

# Using Genome Wide Estimates of Heritability to Examine the Relevance of Gene-Environment Interplay

Ben Domingue & Jason Boardman\*

March 11, 2013

## Abstract

We use genome-wide data from the third generation respondents of the Framingham Heart Study to estimate heritability in body mass index using different quantities of the measured genotype. Heritability decreases rapidly when SNPs implicated by a genome-wide association study are removed but shows essentially no decline when SNPs implicated by a gene-environment interaction in a second genome-wide analysis are removed. This second result is highlighted by our additional finding that the SNPs which explain heritability amongst a subsample defined by higher educational attainment explain no heritability of the heritability in the lower education group, and vice-versa. Finally, we do find consistent heritability estimates when we compare family-based estimates versus those based on measured genotype.

---

\*Institute of Behavioral Science, University of Colorado Boulder

Address all correspondence to: Jason D. Boardman, University of Colorado, Institute of Behavioral Science, 1440 15th Street, Boulder, CO 80309-0483; ph: 303-492-2146; fx: 303-492-2151. Email: boardman@colorado.edu. This paper is part of a larger study funded by the National Institute of Child Health and Human Development (R01HD060726). Research funds were also provided by the NIH/NICHD funded CU Population Center (R24HD066613). From the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. This work was supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195).

Evidence from twin and sibling studies suggests that most behavioral phenotypes of interest to social demographers evidence moderate to large heritability estimates. Traits such as smoking, drinking, obesity, and exercise are all found to be roughly 40-60% heritable. These large estimates of genetic influence have been increasingly criticized because, to date, genome-wide association studies (GWAS) have not uncovered SNPs or SNP clusters that explain more than 1-2% of phenotypic variance. The so called “missing heritability” (Maher, 2008; Manolio et al., 2010) has defined the first generation of GWAS studies and has led to a re-thinking of standard approaches.

From a social science perspective, BMI is an interesting phenotype since it has strong biological and social components. There is strong evidence that genes determine individual differences in physical weight and weight gain (Haberstick et al., 2010; Fox et al., 2007; W. Yang, Kelly, & He, 2007). There is also a great deal of variability in the estimated influence of genotype on BMI; with an average of roughly 60%, heritability estimates for BMI range from as little as 5% to as high as 90% (Loos & Bouchard, 2003). This variation is in line with the GxE perspective that anticipates differential associations between genotype and phenotype across different environments (Shanahan & Hofer, 2005) and some work has demonstrated the social moderation of genetic factors linked to obesity related phenotypes (Lee, Lai, Ordovas, & Parnell, 2011; J. D. Boardman et al., 2012).

More recent models that use genetic similarity among unrelated persons have begun to provide estimates of genetic influence that are similar to traditional behavior genetic results (Yang et al. 2010). These methods have been organized under the umbrella of GCTA and a toolkit for these analyses is available to all researchers.<sup>1</sup> To date, these methods have been used to characterize the relative contribution of additive genetic influences on overall phenotypic variance. No existing study has used these methods to explore the relevance of the gene-environment interaction perspective. The purpose of this study is to use the

---

<sup>1</sup><http://www.complextraitgenomics.com/software/gcta/>

GCTA methods to decompose the variation of BMI into components that are due to main and interactive components. We do this by estimating heritabilities after repeatedly removing SNPs that were identified by various genome-wide analyses as top hits. Our primary finding is that the top hits identified by a genome-wide search for SNPs that differentially predict phenotype by environment account for virtually none of the heritability.

## Methods

The GCTA model (J. Yang, Lee, Goddard, & P.M., 2011) has become a popular alternative to using sibling and twin data to estimate heritability. Rather than using expected genetic similarity, such as of .5 and 1 in the case of dizygotic and monozygotic twins, the GCTA models use the empirical genetic similarity score that characterizes genetic similarity above and beyond what we would expect by chance (e.g., IBS). This NxN genetic relationship matrix is then used to partition variance into components that are due to measured genetic associations or those due to environmental factors.

Our contribution is to focus on the results from removing different blocks of SNPs when calculating GCTA-based heritabilities. That is, we remove blocks of SNPs and subsequently recalculate heritability to see how much of the genetic variation is explained by the removed SNPs. The SNPs are removed in specific orders, typically based on a ranking of their associated p-values from GWAS analyses. The first model is a typical GWAS:

$$Y_i | G_i, G_i^p, E_i, \mathbf{Z}_i \sim N [b_0 + b_1 G_i + b_2 G_i^p + b_3 E_i + \mathbf{b}_4 \mathbf{Z}_i, \sigma_1^2] \quad (1)$$

where bold characters represent multidimensional components (either vectors or matrices). Equation 1 describes BMI ( $Y$ ) as a function of genes ( $G$ ) and other factors. First, a control for parental mating type ( $G^p$ ) is included. Parents may both be homozygous for the minor allele (AA, AA), one may be homozygous for the minor and the other homozygous for the

alternate allele (AA, BB), they may both be heterozygous (AB, AB), etc. In total, there are six potential mating types. The use of trios (genetic data for parents and their offspring) enables researchers to look at within family distributions of alleles and this approach is robust to population stratification. Second, a control for environment ( $E_i$ ), an indicator of whether an individual has obtained a college degree is included. Finally, additional controls for gender and age ( $Z_i$ ) are also included.

We then use a genome-wide gene-environment interaction (GWGEI) model that controls for gene-environment correlation as well as population stratification. This model is proposed by Moreno-Macias, Romieu, London, and Laird (2010) and has been shown to provide valid and reliable GWGEI estimates. The model is:

$$Y_i | G_i, G_i^p, E_i, Z_i \sim N [b_0 + b_1 G_i + b_2 G_i^p + b_3 E_i + \mathbf{b}_4 Z_i + b_5 G_i E_i + b_6 G_i^p E_i, \sigma_2^2] \quad (2)$$

This model differs from the above in the introduction of the interactions. The first interaction ( $b_5 G_i E_i$ ) allows for the effect of genotype to differ by environment. The second interaction ( $b_6 G_i^p E_i$ ) reduces the risk of gene-environment correlation which may have important influences on GxE parameter estimates. This model is comparable to the FBAT approach (Laird, Horvath, & Xu, 2000; Laird & Lange, 2006) that has been successfully used to identify SNPs linked to obesity (Herbert et al. 2006). We estimate all models using the `lm` procedure in R (R Core Team, 2012).

The models above emphasize allelic associations and corresponding interactions one SNP at a time. Researchers have recently adapted existing quantitative genetic modeling techniques to include genetic similarity among unrelated individuals (J. Yang et al., 2010, 2011). These methods (described below) have been organized into the GCTA suite of genome wide association tools. Rather than estimating the cumulative influence of all known causal loci (which are, in principle, unknown), these models estimate a relationship matrix for all unrelated persons. They characterize the genetic relationships between individuals  $j$  and  $k$

individual across all genetic markers  $i$  with minor allele frequency  $p_i$  as:

$$A_{jk} = \frac{1}{n} \sum_{i=1}^n \frac{(x_{ij} - 2p_i)(x_{ik} - 2p_i)}{2p_i(1 - p_i)}. \quad (3)$$

Related pairs will have values that, on average, correspond to the fixed values in traditional behavioral genetic models (e.g., siblings will have an average of .5) but the inclusion of family members can artificially inflate heritability estimates because the shared environment is subsumed in the family coefficient. As such, these researchers recommend eliminating pairs with  $A_{jk}$  estimates in excess of .025. Then an OLS estimate of  $b_1$  in the below model:

$$E [(bmi_j - bmi_k)^2 | A_{jk}] = b_0 + b_1 A_{jk}$$

provides an unbiased estimate of  $-2\sigma_g^2$  and the genetic variance is simply returned as  $-b_1/2$ . Taken as a proportion of the overall phenotypic variance this method provides an assumption free estimate of additive genetic influence and corresponding standard error estimates for each of the parameters.

## Data

The study sample for this project was derived from the Framingham SNP (Single Nucleotide Polymorphism) Health Association Resource (SHARe, version 6) as available through NCBI's database of Phenotypes and Genotypes (dbGaP). The analysis for this study focused on the third generation of the Framingham Heart Study (FHS, Splansky et al., 2007). The original cohort of the FHS was first assessed in 1948 and nearly 25 years later their children and many of their spouses participated in the offspring cohort study (W2). Then, in 2002, roughly 4000 adults who had at least one parent in the offspring cohort took part in the third generation (W3) cohort. This cohort was examined for a variety of different morbidities using clinical and

laboratory assessments. Crucially, study participants were measured for height and weight. Table 1 presents descriptive statistics for the FHS W3 sample that we use in our analysis by educational status. Those without a college degree have an average BMI that is 1.45 units higher than those with a college degree ( $p < .001$ ). This is a moderate effect size and translates to roughly 10 additional pounds for a 140 pound adult who is 5'8". There are no gender differences by educational attainment but we do see that the college educated sample is slightly younger. We include these controls in the genome wide association models described below.

These samples were made available by the Framingham SHARe resource which contains genotypes for all respondents using the Affymetrix 5.0 genotyping platform. After reducing the Framingham SHARe data set to trios with complete (non-missing) genetic information (e.g., genotypes for biological mother, biological father, and focal subject) our analytic sample includes 1,967 W3 respondents. We drop SNPs with minor allele frequencies of less than 5% and those that do not meet Hardy Weinberg criteria.<sup>2</sup> This initial pruning was done in PLINK and 256,884 SNPs met this criteria (full set of SNPs are available upon request).

Descriptives for the phenotype and individuals used here are shown in Table 1. The W3 respondents had higher average BMIs (26.6) than the W2 respondents (25.5). Of the W3 respondents, those with a college degree had lower BMIs than those without (26.0 compared to 27.4). Heritabilities (using the GCTA approach described below) were also computed based on the full W3 sample as well as when it was split by having a college degree. For the full sample, the heritability of BMI was 0.5 although heritabilities were higher (though not significantly so) in the samples split by education.

---

<sup>2</sup>The pruning of the SNPs was done in the full Framingham sample, not in the subsample of the W3 respondents.

Table 1: Descriptive statistics for BMI

	Mean (SD)	N
W2	25.5 (4.18)	1624
W3	26.6 (5.44)	1979
W3 College	26.0 (5.2)	1103
W3 Non-College	27.4 (5.6)	864
	$h^2$ (SE)*	N
W3	0.50 (0.05)	1979
W3 College	0.60 (0.08)	1103
W3 Non-College	0.53 (0.09)	864

\* Based on GCTA estimates.

## Results

Figure 1 compares the declines in heritability as SNPs are removed in blocks of 5000 in four different orders. When no SNPs are removed (the point where all four curves touch on the y-axis), heritabilities are all identical. Consider first the line with the most severe negative slope. This line, labeled GWAS, represents the repeated removal of the SNPs that had the lowest p-values from the GWAS analysis (p-values for the estimated  $b_1$  coefficients from Equation 1). Of these SNPs, the first 50,000 are clearly those that explain nearly all of the heritability. The line above, labeled GWGEI-G, removes blocks of 5000 SNPs as ranked by lowest p-values for the main effect of the SNP from the GWGEI analysis (the  $b_1$  coefficient from Equation 2). The general pattern is roughly similar to removal based on the GWAS analysis.

The line labeled GWGEI-G $\times$ E is the most interesting of the four. This line is based on removing SNPs as ordered by the p-values of the SNP-environment interaction from the

GWGEI analysis (the  $b_5$  coefficient from Equation 2). The first 200,000 SNPs, as ordered by this analysis, explain only a fraction of the overall heritability. This curve can be compared to the curve labeled Random which is based on removing SNPs that are randomly ordered. Essentially, the top hits from the GWGEI-GxE SNPs explain no more of the heritability than randomly chosen SNPs. We believe that this finding raises questions about this type of GWAS work, a claim that we elaborate on in the discussion.

Figure 2 is based on a separate set of GWAS analyses. The same model as in Equation 3 is used except there is no control for environment ( $E_i$  does not appear). Instead, the analysis is run separately on those with and without a college degree. The appropriately labeled curves in Figure 2 correspond to these separate analyses. Note that for both groups, the top hits in the GWAS explain the majority of the heritability using fewer SNPs than in the data as a whole. This can be observed by comparing the No College and College lines to the GWAS line, which is a replication of the line from Figure 1 (note that the scale of the x-axis has changed as well).

In contrast, the curves at the top of Figure 2 remove SNPs for the groups as they are ordered from the GWAS in the other group. So, the line labeled No College, Alternate SNPs computes heritability for the group of individuals who did not finish college based on removing SNPs in the order they were ranked from the GWAS using the college graduates. What is remarkable is that essentially *no* heritability is explained by this process. This finding suggests to us that the GWAS estimates are extremely sensitive to the choice of sample.

## **GCTA compared to family-based heritabilities**

The GCTA approach discussed here utilized genetics data to compute heritability estimates, but the family-based structure of Framingham allows us to compare this estimate to traditional heritability estimates based on family trios (mother, father, child). Using the approach in Rabe-Hesketh, Skrondal, and Gjeesing (2008) and the Stan Development Team (2012)

Figure 1: Heritability as a function of remaining SNPs: Removed SNPs for different curves are ordered by p-values from corresponding genome-wide analyses.

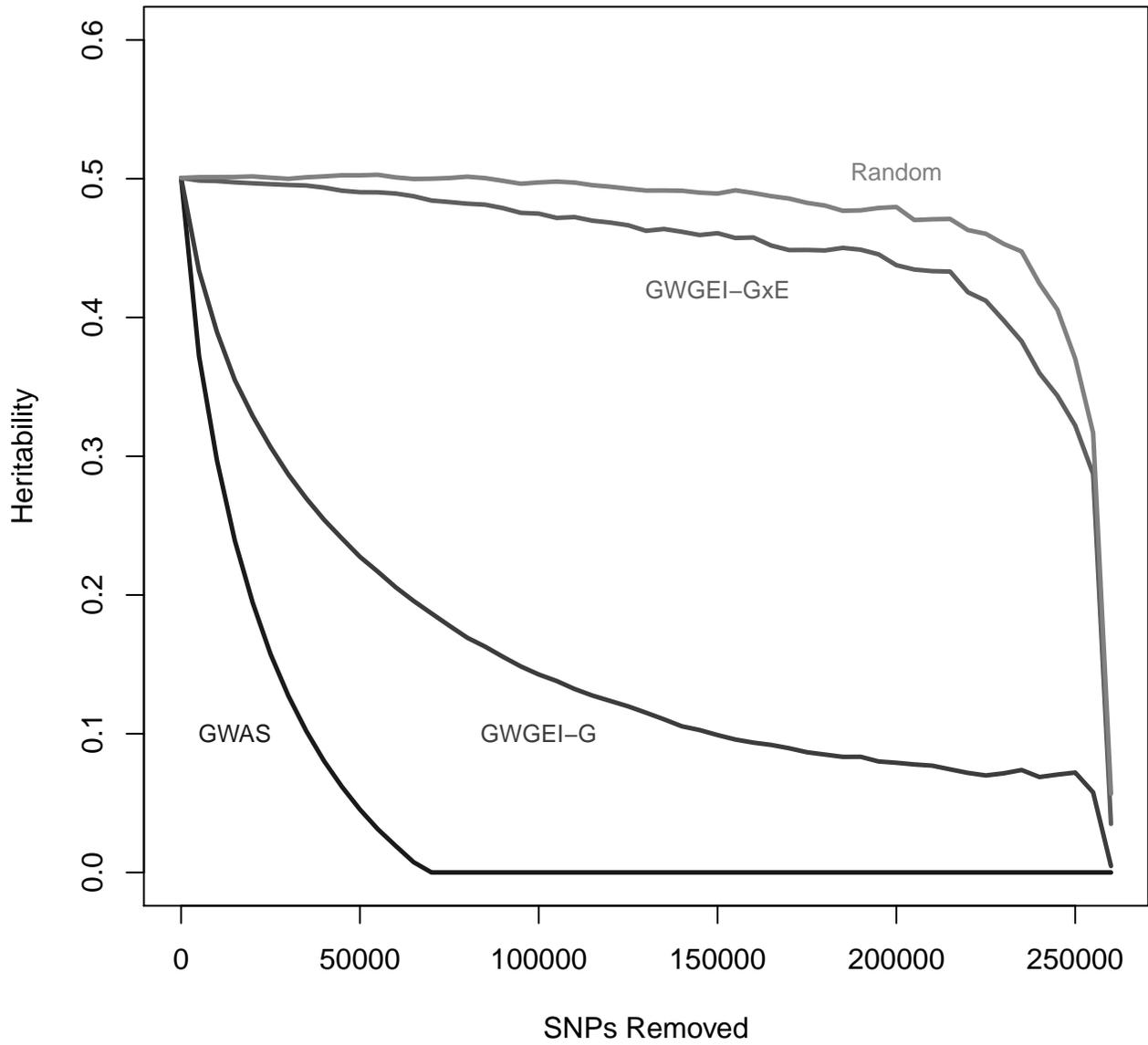


Figure 2: Heritability as a function of remaining SNPs: Removed SNPs for different curves are ordered by p-values from corresponding genome-wide analyses done separately on respondents that had and had not completed college separately.

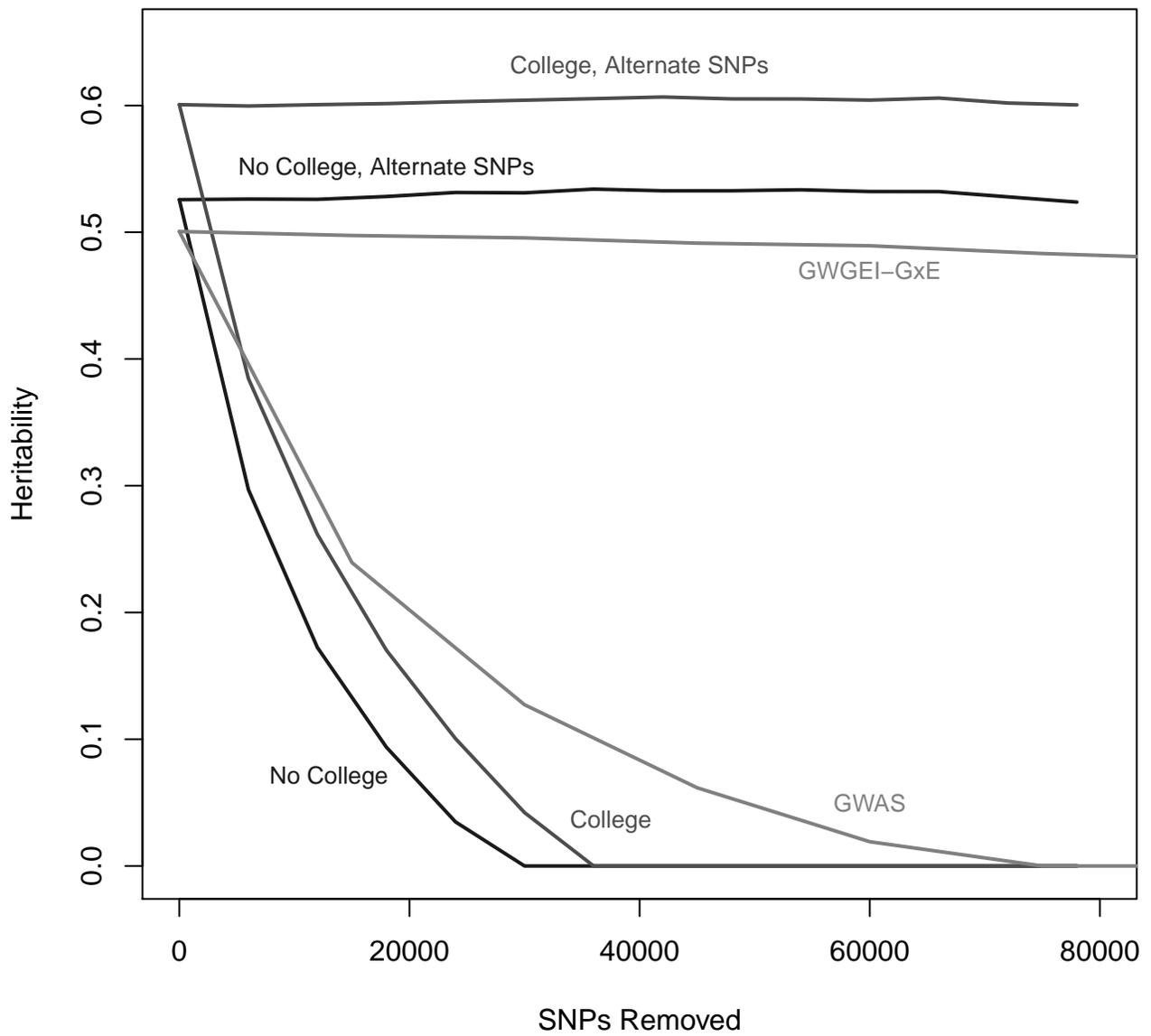
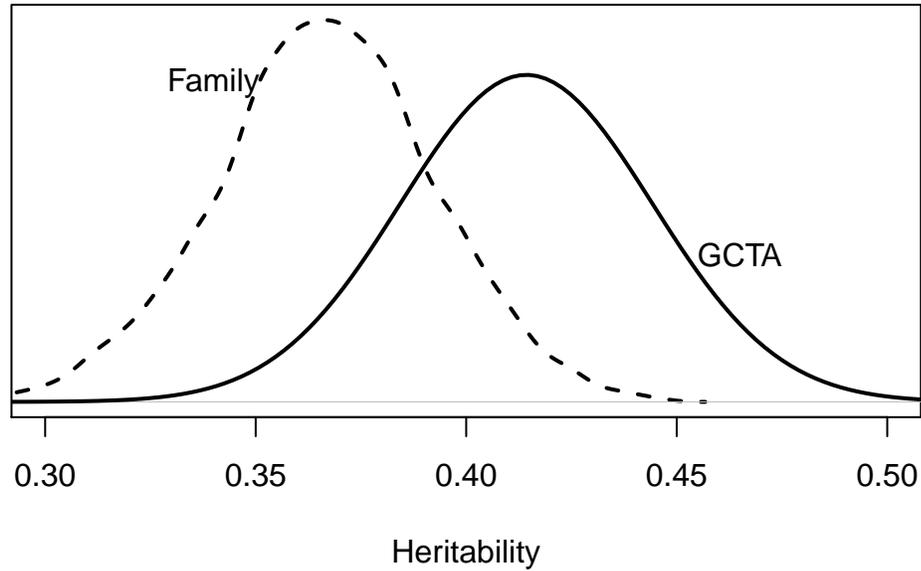


Figure 3: Comparison of GCTA and family-based heritability estimates



software, we obtained a Bayesian estimate for the heritability of BMI. This approach allowed us to also control for age and gender of respondents. Estimates were centered around 0.355 with a 95% CI from 0.34 to 0.4. A GCTA analysis performed using both waves 2 and 3 (N=3603) led to a heritability of 0.42 (0.03). However, this GCTA estimate is not directly comparable due to the family-based estimate due to the presence of the covariates. An additional GCTA estimate that controlled for age and gender was only slightly lower, 0.41 (0.03). A comparison of the estimates for heritability in each approach is shown in Figure 3. We find it reassuring that the two approaches are yielding roughly similar results and suggest some reasons for why the family-based approach might be computing smaller heritability estimates in the discussion.

## Discussion

This paper focused on the heritability that remained in a group of individuals after removing SNPs in different orders. Figure 1 compared the heritability of BMI in the third generation Framingham after removing SNPs as they were ordered by their p-values in different genome-wide association analyses. Our first main result was a demonstration that the top hits indicated by a traditional GWAS explained nearly all of the heritability. In contrast, those hits indicated by a gene-environment interaction explained essentially none of the heritability. The second main result is shown in Figure 2. The key point is that the top hits from a GWAS using only those that graduated from college explained none of the heritability for those that did not attend college. The opposite version (heritability for those who attended college after removing top hits from a GWAS on those that did not attend college) was also true. This suggests that SNP effect estimates are potentially extremely sensitive to environment.<sup>3</sup>

The third main result was a comparison of heritability estimates based on measured genotype versus family structure. The estimates were roughly comparable, which is especially interesting given that the heritability estimates in Figure 3 are based on different sources of information. The family-based estimate uses only indicated familial relationships between waves 2 and 3 while the GCTA estimate is based on measured phenotype. Moreover, the GCTA estimate explicitly excludes pairs with a genetic relationship over some (relatively low) threshold so that family pairs don't bias the estimate due to the shared environment. The fact that the GCTA estimate of heritability is higher than the family-based estimate is interesting. One potential problem is that the family-based estimate isn't accounting for the fact that some families have multiple siblings. However, this would probably bias this estimate upwards and so is unlikely to explain the difference.

The results of this research echo those of J. Boardman et al. (2013) which question

---

<sup>3</sup>It is worth noting that we also found, in J. Boardman et al. (2013), that SNPs are measured with sufficient noise that they fail to replicate in a random split of the Framingham data.

the contribution of genetic studies that focus on specific SNPs for social science in general, especially given the limited sample sizes that characterize most of the studies in question. On the other hand we do think that information based on the whole genome could be quite useful. Heritabilities are one approach that can potentially provide information about genetic causes of behavior, but working strictly with heritabilities might be limiting since they don't allow one to simultaneously control for genetic and environmental factors. One possibility might be the approach suggested in Zhou and Stephens (2012), but the computational demands of this approach are relatively extreme. We hope to explore less demanding alternatives in future research.

## References

- Boardman, J., Domingue, B., Blalock, C., Haberstick, B., Harris, K., & McQueen, M. (2013). *Genome-wide gene-environment interactions for body mass index*.
- Boardman, J. D., Roettger, M. E., Domingue, B. W., McQueen, M. B., Haberstick, B. C., & Harris, K. M. (2012). Gene-environment interactions related to body mass: School policies and social context as environmental moderators. *Journal of Theoretical Politics*, *24*(3), 370–388.
- Fox, C., Heard-Costa, N., Cupples, L., Dupuis, J., Vasan, R., & Atwood, L. (2007). Genome-wide association to body mass index and waist circumference: the Framingham heart study 100k project. *BMC Medical Genetics*, *8*(Supplement 1), S18.
- Haberstick, B., Lessem, J., McQueen, M., Boardman, J., Hopfer, C., Smolen, A., et al. (2010). Stable genes and changing environments: Body mass index across adolescence and young adulthood. *Behavior Genetics*, *40*, 495–504.
- Laird, N., Horvath, S., & Xu, X. (2000). Implementing a unified approach to family based tests of association. *Genetic Epidemiology*, *19*(Supplement 1), S36–S42.

- Laird, N., & Lange, C. (2006). Family-based designs in the age of large-scale gene-association studies. *Nature Review Genetics*, 7, 385–394.
- Lee, Y., Lai, C., Ordovas, J., & Parnell, L. (2011). A database of gene-environment interactions pertaining to blood lipid traits, cardiovascular disease, and type 2 diabetes. *Journal of Data Mining in Genomics and Proteomics*(1), 1–8.
- Loos, R., & Bouchard, C. (2003). Obesity-is it a genetic disorder? *Journal of Internal Medicine*, 254, 401–425.
- Maher, B. (2008). Personal genomes: The case of the missing heritability. *Nature*, 456, 18–21.
- Manolio, T., Collins, F., Cox, N., Goldstein, D., L.A.Hindorff, Hunter, D., et al. (2010). Finding the missing heritability of complex diseases. *Nature*, 461(7265), 747–753.
- Moreno-Macias, H., Romieu, I., London, S., & Laird, N. (2010). Gene-environment interaction tests for family studies with quantitative phenotypes: a review and extension to longitudinal measures. *Human Genomics*, 4(5), 302–326.
- R Core Team. (2012). R: A language and environment for statistical computing [Computer software manual]. Vienna, Austria. Available from <http://www.R-project.org/> (ISBN 3-900051-07-0)
- Rabe-Hesketh, S., Skrondal, A., & Gjeesing, H. (2008). Biometrical modeling of twin and family data using standard mixed model software. *Biometrics*, 64, 280–288.
- Shanahan, M., & Hofer, S. (2005). Social context in gene-environment interactions: Retrospect and prospect. *Journals of Gerontology: Series B*, 60B, 65–76.
- Splansky, G., Yang, D. C. Q., Atwood, L., Cupples, L., Benjamin, E., D'Agostino, R., et al. (2007). The third generational cohort of the national heart, lung, and blood institute's Framingham heart study: Design, recruitment, and initial examination. *American Journal of Epidemiology*, 165(11), 1328–1335.
- Stan Development Team. (2012). Stan: A C++ library for probability and sampling [Computer

- software manual]. Available from <http://mc-stan.org/> (Version 1.0)
- Yang, J., Benjamin, B., McEvoy, B., Gordon, S., Henders, A., Nyholt, D., et al. (2010). Common snps explain a large proportion of the heritability for human height. *Nature Genetics*, *42*(7), 565–569.
- Yang, J., Lee, S., Goddard, M., & P.M., V. (2011). GCTA: A tool for genome-wide complex trait analysis. *American Journal of Human Genetics*, *88*(1), 76–82.
- Yang, W., Kelly, T., & He, J. (2007). Genetic epidemiology of obesity. *Epidemiologic Reviews*, *29*, 49–61.
- Zhou, X., & Stephens, M. (2012). Genome-wide efficient mixed-model analysis for association studies. *Nature Genetics*, *44*(7), 821–824.