

Estimating Genetic Correlation from GWAS Summary Statistics

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Abstract

Discovering relationships between phenotypes is a fundamental goal of epidemiology, with implications for drug development, nosology and treatment. Phenotypic correlations in observational epidemiological studies are often confounded by environmental factors, so genetic correlations between phenotypes may be more easily interpretable. The largest currently available sources of genotype-phenotype data are genome-wide association studies (GWAS); however, existing methods for estimating genetic correlation from GWAS data require genotype and phenotype data for at least one of the phenotypes, which is often impossible to obtain due to restrictions on data sharing. For this reason, only a few dozen genetic correlations have been estimated from GWAS data to date. In this paper, we describe a method based on LD Score regression which estimates genetic correlations directly from GWAS summary statistics and is immune to sample overlap. Since dozens of sets of summary statistics can be freely downloaded from the internet, we can report a much larger number of genetic correlations – more than 700 in this paper alone – than was previously possible. In addition, we relax many common assumptions about genetic architecture, and demonstrate that our method is not confounded when effect size depends on allele frequency or linkage disequilibrium.

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1 Introduction

The (additive) genetic covariance, ρ_g between two phenotypes y_1 and y_2 is the bivariate analogue of heritability, and is defined as the covariance (in the population) between the additive genetic components of y_1 and y_2 . The normalized version of genetic covariance is genetic correlation,

$$r_g := \frac{\rho_g}{\sqrt{h_1^2 h_2^2}}, \quad (1.1)$$

which lies in the interval $[-1, 1]$. Note that genetic correlation is a stronger condition than pleiotropy. To exhibit genetic correlation, it is not sufficient for two phenotypes to be influenced by the same genetic loci: the directions of effect of the variants that influence the phenotypes must also be aligned consistently across the genome.

Existing methods for estimating genetic correlation from GWAS genotype data (*e.g.*, restricted maximum likelihood (REML) as implemented in the software package GCTA [36, 37] – hereafter referred to as GCTA-REML – or polygenic risk scores [9]) require genotype data, which is often impossible to obtain due to restrictions on data sharing. For this reason, papers typically report at most a handful of genetic correlations, usually estimated from samples of at most a few tens of thousands of individuals, and only a few dozen genetic correlations have been estimated using GWAS data to date.

We propose a modification of LD Score regression [4] that can estimate genetic correlation from GWAS summary statistics. Precisely, if $z_{1,j}z_{2,j}$ are the Z -scores for a SNP j from two GWAS, ℓ_j , the LD Score of SNP j , and we assume a simple model of genetic architecture where all SNP effect sizes are drawn *i.i.d.*, we can write

$$\mathbb{E}[z_{1,j}z_{2,j}] = \frac{\rho_g \sqrt{N_1 N_2}}{M} \ell_j + \frac{N_s \rho}{\sqrt{N_1 N_2}}, \quad (1.2)$$

where N_1 and N_2 are the sample sizes of each study, N_s is the number of shared samples, ρ is the phenotypic covariance and ρ_g is the genetic covariance. This equation is derived in the supplementary note, and a similar relationship holds if one or both of the studies is an ascertained study of a binary phenotype. The relationship becomes more complicated if effect sizes are not identically distributed, but instead depend on MAF or linkage disequilibrium, as discussed in [30]; however, we can easily accommodate such dependencies with partitioned LD Score regression (as described in the results and methods sections of this paper and also [11]).

Thus, if we regress the product $z_{1,j}z_{2,j}$ of Z -scores from two GWAS against ℓ_j , the LD Score of SNP j , the slope times a constant estimates genetic covariance. Since sample overlap affects the term $z_{1,j}z_{2,j}$ equally for all SNPs, and the quantity N_s appears only as the intercept term, the LD Score regression estimator of genetic covariance is not biased by sample overlap¹. We can estimate heritability using LD Score regression (as described in [4]), and use these heritability estimates to transform the estimates of genetic covariance into estimates of genetic correlation.

In this paper, we describe a series of simulations that validate these claims. We then replicate the genetic correlations reported by the PGC Cross-Disorder Group in [20], using only the summary statistics from [21], before reporting more than 700 (mostly novel) genetic correlations between phenotypes with publicly available GWAS summary data. We find that phenotypes generally tend

¹Indeed, if ρ is known, for instance if both studies assay the same phenotype and $\rho = 1$, the intercept from this regression times a constant can be used as an estimator of the number of shared samples

to cluster within categories defined by clinical practice and observational epidemiology; nonetheless, we do observe some surprising results. For instance, we estimate genetic correlations close to zero between Alzheimers and schizophrenia, rheumatoid arthritis (RA) and schizophrenia, and smoking traits and schizophrenia, despite reports of psychosis in patients with Alzheimers, reduced risk of RA in patients with schizophrenia and high rate of smoking in patients with schizophrenia.

The computational demands of our method are mild, and we provide an open-source software package, `ldsc`, written in python, which implements the analyses described in this paper and also the analyses from [4, 11] (URLs).

2 Results

2.1 Simulations

In order to check our derivations and verify the robustness of our inference procedure to violations of our modeling assumptions, we performed a variety of simulations.

2.1.1 Sample Overlap

To verify the unbiasedness of our estimation procedure in the presence of sample overlap (which is derived formally in the supplementary note), we simulated two GWAS with quantitative phenotypes, using genotypes from the 4,292 individuals in the Wellcome Trust Case/Control Consortium 1 (WTCCC1, [8]) bipolar disorder cohort for the first GWAS and genotypes from the 4,482 individuals in the WTCCC1 coronary artery disease cohort for the second GWAS. These cohorts contain 2,713 overlapping individuals. Additive genetic effect sizes were drawn from a bivariate point-normal distribution with 10% of SNPs causal and true genetic correlation 0.7. We then estimated genetic correlation using LD Score regression. Results from these simulations are summarized in supplementary table 6.1, and confirm that LD Score regression is not confounded by sample overlap.

2.1.2 Case-Control Ascertainment

We simulated ascertained GWAS in order to evaluate the performance of LD Score regression under various case/control ascertainment schemes. Simulating case/control GWAS under a liability threshold model requires rejection sampling from a large pool of genotypes. For instance, in order to simulate drawing 1,000 cases for a phenotype with prevalence of 1%, one would need on expectation to sample 100,000 genotypes. We do not have access to genotypes for 100,000 individuals, so we used simulated genotypes with a simplified LD structure ($r^2 = 0$ or 1) for simulating ascertainment.

We simulated standard case/control ascertainment following a liability threshold model, and estimated the genetic correlation using LD Score regression. Results from these simulations are summarized in supplementary table 6.2, and confirm that LD Score regression recovers the true heritability and genetic correlation, even with heavy ascertainment. The simplified LD structure should not hinder interpretation of these simulation results, especially since we also provide a proof that unlike GCTA-REML [12], LD Score regression is valid when applied to ascertained samples of binary phenotypes (Supplementary Note).

2.1.3 Misspecified Models of Genetic Architecture

Estimates of heritability and genetic covariance can be biased if the underlying model of genetic architecture is misspecified. For example, Speed, *et. al.* [30] demonstrate that GCTA-REML is confounded by MAF- or LD-dependent genetic architectures. Estimates of genetic correlation are somewhat more robust. Since genetic correlation is estimated as a ratio $\hat{\rho}_g / \sqrt{\hat{h}_1^2 \hat{h}_2^2}$ (or the weighted block jackknife estimator of this ratio, see Methods), model misspecification bias in the numerator and model misspecification bias in the denominator will tend to approximately cancel, unless genetic correlation (not just heritability and genetic covariance) also depends on MAF or LD.

Naive LD Score regression is subject to similar biases as REML; however, it is possible to remove these biases by allowing for MAF- or LD-dependent genetic architectures by using partitioned LD Score regression (see [11] and Methods)

To explore the behavior of LD Score regression under various nonstandard models of genetic architecture, we simulated three genetic architectures with MAF- and LD-dependence. For the first genetic architecture, the MAF- and LD- dependence was the same for both phenotypes and genetic correlation did not vary with MAF or LD. Effect sizes were drawn from a normal distribution so that the magnitude of per-allele effect sizes were uncorrelated with MAF and variants with LD Score below 100 were 4× enriched for heritability.

For the second genetic architecture, we drew per-allele effect sizes for the first phenotype from a normal distribution such that the variance of per-allele effect sizes were uncorrelated with MAF, and variants with LD Score below 100 were 4× enriched for heritability. Per-allele effect sizes for the second phenotype were drawn from a normal distribution such that the variance of per-allele effect size followed $\sqrt{p(1-p)}$, where p is MAF, and variants with LD Score above 100 were 4× enriched for heritability.

For the third genetic architecture, we allowed not only heritability and genetic covariance to depend on MAF and LD, but also genetic correlation. The parameters of these simulations were the same as the second genetic architecture, except that genetic correlation was 0.2 for variants with LD Score less than 100 and 0.8 for variants with LD Score greater than 100.

We estimated heritability, genetic covariance and genetic correlation using both naive LD Score regression and two partitioned LD Score regression models (one with 30 bins, one with 60 bins) that allow for both MAF- and LD-dependence. Results from these simulations are presented (in order) in supplementary tables 6.3, 6.4 and 6.5. The heritability and genetic covariance estimates from naive LD Score regression are badly biased in all cases (which is similar to the results obtained by Speed, *et. al.*), but the bias in the genetic correlation estimates was much less severe, except in the third set of simulations, where genetic correlation varied with LD. As expected, partitioned LD Score regression was able to remove almost all bias introduced by LD- and MAF-dependence, and the increase in standard error was only mild.

2.2 Real Data

2.2.1 Replication of PGC Cross Disorder Results

As a sanity check, we replicated the estimates of genetic correlations between psychiatric phenotypes obtained with raw genotypes and GCTA-REML in the PGC Cross-Disorder Group paper [20], using the summary statistics from [21] downloaded from the PGC website (URLs). For this replication, we used an LD Score with r^2 's from the 1000 Genomes Europeans [6] but with the sum of r^2 's

taken only over SNPs in HapMap 3 [7] (hereafter referred to as HapMap3 LD Score) because this is most similar to the model of genetic architecture fit by GCTA-REML, where only the effects of genotyped SNPs are modeled (see the section “LD Score Regression is Haseman-Elston Regression” in the Supplementary Note). We believe that our partitioned LD Score regression model is more reliable, so we fit the GCTA-REML model simply as a technical demonstration. The genetic correlations estimates in the next section (“Application to a Large Set of Publicly Available Summary Statistics”) are more reliable, since they use the partitioned LD Score regression model and much larger sample sizes. Nonetheless, when we fit the GCTA-REML model using LD Score regression we replicated the results from the PGC Cross-Disorder Group paper closely, and the standard errors were similar to those obtained from GCTA-REML (Figure 1). In general, we expect the standard errors from GCTA-REML to be lower than the LD Score regression standard errors at fixed sample size when the distributional assumptions (normally distributed phenotypes, environmental effects independent of genetic effects in the sample) made by GCTA-REML are met, which will often be the case for non-ascertained studies of quantitative traits. In ascertained studies of binary phenotypes, the distributional assumptions made by GCTA-REML do not hold [12], and so it is not surprising that LD Score regression performs about as well in this example.

2.2.2 Application to a Large Set of Publicly Available Summary Statistics

We applied our method to a large set of publicly available summary statistics, including studies of schizophrenia [22], major depression [24], bipolar disorder [28], autism [21], attention-deficit hyperactivity disorder [19], anorexia [3], height [1], body mass index [31], waist-hip ratio [13], obesity [2], various insulin- and glucose- related traits [16], smoking [35], coronary artery disease [26], type-2 diabetes [18], rheumatoid arthritis [32], plasma lipid traits [34], inflammatory bowel disease [14] and Alzheimer’s disease [15].

We estimated all pairwise genetic correlations between these phenotypes using partitioned LD Score regression. Where information on sample overlap and phenotypic correlation was available, we seeded the regression weights with this information in order to reduce the standard error (Methods, supplementary table **NNN**). LD Score regression heritability estimates are biased downwards by genomic control correction [4], so we report heritability estimates only for those GWAS that did not use GC correction – the GWAS for psychiatric diseases and inflammatory bowel disease

Heritability estimates are displayed in table **NNN**. Note that these are technically estimates of the heritability accounted for by SNPs with 5-50% MAF that appear in 1000 Genomes, denoted $h^2(5-50\%)$ (see Methods). This quantity is not in general the same as the quantity obtained from GCTA-REML described as the “variance explained by genotyped SNPs”, and denoted either h_g^2 or h_{SNP}^2 (indeed, different h_g^2 estimates from different studies are usually not directly comparable to each other, because they depend on the set of SNPs used for computing the kinship matrix).

The full list of 700 genetic correlation estimates are provided in tabular format in supplementary table **NNN**, and are displayed as a heatmap in table **NNN**. We find that phenotypes tend to cluster into categories defined by clinical practice and observational epidemiology; for instance, we observe high genetic correlations between anthropometric traits, between psychiatric traits, between metabolic traits and between autoimmune traits. Reassuringly, most genetic correlations across categories were non-significantly different from zero.

Nevertheless, we do observe some interesting individual results (table **NNN**). A few examples: We estimate genetic correlations close to zero between Alzheimer’s and all of the psychiatric traits. Instead, Alzheimer’s clusters (weakly, but significantly) with the anthropometric traits. We estimate

genetic correlation close to zero between rheumatoid arthritis (RA) and schizophrenia, and between smoking traits and schizophrenia, despite reduced risk of RA in patients with schizophrenia and high rate of smoking in patients with schizophrenia

... etc more examples

3 Discussion

Recap of the highlights

Main point: it is now almost trivial (mod admixed or non european GWAS) to produce the all phenotype by all phenotype matrix of genetic correlations without the ethical issues around sharing genotypes IF people are willing to share INFO (or at least provide a file with QC+ INFO $r^2 > 0.9$ SNPs)

4 Online Methods

4.1 Statistical Framework

See the supplementary note for a thorough derivation of the models behind LD Score regression.

4.2 $h_{5-50\%}^2$

Let S denote the set of all SNPs in 1000 Genomes (or whatever much larger sequenced reference panel future readers are more familiar with); let X_j denote the random variable whose value is the 0-1-2 coded genotype at SNP j , and let y denote a phenotype. Let

$$\beta := \operatorname{argmax}_{\alpha} \left(\operatorname{Cor} \left[y, \sum_{j \in S} X_j \alpha_j \right] \right)^2 \quad (4.1)$$

(note that uniqueness of β is guaranteed because this is a projection). Let S' denote the set of SNPs with $\text{MAF} > 5\%$. Then

$$h_{5-50\%}^2 := \sum_{j \in S'} \beta_j^2. \quad (4.2)$$

We choose 5% as the lower bound, because we can estimate LD Scores for 5% SNPs reasonably well from the $N = 387$ samples in 1000 Genomes. With larger sample sizes in future sequenced reference panels, this lower bound can be pushed lower.

The main distinction between $h_{5-50\%}^2$ and h_g^2 is that the effects of causal 4% SNPs are not counted towards $h_{5-50\%}^2$. This differs from the definition of the quantity h_g^2 estimated by GCTA-REML, in that GCTA-REML considers a set of SNPs g , and then projects the phenotype onto those SNPs, without accounting for SNPs that are not in the set g . Thus if there is a 5% SNP in set g that is in high LD with a 4% SNP that happens to be causal for the phenotype of interest but is not in g , then the effect of the 4% SNP is counted towards h_g^2 (or at least the component of the effect of the 4% SNP that is tagged by the 5% SNP that is in g). There tends not to be very much LD between SNPs with different MAFs, so in the specific case of a MAF cutoff, this distinction likely makes only a small difference.

Technically, we should write $h_{5-50\%, 1kG}^2$ to indicate that we are only accounting for SNPs in 1000 Genomes, but 1000 Genomes has sufficiently good power to observe 5% and higher SNPs that we feel justified in omitting $1kG$ from the subscript for notational simplicity. It is perhaps more important to also note that we are only accounting for autosomal variation. Most GWAS do not report summary statistics for SNPs on the sex chromosomes or in mitochondrial DNA.

Note that estimates of $h_{5-50\%}^2$ should generally be less than pedigree-based estimates of heritability (modulo standard error), since pedigree estimators take into account all forms of genetic variation rare variants, microsatellites, indels, copy number variants, non-autosomal variation, etc).

The genetic covariance and genetic correlation quantitates that we estimate are direct bivariate analogues of $h_{5-50\%}^2$. It is possible that the genetic covariance between two phenotype may be different among $\text{MAF} > 5\%$ variants than among rare variants; however, we could not detect such a phenomenon with GWAS data, since current GWAS only reliably assay common variation.

4.3 Estimation of LD Scores

We estimated LD Scores from the European samples in the 1000 Genomes Project [6] reference panel using the `--l2` flag in the `ldsc` software package by the authors (URLs) as in [4]. We estimated per-allele LD Scores using the `--per-allele` flag in `ldsc`, and we estimated MAF-binned LD Scores using the `--cts-bin` and `--cts-breaks` flags in `ldsc`. Following [4], we estimated LD Scores using a 1 centiMorgan (cM) window (with the `ldsc` flag `--ld-wind-cm 1`). Unlike [4], we used a MAF cutoff of 1% when estimating LD Scores, in order to reduce the impact of LD measurement error on our regressions. Since we only include variants with $\text{MAF} > 5\%$ in LD Score regressions for estimating genetic correlation, and because there is very little LD between variants with $\text{MAF} > 5\%$ and variants with $\text{MAF} < 5\%$, this is unlikely to impact our results.

For the analyses with HapMap 3 [7] LD Scores, we took the sum of r^2 's over the same subset of HapMap 3 SNPs retained for LD Score regression in [4], (that is, HapMap 3 SNPs with $\text{MAF} > 1\%$, excluding centromeres and regions with long-range LD) using the `--keep` flag in `ldsc`.

4.4 Partitioned LD Score Regression

In partitioned LD Score regression, we cut the set of SNPs in our reference panel into bins, for example, we might use five MAF bins, corresponding to MAF 0-10%, 10-20%, ..., 40-50% (as in supplementary table 4 of [20]). We allow the variance explained per SNP to vary from bin to bin, but assume that variance explained per SNP is (roughly) equal within each bin. This amounts to approximating the unknown function that maps MAF to variance explained per SNP with a locally constant approximation. This presents a bias/variance tradeoff: if the mesh of our locally constant approximation is too coarse (*e.g.*, if we were to use two MAF bins instead of five), our locally constant approximation would be poor, and this would result in bias. On the other hand, if we use too many bins, the standard error of our estimates will increase. However, we show in the simulations under the header “Misspecified Models of Genetic Architecture” that we can remove almost all MAF- and LD-bias under realistic parameter settings using only a few tens of bins, which increases the standard error only modestly. MAF- and LD- partitioned LD Scores can be estimated using the `--cts-bin` and `--cts-breaks` flags from our `ldsc` software.

4.5 Genetic Covariance Regression Weights

For heritability estimation, we use the LD Score regression weights derived in the supplementary note from [4]. The optimal regression weights for genetic covariance estimation are

$$\text{Var}[\hat{\beta}_j \hat{\gamma}_j | \ell_j] = \left(\frac{h_1^2 \ell_j}{M} + \frac{1 - h_1^2}{N_1} \right) \left(\frac{h_2^2 \ell_j}{M} + \frac{1 - h_2^2}{N_2} \right) + 2 \left(\frac{\rho_g \ell_j}{M} + \frac{\rho N_s}{N_1 N_2} \right);$$

(Supplementary Note) however, this quantity depends on both heritabilities, the genetic covariance and the number of overlapping samples, which are often not known a priori, so some approximation is required. In order to obtain approximate regression weights, we use heritability estimates from the single-phenotype LD Score regressions, then we assume that N_s is close enough to zero that the term $\rho N_s / N_1 N_2$ is negligible (though this default can be adjusted using the `--overlap` and `--rho` flags in `ldsc`), and estimate a rough genetic covariance (which we only use for the regression weights)

using the aggregate estimator

$$\hat{\rho}_{g,agg} := \frac{1}{\bar{\ell}\sqrt{N_1N_2}} \sum_{j=1}^M z_{1,j}z_{2,j},$$

where $\bar{\ell}$ denotes the mean LD Score among SNPs included in the regression. These regression weights are only an approximation to the optimal weights, but this will not introduce bias into the regression; it will only increase the standard error. The standard errors for LD Score regressions with summary statistics from GWAS with sample size below 10,000 are low enough to be interpretable, so non-optimality of the regression weights does not seem to be a major hindrance.

Users of our **ldsc** software package should note that when attempting to compute the genetic correlation between a trait and itself using the same GWAS data twice, the result will generally be different from one unless the weights are set appropriately. With the default weights (which are set for zero sample overlap), **ldsc** is simply computing the ratio between the slope of and LD Score regression with efficient weights and the slope of an LD Score regression with inefficient regression weights, which is equal to one in expectation, but with noise.

4.6 Weighted Block Jackknife Genetic Correlation

This section describes the inner workings of the `--sumstats-gencor` flag in **ldsc**.

Genetic correlation is defined as a ratio of quantities:

$$r_g := \frac{\rho_g}{\sqrt{h_1^2 h_2^2}}.$$

Instead of the naive estimator of this ratio,

$$\hat{r}_g := \frac{\hat{\rho}_g}{\sqrt{\hat{h}_1^2 \hat{h}_2^2}},$$

we use the weighted block jackknife estimator [5] of the ratio, with the jackknife taken over blocks of adjacent SNPs

$$\hat{r}_{g,jack} := n_b \hat{r}_g - \sum_{i=1}^{n_b} \left(1 - \frac{m_i}{M_g}\right) \hat{r}_{g,i} \quad (4.3)$$

where n_b is the number of blocks, and $\hat{r}_{g,i}$ is the naive estimate of genetic correlation obtained by deleting the i^{th} block of SNPs, m_i is the number of SNPs in block i , and M_g is the number of SNPs included in the regression. The weighted block jackknife ratio estimator is less biased than the naive estimate (though this is not so important at our sample sizes), and comes with a convenient nonparametric variance estimator [5],

$$\widehat{\text{Var}}[\hat{r}_{g,jack}] := \frac{1}{n_b} \sum_{i=1}^{n_b} \frac{1}{h_i - 1} \left((h_i - n_b) \hat{r}_g - (h_i - 1) \hat{r}_{g,i} + \sum_{j=1}^{n_b} \left(1 - \frac{m_i}{M_g} \hat{r}_{g,j}\right) \right), \quad (4.4)$$

where $h_i := M_g/m_i$. Weighted block jackknife standard errors (over blocks of adjacent SNPs) are robust to the correlated error structure of GWAS χ^2 -statistics, so long as the block size exceeds the typical range of LD. See references [4, 11, 17] for examples of papers in the statistical and population genetics literature that use this technique. We checked the reliability of our standard errors via

simulations with real genotypes (Supplementary Table 6.6), and found that the `ldsc` default setting of 2000 blocks genome-wide (which can be adjusted with the `--num-blocks` flag) gives standard error estimates that agree well with the empirical standard deviation across simulation replicates.

In another set of simulations with much lower power (not shown), we observed that the LD Score regression genetic correlation estimates became unstable when either sample size or heritability was so low that at least one of the two heritability estimates was not significantly different from zero. This is a general difficult with attempting to estimate a ratio where the denominator is close to zero, and is not specific to LD Score regression. As a rule of thumb, we recommend discarding (or at least being very cautious with) any genetic correlation estimates where either of the following conditions is met:

1. Either of the heritability estimates is less than 2 SE's from zero, or
2. The block jackknife SE for the genetic correlation estimate is greater than 0.2.

4.7 GWAS Data

4.7.1 Minimum Viable Summary Statistics

The minimum summary data required for estimating genetic correlation with LD Score regression are the following:

1. Genome-wide summary statistics from cohorts with similar ancestry
2. The summary statistics must be *signed* (allele and direction of effect)
3. The summary statistics should *never* be “corrected” via genomic control (GC) correction. Using GC’ed summary statistics will result in downward bias in the LD Score regression estimates of heritability and genetic covariance, and deflated LD Score regression intercepts, though the genetic correlation estimates will be fine.
4. The summary statistics must not be meta-analyzed with targeted genotyping at significant loci (*e.g.*, specialty genotyping arrays like immunochip, exome chip, psychchip, metabochip, or replication cohorts)

The next details are nice to have, but are only used for filtering SNPs:

1. A measure of imputation quality (*e.g.*, INFO) for each SNP
2. Sample size at each SNP (for binary traits, number of cases and number of controls)
3. Sample MAF

If these data are not available, we recommend retaining only HapMap 3 SNPs with reference panel MAF above 5% for the LD Score regression as a workaround (note: for *regression*, not for estimation of the LD Scores), since HapMap3 SNPs seem to be well-imputed in most studies.

4.7.2 Huge Effect Loci

Though the derivation of LD Score regression makes no distributional assumptions about effect sizes, the LD Score regression standard error can become very large if effect sizes are drawn from a highly kurtotic distribution, *i.e.*, if there are huge-effect loci. The `ldsc` default is to remove a window around SNPs with $\chi^2 > 0.01N$ (this can be disabled with the `--no-filter-chisq` flag).

4.7.3 IGAP

IGAP (which provided the summary statistics for Alzheimer’s disease) requests that we include the following text in our methods section:

International Genomics of Alzheimer’s Project (IGAP) is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7,055,881 single nucleotide polymorphisms (SNPs) to meta-analyze four previously-published GWAS datasets consisting of 17,008 Alzheimer’s disease cases and 37,154 controls (The European Alzheimer’s disease Initiative, EADI; the Alzheimer Disease Genetics Consortium, ADGC; The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium, CHARGE; The Genetic and Environmental Risk in AD consortium, GERAD). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer’s disease cases and 11,312 controls. Finally, a meta-analysis was performed combining results from stages 1 and 2.

Note that we only used stage 1 data for LD Score regression.

5 URLs

1. ldsc software:
`github.com/bulik/ldsc`
2. LD block genotype simulation code:
`github.com/bulik/ldsc-sim`
3. This paper:
`github.com/bulik/gencor-text`
4. PGC (psychiatric) summary statistics:
`www.med.unc.edu/pgc/downloads`
5. GIANT (anthropometric) summary statistics:
`www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files`
6. MAGIC (insulin, glucose) summary statistics:
`www.magicinvestigators.org/downloads/`
7. CARDIoGRAM (coronary artery disease) summary statistics:
`www.cardiogramplusc4d.org`
8. DIAGRAM (T2D) summary statistics:
`www.diagram-consortium.org`
9. Rheumatoid Arthritis summary statistics:
`www.broadinstitute.org/ftp/pub/rheumatoid_arthritis/Stahl_etal_2010NG/`
10. IGAP (Alzheimers) summary statistics:
`www.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php`
11. IIBDGC (inflammatory bowel disease) summary statistics:
`www.ibdgenetics.org/downloads.html`
Note that we used a newer version of these data with 1000 Genomes imputation.
12. Plasma Lipid summary statistics:
`www.broadinstitute.org/mpg/pubs/lipids2010/`
13. Beans:
`www.barismo.com`
`www.bluebottlecoffee.com`

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Data on glycaemic traits have been contributed by MAGIC investigators and have been downloaded from www.magicinvestigators.org.

Data on coronary artery disease / myocardial infarction have been contributed by CARDIOGRAMplusC4D investigators and have been downloaded from www.CARDIOGRAMPLUSC4D.ORG

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7 Author Contributions

The caffeine molecule is responsible for everything that is good about this manuscript. BBS and HKF are probably responsible for the other bits. All authors revised and approved the final manuscript.

8 Competing Financial Interests

Unfortunately, we have no financial conflicts of interest to declare.

9 References

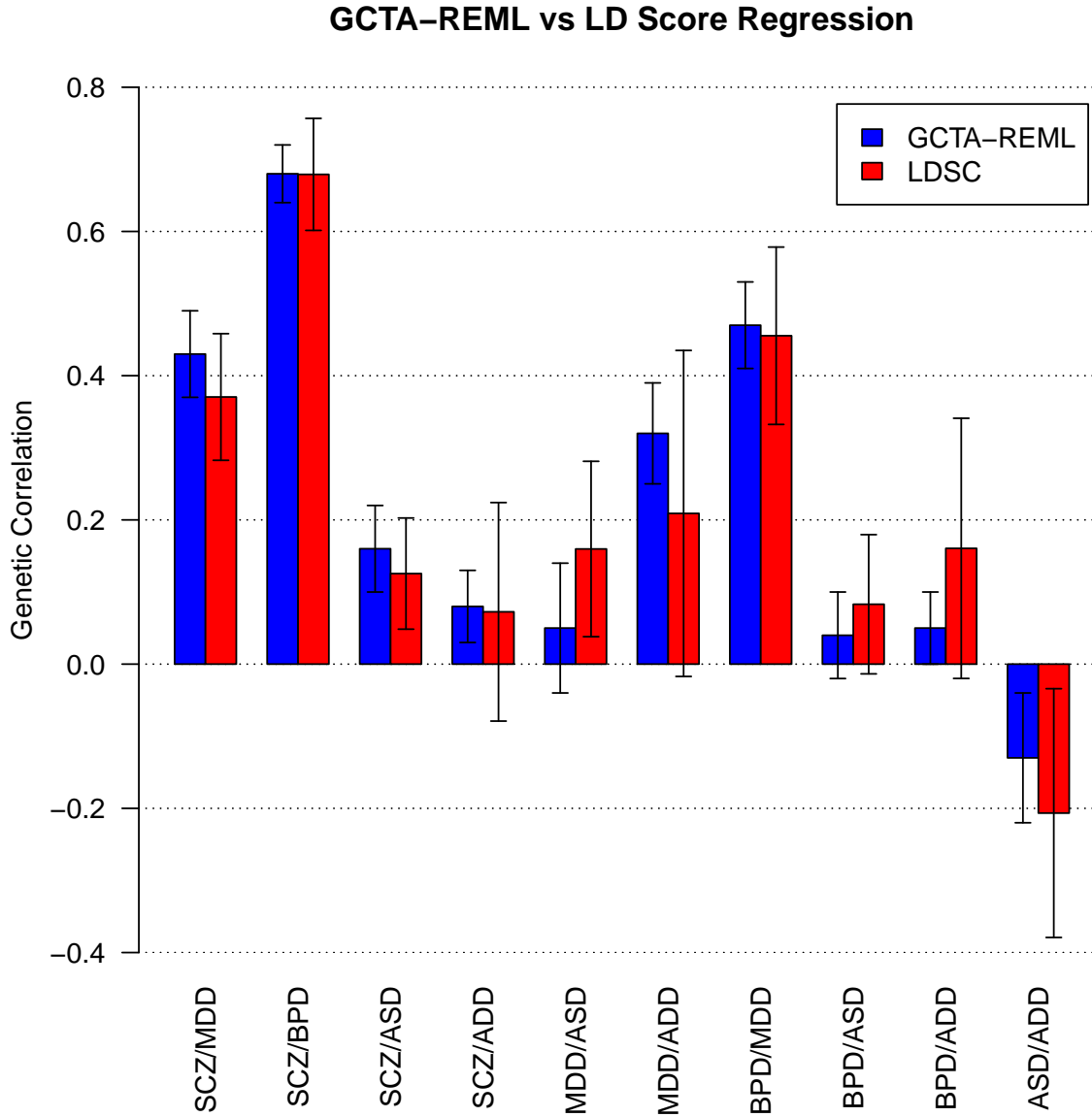
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Figure 1: Replication of PGC Cross Disorder Results



This plot compares LD Score regression estimates of genetic correlation using the summary statistics from [21] (which were generated from approximately the same data as [20]). The horizontal axis indicates pairs of phenotypes, and the vertical axis indicates genetic correlation. The red bars are the LD Score regression estimates, the blue bars are the GCTA-REML estimates from [20], and the black lines indicate one standard error. For this plot, we used a HapMap3 LD Score (Online Methods), since this more closely corresponds to the model fit by GCTA-REML (which only models the effects of genotyped SNPs). This plot should be interpreted as a technical sanity check. The estimates of genetic correlation between psychiatric phenotypes presented under the header "Application to a Large Set of Publicly Available Summary Statistics" use larger sample sizes and rely on fewer assumptions about genetic architecture, and so are more robust.