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## **The Relationship Between Common Variant Schizophrenia Liability and Number of Offspring in the UK Biobank. Comment on Escott-Price et al.**

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### **To the editor:**

Escott-Price and colleagues report an association between genetic liability for schizophrenia and number of children in UK Biobank. They interpret this as consistent with sexual selection. However, the genetic data for UK Biobank was released in two waves (May 2015 and July 2017) (1). Escott-Price and colleagues used the most recent genome-wide association study for schizophrenia, but the reported sample size suggests that only data from the first wave of UK Biobank, comprising ~150,000 participants in total, was used (1). The first release of UK Biobank data was selected on the basis of smoking behaviour (2) and, as we have demonstrated elsewhere (3), this can yield biased estimates in analyses.

We investigated a similar question to Escott-Price and colleagues (4), using different but related methods. Initially, when using the first release of UK Biobank, we found results similar to those reported by Escott-Price and colleagues – a weak positive relationship between genetic liability for schizophrenia and number of children. However, given our concerns about conditioning on this sub-sample (with well-established associations between smoking and both schizophrenia risk and fertility) (5), we repeated our analyses in the full release. Strikingly, these results were quite different, with no clear evidence of a relationship between genetic liability for schizophrenia and number of children (4) The results for the two waves of UK Biobank data, and the full release, using our methods, are shown in Table 1.

Whether genetic risk for psychiatric disorders is associated with a reproductive advantage is an important question, as it may explain the persistence of these disorders despite deleterious effects. One possibility is that the discrepancy between our results and those of Escott-Price and colleagues is due to differences in the methodology we adopted. However, another is that the results reported by Escott-Price and colleagues are an artefact of conditioning on the first, selective, release of UK Biobank data, which could be tested by repeating their exact analysis strategy in the full data release.

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**Table 1. Estimates of the causal effect of genetic liability for schizophrenia on number of children using an inverse variance weighted Mendelian randomization approach.**

	N for outcome data	Number of Children <sup>b</sup> β (95% CI), p-value
<b>Genetic liability for schizophrenia <sup>a</sup></b>		
First release	90,058 to 94,792	0.012 (0.00003, 0.023), 0.05
Second release	228,863 to 240,966	-0.001 (-0.008, 0.006), 0.81
Full UK Biobank data	318,921 to 335,758	0.003 (-0.003, 0.009), 0.39

<sup>a</sup> Schizophrenia genetic data from the Psychiatric Genomics Consortium GWAS (N = 35,123 cases and 109,657 controls; 101 SNPs); <sup>b</sup> Results were multiplied by 0.693 to represent the estimate per doubling in odds of the exposure.