Ancillary Study Proposal Form

Atherosclerosis Risk in Communities (ARIC)

I. Basic Study Information and Projected Impact on ARIC

1. Title of study: ***Association of lipoprotein and cardiac biomarkers with dementia, cognitive change and CVD in ARIC study***

2. Principal investigator(s) (name, address, phone and fax numbers, e-mail address):

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3. Collaborators (must include at least one ARIC investigator):

1. ***Yashashwi Pokharel***
2. ***Melinda Power***
3. ***Andrea Schneider***
4. ***Andreea M. Rawlings***
5. ***Elizabeth Selvin***
6. ***Wensheng Sun***
7. ***Vijay Nambi***
8. ***Salim Virani***
9. ***Ron Hoogeveen***
10. ***Rebecca Gottesman***
11. ***Lisa Wruck***
12. ***Alvaro Alonso***
13. ***Gerardo Heiss***
14. ***Josef Coresh***
15. ***Thomas Mosley***
16. ***Christie Ballantyne***

4. Summary of ARIC centers and tasks involved – Leave cell blank if Not Applicable

Center	Enroll or examine participants (N)	Assay samples (N participants)	Provide samples (N participants)	Analyze data (yes/no)
Forsyth Co. Field Center				
Jackson Field Center				
Minnesota Field Center				
Washington Co. Field				***Yes***

Center				
DNA Central Lab				
MN Chem Lab				
Lipid Central Lab				***Yes***
Hemostasis Central Lab				
ECG Reading Center				
Coordinating Center (UNC)				
Other (specify)				

5. ARIC participant and staff involvement:

   A. Participants:
   Describe number of subjects needed; special characteristics of study population; age and sex distribution. Will participants be contacted, interviewed, examined, or asked to provide specimens? Will the study involve radiation or administration of a drug or contrast? If so, describe participant involvement. Estimate time required of each participant. ***This study will be based on secondary data analysis and will not include additional ARIC participant involvement.***

   B. Stored ARIC specimens:
   Describe materials to be used (e.g., stored plasma, urine, DNA). If blood samples are requested, please review the Criteria for Approval section of the Ancillary Study Policy (http://www.cscc.unc.edu/aric/utility/docfilter.php?study=aric&filter_type=forms&sorter=s_mid) in consideration of your description of the following:

      1. Study participants and material requested:

Yes/No	Cohort	Total Number of Specimens	Full Cohort (or →)	Number of Cases	Number of Controls
	All parent study participants (or ↓)				
	Specify sample and specimens in each sample/stratum				

Type of Specimen	N	Volume Requested	Time point (e.g. visit*)	Specify proposed lab and analytes to be assayed at catch lab (be specific)
Serum		ul		
EDTA plasma		ul		
Citrate plasma		ul		
DNA		ug/ng		
Urine		ul		
Other (specify)				

* Please contact the ARIC in advance and indicate here how many tubes of each visit and type you are requesting: ***N/A***

2. Is the proposed work consistent with the stipulations in the ARIC informed consent form? ☐ Yes ☐ No (The informed consent forms can be obtained from the collaborating ARIC investigator).

3. Are thawed/re-frozen acceptable? ☐ Yes ☐ No

   If No, specify reasons for specific assays:

4. Describe efforts to integrate sample needs with those of other studies to conserve sample and/or limit freeze-thaw cycles.

5. If approved, when will samples be requested for retrieval?

C. ARIC Field Centers:
Describe effort (and estimated time) required of ARIC staff at each participating center. Include consent, collection of samples, etc.
No ARIC samples will be analyzed as this study will be based on secondary data analysis and will not include additional ARIC participant involvement.

D. ARIC Coordinating Center:
Describe effort (and estimated time) required of ARIC Coordinating Center staff. Specifically: ***All ARIC data needed for this project already exist and have been or will be distributed to the Field Center PIs before the start date for the grant. Therefore, ARIC Coordinating Center staff effort will not be required.***

** Unless you provide strong justification, the Coordinating Center must be included and its costs budgeted.*

i. Will the Coordinating Center be involved in data collection, tracking, or preparation of forms or software? or Will these tasks be completed locally by the Ancillary Study, and a data file sent to the Coordinating Center? ***N/A***

ii. If a Reading Center or laboratory is involved, will data be sent directly from the Reading Center or laboratory to the Coordinating Center for processing, or will processing be done locally (either by the Ancillary Study or at the Reading Center/Laboratory)? ***N/A***

iii. Will analyses be done locally by the Ancillary Study or by analysts at the Coordinating Center? If analyses will be done locally, should Coordinating Center verify the analyses? ***Analyses will be done locally by the Ancillary Study PI, Yashashwi Pokharel. Verification of the analyses by the Coordinating Center is not required.***

6. Genomic information (defined as any data from a participant's DNA):
   A. Does your proposal include any genomic materials? (please check one)
   ☐ No (go to question 7) ☒ Yes (see question 6B)

   B. Name the gene(s), genotypes, SNPs to be investigated: ***APOE genotype, already available in ARIC***

   C. Is genetic information used to address a primary aim or secondary aim of ARIC? (please check one or both)

   ☐ Primary aim (heart/vascular disease)
   ☒ Secondary aim (other health conditions)
   List the conditions addressed:
   Alzheimer disease, cognitive function

   D. Should DNA-based results be reported to patients' physicians? Base your response on your knowledge of existing literature and current practice regarding increased risk and availability of treatment for adverse outcomes associated with the gene mutations to be studied. ***No. We are proposing to use existing APOE genotype status data only.***

7. Proposed starting and ending dates: ***July 2014 - June 2016***

8. Estimated cost by year; number of years: ***$44,264-$59,180; 2 years***

9. Source of funding; date of submission:
American Heart Association, Winter 2014-Postdoctoral Fellowship, SouthWest Affiliate; January 17, 2014

10. Does this study involve the support or collaboration of a for-profit corporation, or do you intend to use the data to patent any process, aspect or outcome of the analysis? ***No***

11. What is the advantage, both to ARIC and yourself, of conducting the study within the ARIC cohort versus another population? ***ARIC is uniquely suited to the study of the association between the novel potential risk factors of interest, specialized lipoproteins and cardiac biomarkers and cognition. Combined with existing neuropsychological tools, dementia diagnosis and cardiovascular disease (CVD), existing measures of lipoprotein(a), lipoprotein associated phospholipase A2 (Lp-PLA2) activity and small dense low-density lipoprotein cholesterol (sd-LDL-C) (at visit 4), as well as high-sensitivity cardiac troponin T (hs-cTnT) and high-sensitivity N-terminal–pro–B-type natriuretic peptide (NT-proBNP) (at visits 4 and 5) in the full cohort allow large-scale, methodologically sound investigation of the prospective association in a cost-effective way. The multidimensional nature of the outcome data available (neuropsychological and clinical) and the long duration of follow-up beween measures of exposure and outcome allow comprehensive and theoretically sound assessment of the association, including insight into the mechanisms by which these risk facors may be related to dementia, cognition and future cardiovascular outcomes. From my perspective, I am familiar with the ARIC cohort as I have been writing other ARIC manuscript proposals and I have taken courses from ARIC investigators during my graduate school at UNC Gillings School of Public Health. I also have established relationships with ARIC investigators, including several who have agreed to serve as mentors or collaborators for the AHA grant. I look forward to continued participation with ARIC in the future. The advantage to ARIC participants and to any other population and the scientific community is that study of these novel potential risk factors will advance our understanding of the causes and correlates of cognitive decline and dementia and progression of CVD, and may lead to new targets for intervention or treatment.***

12. Impact on ongoing ARIC studies (main study or other Ancillary Studies): ***None***

13. Provide the following assurances (answer each):

(1) Who (name and position) will report progress of the study in the fall of each year? (Ancillary Study PI or designate preferred) ***Yashashwi Pokharel, PI***

(2) How will confidentiality of ARIC participants be maintained? ***ARIC cohort participants will not be identified in reporting for this study.***

(3) Data collected by the Ancillary Study, will be provided to the ARIC Coordinating Center for integration into the main database. This will include documentation of newly collected data with labels, and/or laboratory results as well as documentation on methods, visits and units used with specific instructions for using the data in analyses. such as exclusions that were applied. After that has been done the Ancillary Study investigators will receive the integrated file containing data from the main study.

The Ancillary Study PI will be given the first and exclusive opportunity to analyze, present and publish data collected under the auspices of the Ancillary Study. After a reasonable time (in general, 12 months after data cleaning is complete or 12 months after acceptance of primary manuscript, whichever is earlier), Ancillary Study data will be made available for additional uses by other ARIC investigators. It is the responsibility of the Ancillary Study PI to state in writing to the ARIC Steering Committee any special circumstances that would warrant an exception to these guidelines for data sharing. In the spirit of encouraging collaboration, reasonable and justified requests for limiting Steering Committee access to the data will be honored, or a compromise will be worked out.

(4) How many papers do you estimate will be written from the Ancillary Study? ***3-5***

(5) Variables/measurements from the ARIC main study database to be analyzed: ***Lipoprotein(a), Lp-PLA2 activity and sd-LDL-C (at visit 4), as well as hs-cTnT and high sensitivity NT-proBNP (at visits 4 and 5), neuropsychological data (visits 4 and 5), dementia diagnosis (visit 5), and covariate data (including but not limited to demographics, blood lipids, vascular risk factors and other health conditions, socioeconomic indicators, APOE status) from visit 4.***

14. If the study will have clinical implications, explain and describe the plan for reporting results to participants and providing recommendations for follow up: ***N/A***

II. Abbreviated Ancillary Study Proposal

Please provide a brief (2 to 4 page) description of the proposed study. Include the following:

Purpose/Aims: ***The purpose of this study is determine the association of lipoprotein and cardiac biomarkers with dementia, cognitive change and CVD in the ARIC cohort.***

Aim 1. To evaluate whether elevated levels of specialized lipid markers (Lp(a), Lp-PLA2 and sd-LDL-C) at ARIC visit 4 are associated with increased risk of dementia or mild cognitive impairment (MCI) (or its subtypes including those with vascular component, Alzheimer disease and other types) at ARIC visit 5.

Aim 2. To evaluate whether cardiac biomarkers (hs-cTnT and NT-proBNP) at ARIC visit 4 are associated with increased risk of dementia or MCI (or its subtypes) at ARIC visit 5

Aim 3. To evaluate whether elevated levels of specialized lipid markers at ARIC visit 4 are associated with increased risk of cognitive decline over visits 4 and 5, as measured by scores on the Delayed Word Recall (DWR), Digit Substitution (DSS), and Word Fluency (WF) tests and a global score summarizing performance on these 3 tests.

Aim 4. To evaluate whether cardiac biomarkers at ARIC visit 4 are associated with increased risk of cognitive decline over ARIC visits 4 and 5, as measured by scores on the Delayed Word Recall (DWR), Digit Substitution (DSS), and Word Fluency (WF) tests and a global score summarizing performance on these 3 tests.

Aim 5. To evaluate whether elevated levels of specialized lipid biomarkers at ARIC visit 4 are associated with increased risk of recurrent CVD events (first recurrent CHD and stroke, CVD mortality) in those with prevalent CVD at ARIC visit 4 when followed up until ARIC visit 5

Aim 6. To evaluate the risk of incident CVD (coronary heart disease [CHD], stroke,congestive heart failure [CHF] and CVD mortality) and recurrent CVD events (first recurrent CHD and stroke, CVD mortality) by patterns of cardiac biomarkers changes between ARIC visits 4 and 5.

Background:

Dementia affects about 5–10% of people ≥ 65 years of age in affluent countries [1]. Cognitive decline and dementia can be debilitating [2–6] and are associated with significant cost to society [7]. Very few, if any, existing interventions retard or prevent the process of cognitive decline. In particular, few existing biomarkers predict cognitive decline and dementia.

Established CVD has been shown to be strongly associated with dementia and cognitive decline [8-11]. Emerging data suggest associations of subclinical atherosclerosis [12–14] and subclinical CVD [15] with cognitive change and dementia. There has been growing interest in conventional cardiovascular risk factors such as low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) as potential biomarkers of cognitive decline and dementia [16-18]. Some studies have indicated an association of conventional lipid markers with cognitive change and dementia [19,20], and others are ongoing. Specialized lipoprotein assessments such as lipoprotein(a) [21–23] and Lp-PLA2 [24] have been shown to be independently associated with CVD, and sd-LDL-C is an emerging atherogenic lipoprotein risk factor that has been associated with higher plaque burden [25] and identification of vascular disease in individuals with lower levels of LDL-C [26]. Lp(a) level in humans has the strictest genetic control among all the lipoproteins [27,28]. Lp(a) screening may be performed in specialized lipid clinics in patients with recurrent CVD [29], yet there are few, if any, studies looking at the association of elevated Lp(a) with recurrent CVD. Lp-PLA 2 is a proinflammatory enzyme secreted by inflammatory cells in atherosclerotic plaques [30,31], and it is primarily bound to LDL in the circulation [32]. It hydrolyzes oxidized phospholipids to generate lysophosphatidylcholine and oxidized fatty acids, which have proinflammatory properties [33]. Lp-PLA2 can be used to improve identification of patients at high or very high risk who will benefit from intensification of lipid-modifying therapies. sd-LDL-C is a potent atherogenic lipoprotein that easily enters the arterial wall, undergoes enhanced localized retention due to binding with arterial wall proteoglycans and exhibits enhanced oxidizability [34-36]. Therefore, sd-LDL-C may have incremental value in CVD risk prediction beyond that of LDL-C.

We hypothesize that elevated levels of specialized lipoproteins such as lipoprotein(a), Lp-PLA2 and sd-LDL-C are associated with increased risk of cognitive decline, MCI and dementia in *the ARIC cohort. We also hypothesize that the association will be stronger for the vascular component of MCI, dementia and cognitive domains usually affected by vascular disease. In addition, we will also test the hypothesis that elevated levels of these specialized lipoproteins are associated with recurrent cardiovascular events.*

Cardiac biomarkers such as hs-cTnT and highly sensitive NT-proBNP have been shown to be associated with cardiovascular events such as CHF, stroke, CHD and cardiovascular mortality [37–43]. Both hs-cTnT and NT-proBNP were independently associated with stroke after adjusting for traditional cardiovascular risk factors [40]. The association of hs-cTnT with cerebrovascular outcomes is likely mediated by nonatherosclerotic mechanisms, and it has been suggested that hs-cTnT may be a marker of subclinical small vessel disease [44]. Atrial fibrillation (AF) is a common contributor to cardioembolic stroke. NT-proBNP and hs-cTnT are both associated with new-onset AF [45–50], recurrent AF [51–53] and poor cardiovascular outcomes in individuals with AF [54,55]. The association of hs-cTnT and NT-proBNP with atherothrombotic stroke may reflect coexisting atherosclerotic cerebrovascular and cardiac disease or some other unknown mechanisms. We hypothesize that higher levels of both these biomarkers are associated with increased risk of cognitive decline, dementia and MCI. There are limited available data on the patterns of changes in these biomarkers over time and their association with CVD. We hypothesize that increasing levels of these biomarkers over time is associated with higher incidence of CVD and also higher recurrence of CVD when compared with normal or decreasing levels.

Summary

Cognitive decline, dementia and recurrent CVD are serious public health problems. New strategies are necessary to take advantage of the various available biomarkers. Evaluation of novel risk factors may lead to improved risk prediction with opportunity for new interventions and treatments. There is sufficient evidence to hypothesize the role of specialized lipid biomarkers and cardiac biomarkers in cognitive decline and dementia as well as CVD. We propose to evaluate systematically and prospectively the relationship of lipoprotein(a) level, Lp-PLA2 activity and sd-LDL-C level, along with novel cardiac biomarkers hs-cTnT and NT-proBNP, to cognitive decline using neuropsychological performance, dementia and MCI diagnosis and recurrent CVD. We will also examine trends in the pattern of changes in cardiac biomarkers over time and incident and recurrent CVD in the large longitudinal ARIC study.

Hypotheses:

A. (Aim1) Higher levels of lipoprotein(a) are associated with increased risk of dementia or MCI.

B. (Aim 1) Higher levels of Lp-PLA2 activity are associated with increased risk of dementia or MCI.

C. (Aim 1) Higher levels of sd-LDL-C are associated with increased risk of dementia or MCI.

D. (Aim 1) Associations of Lp(a), Lp-PLA2 and sd-LDL-C with the vascular component of dementia or MCI will be stronger than with other types, including Alzheimer disease.

E. (Aim 2) Higher levels of hs-cTnT are associated with increased risk of dementia or MCI.

F. (Aim 2) Higher levels of NT-proBNP are associated with increased risk of dementia or MCI.
G. (Aim2) Associations of hs-cTnT and NT-proBNP with the vascular component of dementia or MCI will be stronger than with other types, including Alzheimer disease.
H. (Aim 3) Higher levels of lipoprotein(a) are associated with increased risk of cognitive decline as measured by scores on the DWR, DSS and WF tests and a global score summarizing performance on these 3 tests.
I. (Aim 3) Higher levels of Lp-PLA2 activity are associated with increased risk of cognitive decline.
J. (Aim 3) Higher levels of sd-LDL-C are associated with increased risk of cognitive decline.
K. (Aim 3) Associations of lipoprotein(a), Lp-PLA2 and sd-LDL-C and decline on the DSS test will be strongest, given that this test covers domains usually affected by vascular disease—executive function and psychomotor speed. Associations with DWR, which is expected to be affected more by Alzheimer disease, are expected to be weaker.
L. (Aim 4) Higher levels of hs-cTnT are associated with increased risk of cognitive decline.
M. (Aim 4) Higher levels of NT-proBNP are associated with increased risk of cognitive decline.
N. (Aim 4) Associations of hs-cTnT and NT-proBNP and decline on the DSS test will be strongest, given that this test covers domains usually affected by vascular disease—executive function and psychomotor speed. Associations with DWR, which is expected to be affected more by Alzheimers disease, are expected to be weaker.
O. (Aim 5) Higher levels of lipoprotein(a) are associated with recurrent CVD events (first recurrent CHD and stroke, CVD mortality).
P. (Aim 5) Higher levels of Lp-PLA2 activity are associated with recurrent CVD events.
Q. (Aim 5) Higher levels of sd-LDL-C are associated with recurrent CVD events.
R. (Aim 6) Risk of incident CVD (CHD, stroke, CHF and CVD mortality) increases across the following categories of hs-cTnT changes between visits 4 and 5: within normal range at both visits (lowest risk), decrease, variable change and increase (highest risk).
S. (Aim 6) Risk of incident CVD increases across the following categories of NT-proBNP changes between visits 4 and 5: within normal range at both visits (lowest risk), decrease, variable change and increase (highest risk).
T. (Aim 6) Risk of recurrent CVD (first recurrent CHD and stroke, CV mortality) events increases across the following categories of hsc-TnT changes between visits 4 and 5: within normal range at both visits (lowest risk), decrease, variable change and increase (highest risk).
U. (Aim 6) Risk of recurrent CVD events increases across the following categories of NT-proBNP changes between visits 4 and 5: within normal range at both visits (lowest risk), decrease, variable change and increase (highest risk).

Experimental Design (include sample size justification):

Aim 1. We propose to complete Aim 1 using visit 5 data on dementia or MCI and its subtypes, and specialized blood lipoprotein data from visit 4. We will exclude persons lacking data on the relevant blood lipoproteins and dementia for each proposed analysis. We will begin by considering only visit 5 adjudicated diagnoses of dementia and its subtypes or MCI as cases. We will also explore other definitions allowing for additional dementia cases identified with additional information obtained by telephone interview, informant interview, hospitalization ICD-9 codes or diagnoses from the Medicare billing claims database. Standard ARIC race and center exclusions will be applied. Logistic regression analysis will be used to calculate odds ratio per 1–standard deviation increase in the specialized cardiac biomarkers as well as quantile-based analysis. In a multivariate model, adjustment will be made for age, *gender, race, education, occupation, area-level SES, diabetes, APOE genotype, hypertension, total cholesterol/HDL-C, statin use, body mass index (BMI), a summary of healthy diet, physical activity, health care utilization variables and smoking, all obtained from visit 4. Race, gender, presence of CVD at visit 4 (CHD, stroke and CHF), presence of stroke and education will be assessed for potential as effect modifiers in a multiplicative scale, and if significant interaction is present, we will consider a stratified analysis.*

Aim 2. We propose to complete Aim 2 using visit 5 data on dementia or MCI and its subtypes, and cardiac biomarkers from visit 4. We will exclude persons lacking data on the relevant cardiac biomarkers and dementia for each proposed analysis. We will begin by considering only visit 5 adjudicated diagnoses of dementia and its subtypes or MCI as cases. We will also explore other definitions allowing for additional dementia cases identified with additional information obtained by telephone interview, informant interview, hospitalization ICD-9 codes or diagnoses from the Medicare billing claims database. Standard ARIC race and center exclusions will be applied. Logistic regression analysis will be used to calculate odds ratio per 1–standard deviation increase in the specialized cardiac biomarkers as well as quantile-based analysis. In a multivariate model, adjustment will be made for age, gender, race, education, occupation, area-level SES, diabetes, APOE genotype, hypertension, total cholesterol/HDL-C, statin use, BMI, a summary of healthy diet, physical activity, health care utilization variables and smoking, all obtained from visit 4. Race, gender, presence of CVD at visit 4 (CHD, stroke and CHF), presence of stroke and education will be assessed for potential as effect modifiers in a multiplicative scale, and if significant interaction is present, we will consider a stratified analysis.

Aim 3. We propose to complete Aim 3 using visit 4 and 5 data on the DWR, DSS and WF tests and a global score summarizing performance on these 3 tests, and specialized blood lipoprotein data from visit 4. We will exclude persons lacking data on the relevant blood lipoproteins, education and cognitive evaluation for each proposed analysis. Standard ARIC race and center exclusions will be applied. We will use a generalized estimating equation model per 1–standard deviation increase in the specialized cardiac biomarkers as well as quantile-based based analysis. In a multivariate model, adjustment will be made for age, gender, race, education, occupation, area-level SES, diabetes, APOE genotype, hypertension, total cholesterol/HDL-C, statin use, BMI, time in study, a summary of healthy diet, physical activity, health care utilization variables and smoking, all obtained from visit 4. We will consider use of quadratic terms or splines to allow for nonlinearity of cognitive change over time and age. Race, gender, age, time in study, presence of CVD at visit 4 (CHD, stroke and CHF), presence of stroke and education will be assessed for potential as effect modifiers in a multiplicative scale, and if significant interaction is present, we will consider a stratified analysis.

Aim 4. We propose to complete Aim 4 using visit 4 and 5 data on the DWR, DSS and WF tests and a global score summarizing performance on these 3 tests, and cardiac biomarkers data from visit 4. We will exclude persons lacking data on the relevant cardiac biomarkers, education and cognitive evaluation for each proposed analysis. Standard ARIC race and center exclusions will be applied. We will use a generalized estimating equation model per 1–standard deviation increase in the specialized cardiac biomarkers as well as quantile-based based analysis. In a multivariate model, adjustment will be made for age, gender, race, education, occupation, area-level SES, diabetes, APOE genotype, hypertension, total cholesterol/HDL-C, statin use, BMI, time in study, a summary of healthy diet, physical activity, health care utilization variables and smoking, all obtained from visit 4. We will consider use of quadratic terms or splines to allow for nonlinearity of cognitive change over time and age. Race, gender, age, time in study, presence of CVD at visit 4 (CHD, stroke and CHF), presence of stroke and education will be assessed for potential as effect modifiers in a multiplicative scale, and if significant interaction is present, we will consider a stratified analysis.

Aim 5. We propose to complete Aim 5 using visit 4 and 5 data on recurrent CVD events (first recurrent CHD and stroke, CVD mortality, all per standard ARIC definition), and specialized lipoprotein biomarkers data from visit 4. We will exclude persons lacking data on the relevant lipoprotein biomarkers or prevalent and recurrent CVD events for each proposed analysis. Standard ARIC race and center exclusions will be applied. We will use Cox proportional hazards regression model per 1–standard deviation increase in the specialized cardiac biomarkers as well as quantile-based analysis. In a multivariate model, adjustment will be made for age, gender, race, BMI, diabetes, hypertension, total cholesterol/HDL-C, estimated glomerular filtration rate (e-GFR), smoking, antihypertensive medication use, all obtained from visit 4. Race and gender will be assessed for potential as effect modifers in a multiplicative scale, and if significant interaction is present, we will consider a stratified analysis. We *will also consider assessment for separate outcomes of first recurrent CHD, first recurrent stroke and CVD mortality.*

Aim 6. We propose to complete Aim 6 using visits 4 and 5 data on incident CVD (CHD, stroke, CHF and CVD mortality) and recurrent CVD events (first recurrent CHD and stroke, CVD mortality, all per standard ARIC definition), and changes in cardiac biomarkers data from visits 4 and 5. We will exclude persons lacking data on the relevant cardiac biomarkers or prevalent, incident and recurrent CVD events for each proposed analysis. Standard ARIC race and center exclusions will be applied. We will use Cox proportional hazards regression model. We will categorize hs-cTnT based on undetectable limit of <5 ng/dL. For the group with undetectable levels at visit 4, possible changes at visit 5 include undetectable (<5 ng/dL; unchanged) or detectable (≥5 ng/dL; increase). For the group with detectable levels at visit 4 (≥5 ng/dL), possible changes at visit 5 are as >50% increase (increase), >50% decrease (decrease) or <50% change (variable). This categorization is based on prior published methods. We will also consider quantile-based analysis after developing appropriate quantiles of changes in hs-cTnT between visits 4 and 5. We will categorize NT-proBNP as normal (<120 pg/mL), intermediate (120-300 pg/mL) and high (>300 pg/mL) based on the clinical relevance of NT-proBNP. Possible changes in NT-proBNP between visits 4 and 5 include normal at both visits (unchanged); increased from normal to either intermediate or high levels, or from intermediate to high levels (increase); decreased from either intermediate or high levels to normal levels, or from high to intermediate levels (decrease); and remaining at either intermediate or high levels (variable). We will also consider quantile-based analysis after developing appropriate quantiles of changes in NT-proBNP between visits 4 and 5. In a multivariate model, adjustment will be made for age, gender, race, BMI, diabetes, hypertension, total cholesterol/HDL-C, e-GFR, smoking and antihypertensive medication use, all obtained from visit 4. Race and gender will be assessed for potential as effect modifiers in a multiplicative scale, and if significant interaction is present, we will consider a stratified analysis. We will also consider assessment for separate outcomes of first recurrent CHD, first recurrent stroke, CHF and CVD mortality.

Sample Size Justification. Sample size for all proposed analyses is dictated by availability of existing samples and/or data. Although we have not completed formal power calculations for each analysis at this time, sample sizes for all proposed analyses are generally comparable to those for similar ARIC analyses that are in progress or published, which often find and report statistically significant associations, or published non-ARIC studies using similar methods.

ARIC visit 5 participants may be a healthier subcohort of the original cohort from visit 1, which can possibly introduce selection bias. We will compare participants' characteristics from visits 1 and 5. We will also consider inverse probability of attrition weighting, where we would create logistic regression models to predict death and/or drop-out between visits. The predicted probability of attrition is then used to weight up people who make it to visit 5 to account for people who did not.

Methods, including:

Participant involvement (if any): ***N/A***

Data to be collected by the ancillary study (attach questionnaires and forms): ***N/A***

Analysis Methods: ***N/A***

Literature References

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Please send an electronic copy of the completed proposal to:
Aaron R. Folsom, M.D. (Principal Investigator) folso001@umn.edu

CC: Nell Malone malone@unc.edu

For Coordinating Center Use Only

Approved? ☒ Yes ☐No

Date: 1/2/14

If approved, ancillary study # 2014.04

January 2, 2014

Dear Dr. Pokharel,

APPROVAL DECISION

The ARIC steering committee approves your ancillary study, which is assigned ancillary study number 2014.04. Please refer to this number in future communications.

The committee had the following stipulations:

-Consider reducing the number of aims
-Be sure to work closely with the neurocognitive investigators to use their variable definitions and analytic methods
-Remember to submit manuscript proposals with all relevant authors before undertaking this work

Please read the following expectations about ARIC ancillary studies:

ARIC POLICIES

You must comply with any of the following policies that apply to your study:

- If you are seeking funding, please notify the ARIC coordinating center when you receive the funding or when the ancillary study is not to be initiated due to lack of funding. Also notify the coordinating center when your ancillary study is finished.

- All ancillary studies must file annual reports and eventually share any new data on ARIC subjects with ARIC, as outlined in the ARIC ancillary study policy and NHLBI data sharing policies. In addition, you will need to follow ARIC's manuscript approval policies, as outlined in the ARIC Publication Policies. ARIC study policies can be found at http://www.cscc.unc.edu/aric/.

- If this study involves participant burden, it will need to be approved by the ARIC Observational Study Monitoring Board (OSMB). Please make sure Dr. Wright, the ARIC project officer, has the version of the proposal you want the OSMB to review.

-If this study involves laboratory work, unless exempted, you will need to include blind duplicates identified by the coordinating center in your specimen pool. Please budget funds for the Coordinating Center to draw up the laboratory pull list or to add the appropriate blind duplicates to a list of IDs you provide.

- If you are not affiliated with an ARIC center and require access to data files, or if your study involves biologic samples, you will need to complete a Data and Materials Distribution Agreement (DMDA) available on the ARIC website (Ancillary Studies page), once you obtain funding. Evidence of IRB review for your ancillary study is also required. Please contact Ms. Nell Malone at malone@unc.edu if you need more information.

- If this study involves industry funding, NHLBI will need to review the draft agreement letter between your university and the industry before you (and your school business representative) and company sign the letter. Please contact Dr. Wright to obtain advice and instructions in this regard. Please note that the study cannot start until the agreement letter receives approval by the NHLBI.

BUDGET CONSIDERATIONS

- Please be sure to involve the Coordinating Center in your grant and budget adequate coordinating center costs in your proposal. Please work with Nell Malone malone@unc.edu.

- If this study involves the field centers, please work with the field center PIs as soon as possible to finalize their budgets.

- If this study involves lab samples, please discuss and arrange with the ARIC lab involved the aliquotting, processing, and lab costs.

LETTER FOR GRANT PROPOSAL

A letter for your grant proposal is attached.

Regards,

Aaron R. Folsom, MD

ARIC steering committee chair

COMMENTS, IF ANY, FOLLOW

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January 2, 2014

Yashashwi Pokharel, MD
Baylor College of Medicine,
6565 Fannin Street,
MS A601/ STE B160
Houston, TX 77030

Dear Dr. Pokharel:

I am pleased to convey the approval and enthusiasm of the ARIC steering committee for your ancillary study proposal and AHA post-doctoral fellowship application entitled, “Association of lipoprotein and cardiac biomarkers with dementia, cognitive change and CVD in ARIC study.” Your project is significant and its topic fits nicely with the aims of ARIC.

By approving this project, ARIC is offering to share its data and resources in order for you to accomplish your aims. In return, of course, you are expected to follow ARIC’s ancillary study and publication policies.

We wish you success in this important project.

Sincerely,

Aaron R. Folsom

Aaron R. Folsom, MD
Professor
ARIC Steering Committee Chair