ARIC Manuscript Proposal #2658

PC Reviewed: 10/13/15  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Triglyceride to high-density lipoprotein cholesterol ratio, and index of insulin resistance, and CHD: Impact of sex and race. The ARIC Study

b. Abbreviated Title (Length 26 characters): Insulin resistance and CHD

2. Writing Group:
   Writing group members: Joshua Knowles, Gerald Reaven, Dmitry Kats, Richey Sharrett, Peter Savage, Vijay Nambi, Gerardo Heiss

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
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3. Timeline: The data are available; analyses can begin following approval. Anticipated time to manuscript submitted to the Publication Committee: ~10 months

4. Rationale:
   Insulin resistance, in association with compensatory hyperinsulinemia and associated abnormalities, has been shown to predict cardiovascular disease (CVD) in non-diabetic individuals 1-6. The ability to identify insulin resistant individuals prior to vascular disease would therefore be of clinical significance. Insulin resistance measures per se are not currently part of risk prediction models such as the AHA/ACC Omnibus Risk Calculator 7, the European Atherosclerosis Society SCORE
algorithm\(^8\), or the QRISK2 score\(^9\). Several reasons exist for this omission, the most influential probably being the complexity of the currently available methods to quantify insulin action (euglycemic clamp or insulin suppression test) which make them unsuitable for clinical purposes and population research. While the best surrogate estimates of insulin resistance involve measurement of plasma insulin concentration, the absence of a standardized assay markedly attenuates the clinical utility of this approach\(^10\).

The significant and independent relationship between insulin-mediated glucose uptake and plasma triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) concentrations represents a potential solution to this challenge\(^11\). Although both TG and HDL-C concentrations are significantly related to direct measures of insulin action, the association between the plasma concentration of TG/HDL-C is somewhat greater than with either component by itself\(^11\)-\(^13\).

The potential advantages of using this surrogate to identify insulin resistant individuals at increased risk of CVD include its apparent simplicity and the availability of standardized measures of TG and HDL-C concentration. Furthermore, in relatively small community based studies, this ratio has been shown to predict incident CVD in apparently healthy individuals\(^14, 15\). Importantly, the TG/HDL-C ratio that identifies insulin resistant individuals, with enhanced cardio-metabolic risk, is reportedly different in men and women\(^16\). There are also differences in the specific value of the TG/HDL-C ratio that best identifies insulin resistant individuals from different race/ethnic groups\(^17\), and it has been argued that the TG/HDL-C ratio does not predict insulin resistance in African Americans\(^18\). Thus, even within a given sex and/or ethnic/racial group, there is no consensus as to the TG/HDL-C ratio cut-point that would most effectively estimate insulin resistant individuals in sub-populations. Finally, it is unclear whether the incorporation of TG/HDL-C ratio into risk prediction models would improve classification performance beyond (i) the variables currently used in established risk prediction equations; (ii) fasting triglyceridemia alone; (iii) combinations of triglyceridemia and HDL-C levels other than a ratio formulation.

We propose to address these questions in the Atherosclerosis Risk in Communities (ARIC) study\(^19\)-\(^21\) to provide new information relevant to these unresolved issues. Specifically, we propose to examine: 1) distributional properties of the TG/HDL-C ratio by gender and race, and its association with levels of fasting insulin; 2) optimize gender and race-specific threshold values that identify insulin resistant individuals; 3) compare the cardio-metabolic risk profiles of the subgroups identified using these cut-points; and 4) estimate the association of the triglyceridemia, JHDL-C levels, and the TG/HDL-C ratio with the incidence of CHD (in gender and race groups); 5) Characterize the classification properties in the risk “established” ARIC prediction for incident CHD contributed by each of triglyceridemia, JHDL-C levels, and the TG/HDL-C ratio.

References


17. Li C, Ford ES, Meng YX, Mokdad AH, Reaven GM. Does the association of the triglyceride to high-density lipoprotein cholesterol ratio with fasting serum insulin differ by race/ethnicity? *Cardiovascular diabetology*. 2008;7:4


5. **Main Hypothesis/Study Questions:**
   a. Fasting TG levels are associated with levels of fasting insulin in a monotonically increasing, linear fashion;
   b. Fasting HDL-C levels are (inversely) associated with levels of fasting insulin in a monotonic, linear fashion;
   c. TG/HDL-C levels are associated with levels of fasting insulin in a monotonically increasing, linear fashion;
   d. The circulating levels of the TG/HDL-C ratio are lower in African American women and men (than in their white counterparts), and higher in women (than in men);
   e. Gender and race-specific TG/HDL-C ratio threshold values can be estimated to optimize agreement with the ~75th percentile of fasting insulin;
   f. In each gender and race group levels of fasting TG, HDL-C and the TG/HDL-C ratio are associated with increased risk of (incident) CHD; the magnitude of the association is TG/HDL-C > HDL-C > TG;
   g. The inclusion of TG, HDL-C and the TG/HDL-C ratio to the “established” ARIC CHD risk prediction equation will in each case be associated with modest improvements in goodness of fit, model discrimination, and in reclassification properties. Net reclassification will be greater for the TG/HDL-C ratio than that observed for TG or HDL-C.

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).**

Aims a–e will be addressed in the ARIC Visit 1 data. The analyses for Aims f and g will use ARIC’s Visit 1 as baseline and be based on the extant, derived variable for incidence CHD (INC_CHD-BY), through 2012. The analyses for Aims f and g will be based on the published ARIC CHD risk prediction model and add the proposed indexes of insulin resistance trait as to assess their influence on the conventional measures of model fit, discrimination and reclassification, with a narrowly focused question on a meaningful – and practical – improvement in classification properties.

7.a. **Will the data be used for non-CVD analysis in this manuscript?**  ____ Yes   ___ X___ 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  __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”? __X__ 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.csc.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)?

Ms#2054 - The association of insulin resistance and glucose levels with cardiac structure and function in an older population without diabetes mellitus:  The ARIC study

Ms#2129 - Diabetes and prediabetes and the incidence and progression of subclinical myocardial injury

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

*ancillary studies are listed by number at http://www.csc.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.csc.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.
13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.