ARIC Manuscript Proposal #3535

PC Reviewed: 1/14/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Development and validation of an inflammatory diet score (IDS) and its association with incident cardiovascular disease in the ARIC study

b. Abbreviated Title (Length 26 characters):
IDS and CVD

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

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3. Timeline: 8-9 months, manuscript submission in summer 2020

4. Rationale:

Chronic inflammation is characterized as a state of low-grade, persistent presence of cytokines that can modulate or amplify the inflammatory response that leads to tissue degeneration[1]. Considerable research has shown that diet has an impact on the regulation of inflammation. High fruit and vegetable intake is inversely correlated with the concentration of C-reactive protein (CRP) and interleukin-6 (IL-6)[2], while consumption of red meat is associated with a higher

level of CRP and lower adiponectin[3,4]. Specific nutrients, like β-carotene[5], vitamin C[6,7], and Ω-3 fatty acids[8,9] are shown to be associated with a lower level of inflammation, while others, like saturated fatty acid[10], fat[11,12] have a pro-inflammatory response.

Chronic inflammation also plays an important role in the development of cardiovascular disease (CVD) [13]. Especially for atherosclerosis, inflammation participates in all of its stages from the inception, progression and ultimately thrombosis[14,15]. Diet is a modifiable risk factor for CVD. The Mediterranean diet, the DASH diet, and other healthy dietary patterns are associated with a lower risk of cardiometabolic outcomes[16,17]. Therefore, quantifying the inflammatory potential of the diet will allow us to investigate inflammation as a purported pathway underlying the association between diet and cardiovascular disease risk. A previous meta-analysis documented a positive association between higher dietary inflammatory index (DII) score (i.e., pro-inflammatory diet) and CVD incidence and mortality[18].

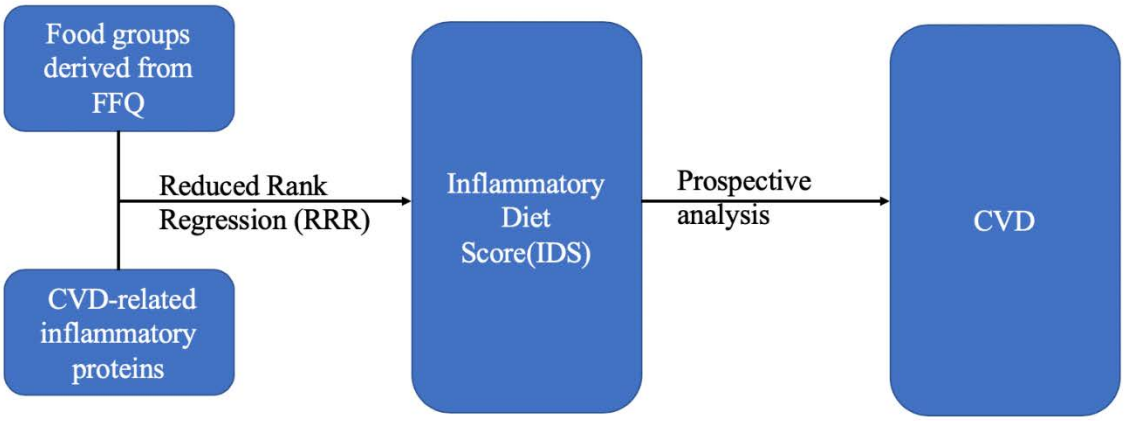
The effects of single nutrients and whole food groups on inflammation have been thoroughly studied, but an aggregated assessment of the inflammatory potential of individuals' diets was proposed in 2009. Researchers from the University of South Carolina first developed a literature-derived, population-based index called dietary inflammatory index (DII) that categorizes individuals' diets on a continuous scale from anti-inflammatory to pro-inflammatory[19]. They scored the peer-reviewed articles available based on the pro- or anti-inflammatory association demonstrated between each dietary component and 6 inflammatory markers (CRP, IL-6, IL-1β, IL-4, and IL-10; and tumor necrosis factor (TNF)-α) and then assigned a score, representing the strength of the evidence, as a weight to each component [19]. In total, 45 dietary factors, mostly nutrients, herbs and spices, and some whole foods like garlic and onions were included[19]. More recently, an empirical dietary inflammatory index (EDII) was developed based exclusively on food groups by researchers from Harvard University. They applied reduced rank regression followed by stepwise linear regression using data from the Nurses' Health Study. They identified 18 components most predictive of 3 plasma inflammatory markers: IL-6, CRP, and tumor necrosis factor-alpha receptor 2 (TNFαR2) [20].

Although these two indexes both were designed to access the inflammatory potential of diet, the validity of DII and EDII is still controversial. DII was reported to have a stronger association with IL-6, while EDII was more strongly associated with adiponectin[21]. The association between the inflammatory potential of diet and disease outcomes measured by these two indexes was different in scale and sometimes different in the direction[21,22]. The limitations of DII mainly come from its heavy focus on nutrients and other food parameters as components of the index. First, reproducibility is an issue since DII includes many components that are not typically available on food frequency questionnaires, such as herbs and spices (saffron, pepper, thyme, oregano, rosemary). Second, the food parameters, which are mostly nutrients, do not capture the interaction between bioactive components that exist in whole foods[19,23]. Third, the weighted literature method is somewhat arbitrary in terms of the scoring algorithm[19,23] and did not take the magnitude of association into account. As for EDII, the limitations are related to comparability and generalizability. EDII was derived and validated in cohorts with similar demographic characteristics and identical dietary measurement assessment methods, which could raise issues of correlated error, overstated validity, and limited generalizability to other populations with different characteristics[20,24]. For both of the indexes, only a limited number of

inflammatory biomarkers (i.e., 6 for DII and 3 for EDII) were evaluated resulting in weaker ability to predict the overall inflammatory potential of diet.

In the proposed study, we will construct a data-driven novel inflammatory diet score (IDS) using *a posteriori* statistical exploratory method. The recently used high-throughput technology (i.e., SOMAscan multiplexed proteomic technology) for the characterization of the human proteome in ARIC study provided us with accurate and reliable measurements of ~350 inflammatory proteins. Candidate proteins selected to derive the novel inflammatory diet score (IDS) will be those most relevant to the etiology of cardiovascular disease. The comprehensive inflammation biomarker panel enables us to explore the association between diet and inflammation in a more comprehensive manner. Furthermore, the ARIC study population is a more representative sample of the general US population than previous research on this topic, and thus the expected results will have broader generalizability.

In the proposed study, we will also relate the novel inflammatory diet score (IDS) to incident cardiovascular disease in ARIC study.



5. Main Hypothesis/Study Questions:

Aim 1: To derive a novel inflammatory diet score (IDS) from proteomics data in a random 2/3 sample of ARIC participants using reduced rank regression (RRR).

Hypothesis 1: The novel IDS can quantify the inflammation potential of diets with higher scores reflecting a proinflammatory diet.

Aim 2: To evaluate the construct validity of our IDS by evaluating its association with individual inflammatory biomarkers and a standardized overall inflammatory biomarker score in a random 1/3 sample of ARIC participants.

Hypothesis 2: The IDS has good construct validity and is significantly associated with inflammatory biomarkers.

Aim 3: To compare our novel IDS to EDII and DII.

Hypothesis 3: There is weak to moderate correlation between our index (IDS) and the previously created indices (DII and EDII).

Aim 4: To determine whether a higher IDS (representing a pro-inflammatory diet) is associated with a higher risk of incident cardiovascular disease.

Hypothesis 4: Participants with a higher IDS have a higher risk of developing CVD.

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

The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing community-based, prospective cohort study. From 1987 to 1989, there were 15,792 middle-aged men and women (45-65 years of age at baseline) enrolled in ARIC study from 4 communities within the U.S: Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis, Minnesota[25]. Follow-up visits occurred in 1990 to 1992 (visit 2), 1993 to 1995 (visit 3), 1996 to 1998 (visit 4), 2011 to 2013 (visit 5), and 2016 to 2017 (visit 6) [25]. Dietary intake was assessed at baseline and visit 3 by trained interviewers using a modified semi-quantitative 66-item Willett food frequency questionnaire[26]. Proteomic data were measured using a Slow Off-rate Modified Aptamer (SOMAmer)-based capture array (SomaLogic) at visit 3. We will conduct cross-sectional analyses of dietary intake and inflammatory biomarkers for aims 1-3 and a prospective analysis of the novel IDS and incident cardiovascular disease for aim 4. Visit 3 will serve as the baseline visit for all analyses given the availability of both proteomic and dietary data at this visit.

Study Design & Analysis

For Aim 1-3 (development and validation of the index):

Study design: A simple random sample of 2/3 of ARIC study participants at visit 3 will be used to develop the index. The remaining 1/3 ARIC cohort will be used for the purpose of validation.

Inclusion Criteria: All participants who (1) attended visit 3 (1993–1995), (2) have dietary intake data, (3) had inflammatory proteins measured by SOMALogic will be eligible for inclusion in the study.

Exclusion Criteria: We will exclude participants (1) with a large amount of missing data (≥10%) on the FFQ; (2) with implausible energy intake [<2510 kJ (<600 kcal) or >17 573 kJ (>4200 kcal per day for men and <2092 kJ (<500 kcal) or >15062 kJ (>3600 kcal) per day for women)]; (3) with extreme body mass index (BMI) (<15 kg/m^2 or >50 kg/m^2), (4) with CRP concentrations >10 mg/L, since it may have been due to acute infection or medication use[30]; (4) who had a history of cancer, cardiovascular disease, diabetes mellitus, rheumatoid or other arthritis, chronic kidney disease at baseline; (5) with missing covariate data (age, sex, physical activity, smoking status, education, BMI, regular aspirin/nonsteroidal anti-inflammatory drug use, menopausal status, postmenopausal hormone use, inflammation-related chronic disease [i.e. hypercholesterolemia, cancer, diabetes, hypertension, heart disease, and rheumatoid or other arthritis]

Exposure: Dietary data collected from FFQ at visit 3. Participants were asked to report the average consumption of each food item of particular portion size in the past year. There are 9 frequency options in the questionnaire from "almost never" to "6 or more times a day"[26]. Total energy intake was obtained through multiplying the consumption amount of food by the nutrient content of corresponding food in USDA data source. The reported frequency for each food item will be converted to daily intake. Single food items from FFQ will be grouped into food categories [27]. We will exclude food items if <1% of our study population consumed ≥1 serving/wk[23].

Outcome:
Inflammatory proteins related to cardiovascular disease[28], including:
Pro-inflammatory: CRP, IFN-γ, IL-1, IL-6, IL-8, MCP-1, MIF, TNF-α, TNFR-1
Anti-inflammatory: Adiponectin, IL-4, IL-10, TGF-β
The concentration of each biomarker will be log-transformed to improve normality of the distribution.
We will construct a **standardized inflammatory biomarker score** for each individual by adding up the z-scores of natural log pro-inflammatory biomarkers and then subtracting the z-scores of natural log anti-inflammatory biomarkers. The algorithm is as follows:

z score(log CRP) + z score(log IFN-γ) + z score(log IL-1) + z score(log IL-6) + z score(log IL-8) + z score(log MCP-1) + z score(log MIF) + z score(log TNF-α) + z score(log TNFR-1)- z score(log adiponectin) - z score(log IL-4) - z score(log IL-10) - z score(log TGF-β)

All the plasma concentrations of inflammatory proteins were assayed using highly sensitive, high throughput aptamer-based protein profiling (SOMAscan® Platform) at visit 3. Previous studies have reported inter-assay CVs (coefficient of variation) around 5% and ICCs (intraclass correlation) around ~0.9 for this assay[29].

Covariates: If available, we will use covariates assessed at visit 3.
1. Confounders:
Sociodemographic data: age, center, education level
Lifestyle factors: smoking status, physical activity
Medical conditions: regular aspirin/nonsteroidal anti-inflammatory drug use, lipid-lowering medication use, inflammation-related chronic disease (i.e. hypercholesterolemia, cancer, hypertension, heart disease, and rheumatoid or other arthritis)
2. Effect Measure Modifiers:
Sex, race, diabetes status, BMI

Statistical Analysis Plan:
1. Construct the inflammatory diet score (IDS) in test dataset (2/3 random sample of ARIC participants)

1) The energy-adjusted intake estimate of each food item will be calculated using the residual method[30]. The food items will be further grouped into food groups and mean daily intake for each food group will be calculated.

2) Reduced rank regression (RRR) will be used to derive a dietary pattern associated with the inflammatory biomarkers. The goal of RRR is to select a set of predictors (food groups) that can explain the maximum variation of the response variables (inflammatory

biomarkers)[31]. The first factor obtained by RRR is a linear function of predictors (food groups) which explains the most variation in the intermediate response variables (inflammatory biomarkers) than the subsequent patterns. This first factor will be used for subsequent analyses [31,32]. The factor score for the first factor will constitute the DIS. The DIS will be a continuous variable with higher scores indicating a more pro-inflammatory diet.

3) We will graphically assess the distribution of each biomarker and the standardized total biomarker score according to IDS. We will calculate correlation coefficients between inflammatory biomarkers (individual biomarkers and the standardized score) and the IDS in test dataset (random 2/3 sample).

2. Validate the IDS in the remaining 1/3 validation dataset

1) We will calculate the IDS for the remaining 1/3 sample of ARIC participants (validation dataset) by multiplying the factor weights for each food category by each individual's reported frequency of consumption of each food category. We will describe the baseline characteristics of the study population according to quartiles of IDS.

2) Multivariable linear regression will be used to assess the association of standardized total inflammatory biomarker score (as well as individual inflammatory biomarkers) and IDS. IDS will be analyzed as quartiles and continuously. Linear trend across IDS quartiles will be assessed by modeling an ordinal variable using the median value within each quartile. The models will be adjusted for the potential confounding factors mentioned above. Potential effect measure modifiers will be assessed by including an EMM × IDS interaction term in the models. As a sensitivity analysis for the standardized total inflammatory biomarker score, we will use factor analysis to create a single score (the first factor) of the inflammatory biomarkers.

3) DII and EDII for each participant in the validation cohort will be calculated using previously described methods. The Spearman's correlation will be used to investigate the correlations between the IDS, DII, and EDIP. We will also calculate the concordance between identical quartiles of the three indices.

For Aim 4 (prospective association with incident CVD):

Study Design: We will use the entire ARIC cohort to study the association of IDS with incident CVD.

Inclusion Criteria: All participants who had dietary intake measurements and those without prevalent CVD at visit 3.

Exclusion Criteria: same as for aims 1-3.

Exposure: The exposure is IDS that we will develop for aim 1 using dietary data at visit 3.

Outcome: Incident CVD is defined as a composite outcome of coronary heart disease (including hospitalized myocardial infarction or fatal CHD), definite or probable stroke, and heart failure (hospitalization or death with ICD-9 code 428 or ICD-10 code I50). The events were ascertained through annual telephone follow-up, active community surveillance, and linkage to the National Death Index for fatal events.

Covariate: same as for aims 1-3.

Statistical Analysis Plan:
1. IDS will be calculated for all eligible ARIC study participants as a sum of the weighted intake of food groups. Weights/factors score will be obtained from the RRR analysis.
2. We will describe the baseline characteristic of the population according to quartiles of the IDS.
3. Cox proportional hazards regression model will be used to examine the association between IDS and incident CVD. The IDS will be analyzed according to quartiles of its distribution with the lowest quartile serving as the reference group. Schoenfeld residuals test and other graphical methods will be used to assess the proportionality assumption. If the hazards are found to be not proportional, we will fit non-proportional hazard or use generalized gamma model instead. The basic model will adjust for total energy intake, age, sex, and race-center. Model 2 will build on model 1 and further adjust for smoking status, education level, and physical activity level. Model 3 will additionally adjust for cancer, hypertension, dyslipidemia, and rheumatoid or other arthritis, and use of aspirin, other NSAIDs, or lipid-lowering medications. We will evaluate model fit using likelihood ratio tests and Akaike Information Criteria (AIC).
4. DII and EDII will also be calculated and we will repeat the Cox regression to determine their associations with incident CVD. The strengths and directions of the associations with incident CVD will be compared between IDS, DII, and EDII.
4. Subgroup analysis will be conducted by sex, race, diabetes, and BMI.
5. Sensitivity analysis: We will analyze IDS as a continuous variable and repeat the Cox proportional hazards regression model.

Limitations:
1. We only have both dietary measurements and protein measurements at visit 3. The one-time measurement of biomarkers and diet may not represent usual diet and inflammatory status.
2. The index is derived based on a panel of biomarkers most relevant to CVD which may limit the generalizability of the IDS as representing the inflammatory potential of the diet with respect to the development of other diseases.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __ √ __ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __ √ __ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. **The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.** ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

   ___X___ Yes _____ No

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

No known related manuscript proposals.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __ X __ Yes ____ No

11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* 2017.27)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at https://www2.cscc.unc.edu/aric/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 http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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