ARIC Manuscript Proposal Form

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1.a. Full Title: Inflammation, Subclinical Markers, and Cardiovascular Disease: the Cross-Cohort Collaboration (CCC)

b. Abbreviated Title (Length 26 characters): CCC-Inflammation and Marker

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3. Timeline:

07/2025-12/2025 data analysis
01/2026-04/2026 manuscript writing and revision
05/2026-07/2026 cohort PnP review
08/2026 submission for publication

4. Rationale:

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide. Despite advances in prevention and treatment, CVD continues to pose a significant burden on global health. It is estimated that CVD accounts for nearly one-third of global deaths annually.[1] The high prevalence, mortality, and disability rates associated with CVD underscore the urgent need for identifying novel therapeutic targets and refining risk stratification strategies.

A growing body of research has established inflammation as a central mechanism in the pathogenesis of chronic CVD. Among inflammatory biomarkers, interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) have received considerable attention. IL-6 is a key upstream cytokine that triggers hepatic production of CRP and plays a direct role in vascular inflammation, endothelial dysfunction, and atherosclerosis.[2] The activation of the NLRP3 inflammasome leads to IL-6 upregulation, which in turn activates the JAK/STAT signaling cascade—resulting in increased CRP production, leukocyte recruitment, foam cell formation, and plaque destabilization.[3]

IL-6 contributes to atherosclerosis by promoting low-density lipoprotein uptake in macrophages and weakening the extracellular matrix, which increases the likelihood of plaque rupture and acute cardiovascular events. In myocardial infarction (MI), IL-6 enhances neutrophil infiltration and alters calcium dynamics via nitric oxide signaling. It also upregulates intercellular adhesion molecule-1 (ICAM-1) and increases plasminogen activator inhibitor (PAI) production, fostering a pro-thrombotic environment. In heart failure (HF), IL-6 exacerbates oxidative stress, impairs myocardial contractility, and promotes cardiac fibrosis. In ischemic stroke, IL-6 contributes to neuronal injury through reactive oxygen species (ROS) production, phospholipid metabolism disruption, and activation of glial and immune cells via JAK/STAT signaling.

C-reactive protein (CRP), as a downstream marker of IL-6 signaling, has also been widely validated as a predictor of cardiovascular risk. Elevated CRP levels have been associated with increased incidence of MI, stroke, and cardiovascular death, even after adjustment for traditional risk factors. The simplicity of its measurement and its reproducibility have made CRP a candidate for risk stratification in clinical settings, though its specificity remains debated. Together, IL-6 and CRP offer a biologically and clinically linked inflammatory axis with potential for both prognostic and therapeutic relevance.

However, despite strong biological plausibility and cross-sectional associations, the predictive value of IL-6 and CRP—individually or jointly—beyond traditional risk factors such as age, sex, blood pressure, and cholesterol levels, remains uncertain. Neither is currently incorporated into standard cardiovascular risk assessment algorithms. Our study aims to bridge this gap by providing robust prospective epidemiologic evidence on the role of IL-6 and CRP in predicting cardiovascular and mortality outcomes, independent of traditional CVD risk factors.

Recent randomized controlled trials have explored IL-6 inhibition as a strategy for cardiovascular risk reduction. The RESCUE trial demonstrated that ziltivekimab,[4] a targeted monoclonal antibody IL-6 inhibitor, significantly reduced biomarkers of inflammation and thrombosis associated with atherosclerosis, prompting large-scale cardiovascular outcome trials such as ZEUS,[5] HERMES,[6] and ARTEMES.[7] While promising, these trials require long durations, high cost, and strict protocol adherence—highlighting the need for complementary, population-based evidence to guide future research and clinical application.

Beyond IL-6 and CRP, additional biomarkers of adipose tissue dysregulation and cardiovascular harm have also shown promise in risk prediction. Systemic inflammation has been linked to increased risk of MI, stroke, and other CV events.[8,9]Adipokines are associated with abnormalities in lipid metabolism and increased cardiovascular risk.[10,11,12] Markers of cardiovascular harm, such as those indicating myocardial injury and stress, serve as strong predictors of adverse outcomes.[13,14]

While these biomarkers have demonstrated cross-sectional associations, their prospective effects on future cardiovascular outcomes and mortality remain relatively underexplored, particularly in large, harmonized cohorts with wide phenotypic diversity. Furthermore, the relationships between these biomarkers and traditional risk factors—such as total cholesterol, LDL cholesterol, and systolic blood pressure (SBP)—are not fully delineated. Clarifying these associations may help establish clinically actionable thresholds and improve their utility in CVD prediction.

Additionally, investigating whether biomarkers mediate the relationship between traditional risk factors and cardiovascular outcomes could offer mechanistic insight and enhance the performance of prediction models. If biomarkers such as IL-6 and CRP act as intermediaries in these pathways, combining them with traditional risk factors may yield more effective risk stratification tools. A large, well-phenotyped pooled cohort is essential to ensure adequate power for mediation analysis, detect subtle associations, and compare the relative effectiveness of biomarkers within the same biological pathway.

To address these gaps, the **Cross Cohort Collaboration (CCC)-Inflammation and Subclinical Markers** project harmonizes data from 25 longitudinal cohort studies from the U.S. and Brazil. Our study aims to: (1) evaluate the prospective associations of IL-6, hs-CRP, and other key biomarkers with prevalent atherosclerosis, incident cardiovascular events and mortality; (2) examine their associations with traditional CVD risk factors in predicting future cardiovascular

events and mortality; and (3) assess their potential mediating roles in the causal pathway from risk factors to cardiovascular and mortality outcomes. By leveraging a large, well-characterized population-based dataset, we aim to generate population-level evidence that can inform future guidelines and support the integration of inflammation-related biomarkers into cardiovascular risk prediction and prevention strategies. We will primarily rely on the previously harmonized **CCC-Obesity** dataset and the associated data already approved for use in prior projects.

5. Main Hypothesis/Study Aims:

1) **Aim 1:** Evaluate the prospective association between elevated levels of IL-6 and hs-CRP and future cardiovascular events and all-cause mortality, and their independent and joint predictive value beyond traditional risk factors.

   Hypothesis: IL-6 and hs-CRP are independent predictors of incident CV events and mortality, with residual risk beyond traditional risk factors such as age, sex, blood pressure, and lipid levels.

2) **Aim 2:** Evaluate the cross-sectional association between elevated levels of IL-6 and hs-CRP and prevalent subclinical atherosclerosis, including CAC score, cIMT, carotid plaque, and ABI level.
   Hypothesis: Elevated levels of IL-6 and hs-CRP are positively associated with greater burden of subclinical atherosclerosis, reflecting early vascular inflammation and injury.
3) **Aim 3:** Evaluate the prospective associations between levels of biomarkers of adipose tissue dysregulation, and cardiovascular harm, and incident cardiovascular events and all-cause mortality, and their independent and joint predictive value beyond traditional risk factors.
   Hypothesis: Higher levels of these biomarkers are independently associated with increased risk of incident cardiovascular events and mortality, beyond traditional risk factors.
4) **Aim 4:** Assess the cross-sectional associations between biomarker reflecting adipose tissue dysregulation and cardiovascular harm and markers of subclinical atherosclerosis, including CAC score, cIMT, carotid plaque, and ABI level.
   Hypothesis: Elevated biomarker levels are positively associated with greater burden of subclinical atherosclerosis at baseline.
5) **Aim 5:** Investigate the potential mediating role of the above biomarkers in the pathway between traditional cardiovascular risk factors and future cardiovascular events and mortality.
   Hypothesis: The relationship between traditional risk factors (e.g., SBP, LDL cholesterol, total cholesterol) and adverse outcomes is partially mediated by biomarkers of systemic inflammation, adipose tissue dysregulation, and cardiovascular injury.

6. Design and analysis - please address the following aspects:

a) Inclusion/exclusion

We will include participants with available data on IL-6, hs-CRP, or subclinical markers of interest (see Exposures), when available, from any visits in ARIC.

b) study design

Prospective observational multi-cohort study design.

c) outcome and other variables of interest with specific reference to the time of their collection

Outcomes:

1. Incident cardiovascular events:
   1.2 Individual conditions: myocardial infarction, stroke, heart failure, atrial fibrillation, and peripheral artery disease
   2.2 composite: CVD, and CHD.
   3.2 Heart failure subtypes: heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) will be characterized where data availability permits.
2. Incident mortality events:
   1.2 all-cause mortality
   2.2 CVD specific mortality and CHD-specific mortality.
3. Prevalent Atherosclerosis: coronary artery calcium (CAC), carotid plaque, carotid intima-media thickness (cIMT), ankle-brachial index (ABI). Availability of those variables in the ARIC study can be checked in *Appendix Table 1*.

   We will utilize the available data summarized above collected at any visits or follow-ups in the ARIC study.

Exposure variables:

1. IL-6
2. hs-CRP
3. Biomarkers including markers of adipokines (leptin, adiponectin, resistin, visfatin), lipoprotein(a), and markers of cardiovascular harm (troponin, NT-proBNP).

The biomarkers of interest were assessed at baseline or during follow-up visits. They will be analyzed both as continuous variables and as categorical variables, using either clinically relevant cutoff points or distribution-based thresholds. Availability of those variables in the ARIC study can be checked in *Appendix Table 1*.

Covariates variables:

1. Demographic and socioeconomic variables (age, sex, race/ethnicity, education, income, study site)

2. Physical measurement variables (body mass index [BMI], waist circumference [WC], waist-hip ratio [WHR], heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP])

4. Lifestyle variables (physical activity, smoking status, alcohol use)

5. Clinical risk factors variables: (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, hemoglobin A1C [HbA1C], and fast blood glucose [FBG])

6. Medication use variables: lipid-lowering medication, anti-hypertensive medication, and anti-hyperglycemic therapy, anti-inflammatory medications.

7. Co-morbidities: chronic kidney disease (CKD).

d) summary of data analysis

General Considerations:

1. Significance Level:

-Set the significance level at $\alpha = 0.05$ for all statistical tests.

2. Handling Missing Data:

-Use multiple imputation techniques to handle missing data.

3. Statistical Software:

-Perform all analyses using statistical software such as R or STATA.

Aim 1: To evaluate the prospective association between elevated levels of IL-6 and hs-CRP and the risk of incident cardiovascular events and all-cause mortality, we will employ Cox proportional hazards regression models. Follow-up time will be calculated from the date of biomarker assessment to the date of the first cardiovascular event, death, or censoring.

Exposure Definition:

IL-6 and hs-CRP will be analyzed as both continuous variables (log-transformed if skewed) and categorical variables (e.g., quartiles or clinically relevant cutoffs). A joint exposure variable will also be created to evaluate combined inflammatory burden.

Model adjustment:

- **Model 1:** Unadjusted
- **Model 2:** Adjusted for demographic variables (age, sex, race/ethnicity) and individual cohort
- **Model 3:** Additionally adjusted for traditional cardiovascular risk factors, including smoking status, systolic blood pressure, antihypertensive and lipid-lowering medication use, total and LDL cholesterol, diabetes status, and BMI
- **Model 4:** Mutually adjusted for IL-6 and hs-CRP to assess their independent effects

Model Performance and Incremental Predictive Value:

The incremental predictive value of IL-6 and hs-CRP over traditional risk factors will be evaluated using:

- Harrell's C-index for model discrimination
- Likelihood ratio tests to compare nested models

Effect Modification and Sensitivity Analyses:

- Stratified analyses by sex, age group, BMI category, baseline CKD status
- Interaction terms will be tested to assess effect modification by traditional risk factors
- Secondary analysis excluding individuals with known CVD to minimize reverse causation

Aim 2:

To evaluate the cross-sectional association between elevated levels of IL-6 and hs-CRP and prevalent subclinical atherosclerosis, we will use multivariable regression models appropriate to each subclinical outcome:

Exposure Definition:

IL-6 and hs-CRP will be analyzed as both continuous variables (log-transformed if skewed) and categorical variables (e.g., quartiles or clinically relevant cutoffs). A joint exposure variable will also be created to evaluate combined inflammatory burden.

Outcomes of Interest:

- **CAC score:** analyzed as both binary (CAC > 0 vs. CAC = 0) using logistic regression and continuous (Agatston score, log-transformed +1) using linear regression
- **cIMT:** modeled as a continuous variable using linear regression
- **Carotid plaque (presence/absence):** modeled using logistic regression
- **ABI:** modeled as continuous and as a binary outcome (e.g., ABI < 0.9 indicating peripheral artery disease)

Model adjustment:

- **Model 1:** Unadjusted
- **Model 2:** Adjusted for demographic variables (age, sex, race/ethnicity) and individual cohort
- **Model 3:** Additionally adjusted for traditional cardiovascular risk factors, including smoking status, systolic blood pressure, antihypertensive and lipid-lowering medication use, total and LDL cholesterol, diabetes status, and BMI
- **Model 4:** Mutually adjusted for IL-6 and hs-CRP to assess their independent effects

Effect Modification and Sensitivity Analyses:

- Stratified analyses by sex, age group, BMI category, and baseline CKD status

- Interaction terms will be tested to assess effect modification by traditional risk factors

Aim 3: To Evaluate the prospective associations between levels of biomarkers of adipose tissue dysregulation, and cardiovascular harm, and incident cardiovascular events and all-cause mortality, and their independent and joint predictive value beyond traditional risk factors, we will employ Cox proportional hazards regression models. Follow-up time will be calculated from the date of biomarker assessment to the date of the first cardiovascular event, death, or censoring.

Exposure Definition:

Each biomarker will be analyzed as both a continuous variable (log-transformed where appropriate to normalize skewed distributions) and as categorical variables (e.g., quartiles or biomarker-specific clinical cutoffs when established).

Model adjustment:

- **Model 1:** Unadjusted
- **Model 2:** Adjusted for demographic variables (age, sex, race/ethnicity) and individual cohort
- **Model 3:** Additionally adjusted for traditional cardiovascular risk factors, including smoking status, systolic blood pressure, antihypertensive and lipid-lowering medication use, total and LDL cholesterol, diabetes status, and BMI
- **Model 4:** Further adjusted for systematic inflammation level.

Model Performance and Incremental Predictive Value:

The incremental predictive value of biomarkers of adipose tissue dysregulation and cardiovascular harm over traditional risk factors will be evaluated using:

- Harrell's C-index for model discrimination
- Likelihood ratio tests to compare nested models

Effect Modification and Sensitivity Analyses:

- Stratified analyses by sex, age group, BMI category, and inflammation level
- Interaction terms will be tested to assess effect modification by traditional risk factors

Aim 4:

To evaluate the cross-sectional association between elevated levels of biomarkers of adipose tissue dysregulation, and cardiovascular harm and prevalent subclinical atherosclerosis, we will use multivariable regression models appropriate to each subclinical outcome:

Exposure Definition:

Each biomarker will be analyzed as both a continuous variable (log-transformed where appropriate to normalize skewed distributions) and as categorical variables (e.g., quartiles or biomarker-specific clinical cutoffs when established).

Outcomes of Interest:

- **CAC score:** analyzed as both binary (CAC > 0 vs. CAC = 0) using logistic regression and continuous (Agatston score, log-transformed +1) using linear regression
- **cIMT:** modeled as a continuous variable using linear regression
- **Carotid plaque (presence/absence):** modeled using logistic regression
- **ABI:** modeled as continuous and as a binary outcome (e.g., ABI < 0.9 indicating peripheral artery disease)

Model adjustment:

- **Model 1:** Unadjusted
- **Model 2:** Adjusted for demographic variables (age, sex, race/ethnicity) and individual cohort
- **Model 3:** Additionally adjusted for traditional cardiovascular risk factors, including smoking status, systolic blood pressure, antihypertensive and lipid-lowering medication use, total and LDL cholesterol, diabetes status, and BMI
- **Model 4:** Further adjusted for systematic inflammation level.

Effect Modification and Sensitivity Analyses:

- Stratified analyses by sex, age group, BMI category, and inflammation level
- Interaction terms will be tested to assess effect modification by traditional risk factors

Aim 5: To investigate the potential mediating role of biomarkers reflecting systemic inflammation (e.g., IL-6, hs-CRP), adipose tissue dysregulation (e.g., adipokines, lipoprotein[a]), and cardiovascular harm (e.g., troponin, NT-proBNP) in the pathway linking traditional cardiovascular risk factors (e.g., SBP, LDL cholesterol, total cholesterol) to incident cardiovascular events and all-cause mortality.

Path Analysis:

We will begin by constructing directed acyclic graphs (DAGs) and conceptual path diagrams to illustrate hypothesized causal relationships among exposures (traditional cardiovascular risk factors), mediators (biomarkers), and outcomes (cardiovascular events and mortality). These diagrams will guide model specification and clarify assumptions.

Causal Mediation Analysis:

We will use counterfactual-based causal mediation techniques to decompose the total effect of each traditional risk factor into:

- Direct effects (not mediated by biomarkers)
- Indirect effects (mediated through biomarkers)

Models will adjust for potential confounders of the exposure–outcome and mediator–outcome relationships, including age, sex, race/ethnicity, diabetes, smoking, BMI, and medication use.

Proportion Mediated and Significance Testing:
We will estimate the proportion of the total effect mediated by each biomarker or biomarker class. Bootstrapped 95% confidence intervals will be generated for all indirect and direct effects. We will also assess whether the mediation varies by subgroups (e.g., sex, obesity status) through interaction terms and stratified models.

e) Any anticipated methodologic limitations or challenges if present
We don't anticipate any methodologic limitations or challenges.

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ☐ Yes ☐ No
(The file ICTDER is distributed to ARIC PIs annually, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ☐ Yes ☒ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☐ Yes ☐ No

9. The lead author or the "sponsoring" ARIC author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ Yes ☐ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?
#3604 Association of Interleukin-6 and Interleukin-18 levels in blood with Global Cardiovascular Disease in Older Adults: Atherosclerosis Risk in Communities Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☐ Yes ☒ No → Skip to question 12

11.b. If yes to 11.a., is the proposal

- ☐ **A. primarily the result of an ancillary study**
- ☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* __

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website□Ancillary Studies□Approved Ancillary Studies]

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

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website□Publications□Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

Reference:

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Appendix Table 1. Availability of key variables in ARIC

Variables	Visit
IL-6	Visit 2, 3, 5
Hs-CRP	Visit 4, 5, 6, 7, 9
Lp(a)	Visit 1, 4, 5
Adipokines	Visit 2, 3, 4, 5, 7
Hs-cTnl Hs-cTNT	Visit 4, 5 Visit 2, 4, 5
NT-pro BNP	Visit 2, 4, 5, 6, 7
CAC score	Visit 7
cIMT	Visit 1 Carotid-MRI
Carotid plaque	Visit 1, 2 Carotid-MRI
ABI	Visit 1, 3, 4, 5, 7