0.087 | 0.249 | 0.205 |

** Kruskal-Wallis equality of proportions test used for age, education, BMI; other tests used Fisher's exact test. Bonferroni = 0.0004; statistically significant FDR values (<20%) in parentheses*