

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplemental Methods

Polygenic risk score calculation

Publicly available genome-wide association study (GWAS) summary statistics for 8 psychiatric disorders and 3 continuously distributed psychiatric or cognitive traits¹⁻¹⁰ were used to derive polygenic risk scores (PRS) in the CATSS individuals. Where multiple discovery GWAS summary statistics files on different ancestry groups were available, the GWAS results restricted to individuals of European ancestry were used. The discovery and target data were independent. CATSS data have been genotyped recently¹¹ and have not been previously contributed to any GWAS consortia. The cohort is too young to have previously taken part in published research studies of adult psychiatric disorders. Additionally, care was taken to ensure that the discovery GWAS did not include any individuals who may be related to those in the target CATSS data by excluding Swedish data (e.g. the PAGES data from the autism GWAS). Each discovery GWAS results file was filtered based on available information for minor allele frequency (MAF>0.05) and imputation quality (INFO>0.8). Indels, asymmetric/ambiguous (AT, TA, CG, GC), multi-allelic and duplicate position SNPs were excluded. Where necessary, SNPs were lifted over to genome build hg19 using the UCSC Liftover tool. SNPs were matched across the target and discovery data based on chromosomal position.

Next, LD-clumping was run using the 1000-Genomes reference population (which was used for imputation of the CATSS data), to obtain a relatively independent set of autosomal SNPs for each set of discovery results, while retaining the most significant SNP in each LD block and maximizing the overlap of SNPs across the discovery and target data. The following parameters were applied in PLINK.v.1.9: --clump-kb 1000 --clump-r2 0.1. The number of clumped SNPs for each discovery study varied from 55,072-89,358.

PRS were then calculated for each individual in CATSS by scoring the number of effect alleles (weighted by the SNP log of the odds ratio or SNP beta) across each discovery set of clumped SNPs in PLINK.v.1.9 (using the command --score no-mean-imputation). The p-value thresholds used for SNP selection were $p < 1$, $p < 0.5$, $p < 0.1$, $p < 0.05$, $p < 0.01$, and $p < 0.001$. The primary analyses are based on the threshold $p < 0.5$. Scores were derived in imputed best guess genotype data after filtering out SNPs with $MAF < 0.05$ and $INFO < 0.8$. The PRS were standardized using z-score transformations; effect sizes can be interpreted as increase in risk of the outcome, per standard deviation increase in PRS. Nagelkerke R^2 differences between null and full models were calculated to obtain estimates of variance explained.

Principal components analysis

A principal components analysis (PCA) was performed to derive population covariates (PCs) in all individuals. First, common autosomal genotyped SNPs passing all QC (N=287,655) were LD-pruned after removing SNPs located in long-range LD regions. Next, relatives were identified using an identity-by-descent analysis

and one of each pair of related individuals ($\pi\text{-hat} > 0.2$) were temporarily excluded. Allele frequencies were obtained for the set of LD-pruned SNPs for unrelated individuals ($N=83,648$ SNPs and $N=7,112$ individuals). PCs were then estimated by calculating variant weights on unrelated individuals and then projecting remaining samples to the PC scales set by these unrelated individuals. All analyses were carried out using PLINK.v.1.9. The first 10 principal components were used as covariates for subsequent analyses.

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eTable 1. Additional Description of the Study Measures

Phenotype	Measure	Description	Range of scale
ASD	A-TAC ASD module (17 items)	Social interaction (6), communication (6) & flexible behavior (5) items	0-17
ADHD	A-TAC ADHD module (19 items)	Inattentive (9) & hyperactive-impulsive (10) items	0-19
ID	A-TAC Learning module (3 items)	Reading difficulties (1), maths difficulties (1) & general learning delay (1) items	0-3
TD	A-TAC Tics module (3 items)	Motor (1) & vocal (2) tic items	0-3
OCD	ATAC Compulsions module (2 items);	A-TAC: Compulsion (1) & obsession (1) items;	0-2;
	BOCS (15 items)	BOCS: Contamination (2), checking (1), superstition (2), morality (1), harming obsessions (2), sexual obsessions (1), somatic obsessions (1), symmetry/ordering (2), rituals (1), hoarding (1), self-harm (1)	0-15
ANX	SCARED (41 items); SDQ Emotion subscale (5 items); ABCL DSM-IV Anxiety subscale (6 items); SCARED (38 items)	SCARED: Panic (13), general anxiety (9), separation anxiety (8), school phobia (4) & social phobia (7) items; Panic (13), general anxiety (9), separation anxiety (8), school phobia (4) & social phobia (4) items (social phobia has 7 items in the 41 item SCARED); SDQ: somatic symptoms (1), worries (1), unhappiness (1), nervousness (1), fearfulness (2); ABCL: worries (3), fears (1), nervousness (1) items	0-82; 0-10; 0-12; 0-76
MDD	SMFQ (13 items); SDQ Emotion subscale (5 items); ABCL DSM-IV Depression subscale (15 items); CES-D (11 items)	SMFQ: low mood (1), anhedonia (1), tired (1), restless (1), low self worth (6), crying (1), cognitive difficulties (1), loneliness (1) items; SDQ: see ANX; ABCL: crying (1), self-harm/suicide (2), low appetite (1), negative self-worth (2), guilt (1), disrupted sleep (3), anhedonia (1), difficulties making decisions (1), passive (1), low energy (1), low mood (1) items; CESD: appetite (1), low mood (3), tiredness (1), disturbed sleep (1), loneliness (1), others unfriendly (2), enjoyment (1), behavior inactivation (1) items	0-26; 0-10; 0-30; 0-33
Mania	MDQ (13 items)	Hyperactivity (2), irritability (1), self confidence (1), reduced need for sleep (1), talkativeness (1), racing thoughts (1), distracted (1), high energy (1), hyper-sociability (1), hypersexual (1), atypical behavior (1), spending too much money (1)	0-13
Psychosis	APSS (7 items)	Paranoia (4), grandiosity (2), visual hallucinations (1)	0-7

ASD: autism spectrum disorders; ADHD: attention-deficit/hyperactivity disorder; ID: intellectual disability; TD: tic disorders; OCD: obsessive-compulsive disorder; ANX: anxiety disorders; MDD: major depressive disorder; ABCL: Adult Behavior Checklist²²; A-TAC: Autism-Tics, AD/HD, and other Comorbidities inventory^{23,24}; APSS: Adolescent Psychotic-Like Symptoms Screener²⁵; BOCS: Brief Obsessions and Compulsions Scale²⁶; CES-D: Center for Epidemiologic Studies Depression scale²⁷; MDQ: Mood Disorders Questionnaire²⁸; NPR: National Patient Register; SCARED: Screen for Anxiety Related Disorders²⁹; SDQ: Strengths and Difficulties Questionnaire²⁰; SMFQ: Short Moods and Feelings Questionnaire²¹.

eTable 2: Summary of Discovery Data Sets Used to Derive Polygenic Risk Scores

Phenotype	Consortium	Sample size	Publication
ASD	PGC + iPSYCH	20,158 cases; 30,031 controls	¹
ADHD	PGC + iPSYCH	20,183 cases; 35,191 controls	²
TD	PGC	4,642 cases; 8,696 controls	Unpublished (manuscript in preparation)
OCD	PGC	2,936 cases; 7,285 controls	³
ANX	ANGST	5,761 cases; 11,765 controls	⁴
MDD	PGC	59,851 cases; 113,154 controls	⁵
BD	PGC	11,974 cases; 51,792 controls	⁶
SCZ	PGC	33,640 cases; 43,456 controls	⁷
ADHD traits	EAGLE	17,666	⁸
Depressive traits	SSGAC	180,866	⁹
General cognition	COGENT	35,298	¹⁰

ADHD: attention-deficit hyperactivity disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; SCZ: schizophrenia; OCD: obsessive-compulsive disorder; TD: Tic disorders; ANX: anxiety disorders; PGC: Psychiatric Genomics Consortium; iPSYCH: Lundbeck Foundation Initiative for Integrative Psychiatric Research; ANGST: Anxiety NeuroGenetics Study; EAGLE: Early Genetics and Lifecourse Epidemiology Consortium; SSGAC: Social Science Genetic Association Consortium; COGENT: Cognitive Genomics Consortium.

Please note: the power of the discovery GWAS (and hence polygenic risk scores derived from these GWAS) is variable, depending on sample size. The highest power comes from GWAS of depressive traits, MDD, SCZ, ADHD, ASD, BD, with more modest power for scores based on general cognition, ADHD traits, ANX, TD, and OCD.

eTable 3. Probandwise Concordances

Disorder	N MZ Concordant Pairs	N MZ Discordant Pairs	N DZ Concordant Pairs	N DZ Discordant Pairs	MZ Probandwise Concordance	DZ Probandwise Concordance
ASD	14	35	11	202	.44	.10
ADHD	73	97	84	597	.60	.22
ID	16	11	7	137	.74	.09
TD	5	24	1	76	.29	.03
OCD	1	34	1	83	.02	.02
ANX	21	100	17	364	.30	.09
MDD	21	101	15	298	.29	.09

ASD: autism spectrum disorders; ADHD: attention-deficit/hyperactivity disorder; ID: intellectual disability; TD: Tic disorders; OCD: obsessive-compulsive disorder; ANX: anxiety disorders; MDD: major depressive disorder.

eTable 4. Twin Model Fit Statistics for Different Models Comparing the Associations Between Clinical Diagnosis and Continuous Traits

ASD & ATAC-ASD (9/12)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	75599.64	25	55601	-454906.04	-----	-----	-----	-----
ADE-s	75751.93	14	55614	-454877.79	Saturated	152.29	13	<.001
ADE	75815.85	12	55616	-454832.95	ADE-s	63.92	2	<.001
AE-s	75751.93	11	55617	-454906.47	ADE-s	0.00	3	1.00
AE	75959.83	9	55619	-454717.60	ADE-s	207.90	5	<.001
E	79055.58	6	55622	-451650.47	ADE-s	3303.65	8	<.001
ADHD & ATAC-ADHD (9/12)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	80878.12	25	55580	-449427.20	-----	-----	-----	-----
ADE-s	80976.35	14	55593	-449453.00	Saturated	98.23	13	<.001
ADE	81013.81	12	55595	-449434.62	ADE-s	37.47	2	<.001
AE-s	80976.35	11	55596	-449481.63	ADE-s	0.00	3	1.00
AE	81173.31	9	55598	-449303.75	ADE-s	196.96	5	<.001
E	84193.10	6	55601	-446312.58	ADE-s	3216.75	8	<.001
ID & ATAC-Learning (9/12)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	75699.50	25	55625	-455035.17	-----	-----	-----	-----
ADE-s	75740.83	14	55638	-455117.88	Saturated	41.33	13	<.001
ADE	75808.44	12	55640	-455069.35	ADE-s	67.61	2	<.001
AE-s	75743.35	11	55641	-455143.98	ADE-s	2.52	3	.47
AE	76333.75	9	55643	-454572.66	ADE-s	592.93	5	<.001
E	78525.53	6	55646	-452409.51	ADE-s	2784.70	8	<.001

TD & ATAC-Tics (9/12)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	78122.01	25	55612	-452488.63	-----	-----	-----	-----
ADE-s	78390.99	14	55625	-452343.68	Saturated	268.98	13	<.001
ADE	78404.15	12	55627	-452349.60	ADE-s	13.16	2	<.01
AE-s	78392.69	11	55628	-452370.60	ADE-s	1.70	3	.64
AE	78495.12	9	55630	-452287.26	ADE-s	104.13	5	<.001
E	79305.99	6	55633	-451505.01	ADE-s	915.00	8	<.001
Drop s for Tic Disorder	78392.75	10	55629	-452380.09	ADE-s	1.76	4	.78
ANX & SCARED (9)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	47327.92	25	43620	-368863.48	-----	-----	-----	-----
ADE-s	47410.78	14	43633	-368904.66	Saturated	82.86	13	<.001
ACE	47408.14	12	43635	-368926.37	Saturated	80.23	15	<.001
AE	47418.05	9	43638	-368945.08	ACE	9.91	3	<.05
CE	47723.29	9	43638	-368639.85	ACE	315.15	3	<.001
E	49506.44	6	43641	-366885.32	ACE	2098.30	6	<.001
Drop C for Anxiety, drop rC and rE	47408.35	10	43637	-368945.25	ACE	0.21	2	.90
ANX & SDO-E-parent (15)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	25775.16	25	35484	-312788.24	-----	-----	-----	-----
ADE-s	25812.20	14	35497	-312875.23	Saturated	37.04	13	<.001
ADE	25814.47	12	35499	-312892.05	ADE-s	2.27	2	.32
AE-s	25812.23	11	35500	-312903.83	ADE-s	0.03	3	1.00
AE	25816.54	9	35502	-312918.60	ADE-s	4.34	5	.50
E	26300.47	6	35505	-312463.29	ADE-s	488.27	8	<.001

ANX & SDQ-E-self (15)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	27457.93	25	35971	-44484.07	-----	-----	-----	-----
ADE-s	27490.09	14	35984	-44477.91	Saturated	32.16	13	<.01
ADE	27492.05	12	35986	-44479.95	ADE-s	1.96	2	.38
AE-s	27490.16	11	35987	-44483.84	ADE-s	0.06	3	1.00
AE	27497.58	9	35989	-44480.42	ADE-s	7.48	5	.19
E	27915.96	6	35992	-44068.04	ADE-s	425.86	8	<.001
Drop rE	27499.40	8	35990	-44480.60	ADE-s	9.30	6	.16
ANX & ABCL-anx (18)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	18751.80	25	32981	-295929.73	-----	-----	-----	-----
ADE-s	18766.53	14	32994	-296039.04	Saturated	14.73	13	.32
ACE	18772.13	12	32996	-296052.52	Saturated	20.33	15	.16
AE	18774.04	9	32999	-296079.24	ACE	1.91	3	.59
CE	18850.35	9	32999	-296002.92	ACE	78.22	3	<.001
E	19348.66	6	33002	-295533.24	ACE	576.52	6	<.001
ANX & SCARED (18)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	20701.85	25	33622	-300095.65	-----	-----	-----	-----
ADE-s	20748.94	14	33635	-300172.60	Saturated	47.08	13	<.001
ADE	20754.03	12	33637	-300186.60	ADE-s	5.09	2	.08
AE-s	20748.94	11	33638	-300201.23	ADE-s	0.00	3	1.00
AE	20764.16	9	33640	-300205.09	ADE-s	15.22	5	<.05
E	21116.41	6	33643	-299881.46	ADE-s	367.47	8	<.001

MDD & SMFQ (9)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	47898.84	25	43694	-368998.61	-----	-----	-----	-----
ADE-s	48060.39	14	43707	-368961.09	Saturated	161.55	13	<.001
ACE	48056.75	12	43709	-368983.82	Saturated	157.90	15	<.001
AE	48061.16	9	43712	-369008.04	ACE	4.41	3	.22
CE	48236.30	9	43712	-368832.89	ACE	179.56	3	<.001
E	49346.94	6	43715	-367750.87	ACE	1290.20	6	<.001
Drop rE	48063.41	8	43713	-369015.32	ACE	6.67	4	.15
MDD & SDQ-E-parent (15)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	25299.73	25	35484	-313263.67	-----	-----	-----	-----
ADE-s	25334.64	14	35497	-313352.79	Saturated	34.92	13	<.01
ACE	25337.37	12	35499	-313369.15	Saturated	37.64	15	<.01
AE	25337.37	9	35502	-313397.77	ACE	0.00	3	1.00
CE	25424.06	9	35502	-313311.08	ACE	86.69	3	<.001
E	25835.23	6	35505	-312928.53	ACE	497.86	6	<.001
MDD & SDQ-E-self (15)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	26962.02	25	35971	-316247.99	-----	-----	-----	-----
ADE-s	26997.22	14	35984	-316336.83	Saturated	35.20	13	<.01
ACE	27001.82	12	35986	-316351.31	Saturated	39.81	15	<.001
AE	27001.95	9	35989	-316379.80	ACE	0.13	3	.99
CE	27080.88	9	35989	-316300.87	ACE	79.06	3	<.001

E	27435.39	6	35992	-315974.99	ACE	433.57	6	<.001
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MDD & ABCL-dep (18)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	18385.45	25	33036	-296820.85	-----	-----	-----	-----
ADE-s	18400.23	14	33049	-296930.11	Saturated	14.78	13	.32
ACE	18405.69	12	33051	-296943.73	Saturated	20.24	15	.16
AE	18405.91	9	33054	-296972.13	ACE	0.22	3	.97
CE	18483.42	9	33054	-296894.62	ACE	77.73	3	<.001
E	18891.61	6	33057	-296515.06	ACE	485.91	6	<.001
MDD & CESD (18)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	19615.60	25	33339	-298481.72	-----	-----	-----	-----
ADE-s	19646.94	14	33352	-298574.41	Saturated	31.35	13	<.01
ACE	19651.22	12	33354	-298589.22	Saturated	35.62	15	<.01
AE	19651.29	9	33357	-298617.77	ACE	0.07	3	1.00
CE	19716.58	9	33357	-298552.47	ACE	65.37	3	<.001
E	20012.23	6	33360	-298285.45	ACE	361.01	6	<.001

ASD: autism spectrum disorders; ADHD: attention-deficit/hyperactivity disorder; ID: intellectual disability; TD: Tic disorders; ANX: anxiety disorders; MDD: major depressive disorder

ATAC: Autism-Tics, AD/HD, and other Comorbidities inventory; SCARED: Screen for Anxiety Related Disorders; SDQ-E-parent: parent-rated Strengths and Difficulties Questionnaire, Emotional problems subscale; SDQ-E-self: self-rated Strengths and Difficulties Questionnaire, Emotional problems subscale; ABCL-anx: Adult Behavior

Checklist, DSM-IV anxiety subscale; SMFQ: Short Mood and Feelings Questionnaire; ABCL-dep: Adult Behavior Checklist, DSM-IV depression subscale; CESD: Center for Epidemiologic Studies Depression Scale

* $\Delta\chi^2$: difference in -2LL between two models, distributed χ^2 ; Δdf : difference in degrees of freedom between two models; p: p-value from likelihood-ratio tests.

All ADE-s and ACE models are compared with the saturated model. The column labelled 'Comparison' shows which models are being compared by the likelihood-ratio test.

The best-fitting model is indicated in bold italics in each case.

eTable 5 Parameter Estimates From the Best-Fitting Twin Models of the Associations Between Continuous Traits and Clinical Diagnoses

ASD & ATAC-ASD (9/12)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
ATAC-ASD	.79 (.78-.80)	-----	-----	.21 (.20-.22)	-.09 (-.10/-.08)	.48 (.44-.53)	.23	.27 (.16-.38)	.07
ASD	.84 (.70-.91)	-----	-----	.16 (.09-.30)	-.06 (-.12/.01)	89%		11%	
ADHD & ATAC-ADHD (9/12)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
ATAC-ADHD	.76 (.75-.78)	-----	-----	.24 (.22-.25)	-.09 (-.10/-.08)	.56 (.53-.59)	.31	.36 (.28-.45)	.12
ADHD	.89 (.88-.89)	-----	-----	.11 (.11-.12)	-.01 (-.05/.03)	89%		11%	
ID & ATAC-Learning (9/12)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
ATAC-Learning	.81 (.80-.82)	-----	-----	.19 (.18-.20)	-.15 (-.16/-.14)	.69 (.64-.73)	.48	.55 (.31-.75)	.30
ID	.94 (.85-.98)	-----	-----	.06 (.02-.15)	-.09 (-.14/-.02)	91%		9%	
TD & ATAC-Tics (9/12)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
ATAC-Tics	.56 (.52-.59)	-----	-----	.44 (.41-.48)	-.09 (-.11/-.07)	.61 (.51-.80)	.37	.31 (.18-.44)	.10
TD	.57 (.32-.77)	-----	-----	.43 (.25-.68)	-----	72%		28%	
ANX & SCARED (9)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
SCARED	.58 (.52-.64)	-----	.08 (.03-.12)	.34 (.32-.36)	-----	.48 (.37-.63)	.23	-----	-----
ANX	.67 (.43-.76)	-----	.00 (.00-.02)	.33 (.24-.44)	-----	100%		-----	-----
ANX & SDQ-E-parent (15)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
SDQ-E-parent	.46 (.42-.49)	-----	-----	.54 (.51-.58)	-----	.46 (.34-.58)	.21	.26 (.11-.40)	.07
ANX	.66 (.55-.76)	-----	-----	.34 (.24-.45)	-----	70%		30%	

ANX & SDQ-E-self (15)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
SDQ-E-self	.42 (.38-.45)	-----	-----	.58 (.55-.62)	-----	.47 (.37-.57)	.22	-----	-----
ANX	.67 (.55-.76)	-----	-----	.33 (.24-.45)	-----	100%		-----	-----
ANX & ABCL-anx (18)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
ABCL-anx	.57 (.53-.61)	-----	-----	.43 (.39-.47)	-----	.47 (.36-.58)	.22	.29 (.13-.44)	.08
ANX	.66 (.54-.75)	-----	-----	.34 (.25-.46)	-----	72%		28%	
ANX & SCARED (18)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
SCARED (18)	.58 (.50-.65)	-----	-----	.42 (.35-.50)	-.07 (-.11/-.03)	.57 (.46-.68)	.32	.15 (-.03-.33)	.02
ANX	.74 (.61-.83)	-----	-----	.26 (.17-.39)	-.06 (-.12/.01)				
MDD & SMFQ (9)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
SMFQ	.56 (.53-.58)	-----	-----	.44 (.42-.47)	-----	.33 (.19-.47)	.11	-----	-----
DEP	.70 (.59-.78)	-----	-----	.30 (.22-.41)	-----	100%		-----	-----
MDD & SDQ-E-parent (15)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
SDQ-E-parent	.46 (.38-.45)	-----	-----	.54 (.51-.58)	-----	.39 (.27-.51)	.15	.35 (.20-.49)	.12
DEP	.68 (.58-.77)	-----	-----	.32 (.23-.42)	-----	60%		40%	
MDD & SDQ-E-self (15)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
SDQ-E-self	.42 (.38-.45)	-----	-----	.58 (.55-.62)	-----	.33 (.20-.46)	.11	.22 (.07-.37)	.05

DEP	.69 (.59-.78)	-----	-----	.31 (.22-.41)	-----	65%		35%	
MDD & ABCL-dep (18)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
ABCL-dep	.51 (.47-.55)	-----	-----	.49 (.45-.53)	-----	.53 (.50-.56)	.28	.32 (.26-.45)	.10
DEP	.67 (.64-.76)	-----	-----	.33 (.30-.36)	-----	70%		30%	
MDD & CESD (18)									
	A	D	C	E	s	rA (% rPH A)	rA ²	rE (% rPH E)	rE ²
CESD	.44 (.39-.49)	-----	-----	.56 (.51-.61)	-----	.58 (.52-.63)	.34	.30 (.11-.41)	.09
DEP	.68 (.63-.73)	-----	-----	.32 (.27-.37)	-----	71%		29%	

ASD: autism spectrum disorders; ADHD: attention-deficit/hyperactivity disorder; ID: intellectual disability; TD: Tic disorders; ANX: anxiety disorders; MDD: major depressive disorder

ATAC: Autism-Tics, AD/HD, and other Comorbidities inventory; SCARED: Screen for Anxiety Related Disorders; SDQ-E-parent: parent-rated Strengths and Difficulties Questionnaire, Emotional problems subscale; SDQ-E-self: self-rated Strengths and Difficulties Questionnaire, Emotional problems subscale; ABCL-anx: Adult Behavior Checklist, DSM-IV anxiety subscale; SMFQ: Short Mood and Feelings Questionnaire; ABCL-dep: Adult Behavior Checklist, DSM-IV depression subscale; CESD: Center for Epidemiologic Studies Depression Scale

A: additive genetic influences; D: non-additive genetic influences; C: shared environmental influences; E: nonshared environmental influences; s: sibling interaction effects; rA: additive genetic correlation; rD: non-additive genetic correlation; rC: shared environmental correlation; rE: nonshared environmental correlation; % rPH A: percentage of the phenotypic correlation explained by A; % rPH C: percentage of the phenotypic correlation explained by C; % rPH D: percentage of the phenotypic correlation explained by D; % rPH E: percentage of the phenotypic correlation explained by E; rA²: squared genetic correlation, which gives the proportion of genetic variance shared between two phenotypes; rE²: squared nonshared environmental correlation, which gives the proportion of nonshared environmental variance shared between two phenotypes

eTable 6. Twin Fit Statistics for Diagnostic Subdomains

ASD & ATAC-Social (9/12)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	77288.36	25	55606	-453265.02	-----	-----	-----	-----
ADE-s	77468.82	14	55619	-453208.60	Saturated	180.45	13	<.001
ADE	77540.54	12	55621	-453155.97	ADE-s	71.71	2	<.001
AE-s	77468.82	11	55622	-453237.23	ADE-s	0.00	3	1.00
AE	77642.00	9	55624	-453083.13	ADE-s	173.18	5	<.001
E	79555.07	6	55627	-451198.68	ADE-s	2086.25	8	<.001
ASD & ATAC-Language (9/12)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	76053.65	25	55614	-454576.07	-----	-----	-----	-----
ADE-s	76085.11	14	55627	-454668.64	Saturated	31.46	13	<.01
ADE	76089.83	12	55629	-454683.00	ADE-s	4.72	2	.09
AE-s	76090.69	11	55630	-454691.69	ADE-s	5.58	3	.13
AE	76261.76	9	55632	-454529.70	ADE-s	176.64	5	<.001
E	79208.43	6	55635	-451621.65	ADE-s	3123.32	8	<.001
ASD & ATAC-Flexibility (9/12)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	77740.44	25	55610	-452851.11	-----	-----	-----	-----
ADE-s	78021.60	14	55623	-452693.99	Saturated	281.16	13	<.001
ADE	78129.28	12	55625	-452605.39	ADE-s	107.68	2	<.001
AE-s	78021.60	11	55626	-452722.61	ADE-s	0.00	3	1.00
AE	78336.40	9	55628	-452426.90	ADE-s	314.79	5	<.001
E	79958.72	6	55631	-450833.20	ADE-s	1937.11	8	<.001

ADHD & ATAC-Hyperactivity/Impulsivity (9/12)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	81867.54	25	55597	-448599.97	-----	-----	-----	-----
ADE-s	81948.02	14	55610	-448643.53	Saturated	80.48	13	<.001
ACE	82310.79	12	55612	-448299.85	Saturated	443.25	15	<.001
ADE	82004.70	12	55612	-448605.93	ADE-s	56.68	2	<.001
AE-s	81948.11	11	55613	-448672.07	ADE-s	0.09	3	.99
AE	82310.79	9	55615	-448328.47	ADE-s	362.76	5	<.001
E	85101.86	6	55618	-445566.02	ADE-s	3153.84	8	<.001
ADHD & ATAC-Inattention (9/12)								
Model	-2LL	Parameters	df	BIC	Comparison	$\Delta\chi^2^*$	Δdf^*	p *
Saturated	81840.90	25	55595	-448607.53	-----	-----	-----	-----
ADE-s	81916.85	14	55608	-448655.62	Saturated	75.94	13	<.001
ACE	82231.49	12	55610	-448360.06	Saturated	390.59	15	<.001
ADE	81980.76	12	55610	-448610.79	ADE-s	63.91	2	<.001
AE-s	81916.85	11	55611	-448684.39	ADE-s	0.00	3	1.00
AE	82231.49	9	55613	-448388.68	ADE-s	314.65	5	<.001
E	84112.87	6	55616	-446535.92	ADE-s	2196.03	8	<.001

* $\Delta\chi^2$: difference in -2LL between two models, distributed χ^2 ; Δdf : difference in degrees of freedom between two models; p: p-value from likelihood-ratio tests

All ADE-s and ACE models are compared with the saturated model. The column labelled 'Comparison' shows which models are being compared by the likelihood-ratio test.

The best-fitting model is indicated in bold italics in each case.

eTable 7: Twin Model Estimates for Diagnostic Subdomains

ASD & ATAC-Social (g/12)									
	A	D	C	E	s	rA (% rPH A)	rD (% rPH D)	rC (% rPH C)	rE (% rPH E)
ATAC-Social	.71 (.69-.73)	-----	-----	.29 (.27-.31)	-.09 (-.11/-.08)	.48 (.43-.55)	-----	-----	.31 (.19-.43)
ASD	.83 (.69-.91)	-----	-----	.17 (.09-.31)	-.05 (-.11/.02)	84%	-----	-----	16%
ASD & ATAC-Language (g/12)									
	A	D	C	E	s	rA (% rPH A)	rD (% rPH D)	rC (% rPH C)	rE (% rPH E)
ATAC-Language	.75 (.74-.77)	-----	-----	.25 (.23-.26)	-.08 (-.09/-.07)	.43 (.39-.47)	-----	-----	.20 (.14-.32)
ASD	.88 (.79-.92)	-----	-----	.12 (.08-.21)	-.08 (-.14/-.02)	91%	-----	-----	9%
ASD & ATAC-Flexibility (g/12)									
	A	D	C	E	s	rA (% rPH A)	rD (% rPH D)	rC (% rPH C)	rE (% rPH E)
ATAC-Flexibility	.74 (.72-.76)	-----	-----	.26 (.24-.28)	-.12 (-.14/-.11)	.47 (.46-.51)	-----	-----	.23 (.10-.35)
ASD	.85 (.72-.91)	-----	-----	.15 (.09-.28)	-.04 (-.10/.03)	89%	-----	-----	11%
ADHD & ATAC-Hyperactivity/Impulsivity (g/12)									
	A	D	C	E	s	rA (% rPH A)	rD (% rPH D)	rC (% rPH C)	rE (% rPH E)
ATAC-HYP/IMP	.79 (.77-.80)	-----	-----	.21 (.20-.23)	-.12 (-.13/-.11)	.49 (.46-.52)	-----	-----	.26 (.17-.35)
ADHD	.89 (.84-.93)	-----	-----	.11 (.07-.16)	.00 (-.05/.04)	91%	-----	-----	9%
ADHD & ATAC-Inattention (g/12)									
	A	D	C	E	s	rA (% rPH A)	rD (% rPH D)	rC (% rPH C)	rE (% rPH E)
ATAC-Inattention	.73 (.71-.74)	-----	-----	.27 (.26-.29)	-.13 (-.14/-.11)	.57 (.54-.60)	-----	-----	.41 (.32-.50)
ADHD	.89 (.83-.93)	-----	-----	.11 (.07-.17)	-.01 (-.05/.04)	86%	-----	-----	14%

ASD: autism spectrum disorders; ADHD: attention-deficit/hyperactivity disorder; A-TAC: Autism-Tics, AD/HD, and other Comorbidities inventory; HYP/IMP: Hyperactivity/Impulsivity subscale.

A: additive genetic influences; D: non-additive genetic influences; C: shared environmental influences; E: nonshared environmental influences; s: sibling interaction effects; rA: additive genetic correlation; rD: non-additive genetic correlation; rC: shared environmental correlation; rE: nonshared environmental correlation; % rPH A:

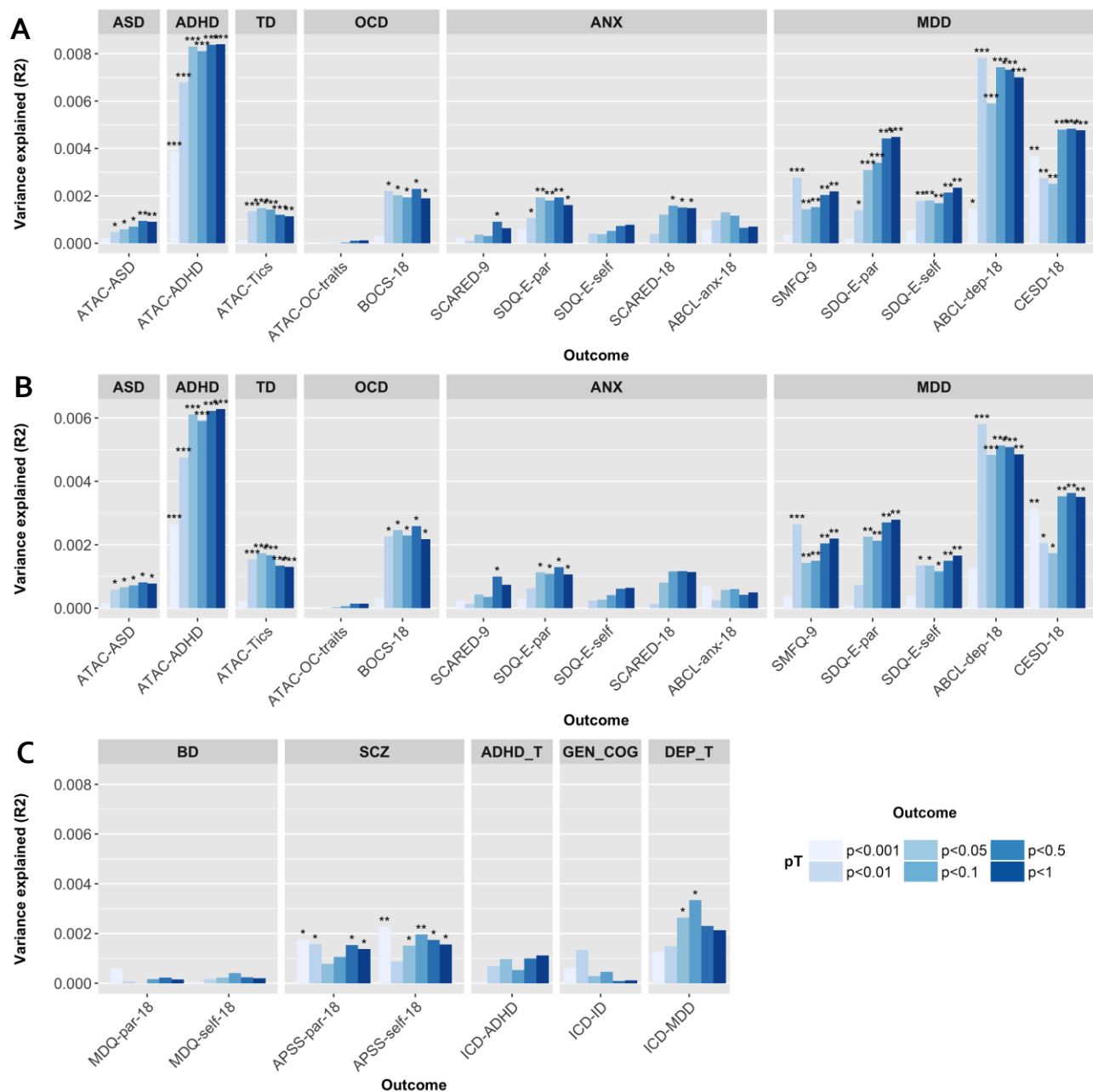
percentage of the phenotypic correlation explained by A; % rPH C: percentage of the phenotypic correlation explained by C; % rPH D: percentage of the phenotypic correlation explained by D; % rPH E: percentage of the phenotypic correlation explained by E.

eTable 8. Association of Polygenic Risk Scores for ADHD and ASD With Traits of Diagnostic Subdomains

PRS	Outcome	Full sample					Excluding those with ICD diagnoses				
		N	Beta	SE	P	R ²	N	Beta	SE	P	R ²
ASD	Social	13397	0.011	0.006	0.042*	3.9E-04	13256	0.009	0.005	0.055	3.2E-04
	Language	13398	0.011	0.006	0.047*	4.2E-04	13256	0.008	0.005	0.15	2.1E-04
	Flexibility	13397	0.022	0.005	6.9E-06***	1.5E-03	13255	0.020	0.005	8.7E-05***	1.4E-03
ADHD	Hyperactivity/ Impulsivity	13395	0.139	0.015	1.9E-19***	7.7E-03	12957	0.109	0.014	2.5E-14***	5.9E-03
	Inattention	13394	0.129	0.016	2.9E-15***	6.0E-03	12957	0.096	0.015	2.6E-10***	4.1E-03

*p<0.05, **p<0.01, ***p<0.001. ASD: autism spectrum disorders; ADHD: attention-deficit/hyperactivity disorder.

eFigure. Results of Sensitivity Analyses



Results of sensitivity analyses using polygenic risk scores (PRS) derived based on variable p-value thresholds (pT), for: a) Associations between PRS with continuous psychiatric outcomes in the full sample; b) PRS associations with the same outcomes as shown in a), after excluding individuals with the relevant ICD diagnosis from each analysis; c) PRS associations with outcomes in the full sample, for late-onset phenotypes, where individuals with ICD diagnoses could not be excluded and for analyses of binary ICD diagnosis outcomes.

Discovery GWAS samples (based on case-control and quantitative trait GWAS) used to derive PRS are listed above each plot. Asterisks indicate significance after false discovery rate (FDR) correction: * $p_{FDR} < 0.05$, ** $p_{FDR} < 0.01$, *** $p_{FDR} < 0.001$. ASD: autism spectrum disorder; ADHD: attention-deficit hyperactivity disorder; TD: Tic disorders; OCD: obsessive-compulsive disorder; ANX: anxiety disorders; MDD: major depressive disorder; BD: bipolar disorder; SCZ: schizophrenia; ADHD_T: ADHD traits; GEN_COG: General cognitive ability; ID: intellectual disability; DEP_T: Depressive traits.