ARIC Manuscript Proposal #2359r

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Status: A
Priority: 2

SC Reviewed: _________
Status: _____
Priority: ____

1.a. Full Title: Population impact of adiposity on the chronic disease burden in African Americans and whites: an application of the parametric g-formula

b. Abbreviated Title (Length 26 characters): BMI and chronic disease burden

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

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Timeline:
Analysis will start as soon as approval is obtained. We plan to complete two manuscripts within 15 months from approval of this manuscript proposal.
3. **Rationale:**

Chronic kidney disease (CKD), peripheral artery disease (PAD), and coronary heart disease (CHD) are important public health concerns in the United States. Approximately 10% (26 million), 6% (8 million) and 3% (5.7 million) of Americans are affected by CKD, PAD and CHD respectively. Given the public health burden associated with these chronic diseases, emphasis has been placed on identifying modifiable risk factors. Adiposity is a risk factor for the aforementioned chronic diseases. Well documented biological pathways through which adiposity affects these diseases include the cardio-metabolic risk factors systolic blood pressure (SBP) and glucose. Human experimental studies provide evidence that reductions in adiposity are associated with reductions in levels of these two cardio-metabolic risk factors. Common categorizations of adiposity include underweight (body mass index (BMI) < 18.5 kg/m$^2$), normal weight (BMI = 18.5-24.9 kg/m$^2$), overweight (BMI = 25-29.9 kg/m$^2$) and obese (BMI ≥ 30 kg/m$^2$), which may be helpful in a clinical setting. Categorically-defined adiposity also has been widely reported as a risk factor for the above chronic diseases. However, evaluation of adiposity on a continuous measurement scale may better describe the associations with health risk at a population level. Shifting the population distribution of risk factors such as adiposity has been emphasized in the work of G. Rose as having the largest potential to reduce disease burden. Several investigators also have demonstrated beneficial effects from small shifts in the population distribution of blood pressure on cardiovascular disease (CVD) events. However, similar work has not been done for adiposity to the best of our knowledge.

Our study objective is therefore to first characterize the association between BMI and the two specified cardio-metabolic risk factors – SBP and glucose – in the observational setting of the biracial Atherosclerosis Risk in Communities (ARIC) study. We will then estimate the change in risk, disability and premature death related to CKD, PAD and CHD associated with a population-wide shift in the distribution of BMI.

To estimate this effect of BMI on the selected outcomes, we propose using the parametric g-formula since it is well suited for estimation of changes in population risk where covariates may be time-varying. The method is well established, yet its application is not yet widespread in the literature. We selected three outcomes (CKD, PAD and CHD) as plausible long-term outcomes influenced by shifts in the population distribution of adiposity, in ways that have been documented. The proposed work is part of a doctoral research proposal.

5. **Specific Aims and Hypotheses:**

1. Characterize the cross-sectional association between BMI and the specified cardio-metabolic risk factors - SBP and fasting glucose in the ARIC cohort. **Hypotheses:** There will be a monotonic linear relationship between BMI and SBP, and between BMI and
fasting glucose, without evidence of a threshold in these relationships over the range of the adiposity distribution included in our analysis (BMI=24-40 kg/m²). The association between BMI and SBP and fasting glucose will be comparable in shape and magnitude across race, sex and age cohort.

2. Compare the effect estimates of the decrement in BMI on the specified cardio-metabolic risk factors - SBP and glucose derived from the human experimental literature to their observational equivalent in the ARIC cohort. *Hypothesis:* The association between BMI and the two specified cardio-metabolic risk factors in the ARIC cohort will be comparable in magnitude to the association found in the human-experimental data, after adjustment for confounders.

3. Estimate the decrement in risk of each of the three specified chronic diseases resulting from two hypothetical favorable shifts (1 kg/m² and 5%) in the population distribution of BMI in the ARIC cohort. *Hypothesis:* Shifting the population distribution of BMI reduces the risk of each of the specified chronic diseases.

4. Estimate the change in the burden of premature mortality and disability in the specified chronic diseases associated with two hypothetical favorable shifts (1 kg/m² and 5%) in the distribution of BMI. *Hypothesis:* Shifts in the population distribution of BMI will be associated with detectable (and beneficial) differences in years of life lost (YLL), years lived with disability (YLD) and disability adjusted life years (DALYs)²⁸,²⁹ for the specified chronic diseases.

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 methodological limitations or challenges if present).

**Study design:**

Inclusions: The analyses will include African American and white ARIC participants with a baseline BMI range of 24-40 kg/m².

Exclusions: ARIC study participants with morbidity/chronic conditions at baseline associated with weight gain or loss will be excluded. These conditions include an eGFR<15 mL/min/1.73 m², heart failure, and cancers. Participants with prevalent chronic diseases (CKD, PAD, and CHD) will be excluded from the relevant analyses.

Overview: The cross-sectional association between general adiposity (BMI) and SBP and glucose in the ARIC population and the human experimental literature will be described. We will estimate the effect of two hypothetical favorable shifts (1 kg/m² and 5%) in the population distribution of BMI on changes in the risk, burden of disability and the burden of mortality for CKD, PAD and CHD.

**Measurements:** Anthropometric measures (height and weight) were ascertained at each of the first four ARIC study visits.

**Outcomes:** The study outcomes correspond to those ascertained and classified by the ARIC
investigators and released as CHD events or as derived variables, consistent with those published by ARIC.

- **Stage 4 CKD and ESRD:** Incidence will be ascertained in participants who did not have prevalent stage 4 CKD or ESRD at baseline examination. Hospitalizations and death certificates with ICD-9-CM codes of 585.4 and 585.6 in any position will be used to identify stage 4 CKD and ESRD respectively.

- **PAD and CHD:** Incidence of PAD and CHD will be ascertained in participants who did not have the relevant condition at baseline. Annual telephone interviews, identification of hospitalizations and deaths during the previous year and surveying discharge lists from local hospitals and death certificates from the state will be used to identify incident cases.
  - **PAD** will be identified as a self-reported diagnosis during annual telephone surveys or from hospitalization ICD-9-CM codes recorded on hospital discharge records (in any position) that include revascularization or lower extremity, amputation procedure, peripheral vascular disease not otherwise specified, and peripheral angiopathy not otherwise specified (ICD-9 CM codes 440.2x, 440.3x, 440.8x, 440.9x, or 443.9x).
  - **CHD** will be defined as a validated (definite or probable) hospitalized myocardial infarction (MI), a definite CHD death, or an unrecognized MI. Unrecognized MI was determined as a major Q wave or a minor Q wave with ischemic ST-T changes on an ECG at one of the follow-up study visits, in comparison to the ECG done at the baseline visit. All final diagnoses for CHD based on this definition were validated by a morbidity and mortality classification committee.

**Covariates:** age, smoking, and use of blood pressure, lipid or glucose lowering medications.

**Statistical Analysis:**

**Aim 1:**

The cross-sectional association between BMI and SBP and glucose will be estimated at each of the four ARIC study visits using the following linear regression model:

\[ Y = \beta_0 + \beta_1(BMI) + \beta_2(smoking) + (e) \]

where \( Y \) will be SBP in one model and glucose in a separate model, \( \beta_0 \) will represent the intercept, \( \beta_1 \) will represent the difference in \( Y \) given a 1-unit increase in BMI controlled for smoking. This association will be stratified by race (African American and white), sex (male and female), and age cohort (45-54 or 55-64 at baseline). We will conduct linear regression analysis of the association with BMI included in the model along with its polynomials to test for linearity.

**Aim 2:**

Estimates of the association between BMI and the two cardio-metabolic risk factors – SBP and glucose have been reported in the human experimental literature. In the human experimental literature,\(^4\text{-}^7\) for every 1-unit decrease in BMI, reductions in SBP ranged from 0.33 to 4.33 mmHg and reductions in fasting glucose ranged from 0.81 to 9.11 mg/dL. The
magnitude of the differences in SBP and glucose predicted using linear regression analysis in ARIC for a 1-unit change in BMI will be compared to the summary meta-analysis estimates and those found in the human experimental literature.

Aim 3:

Two hypothetical shifts (1 kg/m\(^2\) and 5%) in the population distribution of BMI will be applied to the ARIC cohort at baseline. These population shifts will be applied so that reductions will not occur below a BMI of 23 kg/m\(^2\) and not at or above 65 years of age. Next, we will use these shifts to estimate the risk of CKD, PAD and CHD. We have several outcomes so we present this estimation for BMI and CHD as an example and the other combinations will use this same strategy. We will use the parametric g-formula below, which allows the estimation of cumulative incidence for CKD, PAD and CHD before and after the hypothetical shifts in the distribution of BMI:

\[
\sum_{k=1}^{21} \sum_{z_{10}}^{z_{10}} \sum_{z+10}^{z+10} \sum_{v} \Pr[D_k + 1 = 1| z_k, v, D_k = \tilde{C}_k = \tilde{N}_k = 0] \times \prod_{j=1}^{k} \left[ f(d(z_j|z_j*, \tilde{z}_j - 1, v, \tilde{D}_j = \tilde{C}_j = \tilde{N}_j = 0) \times \Pr[D_j = \tilde{N}_j = 0| \tilde{z}_j - 1, v, \tilde{D}_j - 1 = \tilde{C}_j - 1 = \tilde{N}_j - 1 = 0] \right]
\]

where \(k=1,\ldots,21\) denotes 1-year time periods starting at baseline (1987-1990); \(z_k\) is the vector of intervention values following a 1kg/m\(^2\) shift in BMI at baseline of the risk factors \(Z_k\) at time \(k\); \(z_k^{*}\) is the vector of values that would be observed without time \(k\) intervention; \(v\) is the vector of time-independent baseline covariates; \(D_k + 1 = 1\) is the event that CHD is diagnosed between year \(k\) and \(k+1\); \(D_k = 0\) is the event that a subject remains free of CHD through year \(k\); and \(\tilde{N}_k = 0\) is the event that a subject has not died from other causes through exam \(k\).

The following process of estimating risks using the parametric g-formula will be followed. We will fit this regression model for all covariates of the association between BMI and CHD:

\[
[Y=\beta_0+\beta_1(BMI)+ \beta_2(smoking)+ \beta_3(age) + (e)]; \text{ where } Y \text{ will be CHD, } \beta_1 \text{ will represent the difference in } Y \text{ given a 1-unit increase in BMI controlled for the other covariates in the model.}
\]

These regression models will be used to simulate the risk of CHD under the two hypothetical population shifts in BMI (1-kg/m\(^2\) and 5%), according to the following steps. We will estimate the observed distribution of the covariates at baseline and estimate the joint distribution of time-varying covariates at the next time-point using the parametric models. Next we will apply one of the hypothetical population shifts by setting the values for BMI to the values determined by the hypothetical shifts (constrained by a BMI of 23 kg/m\(^2\)) and estimate the predicted probability of CHD using these new values. These steps will be followed for each 1-
year follow-up interval to estimate the predicted risk of CHD under each of the hypothetical population shifts in BMI.

**Aim 4:**

We will estimate the change in disease burden following a shift in BMI for each of the specified chronic diseases (CKD, PAD and CHD). Specifically, we will estimate the change in years of life lost (YLL) and years lived with disability (YLD). Calculating these measures of change in burden requires the estimation of the generalized impact fraction (GIF). The population risk ratio estimated in Aim 3 will be used to estimate

\[ GIF = \frac{\int x^b RR(x)P(x)dx - \int x^b RR(x)P^*(x)dx}{\int x^b RR(x)P(x)dx}, \]

where \( x \) is the level of BMI, \( P(x) \) is the original BMI distribution, and \( P^*(x) \) is the BMI distribution after the shift in the population distribution of BMI. Using the GIF, we will estimate YLL = number of study participants who die from disease*life expectancy at age of death, YLD = number of study participants with disease*length of disease*disability weight and the composite measure, disability adjusted life years (DALYs = YLL + YLD). We will use the disability weights most recently calculated for an array of non-fatal health outcomes by the global burden of disease (GBD) investigators based on surveys given to more than 30,000 respondents.\(^{20,21}\)

**Limitations:**

1. We will include the approximately 20 years of follow-up for ARIC participants following the cohort inception in 1987-89 until 2008. Thus, cohort and period effects could limit the generalizability of the results, as is the case with studies that follow a cohort over prolonged periods of time.

2. Selection bias needs to be considered, since (a) the participants may represent a healthier segment of the source population and of higher socio-demographic status, and (b) attrition occurred over the course of follow-up.

3. Although BMI does not appropriately characterize adiposity, BMI is commonly used in epidemiological studies because of its ease of measurement and as it is the recommended measure of adiposity to capture change over repeated measures.\(^{22}\)

4. Our study is based on the premise that changes in lifestyle in free-living populations are associated with changes in adiposity at the population level. This expectation is based on a body of literature of observational study results consistent with this assumption, as well as clinical trial data that have shown the ability to reduce BMI and weight reduction in the population as a goal of Healthy People 2020.\(^{23}\)

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
8.a. Will the DNA data be used in this manuscript?  ___ Yes  X 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/search.php  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)?

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<thead>
<tr>
<th>MP</th>
<th>Year</th>
<th>Title, Lead</th>
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<tr>
<td>2254</td>
<td>2008</td>
<td>Relationship of Adiposity Trajectories to Later Life Physical Function and Strength - Gwen Windham</td>
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<td>2196</td>
<td>2013</td>
<td>BMI change and trajectories over 25 years: the relationship between spouse pairs – Laura Cobb</td>
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<tr>
<td>2146</td>
<td>2011</td>
<td>Systolic blood pressure trajectories and incident cardiovascular disease – Daichi Shimbo</td>
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<td>2035</td>
<td>2012</td>
<td>Effect of 3-year weight loss on cardiometabolic risk factors in metabolically healthy obese individuals - Zhaohui Cui</td>
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<tr>
<td>815</td>
<td>2001</td>
<td>The associations between weight maintenance and metabolic risk factors for cardiovascular disease – Kimberly Truesdale</td>
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11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ___ Yes  X No

11.b. If yes, is the proposal
   ___ A. primarily the result of an ancillary study (list number*  _  _)
   ___ 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 http://www.cscc.unc.edu/aric/forms/
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.cscu.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.

References


