1a. Full Title: Analysis of single nucleotide polymorphisms from genome-wide association data for adiposity traits

b. Abbreviated Title: GWAS and adiposity

2. Writing Group:
   Kari North
   Keri Monda
   Ellen Demerath
   Linda Kao
   Eric Boerwinkle
   Braxton Mitchell (with the OOA Study)
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Other investigators welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. KN

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3. Timeline:
   Data arrival: End of June, 2008
   Statistical analyses: July – August, 2008
   Manuscript preparation: August – September, 2008
   Manuscript revision: September – October 2008
   Manuscript submission: October – November 2008

4. Rationale:
   Several lines of evidence support the role of genetics in the regulation of body mass, including longitudinal family and twin studies which show that BMI, weight, and weight change are all heritable traits (Adams, Hunt et al. 1993; Austin, Friedlander et al. 1997; Lee, Reed et al. 1997; Bouchard, Perusse et al. 1998; Comuzzie and Allison 1998; Hunt, Katzmarzyk et al. 2002; Loos and Bouchard 2003). However, most forms of obesity do not follow simple Mendelian modes of inheritance and thus investigating potential genetic variants that contribute to common forms of obesity will require large population-based studies. Linkage analyses of family-based data have identified areas of the human genome that are associated with
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
   _X_ A. primarily the result of an ancillary study (AS #2006.03 & #2007.02)
   ___ 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.cscs.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.

References
ARIC investigators in the JHU group will run EIGENSOFT and provide principal components for inclusion in regression models.

Multiple testing: The large number of statistical tests these analyses entail will yield false positive results unless appropriate corrections are made for multiple testing. We will control for this using the Bonferroni correction on an overall $q=0.05$, a standard approach in GWA analyses, resulting in a significant p-value of approximately $0.05 \times 10^{-6}$. Secondarily, we will use the false discovery rate (FDR) (Benjamini, Drai et al. 2001; van den Oord and Sullivan 2003) and permutation-based procedures (Nichols and Holmes 2002).

7.a. Will the data be used for non-CVD analysis in this manuscript?
   ___ Yes
   ___ No

8.a. Will the DNA data be used in this manuscript?
   ___ 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 ICTDER02 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
   ___ 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)?
   #795: Resistin gene polymorphisms and association with obesity and body size measures in African Americans, Mexican Americans, and non-hispanic Whites from two community-based studies
   #814: Association of beta2-adrenergic receptor polymorphisms with asthma and obesity in the Atherosclerosis Risk in Communities Study
   #1041: Obesity resistance in an aging population and the effects of two obesity candidate genes in the Atherosclerosis Risk in Communities Study.
   #1269r: FTO, Obesity and Diabetes.

The above ARIC manuscript proposals all describe studies in which candidate obesity genes will be investigated with adiposity traits. None of these proposals include the use of GWAS data.