1.a. Full Title: Effect of triglycerides on new-onset type 2 diabetes mellitus in the Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): TG and new-onset DM2

2. Writing Group: University of Mississippi School of Medicine
   Writing group members: Honey E. East, Daniel M. Riche, Alan Penman, Kenneth Butler, Margaret Pearson, Tom Mosley. [OTHERS WELCOME.]

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

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3. Timeline: Approximately 6 months from data analysis to manuscript submission:
   - Data collection/analysis no more than 2 months following proposal approval.
   - Discussion/Conclusion preparation no more than 2 months following data analysis.
   - Manuscript submission no more than 1 month following discussion/conclusion review.

4. Rationale:
   The association between elevated triglycerides (TG) and impaired glucose tolerance is well known (for example, in the Metabolic syndrome). Elevated TG and low levels of high-density lipoprotein are associated with increased diabetes prevalence.1 In a 20-year prospective cohort study men who developed type 2 diabetes had higher baseline TG levels.2 The GEMCAS study found that elevated triglycerides was one of only a few risk factors that was statistically predictive of diagnosed diabetes, undiagnosed diabetes,
and impaired fasting glucose. However, the specific details of the predictive nature of elevated TG were not investigated (e.g., at what level are TG levels predictive; does the predictive ability of TG levels differ in men versus women; within what time period are TG levels predictive). In the ARIC study the best predictive model for incident diabetes occurred when lipid markers, including TG, were added to clinical variables and fasting glucose. However, extrapolation of the risk score for the development of diabetes has diminished utility in younger adults. Identification of individual clinical factors which can improve the risk prediction for diabetes development is necessary. The precise utility of TG levels in predicting onset of type 2 diabetes remains unclear.

References

5. Main Hypothesis/Study Questions:

Hypothesis
Higher levels of triglycerides are associated with an increased risk of developing type 2 diabetes mellitus.
If rejecting the null hypothesis:
Define the risk associated with different TG levels, both overall and in race/sex subgroups.

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).

Design: prospective cohort study, with follow-up through visit 4.
Analysis strategy: survival analysis using life table methods and piecewise exponential models to account for the grouped time-to-event data.
Exclusion criteria: Exclude persons who did not return for a follow-up visit, whose race is neither black nor white, who have unknown diabetes status at follow-up or missing TG values.

Dependent variable: incident diabetes, using the new defined variables for incident diabetes when these become available: INCDIABTS21, INCDIABTS31, INCDIABTS41, INCDIA, INCDIABTS, INCDIABTSVISIT.

Main predictors: Baseline (visit 1) triglyceride level (TRGSIU01); values for triglyceride levels at subsequent visits (TRGSIU21, TRGSIU31, TRGSIU41) will be included in the piecewise exponential models.

Covariates for potential inclusion in models: age, sex, race, education, BMI, WHR, hypertension status, systolic and diastolic BP, family history of diabetes, total/LDL/HDL-cholesterol, cigarette smoking status, alcohol consumption, physical activity.

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?  ____ X  ____ Yes  ____ No

(This file ICTDER03 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”? N/A  ____ 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

There are a large number of manuscript proposals looking at risk of incident and prevalent diabetes (below), but none directly overlapping this proposal.

MP 252: Correlates of prevalent diabetes by race.
MP 356: Characteristics associated with undiagnosed diabetes mellitus in the community.
MP 539: Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities Study): a cohort study.
MP 539A: Factor VIII and other hemostasis variables are related to incident diabetes in adults - the Atherosclerosis Risk in Communities (ARIC) Study.
MP 564: Acute phase response lipids/lipoproteins as predictors of incident diabetes mellitus.
MP 668: Delayed Diagnosis of Incident Type 2 Diabetes Mellitus in the ARIC Study.
MP 682: TNFa, IL-6 and incident diabetes mellitus.
MP 784: Serum insulin, obesity, and the incidence of type 2 diabetes in black and white adults.
MP 808B: Identifying Individuals at High Risk for Diabetes: The Atherosclerosis Risk in Communities Study.
MP 853: Low-grade systemic inflammation and the development of type 2 diabetes mellitus - the ARIC study.
MP 862: Fasting plasma free fatty acids and risk of type 2 diabetes: The ARIC study.
MP 931: Dietary fat consumption and incidence of type 2 diabetes.
MP 979: Factors of the metabolic syndrome and incidence of coronary heart disease, stroke and type 2 diabetes.
MP 985: Association between family history of type 2 diabetes mellitus, the multiple metabolic syndrome (MMS), and the risk of developing type 2 diabetes mellitus.
MP 1031: Empirical validation of the metabolic syndrome components and cutpoints through the prediction of CHD and diabetes using partitioning methods.
MP 1052: Increased risk of type 2 diabetes from a family history of coronary heart disease and type 2 diabetes.

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)? Nothing currently.

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 N/A

  ____ 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/

12. 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.