Data supplement for Hindley et al., Charting the Landscape of Genetic Overlap Between Mental Disorders and Related Traits Beyond Genetic Correlation. Am J Psychiatry (doi: 10.1176/appi.ajp.21101051)

CONTENTS

Supplementary Methods

Samples

It has previously been shown that, for methods based on GWAS summary statistics, statistical power depends on the product of SNP-based heritability (h^2_{SNP}) and sample size.[1] We therefore included mental disorder GWAS which had the equivalent statistical power of $n_{effective} > 100{,}000$ when $h^2_{SNP} > 0.06$ (i.e. $n_{effective} * h^2_{SNP} > 100{,}000 * 0.06$). This threshold was derived from simulations showing required sample sizes for robust MiXeR estimates (***Tables S2, S3***). We also excluded lifetime anxiety disorder[2] since this sample used self-reported diagnoses to define cases. Minimal phenotyping procedures have been shown to affect the genetic architecture of complex mental traits.[3] General intelligence, educational attainment, neuroticism and subjective well-being were selected as additional mental traits as they capture a range of different traits and well-powered GWAS for these traits were publicly available. These traits were not intended to represent an exhaustive list. For detailed descriptions of individual samples, please refer to ***Table S1*****.**

Prior to commencing analysis, we QCed all summary statistics. In addition to following the recommended QC steps for the respective consortia from which the data was accessed, we filtered all variants with MAF<0.05 and all variants within the MHC region (6:26000000-34000000) (see https://github.com/precimed/mixer)

Gaussian mixture models

Gaussian mixture models assume that a given dataset can be described as a "mixture" of pre-defined components, each with their own Gaussian (normal) distribution. After defining the mathematical framework of the model, the unknown features of interest for each component, or "model parameters", are estimated using maximum likelihood estimation. This procedure compares observed data with modelled data based on thousands of different potential values for the model parameters. The "likelihood" that the GWAS data is captured by each set of trialled parameters is estimated using a Bayesian statistical

framework, and the set of parameters with the greatest likelihood is identified, representing the model's best-fitting estimates. To test the reliability of the model parameters, model-fit is further quantified using the Akaike Information Criterion (AIC), which measures how much information is lost by the model compared to the observed data. Analogous to traditional "significance testing", the difference in AIC between a "reference" model and the best-fitting model is used as a test of how well the best-fitting model can be distinguished from the reference, with a positive AIC difference indicating that the best-fitting model can be distinguished from the reference. See ***Figure S1*** for a conceptual illustration of how gaussian mixture models are applied in MiXeR.

Bivariate causal mixture model

MiXeR first constructs a univariate mixture model for each phenotype. This assumes that the additive genetic effect of a given variant on a trait (β_j) can be modelled as a mixture of 1) non-causal and 2) causal effects, defined by the trait's polygenicity (π_1 – proportion of variants with causal effects) and discoverability (σ^2_β - variance of effect size per causal variant):

$$\beta_j \sim \pi_0 N(0,0) + \pi_1 N(0,\sigma^2_\beta)$$

The model parameters π_1 and σ^2_β are estimated using maximum likelihood estimation which identifies the "best-fitting" values from thousands of potential values by comparing model predictions to observed data. Since it is a function of a trait's polygenicity and discoverability, SNP-based heritability was estimated from univariate MiXeR model parameters using the following formula, in which H_{total} is the combined heterozygosity of all variants in the reference:

$$h^2_{SNP} = \pi_1 H_{total} \sigma^2_\beta$$

Polygenicity is further expressed as the number of causal variants with strongest effects required to explain 90% h^2_{snp}. A threshold of 90% is applied to prevent extrapolating model parameters into variants with infinitesimally small effects.

MiXeR is extended to a bivariate context by assuming that the additive genetic effect of a given variant on two traits (β_{1j},β_{2j}) can be described as a mixture of four components – 1) shared 'causal' effects, 2) unique 'causal' effects for trait 1, 3) unique 'causal' effects for trait 2 and 4) non-causal effects. Informed by the model parameters from univariate MiXeR (polygenicity and discoverability: π_1, σ^2_1 – trait 1; π_2, σ^2_2 – trait 2), bivariate MiXeR uses maximum likelihood estimation to estimate the polygenicity (π_{12}) and correlation of effect sizes (r_{gs}) for the shared component using the following formula, in which the covariance matrices Σ_1 and Σ_2 are defined by σ^2_1 and σ^2_2, and the covariance matrix Σ_{12} is defined by σ^2_1, σ^2_2 and r_{gs}:

$$(\beta_{1j},\beta_{2j}) \sim \pi_0 N(0,0) + \pi_1 N(0,\Sigma_1) + \pi_2 N(0,\Sigma_2) + \pi_{12} N(0,\Sigma_{12})$$

r_g is derived from these model parameters as follows:

$$r_g = r_{gs}\pi_{12}/\sqrt{(\pi_1 + \pi_{12})(\pi_2 + \pi_{12})}$$

AIC differences for bivariate MiXeR are calculated by comparing the best-fitting model to minimum possible overlap, constrained by r_g and maximum possible overlap, constrained by the polygenicity of the least polygenic trait.

Bayesian Information Criterion (BIC) is an alternative method for model selection.[4] However, BIC is a more conservative measure which has been shown to be overly stringent in scenarios of moderate statistical power. [4] We demonstrated that the AIC was a more appropriate test for the reliability of MiXeR estimates using simulations, showing that the BIC was overly conservative for scenarios of statistical power equivalent to ADHD, DEP and MDD (***Table S3***).

Each analysis comprised 20 iterations, with each iteration utilising 2 million randomly selected variants with MAF of at least 5%, followed by random pruning at an LD threshold of r^2=0.8. Estimates and SDs were computed from each set of 20 iterations.

In order to compute the genetic correlation of the shared component for ADHD and major depression under a scenario of maximum possible overlap we used the equation above, but replaced the values of $\pi 1, \pi 2$, and

$\pi 12$ with equivalent values for total possible overlap, i.e. 0 (unique-ADHD variants) , 8.9K (unique-MD variants), and 5.6K (shared variants).

Please note, MiXeR does not currently incorporate functional categories, gene set enrichments, or MAF- and LD-dependent genetic architectures. 'Causal' variants have been shown to be distributed non-randomly throughout the genome, with a higher density present in transcriptionally active regions and regions with lower levels of LD.[5,6] While this may affect the accuracy of absolute estimates, there is no evidence to suggest this affects the accuracy of the measures relatively, and so is unlikely to substantially affect bivariate measures. Future iterations of the MiXeR model will attempt to control for these additional features.

The current analysis is also restricted to common genetic variants. Large proportions of the broad-sense heritability of mental disorders are not explained by common variants and the heritability tagged by common variants may represent the effect of hidden rare variants. Consequently, the 'causal' variants quantified by MiXeR may not always represent variants underlying the direct 'causal' mechanism, rather variants which are associated with the phenotype beyond the confounding effect of LD.

Visualising parameter optimisation and evaluating model fit

Parameter optimization for the number of shared 'causal' variants π_{12} was visualised using log-likelihood plots, which plot the negative log-likelihood function (*y axis*) against the modelled number of shared causal variants (*x axis*). The predicted number of shared causal variants is represented as the lowest point (i.e. the lowest negative log-likelihood) on the log-likelihood curve (***Figure S1***). Minimum (constrained by genetic correlation between the two traits) and maximum possible overlap (constrained by the polygenicity of the least polygenic trait) were represented on the log-likelihood plots as the minimum and maximum values plotted along the x-axis (number of causal variants), which are used by the Akaike Information Criterion test as comparators against the estimated number of shared 'causal' variants after parameter optimisation. A positive AIC difference is represented by a clear descending curve from the minimum number of shared

causal variants to the lowest point and a clear ascending curve to the maximum number of shared causal variants (***Figure S1a***). A negative AIC difference may be due to an apparent convergence towards minimum or maximum overlap. This is observed in ***Figure S1b***, which converges towards maximum possible overlap, resulting in a positive AIC difference when comparing minimum overlap to modelled fit, but a negative AIC difference when compared to maximum overlap. This scenario can therefore be interpreted as evidence of extensive genetic overlap between the two traits, but greater power is required to improve the precision of the estimate given its proximity to complete genetic overlap. A negative AIC difference may also be observed for both minimum and maximum overlap, as in ***Figure 1c***. This indicates poor parameter optimisation, most likely due to the power of the analysis. The estimates should therefore be interpreted with caution.

Conditional QQ plots, a common method for visualising cross-trait enrichment of genetic associations between two traits, for both modelled and input data were also constructed (***Supplementary Methods*** and ***Figure S2***).[7] The proximity of the modelled QQ plots (dotted line) to observed QQ plots (solid lines) is a qualitative indicator of model fit (Figure 1A, panels 2-3).

LAVA local correlations

Genetic loci included in the bivariate analysis were filtered according to their local h^2_{SNP} using a significance threshold of $p<1e^{-4}$, consistent with LAVA's standard settings.[8]

MiXeR simulations to evaluate effect of GWAS statistical power on MiXeR model fit

We performed simulated MiXeR analyses at 4 levels of statistical power (h^2_{SNP}=0.06, 0.12, 0.24 and 0.48 with constant sample size of n=100,000 and constant polygenicity of pi=0.003), and 5 scenarios of genetic overlap (0, 0.25, 0.5, 0.75 and 1). Simulation settings were chosen to reflect the phenotypes included in the current analysis."

Supplementary Results

Univariate MiXeR

h^2_{SNP} possessed a similar but different trend to polygenicity. Schizophrenia (h^2_{SNP}=0.38, sd=0.0041) and ADHD possessed highest h^2_{SNP} (h^2_{SNP}=0.23, sd=0.0034), followed by BIP, intelligence and EDU (h^2_{SNP}=0.10-0.20). Neuroticism, SWB and MD had the lowest h^2_{snp} (h^2_{SNP}=0.05-0.10) (***Table S4***). Height had substantially higher h^2_{SNP} than mental traits (h^2_{SNP}=0.63, sd=0.0067). MiXeR estimates closely matched previously reported LDSC-based h^2_{SNP} (***Table S4)***.

Univariate MiXeR estimated the discoverability of each trait, defined as the average explained variance per causal variant (*heritability/polygenicity*) (***Table S4***). Given their low heritability and high polygenicity, major depression ($\sigma_2\beta$=7.40e^{-6}, s.d.=3.20e^{-7}) and personality traits ($\sigma_2\beta$=1.31e^{-5}-6.24e^{-6}) were less discoverable than other mental disorders ($\sigma_2\beta$=3.37e^{-5}-6.31e^{-5}), general intelligence ($\sigma_2\beta$=2.62e^{-5}, s.d.=7.07e^{-7}) and educational attainment ($\sigma_2\beta$=1.40e^{-5}, s.d.=2.81e^{-7}). In contrast, height's high heritability and low polygenicity meant that it was an order of magnitude more discoverable ($\sigma_2\beta$=2.39e^{-4}, s.d.=5.51e^{-6}).

Power analysis revealed large differences in the statistical power of the current GWASs. Given its high discoverability and large sample size, height was the only GWAS sufficiently powered to explain over 50% of its h^2_{SNP} at genome-wide significance, and a sample size of 3 million was predicted to explain 90% heritability. In contrast, all mental disorders and traits currently explained less than 10% h^2_{SNP} and were estimated to require effective sample sizes of over 10 million participants to explain 90% heritability. Due to their low discoverability, major depression and personality traits required sample sizes of greater than 60 million to discover 90% h^2_{SNP} (***Table S4***; ***Figure S2***).

All univariate AIC differences were positive, indicating that the "causal mixture" model was a substantially better fit to the data than an infinitesimal model (AIC=2.22-12486.61).

Mental disorders by cognitive and personality traits

Schizophrenia and BIP displayed divergent patterns of genetic correlations with intelligence and EDU despite their highly similar genetic architectures, in line with previous reports.[9] Intelligence was more strongly negatively correlated with schizophrenia (r_g=-0.24, sd=0.005) compared to BIP (r_g=-0.09, sd=0.009) while EDU was more strongly positively correlated with BIP (r_g=0.12, sd=0.008) than with schizophrenia (r_g=0.02, sd=0.007). In contrast, MD was negatively correlated with both EDU (r_g=-0.12, sd=0.007) and intelligence (r_g=-0.04, sd=0.024). Genetic correlation of shared variants closely matched genome-wide genetic correlations for schizophrenia, BIP and MD. However, given ADHD's lower polygenicity compared to cognitive traits, 'causal' variants shared between ADHD and each of intelligence and EDU were more strongly negatively correlated (r_{gs}=-0.60, sd=0.03; r_{gs}=-0.88, sd=0.04, respectively) than corresponding genome-wide genetic correlations (r_g=-0.42, sd=0.012; r_g=0.57, sd=0.007, respectively).

LAVA results also showed prominent mixed effect directions between BIP, SCZ, MD and cognitive traits. Consistent with genetic correlations, there were fewer positively correlated loci for SCZ and intelligence (17/43, 40%) than BIP and intelligence (17/32, 53%), while there were more positively correlated loci for BIP and EDU (38/51, 75%) than for SCZ (42/70, 58%). MD and intelligence proportions were also consistent with MiXeR genetic correlations, with 17/44 positively correlated (39%). There was a predominance of positively correlated loci between MD and EDU (17/30, 57%), somewhat divergent from negative genetic correlations. Interestingly, we saw a similar pattern of a high proportion of negative local genetic correlation between ADHD and intelligence (0/1, 0%) and educational attainment (1/11, 9%), consistent with MiXeR genetic correlation of shared variants.

Among mental disorders and personality traits, MD and neuroticism shared the strongest genetic correlation (r_g=0.68, sd=0.006) but displayed the largest number of unique variants. There were 2.4K (sd=0.5K) unique neuroticism variants and 4.7K (sd=0.7K) unique MD variants. Accordingly, there was a marked difference between genome-wide genetic correlation (r_g=0.68, sd=0.006) and genetic correlation of shared variants

(r_{gs}=0.92, sd=0.04). MD was strongly negatively correlated with SWB (r_g=-0.65, sd=0.008) but since there was almost complete genetic overlap, the genetic correlation of shared variants was comparable (r_{gs}=-0.75, sd=0.03). All other analyses displayed moderate genetic correlations and extensive genetic overlap, indicative of a predominance of mixed effect directions. This was illustrated by the proportion of shared 'causal' variants with concordant effects, which varied between 0.16 (sd=0.031) for ADHD and EDU and 0.88 (sd=0.037) for MD and neuroticism.

LAVA local correlations also showed a predominance of mixed effect directions between neuroticism and SCZ (31/45, 69%), BIP (15/25, 60%), and ADHD (4/6, 67%). Interestingly, there was a high proportion of loci with positive local genetic correlations between MD and NEUR, consistent with MiXeR estimates of the correlation of shared variants (55/58, 95%). There was less consistency between LAVA and MiXeR results for SWB. This is likely because there were few loci with significant local correlations due to the smaller sample size and lower heritability of SWB, including no significant loci with BIP. 0/11 had positive local correlations with SCZ (0%), 1/10 with MD (10%) and 1/2 with ADHD (50%).

Height by mental disorders

Since there were few shared variants, there were large differences between genome-wide genetic correlations and genetic correlations of shared variants. This was most pronounced for height and ADHD (r_g=-0.09; r_{gs}=-0.63). While this suggests that shared variants between these traits are highly correlated, the small number of shared variants (0.7K) represent a small proportion of explained variance for both traits and the precision of these estimates was low (***Table S8***).

MiXeR simulations to evaluate effect of GWAS statistical power on MiXeR model fit

We performed simulations to evaluate the effect of GWAS statistical power on MiXeR model fit (***Table S3***). These showed that MiXeR estimates were not reliable for GWAS with an equivalent statistical power of $n_{effective\_} \leq 100{,}000$ when $h^2_{SNP} \leq 0.06$ (i.e. $n_{effective} * h^2_{SNP} \leq 100{,}000 * 0.06$). The precision of MiXeR estimates improved as power increased, supported by positive AIC differences. This indicates that AIC

differences are sensitive to changes in statistical power and successfully differentiate good model fit from bad model fit.

Supplementary Discussion

The *p* factor and GenomicSEM

The extensive genetic overlaps observed among mental disorders may be consistent with the concept of the "*p* factor", the hypothesised "single dimension of psychopathology".[10,11] However, genetic variants associated with the *p* factor would be expected to display a consistent effect direction across included disorders. This is better addressed by methodologies such as GenomicSEM, which constructs a common genetic factor across multiple phenotypes using genome-wide genetic correlations. However, GenomicSEM is unable to identify shared genetic variants in the context of mixed effect directions. Since we aimed to chart genetic overlap beyond genome-wide genetic correlation and accounting for mixed effect directions, we applied MiXeR and LAVA.

Supplementary Figures

FIGURE S1. *How does MiXeR work? 'Causal' variants for a single trait are represented by red stars, null variants are represented by green circles, blue squares represent causal variants for a second trait and yellow triangles represent shared causal variants. Effect sizes are represented on the "y-axis". Venn diagrams: size of circles indicates polygenicity, colours illustrate genome-wide genetic correlation (r_g, unique regions of Venn diagrams) and correlation of shared variants (r_{gs}, shared region of Venn diagrams), numbers inside circles are estimated number of causal SNPs in 1000s. AIC = Akaike Information Criterion*

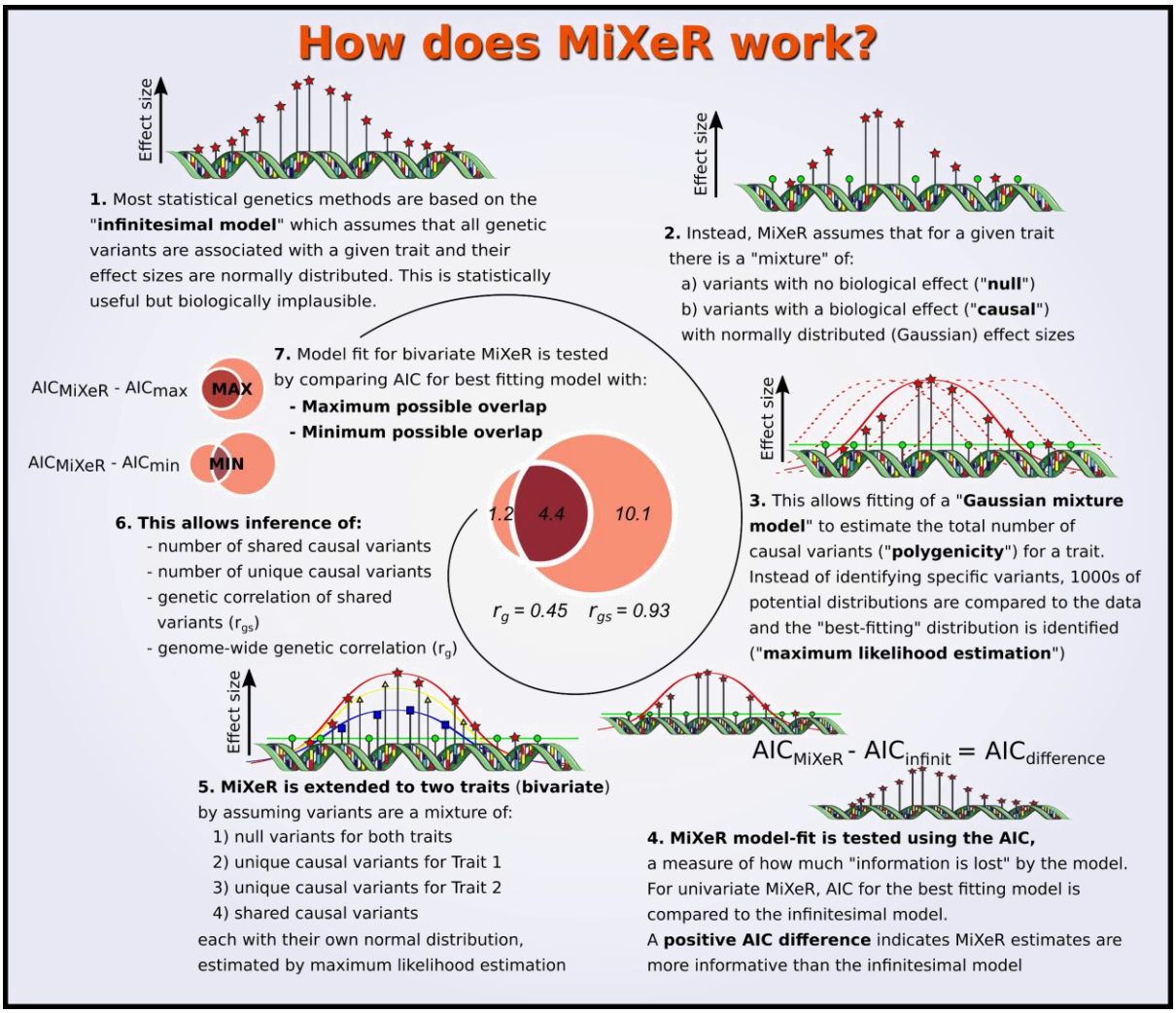


FIGURE S2. *Evaluating MiXeR model fit. MiXeR log-likelihood plots and conditional QQ plots for a. schizophrenia (SCZ) and height, b. SCZ and bipolar disorder (BIP) and c. BIP and autism spectrum disorder (ASD).* ***i.)*** *Log-likelihood plots plotting -log-likelihood (y-axis) against the modelled number of causal variants. The lowest point on the curve indicates the number of causal variants after parameter optimization. The minimum and maximum number of causal variants is represented by the minimum and maximum points along the x axis. The dotted lines represent each iteration of the analysis, and the solid line indicates the mean values across all 20 iterations. Note the y-axis scale differs across the 3 plots.* ***a.*** *Example of good model fit, with clear convergence of the log-likelihood function between the minimum and maximum possible overlap, supported by positive AIC differences when comparing modelled overlap versus minimum (AIC=19.18) and maximum overlap (AIC=147.86).* ***b.*** *Example of convergence towards maximum possible overlap. The AIC value was therefore positive when compared to minimum overlap (AIC=14.41), but not maximum overlap (AIC=-0.43).* ***c.*** *Example of poor model fit, with no clear convergence. The AIC was therefore negative for both minimum (AIC=-0.48) and maximum overlap (AIC=-0.67).* ***ii.*** *MiXeR modelled conditional QQ plots (dotted line) versus real-life conditional QQ plots (solid lines) for each pair of traits, visualising how accurately MiXeR model predictions map on to real-life data. Model fit is qualitatively assessed, with deteriorating model fit from a) to c).*

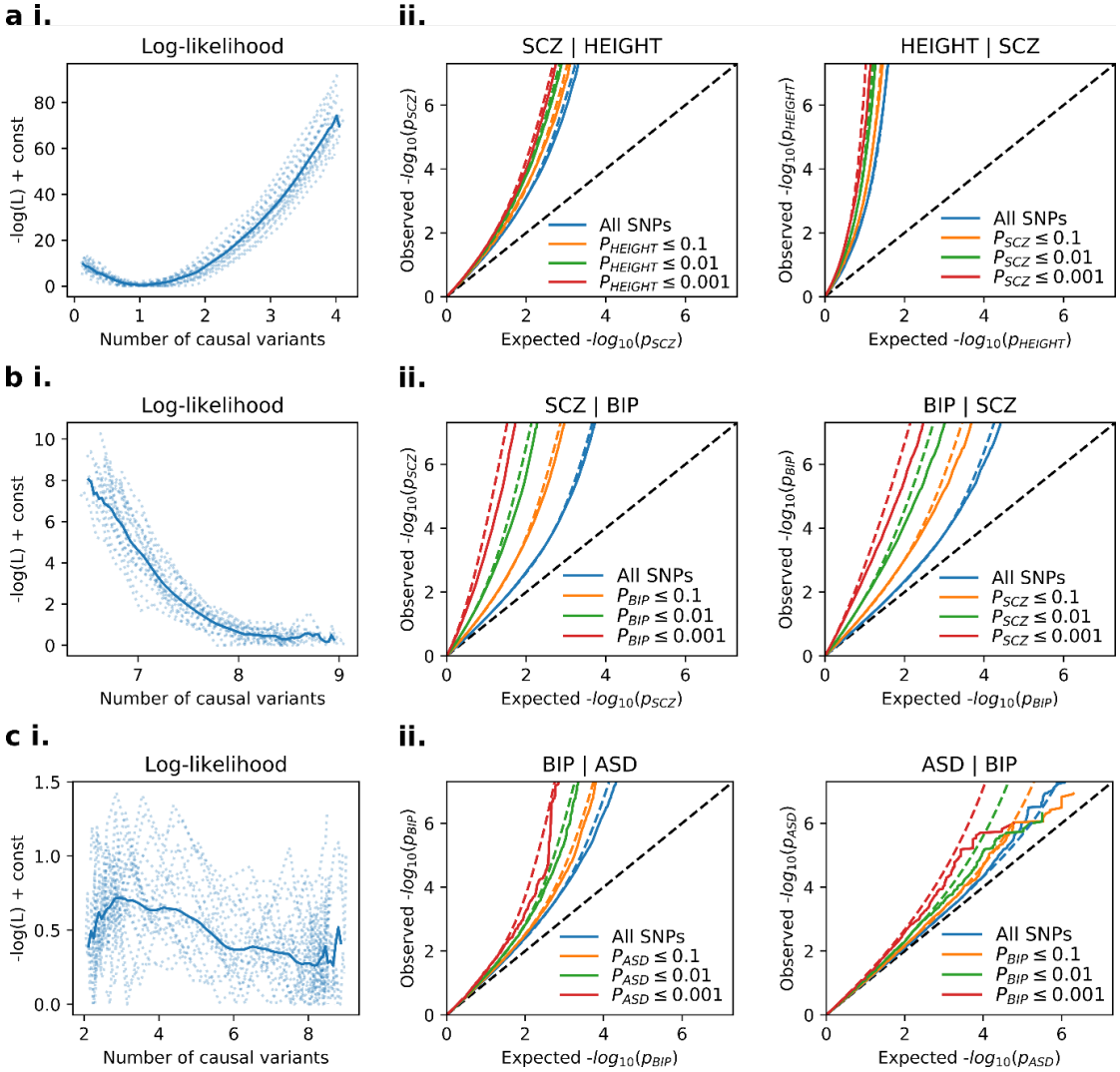


FIGURE S3. *Univariate MiXeR Power plots. The estimated variance explained by genome-wide significant SNPs (y axis) plotted against effective sample size. The explained variance at current n for input GWASs is represented by the star symbol. The sample size required to explain 90% variance is represented by the circle and marked by the dashed line.*

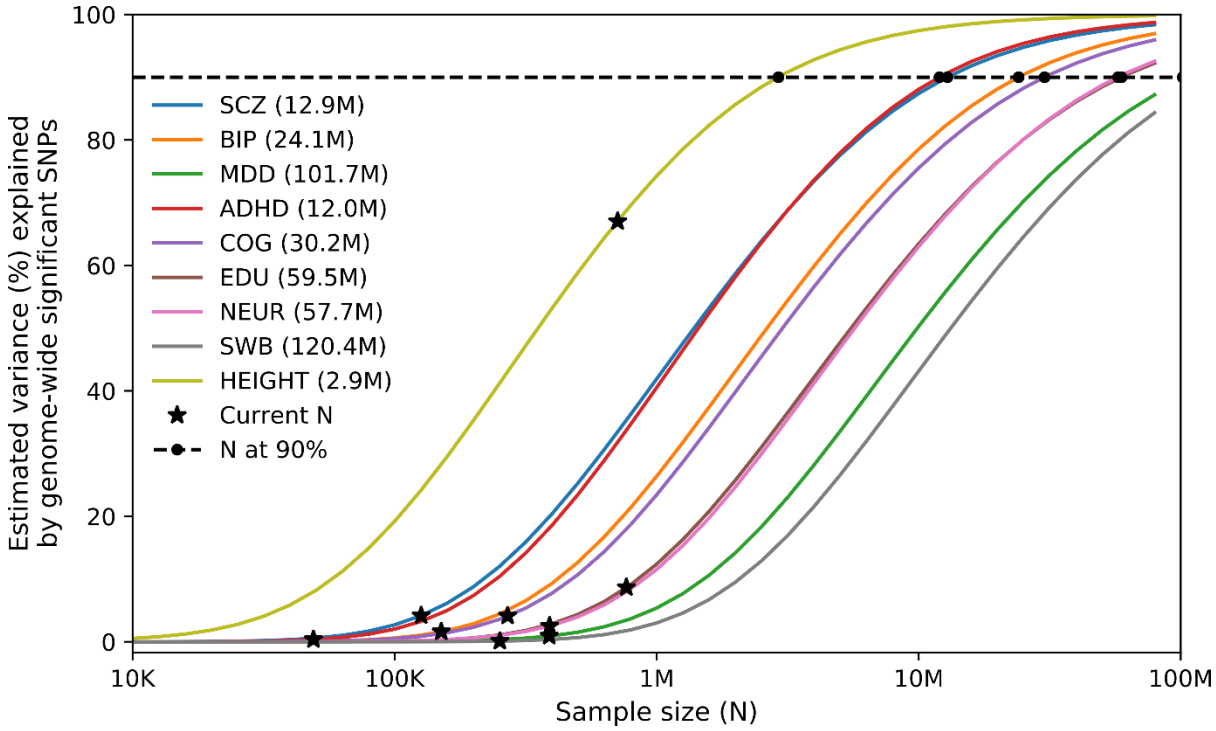


FIGURE S4. *Density plots illustrating the number of variants with a given effect size (β) for each disorder (x and y axes) as modelled by MiXeR, from no variants (dark blue) to 1000 variants (yellow). Unique causal variants for a given disorder are illustrated by the horizontal and vertical lines along each axis. Shared variants are illustrated by variants within the four quadrants (i.e. non-null for both traits). Positive correlations are indicated by a predominance of variants within the top right and bottom left quadrants, representing concordant effects on the two disorders, as opposed to variants in the top left and bottom right quadrants which represent discordant effects on the two disorders.*

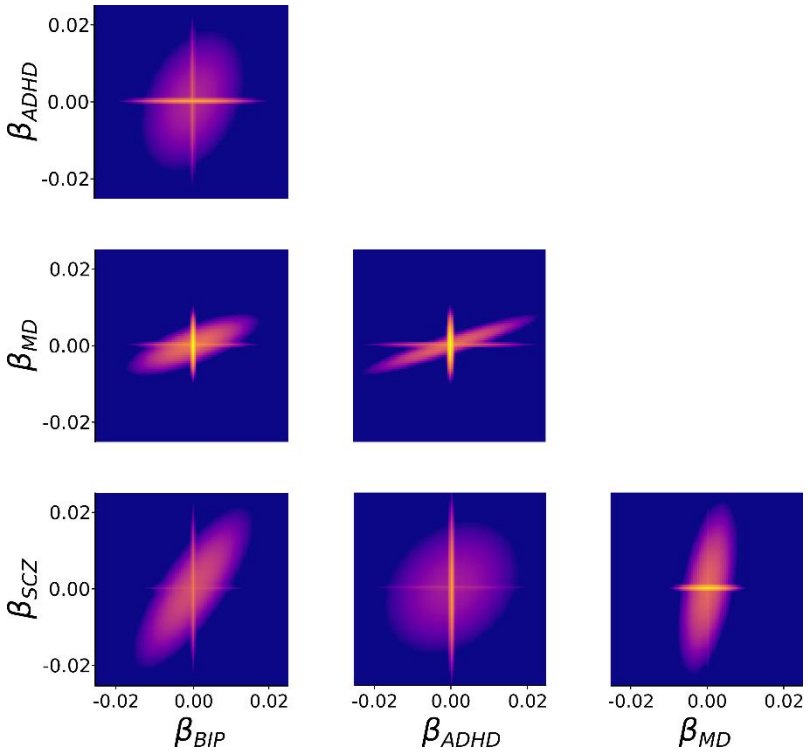
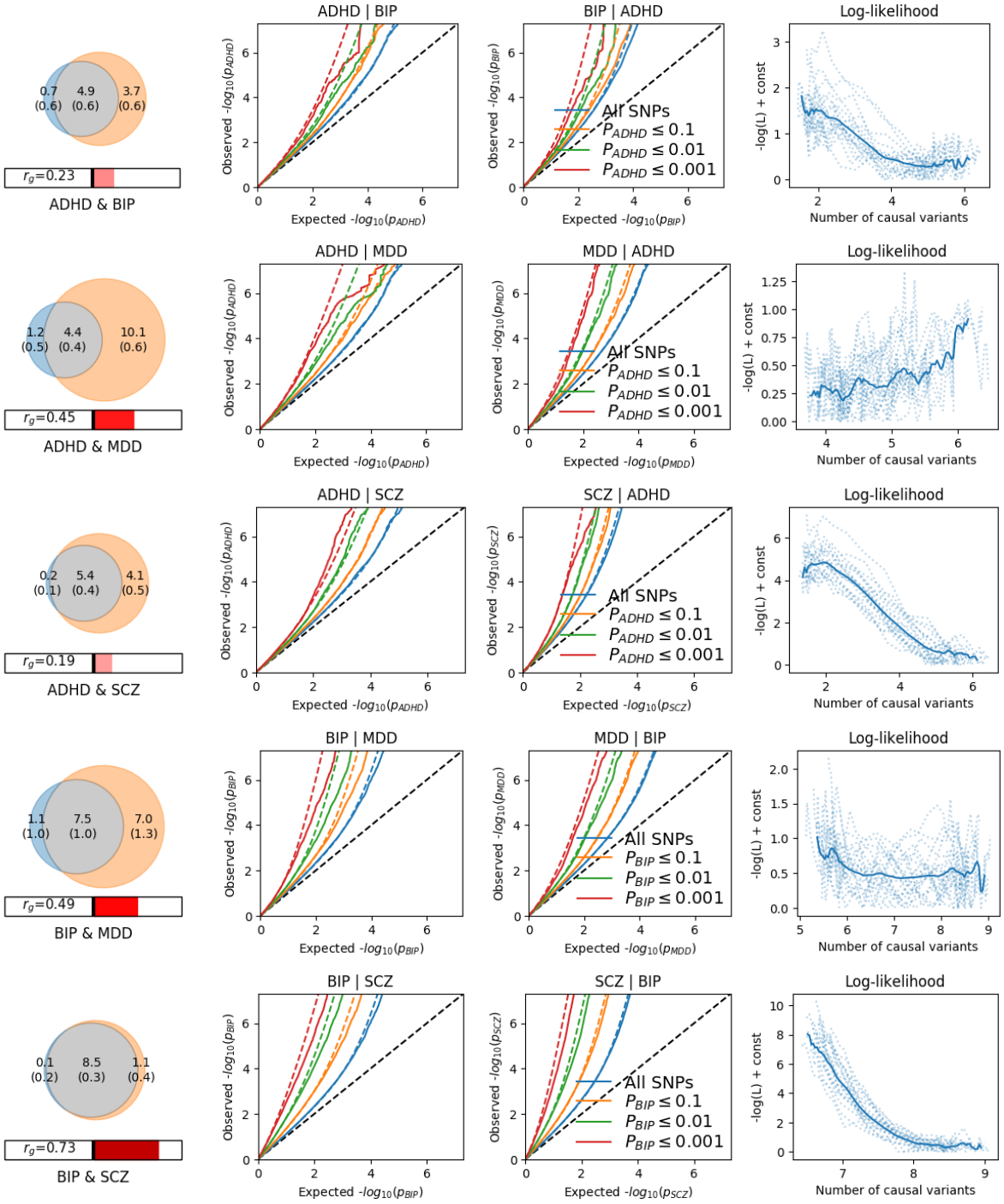
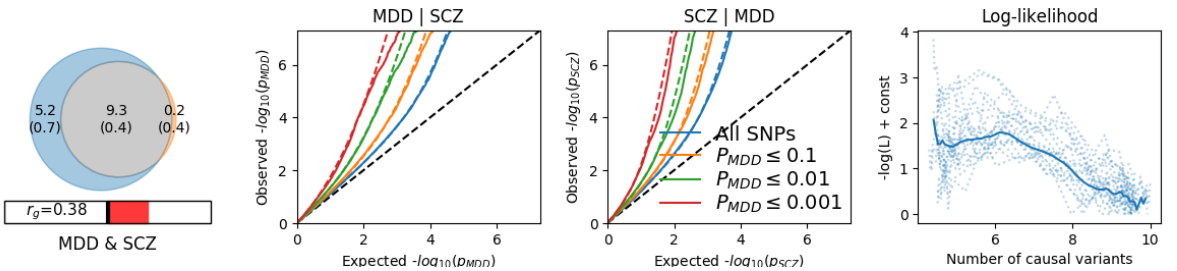


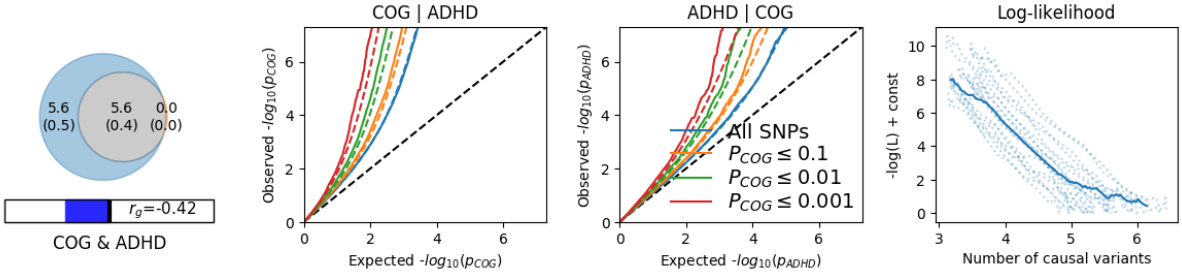
FIGURE S5. *Bivariate MiXeR conditional QQ plots showing real-life vs modelled cross trait enrichment and log-likelihood plots, plotting the adjusted negative log-likelihood function against the number of shared 'causal' variants, constrained to minimum and maximum possible overlap.* ***a.*** *Mental disorders by mental disorders;* ***b.*** *Mental disorders by cognitive traits;* ***c.*** *Mental disorders by personality traits;* ***d.*** *General intelligence by educational attainment;* ***e.*** *Neuroticism by subjective well-being;* ***f.*** *Cognitive traits by personality traits;* ***g.*** *Height by mental disorders/cognitive traits/personality traits.*

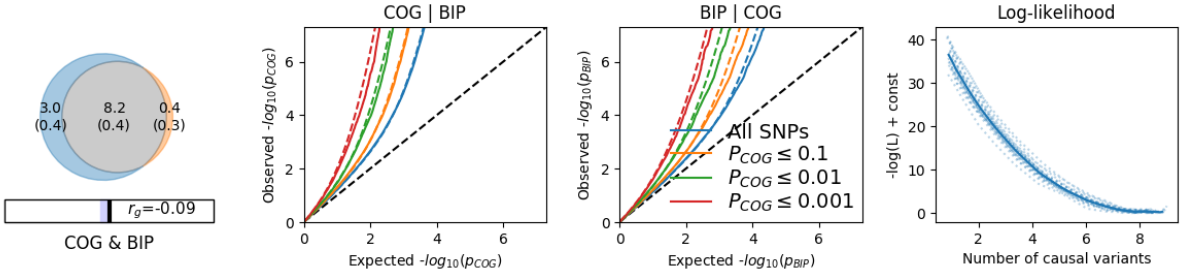
a. Mental disorder by mental disorder

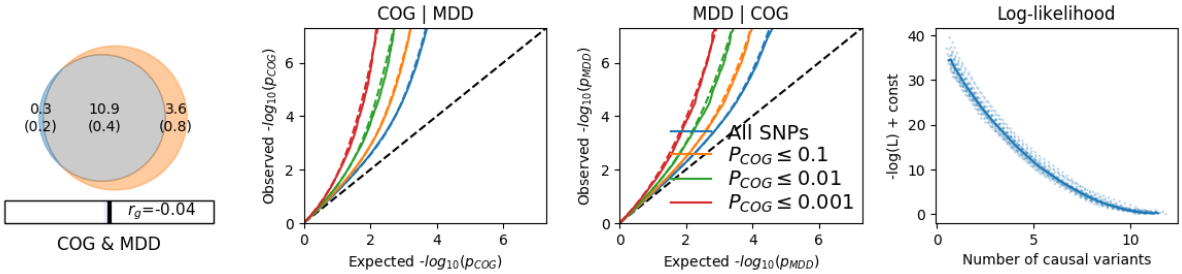


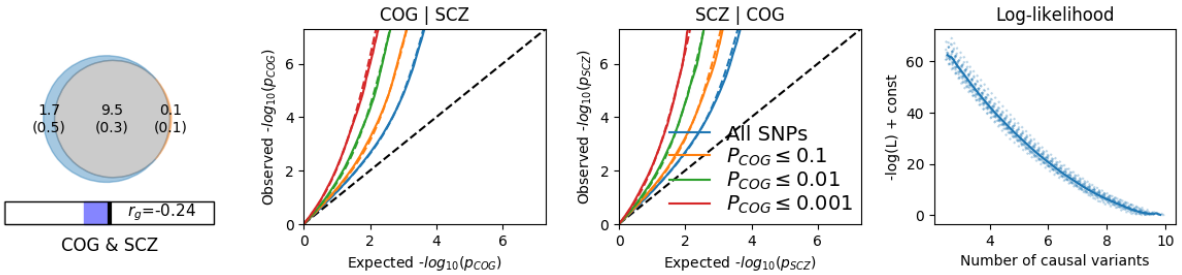


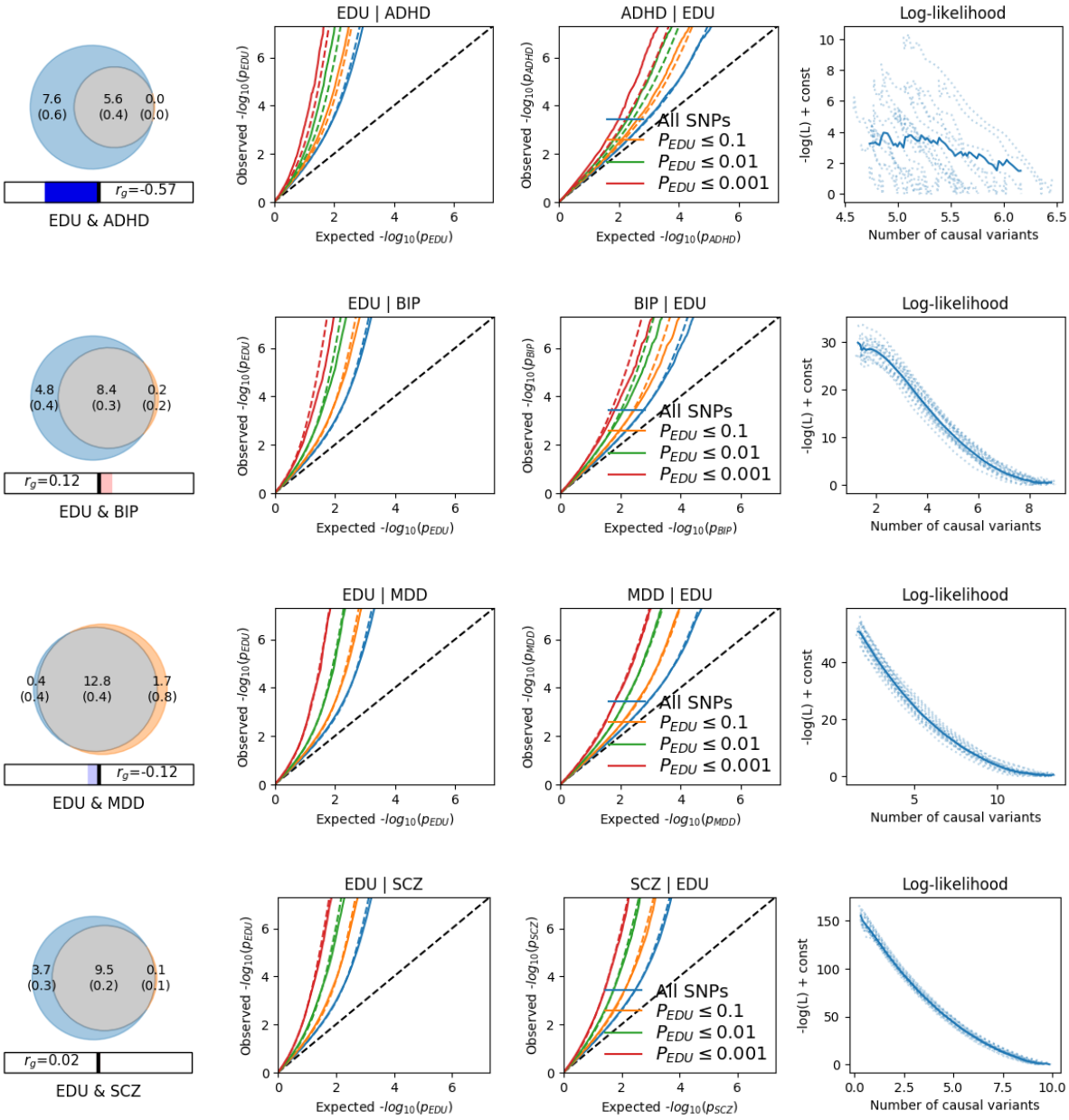
b. Mental disorder by cognitive traits



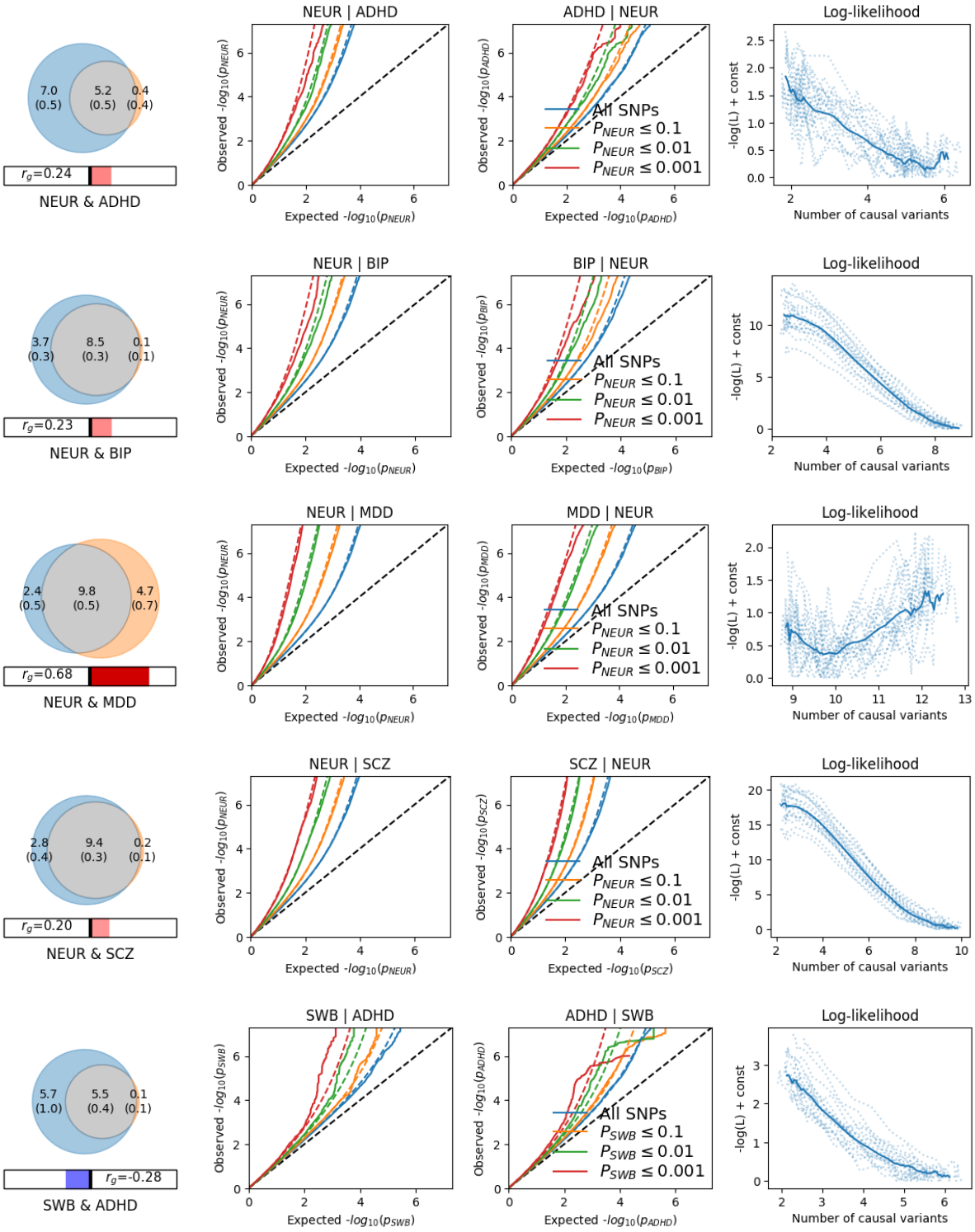


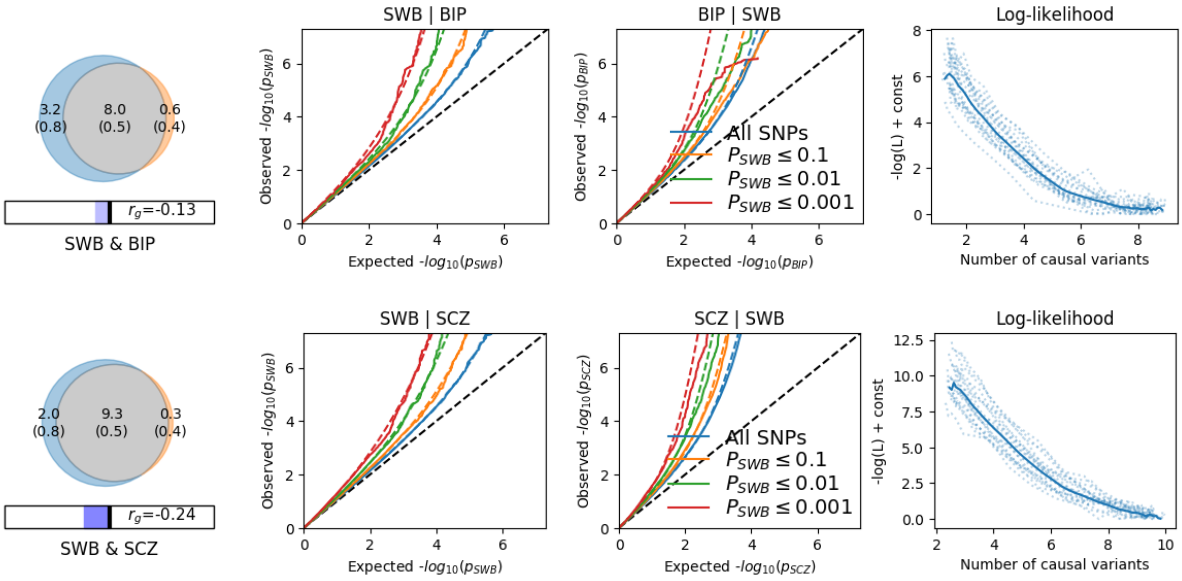




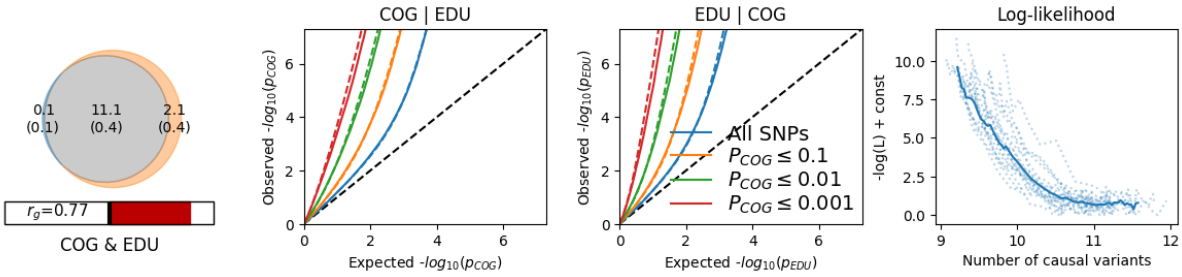

7.6
(0.6)
5.6
(0.4)
0.0
(0.0)
r_g=-0.57
EDU & ADHD
EDU | ADHD
ADHD | EDU
Log-likelihood
Observed -$log_{10}(p_{EDU})$
Expected -$log_{10}(p_{EDU})$
Observed -$log_{10}(p_{ADHD})$
Expected -$log_{10}(p_{ADHD})$
All SNPs
$P_{EDU} \leq 0.1$
$P_{EDU} \leq 0.01$
$P_{EDU} \leq 0.001$
-log(L) + const
Number of causal variants
4.8
(0.4)
8.4
(0.3)
0.2
(0.2)
r_g=0.12
EDU & BIP
EDU | BIP
BIP | EDU
Observed -$log_{10}(p_{BIP})$
Expected -$log_{10}(p_{BIP})$
0.4
(0.4)
12.8
(0.4)
1.7
(0.8)
r_g=-0.12
EDU & MDD
EDU | MDD
MDD | EDU
Observed -$log_{10}(p_{MDD})$
Expected -$log_{10}(p_{MDD})$
3.7
(0.3)
9.5
(0.2)
0.1
(0.1)
r_g=0.02
EDU & SCZ
EDU | SCZ
SCZ | EDU
Observed -$log_{10}(p_{SCZ})$
Expected -$log_{10}(p_{SCZ})$

c. Mental disorders by personality traits

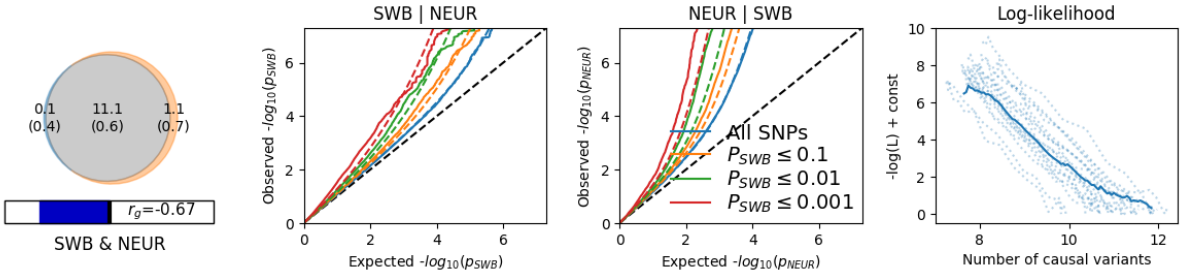




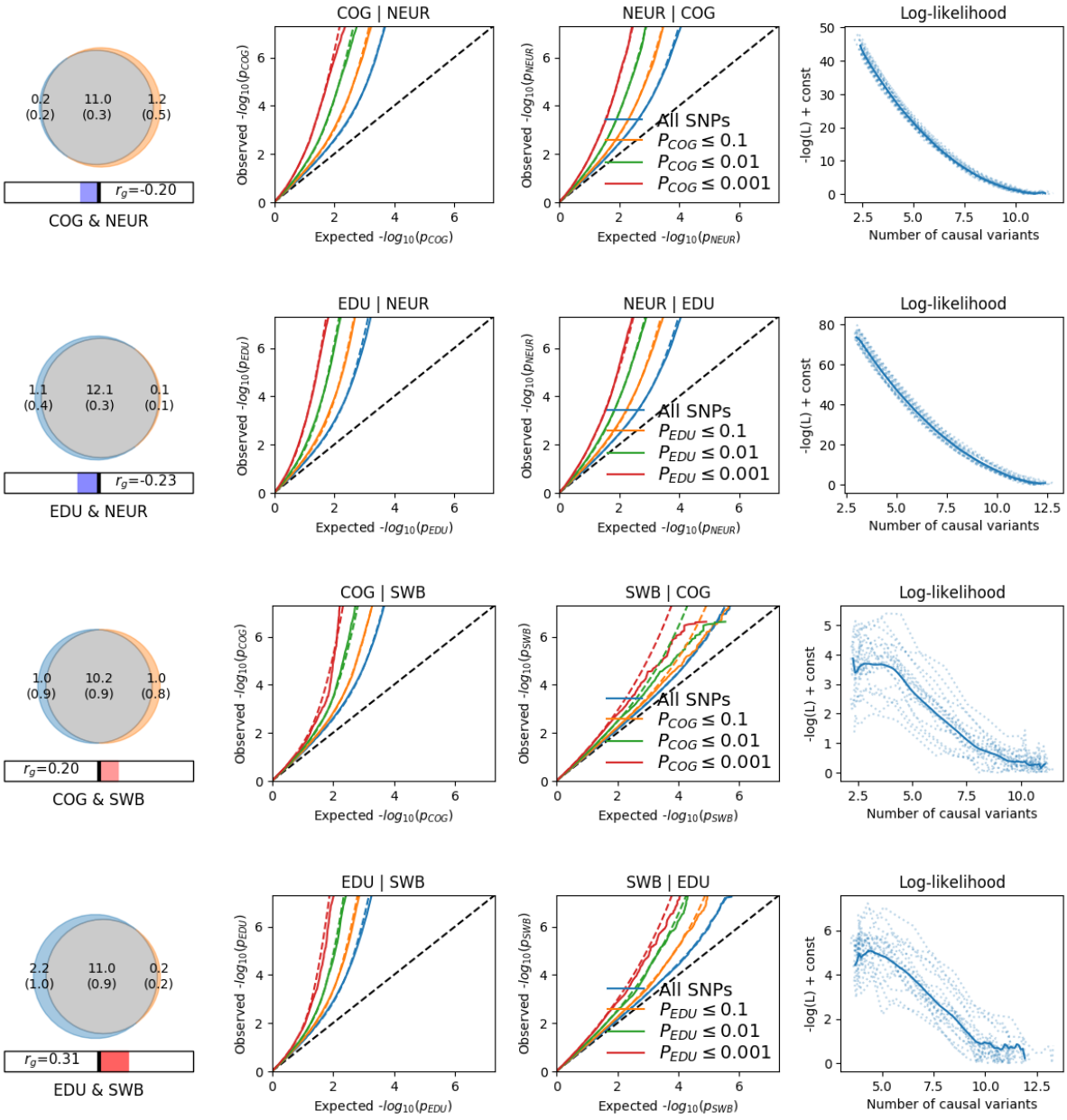
d. General intelligence by educational attainment



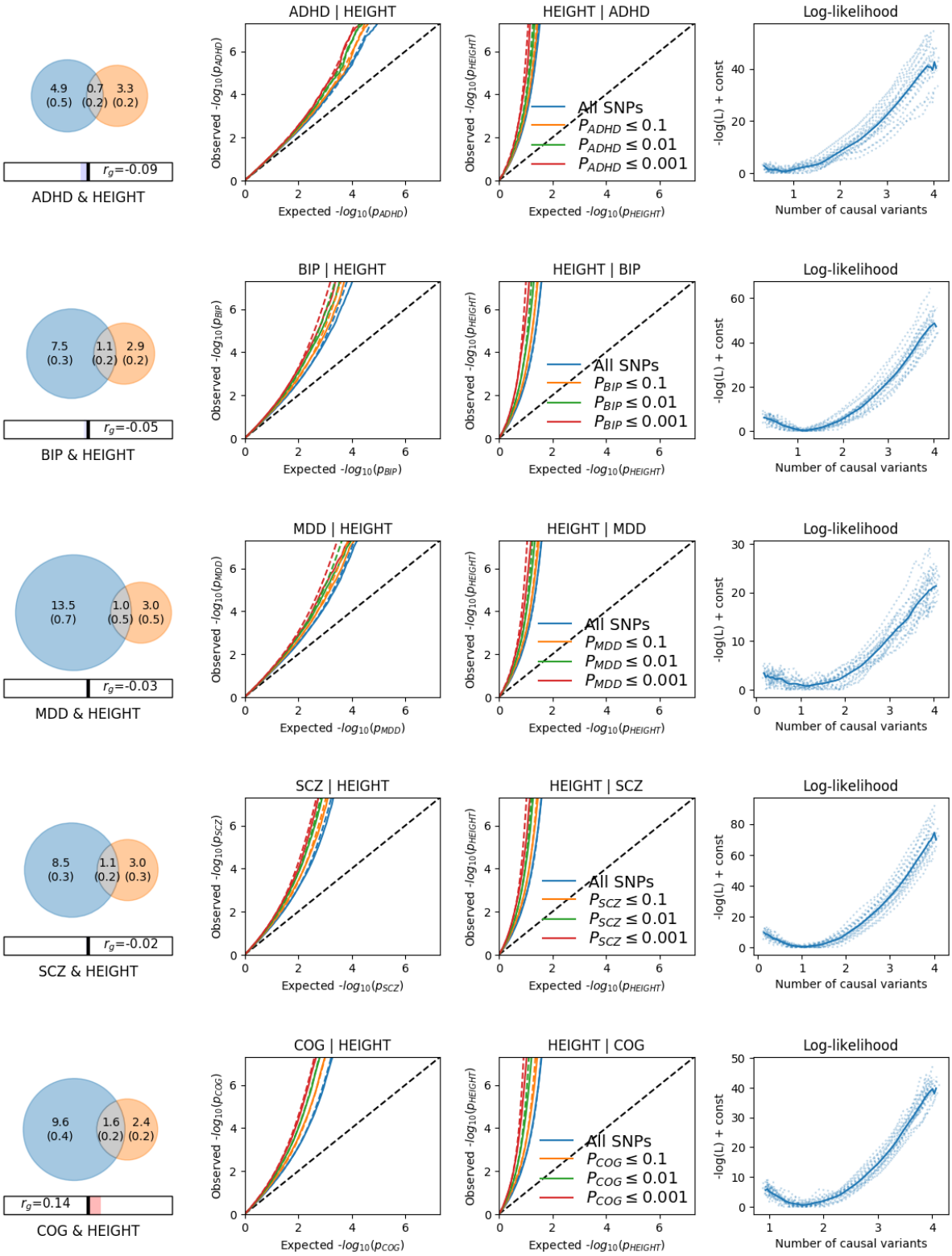
e. Subjective well-being by neuroticism

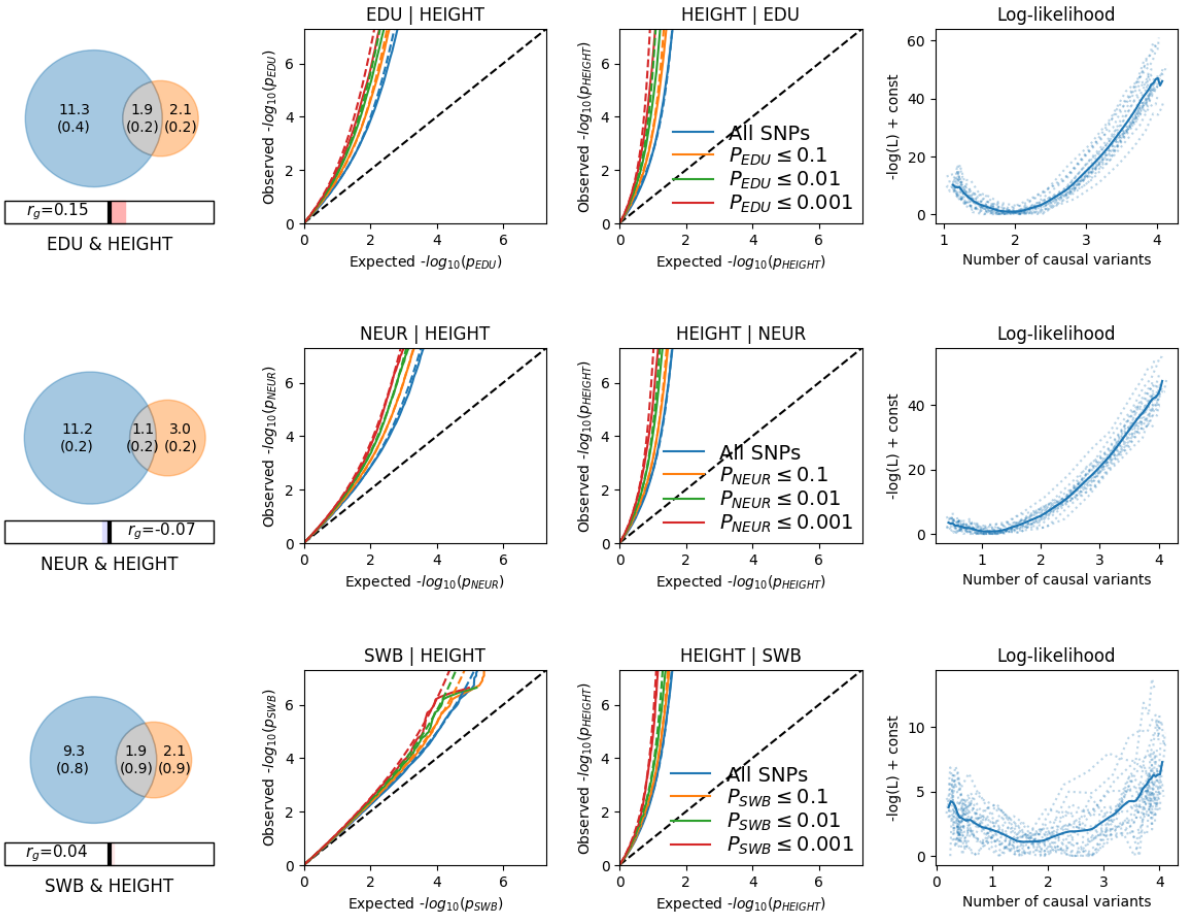


f. Cognitive traits by personality traits



g. Height by disorders/mental traits




11.3 (0.4)
1.9 (0.2)
2.1 (0.2)
r_g=0.15
EDU & HEIGHT
EDU | HEIGHT
HEIGHT | EDU
Log-likelihood
Observed -log10(p_{EDU})
Expected -log10(p_{EDU})
Observed -log10(p_{HEIGHT})
Expected -log10(p_{HEIGHT})
All SNPs
$P_{EDU} \leq 0.1$
$P_{EDU} \leq 0.01$
$P_{EDU} \leq 0.001$
-log(L) + const
Number of causal variants
11.2 (0.2)
1.1 (0.2)
3.0 (0.2)
r_g=-0.07
NEUR & HEIGHT
NEUR | HEIGHT
HEIGHT | NEUR
Observed -log10(p_{NEUR})
Expected -log10(p_{NEUR})
$P_{NEUR} \leq 0.1$
$P_{NEUR} \leq 0.01$
$P_{NEUR} \leq 0.001$
9.3 (0.8)
1.9 (0.9)
2.1 (0.9)
r_g=0.04
SWB & HEIGHT
SWB | HEIGHT
HEIGHT | SWB
Observed -log10(p_{SWB})
Expected -log10(p_{SWB})
$P_{SWB} \leq 0.1$
$P_{SWB} \leq 0.01$
$P_{SWB} \leq 0.001$

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