Supplementary Data 1

Multivariate analysis of 1.5 million people identifies genetic associations with traits related to self-regulation and addiction

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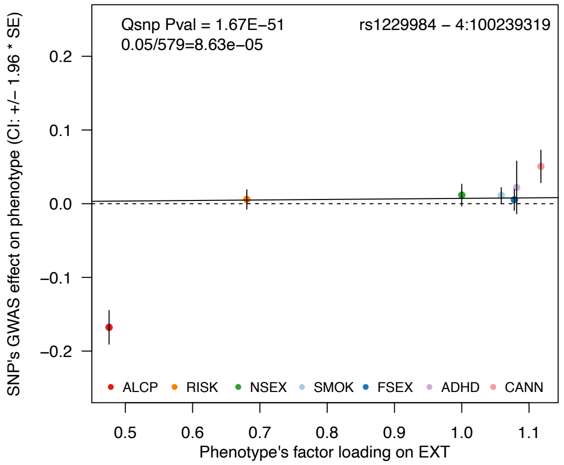
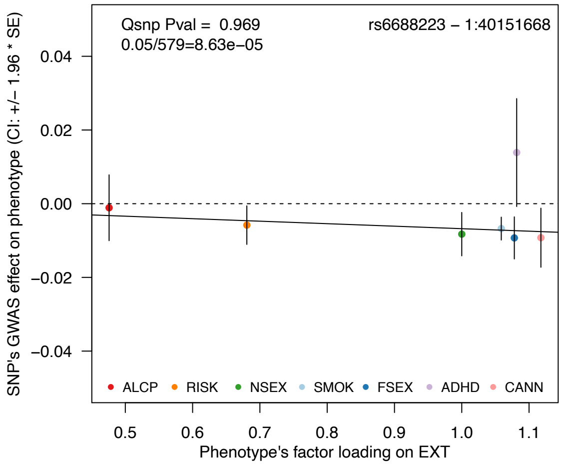
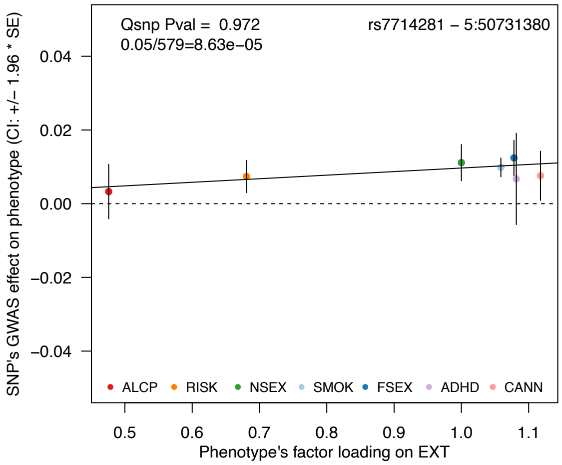


Supplementary Data 1A | Heterogeneity plot for rs1229984 in *ADH1B*. Scatterplot of the SNP's GWAS effect (i.e., the regression coefficient from a generalized linear regression) on the seven Genomic SEM phenotypes against their respective factor loadings on the externalizing factor (*EXT*). Both the GWAS effects and the factor loadings are "standardized" with respect to the total phenotypic variance of the respective seven indicator phenotypes (i.e., only standardized with respect to the outcomes). Error bars represent 95% confidence intervals centered on the GWAS effect size, computed as $\pm 1.96 \times SE$. The exact number of independent samples used to derive the estimates are: ADHD (*N* = 53,293), ALCP *(N* = 164,864), CANN (*N* = 186,875), FSEX (*N* = 357,187), NSEX (*N* = 336,121), RISK (N = 426,379), and SMOK (*N* = 1,251,809). The solid black line shows the fitted regression line from an inverse-variance weighted least squares regression of the GWAS effects on the factor loadings, with the model intercept fixed to zero.


Qsnp Pval = 0.969
0.05/579=8.63e−05
rs6688223 – 1:40151668
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 0.972
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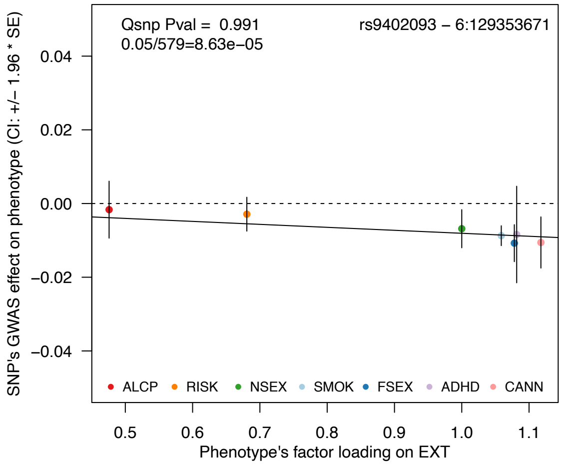
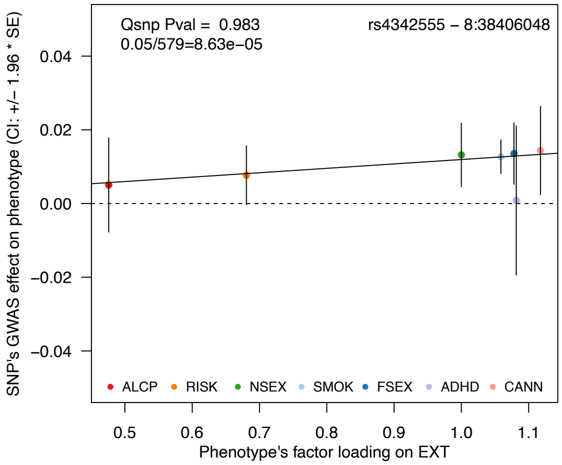
rs7714281 – 5:50731380
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 0.991
0.05/579=8.63e−05
rs9402093 – 6:129353671
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT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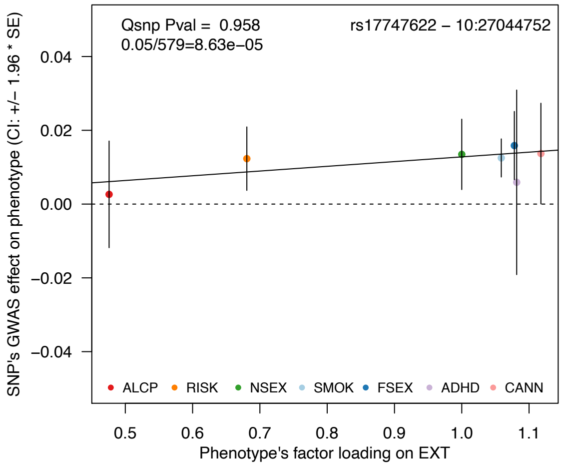
0.05/579=8.63e−05
rs4342555 – 8:38406048
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 0.958
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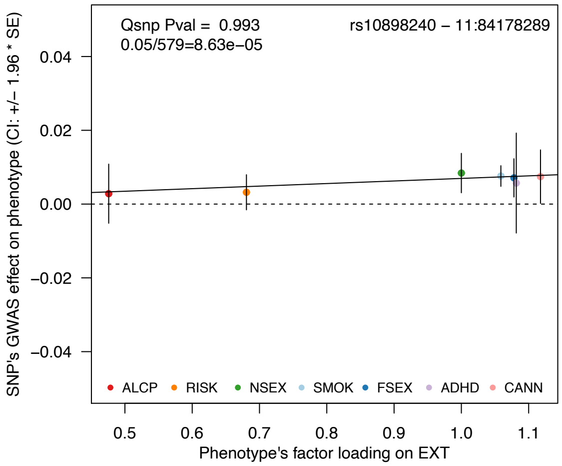
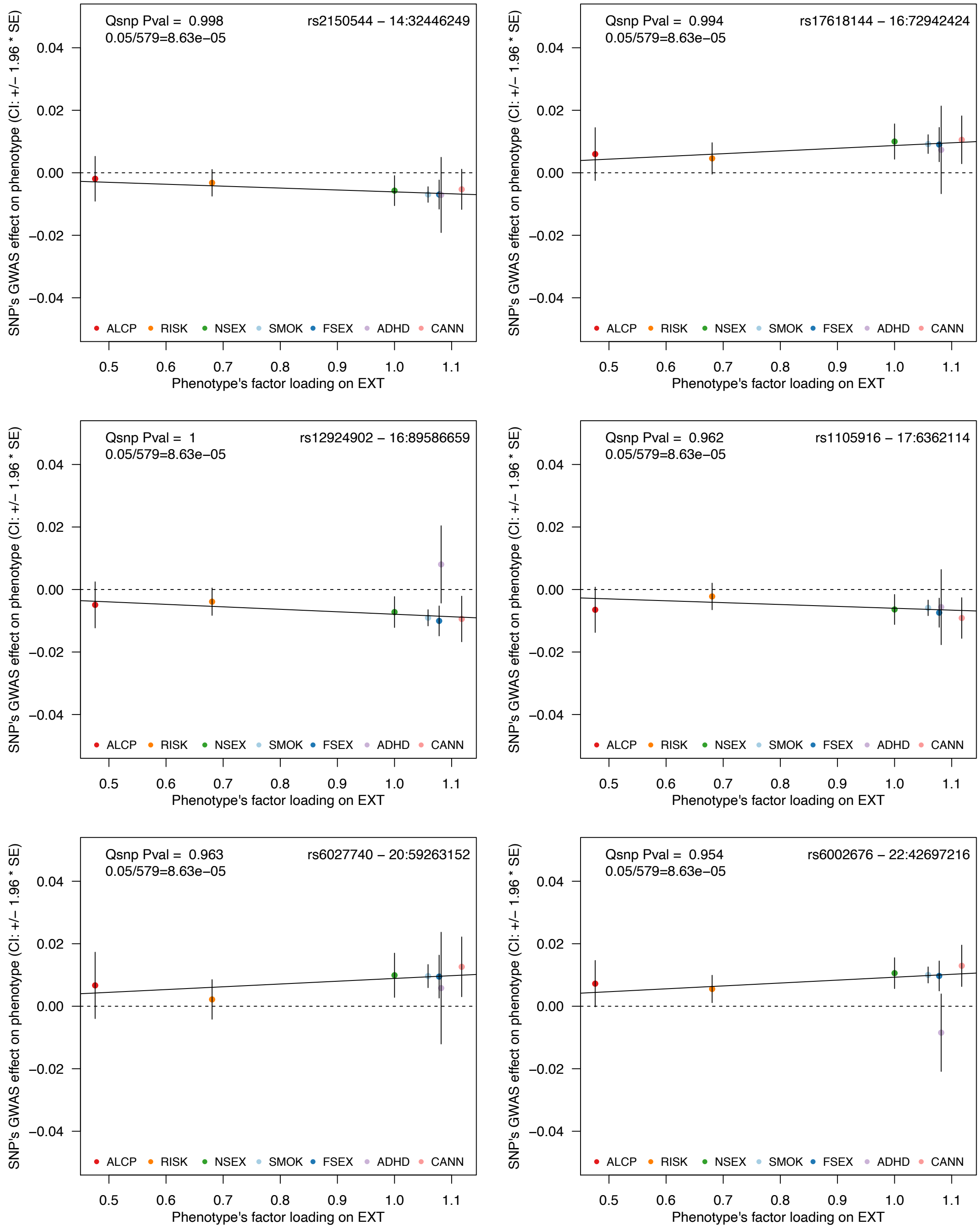
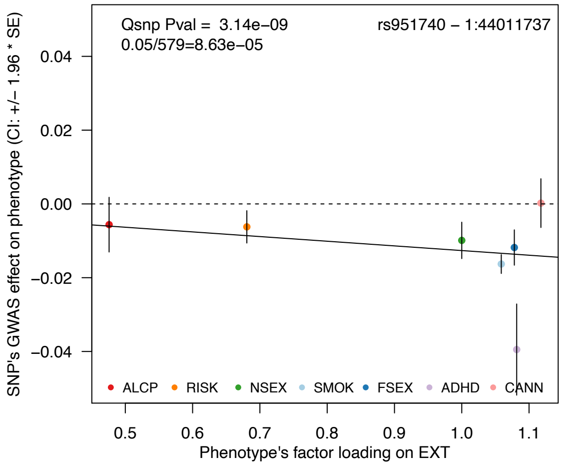
rs17747622 – 10:27044752
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

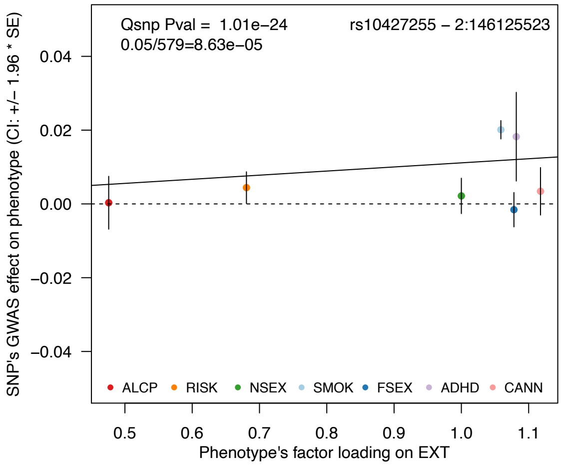

Qsnp Pval = 0.993
0.05/579=8.63e−05
rs10898240 – 11:84178289
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

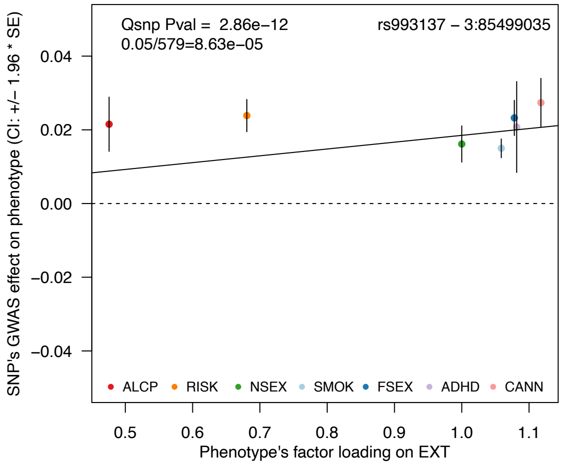


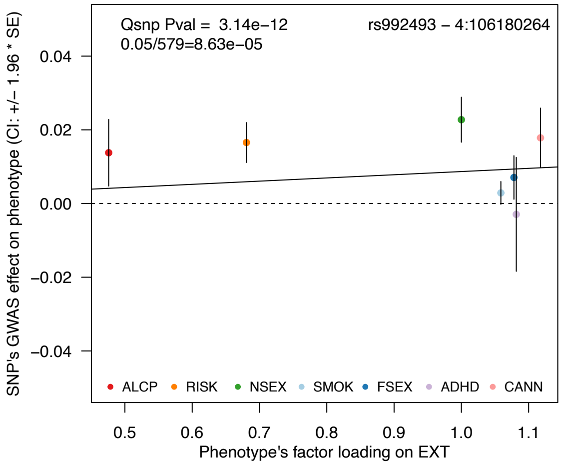
Supplementary Data 1B | Heterogeneity plot for 12 *EXT* SNPs without evidence of heterogeneity ($P_Q > 0.95$). Scatterplot of the SNP's GWAS effects (i.e., the regression coefficient from a generalized linear regression) on the seven Genomic SEM phenotypes against their respective factor loadings on the externalizing factor (*EXT*). Both the GWAS effects and the factor loadings are "standardized" with respect to the total phenotypic variance of the respective seven indicator phenotypes (i.e., only standardized with respect to the outcomes). Error bars represent

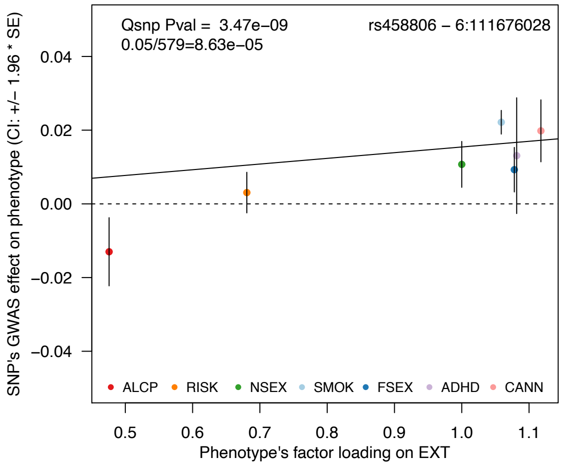
95% confidence intervals centered on the GWAS effect size, computed as $\pm 1.96 \times SE$ The exact number of independent samples used to derive the GWAS effect sizes are: ADHD (*N* = 53,293), ALCP *(N* = 164,864), CANN (*N* = 186,875), FSEX (*N* = 357,187), NSEX (*N* = 336,121), RISK (N = 426,379), and SMOK (*N* = 1,251,809). The solid black line shows the fitted regression line from an inverse-variance weighted least squares regression of the GWAS effects on the factor loadings, with the model intercept fixed to zero.

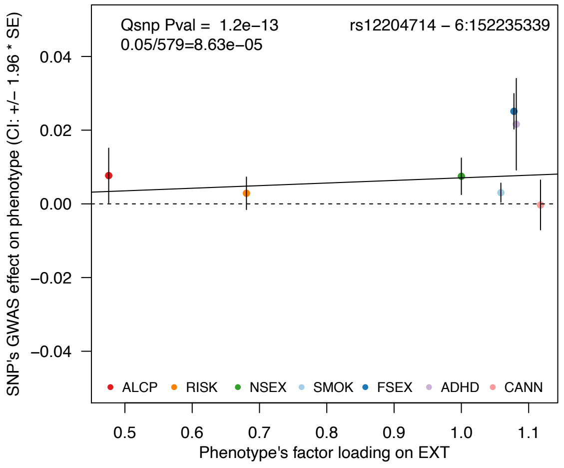

Qsnp Pval = 3.14e−09
0.05/579=8.63e−05
rs951740 – 1:44011737
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

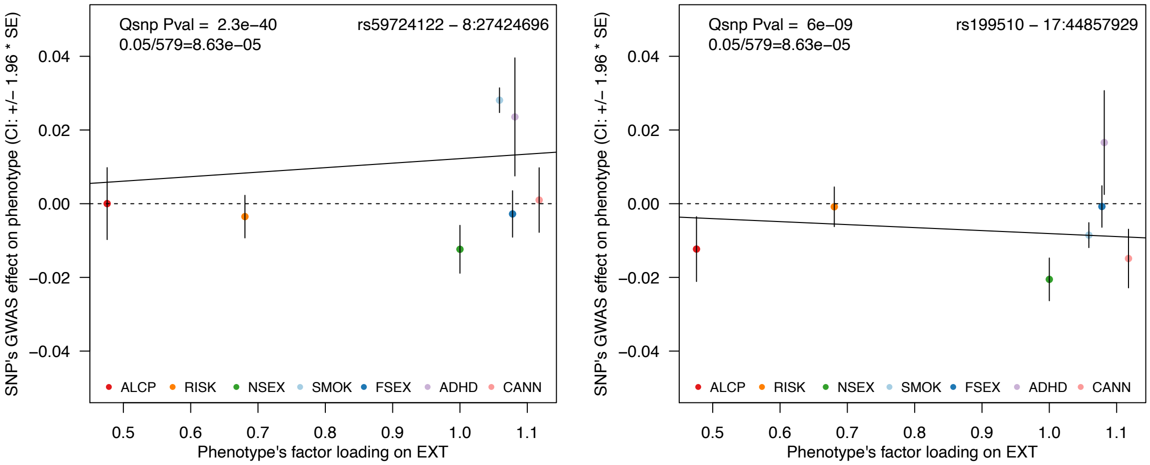

Qsnp Pval = 1.01e−24
0.05/579=8.63e−05
rs10427255 – 2:146125523
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 2.86e−12
0.05/579=8.63e−05
rs993137 – 3:85499035
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

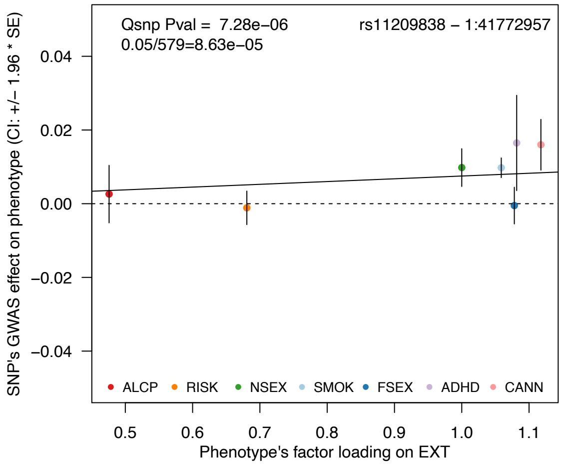

Qsnp Pval = 3.14e−12
0.05/579=8.63e−05
rs992493 – 4:106180264
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

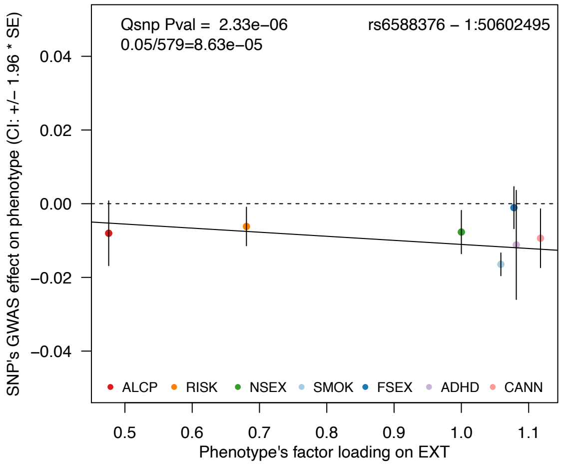

Qsnp Pval = 3.47e−09
0.05/579=8.63e−05
rs458806 – 6:111676028
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

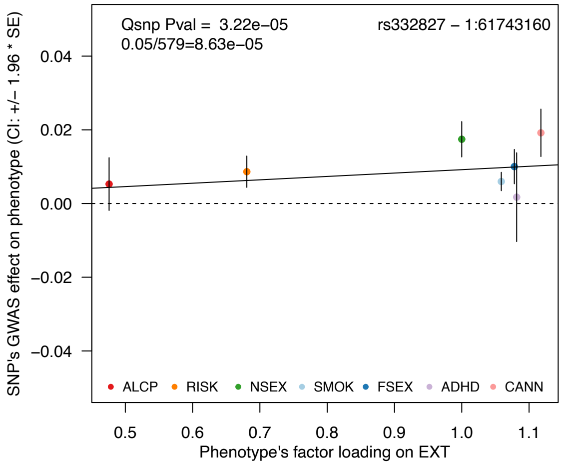

Qsnp Pval = 1.2e−13
0.05/579=8.63e−05
rs12204714 – 6:152235339
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

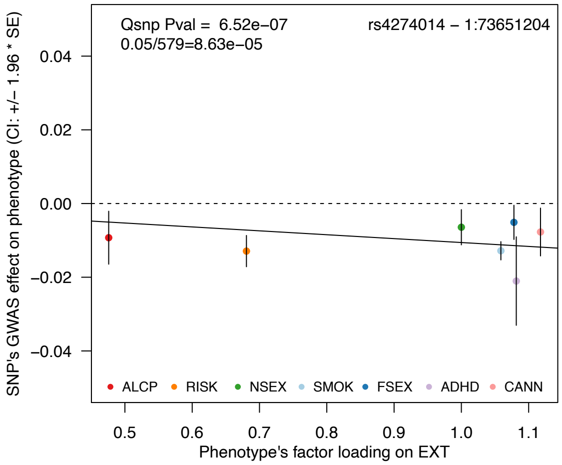


Supplementary Data 1C | Heterogeneity plot for eight *EXT* SNPs that are genome-wide significant Q_{SNP}. Scatterplot of the SNP's GWAS effects (i.e., the regression coefficient from a generalized linear regression) on the seven Genomic SEM phenotypes against their respective factor loadings on the externalizing factor (*EXT*). Both the GWAS effects and the factor loadings are "standardized" with respect to the total phenotypic variance of the respective seven indicator phenotypes (i.e., only standardized with respect to the outcomes). Error bars represent 95% confidence intervals centered on the GWAS effect size, computed as $\pm 1.96 \times SE$ The exact number of independent samples used to derive the GWAS effect sizes are: ADHD (*N* = 53,293), ALCP *(N* = 164,864), CANN (*N* = 186,875), FSEX (*N* = 357,187), NSEX (*N* = 336,121), RISK (N = 426,379), and SMOK (*N* = 1,251,809). The solid black line shows the fitted regression line from an inverse-variance weighted least squares regression of the GWAS effects on the factor loadings, with the model intercept fixed to zero.


Qsnp Pval = 7.28e−06
0.05/579=8.63e−05
rs11209838 – 1:41772957
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 2.33e−06
0.05/579=8.63e−05
rs6588376 – 1:50602495
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 3.22e−05
0.05/579=8.63e−05
rs332827 – 1:61743160
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 6.52e−07
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SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
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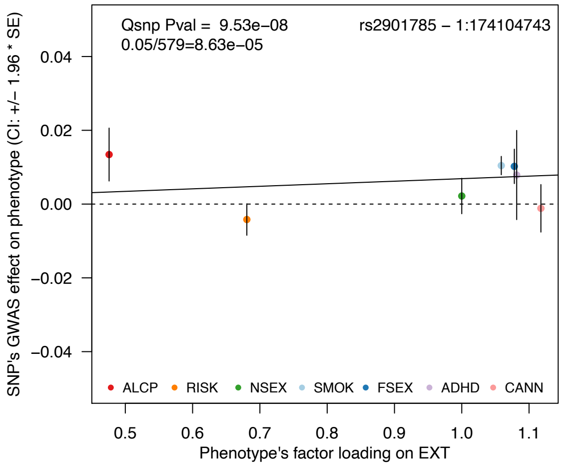
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT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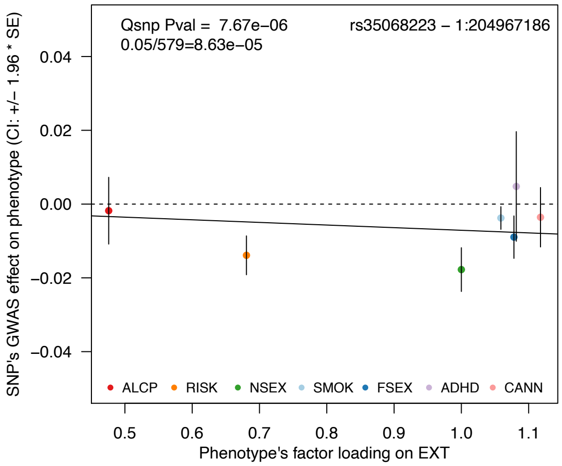
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT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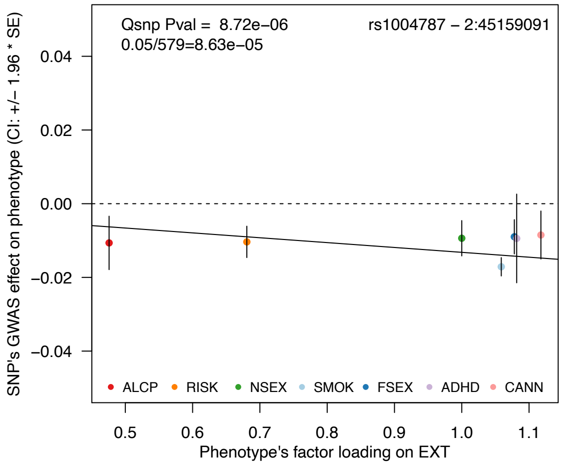
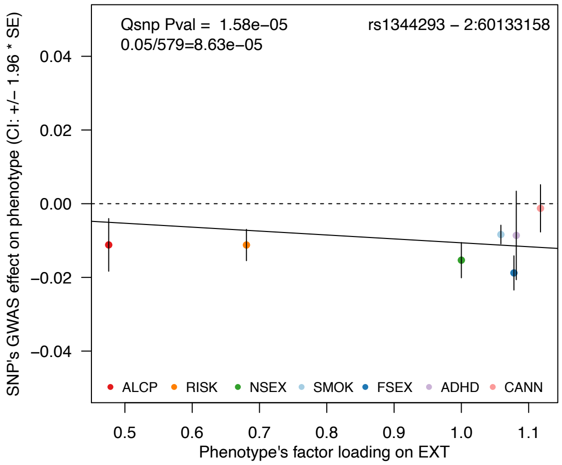
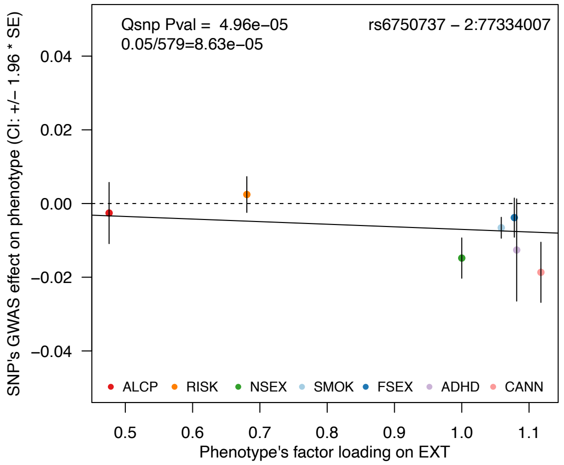
0.05/579=8.63e−05
rs35068223 – 1:204967186
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 8.72e−06
0.05/579=8.63e−05
rs1004787 – 2:45159091
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 1.58e−05
0.05/579=8.63e−05
rs1344293 – 2:60133158
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT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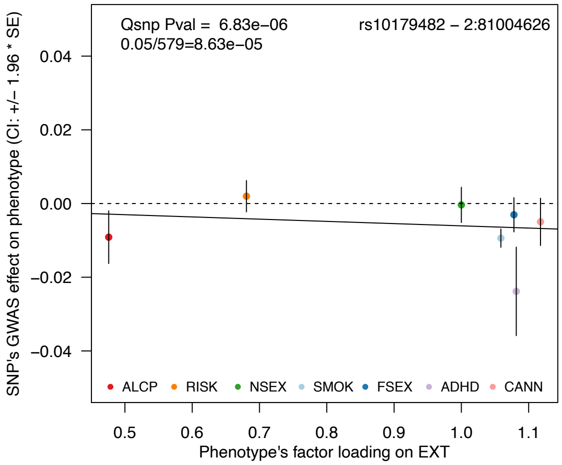
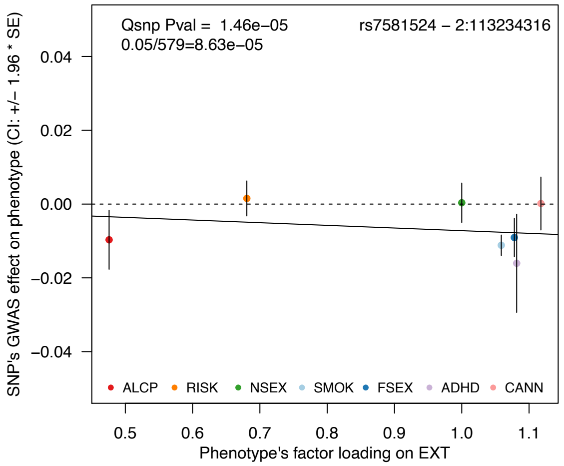
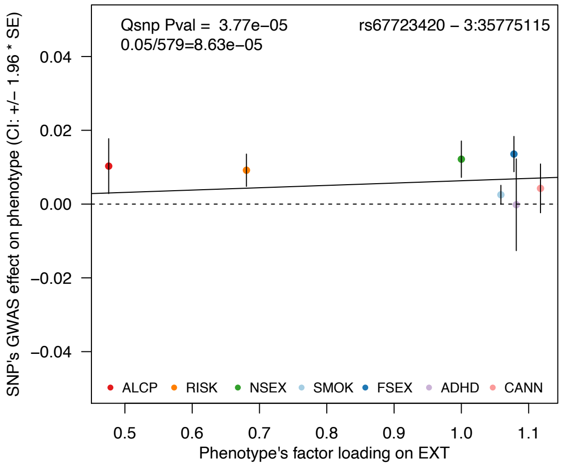
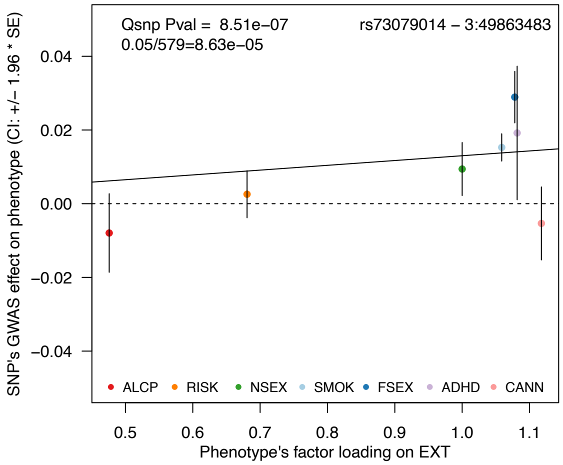
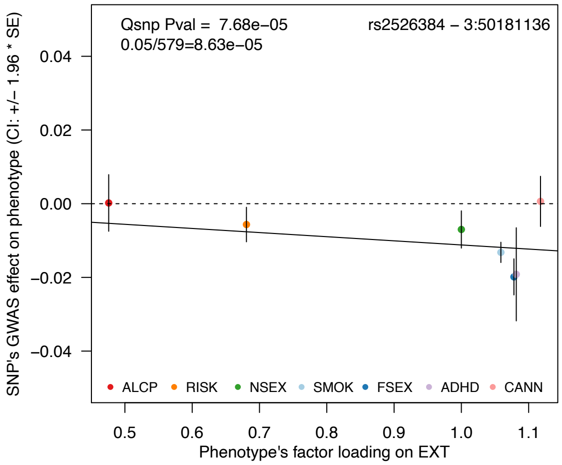
rs6750737 – 2:77334007
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

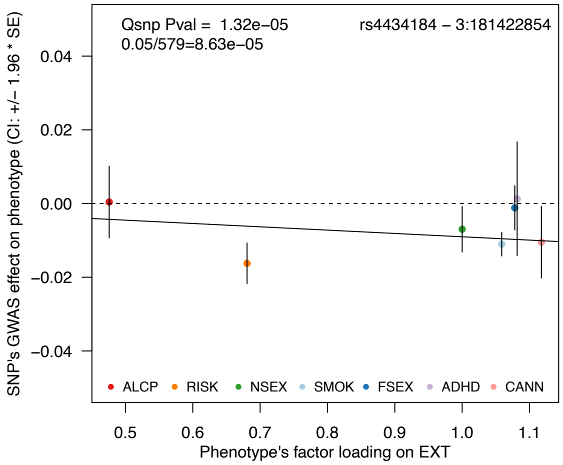

Qsnp Pval = 6.83e−06
0.05/579=8.63e−05
rs10179482 – 2:81004626
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

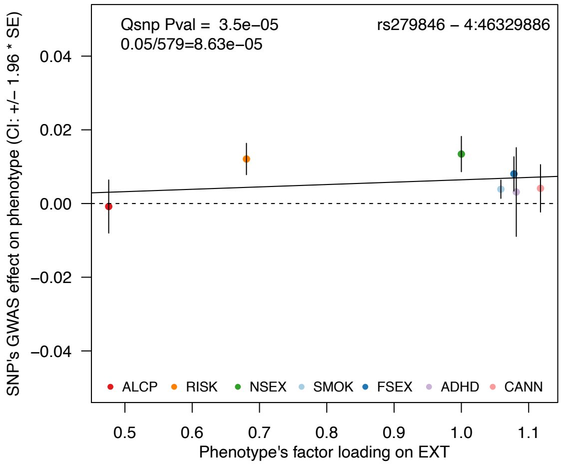

Qsnp Pval = 1.46e−05
0.05/579=8.63e−05
rs7581524 – 2:113234316
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

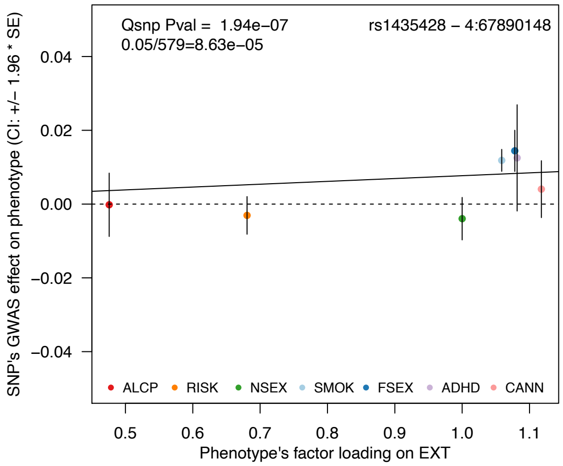

Qsnp Pval = 3.77e−05
0.05/579=8.63e−05
rs67723420 – 3:35775115
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

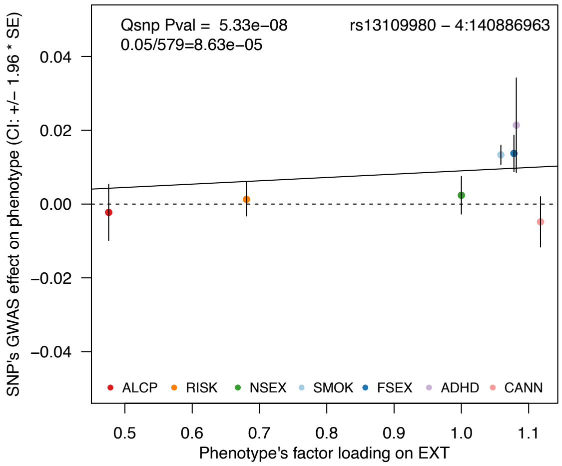

Qsnp Pval = 8.51e−07
0.05/579=8.63e−05
rs73079014 – 3:49863483
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP RISK NSEX SMOK FSEX ADHD CANN
0.5 0.6 0.7 0.8 0.9 1.0 1.1
Phenotype's factor loading on EXT

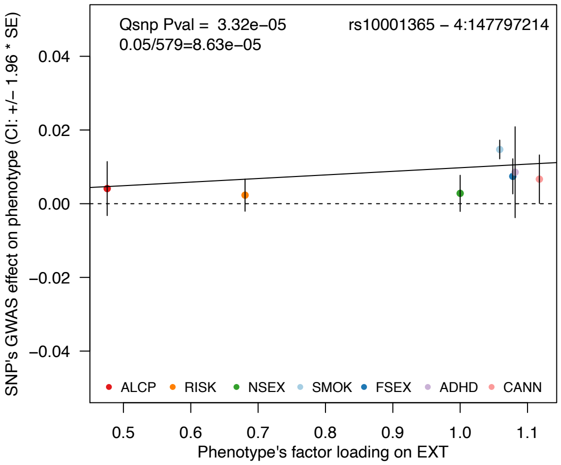

Qsnp Pval = 7.68e−05
0.05/579=8.63e−05
rs2526384 – 3:50181136
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP RISK NSEX SMOK FSEX ADHD CANN
0.5 0.6 0.7 0.8 0.9 1.0 1.1
Phenotype's factor loading on EXT

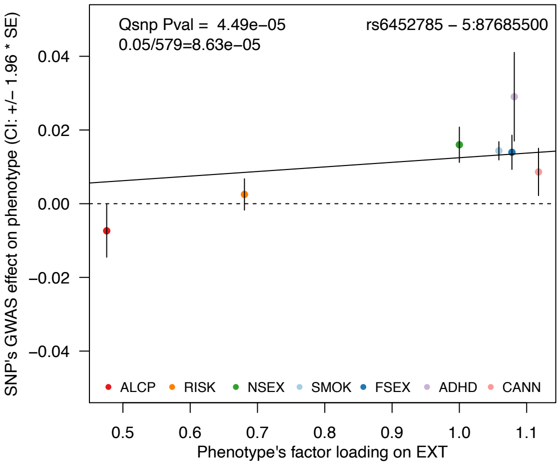

Qsnp Pval = 1.32e−05
0.05/579=8.63e−05
rs4434184 – 3:181422854
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP RISK NSEX SMOK FSEX ADHD CANN
0.5 0.6 0.7 0.8 0.9 1.0 1.1
Phenotype's factor loading on EXT

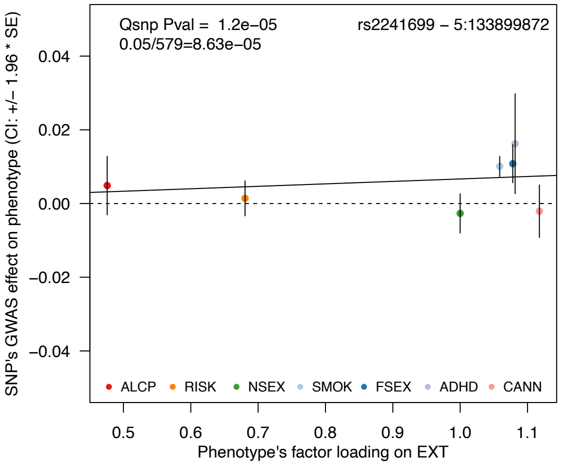

Qsnp Pval = 3.5e−05
0.05/579=8.63e−05
rs279846 – 4:46329886
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP RISK NSEX SMOK FSEX ADHD CANN
0.5 0.6 0.7 0.8 0.9 1.0 1.1
Phenotype's factor loading on EXT

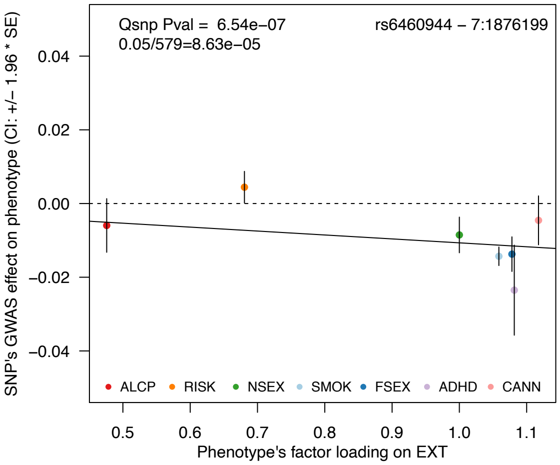

Qsnp Pval = 1.94e−07
0.05/579=8.63e−05
rs1435428 – 4:67890148
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP RISK NSEX SMOK FSEX ADHD CANN
0.5 0.6 0.7 0.8 0.9 1.0 1.1
Phenotype's factor loading on EXT

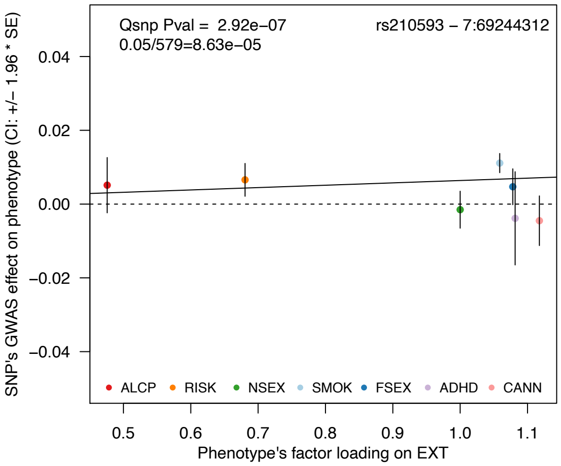

Qsnp Pval = 5.33e−08
0.05/579=8.63e−05
rs13109980 – 4:140886963
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP RISK NSEX SMOK FSEX ADHD CANN
0.5 0.6 0.7 0.8 0.9 1.0 1.1
Phenotype's factor loading on EXT

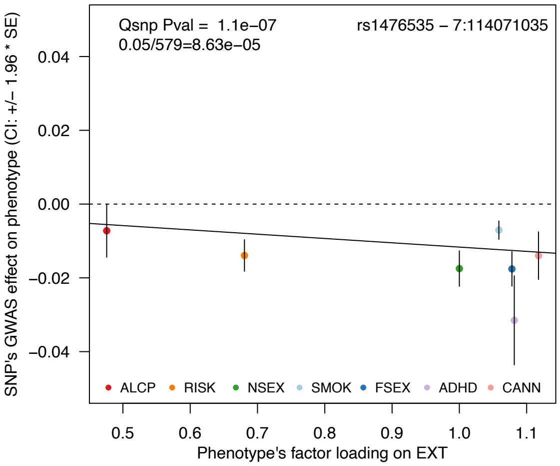

Qsnp Pval = 3.32e−05
0.05/579=8.63e−05
rs10001365 – 4:147797214
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

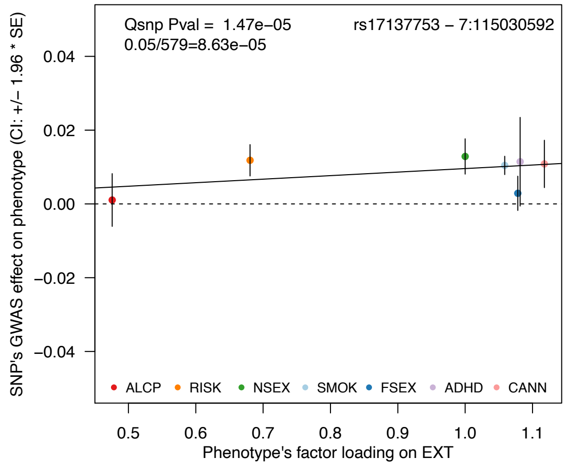

Qsnp Pval = 4.49e−05
0.05/579=8.63e−05
rs6452785 – 5:87685500
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

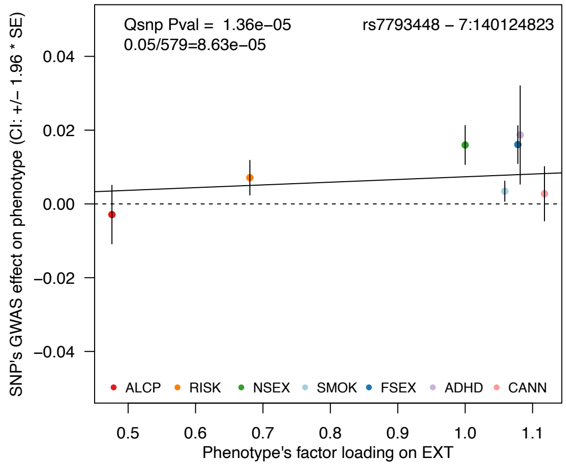

Qsnp Pval = 1.2e−05
0.05/579=8.63e−05
rs2241699 – 5:133899872
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

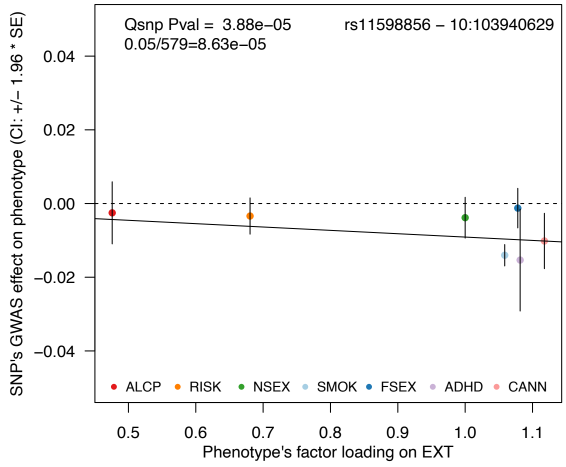

Qsnp Pval = 6.54e−07
0.05/579=8.63e−05
rs6460944 – 7:1876199
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

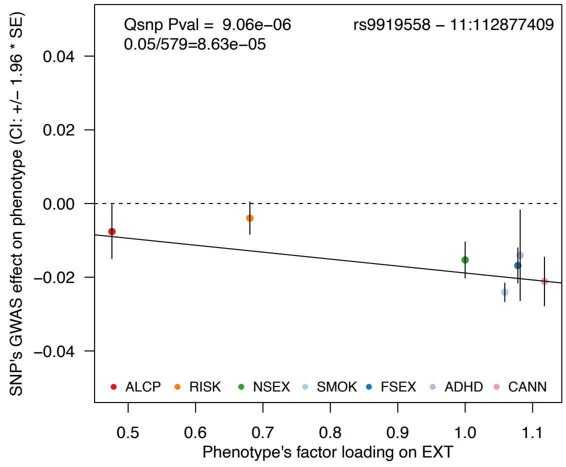

Qsnp Pval = 2.92e−07
0.05/579=8.63e−05
rs210593 – 7:69244312
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

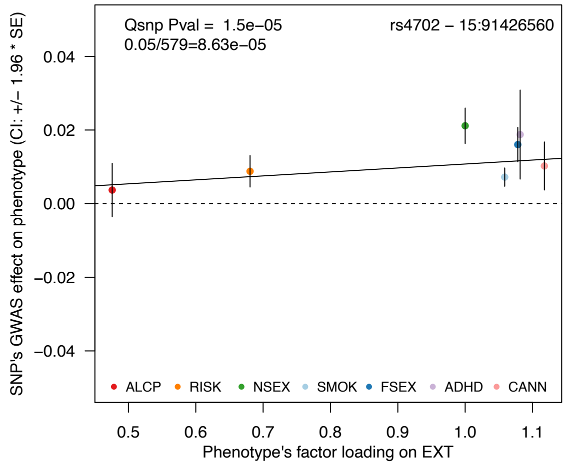

Qsnp Pval = 1.1e−07
0.05/579=8.63e−05
rs1476535 – 7:114071035
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

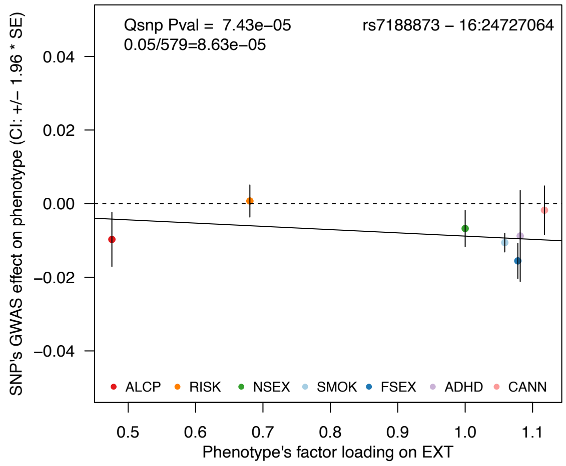

Qsnp Pval = 1.47e−05
0.05/579=8.63e−05
rs17137753 – 7:115030592
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT

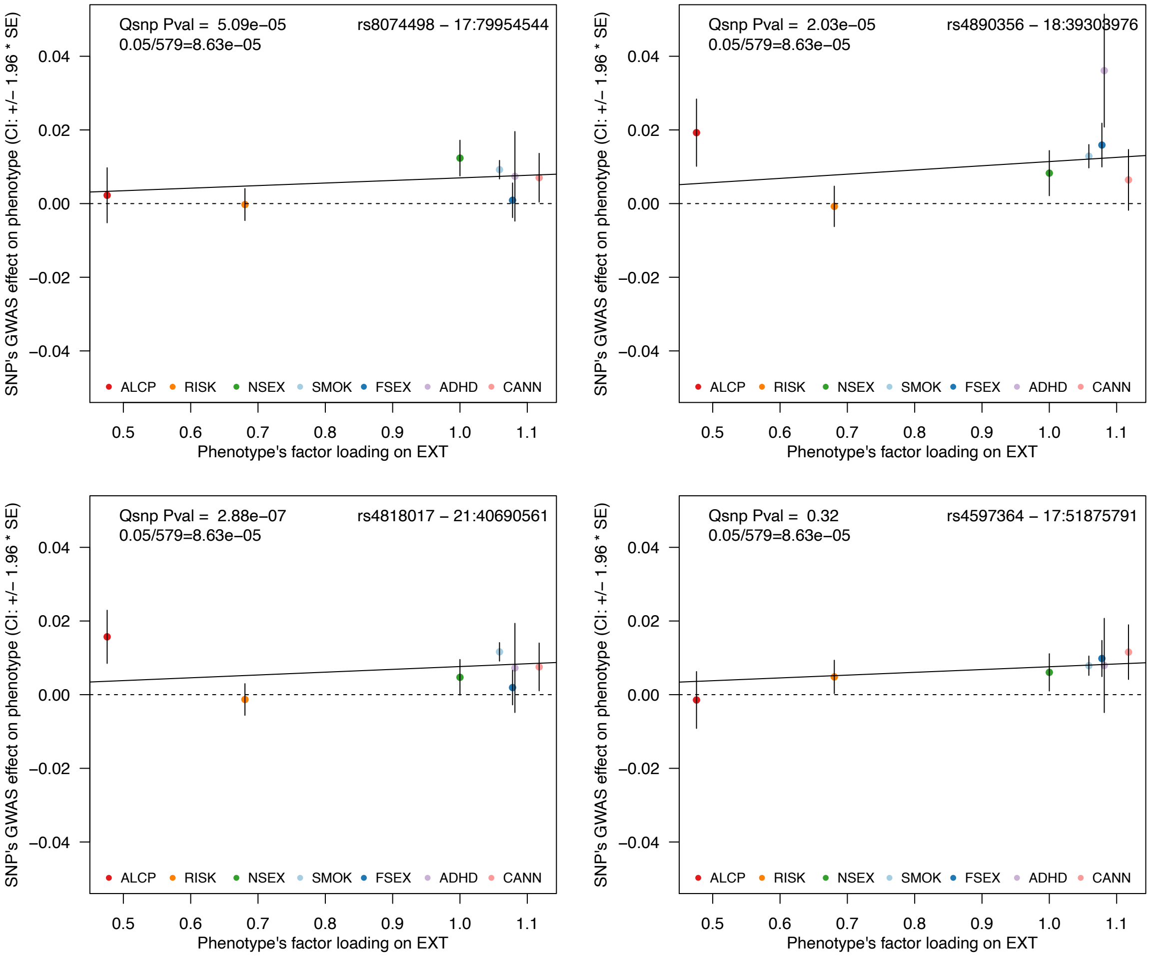

Qsnp Pval = 1.36e−05
0.05/579=8.63e−05
rs7793448 – 7:140124823
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 3.88e−05
0.05/579=8.63e−05
rs11598856 – 10:103940629
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 9.06e−06
0.05/579=8.63e−05
rs9919558 – 11:112877409
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 1.5e−05
0.05/579=8.63e−05
rs4702 – 15:91426560
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT


Qsnp Pval = 7.43e−05
0.05/579=8.63e−05
rs7188873 – 16:24727064
SNP's GWAS effect on phenotype (CI: +/− 1.96 * SE)
0.04
0.02
0.00
−0.02
−0.04
ALCP
RISK
NSEX
SMOK
FSEX
ADHD
CANN
0.5
0.6
0.7
0.8
0.9
1.0
1.1
Phenotype's factor loading on EXT



Supplementary Data 1D | Heterogeneity plot for 33 *EXT* SNPs that are not genome-wide significant Q_{SNP} but instead at $P(Q) < 0.05/579$. Scatterplot of the SNP's GWAS effects (i.e., the regression coefficient from a generalized linear regression) on the seven Genomic SEM phenotypes against their respective factor loadings on the externalizing factor (*EXT*). Both the GWAS effects and the factor loadings are "standardized" with respect to the total phenotypic variance of the respective seven indicator phenotypes (i.e., only standardized with respect to the outcomes). Error bars represent 95% confidence intervals centered on the GWAS effect size, computed as $\pm 1.96 \times SE$. The exact number of independent samples used to derive the GWAS effect sizes are: ADHD (*N* = 53,293), ALCP (*N* = 164,864), CANN (*N* = 186,875), FSEX (*N* = 357,187), NSEX (*N* = 336,121), RISK (N = 426,379), and SMOK (*N* = 1,251,809). The solid black line shows the fitted regression line from an inverse-variance weighted least squares regression of the GWAS effects on the factor loadings, with the model intercept fixed to zero.