1) Protocol Title

Title: MRI Measures of Cerebrovascular Injury and AD atrophy in a Study of Latinos

Protocol Version Date: Version 1.2, 10/09/2017

2) Objectives

We will perform Magnetic Resonance Imaging (MRI) analysis of individuals participating in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Leveraging the HCHS/SOL cohort affords an efficient and unique opportunity to examine the impact of disparities in vascular risk factors on brain health within a large, understudied population of diverse Latinos spanning the age range of risk for stroke and dementia. Given the heterogeneity of racial ancestry among Latinos in HCHS/SOL, we will characterize the biological substrates of stroke, Mild Cognitive Impairment (MCI), and dementia among the various racial admixtures in this deeply phenotyped cohort. Utilizing cutting edge MRI techniques, we propose to examine the relationship between prevalent vascular risk factors and brain structure throughout the age continuum as well as examine the impact of these measures on cognitive measures amongst middle-aged and older HCHS/SOL participants acquired through a separate grant (Study of Latinos, Investigation of Neurocognitive Aging, abbreviated as SOL-INCA). Moreover, we will extend the scientific impact of these novel imaging and cognitive measures to examine potentially new genetic influences that could lead to new therapeutic directions in stroke and Alzheimer's Disease (AD) treatment which may reduce brain health disparity in this population. The following aims are developed to accomplish these overarching goals:

Aim 1. Comprehensive MRI quantification of 2800 Latinos with normal and impaired cognition (MCI) throughout the age-range of HCHS/SOL. Quantification includes measures of vascular brain injury [i.e. White Matter Hyperintensities (WMH) and integrity, MRI evidence of cerebral infarction] as well as measures of cortical volume, cortical thickness and hippocampal volume to estimate AD patterns of cerebral atrophy.

H1: The extent of MRI measures of vascular brain injury will be associated with the extent of vascular risk[1] even at an early age[2, 3], potentially explaining some of the disparities in stroke in this population.

H2: Vascular brain injury will contribute significantly to the extent of cognitive impairment (MCI) amongst older individuals after adjusting for known AD genetic risk factors (e.g. ApoE genotype) and AD patterns of cerebral atrophy[4, 5], potentially explaining some of the disparities in dementia in this population.

Aim 2. Leverage fine-scale population structure to identify novel genetic loci for MRI-defined vascular injury and structural endophenotypes and their neurocognitive outcomes (in SOL-INCA subgroup). We will use methods of association testing that incorporate global and fine-scale population structure to characterize pan-ethnic and ethnic-specific loci for vascular injury endophenotypes, MCI, AD and related dementias.

H1: There is overlap in the genetic architecture of brain MRI endophenotypes across ethnically-diverse Latino populations, which can be leveraged to fine-map novel genetic loci for brain MRI endophenotypes.

H2: There is overlap in the genetic architecture of brain MRI, MCI, AD and related dementia endophenotypes, which will improve the power to detect associations and help understand the important underlying biological mechanisms.

3) Background

Why Study Vascular Brain Injury in Latinos?

Understanding the biology of brain vascular injury, MCI and AD within the Latino population is relevant for at least three reasons. First, by 2050 nearly one-in-three older Americans will be Latino[6] and at increased risk for cerebral vascular disease (CVD) and dementia[7-11], including AD. We hypothesize that CVD may have greater impact on cognition within HCHS/SOL, particularly for Cuban, Dominican and Puerto Rican Latinos.[7-9, 12] Second, while dementia has traditionally thought to be mostly due to AD[13], recent consensus[14] suggests that most dementia is due to a combination pathologies, particularly the combination of AD and CVD [14-16]. The impact of CVD on AD incidence is also supported by multiple epidemiological studies that find vascular risk factors (VRFs) are strong predictors of AD[17, 18] and that AD dementia risk increases in association with increasing numbers of individual VRFs[7, 19]. VRFs are highly prevalent among older individuals[20, 21] and are associated with cognitive decline[22], incident MCI and dementia[23], independent of AD pathology[24, 25]. MRI measures of vascular brain injury such as infarction and white matter hyperintensities (WMH) are similarly associated with increased risk for dementia [23, 26-30]. Furthermore, these MRI features (endophenotypes) appear to be under genetic influence that differs by race and ethnicity[31-37]. Third, brain injury associated with VRFs begins early in life[2, 3] and is predictive of future stroke and mortality[23]. Stroke is the leading cause of disability in the US[38] and is more prevalent among Latinos[38]. Despite declining mortality from stroke—assumed due to improved control of VRFs—a substantial proportion of the population are in less than ideal cardiovascular health, particularly Blacks and Mexican Americans[38(Chart 2-5)]. Further, the impact of VRFs on stroke incidence differs by race and ethnicity suggesting the need for tailored prevention strategies[39]. Understanding the impact of VRFs on brain injury among various Latino communities throughout the life span may improve risk stratification[40] leading to further tailoring of preventative strategies specific to this higher risk population that will likely reduce disparities in disease, disability and mortality.

Why Study the Genetics of MRI and Cognitive Endophenotypes in Latinos?

Genome-wide association studies (GWAS) are identifying increasing numbers of loci for AD and its MRI endophenotypes. Yet, with few exceptions[41, 42], these discoveries are emerging from studies of Whites. Risk alleles for brain MRI endophenotypes and their related cognitive and clinical outcomes have not been widely explored among diverse Latino populations. This study, therefore, would provide a unique opportunity to leverage the rich collection of newly acquired genetic data to identify novel genetic loci for MRI-defined CVD and structural endophenotypes and cognitive outcomes. We hypothesize that there is a substantial overlap in the genetic architecture of MCI, AD and brain MRI endophenotypes. These quantitative, heritable traits, which lie in the causal

pathway to the disease but are closer to the genes than the clinical phenotype, will improve power to detect associations to elucidate the biological mechanisms that underlie disease.[43] We also expect that there is substantial overlapping genetic component influencing brain MRI endophenotypes across diverse populations, but there may also exist important population-specific loci and variants. An effective strategy to characterize loci for these traits will combine evidence across multi-ethnic populations, capitalizing on their shared genetic architecture.

How will this study help extend knowledge of CVD, genetics, brain injury and cognition?

The proposed project offers a unique opportunity to study a large and representative group of Latinos and will extend current scientific knowledge by contributing to a growing and increasingly diverse MRI and genetics database from other community based studies such as the Framingham Heart Study (FHS), Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Chicago Healthy Aging Project (CHAP), Washington Heights Inwood Columbia Aging Project (WHICAP) and the Northern Manhattan Stroke Study (NOMAS) that have similar imaging variables. Dr. DeCarli and the IDeA laboratory have contributed MRI data to a majority of these studies. Drs. DeCarli and Fornage are active, senior members and Dr. González is a newer member of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium which utilizes these data for multi-racial and ethnic studies[37]. Fully understanding the public health consequences of VRFs on brain as well the genetic influences on brain health and MCI or AD requires large collaborative study groups. Until now, these groups has been limited to data from Caribbean Latinos (e.g. WHICAP and NOMAS), despite the fact that Mexican Americans constitute the majority of Latino Americans[44]. This project, therefore, will likely advance understanding of the prevalence, cognitive consequences and potential differences in genetic architecture of vascular brain injury within the community based and representative Latino population of HCHS/SOL. This information could lead to tailored approaches to treatment to reduce disease disparities among an understudied and diverse cohort of Latinos[39].

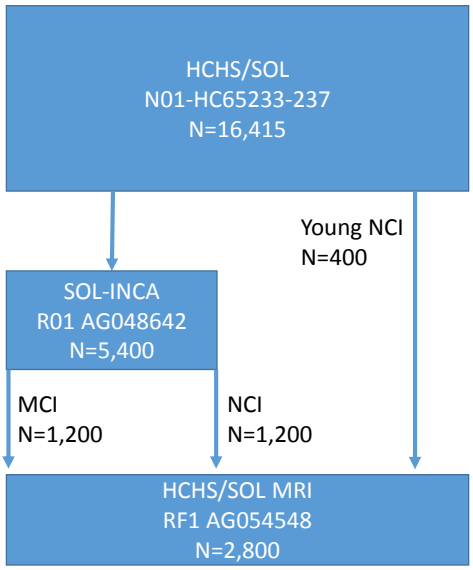
Summary

Rapid Latino population growth coupled with profiles of higher CVD risk suggest that stroke and dementia among Latinos will have an increasing impact on economic, public health, family, and personal disease burden. Moreover, the disproportionate rate of increase of AD and related dementias affecting Latinos will likely exceed existing projections based primarily on Whites[13, 45]. Given the higher VRF prevalence, however, much of this potential disability among Latinos could be avoided by optimal treatment[38]. This study, therefore, could have profound public health impact by filling knowledge gaps regarding brain health and disease by identifying the extent to which VRFs impact brain structure and function as well as potential new genetic influences. As such, the results of this study could guide future public health recommendations to reduce health disparities among the U.S. Latino population.

4) Inclusion and Exclusion Criteria

Overview

Figure 1. Study Cohorts



This protocol is designed to acquire brain MRIs from a subset of individuals participating in the Hispanic Community Health Study/ Study on Latinos (HCHS/SOL) for which the sample design, cohort selection and study implementation parameters have been previously described in detail [46, 47] (Figure 1). In brief, HCHS/SOL is a contract program sponsored by the National Heart Lung and Blood Institute (NHLBI). It consists of 4 recruitment sites located in or near San Diego, Chicago, the Bronx and Miami. There is also a coordinating center located at University of North Carolina, Chapel Hill. The main study supported by NHLBI seeks to examine health risk factors amongst a diverse community sample of Latinos through recruitment and evaluation of 16,451 individuals 18-74 years of age at recruitment with 62.5% being above the age of 44 at the time of recruitment. The study, which began in 2006, has completed two evaluations and a third is in the planning stage. In addition to the main study, a second study, the Study of Latinos, Investigation of Neurocognitive Aging (SOL-INCA; Hector Gonzalez, PI, R01AG048642) was funded in September of 2015. The aims of this ancillary study are to evaluate the cognitive performance of nearly all individuals above 60 years of age (approximately 6,600). These individuals will serve as the main source of subjects for this MRI sub-study (HCHS/SOL MRI, Charles DeCarli, PI, RF1 AG054548). As many as 400 additional younger individuals 25-52 years of age will also be randomly selected from the main HCHS/SOL cohort for this study.

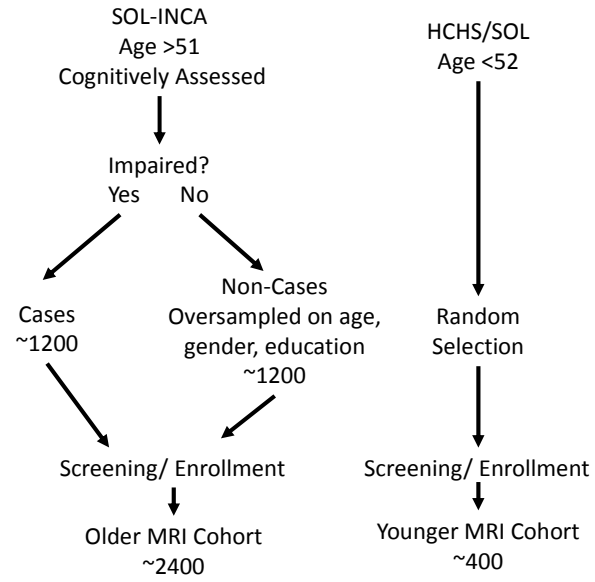
Inclusion Criteria

We plan to study approximately 2800 individuals with cognitive status that will range from normal to mild cognitive impairment. The main inclusion criteria for enrollment are participation in Visit 2 of the Hispanic Community Health Study/ Study of Latinos (HCHS/SOL), however, informed and written consent for this project will be separate from the main HCHS/SOL consent. The project protocols and procedures will require local IRB approval for each of the four Field Centers as well as the two reading centers (see Research Strategy for details). Annual IRB re-approval for the parent HCHS/SOL study, SOL-INCA, and this project will be assured.

Exact subject selection criteria will be based on two factors. First, participation in the associated R01, AG048642 (SOL-INCA) by the Co-PI of this proposal, Dr. González will lead to selection of adults older than 51 years of age. Second, participation through random selection by the HCHS/SOL coordinating center of 400 individuals less than 52 years of age.

The sampling strategy for this project builds on four objectives: 1) Including all identified cognitively impaired cases through SOL-INCA (RO1 AG048642, Gonzalez, PI); 2) Randomization of cognitive normal respondents into two groups (MRI and non-MRI eligible); 3) Oversampling on cognitively normal MRI eligible participants with respect to older age, gender and education; 4) Maintaining the integrity of the HCHS-SOL design to permit generalization to the target Latino populations. Cognitive function and impairment be assessed and determined in SOL-INCA. Briefly, respondents scoring below 1 standard deviation on any of the cognitive test scores with memory or concentration complaints of cognitive decline and no or minimal functional impairment considered "cases" based on NIA and the Diagnostic and Statistical Manual Version 5 criteria.[48, 49] Participants not satisfying these criteria will be eligible for non-cases sampling selection into the MRI study. In addition, a subpopulation of younger participants at Visit 2 (<52 years) will also sampled for this MRI study (See Figure 2). To generate our control subsample, a list of non-cases similar in size to the cases will be generated. Non-cases will be randomly selected, using random ordering procedures established at the UNC coordinating center, from within prevalence calibrated age, sex, education, and possibly Latino background strata. In addition to the above selected cases and controls, a random sample of participants aged <52 and participating in the second HCHS/SOL visit will also be selected using random selection from stratifications based on study site, gender and Latino background. If the SOL-INCA and MRI enrollment rates are different than assumptions, or case composition reveals specific criteria (e.g. CVD or genetic risks) that require additional oversampling, sample selection criteria will be subsequently corrected.

Figure 2. Inclusion Criteria



Inclusion of a Vulnerable Population

Slightly less than half of the subjects enrolled in this study will be cognitively impaired and may become demented, hence they are vulnerable in this context. It is important and justified to study these subjects because we are studying the disorders that caused the cognitive impairments of these subjects. Because there is no other suitable population, to exclude these people from study would deny them, and others affected by the same diseases, the potential benefits of this type of study. Policies and procedures to assess capacity and to gather subject consent or assent with the assistance of a designated representative, however, have been developed and will be employed with this study.

Assessment of Capacity

Consent will be obtained after the study protocol, including the purposes and procedures, risks and benefits of the study are explained. The voluntary nature of participation will be emphasized. A staff member will review the consent form in detail with participants and will invite questions along the way. Written informed

consent will be obtained. A copy of the form will be retained by the subject, and the original will be added to the research participant chart. We will maintain a tracking data base that records and consequently checks that informed consent has been obtained.

A special problem, but one that we have dealt with continually in this line of research, is obtaining consent from people of diminished capacity. While this capacity to consent will not be at issue during recruitment of our MCI subjects or normal controls, progressive cognitive decline is part of the natural history of MCI (and occasionally our normal controls) and therefore may be an issue during follow-up evaluations. Because it is such a pervasive issue with our research, we have developed a policy and procedure for assessing capacity to consent to research. Our current protocol for obtaining consent includes specific procedures for explicitly determining both the understanding of the research study and the willingness to participate. If the subject is unable to understand the consenting process or has great difficulty, then diminished capacity is suggested.

When there is any indication to suggest diminished capacity, we begin by discussing the research directly with the subject to the extent possible to gain as fair an idea as possible of what their understanding of the study and their inclination to participate. The individual's knowledge of the study is supported by the use of a 'Simplified Study Summary' where the procedures of the study are outlined in single sentences. The individual obtaining consent systematically tests understanding of the protocol in a structured way and uses this to make a judgment about the mental capacity of the subject to consent to that particular protocol. If the subject lacks capacity, we still ask that the subject assent to study participation. If he or she refuses to do so, we will not enroll the subject. In addition, we review the consent form with the research participant's legal guardian (if one exists), proxy, next of kin, or familial caregiver according to State Law and require that that person consent to the study as well. If either party refuses we do not enroll the subject. One further point is that we do not obtain "blanket" consent. The procedures involved in this protocol are distinct from other protocols and, therefore, a separate consent will be obtained for all subjects. Finally, capacity to consent is reassessed during each evaluation. Should the study participant lose capacity to consent, assent with co-signature of the appropriate designee is pursued.

Exclusion Criteria

After recruitment and signing of the consent, each subject will be evaluated for MRI eligibility using a "prescreening questionnaire" given in either English or Spanish (see appendix). Those found ineligible for MRI will be excluded from this study. However, other exclusions will include Central Nervous System (CNS) infection, tumor, traumatic brain injury of moderate or greater severity; unstable major medical illness; psychosis not secondary to neurological disease; history of drug or alcohol abuse within 5 years; and sensory or motor defect that precludes neuropsychological testing. Individuals with vascular risk factors including clinically identified vascular events such as TIA, stroke, coronary artery disease, etc. will not be excluded from enrollment.

Many of the subjects will be cognitively impaired, hence vulnerable in this context. It is important and justified to study these subjects because we are studying the

disorders that caused the cognitive impairments of these subjects. Because there is no other suitable population, to exclude these people from study would deny them, and others affected by the same diseases, the potential benefits of this type of study.

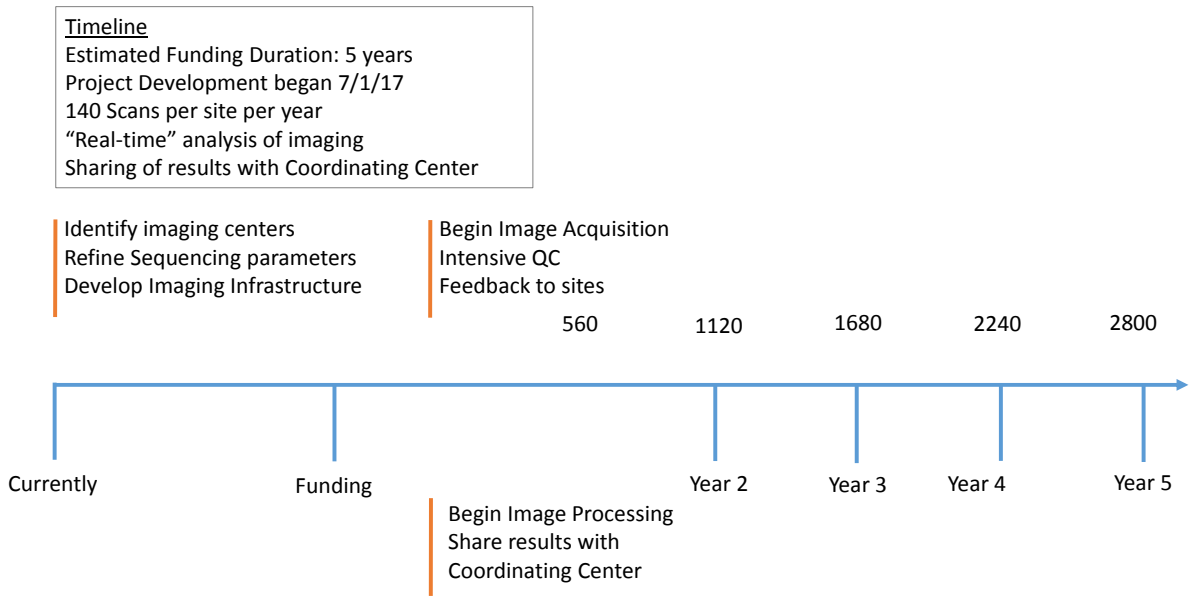
Children, pregnant women, and prisoners will be excluded from this study.

5) Study Timelines

This is a cross-sectional study. Subject participation in this part of the study is only for a single MRI visit. No follow-up is required for this study. The timeline for image acquisition is reviewed below (Figure 3).

Prior to funding, Dr. DeCarli and the UCD team identified imaging centers and developed MRI sequence parameters to assure prompt implementation of the protocol. An organizational and training session is scheduled for spring/summer of 2017. Each site will be expected to obtain consent and obtain 140 subject MRIs a year.

Figure 3 Study Timeline



6) Study Endpoints

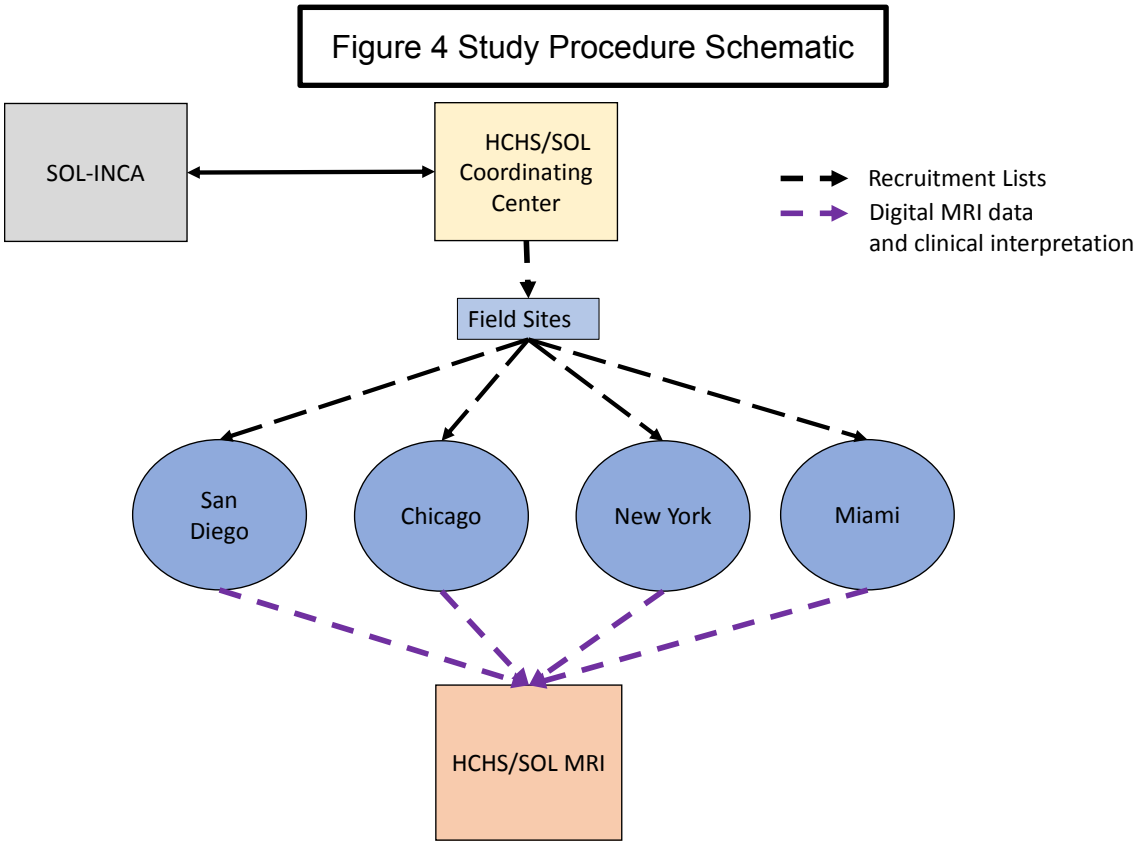
Acquisition of MRI for the proposed 2800 individuals is the primary endpoint of the study. MRIs will be analyzed to obtain various measures of brain structure to associate with demographic, vascular risk, cognitive and genomic data obtained as part of the parent HCHS/SOL study and the SOL/INCA sub-study.

Given that this is a MRI study, no safety endpoints are planned.

7) Procedures Involved

The logistics of MRI acquisition, tracking and quality control has been developed by Dr. DeCarli and the Imaging of Dementia and Aging (IDeA) laboratory at UC Davis through decades of experience. Schematics of how the MRIs will be acquired from the 4 HCHS/SOL sites are summarized in Figures 4 and 5. In brief, the HCHS/SOL coordinating center in collaboration with SOL/INCA will identify candidates for MRI-

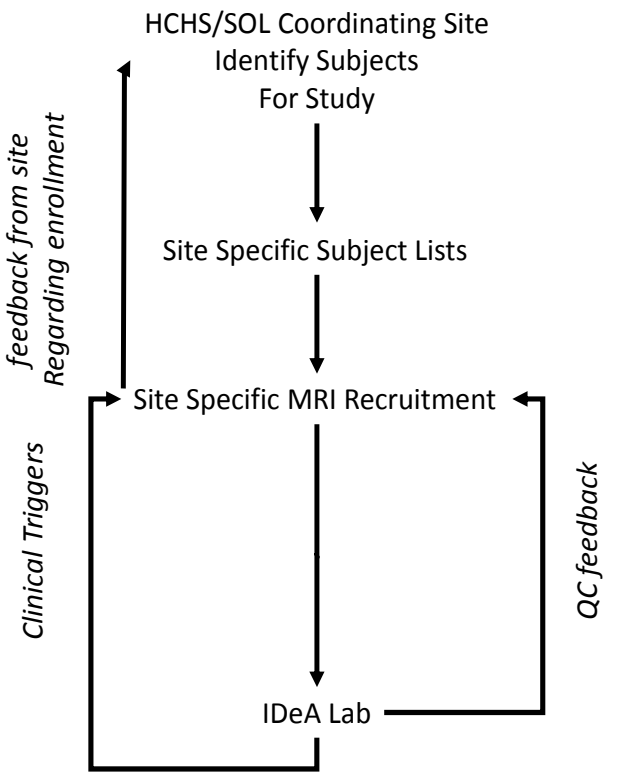
Figure 4 Study Procedure Schematic



qualified subjects in collaboration with the already identified MRI facilities. Field Centers (FCs) will update the coordinating site on status of subject enrollment and denials on a monthly basis. The MRI Centers in collaboration with the FCs will transfer de-identified subject imaging data to the IDeA lab through previously arranged, HIPAA secure electronic data transfer protocols (e.g. Digital Imaging and Communications in Medicine or DICOM servers). The IDeA laboratory has already identified radiologists to perform clinical review of each subject. Each site will attach a DICOM version of each clinical review that also will be transferred to the IDeA lab and stored as an annotation file to each subject within the imaging database. Similarly, the clinical interpretation of each MRI will be reviewed by the PI or his designee to assess clinical relevance. Clinically relevant findings will be communicated to each FC according to a predefined set of notification criteria. The IDeA laboratory will receive the DICOM data, convert to image volume data and compile into an imaging archive. Each image volume then receives quality control with the results stored in a QC database. The IDeA laboratory will monitor enrollment, MRI acquisition, create monthly FC specific progress reports, and coordinate clinical reporting with HCHS/SOL Coordinating Site.

MRI alerts: Subjects with clinically relevant MRI abnormalities (e.g. tumors, vascular anomalies, large clinically undetected cerebral infarction) will be identified, appropriately informed and referred for care by licensed study clinical investigators. Drs. DeCarli and Dr. Lipton (Bronx) are board certified neurologists who will collaborate in making appropriate referrals when needed.

Figure 5 Study Procedure Flow Chart

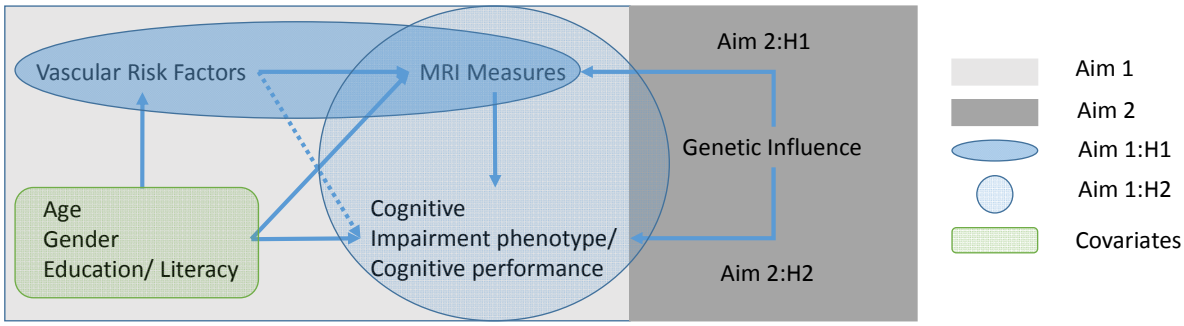


8) Data and/or Specimen Management and Confidentiality

To preserve confidentiality, individuals will be assigned research identification (ID) numbers. Creation of the research identification numbers will be done by the HCHS/SOL Coordinating Center. The ID linking databases will be securely stored at each field site. Only coded data/images will be sent from each field site. All MRI data, including the clinical assessment, will be stored in DICOM format and transferred through secure DICOM servers from each site to the IDeA laboratory for analysis. All DICOM files, constructed images, process files and summary reports will be stored in the IDeA laboratory in the UC Davis Center for Neuroscience. The servers that host these data have no direct connection to the internet and sit behind a UCD Center for Neuroscience firewall assuring the highest level of data protection. In addition, all data on the IDeA servers is mirrored and weekly backups are created offsite to assure protection against system malfunction.

Summary measures of the MRI data analysis will be sent to the HCHS/SOL Coordinating Center on a monthly basis. The HCHS/SOL Coordinating Center is the governance arm of the HCHS/SOL program and will oversee data sharing to authorized users of the HCHS/SOL data. In addition, Dr. DeCarli and Dr. Gonzalez will work with the HCHS/SOL Coordinating Center to establish a publications committee to facilitate distribution of data related to this protocol and publication of manuscripts.

Figure 6 Overall Data Analysis Schematic



Data analytic plan

Overview

Analyses for **Aim 1** will focus on vascular risk predictors of brain injury, co-varying for age and gender and education when considering the role of brain structure on cognition. Given the number of MRI measures potentially available, we have chosen to focus on those most relevant to stroke risk and cognition and which have been reported for other community cohorts of European or African descent[23, 50-57]. Fortunately, we have prior experience on the study of brain structure and cognition within a diverse population[58]. Analyses for **Aim 2** will focus on identifying novel genetic loci for MRI-defined CVD and structural endophenotypes and their neurocognitive outcomes (in the SOL-INCA subgroup). We will use methods of association testing that incorporate global and fine-scale population structure to characterize pan-ethnic and ethnic-specific loci for CVD endophenotypes, MCI and dementia. These analyses will similarly focus on the most relevant MRI measures identified in Aim 1. Figure 6 summarizes the overall analytic approach for the specified aims and hypotheses. Solid lines indicate presumed mechanistic association, whereas the dotted line indicates potential association.

Planned Analyses for Aim 1. For this aim, we will assess MRI measures of vascular brain injury (i.e. WMH and integrity and MRI infarction) as well as measures of cortical volume, cortical thickness and hippocampal volume to estimate AD patterns of cerebral atrophy. *The primary outcome measures for* **H1** *will be: 1) total WMH volume, 2) presence and number of MRI infarctions and cerebral microbleeds. Secondary outcomes for this aim will also include: 1) regional measures of white matter microintegrity as evidenced by FA magnitudes in cerebral white matter areas pre-defined to be associated with vascular injury[2, 3, 54, 59] and 2) regional rCBF as measured by blood flow MRI. The primary outcome measures for* **H2** *will be: 1) the "AD signature" measure derived for each participant [4] and 2) Hippocampal volume.*

Statistical methods: Our modeling approach will reflect the analytic plan of Figure 6. First, we will independently examine the direct associations between VRFs, brain injury measures, cognitive performance, and AD markers of cerebral atrophy. We will use generalized linear model (GLM)[60] to identify individual VRFs that are associated with each of the primary and secondary MRI measures of brain injury. Interactions between cognitive impairment status and each VRF in predicting outcome measures will also be tested in follow-up models to examine differential brain injury estimates between MCI and cognitively normal. All crude and covariate adjusted GLMs will appropriately reflect the distributions of the outcome variables, and appropriate methods for testing assumptions and model fit will be considered.[60-62] We will follow the same process to examine relationships between VRFs and AD markers of atrophy and cognitive performance. Interactions between VRFs and impairment status will only be considered

in the case of AD markers. Similarly we will use GLMs to sequentially test the associations between individual indicators of vascular brain injury and measures of cerebral atrophy, individual cognitive task performance and cognitive impairment phenotype. Fully adjusted models will also account for AD specific genetic risk factors, and through interactions examine differential cerebral atrophy estimates among MCI and cognitively normal respondents. Second, we will specify structural equation modeling to simultaneously test all hypothesized associations between independent variables and outcome within a single framework.[63] SEM is a flexible analytic method permits the specification of both simple path analyses of association between manifest variables as well as complex measurement and structural models to examine relationships between both manifest and latent variables and any interactions thereof.[64, 65] SEM's flexibility is demonstrated by its capacity to test mediation and moderation effects. [66-69]

When AD markers of cerebral atrophy outcomes are considered as exogenous outcomes, our model will be estimated using the whole sample and as multi-group models based on participants' cognitive impairment status. Through multi-group SEMs we can formally test the equivalence of the structure and magnitude of the relationships across cognitively normal and impaired groups, and appropriate steps will be undertaken to test for invariance when latent constructs are included. [70-72] Follow-up analyses will re-specify our structural equation model to examine the mediation effects of brain injury measures in the relationship between VRFs and measures of AD brain atrophy and cognitive function. We will estimate and examine all direct, indirect, and total effects. Bootstrap techniques will be used to assess statistical significance and generate confidence intervals for indirect effects. Model fit will be assessed using a series of standard statistics including overall, incremental and comparative fit indices. [71, 73] We will use Full Information Maximum Likelihood (FIML) method to conduct all SEM analyses in MPLUS version 7, and account for the complex design of the MRI sample. FIML accounts for all available data in estimating model parameters. FIML is capable of generating unbiased population estimates in the presence of missing data, has superior properties compared to extant prevalent methods and is more computationally feasible and requires less modeling assumptions relative to multiple imputation methods. [74-76]
Power Analysis: We will use G*Power (v.3.1.7) to conduct our power analysis for aim 1. Under the normal distribution, we estimated that a sample as small as N=500 would allow us to recover a small effect size corresponding to an increase in explained variance (R^2) as small as 2% when testing one additional predictor in a multivariate model with 8 total predictors, assuming a standard power of 0.8 and a type-I error alpha=0.01. Under conditions of testing a combined set of multiple (X=9; equating to the number of VRFs considered) additional covariates, we estimated that a sample size as small as N=1000 would be sufficient to recover an equally small effect size, assuming a total number of 15 tested covariates and similarly set power and type-I error. We considered multiple scenarios for each of the Logit and Poisson models using three different assumptions for the distribution of main predictor: standard normal (S1), binomial (S2: 10% prevalence), and binomial (S3: 30% prevalence). Under each assumption and for each distribution we considered 1) multiple probabilities (under the Logit) and base rates (under the Poisson), and estimated recoverable estimates of Odds Ratios and Relative Rates for crude and adjusted models. When adjusted models were considered we set the explained variance (R^2) contributed by the model covariates (not including the predictor) to a conservative 40%. All parameters were estimated assuming a sample size equivalent to our proposed N=2400, a standard power of 0.8 and a type-I error set to 0.01.

Predictor (X)	S1	S2	S3		S1	S2	S3
GLM: Logit		**OR**		**GLM: Poisson**		**RR**	
(1) Probability (at X=0)=0.05				**(1) Base Rate (at X=0)=0.5**			
Crude	1.37	2.30	1.82	Crude	1.11	1.35	1.21
Adjusted: R^2=0.40	1.50	2.79	2.12	Adjusted: R^2=0.40	1.14	1.45	1.27
(2) Probability (at X=0)=0.2				**(2) Base Rate (at X=0)=1**			
Crude	1.20	1.70	1.43	Crude	1.08	1.24	1.15
Adjusted: R^2=0.40	1.26	1.95	1.58	Adjusted: R^2=0.40	1.10	1.32	1.19
(3) Probability (at X=0)=0.2				**(3) Base Rate (at X=0)=2**			
Crude	1.16	1.60	1.36	Crude	1.06	1.17	1.11
Adjusted: R^2=0.40	1.21	1.83	1.49	Adjusted: R^2=0.40	1.07	1.22	1.14

Planned Analyses for Aim 2. Leverage fine-scale population structure to identify novel genetic loci for MRI-defined CVD and structural endophenotypes and their cognitive outcomes (in SOL-INCA subgroup). We will use methods of association testing that incorporate global and fine-scale population structure to characterize pan-ethnic and ethnic-specific loci for CVD endophenotypes, MCI and dementia.

H1: There is overlap in the genetic architecture of brain MRI endophenotypes across ethnically-diverse Latino populations, which can be leveraged to fine-map novel genetic loci for brain MRI endophenotypes.

H2: There is overlap in the genetic architecture of brain MRI endophenotypes, MCI, and dementia, which will improve power to detect associations and help understand the important underlying biological mechanisms.

Genetic data available in SOL: We will take advantage of multiple sources of SOL genotype data: The genome-wide SOL Custom SNP array, which is based on the Illumina Omni2.5 but has 150,000 additional custom SNPs designed to improve coverage of American Indian-specific variants and various genes of interest; Imputations to the 1000 Genomes reference panel (Phase 1) have been completed by the SOL Genetic Analysis Center (GAC) led by Drs. B. Weir and C. Laurie and are available to this study; the NHGRI-PAGE-I Metabochip array; the NHGRI-PAGE-II array, which is a custom array of approximately 200,000 SNPs designed to comprehensively capture DNA sequence variation at established CVD-related loci across ethnically diverse populations and will be genotyped on the SOL cohort through the CALiCo-PAGE ancillary study (K. North, PI; M. Fornage, Co-I).

Imputation with improved population-specific reference panels: The 1000 Genomes (1000G) reference haplotypes are the most commonly used reference panel for imputation and provide a robust means of imputation of common variants (Minor Allele Frequency (MAF) >1%) in diverse populations.[77, 78] However, for rare variants and for variants that are specific to populations not well represented in the 1000G, its utility is more limited. Several studies have shown that population-matched reference panels combining the 1000G data and sequence data derived from large scale projects such as the Exome Sequencing Project (ESP) enhance the quality of imputation for rare variants, including those from admixed populations.[79-81] In an effort to improve on the current 1000G reference panel, the Haplotype Reference Consortium has assembled whole

genome sequence data on over 30,000 subjects (mostly of European descent) to create a very large reference panel of human haplotypes. The first release (July 2015) consist of 64,976 haplotypes at 39,235,157 SNPs, all with an estimated minor allele count of >= 5.[82] The increasing availability of whole genome and whole exome sequence data provide important resources for improving population-specific imputation reference panels. This strategy was recently described in the ESP, where exome sequence data was combined to the 1000G data to generate an African-American reference panel that outperformed the 1000G reference panel for imputation of rare variants in African-Americans.[81] We will ensure that subjects included in the reference panels are not included in our target study sample and are not first degree relatives of samples in our target study. Prior to imputation, we will pre-phase our study samples using SHAPEIT2.[83] To improve phasing accuracy, we will also consider a long range phasing based on pairwise sharing of haplotypes inferred to be IBD.[84] Imputations will be performed using IMPUTE2 in 5Mb non-overlapping windows using a 250 kb buffer and following best practices recommended by the developers.[85] Alternatively, the piecewise IBS-based method implemented in MACH-Admix has been shown to be efficient and flexible.[86] Post-imputation QC will be performed including examination of imputation info score and Hardy-Weinberg equilibrium (HWE). SNPs with poor imputation quality (score<0.5) and HWE ($p < 10^{-6}$) will be filtered out prior to analysis.

Statistical methods of association testing: We will use a mixed model approach developed by the SOL GAC statistical team to test for genetic association with brain MRI phenotypes. PCs will be included as fixed effects. Typically, the first 5 PCs are sufficient to control for population structure in SOL. Genetic analysis group will also be included as fixed effects. Additional fixed effects will include relevant covariates such as age, sex, recruitment center, total intracranial volume, and APOE genotype (for cognitive measures) as appropriate. Sampling weights to deal with the survey sampling design of the study will also be included as fixed effects. KCs estimates, household membership, and census block group membership will be included as random effects. To test for possible differences across genetic analysis groups, we will include a group-by-SNP interaction term. Alternatively, we may performed stratified analyses by genetic analysis group and carry out a meta-analysis testing for heterogeneity using Cochran's Q statistics. Because we do not know a priori how brain MRI phenotypes' distributions will compare among cognitively normal and cognitively impaired individuals, we will perform analyses separately in the 2 sub-cohorts and combine results by meta-analysis.

Power Analysis: Power was calculated using Quanto assuming a standard normal distribution for the quantitative MRI endophenotypes for samples sizes of 1600, 1200, and 2800, corresponding to the 2 sub-cohorts of cognitively normal and cognitively, impaired individuals, respectively, as well as the combined sample; and assuming an $\alpha=5x10^{-8}$. Power is given for effect sizes expressed in standard deviation units (SD) and ranging from 0.5 to 2 (roughly equivalent to 0.5% to 2.5% variance explained depending on MAF and N).

Minimal detectable effect in SD		MRI traits in cognitively impaired individuals		MRI traits in cognitively normal individuals		MRI traits in all scanned individuals	
	N	1200		1600		2800	
	MAF	0.01	0.05	0.01	0.05	0.01	0.05
0.5	Power	0.13	46.79	0.42	77.63	4.24	99.7
1.0	Power	29.03	99.99	58.14	99.99	97.89	99.99
2.0	Power	99.99	99.99	99.99	99.99	99.99	99.99

We have a good to excellent power to detect a variant of low frequency with a small to moderate effect in each of the subgroups and in the combined sample. We have an excellent power to detect a common variant with a small to moderate effect in each of the subgroups and in the combined sample.

Replication and generalizability to other ethnic groups: The proposed project is uniquely poised to identify novel genetic loci influencing brain MRI endophenotypes in Latinos. Replication and validation of the discoveries in independent samples as well as generalizability of these discoveries in populations of other ancestries are important goals of this application. The investigators of this proposed application have a strong record of collaborations in large neurogenetics consortia, including CHARGE, ADSP, ISGC and other studies. These collaborations provide ample opportunities to expand and generalize our findings through meta-analyses. We will use meta-analytical techniques specifically designed for data from populations of differing ethnic/racial background. For example, Morris et. al.[87] developed a method that combines association results from different ethnic groups by taking advantage of the expected similarity in allelic effects between the most closely related populations. This method has been implemented in the MANTRA software. The method by Wang et al.[88] also provides a natural framework for combining association evidence from multiple racial/ethnic groups. It quantifies the degree of over-representation of associated variants in a pre-defined genomic region (e.g., gene), given a pre-specified definition of statistical significance. It can be applied to both dichotomous and quantitative traits, and allows for the presence of allelic heterogeneity between the groups. More recently, an Empirical Bayesian approach, implemented in the program XPEB, has been developed, which efficiently integrates association evidence from a larger population sample such as European ancestry (EUR) with that of (smaller) minority sample in an adaptive manner.[89] The algorithm uses summary statistics from association analyses, one in a target minority sample and one from an auxiliary sample (typically a large EUR); and computes local false-discovery rates for each variant based on the posterior probability that the variant is not associated in the minority population given its summary statistic in the EUR and minority analyses.[89] XPEB has the ability to safeguard against inflated FDR in the presence of genetic heterogeneity by discarding information from the auxiliary sample. Conversely, when the loci coincide in the 2 groups, XPEB approximates the power of a fixed-effect meta-analysis.[89]

9) Data and/or Specimen Banking

Summary Data Management

In order to manage the large amount of data generated from MRI analysis of community based studies, the IDeA laboratory has developed an extensive database structure for acquisition, permanent storage and reporting of MRI

summary measures. We use custom desktop software that is integrated with a MySQL database to do analyses and report the results. The database is divided into 3 modules: core, pipeline management, and ROI. The database module tracks studies, subjects, scans and their metadata. The pipeline management module tracks each scan within its post-processing pipelines. The ROI module contains all of the various ROI statistics that are created with analysis. The main interface allows for subject selection from the database using a search engine that can identify individual subjects or groups of subjects depending on search specific language context. A variety of reports are available once a subject list is created. These include tracking via the image library inventory or specified ROI measures such as tissue volumes, regional cortical thicknesses, diffusion or perfusion parameters. Data is output by study title, ID, image date and analysis results as a coma delimited file. When image voxel based analyses are required (e.g. gray matter density[2, 3] or multimodal analyses[1, 30, 90-92]), a separate "project directory" is established from links to the image archive for the primary analysis. However, even these data may be summarized and reported via development of "statistical ROIs"[2, 3, 93, 94] that can be seamlessly integrated into the data extraction and reporting pipeline. Importantly, this data management system, along with our detailed processing pipeline, enable comprehensive tracking, reporting and sharing of each step along the pathway of data analysis within our laboratory by adopting a "reproducible science" approach that entails exhaustive documentation of each step of the data receipt from DICOM file storage to summary measure reporting. Summary MRI measures as well as MRI alerts will be electronically transferred to the HCHS/SOL coordinating center on a monthly basis or more often as needed.

Data Sharing

All subjects participating in this project will be asked to sign a data sharing agreement as part of their consent. This allows de-identified data from this project, such as summary MRI data or constructed, but de-identified image volumes to be shared with investigators either associated with the project or investigators and research sponsors outside of the project. Raw digital imaging data will be shared through a UC Davis approved materials transfer agreement and are subject to the rules and regulations stipulated by the University of California system as well as HCHS/SOL mandates. These data are shared with additional pseudo-ids to further prevent subject identification.

The data will be transferred via DICOM servers to the IDeA laboratory. DICOM servers are confidential point-to-point connections commonly used to transfer research participant imaging data. These data, however, will be de-identified and therefore will contain no Personal Health Information (PHI).

All summary data from this project will be securely transmitted electronically to the HCHS/SOL Coordinating Center at UNC-Chapel Hill. Under the current Data Use Agreement (DUA), only HCHS/SOL investigators and collaborating researchers who have entered into the DUA would have access to the de-identified data. Access to the HCHS/SOL data is only provided through secure electronic communications. Under this DUA, HCHS/SOL as well as SOL/INCA data can only be stored and used, including data analyses, on secure local servers and cannot be stored on personal computers. Lastly, staff with access to sensitive participant

data will have completed the online NIH Computer Security Awareness Training prior to accessing SOL, SOL-INCA data and data from this project.

10) Provisions to Monitor the Data to Ensure the Safety of Subjects

To assure research participant safety, each MRI will be evaluated by a local radiologist. In addition, all clinical assessments will be transferred to the IDeA laboratory along with the radiological interpretation. Dr. DeCarli or suitable designee will review the report and the images. Subjects with clinically relevant MRI abnormalities (e.g. tumors, vascular anomalies, large clinically undetected cerebral infarction) will be identified and the Field Center at which the MRI was obtained will be notified. As part of the consenting process, each subject will designate the mode of notification, if needed, either directly or through contact with a specified physician. Should a MRI "alert" be generated, the PI will follow the subject directive so that the subject is appropriately informed. Dr. DeCarli and Dr. Lipton (Bronx) are board certified neurologists who will collaborate in making appropriate referrals when needed.

11) Withdrawal of Subjects

Participation in this study is dependent on subject willingness as well as safety to undergo MRI. As a consequence, some subjects will agree to participation and sign consent, but be unable to participate due to contraindications to MRI. These subjects will be considered "withdrawn" from the study. These individuals will be tracked at each Field Center with the data being shared with the HCHS/SOL coordinating center.

12) Risks to Subjects

Protection of human subjects is of the utmost concern to the investigators of this project. The policies and procedures described here apply to all personnel and sites conducting research under the auspices of this project, including collaborations that use project related materials.

This project was reviewed for scientific merit in relation to participant burden and was approved by the HCHS/SOL Ancillary Studies Committee, Steering committee (see enclosed approval letter from Dr. Olson, Chair of the SOL Steering Committee) and the Observational Study Monitoring Board (OSMB).

There are a number of potential, albeit, minor risks associated with participation in this protocol. These are reviewed individually.

Potential risks

MRI

The primary risks of MR imaging occur in individuals with pacemakers, metal clips in the brain, and large ferromagnetic implants. Some people find the scanner claustrophobic and cannot tolerate it for this reason. Any individual with a contraindication for clinical brain MRI will be excluded from this study. There are no other known risks associated with MR imaging. To mitigate the risks we do the following: All subjects will answer detailed questions about potential ferro-magnetic implants or shrapnel that could result in injury during MRI. In addition,

all subjects are directly observed during the imaging procedure and are in constant communication with the MRI technician in the rare case of claustrophobia.

Identification of clinical problems
There is potential that important clinical problems will be identified after the MRI. As a consequence, all MRI scans will be reviewed by local radiologists to identify serious abnormalities like brain tumors or aneurisms, and these findings will be reported to participants and their medical care providers. Drs. DeCarli and Lipton are all experienced neurologists and will carefully review any problems identified by the Field Center radiologists to determine if intervention is required. In the event that concerns are identified, they will be immediately referred to their local health care providers for further diagnosis and treatment. The project neurologists will also be available to answer questions raised by the subjects and their health providers regarding the identified MRI abnormality.

Confidentiality
The most serious risks associated with this study relate to loss of privacy or the potential exposure of personal medical information, particularly data related to risks for mild cognitive impairment, Alzheimer's disease or other forms of dementia. The improper release of such information could clearly have negative effects on the research participant, for example adversely affecting his or her ability to obtain health or life insurance, and could possibly carry negative effects for blood relatives as well.

Data Sharing
The risks related to data sharing involve accidental disclosure of personal information and loss of privacy. Physical files are kept in close proximity to office staff during business hours, and are in locked rooms at other times. Computer files are password protected. Data transmitted over the internet will never contain names or unique identifiers. When files are distributed for analysis, HIPAA specified identifiers are removed. We will study people who are completely healthy as well as persons who are cognitively impaired. Thus, inadvertent disclosure of the fact of a subject's participation in this protocol would not convey any information about their health status. The data files have no names on them so even in the unlikely event that someone accessed these files, they still would convey no unique identifier unless the unauthorized user also somehow gained access to the ID/name key which will be stored offsite at the HCHS/SOL coordinating center.

13) Potential Benefits to Subjects

Dementia is a leading cause of disability in older adults and is associated with devastating personal, social, and economic burden. The data collected as part of this study will help identify trajectories of cognitive decline leading to cognitive and functional impairment and AD. It will also shed light on how variables associated with vascular disease influence cognitive function in older individuals.

The research procedures of this grant do not generally directly benefit participants (except insofar as many procedures end up rendering a clinical diagnosis and possibly improving the quality of their medical care at no charge to

subjects). The potential risks of participation are low to moderate, and can be very effectively mitigated. Participants are told that they are very unlikely to accrue personal, tangible benefit from their research participation. Nonetheless, participation is very rewarding for many because it is a way that they can contribute to the fight against the disorders that have hurt them. Thus, there is a low degree of personal benefit, a substantial degree of general societal benefit to be weighed in relation to lesser, highly controllable risks.

14) Multi-Site Research

This is a multi-site study where Dr. DeCarli is the lead investigator and Dr. Gonzalez is the Co-Principal Investigator. There are 4 Field Centers, the Coordinating Center, and the IDeA laboratory (located at UC Davis) that will be actively involved in subject selection, data collection and measurement. The IDeA lab at UC Davis is only receiving coded data for analysis. The Informed Consent process will take place at the individual field sites. Fortunately, this protocol takes advantage of the HCHS/SOL infrastructure managed by the Coordinating Center. Specific aspects of this protocol, however, are summarized here.

Site Communication

Site communication will be maintained in two ways. First, all Key Personnel of the grant will participate in monthly conference calls. The agenda for these calls will be established by Drs. DeCarli and Gonzalez in consultation with the Coordinating Center. In addition, Key Personnel will elect volunteers to serve on the publications committee that will oversee appropriate use of the measures provided by this protocol.

Finally, HCHS/SOL has a yearly investigator meeting that Drs. DeCarli and Gonzalez will attend along with the Key Personnel of the HCHS/SOL MRI grant. A HCHS/SOL MRI break-out meeting will be part of the overall agenda. This will serve as an opportunity to present updates as to study progress and logistical concerns. In addition, as data permits, investigators may present research findings at the main HCHS/SOL meeting.

Minutes of the monthly teleconferences and yearly break-out meetings will be kept, reviewed by Drs. DeCarli and Gonzalez and then shared with the Coordinating Center and made available to all Field Centers.

In addition, we will establish a Website similar to, or associated with, HCHS/SOL https://www2.cscc.unc.edu/hchs/. This will serve as a resource page for study progress, downloading of important files such as SOP, protocol addendums, MRI screening forms, etc.

As noted above, these procedures and resources will enable rapid communication of study problems and interim results. They will also facilitate dissemination of results through the publication committee. In addition, with the assistance of the Coordinating Center:

- All sites will have the most current version of the protocol, consent document, and HIPAA authorization.

- All required approvals will be obtained at each site (including approval by the site's IRB of record) prior to first subject enrollment.
- All modifications to the protocol will be communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.
- All Field Centers will safeguard data as required by local information security policies.
- All local site investigators conduct the study appropriately.
- All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Study Closure

This study will require five years to complete. Results of this study, however, may indicate the need for competitive renewal of the grant to continue research. Should the study close, there will be a final investigators meeting that will bring together all the Key Personnel to review the progress of the study, a summary of significant results and publications. The Field Centers will then be encouraged to communicate this information to the participants.

15) Sharing of Results with Subjects

Sharing of MRI results with subjects will only occur under the auspice of "MRI Alerts" where clinically relevant findings, as described above, are revealed to the subject or their designated physician.

Findings arising from the study, however, will be shared with participants through scientific publications, website postings, and public forums. The Field Centers also will be encouraged to share significant findings with participants through community talks, brochures and providing copies of publications.

16) Provisions to Protect the Privacy Interests of Subjects

The investigators of this study take the risk to subject confidentiality very seriously and have implemented a variety of measures to protect the confidentiality of data and the identities of our subjects. In addition to several layers of safeguards for the electronic data (electronic firewalls, password protection of files, limiting access privileges, structural isolation of particularly sensitive components of the data base, use of pseudo ID numbers for sensitive data), normal prudence is observed with regard to the subject's physical records as well, albeit, for this project, physical records will likely be limited to the occasional clinical MRI report to be mailed or faxed to a research participant's physicians. Physical records will be in locked or directly supervised areas during business hours and always under lock and key during off hours. All new staff will be specifically instructed in confidentiality issues. A Federal certificate of confidentiality has been applied for in order to add another set of protections against legal intrusions on subject privacy.

All summary data from this project will be securely transmitted electronically to the HCHS/SOL Coordinating Center at UNC-Chapel Hill. Under the current Data Use Agreement (DUA), only HCHS/SOL investigators and collaborating researchers who have entered into the DUA would have access to the de-identified data.

Access to the HCHS/SOL data is only provided through secure electronic communications. Under this DUA, HCHS/SOL as well as SOL/INCA data can only be stored and used, including data analyses on secure local servers and cannot be stored on personal computers. Lastly, staff with access to sensitive participant data will have completed the online NIH Computer Security Awareness Training prior to accessing SOL, SOL-INCA data and data from this project.

17) Compensation for Research-Related Injury

It is important that subjects promptly tell the person in charge of the research if they believe that they have been injured because of taking part in this study. For subjects who are injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to an insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury.

18) Economic Burden to Subjects

There is no expected economic burden to subjects.

19) Drugs or Devices

No drugs or devices are used in this study.

20) ClinicalTrials.gov Registration

FDAAA 801 establishes penalties for Responsible Parties who fail to comply withClinicalTrials.gov registration or results submission requirements. **Penalties include civil monetary penalties and, for federally funded studies, the withholding of grant funds.**

Section 1: NIH Funded Studies

If yes to BOTH, the study must be registered on Clinicaltrials.gov.

Yes	
☒	This study is funded by the NIH. (If this study is not funded by NIH, go to Section 2.)
☐	One or more human subjects will be prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Section 2: Studies subject to FDA jurisdiction

If yes to ANY the study must be registered on Clinicaltrials.gov.

Yes	
☐	This is a prospective clinical study of health outcomes in human subjects that compares an intervention with an FDA-regulated device against a

	control. This is not a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes.
☐	This is a pediatric postmarket surveillance of a device as required under section 522 of the Federal Food, Drug, and Cosmetic Act.
☐	This is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act.

To view a flowchart describing applicable clinical trials subject to FDA jurisdiction click here.

Section 3: Publishing the results

If yes to BOTH the study must be registered on Clinicaltrials.gov.

Yes	
☐	This study prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention *and* a health outcome.
☐	The PI has access to and control over all the data from the clinical trial and has the right to publish the results of the trial and plans to publish the results in a journal that follows the ICMJE recommendations.

This requirement includes studies of behavioral interventions.

Section 4: Registration on Clinicaltrials.gov is not required

Yes	
☒	I have read sections 1-3 above and registration on clinicaltrials.gov is not required for this research.

21) Criteria for 10 Year Approval

If yes to all items below this research may qualify for a 10-year approval period.

Yes	
☒	This research involves no more than minimal risk.
☐	This research does not receive any federal or state government funding or funding from a private funder who requires annual review per contract.
☒	This research is not subject to FDA jurisdiction.
☒	This research does not include prisoners as participants.
☒	This research is not part of an IRB reliance.
☒	This research is not subject to SCRO oversight.
☒	This research is not subject to oversight by the Research Advisory Panel

	of California (RAP of C).
☒	This research does not involve identifiable information held by the State of California Department or Agency
☐	This research does not involve personnel supported by federal training, center, or program grants.
☒	No personnel involved in the design, conduct, or reporting of this research have a financial interest (RFI) in this study.

REFERENCES

1. Maillard P, Carmichael OT, Reed B, Mungas D, DeCarli C. Cooccurrence of vascular risk factors and late-life white-matter integrity changes. Neurobiol Aging 2015;36:1670-1677.
2. Maillard P, Seshadri S, Beiser A, et al. Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study. Lancet Neurol 2012;11:1039-1047.
3. Weinstein G, Maillard P, Himali JJ, et al. Glucose indices are associated with cognitive and structural brain measures in young adults. Neurology 2015;84:2329-2337.
4. Dickerson BC, Bakkour A, Salat DH, et al. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cereb Cortex 2009;19:497-510.
5. Jack CR, Jr., Petersen RC, Xu YC, et al. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease [see comments]. Neurology 1997;49:786-794.
6. Government US. Facts on Hispanic Elderly [online]. Available at: http://www.aoa.gov/Aging_Statistics/minority_aging/Facts-on-Hispanic-Elderly.aspx. Accessed August 13, 2013.
7. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology 2005;65:545-551.
8. Luchsinger JA, Reitz C, Patel B, Tang MX, Manly JJ, Mayeux R. Relation of diabetes to mild cognitive impairment. Arch Neurol 2007;64:570-575.
9. Reitz C, Tang MX, Manly J, Mayeux R, Luchsinger JA. Hypertension and the risk of mild cognitive impairment. Arch Neurol 2007;64:1734-1740.
10. Luchsinger JA, Brickman AM, Reitz C, et al. Subclinical cerebrovascular disease in mild cognitive impairment. Neurology 2009;73:450-456.
11. Luchsinger JA, Gustafson DR. Adiposity, type 2 diabetes, and Alzheimer's disease. J Alzheimers Dis 2009;16:693-704.
12. Haan MN, Mungas DM, Gonzalez HM, Ortiz TA, Acharya A, Jagust WJ. Prevalence of dementia in older latinos: the influence of type 2 diabetes mellitus, stroke and genetic factors. J Am Geriatr Soc 2003;51:169-177.

13. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. State-specific projections through 2025 of Alzheimer disease prevalence. Neurology 2004;62:1645.
14. Montine TJ, Koroshetz WJ, Babcock D, et al. Recommendations of the Alzheimer's disease-related dementias conference. Neurology 2014;83:851-860.
15. Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology 2006;66:1837-1844.
16. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197-2204.
17. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol 2006;5:735-741.
18. Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MM. Association of diabetes mellitus and dementia: the Rotterdam Study. Diabetologia 1996;39:1392-1397.
19. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005;64:277-281.
20. Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. Jama 2002;287:1003-1010.
21. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. Lancet Neurol 2007;6:1106-1114.
22. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology 2011;77:461-468.
23. Debette S, Beiser A, Decarli C, et al. Association of MRI Markers of Vascular Brain Injury With Incident Stroke, Mild Cognitive Impairment, Dementia, and Mortality. The Framingham Offspring Study. Stroke 2010.
24. Schneider JA, Wilson RS, Bienias JL, Evans DA, Bennett DA. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. Neurology 2004;62:1148-1155.
25. Arvanitakis Z, Schneider JA, Wilson RS, et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. Neurology 2006;67:1960-1965.
26. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study [see comments]. Annals of Neurology 2000;47:145-151.
27. de Leeuw FE, de Groot JC, Oudkerk M, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. Brain 2002;125:765-772.
28. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke 2002;33:21-25.

29. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348:1215-1222.
30. Maillard P, Carmichael O, Fletcher E, Reed B, Mungas D, DeCarli C. Coevolution of white matter hyperintensities and cognition in the elderly. Neurology 2012;79:442-448.
31. Debette S, Bis JC, Fornage M, et al. Genome-Wide Association Studies of MRI-Defined Brain Infarcts. Meta-Analysis From the CHARGE Consortium. Stroke 2009.
32. Fornage M, Debette S, Bis JC, et al. Genome-wide association studies of cerebral white matter lesion burden: the CHARGE consortium. Ann Neurol 2011;69:928-939.
33. Pasaniuc B, Zaitlen N, Lettre G, et al. Enhanced statistical tests for GWAS in admixed populations: assessment using African Americans from CARe and a Breast Cancer Consortium. PLoS genetics 2011;7:e1001371.
34. Bis JC, Decarli C, Smith AV, et al. Common variants at 12q14 and 12q24 are associated with hippocampal volume. Nat Genet 2012;44:545-551.
35. Ikram MA, Fornage M, Smith AV, et al. Common variants at 6q22 and 17q21 are associated with intracranial volume. Nat Genet 2012;44:539-544.
36. Ibrahim-Verbaas CA, Fornage M, Bis JC, et al. Predicting stroke through genetic risk functions: the CHARGE Risk Score Project. Stroke 2014;45:403-412.
37. Verhaaren BF, Debette S, Bis JC, et al. Multi-Ethnic Genome-Wide Association Study of Cerebral White Matter Hyperintensities on MRI. Circulation Cardiovascular genetics 2015.
38. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015;131:e29-322.
39. Sacco RL, Boden-Albala B, Abel G, et al. Race-ethnic disparities in the impact of stroke risk factors: the northern Manhattan stroke study. Stroke 2001;32:1725-1731.
40. Pikula A, Beiser AS, DeCarli C, et al. Multiple biomarkers and risk of clinical and subclinical vascular brain injury: the Framingham Offspring Study. Circulation 2012;125:2100-2107.
41. Lee JH, Cheng R, Barral S, et al. Identification of novel loci for Alzheimer disease and replication of CLU, PICALM, and BIN1 in Caribbean Hispanic individuals. Archives of neurology 2011;68:320-328.
42. Reitz C, Jun G, Naj A, et al. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E 4,and the risk of late-onset Alzheimer disease in African Americans. Jama 2013;309:1483-1492.
43. During EH, Osorio RS, Elahi FM, Mosconi L, de Leon MJ. The concept of FDG-PET endophenotype in Alzheimer's disease. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2011;32:559-569.
44. Bureau UC. 2010 Census, Summary File 1. Washington, D.C.: US Census Bureau, 2010.

45. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003;60:1119-1122.
46. Lavange LM, Kalsbeek WD, Sorlie PD, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol 2010;20:642-649.
47. Sorlie PD, Aviles-Santa LM, Wassertheil-Smoller S, et al. Design and implementation of the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol 2010;20:629-641.
48. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 2011;7:263-269.
49. APA. Diagnostic and Statistcal Manual of Mental Disorders-5. Washington, DC: American Psychiatric Association, 2013.
50. Seshadri S, Wolf PA, Beiser A, et al. Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. Neurology 2004;63:1591-1599.
51. DeCarli C, Massaro J, Harvey D, et al. Measures of brain morphology and infarction in the framingham heart study: establishing what is normal. Neurobiol Aging 2005;26:491-510.
52. Yoshita M, Fletcher E, Harvey D, et al. Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. Neurology 2006;67:2192-2198.
53. Das RR, Seshadri S, Beiser AS, et al. Prevalence and correlates of silent cerebral infarcts in the Framingham offspring study. Stroke 2008;39:2929-2935.
54. Lee DY, Fletcher E, Martinez O, et al. Vascular and degenerative processes differentially affect regional interhemispheric connections in normal aging, mild cognitive impairment, and Alzheimer disease. Stroke 2010;41:1791-1797.
55. Au R, Massaro JM, Wolf PA, et al. Association of white matter hyperintensity volume with decreased cognitive functioning: the Framingham Heart Study. Arch Neurol 2006;63:246-250.
56. Longstreth WT, Jr., Dulberg C, Manolio TA, et al. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. Stroke 2002;33:2376-2382.
57. Knopman DS, Griswold ME, Lirette ST, et al. Vascular Imaging Abnormalities and Cognition: Mediation by Cortical Volume in Nondemented Individuals: Atherosclerosis Risk in Communities-Neurocognitive Study. Stroke 2015.
58. Mungas D, Reed BR, Farias ST, Decarli C. Age and education effects on relationships of cognitive test scores with brain structure in demographically diverse older persons. Psychol Aging 2009;24:116-128.

59. Lee DY, Fletcher E, Martinez O, et al. Regional pattern of white matter microstructural changes in normal aging, MCI, and AD. Neurology 2009;73:1722-1728.
60. McCullagh P, Nelder JA. Generalized linear models. London; New York: Chapman and Hall, 1983.
61. Hardin JW, Hilbe JW. Generalized Linear Models and Extensions. Stata Press books 2012.
62. Cameron CA, Trivedi PK. Microeconometrics Using Stata, Revised ed: Stata Press, 2010.
63. Bollen KA. Structural equations with latent variables. New York: Wiley, 1989.
64. Muthén B. A general structural equation model with dichotomous, ordered categorical, and continuous latent variable indicators. Psychometrika 1984;49:115-132.
65. Muthén BO. Beyond SEM: General latent variable modeling. Behaviormetrika 2002;29:81.
66. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. Annu Rev Psychol 2007;58:593-614.
67. Muthén B. Applications of causally defined direct and indirect effects in mediation analysis using SEM in Mplus. 2011.
68. Preacher KJ, Rucker DD, Hayes AF. Addressing Moderated Mediation Hypotheses: Theory, Methods, and Prescriptions. Multivariate Behav Res 2007;42:185-227.
69. Hayes AF, Preacher KJ. Quantifying and Testing Indirect Effects in Simple Mediation Models When the Constituent Paths Are Nonlinear. Multivariate Behavioral Research 2010;45:627-660.
70. Kim ES, Yoon M. Testing Measurement Invariance: A Comparison of Multiple-Group Categorical CFA and IRT. Structural Equation Modeling-a Multidisciplinary Journal 2011;18:212-228.
71. Barrett P. Structural equation modelling: Adjudging model fit. Personality and Individual Differences 2007;42:815-824.
72. Van De Schoot R, Hoijtink H, Deković M. Testing inequality constrained hypotheses in SEM models. Structural Equation Modeling 2010;17:443-463.
73. Yu C-Y. Evaluating cutoff criteria of model fit indices for latent variable models with binary and continuous outcomes: University of California Los Angeles, 2002.
74. Enders CK. Applied missing data analysis2010.
75. Schafer JL, Graham JW. Missing data: Our view of the state of the art. Psychological Methods 2002;7:147-177.
76. Graham JW. Missing Data Analysis: Making It Work in the Real World. Annual Review of Psychology 2009;60:549-576.
77. Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. Nature methods 2012;9:179-181.
78. Howie B, Marchini J, Stephens M. Genotype imputation with thousands of genomes. G3 2011;1:457-470.
79. Deelen P, Menelaou A, van Leeuwen EM, et al. Improved imputation quality of low-frequency and rare variants in European samples using the 'Genome

of The Netherlands'. European journal of human genetics : EJHG 2014;22:1321-1326.
80. Delaneau O, Marchini J, Genomes Project C, Genomes Project C. Integrating sequence and array data to create an improved 1000 Genomes Project haplotype reference panel. Nature communications 2014;5:3934.
81. Duan Q, Liu EY, Auer PL, et al. Imputation of coding variants in African Americans: better performance using data from the exome sequencing project. Bioinformatics 2013;29:2744-2749.
82. The Haplotype Reference Consortium. http://www.haplotype-reference-consortium.org/ [online]. Available at: http://www.haplotype-reference-consortium.org/.
83. Delaneau O, Zagury JF, Marchini J. Improved whole-chromosome phasing for disease and population genetic studies. Nature methods 2013;10:5-6.
84. Palin K, Campbell H, Wright AF, Wilson JF, Durbin R. Identity-by-descent-based phasing and imputation in founder populations using graphical models. Genetic epidemiology 2011;35:853-860.
85. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS genetics 2009;5:e1000529.
86. Liu EY, Li M, Wang W, Li Y. MaCH-admix: genotype imputation for admixed populations. Genetic epidemiology 2013;37:25-37.
87. Morris AP. Transethnic meta-analysis of genomewide association studies. Genetic epidemiology 2011;35:809-822.
88. Wang X, Liu X, Sim X, et al. A statistical method for region-based meta-analysis of genome-wide association studies in genetically diverse populations. European journal of human genetics : EJHG 2012;20:469-475.
89. Coram MA, Candille SI, Duan Q, et al. Leveraging Multi-ethnic Evidence for Mapping Complex Traits in Minority Populations: An Empirical Bayes Approach. American journal of human genetics 2015;96:740-752.
90. Maillard P, Fletcher E, Harvey D, et al. White matter hyperintensity penumbra. Stroke 2011;42:1917-1922.
91. Maillard P, Carmichael O, Harvey D, et al. FLAIR and diffusion MRI signals are independent predictors of white matter hyperintensities. AJNR Am J Neuroradiol 2013;34:54-61.
92. Maillard P, Fletcher E, Lockhart SN, et al. White matter hyperintensities and their penumbra lie along a continuum of injury in the aging brain. Stroke 2014;45:1721-1726.
93. Fletcher E, Knaack A, Singh B, et al. Combining boundary-based methods with tensor-based morphometry in the measurement of longitudinal brain change. IEEE transactions on medical imaging 2013;32:223-236.
94. Fletcher E, Carmichael O, Pasternak O, Maier-Hein KH, DeCarli C. Early Brain Loss in Circuits Affected by Alzheimer's Disease is Predicted by Fornix Microstructure but may be Independent of Gray Matter. Front Aging Neurosci 2014;6:106.