ARIC Manuscript Proposal # 3148

PC Reviewed: 4/10/18   **Status: _____**   **Priority: 2**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title:
Association of physical activity and Serum metabolomics in the Atherosclerosis Risk in Communities (ARIC) Study

   b. Abbreviated Title (Length 26 characters):
Physical activity and Metabolomics

2.   Writing Group:
     Writing group members:
Jun Xu, Kelley P. Gabriel, Eric Boerwinkle and Bing Yu
Others are welcome.

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

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3.   Timeline:
The data collection of metabolomics and physical activity are already accomplished and there is no other data collection work needed. When the proposal is approved, data analysis process will start. The manuscript will be prepared when data analysis is done (~ 3-6 months).

4.   Rationale:

Sedentary life style with insufficient habitual physical activity has been associated with multiple health related problems, such as obesity, fatal and non-fatal cardiovascular disease, type II diabetes and other metabolic syndromes[1-3]. Prior epidemiological evidence has demonstrated a dose response relationship of moderate to vigorous intensity physical activity (MVPA) with multiple health outcomes including all-cause mortality[4], however, the biological mechanism remains unclear. Human metabolome, throughout characterization of small molecule metabolites, may enhance the understanding of association between physical activity and alternation of human metabolism[2,5,6].

To date, few studies have described the associations between physical activity and various circulating metabolites. Xiao et.al reported that 11 metabolites, including 2-hydroxybutyrate (AHB), mannose, betaine, threonate, tiglyl-carnitine, gamma-glutamylvaline and metabolites in the valine, leucine and isoleucine metabolism pathways (3-methyl-2- oxovalerate, 3-methyl-2-oxobutyrate, isoleucine, valine and 2-hydroxy-3-methylvalerate), were associated with total activity in Asian population[5]. A study by Kujala et al. reported that isoleucine, glucose, glycoprotein and lipids linking with physical activity in European population[6]. No study has investigated the associations between physical activity and metabolites in African-Americans (AAs), who have a higher rate of morbidity and mortality (i.e. obesity[7], diabetes[8], and cardiovascular disease[9]) compared to European-Americans (EAs) in U.S. The identification of metabolic makers in circulating system that relate to physical activity and further understand their potential biological mechanisms, may help establish potential interventions.

Here, we propose to evaluate the cross-sectional association of physical activity with serum metabolites in 2472 AAs and 1551 EAs enrolled in the Atherosclerosis Risk in Communities (ARIC) study. Data collected at the Visit 1 (1987-89) when the cohort was aged 45 to 64 years will be used to address the study questions and hypotheses.

5.   Main Hypothesis/Study Questions:
1. Serum metabolite levels are associated with higher reported leisure time MVPA (MET·hr·wk^{-1}) independent of traditional risk factors, such as sex, gender, body mass index (BMI), kidney function and smoking.

2. Serum metabolite levels are associated with being classified as Ideal Physical Activity based on the Life's Simple 7 metric independent of traditional risk factors, such as sex, gender, BMI and smoking.

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).

Study design:
 This study is a cross-sectional study design using information from both EAs and AAs in the ARIC study visit 1.

Exclusion criteria:

The individuals will be excluded from this study, whose metabolites data and physical activity information are missing, as well as other covariates.

Variables:

Outcome variables:

1) Reported leisure-time MVPA. The summary variable rescored to be expressed as MET·hr·wk^{-1} will be used [10].

2) AHA Recommendations for Ideal Physical Activity (from Life's Simple 7) will be analyzed as an ordinal variable, classing as poor (0 min/wk of moderate or vigorous exercise), intermediate (1 to 149 min/wk of moderate intensity or 1 to 74 min/wk of vigorous intensity or 1 to 149min/wk moderate plus vigorous intensity), and ideal ($\geq$150 min/wk of moderate intensity or $\geq$75 min/wk of vigorous intensity or $\geq$150 min/wk of moderate plus vigorous intensity).

Exposure variables: 245 named metabolites primarily
Metabolites will be excluded if satisfying the following:
   1) Only detected in one batch;
   2) The proportion of missing value of the samples is higher than 25% in either batch;
   3) The Pearson correlation coefficient between Batch 1 (2010) and Batch 2(2014) measurements on the same stored sample is less than 0.3.

Covariates:
Age, gender, study center, race, BMI, cigarette smoking (current smoker, former smoker, and never smoker), estimated glomerular filtration rate (eGFR) and batch effect.

Statistical data analysis:

Statistical analysis will be conducted within AAs and EAs respectively followed by fix-effect inverse variance meta-analysis. Metabolites will be winsorized at 1% and standardized (mean = 0. SD = 1) prior to the analyses. Linear regression will be conducted in each race group adjusting for age, gender, BMI, cigarette smoking status, center, eGFR, and batch effect (if applicable) for total sport physical activity and MVPA respectively. In terms of meeting criteria of AHA Recommendations for Ideal Physical Activity, ordinal logistic regression will be applied following the same analytical strategy mentioned above. The Benjamini–Hochberg procedure (BH step-up procedure) will be used to control false discovery rate (FDR) at level of 0.05 to correct for multiple testing. We will evaluate the consistency across all three different measures of physical activity, and examine the correlations among significant metabolites (i.e. significant in each measures). We will also examine the potential effect modification by sex using stratified analysis and interaction term.

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"? ____ 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)?**

AS#2926 Hibler et al. Physical activity and DNA methylation: an epigenome-wide association
study
AS#3087 Wang et al. Associations of the Human Metabolome and Blood Pressure in the
Atherosclerosis Risk in
Communities (ARIC) Study

**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* _2008.16 and
2014.20_____)**
     **___   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.**
Agreed.

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.
Agreed.

Reference

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2. Fukai K, Harada S, Iida M, et al. Metabolic profiling of total physical activity and sedentary behavior in community-dwelling men. *PloS one*. 2016;11(10):e0164877.

3. Kyu HH, Bachman VF, Alexander LT, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: Systematic review and dose-response meta-analysis for the global burden of disease study 2013. *BMJ*. 2016;354:i3857.

4. Sattelmair J, Pertman J, Ding EL, Kohl HW,3rd, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: A meta-analysis. *Circulation*. 2011;124(7):789-795.

5. Xiao Q, Moore SC, Keadle SK, et al. Objectively measured physical activity and plasma metabolomics in the shanghai physical activity study. *Int J Epidemiol*. 2016;45(5):1433-1444.

6. Kujala UM, Makinen VP, Heinonen I, et al. Long-term leisure-time physical activity and serum metabolome. *Circulation*. 2013;127(3):340-348.

7. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the united states, 2011-2012. *JAMA*. 2014;311(8):806-814.

8. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the united states, 1988-2012. *JAMA*. 2015;314(10):1021-1029.

9. Bauer UE, Briss PA, Goodman RA, Bowman BA. Prevention of chronic disease in the 21st century: Elimination of the leading preventable causes of premature death and disability in the USA. *The Lancet*. 2014;384(9937):45-52.

10. Kats D, Palta P, Gabriel KP, Camplain R, Heiss G, Evenson K. *Abstract MP75: Characterization of Physical Activity Patterns From Mid-Life to Older Adulthood: The Atherosclerosis Risk in Communities (ARIC) Study*. 2015.