Combined polygenic risk scores of different psychiatric traits predict general and specific psychopathology in childhood

RUNNING TITLE

PRSs predict general and specific psychopathology

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ABSTRACT

Background: Polygenic risk scores (PRSs) are increasingly used in psychiatric research to operationalize genetic propensity towards a particular mental disorder. PRSs hold promise as early predictors of psychiatric symptoms in clinical settings, but, before a PRS can be clinically used, their specificity towards a psychiatric domain needs to be evaluated and their explanatory power increased. In this study we tested whether PRSs associate more with general or specific psychopathology in school-aged children. In addition, we tested whether psychiatric PRSs can be combined into a multi-PRS score for improved performance.

Methods: We computed 16 PRSs based on GWASs of psychiatric outcomes, but also neuroticism and cognitive ability. Study participants were 9267 school-aged children from three population-based cohorts of the DREAM-BIG consortium: ALSPAC (England), The Generation R Study (the Netherlands) and MAVAN (Canada). We associated each PRS with general and specific psychopathology factors, derived from a bifactor model based on self-, parental-, teacher-, and observer reports. After fitting each PRS in separate models, we also tested a multi-PRS model, in which all PRSs are entered simultaneously as predictors of the general psychopathology factor.

Results: Seven PRSs were associated with the general psychopathology factor after multiple testing adjustment, two with specific externalizing and four with specific internalizing psychopathology. PRSs predicted general psychopathology independent of each other, with the exception of depression and depressive symptom PRSs. Each PRS associated with a specific psychopathology domain, was also associated with general child psychopathology.

Conclusions: The results suggest that PRSs based on current GWASs of psychiatric outcomes tend to be associated with general psychopathology, or both general and
specific psychiatric symptoms, but not with one specific psychopathology domain only. Furthermore, PRSs can be combined to improve predictive ability. PRS users should therefore be conscious of non-specificity and consider using multiple PRS simultaneously, when predicting psychiatric disorders.
KEYWORDS

Polygenic risk score; child psychopathology; general psychopathology; internalizing; externalizing; meta-analysis; comorbidity; ALSPAC; Generation R; MAVAN

ABBREVIATIONS

PRS: Polygenic Risk Score
GWAS: Genome-Wide Association Study
SNP: Single Nucleotide Polymorphism
ADHD: Attention-Deficit Hyperactivity Disorder
DREAM-BIG: Developmental Research in Environmental Adversity, Mental health, Biological susceptibility and Gender
ALSPAC: Avon Longitudinal Study of Parents and Children
GenR: Generation R
MAVAN: Maternal Adversity, Vulnerability and Neurodevelopment
Introduction

Many psychiatric disorders have a strong genetic basis (Polderman et al., 2015), thus uncovering the genetic pathways underlying the heritability of psychopathology holds the promise of individualized prediction and treatment. While most genome-wide associations studies of psychiatric disorders (GWAS) investigate distinct disorders, effects are often not unique to a specific disorder. For instance, GWAS-derived genetic correlations among psychiatric disorders average 0.41 (Anttila et al., 2018). Furthermore, a GWAS meta-analysis of eight disorders (attention-deficit/hyperactivity disorder (ADHD), anorexia, autism, bipolar, depression, obsessive-compulsive disorder, schizophrenia and Tourette’s) found 23 loci with strong evidence for association with at least four out of the eight disorders (Lee et al., 2019).

The non-specificity of GWAS findings overall raises the issue of whether specific polygenic risk scores (PRS) based on these GWASs can in fact predict specific psychiatric symptoms or disorders. PRSs are increasingly used in psychiatric research to operationalize the genetic predisposition towards a single disorder. They also hold promise as clinical tools to aid in prediction and prevention, by quantifying psychiatric risk before first symptoms develop (Wray et al., 2020). However, before clinical adoption is entertained, it is crucial for both researchers and clinicians to understand what symptoms or disorders a given psychiatric PRS is in fact predicting. However, a comprehensive overview of the specificity of PRSs is missing. This gap is even more pertinent in the context of child psychiatry, where symptoms are not as differentiated and often shift (Finsaas, Bufferd, Dougherty, Carlson, & Klein, 2018; Rutter, Kim-Cohen, & Maughan, 2006). Childhood manifestations of genetic risks towards psychiatric disorders are especially important to study for the development of early prediction systems.
A few studies have evaluated the specificity of PRSs, e.g., a PRS of schizophrenia predicted post-traumatic stress, bipolar and anxiety disorders (Zheutlin et al., 2019). Furthermore, an ADHD PRS was more strongly associated with a general psychopathology factor, encompassing symptoms from multiple domains, than a specific ADHD factor, which was specified to be independent of other psychiatric symptoms (Brikell et al., 2018). In another study a principal component of eight different PRSs was associated with general psychopathology (Allegrini et al., 2019). However, a comprehensive overview of different PRSs, which reports the degree to which they associate with general or specific psychopathology in childhood is missing.

In this study we examined i) whether individual PRSs derived from GWASs of specific psychiatric disorders, cognitive traits and neuroticism are predictive of general and/or specific psychopathologies in school-aged children; and, ii) the independent contribution of each PRS towards general psychopathology when combined with other PRSs. We hypothesized that—in addition to predicting their corresponding specific domain—each PRS is also associated with a general psychopathology factor. We further hypothesized that these associations will be substantially attenuated in mutually adjusted models.

Finally, while the prospective meta-analysis design is commonly used in GWAS, most PRS effects are typically tested in one sample. Given the importance of reliable and generalizable estimation of PRS associations, we studied these questions in the Developmental Research in Environmental Adversity, Mental health, Biological susceptibility and Gender (DREAM-BIG) project, a multi-center consortium which consists of comparable population-based cohorts with harmonized measures of psychopathology and genetics (Sallis et al., 2019; Szekely et al., 2020).
Methods

Participants

This study features three population-based prenatal cohorts from the DREAM-BIG consortium: the Avon Longitudinal Study of Parents and Children (ALSPAC) from England (Boyd et al., 2013; Fraser et al., 2013), Generation R (GenR) from the Netherlands (Kooijman et al., 2016), and the Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) study from Canada (O’Donnell et al., 2014). Participants in each study were included in the analytical sample if they had information on at least one psychopathology subscale and genotyped with a genome-wide SNP array. Ethical approval was obtained by local ethics committees (ALSPAC Ethics and Law Committee, Medical Ethics Committee of the Erasmus Medical Center, Douglas Mental Health University Institute and St-Joseph’s Hospital). Sibling relationships were removed by randomly excluding one sibling per family to avoid shared environment confounding. Only participants with European ancestry were included due to difficulties in applying PRSs derived from source GWAS of mostly European ancestry populations to other populations (Martin et al., 2019).

ALSPAC had 11,612 children with information on psychopathology, 6575 having genetic information. In GenR psychiatric information was available for 7946 children, 2418 were genotyped and of European ancestry. MAVAN had 408 children with information on psychopathology, 274 had genetic information. The total sample size in meta-analyses was 9267 (Table 1). See Supplemental Information 1 for further methods information.

[Insert Table 1]
Measures

Polygenic Risk Scores Selection

We computed PRSs for 16 different psychiatric disorders and related phenotypes including neuroticism and cognitive ability (Figure 1). We performed a systematic search of appropriate source GWAS on June 26th 2019 by examining all GWAS listed in the psychiatric genetic consortium (PGC) data index (https://www.med.unc.edu/pgc/data-index/), in any consortia linked in the PGC data index (ANGST, Converge, Eagle, GPC, SSGAC, CCACE), and in the UK Biobank data fields “20544: Mental health problems ever diagnosed by a professional” and “1200: Sleeplessness/insomnia”. We further added an EAGLE GWAS on total psychiatric problems.(Neumann et al., 2020) See Supplemental Information 1-2 for a complete PRS list.

[Insert Figure 1]

Genotyping

Each cohort genotyped participants using SNP arrays and applied cohort-specific QC (Supplemental Information 1). All cohorts imputed the data to the HRC 1.1 reference panel using either the Michigan Imputation Server(Das et al., 2016) for ALSPAC and GenR or Sanger Imputation Service for MAVAN (McCarthy et al., 2016). SNPs with a minor allele frequency below 1% or imputation quality (R²) below 0.80 were excluded prior to computation of the PRS. In ALSPAC and GenR PRSs were calculated with PRSice 2(Choi & O'Reilly, 2019) using the default option of clumping correlated SNPs within a 250kb window at a r² threshold of 0.1. In MAVAN an equivalent computation was performed with PRSoS using clumping setting of r² = 0.25 within a window of 500kb.(Chen et al., 2018) All cohorts calculated PRSs at the following p-value thresholds: 1, 0.5, 0.4, 0.3, 0.2, 0.1, 0.05, 0.01, 1x10⁻³, 1x10⁻⁴, 1x10⁻⁵, 1x10⁻⁶, 1x10⁻⁷, 5x10⁻⁸, 1x10⁻⁸.
Child Psychopathology

Each cohort had repeatedly collected several measures of psychopathology from 4 through 8 years of age. As children may behave differently in various environments (e.g. home vs school) and self-report at a young age is insufficient, we combined various instruments, including parental-, teacher-, self- and observer-rated, and diagnostic measures. See Sallis et al. (2019) and Supplemental Information for a complete description of instruments.

We estimated child psychopathology factors scores from a bifactor model, as described previously (Sallis et al., 2019). Briefly, we used a bifactor model to define a general psychopathology factor, which underlies all measured psychopathology subscales, and two orthogonal specific internalizing and externalizing factors. These specific factors underlie the subscales of one domain only and represent internalizing or externalizing specific variance, which is not shared with the other domain or other psychopathology.

Statistical Analysis

Separate PRS Models

We first analyzed the associations between each PRS and the three outcomes, i.e. general and specific internalizing and externalizing psychopathology, separately. We regressed child psychopathology factors scores on each PRS at every threshold in separate regression models in each cohort. All analyses were adjusted for sex and the first four components of ancestry (and average assessment age in GenR only).

Standardized regression coefficients and standard errors were extracted and meta-analyzed across all cohorts. We applied a random-effect meta-analysis using the Han and
Eskin method, which accounts for study heterogeneity, while retaining power comparable to fixed effects (Han & Eskin, 2011). We adjusted for multiple testing, by estimating the number of effective tests by accounting for the correlation between all PRSs and all thresholds. We used the largest cohort (ALSPAC) to derive the correlation structure between the variables (Figure S1). Using the Li & Ji (2005) method, as implemented in the poolR package (Cinar & Viechtbauer), we estimated that the number of independent tests is 99, resulting in a Bonferroni adjusted p-value threshold of 0.05/99=5.0x10^{-4}. To test for differences in association strength between the specific factors and the general psychopathology factor, we applied z-tests.

**Mutually Adjusted PRS Model**

Next, we included all PRSs at their most significant threshold (based on the single models above) in a mutually adjusted PRS model to estimate the independent contribution of each PRS to general psychopathology in each cohort. More specifically, we fitted a regression model including all 16 PRSs (listed in Table 3), as predictors of the general psychopathology factor. Within all PRSs of the same phenotype, only the threshold which showed the lowest p-value PRS in the separate models was selected for the mutually adjusted analysis. Mutually adjusted PRS models were adjusted for the same covariates and meta-analyzed using the same approach as the separate PRS models. Associations were considered significant at a threshold of p<0.05, as only one model was tested. To quantify the variance in the general psychopathology that the top independently associated PRSs (p<0.05) jointly explained, we computed predicted general psychopathology factor scores in each cohort using the regression weights obtained from meta-analyses. These scores were then associated with the observed general psychopathology factor scores to obtain a measure of explained variance.
**Results**

Seven PRSs were associated with general psychopathology in unadjusted models (Table 2), two PRSs were associated with the specific externalizing factor and four with the specific internalizing factor (Table 4). The PRSs for cognitive ability, ADHD, major depression, neuroticism, schizophrenia, insomnia and depressive symptoms were all associated with general psychopathology. Associations were in the expected directions, with a PRS for higher cognitive ability predicting lower general psychopathology, while a higher genetic risk for a psychiatric disorder or neuroticism was associated with a higher propensity for general psychopathology. The nominally significant PRSs jointly explained 2.39% of the general psychopathology factor variance (weighted average across three cohorts). Interestingly, all associated PRSs showed contributions to general psychopathology independent of each other, with the exception of major depression and depressive symptoms (Table 3). These PRSs correlated only modestly (r=0.23). The lack of independent association for the PRSs for major depression and depressive symptoms was not explained by the inclusion of two depression-related PRS in the model but rather by the inclusion of non-depression PRSs.

[Insert Table 2-3]

For the specific externalizing psychopathology, only the ADHD and cognitive ability PRSs contributed robustly (Table 4). A genetic predisposition towards ADHD and lower cognitive ability was less predictive of specific externalizing psychopathology than of general psychopathology.

For specific internalizing psychopathology, we observed associations with the PRSs for neuroticism, ADHD, major depression, and schizophrenia (Table 4). The effect size of
the neuroticism PRS was similar for the specific internalizing factor and for general psychopathology. However, the ADHD, major depression and schizophrenia PRSs effect sizes for specific internalizing factor were lower than for general psychopathology factor. It should be noted, that the evidence for effect size difference between general and specific psychopathology was weak for all effect size comparisons.

[Insert Table 4]
Discussion

In this study we identified several PRSs associated with general and specific internalizing/externalizing psychopathology in children across three independent cohorts. Seven PRSs, representing the genetic propensity towards cognitive ability, ADHD, major depression, neuroticism, schizophrenia, insomnia and depressive symptoms, were associated with general psychopathology in school-aged children. All but two (major depression and depressive symptoms) PRSs contributed independently towards general psychopathology. Only two PRSs were associated with specific externalizing psychopathology: ADHD and cognitive ability. Four PRSs were associated with specific internalizing psychopathology: neuroticism, ADHD, major depressive disorder and schizophrenia. In general, the PRS associations support the validity of the bifactor structure of child psychopathology, with genetic predictors from various psychiatric domains being associated with general psychopathology and a narrower, more domain specific set of PRSs associating with specific psychopathology.

The main finding of this study is that PRSs for psychiatric and psychological traits are unlikely to be associated with specific psychopathology exclusively in childhood. PRSs associated with school-age psychopathology tended to either associate with general psychopathology only, or both general and specific psychopathology, but not with specific psychopathology only. It follows from our findings, that a PRS based on the GWAS of a specific psychiatric disorder may be a good predictor for that disorder, but is also very likely to be predictive of symptoms of other psychiatric domains. In fact, effect sizes tended to be larger for general than specific psychopathology. This may indicate that PRSs for psychiatric disorders heavily weigh SNPs, which have extensive cross-disorder effects in childhood. On the one hand, this reflects the comorbid nature of psychiatric disorders. On
the other hand, this makes interpretation of PRS associations difficult. A child scoring high on a PRS of a specific psychiatric disorder could actually develop many distinct symptoms from different domains. The development of more specific PRSs are therefore needed for more detailed projections of symptom profiles. Such PRSs could be potentially obtained by performing GWAS of specific disorders adjusted for general psychopathology. Until then, researchers and clinicians must take these cross-phenotype associations into account when interpreting results of PRS studies. Caution is especially warranted when using a PRS as genetic instrument for specific disorders or symptoms in Mendelian randomization studies. Most PRSs would likely violate the exclusion assumption, i.e. they may affect the outcome via pathways that do not involve the specific disorder they were computed to predict.

Another implication of the results is that in the pursuit of improving genetic predictions of psychiatric disorders, researchers should not only consider computing PRSs based on GWAS of the trait they intend to predict, but also consider PRSs of related traits. As example, while not a psychiatric phenotype, cognitive ability was one of the best predictors of general and specific externalizing psychopathology. This does not mean that conceptually cognition-related SNPs are more associated with general psychopathology than psychiatric SNPs. Rather, the robust association may also be explained by a PRS stemming from a large sample size GWAS of cognitive ability. Thus, PRSs of related traits may be especially useful, when large source GWAS of the target trait are lacking.

Most PRSs associated with general psychopathology had unique effects, with the exception of depression PRSs. Thus, the third implication of our study is that multiple PRSs should be used jointly for improved prediction of general psychopathology. However, currently the inclusion of depression PRSs may be redundant, as SNPs included in the
depression PRSs with general effects can be expressed quite well as linear combination of
general effects from other PRSs.

A strength of this study was the prospective meta-analysis study design. Our study
is the first attempt to harmonize genetic risk scores and latent constructs of child
psychopathology in multiple independent cohorts that used different measures to assess
these developmental problems. We benefited in particular from the inclusion of a wide
range of measures, the inclusion of repeated assessments and multiple informants.
Besides the improved precision through increased sample size, we also expect the results
to generalize better to other populations of European ancestry compared to a single cohort
study. Further investigations are needed in non-European ancestry populations to
determine to what extent the results generalize in other ancestries. Another strength is the
systematic search and selection of PRSs. This enabled us to test a wide variety of PRSs
and form conclusions based on the current state of psychiatric PRSs as a whole.

While the study was well powered to identify whether a PRS is associated with
general or specific psychopathology, the power to detect differences in the association
strength between general and specific pathways was more limited. Also the variance
explained in general psychopathology while improved by inclusion of multiple PRSs, does
still not reach the estimated SNP heritability of 18 to 36% (Alnæs et al., 2018; Neumann et
al., 2016). However, the insights gained from this study in regard to specificity and
independence of PRSs will hopefully in combination with better powered source GWAS
help in the development of multi-PRS scores with high explanatory power and clinical
utility.

In conclusion, our findings demonstrate that many PRSs for psychiatric traits are
associated with general psychopathology in school-aged children. These effects were
mostly independent of each other with the exception of depression-related PRS effects.
Several PRSs were also associated with specific externalizing and specific internalizing psychopathology. However, no PRS predicted specific psychopathology without being associated with general psychopathology. Finally, we recommend that researchers should use a combination of multiple PRSs when predicting child psychiatric symptoms.
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GenR
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Table 1: Cohort characteristics

| Characteristic       | Category           | ALSPAC M (SD) or % | GenR M (SD) or % | MAVAN M (SD) or % |
|----------------------|--------------------|--------------------|------------------|------------------|
| Sex                  | Female             | 48.9%              | 51.0%            | 49.3%            |
|                      | Male               | 51.1%              | 49.0%            | 50.7%            |
| Maternal Age at Birth|                    |                    |                  |                  |
|                      | CSE/None           | 14.0%              | None/Primary     | 0.5%             | Low 14.4%        |
|                      | Vocational         | 8.7%               |                  |                  |
|                      | A-level            | 25.6%              | Secondary        | 28.1%            | Medium 33.5%     |
|                      | University         | 16.6%              | University       | 71.5%            | High 52.1%       |
| Income               | Quintile 1         | 15.8%              | <1,600€ p.m.     | 5.1%             | <15,000CAD p.y.  | 5.6%            |
|                      | Quintile 2         | 18.7%              | <2,400€ p.m.     | 9.0%             | <30,000CAD p.y.  | 13.6%           |
|                      | Quintile 3         | 20.8%              | <3,200€ p.m.     | 18.5%            | <45,000CAD p.y.  | 11.3%           |
|                      | Quintile 4         | 21.8%              | <4,800€ p.m.     | 34.9%            | <90,000CAD p.y.  | 33.8%           |
|                      | Quintile 5         | 22.9%              | ≥4,800€ p.m.     | 32.5%            | ≥ 90,000CAD p.y. | 35.7%           |

M mean

SD Standard Deviation
| GWAS phenotype for PRS | PRS p cutoff | ALSPAC (n=6575) | GenR (n= 2418) | MAVAN (n=274) | Meta-Analysis (n=9267) |
|------------------------|-------------|----------------|----------------|--------------|------------------------|
|                        |             | β   SE | β   SE | β   SE | β   τ   SE   p    |
| Cognitive ability      | 1           | -0.12 0.01 | -0.05 0.02 | -0.03 0.08 | -0.079 0.046 0.032 3.9E-25* |
| ADHD                   | 3E-01       | 0.11 0.01 | 0.06 0.02 | 0.15 0.07 | 0.095 0.024 0.019 2.7E-23* |
| Major Depression       | 5E-02       | 0.07 0.01 | 0.04 0.02 | 0.08 0.07 | 0.060 0.000 0.010 2.7E-09* |
| Neuroticism            | 1E-02       | 0.05 0.01 | 0.07 0.02 | 0.09 0.08 | 0.056 0.000 0.010 2.6E-08* |
| Schizophrenia          | 5E-02       | 0.05 0.01 | 0.05 0.02 | -0.14 0.19 | 0.051 0.000 0.010 4.4E-07* |
| Insomnia               | 2E-01       | 0.06 0.01 | 0.02 0.02 | 0.00 0.06 | 0.041 0.022 0.019 5.7E-07* |
| Depressive symptoms    | 3E-01       | 0.05 0.01 | 0.00 0.02 | 0.05 0.07 | 0.034 0.025 0.020 3.5E-05* |
| Alcohol abuse          | 2E-01       | 0.04 0.01 | -0.02 0.02 | -0.01 0.07 | 0.009 0.041 0.029 2.5E-03 |
| Bipolar                | 1E-04       | 0.03 0.01 | 0.02 0.02 | 0.12 0.06 | 0.027 0.010 0.012 9.9E-03 |
| Cross-disorder         | 1E-01       | 0.03 0.01 | 0.00 0.02 | 0.21 0.14 | 0.023 0.023 0.019 1.2E-02 |
| Autism                 | 1E-01       | -0.01 0.01 | 0.07 0.02 | -0.07 0.07 | 0.015 0.050 0.034 1.6E-02 |
| Total problems         | 2E-01       | 0.02 0.01 | 0.02 0.02 | 0.02 0.10 | 0.021 0.000 0.010 4.1E-02 |
| Generalized anxiety    | 1E-02       | 0.02 0.01 | 0.03 0.02 | 0.02 0.07 | 0.020 0.000 0.010 5.5E-02 |
| Social anxiety         | 1E-02       | -0.02 0.01 | -0.01 0.02 | 0.10 0.06 | -0.007 0.024 0.019 1.0E-01 |
| Phobia                 | 2E-01       | 0.01 0.01 | 0.02 0.02 | 0.04 0.07 | 0.015 0.000 0.010 1.6E-01 |
| Panic                  | 1E-05       | 0.00 0.01 | 0.04 0.02 | 0.09 0.06 | 0.022 0.020 0.017 2.0E-01 |

**Table 2: General psychopathology factor regressed on PRS (each PRS in separate model)**

- **PRS p cutoff**: P-value of PRS threshold with most significant association with outcome
- **β**: Standardized regression coefficient in standard deviations
- **SE**: Standard Error
- **τ**: Random effect of study in standard deviations
- **p**: P-value of regression coefficient

*Significant p-value after multiple testing adjustment (p<5.0E-04)

**Note**: Standard errors for the schizophrenia, cross-disorder (which includes schizopohrenia) and bipolar PRS were inflated in the MAVAN cohort due to multicollinearity with genetic ancestry. Estimates are unbiased, but have higher uncertainty. Uncertainty is taken into account in the pooled estimates.
Table 3: General psychopathology factor regressed on PRS (mutually adjusted PRS model)

| GWAS phenotype for PRS | PRS p cutoff | ALSPAC (n=6575) | GenR (n=2418) | MAVAN (n=274) | Meta-Analysis (n=9267) |
|-----------------------|-------------|-----------------|--------------|---------------|-----------------------|
|                       |             | β    SE        | β    SE      | β    SE       | β    τ    SE    p    |
| Cognitive ability     | 1           | -0.10 0.01     | -0.04 0.02   | 0.02 0.08     | -0.059 0.040 0.029 3.1E-15* |
| ADHD                  | 3E-01       | 0.10 0.01      | 0.05 0.02    | 0.19 0.09     | 0.084 0.035 0.026 3.3E-17* |
| Major Depression      | 5E-02       | 0.02 0.01      | 0.00 0.02    | 0.04 0.08     | 0.018 0.000 0.011 1.1E-01 |
| Neuroticism           | 1E-02       | 0.02 0.01      | 0.06 0.02    | 0.07 0.08     | 0.038 0.024 0.020 8.2E-03* |
| Schizophrenia         | 5E-02       | 0.03 0.01      | 0.04 0.02    | -0.25 0.22    | 0.034 0.000 0.010 1.7E-03* |
| Insomnia              | 2E-01       | 0.04 0.01      | 0.00 0.02    | 0.00 0.07     | 0.023 0.014 0.014 9.4E-03* |
| Depressive symptoms   | 3E-01       | 0.02 0.01      | -0.02 0.02   | 0.04 0.08     | 0.007 0.021 0.018 2.2E-01 |
| Alcohol abuse         | 2E-01       | 0.02 0.01      | -0.03 0.02   | -0.10 0.07    | -0.015 0.039 0.028 1.3E-01 |
| Bipolar               | 1E-04       | 0.01 0.01      | 0.00 0.02    | 0.05 0.07     | 0.010 0.000 0.010 3.5E-01 |
| Cross-disorder        | 1E-01       | 0.00 0.01      | 0.00 0.02    | 0.19 0.15     | 0.002 0.000 0.010 8.8E-01 |
| Autism                | 1E-01       | -0.03 0.01     | 0.04 0.02    | -0.11 0.08    | -0.011 0.051 0.035 1.6E-02 |
| Total problems        | 2E-01       | 0.01 0.01      | 0.01 0.02    | -0.02 0.11    | 0.009 0.000 0.010 4.3E-01 |
| Generalized anxiety   | 1E-02       | 0.00 0.01      | 0.02 0.02    | 0.04 0.07     | 0.008 0.000 0.010 4.5E-01 |
| Social anxiety        | 1E-02       | -0.03 0.01     | -0.01 0.02   | 0.10 0.07     | -0.015 0.020 0.017 3.5E-02 |
| Panic                 | 2E-01       | 0.01 0.01      | 0.04 0.02    | 0.08 0.06     | 0.020 0.011 0.013 9.0E-02 |
| Phobia                | 1E-05       | -0.01 0.01     | 0.02 0.02    | -0.04 0.07    | -0.006 0.003 0.010 5.8E-01 |

**PRS p cutoff** P-value of PRS threshold with most significant association with outcome

**β** Standardized regression coefficient in standard deviations

**τ** Random effect of study in standard deviations

**SE** Standard Error

**p** P-value of regression coefficient

*PRS with nominal significance in mutually adjusted model and multiple testing adjusted significance in separate PRS models*

**Note:** Standard errors for the schizophrenia, cross-disorder (which includes schizophrenia) and bipolar PRS were inflated in the MAVAN cohort due to multicollinearity with genetic ancestry. Estimates are unbiased, but have higher uncertainty. Uncertainty is taken into account in the pooled estimates.
Table 4: Specific psychopathology factors regressed on PRS (single PRS model)

| GWAS phenotype for PRS | PRS p cutoff | ALSPAC (n=6575) | GenR (n=2418) | MAVAN (n=274) | Meta-Analysis (n=9267) | Ext/Int-Gen Δp |
|------------------------|-------------|----------------|-------------|-------------|----------------|-----------------|
|                        |             | β   SE  | β   SE  | β   SE  | β   SE  | τ   SE  | p   |
| **Externalizing**      |             |       |       |       |       |       |     |
| ADHD                   | 5E-01       | 0.00  0.01 | 0.13  0.02 | 0.03  0.08 | 0.059 0.084 0.054 4.4E-09* | 5.3E-01 |
| Cognitive ability      | 5E-02       | -0.02 0.01 | -0.09 0.02 | -0.03 0.07 | -0.048 0.046 0.032 6.2E-05* | 4.9E-01 |
| Total problems         | 1           | 0.01  0.01 | 0.08  0.02 | 0.04  0.10 | 0.044 0.046 0.033 6.4E-04 | 5.2E-01 |
| Autism                 | 4E-01       | 0.04  0.01 | 0.04  0.02 | 0.05  0.07 | 0.036 0.000 0.010 6.5E-04 | 5.6E-01 |
| Bipolar                | 5E-01       | 0.03  0.01 | 0.04  0.02 | 0.01  0.33 | 0.036 0.000 0.011 9.7E-04 | 5.9E-01 |
| Panic                  | 1E-03       | 0.03  0.01 | 0.02  0.02 | 0.02  0.03 | 0.027 0.000 0.010 1.3E-02 | 8.0E-01 |
| Cross-disorder         | 3E-01       | -0.04 0.01 | 0.02  0.02 | 0.02  0.18 | -0.010 0.035 0.027 1.6E-02 | 3.1E-01 |
| Depressive symptoms    | 1E-05       | -0.03 0.01 | -0.01 0.02 | 0.03  0.06 | -0.025 0.000 0.010 1.9E-02 | 8.8E-03* |
| Alcohol abuse          | 1E-05       | 0.03  0.01 | 0.02  0.02 | 0.06  0.07 | 0.024 0.000 0.010 2.8E-02 | 6.2E-01 |
| Major Depression       | 5E-02       | 0.00  0.01 | 0.07  0.02 | 0.00  0.07 | 0.025 0.041 0.029 2.9E-02 | 2.6E-01 |
| Social anxiety         | 1E-02       | 0.03  0.01 | 0.02  0.02 | -0.04 0.07 | 0.023 0.000 0.010 3.6E-02 | 1.7E-01 |
| Phobia                 | 1E-05       | 0.02  0.01 | 0.02  0.02 | -0.07 0.06 | 0.017 0.007 0.012 1.1E-01 | 9.0E-01 |
| Schizophrenia          | 1E-04       | -0.02 0.01 | -0.01 0.02 | -0.01 0.09 | -0.015 0.000 0.010 1.9E-01 | 5.4E-06* |
| Insomnia               | 1E-05       | -0.01 0.01 | 0.00  0.02 | -0.12 0.06 | -0.013 0.018 0.016 3.9E-01 | 2.8E-02* |
| Neuroticism            | 1E-03       | -0.01 0.01 | -0.01 0.02 | 0.11  0.07 | -0.004 0.018 0.017 4.3E-01 | 1.8E-03* |
| Generalized anxiety    | 1E-02       | 0.00  0.01 | 0.04  0.02 | 0.12  0.07 | 0.020 0.017 0.110 8.0E-01 | 2.5E-02* |
| **Internalizing**      |             |       |       |       |       |       |     |
| Neuroticism            | 3E-01       | 0.07  0.01 | 0.04  0.02 | 0.13  0.07 | 0.061 0.003 0.011 5.8E-09* | 7.5E-01 |
| ADHD                   | 5E-02       | -0.03 0.01 | 0.08  0.02 | 0.06  0.07 | 0.031 0.071 0.046 2.1E-04* | 2.0E-01 |
| Major Depression       | 2E-01       | 0.04  0.01 | 0.03  0.02 | 0.04  0.07 | 0.037 0.000 0.010 4.3E-04* | 1.2E-01 |
| Schizophrenia          | 4E-01       | 0.05  0.01 | 0.00  0.02 | 0.45  0.24 | 0.033 0.038 0.029 4.7E-04* | 5.5E-01 |
| Generalized anxiety    | 2E-01       | 0.04  0.01 | 0.02  0.02 | 0.09  0.06 | 0.037 0.000 0.010 5.4E-04 | 2.5E-01 |
| Cognitive ability      | 1E-04       | 0.02  0.01 | -0.08 0.02 | -0.05 0.06 | -0.031 0.066 0.043 6.5E-04 | 3.7E-01 |
| Depressive symptoms    | 3E-01       | 0.03  0.01 | 0.06  0.02 | 0.02  0.08 | 0.035 0.000 0.010 1.0E-03 | 9.7E-01 |
| Cross-disorder         | 2E-01       | 0.04  0.01 | 0.00  0.02 | 0.01  0.16 | 0.025 0.021 0.019 3.0E-03 | 9.4E-01 |
| Social anxiety         | 1           | 0.02  0.01 | 0.04  0.02 | -0.02 0.06 | 0.026 0.000 0.010 1.5E-02 | 1.3E-01 |
| Autism                 | 1E-02       | 0.02  0.01 | 0.05  0.02 | 0.05  0.07 | 0.024 0.000 0.010 2.3E-02 | 8.0E-01 |
| Total problems         | 1           | 0.00  0.01 | 0.06  0.02 | 0.22  0.10 | 0.047 0.046 0.033 2.1E-02 | 4.7E-01 |
| Bipolar                | 1E-04       | 0.04  0.01 | -0.02 0.02 | -0.02 0.07 | 0.009 0.030 0.023 3.0E-02 | 4.9E-01 |
| Phobia                 | 1           | 0.01  0.01 | 0.05  0.02 | -0.01 0.07 | 0.025 0.019 0.017 5.6E-02 | 6.1E-01 |
| Insomnia               | 1E-01       | 0.01  0.01 | 0.02  0.02 | 0.04  0.06 | 0.016 0.000 0.010 1.5E-01 | 2.4E-01 |
| Panic                  | 5E-01       | 0.01  0.01 | 0.03  0.02 | -0.03 0.06 | 0.015 0.000 0.010 1.9E-01 | 7.3E-01 |
| Alcohol abuse          | 1E-04       | -0.01 0.01 | -0.01 0.02 | 0.00  0.06 | -0.013 0.000 0.010 2.5E-01 | 4.8E-01 |

**PRS p cutoff** P-value of PRS threshold with most significant association with outcome
β  Standardized regression coefficient in standard deviations
τ  Random effect of study in standard deviations
SE  Standard Error
p  P-value of regression coefficient

Ext/Int-Gen Δp  P-value for difference in estimates between general and specific factor
*  Significant p-value after multiple testing adjustment (p<5.0E-04) or nominal significance (p<0.05) for Ext/Int-Gen Δp

Note: Standard errors for the schizophrenia, cross-disorder (which includes schizophrenia) and bipolar PRS were inflated in the MAVAN cohort due to multicollinearity with genetic ancestry. Estimates are unbiased, but have higher uncertainty. Uncertainty is taken into account in the pooled estimates.
GWAS Database:
PGC Data Index
Consortia linked in PGC Data Index (ANGST, Converge, Eagle, GPC, SSGAC, CCACE)
UKB "20544: Mental health problems ever diagnosed by a professional"
and "1200: Sleeplessness / insomnia" data field
Unpublished EAGLE GWAS

GWAS of psychiatric disorders, neuroticism or cognitive ability: 47

GWAS with sufficient sample size: 22

Select only 1 GWAS per construct with highest n or highest number of cases

Final GWAS selection: 16

Inclusion:
Psychiatric Disorder (Diagnosis or continuous)
Combination of disorders
Neuroticism
Cognitive Ability

Exclusion:
Single symptoms/components

Remove GWAS with n<30,000

If case-control:
Additional exclusion if number of cases n<1000

Removal of pooled schizophrenia and bipolar GWAS due to high correlation with original GWAS