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Online supplement

To investigate whether the larger estimate of effect size (R^2) from the schizophrenia analysis (compared with the bipolar disorder analysis) is an artefact of power from a larger discovery sample, we repeated our analysis using as discovery data the results data from the International Schizophrenia Consortium (ISC).[6] The ISC data comprises 3322 European individuals with schizophrenia and 3587 controls, and forms part of the Psychiatric Genome-wide Association Study (GWAS) Consortium (PGC) of schizophrenia, and is therefore a less powerful discovery sample than the full PGC study. The number of single nucleotide polymorphisms (SNPs) that overlapped with our attention-deficit hyperactivity disorder (ADHD) study was much reduced, so for direct comparison with results from the PGC schizophrenia data, a set of SNPs was identified that were present in both the PGC study of schizophrenia and the ISC. Results are shown in Table DS1 and, along with the results in Table 1, indicate that (1) the inclusion of more SNPs in the analysis provides for a more significant analysis of the data, and (2) the inclusion of larger discovery samples increase the power for detecting a difference between ADHD and controls. We also found that using the ISC data as the discovery sample (fewer individuals and SNPs), larger estimates of R^2 were obtained than that found when employing the PGC study of bipolar disorder as the discovery sample. Therefore the discovery sample size is not a major factor driving the lower effect sizes seen here with bipolar disorder score alleles.

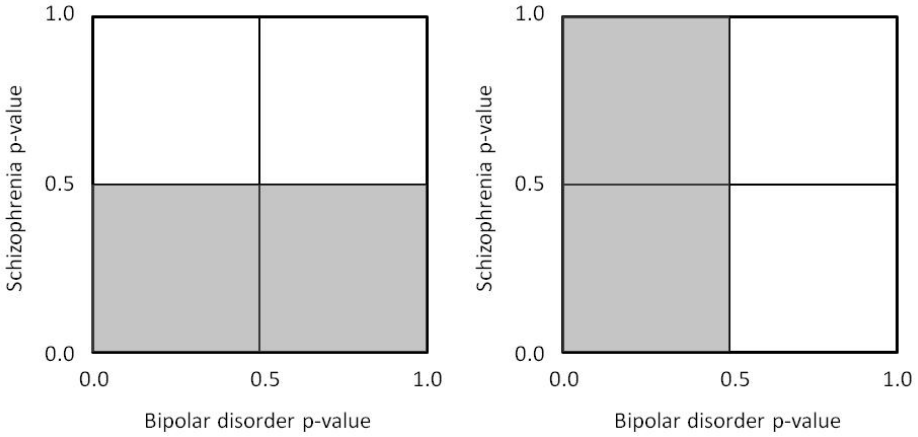
Table DS1 Summary of results in the target sample, comparing ADHD cases *v*. controls for a smaller set of SNPs available also in the ISC sample

Discovery sample	SNP selection criteria	SNPs	ADHD *v*. controls		
		n	*z*-statistic	R^2 %	*p*
ISC	ISC *P*<0.5	15,470	2.22	0.15	0.0264
ISC	SNPs in PGC SZ and ISC, ISC *P*<0.5	14,532	1.97	0.12	0.0490
PGC SZ	SNPs in PGC SZ and ISC, PGC SZ *P*<0.5	15,085	2.91	0.26	0.00357

ADHD, attention-deficit hyperactivity disorder; SNP, single nucleotide polymorphism; ISC, International Schizophrenia Consortium; PGC SZ, Psychiatric GWAS Consortium study of schizophrenia.

In all analyses, the ADHD cases had more risk alleles than the controls. All *z*-statistics are distributed with one degree of freedom and all *P*-values are two-tailed.

A B



C D

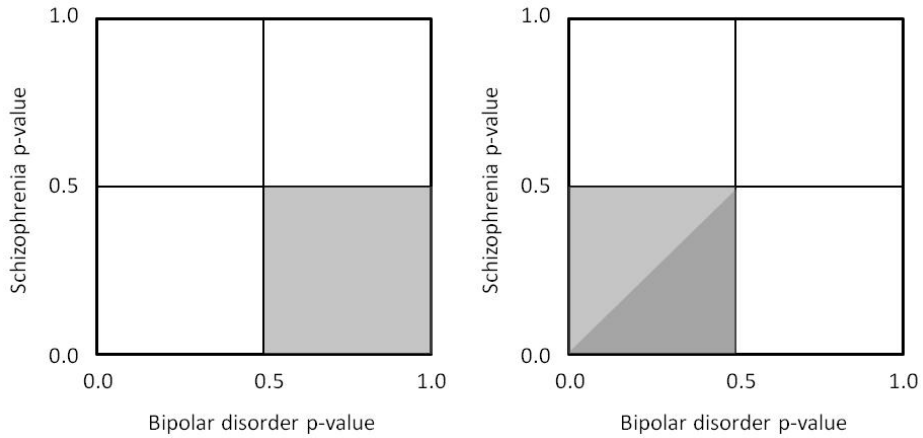


Fig. DS1 Diagram of single nucleotide polymorphism (SNP) selection for polygenic score analysis.

Single nucleotide polymorphisms are selected (in regions shaded grey) if they are associated at the following levels of significance: (A) schizophrenia *v*. controls $P<0.5$; (B) bipolar disorder *v*. controls $P<0.5$; (C) schizophrenia *v*. controls $P<0.5$ and bipolar disorder *v*. controls $P\geq0.5$; (D) schizophrenia *v*. controls $P<0.5$ and bipolar disorder *v*. controls $P<0.5$ (total region shaded). The SNPs selected in (D) are further divided according to whether the alleles associated with schizophrenia and bipolar disorder were (1) the same (light grey), or (2) different (dark grey). The diagram is designed to enable visual interpretation of the SNP selection. In reality, the cell sizes vary. Note that not every SNP is available for analysis in each of the three samples: attention-deficit hyperactivity disorder, schizophrenia and bipolar disorder.

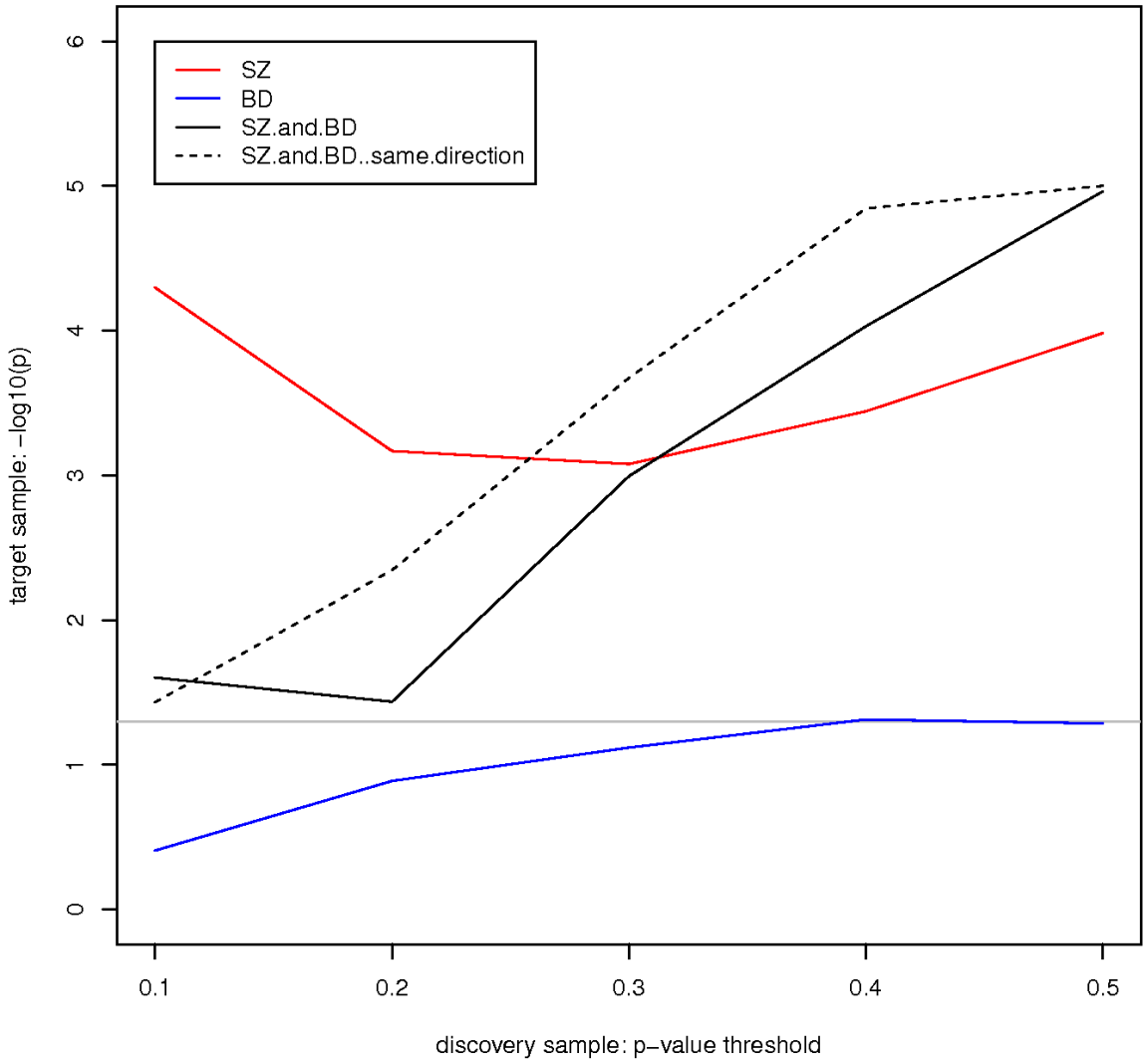


Fig. DS2 Results from polygenic score analysis of attention-deficit hyperactivity disorder (ADHD) *v*. controls, using a range of *P*-value inclusion thresholds.

Those findings that were significant in Table 1 are presented using different significance thresholds, namely 0.1, 0.2, 0.3, 0.4 and 0.5. Note that for analyses that involve the joint distribution of schizophrenia (SZ) and bipolar disorder (BD) data, the same threshold is applied to both the schizophrenia and bipolar disorder data. Consistent with the findings of the International Schizophrenia Consortium, $P<0.5$ gives most evidence for discrimination of ADHD cases from controls. The horizontal grey line indicates a *P*-value of 0.05 when comparing ADHD *v*. controls.

Relationship between sample used in current analysis and that in analysis by Psychiatric Genomics Collaboration Cross Disorders Group

Large-scale, collaborative analyses of psychiatric GWAS data are being undertaken under the auspices of the Psychiatric Genomics Consortium (PGC; previously known as the Psychiatric GWAS Consortium), to which we refer within the main text of this manuscript. This includes analyses across phenotypes, which are being conducted by the Cross Disorders Group (CDG) of PGC, to which we refer within the main text of this manuscript. The PGC CDG analyses are not yet published.

With the exception of 196 attention-deficit hyperactivity (ADHD) cases, our ADHD and control samples were not included in the PGC sample and, so, the data in the current analysis are essentially independent (i.e. PGC is not analysing the same data).

Our ADHD sample reported in the current manuscript is of UK/Irish origin and ascertained and assessed using a consistent approach (i.e. clinically and genetically relatively homogeneous). The PGC CDG ADHD sample is a meta-analysis of various data sets collected by differing groups in differing countries, some of which have very different clinical populations of patients with ADHD from UK/Ireland. Thus, the PGC sample has the potential for greater clinical and genetic heterogeneity.

Further, we note that the PGC CDG analyses of the ADHD sample comprise many 'pseudo controls' constructed from parent–offspring trio data. It is known that estimates of heritability from case *v*. pseudo control analyses tend to underestimate the truth,[24] and this is also likely to influence estimates of genetic overlap with other traits. Our ADHD sample comprises unrelated cases and controls, whereas the PGC ADHD sample is largely family-based, so our sample is more likely to have power to show genetic overlap with schizophrenia and bipolar disorder.

Additional reference

24 Klei L, Sanders SJ, Murtha MT, Hus V, Lowe JK, Willsey AJ, et al. Common genetic variants, acting additively, are a major source of risk for autism. *Mol Autism* 2012; **3**: 9.