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Table 1: Literature review: SNP heritability of child and adolescent emotional problems

Reference	Year	Trait	Sample	Measure	Age	Reporter	N	SNP heritability	SE	P value
Benke et al.	2014	Emotional problems	Gen R	CBCL 1.5-5 internalising scale	3	Primary caregiver	2037	0.26	NA	0.07
			NTR	CBCL 2-3 internalising scale	3	Mother	1475	0.18	NA	0.3
			Raine	CBCL 2-3 internalising scale	2	Primary caregiver	1084	0.13	NA	0.33
Pappa et al.	2015	Emotional problems	NTR / Gen R	CBCL internalising	7	Parent	3175	0.12	0.1	
Sallis et al.	2017	Depressive Symptoms	ALSPAC	Short Moods and Feelings Questionnaire (SMFQ)	11	Child	5480	0.07	0.1	
					13	Child	5055	0.17	0.1	
					14	Child	4615	0.02	0.1	
					17	Child	3605	0.08	0.1	
					18	Child	3289	0.03	0.1	
					19	Child	2433	0.05	0.1	
					10	Parent	5571	0.04	0.1	
					12	Parent	5119	0.12	0.1	
					13	Parent	5031	0.07	0.1	
					17	Parent	3990	0.04	0.1	

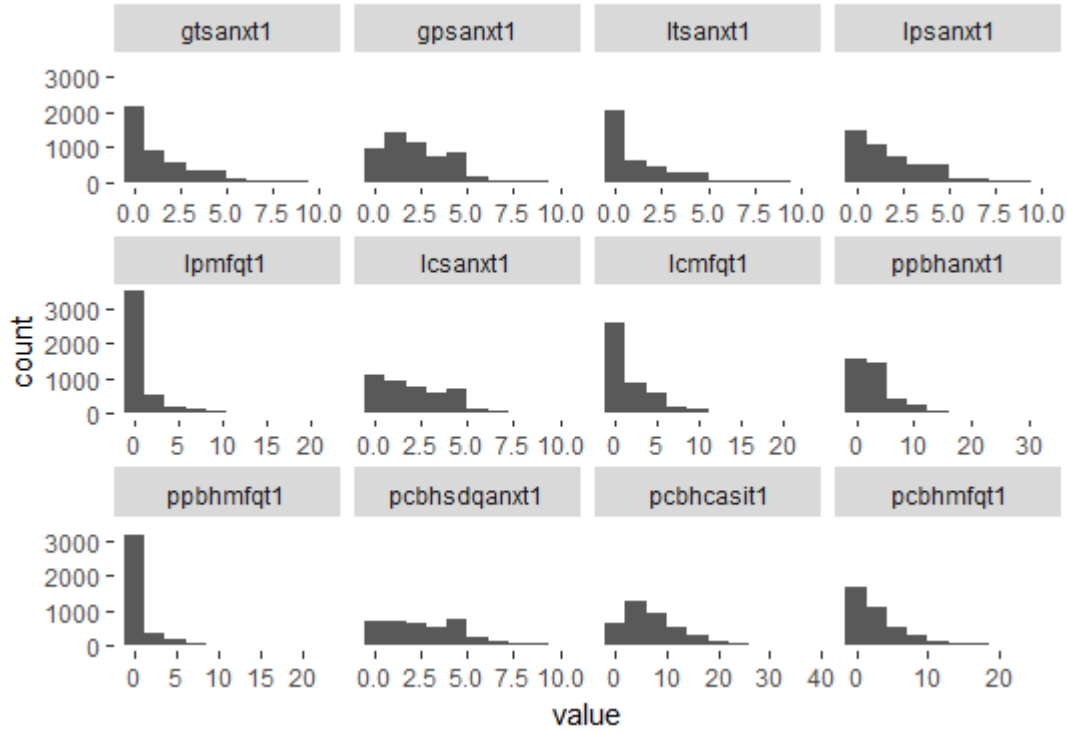
Note: Gen R= Generation R; NTR= Netherlands Twin Register; ALSPAC= Avon Longitudinal Study of Parents and Children; CBCL = Child Behaviour Checklist.

Three studies in samples other than TEDS have estimated SNP heritabilities for quantitative measures of childhood anxiety and depression, known as emotional problems, or internalising'. The average SNP heritability estimate from these studies is 10%. Although this is twice as high as the average in this study from the TEDS sample (5%), 10% SNP heritability is still well below half of the twin estimates of these phenotypes in the literature (40-60% in TEDS). Larger samples are needed to clarify this inconsistent and underpowered literature. For example, the study of pre-school internalising symptoms (Benke et al., 2014) had maximum 35% power with a sample of 2000 if true SNP heritability was half of the twin estimate they cite (50%), and a minimum of 10% power with a sample of 1000 and heritability of 20%. Moreover, the large ranges within the studies makes the estimates difficult to interpret.

Table 2: Descriptive statistics for the 12 TEDS anxiety and depression scales

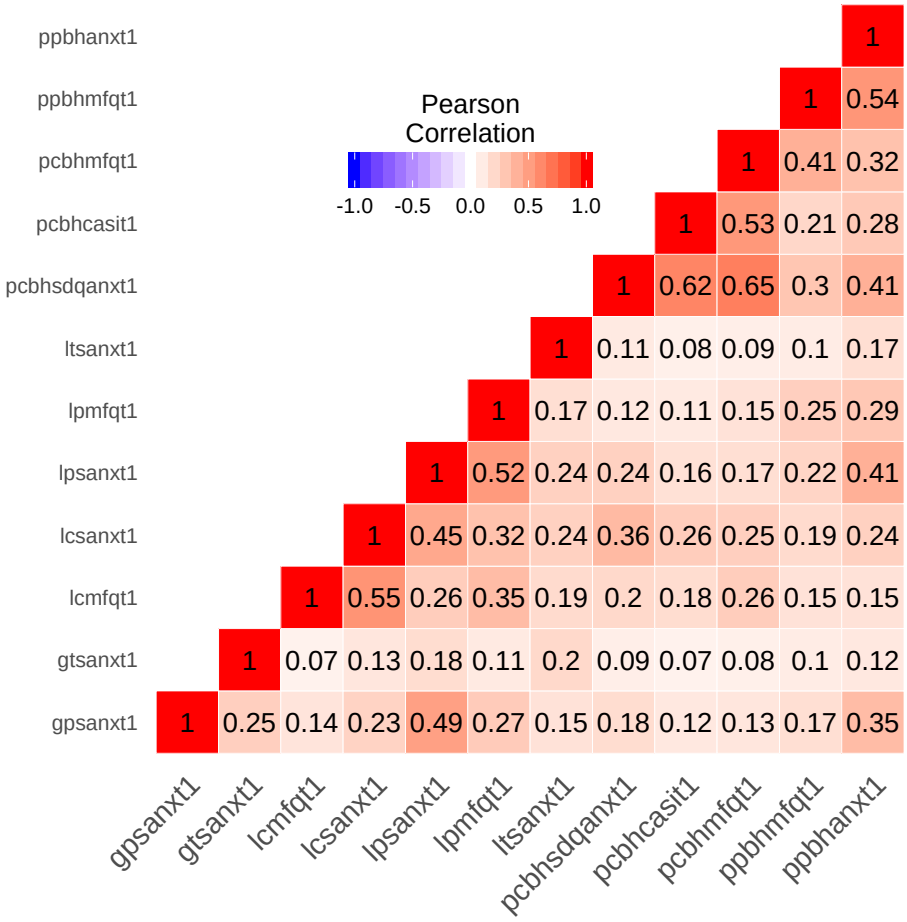
	Measure	**Sample size (twin pairs)**	**Number of items**	**Mean**	**Standard deviation**
1	Parent-rated SDQ at 7	5367	5	2.13	1.80
2	Teacher-rated SDQ at 7	4419	5	1.30	1.77
3	Parent-rated MFQ at 12	4486	11	1.13	2.24
4	Parent-rated SDQ at 12	4487	5	1.77	1.91
5	Self-rated MFQ at 12	4493	11	2.30	3.28
6	Self-rated SDQ at 12	4475	5	2.17	2.05
7	Teacher-rated SDQ at 12	3713	5	1.16	1.77
8	Parent-rated ARBQ at 16	3845	19	3.43	4.08
9	Parent-rated MFQ at 16	3844	11	0.96	2.28
10	Self-rated CASI at 16	3831	18	7.85	5.86
11	Self-rated MFQ at 16	3832	13	3.59	4.37
12	Self-rated SDQ at 16	3830	5	2.76	2.27

Figure 1: Histograms of TEDS anxiety and depression scales



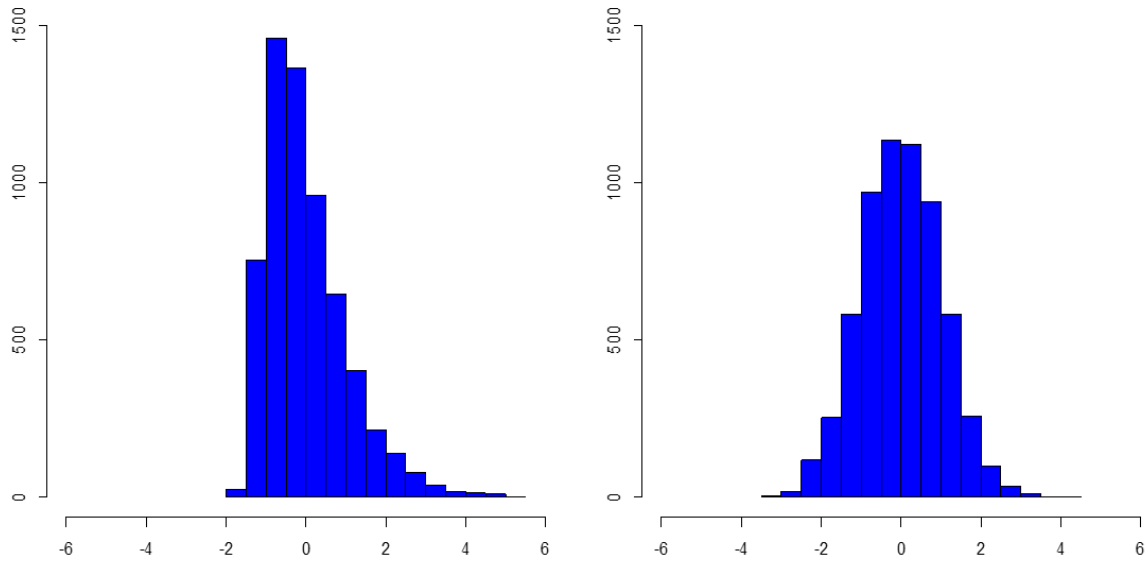
Note: 'gtsanxt1'= Teacher-rated SDQ at 7, 'gpsanxt1'= Parent-rated SDQ at 7, 'ltsanxt1'= Teacher-rated SDQ at 12, 'lpsanxt1' = Parent-rated SDQ at 12, 'lpmfqt1'= Parent-rated MFQ at 12, 'lcsanxt1'= Self-rated SDQ at 12 ,'lcmfqt1'= Self-rated MFQ at 12, 'ppbhanxt1'= Parent-rated ARBQ at 16, 'ppbhmfqt1= Parent-rated MFQ at 16', 'pcbhsdqanxt1'= Self-rated SDQ at 16,'pcbhcasit1'= Self-rated CASI at 16, 'pcbhmfqt1'= Self-rated MFQ at 16.

Figure 2: Phenotypic correlations of the 12 anxiety and depression scales at ages 7, 12 and 16



Note: correlations were calculated in R, before any data cleaning, and including only the people with genotype data and complete data for these 12 scales. See Note of Supplementary Figure 1 for variable names.

Figure 3: histograms of CFA- (left) and IRT-derived (right) stable emotional problems scores



Note that the correlation between CFA and IRT factor scores is 0.92.

CFA model fit and factor loadings

Table 3: Twin correlations for emotional problems stable latent factor from CFA

Twin correlations	
MZ	0.85
DZ	0.489

Table 4: Model Fit

The single-factor model did not provide a good fit to the data. CFI and TLI were less than 0.9, suggesting worse fit than a restricted baseline model, and RMSEA was significantly greater than 0.05, suggesting poor fit. However, poor fit might be expected: it could reflect the lack of stability of anxiety across childhood (as indicated by the low correlations across our measures (heat map above), and the low stability in the literature), or it could reflect the higher than modelled associations within raters and within time-points.

Fit indices for the CFA model of childhood emotional problems	
CFI	0. 68
TLI	0. 69
RMSEA	0.08

Note: RMSEA = Root-Mean-Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index.

Table 5: Standardised Factor Loadings

With regard to the CFA model, all measures load significantly onto the stable emotional problems factor. All measures loaded ≥0.5, apart from the two teacher-rated measures, and self-rated MFQ at 12.

Measure	Factor Loading	SE
Parent-rated SDQ at 7	0.51	0.00
Teacher-rated SDQ at 7	0.42	0.01
Self-rated MFQ at 12	0.33	0.01
Self-rated SDQ at 12	0.61	0.01
Parent-rated SDQ at 12	0.50	0.01
Parent-rated MFQ at 12	0.62	0.01
Teacher-rated SDQ at 12	0.49	0.01
Self-rated SDQ at 16	0.61	0.01

Self-rated CASI at 16	0.56	0.01
Self-rated MFQ at 16	0.73	0.01
Parent-rated MFQ at 16	0.59	0.01
Parent-rated ARBQ at age 16	0.68	0.01

Table 6: Residual variances

Measure	Residual variance	SE
Parent-rated SDQ at 7	0.74	0.00
Teacher-rated SDQ at 7	0.82	0.01
Self-rated MFQ at 12	0.89	0.01
Self-rated SDQ at 12	0.63	0.01
Parent-rated SDQ at 12	0.75	0.01
Parent-rated MFQ at 12	0.61	0.01
Teacher-rated SDQ at 12	0.76	0.01
Self-rated SDQ at 16	0.63	0.01
Self-rated CASI at 16	0.69	0.01
Self-rated MFQ at 16	0.47	0.01
Parent-rated MFQ at 16	0.65	0.01
Parent-rated ARBQ at age 16	0.54	0.01

Full genotyping information

DNA from 3665 individuals extracted from buccal cheek swabs was hybridized to AffymetrixGeneChip 6.0 SNP genotyping arrays using standard WTCCC2 experimental protocols. 4649 other individuals of European ancestry were genotyped on HumanOmniExpressExome-8v1.2 arrays at the Molecular Genetics Laboratories of the Medical Research Council Social, Genetic Developmental Psychiatry Centre, based on DNA extracted from saliva samples.

After initial quality control and genotype calling, the same quality control was conducted on the samples genotyped on the Affymetrix and Illumina platforms separately using PLINK (Purcell et al. 2007; Chang et al. 2015), R (GBIF.ORG n.d.), and vcftools (Danecek et al. 2011). Samples were removed based on call rate (<0.99), suspected non-European ancestry, heterozygosity, array signal intensity, and relatedness. SNPs were excluded if minor allele frequency was <0.5% , if more than 1% of genotype data were missing, or if the Hardy Weinberg p-value was lower than 10-5. Non-autosomal markers and indels were removed. Associations between the SNP and the platform, batch, or plate on which samples were genotyped were calculated; SNPs with p-values less than 10-3 were excluded. A total sample of 6710 individuals remained after quality control – 3093 individuals and 525 859 SNPs genotyped on the Affymetrix platform and 3617 individuals and 600 034 SNPs genotyped on the Illumina platform.

Genotypes from the two platforms were separately imputed using the Haplotype Reference Consortium 5 and Minimac3 1.0.13 (Howie et al. 2012; Fuchsberger et al. 2015) before merging genotype data obtained from both arrays.

We performed principal component analysis on a subset of 42 859 common (MAF>5%) autosomal HapMap3 SNPs (International HapMap 3 Consortium et al. 2010), after stringent pruning to remove markers in linkage disequilibrium (r2 >0.1) and excluding high linkage disequilibrium genomic regions so as to ensure that only genome-wide effects were detected.

SNP heritability: supplementary methods

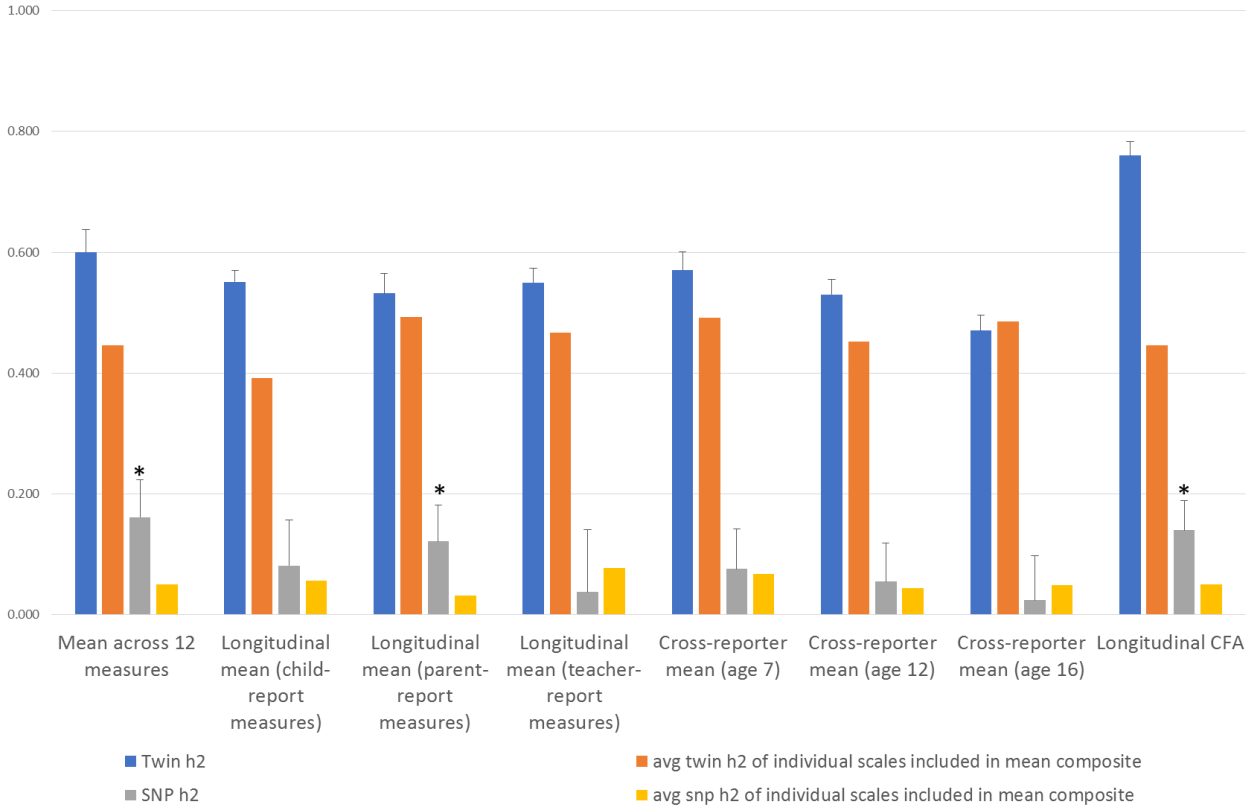
SNP heritabilities were estimated using genomic relatedness matrix restricted maximum likelihood (GREML), implemented in the Genome-wide Complex Trait Analysis (GCTA) program (Yang et al. 2011). This estimates genetic influence directly using genome-wide genotypes in large samples of unrelated individuals. First, genetic similarity for each pair of unrelated individuals across all genotyped or imputed genetic markers is calculated. Each pair's genetic similarity is then used to predict their phenotypic similarity. In the present study, one from each pair of individuals with pairwise identity-by-descent (IBD) of >0.025 (third degree relatives) were removed, so that chance genetic similarity could be used as a random effect in a linear mixed model. Comparing a matrix of pairwise genomic similarity to a matrix of pairwise phenotypic similarity using a random-effects mixed linear model, the variance of a trait can be decomposed into genetic and residual components.

Table 7: Full twin and SNP heritability results:

Measure	**Twin h2**	**SNP h2**	**Twin SE**	**Twin 95% CI**	**SNP SE**	**SNP 95% CI**	**Twin N (pairs)**	**SNP N (indiv)**	**p (SNP h2)**
Stable CFA score (simultaneous)	0.701	n/a	0.047	[0.608-0.792]	n/a	n/a	6110	n/a	n/a
Stable CFA score (extracted FS)	0.760	0.14	0.023	[0.715-0.805]	0.049	[0.044-0.236]	6110	6002	0.002*
Stable IRT score (simultaneous)	0.611	n/a	0.043	[0.527-0.695]	n/a	n/a	6110	n/a	n/a
Stable IRT score (extracted FS)	0.620	0.095	0.023	[0.575-0.665]	0.048	[0.001-0.189]	6110	6001	0.025*
Parent-rated SDQ anxiety at 7	0.475	0.009	0.037	[0.402-0.548]	0.053	[-0.095-0.113]	5359	5272	0.438
Teacher-rated SDQ anxiety at 7	0.509	0.126	0.018	[0.474-0.544]	0.065	[-0.001-0.253]	4419	4336	0.023*
Self-rated MFQ at 12	0.283	0.039	0.051	[0.183-0.383]	0.064	[-0.086-0.164]	4490	4414	0.27
Self-rated SDQ anxiety at 12	0.399	0.082	0.026	[0.348-0.450]	0.065	[-0.045-0.209]	4475	4396	0.106
Parent-rated SDQ anxiety at 12	0.531	0.022	0.041	[0.451-0.611]	0.062	[-0.100-0.144]	4482	4408	0.364
Parent-rated MFQ at 12	0.478	0.029	0.038	[0.404-0.552]	0.063	[-0.094-0.152]	4482	4407	0.326
Teacher-rated SDQ anxiety at 12	0.426	0.029	0.023	[0.381-0.471]	0.077	[-0.122-0.180]	3695	3652	0.359
Self-rated SDQ anxiety at 16	0.428	0.094	0.018	[0.393-0.463]	0.075	[-0.053-0.241]	3822	3759	0.108
Self-rated CASI at 16	0.445	0.069	0.019	[0.408-0.482]	0.076	[-0.080-0.218]	3824	3760	0.187
Self-rated MFQ at 16	0.403	0	0.024	[0.356-0.450]	0.074	[-0.145-0.145]	3824	3761	0.5
Parent-rated MFQ at 16	0.567	0.099	0.031	[0.506-0.628]	0.073	[-0.044-0.242]	3838	3774	0.08
Parent-rated ARBQ at age 16	0.413	0	0.039	[0.337-0.489]	0.066	[-0.129-0.129]	3840	3775	0.499

Note: 'h2' = heritability; 'SE' = standard error; '95% CI' = 95% confidence intervals; 'p' = the p-value associated with the SNP heritability estimate, and whether $p<0.05$ (indicated with '*'); 'FS' = stable emotional problems factor scores extracted from latent modelling; 'simultaneous' = simultaneous latent trait-twin modelling.

Figure 4: Twin and SNP heritability results for a simple mean approach to aggregating emotional problems measures, with sensitivity analyses to investigate rater effects



Note: means were calculated only for individuals with data present on at least half of the variables. Twin and SNP heritability results for the means (blue and grey) are compared to average heritabilities of the constituent individual measures (orange and yellow). '*' indicates a significant SNP heritability estimate.

Supplementary Figure 4 shows that the simpler approach of creating a mean of the 12 anxiety and depression measures yields similar results to a latent modelling approach (comparing the first and eighth sections of the plot). As such, the finding of higher twin and SNP heritabilities holds for even a crude composite measure that adds up common *and* measure-specific error (rather than latent modelling to remove error). This bolsters the argument that aggregating across time and across raters taps into a more heritable, core 'trait' aspect of emotional development.

To explore the whether the effect of extracting longitudinal stability increasing heritability remained when using single-rater composites, we created longitudinal means for child-, parent- and teacher-reports separately (sections 2-4 of the plot). Results suggest that this is the case. Twin estimates increased from ~45% to ~55%. SNP heritability point estimates increased for child- and parent-report longitudinal means (with longitudinal aggregation boosting SNP heritability of parent-report measures into statistical significance), but not for the teacher-report composite. Given the similar point estimates and large standard error intervals around SNP heritability estimates, it would be inappropriate to compare SNP heritability estimates.

To investigate the contribution of trans-situational variance (i.e. rater agreement on childhood emotional problems), we created means of anxiety and depression measures across reporters but at individual ages (sections 5-7 of the plot). Results suggest that combining cross-sectional measures across reporters increases twin and SNP heritability estimates at ages 7 and 12, but

not at 16. Again, standard errors for SNP heritability estimates are large, such that we cannot compare estimates for different composite measures, and we cannot say that aggregation across raters *significantly* increases SNP heritability. The heritability increase resulting from aggregating measures using a simple mean approach is weaker for SNP heritability than for twin estimates, but this is partly because the sample sizes for SNP heritability estimation were ~4000 (rather than over 6000 for latent modelling with maximum likelihood). The restriction of the mean composite approach to individuals with complete data is a disadvantage in comparison to the latent modelling approach. The finding that latent modelling is more powerful than simple approaches replicates evidence from the Netherlands Twin Register: a latent anxious depression phenotype was substantially more heritable than the scores observed at any age, but measure created by simply summing data from the different ages was considerably less heritable (Lubke et al. 2016).

Overall, results suggest that both the mean composite and latent factor across time and across reporters shows increased heritability as a result of tapping into longitudinally stable aspects of behaviour that are also agreed upon by different raters. Future research could more thoroughly and explicitly test the structure of age-, scale-, and rater-specific influences on emotional problems. For example, in the Trait-State-Occasion model, significant covariances between observed variable error terms indicates that trait stability is inflated by shared method variance cross waves.

Investigation of the contribution of individuals with persistent emotional problems to the increased heritability of our stable phenotype.

In studies of adults, recurrent depression is more severe and heritable than single episode depression. It follows that the heritability for stable childhood emotional problems could be higher because we are capturing the higher heritability of severe recurrent symptoms, rather than stability at any level of emotional symptoms. This is especially worth investigating given the high genetic correlation of our stable childhood emotional problems phenotype with adult depression.

To test this idea, we calculated how many of the 12 measures each individual was an outlier for. Outliers were defined as individuals with z-scores >=1.96 (i.e. cutting off the top 1% of scores). We removed twin pairs for whom twin 1 or 2 was an outlier for >6 of the 12 scales (i.e. removed 21 pairs). Then, we re-calculated the twin heritability of a single common factor (from CFA).

We found a lower twin heritability for stable emotional problems when excluding individuals with persistent problems (0.50 (se=0.05) vs 0.70 (se=0.05) for the CFA factor scores using all 6110 pairs). This suggests that a small number of young people with enduring severe emotional symptoms could be disproportionately contributing to the high heritability of stable emotional problems. However, 95% CIs for the two estimates just overlap (.40-.60 and .60-.80), so the difference is not statistically significant.

Adjusting the definition of outliers to z>=1.64 (the top 5% of scores) led to the removal of 43 twin pairs for whom at least one twin was an outlier on more than half of the measures. The heritability estimate hardly decreased below 0.50 (0.49 (se=0.05)), but the upper 95% CI decreased to .57, such that the CIs no longer overlapped with the estimates from the full sample. Overall, there is no strong evidence that individuals with severe persistent symptoms are inflating heritability estimates.

Figures 5 and 6: Polygenic score results

The PRSice 2 plots below demonstrate that the R^2 is not dramatically better at the best p-value threshold than at the others. This is indicative of reliable prediction for a polygenic trait.

Figure 4: Prediction of CFA scores using UK Biobank anxiety polygenic score

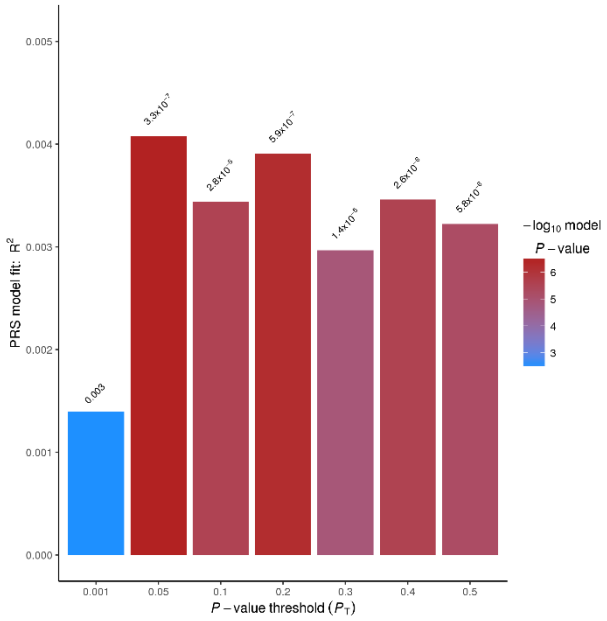


Figure 5: Prediction of IRT scores using UK Biobank anxiety polygenic score

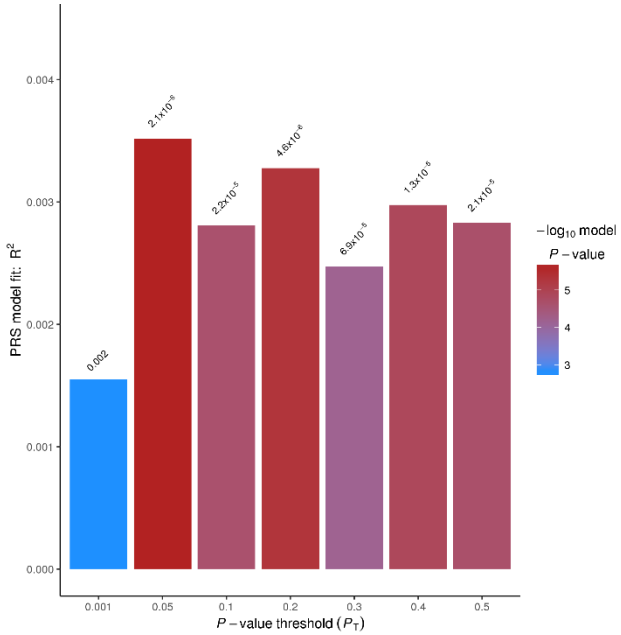


Table 8: variance explained by polygenic scores for MDD, derived from summary statistics for a subset of 10,000 variants in the PGC sample including 23&Me.

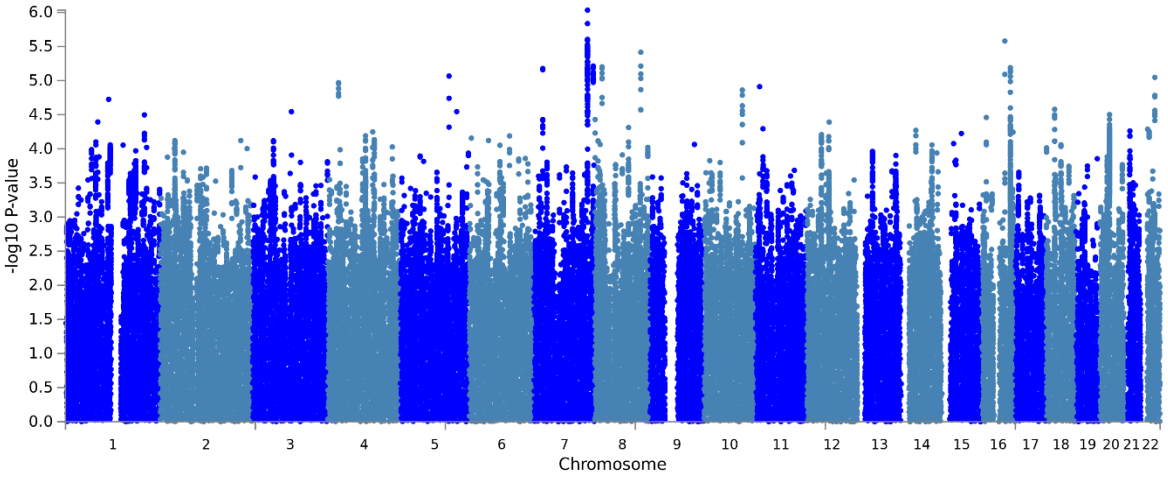
	R^2	**P-value**	**Empirical P-value**
Stable CFA score	0.0041	0.0000	0.0001*
Stable IRT score	0.0031	0.0000	0.0002*
Parent-rated SDQ at 7	0.0006	0.0754	0.1268
Teacher-rated SDQ at 7	0.0023	0.0015	0.0026*
Self-rated MFQ at 12	0.0051	0.0000	0.0001*
Self-rated SDQ at 12	0.0024	0.0010	0.0020*
Parent-rated SDQ at 12	0.0009	0.0411	0.0743
Parent-rated MFQ at 12	0.0014	0.0113	0.0213*
Teacher-rated SDQ at 12	0.0005	0.1633	0.2582
Self-rated SDQ at 16	0.0022	0.0021	0.0038*
Self-rated CASI at 16	0.0034	0.0001	0.0005*
Self-rated MFQ at 16	0.0020	0.0042	0.0091*
Parent-rated MFQ at 16	0.0014	0.0202	0.0366*
Parent-rated ARBQ at 16	0.0021	0.0036	0.0067*

Note: '*' indicates target TEDS phenotypes that were significantly predicted by polygenic scores at the more stringent empirical p-value thresholds.

Figures 7 and 8: Genome-wide association results

No significant SNPs were identified. There are no SNPs that exceed a –log10 p-value of more than 6. This was expected, given the relatively small sample (6110), and the lack of associations in previous, similarly powered studies of emotional problems (e.g. Benke et al., 2014 meta-analysis of preschool emotional problems, N=4596).

IRT score GWAS: FUMA plot:



CFA score GWAS: FUMA plot:

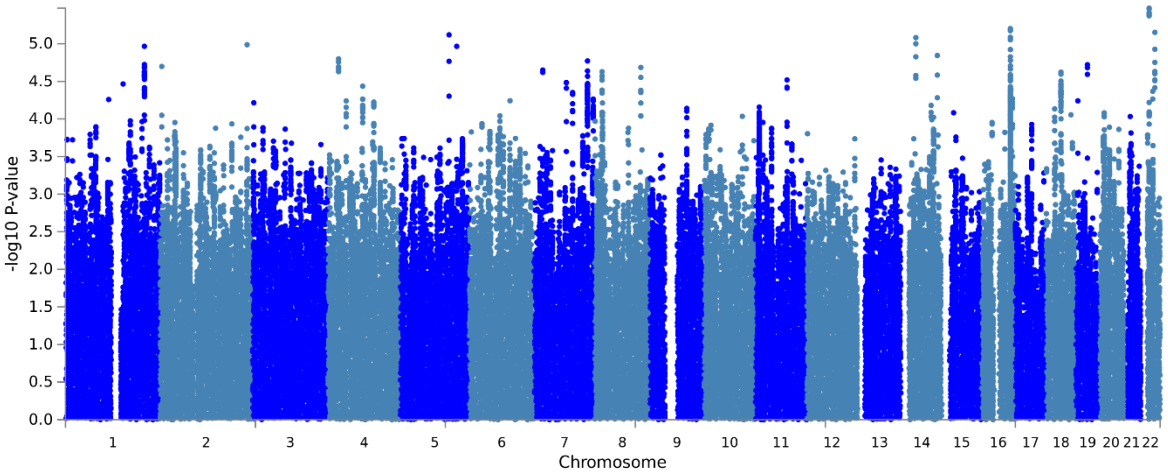


Table 9: Genetic correlations between stable emotional problems (from CFA) and psychiatric traits, obtained using LD Score regression.

Trait	PMID	rg	se	z	p	h2_obs	h2_obs_se
Depressive symptoms	27089181	0.64	0.19	3.37	0.0008**	0.05	0
Adult depression (PGC) †		0.48	0.14	3.35	0.0008**	0	0
Adult anxiety (UK Biobank) †		0.45	0.15	2.92	0.0035**	0.11	0.01
Subjective well being	27089181	-0.36	0.15	-2.36	0.0182*	0.02	0
Major depressive disorder	22472876	0.37	0.2	1.9	0.0574	0.18	0.03
Schizophrenia	25056061	0.16	0.09	1.8	0.0718	0.45	0.02
PGC cross-disorder analysis	23453885	0.21	0.14	1.49	0.1368	0.18	0.01
Attention deficit hyperactivity disorder (GC)	27663945	0.34	0.3	1.14	0.2528	0.08	0.03
Attention deficit hyperactivity disorder (No GC)	27663945	0.34	0.3	1.14	0.2538	0.08	0.03
Attention deficit hyperactivity disorder	20732625	-0.27	0.3	-0.9	0.3677	0.22	0.1
Autism spectrum disorder	0	-0.06	0.15	-0.39	0.6972	0.46	0.05
Bipolar disorder	21926972	0.02	0.14	0.14	0.8857	0.45	0.04
Anorexia Nervosa	24514567	-0.01	0.13	-0.06	0.9528	0.4	0.04

Note: Pairs of traits are ordered according to the p-value of their genetic correlation. * = significant at p<0.05, **= significant at p<0.00385 i.e. (0.05/13) to correct for multiple tests; †= genetic correlation analysis performed separately (using LDSR) because phenotype was *not* in LD Hub.

The genetic correlations between our CFA-derived stable scores, and case-control depression, depressive symptoms, case-control generalised anxiety, and wellbeing, are significant at p<0.05. The negative genetic correlation with wellbeing did not remain significant at the more stringent threshold (p<0. 00385). Genetic correlations have many possible interpretations other than true biological pleiotropy (Martin et al. 2017). For example, the relationship between adult depression and childhood stable emotional problems could be mediated by shared genetic risk with low levels of well-being. It has been suggested that the genetic correlation between MDD and depressive symptoms in the population could be accounted for by shared genetic risk with low levels of subjective well-being (Direk et al. 2017). Another issue is that nosological issues involving heterogeneity, comorbidity and misclassification might inflate phenotypic and genetic correlations.

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