**ARIC Manuscript Proposal #3208**

**PC Reviewed: 8/14/18** **Status: _____** **Priority: 2**
**SC Reviewed: _____** **Status: _____** **Priority: ____**

**1.a. Full Title**: Novel DNA methylation sites of glucose and insulin homeostasis and their integrative cross-omics analysis

**b. Abbreviated Title (Length 26 characters)**: DNAm & glycemia look-up

**2. Writing Group**:
Writing group members:

This paper will present primary results from the Rotterdam Study, Netherlands Twin Registry, and UK Adult Twin Registry (TwinsUK). The CHARGE consortium (which includes ARIC data) has conducted a meta-analysis of epigenome-wide association studies of fasting glucose and insulin and is providing look-up information for 15 CpG sites for replication purposes.

The first author on the paper is Jun Liu, Department of Epidemiology, Erasmus University Medical Centre, Rotterdam, the Netherlands (j.liu.1@erasmusmc.nl). The complete authorship list from all cohorts and authorship order is still to be determined.

ARIC co-authors:
Jim Pankow
Jan Bressler

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

**First author**:

Phone: Fax:
E-mail:

**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).

Name: Jim Pankow (co-author and ARIC cohort contact)
Address: University of Minnesota
1300 S. 2nd St., Suite 300
Minneapolis, MN 55454

Phone: 612-624-2883 Fax:
E-mail: panko001@umn.edu

**3. Timeline**: Submission for publication in late summer 2018

**4. Rationale**:

Type 2 diabetes (T2D) is one of the most common metabolic diseases in the world, characterized by disturbances in glucose and insulin metabolism that are in part genetically driven. More recently, DNA methylation has been associated with T2D but also with fasting glucose and insulin and the methylation risk score of T2D have predicted incident cases beyond traditional risk factors including obesity and waist-hip ratio. DNA methylation can result in gene silencing and thus determine gene expression and subsequent cellular functions. It is possible that the epigenetic modifications may occur in early phases of the pathology of T2D. However, differential DNA methylation may also be a consequence of T2D (or its treatments) rather than a cause of the pathology, requiring research focusing on the early process of the disease, e.g. in the population free of diabetes.

**5. Main Hypothesis/Study Questions**:

The overall objective is to determine whether DNA methylation is associated with fasting glucose and insulin after accounting for obesity.

**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).**

All statistical analyses will be performed using R statistical software. Insulin will be natural log transformed. Linear regression analysis will be used to test the association between fasting glucose or insulin with each methylation site. We will fit two models: 1) the baseline model adjusting for age, sex, technical covariates (array number and position on the array), white blood cell proportions (lymphocytes, monocytes, and granulocytes) and smoking, and 2) a second model additionally adjusting for BMI. All cohort-specific results for each model will then meta-analysed using inverse variance-weighted fixed effects meta-analysis as implemented in the "metafor" R package. In the replication phase, Bonferroni P-value < 0.0033 (0.05 corrected by 15 loci tested for associations) was considered to indicate significance.

**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? _x___ 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"? __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.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)?**

Diabetes is listed as one of the phenotypic domains in MS1928 (Genome-wide methylation analyses of cardiovascular disease and its risk factors). MS1928 is an "umbrella" proposal that has served as a placeholder until domain-specific proposals are developed.

**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 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.