ARIC Manuscript Proposal #1974

PC Reviewed: 8/14/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: The association of GWAS diabetes SNPs with the Incidence of Normal Weight Type 2 Diabetes

b. Abbreviated Title (Length 26 characters): Diabetes SNPs in MONW

2. Writing Group:
Laura J. Rasmussen-Torvik, Alain Bertoni, Donald Bowden, Peter de Chavez, Alan Dyer, Sherita H. Golden, James Meigs, Caroline Fox, James Pankow, Kiang Liu, Jason Vassay, Mercedes R. Carnethon

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

First author:
Address: Laura Rasmussen-Torvik
680 N. Lake Shore Drive, Suite 1400
Chicago, IL 60611

Phone: 312-503-3596  Fax: 312-908-9588
E-mail: ljrtorvik@northwestern.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: James Pankow
Address: Division of Epidemiology and Community Health
1300 S. Second St., Suite 300
Minneapolis, MN 55454

Phone: (612) 624-2883  Fax: 612-624-0315
E-mail: panko001@umn.edu

3. Timeline: Abstract by 8/12
4. **Rationale:**
The metabolically obese normal weight (MONW) phenotype is a clustering of obesity-related metabolic disorders (e.g., type 2 diabetes [T2DM], hypertriglyceridemia, hypertension) in persons with normal to slightly elevated body mass index (BMI<28 kg/m$^2$).\(^1\) T2DM in normal weight persons is an intriguing and understudied representation of the MONW phenotype. Between 5-15% of persons with T2DM have BMI<25 kg/m$^2$ (the contemporary cut-point to define normal weight), but for unknown reasons, that number is growing.\(^2\),\(^3\) Previous attempts to identify characteristics associated with the development of T2DM in the absence of overweight were hindered by the relatively small numbers of persons who are normal weight with T2DM in any single cohort. We propose to pool together data from multiple existing longitudinal cohort studies to conduct an epidemiologic study of demographic, clinical and genetic factors associated with the development of T2DM in normal weight participants. The resulting pooled dataset will include a large, diverse (e.g., race/ethnic, gender, and age) sample of persons who can be classified at the time of incident T2DM as normal weight (BMI<25 kg/m$^2$) or overweight/obese (BMI≥25 kg/m$^2$). Preliminary analyses indicate that across all 3 cohorts (including ARIC) there are 2110 cases of incident T2DM, 230 incident cases among normal weight participants. Additional meta-analysis with the CHS and Framingham Offspring studies may be pursued in the future.

The objective of the present proposal is to identify a genetic model for T2DM in normal weight persons. Clustering of T2DM within families is apparent. Shared environment, which includes health behaviors such as eating patterns and physical activity behaviors, is at least partially responsible for the excess rate of T2DM in first degree relatives of persons with T2DM. Offspring of persons with T2DM also demonstrate adverse metabolic changes including hyperinsulinemia, hypertriglyceridemia, abdominal adiposity, endothelial dysfunction and autonomic nervous system dysfunction before expressing T2DM.\(^4\)\(^-\)\(^7\) The search for genetic determinants of T2DM has been challenging because T2DM is a complex disorder involving the dysregulation of many organ systems and metabolic processes in the body and interactions with health behaviors.

A large GWAS meta-analysis has demonstrated variants in at least 32 genes to be reproducibly associated with type 2 diabetes in Caucasians\(^8\). These variants are summarized in a table from this publication attached to the end of this document. Prevalence (Minor Allele Frequency) of these variants typically ranges from about .10-.50. Investigators hypothesize that many of the genes below are associated with altered insulin secretion. However, since obesity is so strongly associated with insulin resistance, it is difficult to determine a precise mechanism of action. If we determine that the association between genotype and incident T2DM varies by weight status at the time of diabetes identification, it would provide important information about the mechanism by which these candidate genes are associated with T2DM.
5. Main Hypothesis/Study Questions:

We hypothesize that the association between some of 32 single nucleotide polymorphisms (SNPs) identified through type 2 diabetes GWAS and incident T2DM, will vary by weight status at the time T2DM is identified. Rs7903146 will be the first SNO examined. We will carry out this investigation primarily in white participants, but will explore the nature of association in participants of other ethnic and racial groups, particularly if data from the exome or metabochip illuminate causal variants in these regions.

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).

Participant sample. The cohort studies used in this investigation are the Atherosclerosis Risk in Communities (ARIC), Coronary Artery Risk Development in Young Adults (CARDIA), and the Multi-Ethnic Study of Atherosclerosis (MESA). Data from these studies will be directly pooled for analysis, as small numbers of incident normal weight diabetes cases in the individual cohorts prevent individual analysis in the cohorts. Results from CHS and the Framingham Offspring Study may be included in meta-analyses in the future.

Type 2 Diabetes (T2DM) will be defined according to the American Diabetes Association (ADA) 2003 fasting glucose criterion (>126 mg/dL) or report of oral hypoglycemic mediation or insulin. We chose each of the studies because fasting glucose was available at baseline and at least one follow-up examination. We have already developed an incident diabetes phenotype in ARIC through work in the non-genetic aims of our ancillary study (see paper proposal #1699).

Covariates
Body weight (kg) and height (m) will be abstracted from each clinical examination. Participants will be categorized as normal weight (BMI<25 kg/m^2) or overweight/obese (BMI ≥25 kg/m^2) at the time T2DM is initially identified in each study.

Genetic factors:
Please see the table at the end of the document excerpted from the Voight paper ⁸ for the specific SNPs that will be requested from each cohort. In the event that a SNP is not available in a given cohort, the SNAP browser (http://www.broadinstitute.org/mpg/snap/) will be used to select a suitable proxy SNP. Only genotyped SNPs will be used. Depending on single SNP results, we may also combine the SNPs into a gene score for additional analysis.

Because genetic analyses are unlikely to be confounded, we will adjust analyses for age, sex and study center only. Variables will be taken from the baseline examination.

**Analysis Plan and Methods:**

We will test whether the association of genotype on incident T2DM differs by weight status at the time of diabetes identification. Multinomial (polytomous) logistic regression was utilized to obtain odds ratios (point and 95% confidence interval estimates) for those who developed normal weight diabetes and overweight/obese diabetes, relative to those who did not develop diabetes across the study period according to SNP genotype while adjusting for baseline age, sex, center and race. This is the same analytic approach being used in the non-genetic analyses in this project.

We will model SNPs additively for analysis. We will not adjust these analyses for multiple testing given the impact on power of doing so, but will instead interpret any positive findings cautiously, giving greater weight to results that are significant at the 0.01 or 0.001 level than are significant at the 0.05 level. We may also sum the number of risk-increasing alleles across the 32 SNPs for each individual to generate a diabetes genetic risk score and test the association of this score with incident diabetes.

In a secondary analysis, we will examine the associations of the 32 SNPs with prevalent diabetes at study baseline(s), also using multinomial logistic regression.

As part of Dr. Carnethon’s ancillary study, we have paid to obtain the ARIC cohort dataset at NU. We will request that Dr. Pankow extract the SNPs of interest from the ARIC GWAS data and provide them to us so we may use SAS for analysis locally.
## SNP Table from Voight et al. 8

### Supplementary Table 1: DMAR/DAR Stage 1, for this study (Genome-Wide Meta-Analysis results for SNP of interest)

<table>
<thead>
<tr>
<th>Rank</th>
<th>SNP</th>
<th>Chrm</th>
<th>Start (basepairs)</th>
<th>Ref</th>
<th>Alt</th>
<th>Frequency of alternate allele</th>
<th>Minor Allele MAF</th>
<th>Frequency of alternate allele</th>
<th>Minor Allele MAF</th>
<th>P-value</th>
<th>Odds Ratio CI 95% Lower</th>
<th>Odds Ratio CI 95% Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>rs3660950</td>
<td>2</td>
<td>2,012,642</td>
<td>A</td>
<td>G</td>
<td>0.060 (0.255)</td>
<td>0.38</td>
<td>0.255</td>
<td>0.62</td>
<td>1.21</td>
<td>0.899 (0.691-1.18)</td>
<td>1.38 (1.18-1.61)</td>
</tr>
<tr>
<td>11</td>
<td>rs1845287</td>
<td>2</td>
<td>27,012,072</td>
<td>C</td>
<td>T</td>
<td>0.688 (0.996)</td>
<td>0.52</td>
<td>0.996</td>
<td>0.44</td>
<td>0.71</td>
<td>0.52 (0.34-0.80)</td>
<td>0.80 (0.58-1.11)</td>
</tr>
<tr>
<td>13</td>
<td>rs5223587</td>
<td>2</td>
<td>31,354,560</td>
<td>A</td>
<td>G</td>
<td>0.032 (0.052)</td>
<td>0.35</td>
<td>0.052</td>
<td>0.67</td>
<td>2.15</td>
<td>1.02 (0.55-2.66)</td>
<td>1.89 (0.85-4.20)</td>
</tr>
<tr>
<td>16</td>
<td>rs1513292</td>
<td>2</td>
<td>36,132,125</td>
<td>C</td>
<td>A</td>
<td>0.017 (0.011)</td>
<td>0.65</td>
<td>0.011</td>
<td>0.99</td>
<td>0.80</td>
<td>0.59 (0.35-0.98)</td>
<td>0.89 (0.54-1.46)</td>
</tr>
<tr>
<td>18</td>
<td>rs221925</td>
<td>2</td>
<td>40,949,644</td>
<td>C</td>
<td>T</td>
<td>0.796 (0.154)</td>
<td>0.21</td>
<td>0.154</td>
<td>0.90</td>
<td>0.19</td>
<td>2.13 (1.13-3.98)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>19</td>
<td>rs3831018</td>
<td>2</td>
<td>48,834,759</td>
<td>A</td>
<td>G</td>
<td>0.037 (0.056)</td>
<td>0.34</td>
<td>0.056</td>
<td>0.66</td>
<td>2.21</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>20</td>
<td>rs2358216</td>
<td>2</td>
<td>53,851,912</td>
<td>C</td>
<td>A</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>21</td>
<td>rs1604933</td>
<td>2</td>
<td>61,765,100</td>
<td>C</td>
<td>A</td>
<td>0.037 (0.056)</td>
<td>0.34</td>
<td>0.056</td>
<td>0.66</td>
<td>2.21</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>22</td>
<td>rs1668458</td>
<td>2</td>
<td>69,860,759</td>
<td>C</td>
<td>G</td>
<td>0.037 (0.056)</td>
<td>0.34</td>
<td>0.056</td>
<td>0.66</td>
<td>2.21</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>23</td>
<td>rs3983316</td>
<td>2</td>
<td>75,465,759</td>
<td>C</td>
<td>A</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>24</td>
<td>rs1537543</td>
<td>2</td>
<td>81,531,000</td>
<td>A</td>
<td>G</td>
<td>0.184 (0.085)</td>
<td>0.18</td>
<td>0.085</td>
<td>0.82</td>
<td>0.73</td>
<td>0.52 (0.32-0.86)</td>
<td>0.82 (0.52-1.32)</td>
</tr>
<tr>
<td>25</td>
<td>rs3515703</td>
<td>2</td>
<td>85,532,759</td>
<td>A</td>
<td>G</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>26</td>
<td>rs1209698</td>
<td>2</td>
<td>91,532,000</td>
<td>A</td>
<td>G</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>27</td>
<td>rs1210151</td>
<td>2</td>
<td>96,529,759</td>
<td>C</td>
<td>A</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>28</td>
<td>rs1210271</td>
<td>2</td>
<td>101,532,000</td>
<td>A</td>
<td>G</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>29</td>
<td>rs1057900</td>
<td>2</td>
<td>107,532,000</td>
<td>A</td>
<td>G</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>30</td>
<td>rs1210271</td>
<td>2</td>
<td>101,532,000</td>
<td>A</td>
<td>G</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>31</td>
<td>rs1210271</td>
<td>2</td>
<td>101,532,000</td>
<td>A</td>
<td>G</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>32</td>
<td>rs1210271</td>
<td>2</td>
<td>101,532,000</td>
<td>A</td>
<td>G</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>33</td>
<td>rs1210271</td>
<td>2</td>
<td>101,532,000</td>
<td>A</td>
<td>G</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>34</td>
<td>rs1210271</td>
<td>2</td>
<td>101,532,000</td>
<td>A</td>
<td>G</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>35</td>
<td>rs1210271</td>
<td>2</td>
<td>101,532,000</td>
<td>A</td>
<td>G</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
<tr>
<td>36</td>
<td>rs1210271</td>
<td>2</td>
<td>101,532,000</td>
<td>A</td>
<td>G</td>
<td>0.034 (0.048)</td>
<td>0.36</td>
<td>0.048</td>
<td>0.64</td>
<td>2.27</td>
<td>1.15 (0.58-2.29)</td>
<td>2.25 (1.13-4.49)</td>
</tr>
</tbody>
</table>
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  __x__ 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.cscce.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)?

#1273 GRS for diabetes

#1470 GWAS of Prevalent Diabetes

Dr. Pankow (the Senior ARIC author on this manuscript) is the lead and senior author (respectively) on the above two manuscripts and he does not anticipate problematic overlap.

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* 2008.13
Epidemiologic Studies of Type 1 Diabetes in Normal Weight Adults )

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/

11. 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

1. Ruderman NB, Schneider SH, Berchtold P. The "metabolically-obese,"

2. St-Onge MP, Janssen I, Heymsfield SB. Metabolic syndrome in normal-
weight Americans: new definition of the metabolically obese, normal-

3. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically
obese, normal-weight individual revisited. Diabetes. May 1, 1998

4. Ruotsalainen E, Vauhkonen I, Salmenniemi U, et al. Markers of
endothelial dysfunction and low-grade inflammation are associated in the
Proof.

resistance and metabolic syndrome in children of parents with diabetes

of mothers with young-onset type 2 diabetes. Diabetologia.
2006;49(8):1876-1880.

offsprings of diabetics detected by spectral analysis of heart rate

8. Voight BF, Scott LJ, Steinthorsdottir V, et al. Twelve type 2 diabetes
susceptibility loci identified through large-scale association analysis. Nat