1a. Full Title: Obesity-related genetic variant and brain volume: an individual-level meta-analysis without sharing participant data from NEURO-CHARGE

b. Abbreviated Title (Length 26 characters): Partial-derivative meta-analysis

2. Writing Group: Myriam Fornage, Tom Mosley
   Writing group members: Members of the Neuro-CHARGE WG (final authorship to be defined). Lead authors are from the Rotterdam Study (Arfan Ikram)

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

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3. Timeline: Draft manuscript anticipated 1st quarter of 2015

4. Rationale: Genome-wide association studies of obesity have identified a common variant at the FTO/IRX3 locus influencing weight, but its effect on the brain remains unclear. Here we investigate this variant in relation to total brain volume and intracranial volume using a novel meta-analytic approach termed ‘partial derivatives meta-analysis’. This study serves as a proof of principle study of performing individual-level meta-analysis across studies without sharing participant data.
5. **Main Hypothesis/Study Questions:**
To examine the association of rs9939609 with brain volume (from the ancillary Brain MRI study) adjusting for Total Intracranial Volume, age, age\(^2\), BMI and BMI\(^2\) using a novel meta-analytic method termed ‘partial derivatives meta-analysis’.

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).**

a. **Partial derivatives**
Regression models estimate the effects of predictor variables on the outcome variable by determining the combination of beta coefficients that minimize errors between the observed and predicted values, i.e. fitting the best model to the available data. The beta coefficients are calculated by simultaneously solving a set of equations that try to find this “best” value for each of the predictor variables, by setting the partial derivatives of these equations to zero. Partial derivatives meta-analysis, a strategy to exchange between studies the partial derivative equations that are used for calculating effect estimates, is mathematically equivalent to individual-level meta-analysis. Also, using partial derivatives meta-analysis, models can be adjusted afterwards without secondary analyses, and small studies that would otherwise have been excluded can participate.

b. **Exclusion criteria**
- Prevalent clinical stroke at time of MRI-scanning. If data on clinical stroke are missing, then exclude if infarcts on MRI involving the cortical grey matter are present.
- Possible Dementia (based on cognitive testing) at time of MRI-scanning.

c. **Analyses**
- Linear regressions and meta-analysis:
  - Basic model: \([\text{TBV or ICV}] \sim \text{age, sex, and rs9939609}\)
  - Exploration of additional covariates: age2, bmi, bmi2, TBV/ICV (if applicable), pc1-3 (study-specific), study site
  - Sex stratification

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\(_\text{OTH}\) = “CVD Research” for non-DNA analysis, and for DNA analysis RES\(_\text{DNA}\) = “CVD Research” would be used?  **___ Yes _X__ 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.csc.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)? None. This is a novel methodologic approach

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

ARIC brain MRI

11.b. If yes, is the proposal
__X__ A. primarily the result of an ancillary study (list number* 1999.01)
____ 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.csc.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.

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.csc.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.