# Supplementary Material: Gene-environment interplay in associations between maternal drinking and offspring emotional and behavioral problems

[**Supplementary Tables** 3](#_Toc145498269)

[Table S 1. Selective attrition on main study variables 3](#_Toc145498270)

[Table S2: Model-fitting: Tier 1 covariates 3](#_Toc145498271)

[Table S3: Model-fitting: Tier 2 covariates 4](#_Toc145498272)

[Table S4: Model-fitting: Tier 3 covariates 4](#_Toc145498273)

[Table S5: Model-fitting: Multi-level models 5](#_Toc145498274)

[Table S6: Top SNPs from single-SNP models 5](#_Toc145498275)

[Table S7: Model-fitting (xPGS): Tier 1 covariates 6](#_Toc145498276)

[Table S8: Model-fitting (xPGS): Tier 2 covariates 6](#_Toc145498277)

[Table S9: Model-fitting (xPGS): Tier 3 covariates 6](#_Toc145498278)

[Table S10: Model-fitting (xPGS): Multi-level models 6](#_Toc145498279)

[Table S11: FDR corrected p-values for xPGS results 6](#_Toc145498280)

[Table S12: Sensitivity analysis: within-wave main effects of maternal at-risk drinking in models incorporating Tier 2 covariates with and without maternal prenatal smoking 7](#_Toc145498281)

[Table S13: Sensitivity analysis: within-wave interaction effects of maternal at-risk drinking with PGS moderators in models incorporating Tier 2 covariates with and without maternal prenatal smoking 7](#_Toc145498282)

[**Supplementary figures** 9](#_Toc145498283)

[Figure S 1. Exposure-by-xPGS interaction effects in the most adjusted models presented as changes in the overall effect of the exposure at different values of the xPGS moderator 9](#_Toc145498284)

[**Supplementary methods** 10](#_Toc145498285)

[Methods S1: Items from the child behavior checklist included in the MoBa questionnaires completed when the children were 1.5, 3 and 5 years old. 10](#_Toc145498286)

[Methods S2: Deviations from pre-registration 11](#_Toc145498287)

[Methods S3: R packages used in analyses 12](#_Toc145498301)

## **Supplementary Tables**

## Table S 1. Selective attrition on main study variables

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Measure | Mean (continued participation) | Mean (discontinued participation) | Difference | 95% CI (lower) | (upper) | t | p-value |
| CBCL emotional (18m) | 1.297 | 1.361 | -0.064 | -0.083 | -0.046 | -6.863 | 0.000 |
| CBCL behavioural (18m) | 3.851 | 4.033 | -0.182 | -0.214 | -0.149 | -11.032 | 0.000 |
| Maternal at-risk drinking (18m) | 0.172 | 0.225 | -0.053 | -0.061 | -0.044 | -12.186 | 0.000 |
| Neurot. PGS (child) | -0.010 | 0.002 | -0.011 | -0.028 | 0.006 | -1.310 | 0.190 |
| PTSD PGS (child) | -0.013 | 0.002 | -0.014 | -0.031 | 0.002 | -1.693 | 0.090 |
| ADHD PGS (child) | -0.034 | 0.002 | -0.035 | -0.052 | -0.019 | -4.173 | 0.000 |
| Height PGS (child) | 0.014 | -0.003 | 0.017 | 0.000 | 0.033 | 1.972 | 0.049 |

Notes: Continued participation is defined as providing data at both the first and final included wave; discontinued participation is defined as providing data at the first but not the final included wave; PGS = polygenic score

## Table S2: Model-fitting: Tier 1 covariates

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | PGS moderator | Model | AIC | BIC | Chisq | Chisq diff | Df diff | p-value |
| cbcl\_ext\_c | neurot2018 | unconstrained | -1648337 | -1647990 | 242.056 |  |  |  |
| cbcl\_ext\_c | neurot2018 | betas | -1648327 | -1648038 | 264.487 | 19.069 | 6 | 0.004 |
| cbcl\_ext\_c | neurot2018 | betas+resids | -1648330 | -1648060 | 265.199 | 18.845 | 8 | 0.016 |
| cbcl\_int\_c | neurot2018 | unconstrained | -1654637 | -1654290 | 71.466 |  |  |  |
| cbcl\_int\_c | neurot2018 | betas | -1654634 | -1654345 | 86.125 | 12.914 | 6 | 0.044 |
| cbcl\_int\_c | neurot2018 | betas+resids | -1654637 | -1654367 | 87.587 | 11.716 | 8 | 0.164 |
| cbcl\_ext\_c | ptsd2019 | unconstrained | -1643036 | -1642689 | 242.092 |  |  |  |
| cbcl\_ext\_c | ptsd2019 | betas | -1643031 | -1642742 | 259.136 | 14.370 | 6 | 0.026 |
| cbcl\_ext\_c | ptsd2019 | betas+resids | -1643034 | -1642764 | 259.889 | 14.408 | 8 | 0.072 |
| cbcl\_int\_c | ptsd2019 | unconstrained | -1649326 | -1648979 | 66.529 |  |  |  |
| cbcl\_int\_c | ptsd2019 | betas | -1649322 | -1649033 | 82.757 | 14.998 | 6 | 0.020 |
| cbcl\_int\_c | ptsd2019 | betas+resids | -1649325 | -1649055 | 84.105 | 13.153 | 8 | 0.107 |
| cbcl\_ext\_c | adhd | unconstrained | -1643172 | -1642825 | 236.272 |  |  |  |
| cbcl\_ext\_c | adhd | betas | -1643141 | -1642852 | 278.905 | 36.406 | 6 | 0.000 |
| cbcl\_ext\_c | adhd | betas+resids | -1643145 | -1642875 | 279.124 | 34.991 | 8 | 0.000 |
| cbcl\_int\_c | adhd | unconstrained | -1649201 | -1648854 | 71.531 |  |  |  |
| cbcl\_int\_c | adhd | betas | -1649192 | -1648903 | 92.401 | 18.641 | 6 | 0.005 |
| cbcl\_int\_c | adhd | betas+resids | -1649195 | -1648925 | 93.778 | 16.307 | 8 | 0.038 |
| cbcl\_ext\_c | height2 | unconstrained | -1639807 | -1639460 | 251.032 |  |  |  |
| cbcl\_ext\_c | height2 | betas | -1639801 | -1639512 | 268.883 | 15.039 | 6 | 0.020 |
| cbcl\_ext\_c | height2 | betas+resids | -1639804 | -1639534 | 269.769 | 15.162 | 8 | 0.056 |
| cbcl\_int\_c | height2 | unconstrained | -1646142 | -1645794 | 66.119 |  |  |  |
| cbcl\_int\_c | height2 | betas | -1646137 | -1645848 | 82.288 | 14.408 | 6 | 0.025 |
| cbcl\_int\_c | height2 | betas+resids | -1646140 | -1645870 | 83.626 | 12.813 | 8 | 0.118 |

## Table S3: Model-fitting: Tier 2 covariates

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | PGS moderator | Model | AIC | BIC | Chisq | Chisq diff | Df diff | p-value |
| cbcl\_ext\_c | neurot2018 | unconstrained | -3153435 | -3153001 | 158.859 |  |  |  |
| cbcl\_ext\_c | neurot2018 | betas | -3153423 | -3153047 | 182.594 | 21.173 | 6 | 0.002 |
| cbcl\_ext\_c | neurot2018 | betas+resids | -3153426 | -3153070 | 183.703 | 21.063 | 8 | 0.007 |
| cbcl\_int\_c | neurot2018 | unconstrained | -3159661 | -3159227 | 61.708 |  |  |  |
| cbcl\_int\_c | neurot2018 | betas | -3159656 | -3159280 | 78.390 | 14.721 | 6 | 0.023 |
| cbcl\_int\_c | neurot2018 | betas+resids | -3159659 | -3159302 | 80.068 | 13.409 | 8 | 0.099 |
| cbcl\_ext\_c | ptsd2019 | unconstrained | -3144753 | -3144319 | 160.745 |  |  |  |
| cbcl\_ext\_c | ptsd2019 | betas | -3144750 | -3144374 | 175.521 | 13.027 | 6 | 0.043 |
| cbcl\_ext\_c | ptsd2019 | betas+resids | -3144753 | -3144396 | 176.616 | 13.339 | 8 | 0.101 |
| cbcl\_int\_c | ptsd2019 | unconstrained | -3151027 | -3150593 | 54.697 |  |  |  |
| cbcl\_int\_c | ptsd2019 | betas | -3151024 | -3150648 | 69.947 | 14.228 | 6 | 0.027 |
| cbcl\_int\_c | ptsd2019 | betas+resids | -3151026 | -3150670 | 71.405 | 12.637 | 8 | 0.125 |
| cbcl\_ext\_c | adhd | unconstrained | -3144651 | -3144217 | 155.866 |  |  |  |
| cbcl\_ext\_c | adhd | betas | -3144621 | -3144245 | 197.638 | 37.077 | 6 | 0.000 |
| cbcl\_ext\_c | adhd | betas+resids | -3144624 | -3144268 | 198.073 | 35.544 | 8 | 0.000 |
| cbcl\_int\_c | adhd | unconstrained | -3150539 | -3150105 | 60.343 |  |  |  |
| cbcl\_int\_c | adhd | betas | -3150531 | -3150155 | 79.756 | 17.877 | 6 | 0.007 |
| cbcl\_int\_c | adhd | betas+resids | -3150534 | -3150177 | 81.488 | 15.870 | 8 | 0.044 |
| cbcl\_ext\_c | height2 | unconstrained | -3135289 | -3134855 | 168.254 |  |  |  |
| cbcl\_ext\_c | height2 | betas | -3135286 | -3134910 | 183.778 | 13.572 | 6 | 0.035 |
| cbcl\_ext\_c | height2 | betas+resids | -3135288 | -3134932 | 184.968 | 13.970 | 8 | 0.083 |
| cbcl\_int\_c | height2 | unconstrained | -3141545 | -3141111 | 54.082 |  |  |  |
| cbcl\_int\_c | height2 | betas | -3141542 | -3141166 | 69.540 | 14.055 | 6 | 0.029 |
| cbcl\_int\_c | height2 | betas+resids | -3141544 | -3141187 | 71.149 | 12.693 | 8 | 0.123 |

## Table S4: Model-fitting: Tier 3 covariates

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | PGS moderator | Model | AIC | BIC | Chisq | Chisq diff | Df diff | p-value |
| cbcl\_ext\_c | neurot2018 | unconstrained | -4667546 | -4666939 | 172.055 |  |  |  |
| cbcl\_ext\_c | neurot2018 | betas | -4667539 | -4666990 | 191.054 | 16.854 | 6 | 0.010 |
| cbcl\_ext\_c | neurot2018 | betas+resids | -4667542 | -4667012 | 192.161 | 17.018 | 8 | 0.030 |
| cbcl\_int\_c | neurot2018 | unconstrained | -4673799 | -4673192 | 68.701 |  |  |  |
| cbcl\_int\_c | neurot2018 | betas | -4673791 | -4673241 | 88.612 | 17.888 | 6 | 0.007 |
| cbcl\_int\_c | neurot2018 | betas+resids | -4673793 | -4673263 | 90.364 | 16.019 | 8 | 0.042 |
| cbcl\_ext\_c | ptsd2019 | unconstrained | -4701287 | -4700680 | 177.030 |  |  |  |
| cbcl\_ext\_c | ptsd2019 | betas | -4701285 | -4700735 | 191.251 | 12.550 | 6 | 0.051 |
| cbcl\_ext\_c | ptsd2019 | betas+resids | -4701288 | -4700757 | 192.355 | 12.925 | 8 | 0.114 |
| cbcl\_int\_c | ptsd2019 | unconstrained | -4707634 | -4707027 | 67.450 |  |  |  |
| cbcl\_int\_c | ptsd2019 | betas | -4707630 | -4707081 | 83.259 | 14.496 | 6 | 0.025 |
| cbcl\_int\_c | ptsd2019 | betas+resids | -4707632 | -4707102 | 84.887 | 13.063 | 8 | 0.110 |
| cbcl\_ext\_c | adhd | unconstrained | -4676956 | -4676349 | 173.023 |  |  |  |
| cbcl\_ext\_c | adhd | betas | -4676920 | -4676371 | 221.039 | 42.364 | 6 | 0.000 |
| cbcl\_ext\_c | adhd | betas+resids | -4676924 | -4676393 | 221.494 | 40.736 | 8 | 0.000 |
| cbcl\_int\_c | adhd | unconstrained | -4682853 | -4682246 | 84.585 |  |  |  |
| cbcl\_int\_c | adhd | betas | -4682841 | -4682292 | 108.655 | 21.994 | 6 | 0.001 |
| cbcl\_int\_c | adhd | betas+resids | -4682844 | -4682313 | 110.444 | 19.351 | 8 | 0.013 |
| cbcl\_ext\_c | height2 | unconstrained | -4657766 | -4657159 | 179.784 |  |  |  |
| cbcl\_ext\_c | height2 | betas | -4657763 | -4657213 | 195.433 | 13.627 | 6 | 0.034 |
| cbcl\_ext\_c | height2 | betas+resids | -4657766 | -4657235 | 196.618 | 14.072 | 8 | 0.080 |
| cbcl\_int\_c | height2 | unconstrained | -4664054 | -4663447 | 60.516 |  |  |  |
| cbcl\_int\_c | height2 | betas | -4664054 | -4663504 | 73.025 | 11.378 | 6 | 0.077 |
| cbcl\_int\_c | height2 | betas+resids | -4664056 | -4663526 | 74.526 | 10.443 | 8 | 0.235 |

## Table S5: Model-fitting: Multi-level models

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | PGS moderator | Model | AIC | BIC | Chisq | Chisq diff | Df diff | p-value |
| cbcl\_ext\_c | neurot2018 | unconstrained | 3557411 | 3558938 |  |  |  |  |
| cbcl\_ext\_c | neurot2018 | betas | 3557413 | 3558844 |  | 23.031 | 10 | 0.011 |
| cbcl\_ext\_c | neurot2018 | betas+resids | 3557382 | 3558775 |  | -0.193 | 14 | 1.000 |
| cbcl\_int\_c | neurot2018 | unconstrained | 3552326 | 3553853 |  |  |  |  |
| cbcl\_int\_c | neurot2018 | betas | 3552327 | 3553759 |  | 23.546 | 10 | 0.009 |
| cbcl\_int\_c | neurot2018 | betas+resids | 3552319 | 3553712 |  | 18.380 | 14 | 0.190 |
| cbcl\_ext\_c | ptsd2019 | unconstrained | 3558520 | 3560047 |  |  |  |  |
| cbcl\_ext\_c | ptsd2019 | betas | 3558516 | 3559947 |  | 16.909 | 10 | 0.076 |
| cbcl\_ext\_c | ptsd2019 | betas+resids | 3558486 | 3559879 |  | -6.733 | 14 | 1.000 |
| cbcl\_int\_c | ptsd2019 | unconstrained | 3553470 | 3554997 |  |  |  |  |
| cbcl\_int\_c | ptsd2019 | betas | 3553474 | 3554905 |  | 26.692 | 10 | 0.003 |
| cbcl\_int\_c | ptsd2019 | betas+resids | 3553467 | 3554860 |  | 21.889 | 14 | 0.081 |
| cbcl\_ext\_c | adhd | unconstrained | 3558590 | 3560118 |  |  |  |  |
| cbcl\_ext\_c | adhd | betas | 3558630 | 3560061 |  | 62.883 | 10 | 0.000 |
| cbcl\_ext\_c | adhd | betas+resids | 3558605 | 3559998 |  | 53.087 | 14 | 0.000 |
| cbcl\_int\_c | adhd | unconstrained | 3553780 | 3555308 |  |  |  |  |
| cbcl\_int\_c | adhd | betas | 3553791 | 3555222 |  | 33.773 | 10 | 0.000 |
| cbcl\_int\_c | adhd | betas+resids | 3553782 | 3555175 |  | 25.659 | 14 | 0.029 |
| cbcl\_ext\_c | height2 | unconstrained | 3551702 | 3553229 |  |  |  |  |
| cbcl\_ext\_c | height2 | betas | 3551702 | 3553134 |  | 21.103 | 10 | 0.020 |
| cbcl\_ext\_c | height2 | betas+resids | 3551679 | 3553072 |  | 6.097 | 14 | 0.964 |
| cbcl\_int\_c | height2 | unconstrained | 3546604 | 3548132 |  |  |  |  |
| cbcl\_int\_c | height2 | betas | 3546602 | 3548033 |  | 18.669 | 10 | 0.045 |
| cbcl\_int\_c | height2 | betas+resids | 3546593 | 3547986 |  | 14.278 | 14 | 0.429 |

## Table S6: Top SNPs from single-SNP models

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| PGS trait | SNP ID | Chromosome | Position | A1 | Outcome | Beta | p-value |
| ptsd2019 | rs114357244 | 3 | 160592059 | G | cbcl\_int\_c\_3yr | 0.176 | 2.70 x 10-6 |
| neurot2018 | rs17597288 | 18 | 53177208 | G | cbcl\_int\_c\_3yr | -0.064 | 3.10 x 10-6 |
| neurot2018 | rs11075952 | 16 | 72999690 | C | cbcl\_ext\_c\_5yr | -0.060 | 9.80 x 10-6 |
| adhd | rs9921395 | 16 | 73001957 | A | cbcl\_ext\_c\_5yr | -0.059 | 1.19 x 10-5 |
| ptsd2019 | rs141912297 | 3 | 35789001 | A | cbcl\_int\_c\_18m | 0.155 | 1.20 x 10-5 |
| adhd | rs11059055 | 12 | 127761495 | T | cbcl\_int\_c\_18m | 0.067 | 1.40 x 10-5 |
| neurot2018 | rs11059050 | 12 | 127754915 | T | cbcl\_int\_c\_18m | 0.057 | 2..40 x 10-5 |
| neurot2018 | rs2705570 | 21 | 42422020 | G | cbcl\_ext\_c\_5yr | 0.064 | 2.46 x 10-5 |
| ptsd2019 | rs9603415 | 13 | 39325655 | A | cbcl\_int\_c\_5yr | 0.169 | 2.64 x 10-5 |
| ptsd2019 | rs12962469 | 18 | 36480665 | A | cbcl\_int\_c\_3yr | 0.070 | 3.51 x 10-5 |
| ptsd2019 | rs6093648 | 20 | 41094598 | T | cbcl\_int\_c\_18m | 0.037 | 3.83 x 10-5 |
| adhd | rs7581057 | 2 | 115958079 | G | cbcl\_ext\_c\_3yr | 0.091 | 3.90 x 10-5 |
| ptsd2019 | rs2567469 | 17 | 70739580 | T | cbcl\_ext\_c\_3yr | -0.040 | 4.46 x 10-5 |
| neurot2018 | rs35824449 | 5 | 29893311 | A | cbcl\_ext\_c\_18m | -0.037 | 6.00 x 10-5 |
| ptsd2019 | rs11251073 | 10 | 2197460 | A | cbcl\_int\_c\_18m | 0.033 | 6.75 x 10-5 |

## Table S7: Model-fitting (xPGS): Tier 1 covariates

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | PGS moderator | Model | AIC | BIC | Chisq | Chisq diff | Df diff | p-value |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | unconstrained | -445615.2 | -445308.6 | 84.885 |  |  |  |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | betas | -445617.4 | -445361.9 | 94.679 | 8.353 | 6 | 0.213 |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | betas+resids | -445619.9 | -445381.5 | 96.187 | 9.001 | 8 | 0.342 |
| cbcl\_int\_c | All SNPs (Emo. probs.) | unconstrained | -460553.5 | -460246.9 | 26.671 |  |  |  |
| cbcl\_int\_c | All SNPs (Emo. probs.) | betas | -460551.5 | -460296.0 | 40.728 | 12.305 | 6 | 0.055 |
| cbcl\_int\_c | All SNPs (Emo. probs.) | betas+resids | -460538.1 | -460299.7 | 58.064 | 21.374 | 8 | 0.006 |

## Table S8: Model-fitting (xPGS): Tier 2 covariates

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | PGS moderator | Model | AIC | BIC | Chisq | Chisq diff | Df diff | p-value |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | unconstrained | -905491.5 | -905108.3 | 58.278 |  |  |  |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | betas | -905491.3 | -905159.1 | 70.555 | 10.804 | 6 | 0.095 |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | betas+resids | -905493.9 | -905178.8 | 71.867 | 11.017 | 8 | 0.201 |
| cbcl\_int\_c | All SNPs (Emo. probs.) | unconstrained | -921845.5 | -921462.3 | 30.949 |  |  |  |
| cbcl\_int\_c | All SNPs (Emo. probs.) | betas | -921848.2 | -921516.0 | 40.290 | 8.547 | 6 | 0.201 |
| cbcl\_int\_c | All SNPs (Emo. probs.) | betas+resids | -921835.8 | -921520.7 | 56.631 | 17.862 | 8 | 0.022 |

## Table S9: Model-fitting (xPGS): Tier 3 covariates

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | PGS moderator | Model | AIC | BIC | Chisq | Chisq diff | Df diff | p-value |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | unconstrained | -1354521 | -1353984 | 70.247 |  |  |  |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | betas | -1354527 | -1354041 | 76.357 | 5.346 | 6 | 0.500 |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | betas+resids | -1354529 | -1354061 | 77.697 | 5.994 | 8 | 0.648 |
| cbcl\_int\_c | All SNPs (Emo. probs.) | unconstrained | -1370860 | -1370323 | 43.903 |  |  |  |
| cbcl\_int\_c | All SNPs (Emo. probs.) | betas | -1370865 | -1370380 | 50.261 | 6.062 | 6 | 0.416 |
| cbcl\_int\_c | All SNPs (Emo. probs.) | betas+resids | -1370853 | -1370384 | 66.550 | 15.955 | 8 | 0.043 |

## Table S10: Model-fitting (xPGS): Multi-level models

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | PGS moderator | Model | AIC | BIC | Chisq | Chisq diff | Df diff | p-value |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | unconstrained | 1089465 | 1090817 |  |  |  |  |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | betas | 1089457 | 1090724 |  | 12.204 | 10 | 0.272 |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | betas+resids | 1089475 | 1090708 |  | 31.853 | 14 | 0.004 |
| cbcl\_int\_c | All SNPs (Emo. probs.) | unconstrained | 1098718 | 1100070 |  |  |  |  |
| cbcl\_int\_c | All SNPs (Emo. probs.) | betas |  |  |  |  |  |  |
| cbcl\_int\_c | All SNPs (Emo. probs.) | betas+resids | 1098732 | 1099965 |  | 34.453 | 14 | 0.002 |

Note: missing values (other than in the case of baseline unconstrained models) indicate that models did not converge with standard setup

## Table S11: FDR corrected p-values for xPGS results

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome | PGS moderator | Accepted constraints | Wave | Beta | p-value | FDR-corrected p-value |
| cbcl\_ext\_c | All SNPs (Beh. probs.) | Betas only | all | -0.002 | 0.755 | 0.755 |
| cbcl\_int\_c | All SNPs (Emo. probs.) | None | 18m | 0.019 | 0.136 | 0.272 |
| cbcl\_int\_c | All SNPs (Emo. probs.) | None | 3yr | 0.040 | 0.003 | 0.012 |
| cbcl\_int\_c | All SNPs (Emo. probs.) | None | 5yr | 0.017 | 0.235 | 0.313 |

## 

## Table S12: Sensitivity analysis: within-wave main effects of maternal at-risk drinking in models incorporating Tier 2 covariates with and without maternal prenatal smoking

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **Wave** | **Model** | **β** | **SE** | ***p*** | **95% CI** | |
|  |  |  |  |  |  |  |  |
| CBCL behavioural | 18m | Tier 2 covariates | 0.064 | 0.010 | 0.000 | 0.045 | 0.083 |
| CBCL behavioural | 3yr | Tier 2 covariates | 0.026 | 0.010 | 0.006 | 0.008 | 0.045 |
| CBCL behavioural | 5yr | Tier 2 covariates | 0.060 | 0.014 | 0.000 | 0.031 | 0.088 |
| CBCL behavioural | 18m | Tier 2 covariates + prenatal m. smoking | 0.057 | 0.010 | 0.000 | 0.038 | 0.076 |
| CBCL behavioural | 3yr | Tier 2 covariates + prenatal m. smoking | 0.020 | 0.010 | 0.039 | 0.001 | 0.039 |
| CBCL behavioural | 5yr | Tier 2 covariates + prenatal m. smoking | 0.054 | 0.014 | 0.000 | 0.025 | 0.082 |
| CBCL emotional | 18m | Tier 2 covariates | 0.058 | 0.011 | 0.000 | 0.037 | 0.080 |
| CBCL emotional | 3yr | Tier 2 covariates | 0.025 | 0.010 | 0.015 | 0.005 | 0.046 |
| CBCL emotional | 5yr | Tier 2 covariates | 0.008 | 0.014 | 0.554 | -0.019 | 0.035 |
| CBCL emotional | 18m | Tier 2 covariates + prenatal m. smoking | 0.051 | 0.011 | 0.000 | 0.029 | 0.072 |
| CBCL emotional | 3yr | Tier 2 covariates + prenatal m. smoking | 0.019 | 0.010 | 0.066 | -0.001 | 0.039 |
| CBCL emotional | 5yr | Tier 2 covariates + prenatal m. smoking | 0.005 | 0.014 | 0.741 | -0.022 | 0.031 |
| CBCL behavioural | 18m | Tier 2 covariates | 0.063 | 0.010 | 0.000 | 0.044 | 0.082 |
| CBCL behavioural | 3yr | Tier 2 covariates | 0.027 | 0.010 | 0.005 | 0.008 | 0.046 |
| CBCL behavioural | 5yr | Tier 2 covariates | 0.057 | 0.015 | 0.000 | 0.028 | 0.086 |
| CBCL behavioural | 18m | Tier 2 covariates + prenatal m. smoking | 0.057 | 0.010 | 0.000 | 0.038 | 0.076 |
| CBCL behavioural | 3yr | Tier 2 covariates + prenatal m. smoking | 0.020 | 0.010 | 0.034 | 0.002 | 0.039 |
| CBCL behavioural | 5yr | Tier 2 covariates + prenatal m. smoking | 0.051 | 0.015 | 0.000 | 0.023 | 0.080 |
| CBCL emotional | 18m | Tier 2 covariates | 0.059 | 0.011 | 0.000 | 0.037 | 0.081 |
| CBCL emotional | 3yr | Tier 2 covariates | 0.026 | 0.010 | 0.013 | 0.005 | 0.046 |
| CBCL emotional | 5yr | Tier 2 covariates | 0.008 | 0.014 | 0.576 | -0.019 | 0.035 |
| CBCL emotional | 18m | Tier 2 covariates + prenatal m. smoking | 0.052 | 0.011 | 0.000 | 0.030 | 0.074 |
| CBCL emotional | 3yr | Tier 2 covariates + prenatal m. smoking | 0.019 | 0.010 | 0.063 | -0.001 | 0.040 |
| CBCL emotional | 5yr | Tier 2 covariates + prenatal m. smoking | 0.004 | 0.014 | 0.754 | -0.023 | 0.031 |
| CBCL behavioural | 18m | Tier 2 covariates | 0.063 | 0.010 | 0.000 | 0.044 | 0.082 |
| CBCL behavioural | 3yr | Tier 2 covariates | 0.027 | 0.010 | 0.005 | 0.008 | 0.046 |
| CBCL behavioural | 5yr | Tier 2 covariates | 0.057 | 0.014 | 0.000 | 0.029 | 0.085 |
| CBCL behavioural | 18m | Tier 2 covariates + prenatal m. smoking | 0.057 | 0.010 | 0.000 | 0.038 | 0.076 |
| CBCL behavioural | 3yr | Tier 2 covariates + prenatal m. smoking | 0.021 | 0.010 | 0.031 | 0.002 | 0.040 |
| CBCL behavioural | 5yr | Tier 2 covariates + prenatal m. smoking | 0.051 | 0.014 | 0.000 | 0.023 | 0.079 |
| CBCL emotional | 18m | Tier 2 covariates | 0.059 | 0.011 | 0.000 | 0.037 | 0.080 |
| CBCL emotional | 3yr | Tier 2 covariates | 0.026 | 0.010 | 0.012 | 0.006 | 0.047 |
| CBCL emotional | 5yr | Tier 2 covariates | 0.008 | 0.014 | 0.532 | -0.018 | 0.035 |
| CBCL emotional | 18m | Tier 2 covariates + prenatal m. smoking | 0.051 | 0.011 | 0.000 | 0.029 | 0.073 |
| CBCL emotional | 3yr | Tier 2 covariates + prenatal m. smoking | 0.020 | 0.010 | 0.058 | -0.001 | 0.040 |
| CBCL emotional | 5yr | Tier 2 covariates + prenatal m. smoking | 0.005 | 0.014 | 0.725 | -0.022 | 0.031 |
| CBCL behavioural | 18m | Tier 2 covariates | 0.065 | 0.010 | 0.000 | 0.046 | 0.084 |
| CBCL behavioural | 3yr | Tier 2 covariates | 0.028 | 0.010 | 0.003 | 0.010 | 0.047 |
| CBCL behavioural | 5yr | Tier 2 covariates | 0.060 | 0.015 | 0.000 | 0.032 | 0.089 |
| CBCL behavioural | 18m | Tier 2 covariates + prenatal m. smoking | 0.058 | 0.010 | 0.000 | 0.039 | 0.077 |
| CBCL behavioural | 3yr | Tier 2 covariates + prenatal m. smoking | 0.022 | 0.010 | 0.024 | 0.003 | 0.041 |
| CBCL behavioural | 5yr | Tier 2 covariates + prenatal m. smoking | 0.054 | 0.015 | 0.000 | 0.026 | 0.083 |
| CBCL emotional | 18m | Tier 2 covariates | 0.059 | 0.011 | 0.000 | 0.038 | 0.081 |
| CBCL emotional | 3yr | Tier 2 covariates | 0.025 | 0.010 | 0.019 | 0.004 | 0.045 |
| CBCL emotional | 5yr | Tier 2 covariates | 0.011 | 0.014 | 0.426 | -0.016 | 0.038 |
| CBCL emotional | 18m | Tier 2 covariates + prenatal m. smoking | 0.052 | 0.011 | 0.000 | 0.030 | 0.073 |
| CBCL emotional | 3yr | Tier 2 covariates + prenatal m. smoking | 0.018 | 0.010 | 0.080 | -0.002 | 0.039 |
| CBCL emotional | 5yr | Tier 2 covariates + prenatal m. smoking | 0.007 | 0.014 | 0.591 | -0.020 | 0.034 |

## Table S13: Sensitivity analysis: within-wave interaction effects of maternal at-risk drinking with PGS moderators in models incorporating Tier 2 covariates with and without maternal prenatal smoking

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **Wave** | **Model** | **PGS Moderator** | **β** | **SE** | ***p*** | **95% CI** | |
|  |  |  |  |  |  |  |  |  |
| CBCL beh. | 18m | Tier 2 covariates | Neuroticism | -0.004 | 0.006 | 0.544 | -0.017 | 0.009 |
| CBCL beh. | 3yr | Tier 2 covariates | Neuroticism | 0.015 | 0.006 | 0.016 | 0.003 | 0.028 |
| CBCL beh. | 5yr | Tier 2 covariates | Neuroticism | 0.007 | 0.008 | 0.426 | -0.010 | 0.023 |
| CBCL beh. | 18m | Tier 2 covariates + prenatal m. smoking | Neuroticism | -0.004 | 0.006 | 0.521 | -0.017 | 0.008 |
| CBCL beh. | 3yr | Tier 2 covariates + prenatal m. smoking | Neuroticism | 0.015 | 0.006 | 0.016 | 0.003 | 0.028 |
| CBCL beh. | 5yr | Tier 2 covariates + prenatal m. smoking | Neuroticism | 0.007 | 0.008 | 0.409 | -0.010 | 0.024 |
| CBCL emo. | 18m | Tier 2 covariates | Neuroticism | 0.008 | 0.007 | 0.304 | -0.007 | 0.022 |
| CBCL emo. | 3yr | Tier 2 covariates | Neuroticism | -0.002 | 0.007 | 0.785 | -0.016 | 0.012 |
| CBCL emo. | 5yr | Tier 2 covariates | Neuroticism | 0.007 | 0.009 | 0.464 | -0.011 | 0.024 |
| CBCL emo. | 18m | Tier 2 covariates + prenatal m. smoking | Neuroticism | 0.007 | 0.007 | 0.326 | -0.007 | 0.022 |
| CBCL emo. | 3yr | Tier 2 covariates + prenatal m. smoking | Neuroticism | -0.002 | 0.007 | 0.771 | -0.016 | 0.012 |
| CBCL emo. | 5yr | Tier 2 covariates + prenatal m. smoking | Neuroticism | 0.007 | 0.009 | 0.464 | -0.011 | 0.024 |
| CBCL beh. | 18m | Tier 2 covariates | PTSD | 0.001 | 0.006 | 0.850 | -0.011 | 0.013 |
| CBCL beh. | 3yr | Tier 2 covariates | PTSD | 0.004 | 0.006 | 0.539 | -0.009 | 0.016 |
| CBCL beh. | 5yr | Tier 2 covariates | PTSD | -0.002 | 0.008 | 0.810 | -0.019 | 0.015 |
| CBCL beh. | 18m | Tier 2 covariates + prenatal m. smoking | PTSD | 0.001 | 0.006 | 0.874 | -0.011 | 0.013 |
| CBCL beh. | 3yr | Tier 2 covariates + prenatal m. smoking | PTSD | 0.004 | 0.006 | 0.527 | -0.008 | 0.016 |
| CBCL beh. | 5yr | Tier 2 covariates + prenatal m. smoking | PTSD | -0.001 | 0.008 | 0.862 | -0.018 | 0.015 |
| CBCL emo. | 18m | Tier 2 covariates | PTSD | -0.007 | 0.007 | 0.309 | -0.021 | 0.007 |
| CBCL emo. | 3yr | Tier 2 covariates | PTSD | -0.013 | 0.007 | 0.061 | -0.026 | 0.001 |
| CBCL emo. | 5yr | Tier 2 covariates | PTSD | -0.003 | 0.008 | 0.746 | -0.019 | 0.013 |
| CBCL emo. | 18m | Tier 2 covariates + prenatal m. smoking | PTSD | -0.007 | 0.007 | 0.301 | -0.021 | 0.007 |
| CBCL emo. | 3yr | Tier 2 covariates + prenatal m. smoking | PTSD | -0.013 | 0.007 | 0.061 | -0.026 | 0.001 |
| CBCL emo. | 5yr | Tier 2 covariates + prenatal m. smoking | PTSD | -0.002 | 0.008 | 0.771 | -0.018 | 0.014 |
| CBCL beh. | 18m | Tier 2 covariates | ADHD | 0.004 | 0.007 | 0.520 | -0.009 | 0.017 |
| CBCL beh. | 3yr | Tier 2 covariates | ADHD | -0.007 | 0.007 | 0.287 | -0.020 | 0.006 |
| CBCL beh. | 5yr | Tier 2 covariates | ADHD | 0.012 | 0.008 | 0.139 | -0.004 | 0.029 |
| CBCL beh. | 18m | Tier 2 covariates + prenatal m. smoking | ADHD | 0.004 | 0.006 | 0.556 | -0.009 | 0.017 |
| CBCL beh. | 3yr | Tier 2 covariates + prenatal m. smoking | ADHD | -0.007 | 0.007 | 0.269 | -0.020 | 0.006 |
| CBCL beh. | 5yr | Tier 2 covariates + prenatal m. smoking | ADHD | 0.013 | 0.008 | 0.139 | -0.004 | 0.029 |
| CBCL emo. | 18m | Tier 2 covariates | ADHD | -0.004 | 0.007 | 0.542 | -0.018 | 0.010 |
| CBCL emo. | 3yr | Tier 2 covariates | ADHD | -0.002 | 0.007 | 0.763 | -0.016 | 0.011 |
| CBCL emo. | 5yr | Tier 2 covariates | ADHD | 0.007 | 0.009 | 0.415 | -0.010 | 0.025 |
| CBCL emo. | 18m | Tier 2 covariates + prenatal m. smoking | ADHD | -0.005 | 0.007 | 0.497 | -0.019 | 0.009 |
| CBCL emo. | 3yr | Tier 2 covariates + prenatal m. smoking | ADHD | -0.002 | 0.007 | 0.729 | -0.016 | 0.011 |
| CBCL emo. | 5yr | Tier 2 covariates + prenatal m. smoking | ADHD | 0.007 | 0.009 | 0.422 | -0.010 | 0.025 |
| CBCL beh. | 18m | Tier 2 covariates | Height | -0.005 | 0.006 | 0.397 | -0.018 | 0.007 |
| CBCL beh. | 3yr | Tier 2 covariates | Height | -0.002 | 0.007 | 0.780 | -0.015 | 0.011 |
| CBCL beh. | 5yr | Tier 2 covariates | Height | 0.003 | 0.009 | 0.786 | -0.016 | 0.021 |
| CBCL beh. | 18m | Tier 2 covariates + prenatal m. smoking | Height | -0.005 | 0.006 | 0.405 | -0.018 | 0.007 |
| CBCL beh. | 3yr | Tier 2 covariates + prenatal m. smoking | Height | -0.002 | 0.007 | 0.790 | -0.015 | 0.011 |
| CBCL beh. | 5yr | Tier 2 covariates + prenatal m. smoking | Height | 0.001 | 0.009 | 0.874 | -0.017 | 0.020 |
| CBCL emo. | 18m | Tier 2 covariates | Height | -0.006 | 0.007 | 0.440 | -0.020 | 0.009 |
| CBCL emo. | 3yr | Tier 2 covariates | Height | -0.002 | 0.007 | 0.804 | -0.016 | 0.012 |
| CBCL emo. | 5yr | Tier 2 covariates | Height | 0.004 | 0.009 | 0.670 | -0.014 | 0.022 |
| CBCL emo. | 18m | Tier 2 covariates + prenatal m. smoking | Height | -0.005 | 0.007 | 0.448 | -0.019 | 0.009 |
| CBCL emo. | 3yr | Tier 2 covariates + prenatal m. smoking | Height | -0.002 | 0.007 | 0.821 | -0.016 | 0.012 |
| CBCL emo. | 5yr | Tier 2 covariates + prenatal m. smoking | Height | 0.004 | 0.009 | 0.699 | -0.015 | 0.022 |

## **Supplementary figures**



## Figure S 1. Exposure-by-xPGS interaction effects in the most adjusted models presented as changes in the overall effect of the exposure at different values of the xPGS moderator

Notes: xPGS were computed based on interaction effect estimates for all independent SNPs from ADHD, PTSD, and neuroticism (N=17,133) averaged across all waves of an outcome

## **Supplementary methods**

## Methods S1: Items from the child behavior checklist included in the MoBa questionnaires completed when the children were 1.5, 3 and 5 years old.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **1.5 years** | **3 years** | **5 years** |
| **Emotional problems** |  |  |  |
| *Somatic complaints* |  |  |  |
| Doesn’t eat well | X | X | X |
| Stomach aches or cramps (without medical cause) |  | X | X |
| Constipated, doesn’t move bowels |  | X |  |
| Vomiting, throwing up (without medical cause) |  | X | X |
| *Anxious/depressed* |  |  |  |
| Too fearful or anxious | X | X | X |
| Clings to adults or too dependent | X | X | X |
| Gets too upset when separated from parents | X | X | X |
| Nervous, high strung, or tense |  |  | X |
| Unhappy, sad or depressed |  |  | X |
| Feelings are easily hurt |  |  | X |
| Self-conscious or easily embarrassed |  |  | X |
| *Emotionally reactive* |  |  |  |
| Disturbed by any change in routine | X | X | X |
| Sudden changes in moods or feelings |  | X |  |
| **Behavior problems** |  |  |  |
| *Attention problems* |  |  |  |
| Can’t concentrate, can’t pay attention for long | X | X | X |
| Quickly shifts from one activity to another | X | X | X |
| Can’t sit still, restless or overactive | X | X | X |
| Poorly coordinated or clumsy |  | X | X |
| *Aggressive behavior* |  |  |  |
| Gets in many fights | X | X | X |
| Hits others | X | X | X |
| Defiant | X | X | X |
| Doesn’t seem to feel guilty after misbehaving | X | X | X |
| Punishment doesn’t change his/her behavior | X | X | X |
| Can’t stand waiting, wants everything now |  | X | X |
| Demands must be met immediately |  | X | X |

## Methods S2: Deviations from pre-registration

|  |  |  |  |
| --- | --- | --- | --- |
| Pre-registered step | | Deviation | Justification |
| Inclusion criterion: “We will include genotyped individuals from MoBa with data available on at least one exposure or outcome variable” | | Removed restriction to genotyped individuals | Maximum likelihood estimation allows for non-genotyped individuals to contribute to estimates of parameters not reliant on genetic data (e.g., main effects), improving the precision of these estimates without affecting other parameters. Relaxing this inclusion criterion could not, by definition, influence the GxE results and thus there is no risk that this deviation inflates the alpha beyond the level set at the time of the preregistration. |
| Constraint to test in model fitting: “equality of residuals of exposure across wave” | | This constraint was not tested | Stability of exposure residuals across time not relevant to any tested hypothesis, and could result in other constraints (i.e., outcome residuals being equal across time) being rejected unnecessarily. Given the irrelevance to the hypothesis testing, there is no risk that this deviation inflates the alpha beyond the level set at the time of the preregistration. |
| xPGS analyses: “we will create xPGS at the p-value thresholds listed above, using the p values from the single SNP interaction models. Effect size weights will come from the original discovery GWAS as per xPGS paper. PGS-PCA will again be used to derive the first principal component from the scores at all 11 thresholds for use in the analysis.” | Single SNP models were only run for SNPs included at the p-value threshold most associated with the first principal component from the PGS-PCA of the original scores. Further, we created a single xPGS using eligible SNPs from across all of the PGS traits indexing environmental sensitivity (i.e., ADHD, neuroticism, PTSD), rather than one for each. Finally, we used effect size weights from our single SNP models, rather than those from the original GWAS as pre-specified. Also, it was not noted in the pre-registration that the xPGS would be specific to the outcome – i.e., xPGS used in analyses of emotional problems came were derived based on results of single SNP models with emotional problems outcomes, and vice versa for behavioural problems. | | We opted to update the xPGS approach to better fit our needs, rather than adhering completely to the approach outlined in the original paper (cited in the main text). In particular, this meant a) restricting to SNPs deemed most likely to contain interaction effects before running the single SNP models to reduce our multiple testing burden; b) capitalizing on our decision to use a split-sample to allow us to use effect sizes from the SNP-wise interaction models, rather than (main effect) estimates from the original GWAS, while still guarding against overfitting. In doing this, we also realised that the original GWAS source of each SNP had become irrelevant, since once the SNP had been included, no further information from the original GWAS was retained. This allowed us to create a single xPGS score from across all three relevant GWAS traits, clumping the SNPs from all single SNP models, indexing genetically-influenced environmental sensitivity for each outcome (behavioural and emotional problems).  The adapted approach is inherently more sensible for the data and question at hand. We feel it also represents an incremental but meaningful methodological improvement to the xPGS approach. There is limited risk that this deviation inflates the alpha beyond the level set at the time of the preregistration. Our deliberate caution in interpreting the xPGS results is proportionate to this risk (and the relatively isolated nature of the significant finding from this set of results)ß. |

## Methods S3: R packages used in analyses

| **Package** | **Version** | **Citation** |
| --- | --- | --- |
| ggthemes | 4.2.4 | Arnold (2021) |
| grateful | 0.1.11 | Rodríguez-Sánchez, Jackson, and Hutchins (2022) |
| lavaan | 0.6.8 | Rosseel (2012) |
| MplusAutomation | 0.8 | Hallquist and Wiley (2018) |
| patchwork | 1.1.1 | Pedersen (2020) |
| phenotools | 0.2.7 | Hannigan (2022) |
| tictoc | 1.0.1 | Izrailev (2021) |
| tidyverse | 1.3.0 | Wickham et al. (2019) |

Arnold, Jeffrey B. 2021. Ggthemes: Extra Themes, Scales and Geoms for ’Ggplot2’. <https://CRAN.R-project.org/package=ggthemes>.

Hallquist, Michael N., and Joshua F. Wiley. 2018. “MplusAutomation: An R Package for Facilitating Large-Scale Latent Variable Analyses in Mplus.” Structural Equation Modeling, 1–18. <https://doi.org/10.1080/10705511.2017.1402334>.

Hannigan, Laurie. 2022. Phenotools: Facilitates Reproducible Workflows with Data from MoBa and Linked Registry Sources. <https://github.com/psychgen/phenotools>.

Izrailev, Sergei. 2021. Tictoc: Functions for Timing r Scripts, as Well as Implementations of Stack and List Structures. <https://CRAN.R-project.org/package=tictoc>.

Pedersen, Thomas Lin. 2020. Patchwork: The Composer of Plots. <https://CRAN.R-project.org/package=patchwork>.

Rodríguez-Sánchez, Francisco, Connor P. Jackson, and Shaurita D. Hutchins. 2022. Grateful: Facilitate Citation of r Packages. <https://github.com/Pakillo/grateful>.

Rosseel, Yves. 2012. “lavaan: An R Package for Structural Equation Modeling.” Journal of Statistical Software 48 (2): 1–36. <https://www.jstatsoft.org/v48/i02/>.

Wickham, Hadley, Mara Averick, Jennifer Bryan, Winston Chang, Lucy D’Agostino McGowan, Romain François, Garrett Grolemund, et al. 2019. “Welcome to the tidyverse.” Journal of Open Source Software 4 (43): 1686. <https://doi.org/10.21105/joss.01686>.