ARIC Manuscript Proposal # 1567

PC Reviewed: 10/13/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: STAMPEED metabolic syndrome genome-wide association meta-analysis

b. Abbreviated Title (Length 26 characters): metabolic syndrome GWAS

2. Writing Group: STAMPEED Consortium Metabolic Syndrome Working Group
ARIC writing group members: Jim Pankow, Nora Franceschini, Kari North, Aravinda Chakravarti, Eric Boerwinkle, David Couper

Up to six additional authors from each of the other consortium studies will be added. There are currently seven studies that have agreed to contribute to the STAMPEED meta-analysis: Advance, ARIC, CHS, FHS-SCAN, GeneStar, GENOA, and Northern Finland Birth Cohort Study.

Jim Pankow is serving as the ARIC representative on the primary STAMPEED writing group for the paper.

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

(Note: first author(s) on consortium manuscript have yet to be determined)

F**irst author**: **Jim Pankow**
Address: Division of Epidemiology and Community Health
University of Minnesota
1300 South Second Street, Suite 300
Minneapolis, MN 55454

Phone: 612-624-2883 Fax: 612-624-0315
E-mail: pankow@umn.edu

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:
Address:

Phone: Fax:
E-mail:

3. Timeline:

Initial analysis:	July 2009
First draft:	November 2009
Submitted for publication:	December 2009

4. Rationale:

Recent genome-wide association studies, including those conducted in ARIC, have identified dozens of new loci influencing quantitative cardiovascular disease risk factors, including measures of obesity, lipids, blood pressure, and glucose. For a few loci, genome-wide significance has been achieved for multiple traits (e.g., *GCKR* with fasting triglycerides and glucose), suggesting that these loci have pleiotropic effects. Evidence of pleiotropy is also provided by twin and family studies that have found significant heritability for metabolic syndrome indices as well as significant genetic correlations between pairs of metabolic traits (Tang et al., 2004; Zhang et al., 2009).

5. Main Hypothesis/Study Questions:

We hypothesize that GWAS of combinations of metabolic syndrome traits will reveal pleiotropic loci not previously identified by single trait analyses.

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).

The overall aim is to conduct a GWAS analysis for pairwise combinations of 5 risk factor variables for metabolic syndrome (MetS), as well as a MetS affection status variable according to standard criteria – a total of 11 dichotomous phenotypes.

GWAS analysis will be conducted by investigators within each cohort and summary results will be submitted for inclusion in the STAMPEED meta-analysis at Washington University. Analysis will follow a uniform plan specified by the STAMPEED investigators. For ARIC, individuals who did not consent to genetic research, those of self-reported race other than "white" and those that failed quality control for genotyping will be excluded.

Each of five traits will be dichotomized as affected (1) exceeding the specified threshold, not affected (0) below the threshold, or missing.

Definitions of "affected" for each trait:
Waist: ≥ 102 cm (≥ 40 inches) in men or ≥ 88 cm (≥ 35 inches) in women
Triglycerides[1]: fasting TG ≥ 150 mg/dl (≥ 1.69 mmol/L)
HDL: < 40 mg/dl (< 1.04 mmol/L) in men or < 50 mg/dl (< 1.29 mmol/L) in women

Blood pressure[2]: SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or anti-hypertensive meds[3]
Glucose[1]: fasting glucose ≥ 100 mg/dl (≥ 5.5 mmol/L) or hypoglycemic meds

[1] If not fasting (min 8 hrs), set to missing.

[2] measurements must be or sitting or supine, not standing

[3] subjects on anti-hypertensive meds considered affected if either their BP is still in the elevated range, or there is in the database a notation that they have been diagnosed with hypertension. If neither of these two situations apply, then their BP status should be coded as missing.

We will define 10 new phenotypes Pi, i=1, 10, based on all pairwise combinations of these five traits (e.g., WC – TG). We will also define a metabolic syndrome phenotype for comparison:

METS=1 if sum (WC, TG, HDL, BP, GLU) ≥ 3 (with no more than 2 /5 traits missing), i.e.,
METS=1 if sum >= 3, given 5 valid measures
METS=1 if sum >= 3, given 4 valid measures
METS=1 if sum >= 3, given 3 valid measures
METS=0 if sum (WC, TG, HDL, BP, GLU) < 3
METS=0 if sum (WC, TG, HDL, BP, GLU) < 3, given 5 valid measures
METS=0 if sum (WC, TG, HDL, BP, GLU) < 2, given 4 valid measures
METS=0 if sum (WC, TG, HDL, BP, GLU) = 0, given 3 valid measures
else **METS=.** (missing)

Therefore, a total of 11 phenotypes will be analyzed P1 . . . P10, PMetS

Analysis will include all genotyped autosomal SNPs + imputed SNPs. For imputed SNPs, we will use dosage rather than "best guess" genotypes. SNP exclusions will include MAF <1% and $r^2 < 0.30$ (MACH).

In ARIC, we will analyze the imputed genotype by regression of the outcome onto estimated genotypic probabilities, using ProbABEL package from the ABEL set of programs for the imputed genotypes (mga.bionet.nsc.ru/~**yurii**/ABEL/). Logistic regression will be used to analyze the 11 traits of interest under the following model:

Pi = SNP + age + age^2 + sex + center + principal components of population substructure

The SNP effect is modeled under an additive assumption. The beta coefficient with its standard error for the SNP effect will be reported for the meta analysis.

The Der Simonian and Laird (1986) meta-random effects model will be used to combine beta-coefficients and their corresponding standard errors of effect, as provided by the R function meta.DSL. Each study will provide beta-coefficients and standard errors for each SNP (imputed or genotyped) using the logistic regression for these binary phenotypes. The Der Simonian and Laird approach provides a separate homogeneity test (to verify that the studies are in fact sufficiently homogeneous to allow pooling), in addition to a

final meta-analysis estimate of the pooled beta effect, and pooled standard error, which yields a pooled test of significance of the overall beta-coefficient.

Because some STAMPEED studies may contain overlapping subjects (e.g. ARIC was a parent study to the NHLBI Family Heart Study), some of the GWAS results may be correlated across studies. Also, we may be analyzing correlated phenotypes to look for additional pleiotropic effects. In these cases, we will also use a correlated meta-analysis approach, which corrects the traditional meta-analysis z-test combining p-values for background correlation in the GWAS (Province, 2005).

We will adjust for multiple testing using a genome-wide alpha of 5.0×10^{-8}.

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? __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/search.php

_____ Yes ___x____ 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)?

ARIC GWAS working group chairs for each of the component risk factors (i.e., diabetes, lipids, blood pressure, and adiposity working groups) were contacted to determine if they have any objections to ARIC's participation in this STAMPEED meta-analysis and to determine overlap between STAMPEED's plan and plans developed by the working

groups. The lipids working group indicated plans to analyze and publish a GWAS for a combined triglycerides – HDL phenotype, but no other conflicts were received. As a general rule, priority will be given to ARIC publication of single trait GWAS analyses should the top loci for single traits overlap with those found for pairwise analyses in STAMPEED. ARIC authors on this paper include at least one representative from the diabetes, lipids, blood pressure, and adiposity working groups.

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

2006.03 (STAMPEED and GENEVA genotype funding in Caucasians)

11.b. If yes, is the proposal

__x_ 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/
see above

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.

References:

Der Simonian R, Laird N (1986) Meta-analysis in clinical Trials. Controlled Clinical Trials 7:177-188.

Province MA (2005) Meta-analyses of correlated genomic scans. Genetic Epidemiology 29:137

Tang W et al. (2006). Familial clustering for features of the metabolic syndrome: the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study. Diabetes Care 29: 631-636.

Zhang S et al. (2009). Genetic and environmental contributions to phenotypic components of metabolic syndrome: a population-based twin study. Obesity 17: 1581-7.