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Genomic meta-analyses of binge-eating behavior and anorexia nervosa yield insights into the unique and shared biology of eating disorder phenotypes

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Eating disorders—including anorexia nervosa (AN), bulimia nervosa and binge-eating disorder—are clinically distinct but exhibit symptom overlap and diagnostic crossover. Genomic analyses have mostly examined AN. Here we conducted a genomic meta-analysis of case–control studies of binge-eating behavior (BE; 39,279 cases, 1,227,436 controls), alongside analyses of AN (24,223 cases, 1,243,971 controls) and its subtypes (all European ancestries). We identified six BE-associated loci, including loci associated with a higher body mass index and impulse-control behaviors. AN genome-wide association studies yielded eight loci, validating six loci. Subsequent polygenic risk score analysis demonstrated an association with AN in two East Asian ancestry studies. BE and AN exhibited similar positive genetic correlations with psychiatric disorders but opposing genetic correlations with anthropometric traits. Most of the genetic signal in BE and AN was not shared with body mass index. We have extended eating disorder genomics beyond AN; future work will incorporate multiple diagnoses and global ancestries.

The primary eating disorders—anorexia nervosa (AN), bulimia nervosa and binge-eating (BE) disorder—are diagnostically distinct yet show considerable overlap and diagnostic migration over time[1–3]. AN, characterized by low weight, fear of weight gain and an inability to recognize the seriousness of the low weight, has two subtypes: restricting (AN-R) and BE/purging (AN-BP), featuring BE and/or purging behaviors. Bulimia nervosa occurs in individuals with a normal or high weight and is characterized by BE and compensatory behaviors (for example, fasting, self-induced vomiting, laxative use and diuretic use). BE disorder also includes BE at normal or high weights but without recurrent compensatory behaviors[1].

Genome-wide association studies (GWASs) of eating disorders have focused primarily on AN[4–7], with few GWASs of other eating disorder-related phenotypes[8,9]. The most recent AN GWAS[6] included 16,992 cases and identified eight genome-wide significant loci. Single-nucleotide polymorphism-based genetic correlations (SNP-r_gs) with other psychiatric disorders were high and also suggested that metabolic and anthropometric factors might underlie AN pathophysiology[6,7]. The metabolic aspect of AN is reflected by a positive SNP-r_g with high-density lipoprotein cholesterol and negative SNP-r_gs with insulin resistance, leptin and type 2 diabetes. Importantly, these SNP-r_gs were independent of body mass index (BMI), which is relevant given that a low BMI is pathognomonic of AN.

Here, we expand the genetic landscape of eating disorders beyond AN. AN and bulimia nervosa show moderate family- and twin-based genetic correlations[10,11], suggesting shared genetic risk. This may partially reflect BE, a transdiagnostic symptom common to both bulimia nervosa and AN-BP. Psychiatric diagnoses defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) may not capture biological realities or patient experiences, given that disorders often exist on a continuum, overlap, co-occur, present heterogeneously and morph over time[12].

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Table 1 | Phenotype definitions

Phenotype	Inclusion criteria: self-report or questionnaires	Inclusion criteria: diagnostic codes
BE-BROAD BE broadly defined (including BE-NARROW)	1. Eating an unusually large amount of food in a short period of time with loss of control; frequency and duration criteria not required, or 2. If assessed by a single item such as "Have you ever experienced BE?"*, or 3. A self-reported diagnosis of bulimia nervosa or BE disorder, confirmation by healthcare professional not required**	307.51 (ICD-9, DSM-III-R, DSM-IV) F50.2, F50.3 (ICD-10) 307.51 [F50.2, F50.3] (DSM-5) F50.81 (ICD-10-CM)
BE-NARROW BE narrowly defined	1. Eating an unusually large amount of food in a short period of time with loss of control, and these episodes occurred on average at least once a week for at least 3 months, or 2. A clinical diagnosis of bulimia nervosa or BE disorder via hospital/register records or a structured clinical interview, or 3. A self-reported diagnosis of bulimia nervosa or BE disorder with confirmation by a healthcare professional	307.51 (ICD-9, DSM-III-R, DSM-IV) F50.2, F50.3 (ICD-10) 307.51 [F50.2, F50.3] (DSM-5) F50.81 (ICD-10-CM)
AN AN—no subtype specified (including AN-R and AN-BP)	1. A clinical diagnosis of AN or AN-BP subtype or AN-R subtype via hospital or register records, structured clinical interviews or online questionnaires on the basis of standardized criteria, or 2. A self-reported diagnosis of AN or AN-BP subtype or AN-R subtype; confirmation by healthcare professional not required Note: atypical AN (without low body weight) was not specifically excluded from our analyses but has been historically ill defined and was not ascertained for in most studies. As such, our AN data primarily reflect typical AN	306.50 (ICD-8) 307.1 (ICD-9, DSM-III-R, DSM-IV) F50.0 (ICD-10) F50.1 (ICD-10) 307.1 [F50.1] (DSM-5)
AN-R AN-R subtype	1. A clinical diagnosis of AN-R subtype via hospital or register records, structured clinical interviews or online questionnaires on the basis of standardized criteria, or 2. A self-reported diagnosis of AN-R subtype; confirmation by healthcare professional not required	F50.01 (ICD-10) 307.1 [F50.01] (DSM-5)
AN-BP AN-BP subtype	1. A clinical diagnosis of AN-BP subtype via hospital or register records, structured clinical interviews or online questionnaires on the basis of standardized criteria, or 2. A self-reported diagnosis of AN-BP subtype; confirmation by healthcare professional not required	F50.02 (ICD-10) 307.1 [F50.02] (DSM-5)
Controls	1. No history of any eating disorder and no history of BE (broadly or narrowly defined), or 2. No history of any eating disorder, or 3. Unscreened (that is, these individuals may have had an eating disorder or BE)	

Diagnostic codes are shown with the coding system in round brackets and equivalent codes in square brackets. Note that diagnostic codes relate to 'diagnosis' criteria and that some criteria for BE do not require a diagnosis. Control definitions are shown in order of preference. Footnotes: *If assessed with terms such as 'psychological overeating', 'compulsive eating', and so on, these individuals will not be included as BE-BROAD cases. **If Other Specified Feeding or Eating Disorder or Eating Disorder Not Otherwise Specified is diagnosed, these are included only if clearly stated 'subthreshold bulimia nervosa' or 'subthreshold binge-eating disorder'.

Focusing on diagnostic thresholds can bias research towards severe cases and exclude those with substantial pathology and impairment. Symptom-based approaches can complement diagnostic approaches and advance the science of eating disorders[13]. We present a GWAS of the transdiagnostic symptom of BE behavior, an augmented AN GWAS and GWASs of explicitly defined AN-R and AN-BP.

Results

Summary of phenotypes

The genetic ancestry and genetically derived sex of the participants are presented in Supplementary Table 1. We operationalized five phenotypes (Table 1): broadly defined BE (BE-BROAD), narrowly defined BE (BE-NARROW), AN, AN-R and AN-BP. We focus on BE-BROAD (owing to greater statistical power than BE-NARROW; Supplementary Results 1) and AN. Analyses of other phenotypes are presented in Supplementary Results 2. We contrast BE-BROAD with GWAS of a model-derived proxy BE disorder phenotype from the Million Veteran Program[9] (Supplementary Results 3).

GWAS meta-analyses

For BE-BROAD (17 European-ancestry datasets, 39,279 cases, 1,227,436 controls), we identified six independently associated loci (Fig. 1, Table 2, Supplementary Figs. 1–6 and Supplementary Tables 1 and 2). The liability-scale SNP-based heritability (h^2_{SNP}) was 5% (standard error (SE) of 0.4%, assuming population prevalence of 4.5%[14]) with a linkage disequilibrium score regression (LDSC) intercept of 1.03 and an attenuation ratio of 0.14 (SE of 0.04; Supplementary Table 3), suggesting that inflation was primarily due to polygenicity[15].

For AN (26 European-ancestry datasets, 24,223 cases, 1,243,971 controls) we identified eight independently associated loci—six known[6] and two additional (Fig. 1, Table 2, Supplementary Figs. 7–14 and Supplementary Tables 1 and 2). Three previously significant loci (on chromosome 2 and 3 (ref. 6), and on chromosome 12 (ref. 7)) did not reach genome-wide significance ($P = 2 \times 10^{-7}$–6×10^{-7}). The liability-scale h^2_{SNP} was 13% (SE of 0.7%, assuming a population prevalence of 1.5%[16]), the intercept was 1.02, significantly >1, and the attenuation ratio was 0.07 (SE of 0.03), suggesting polygenicity (Supplementary Table 3).

Analyses of chromosome X yielded no genome-wide significant loci for BE-BROAD nor AN, although one genome-wide significant locus was identified for BE-NARROW (Supplementary Results 2, Supplementary Fig. 15 and Supplementary Tables 4 and 5).

Given known sex differences in eating disorders, and mostly female cases in our data (96% in BE-BROAD, 94% in AN), we conducted female-only GWASs as sensitivity analyses. Results mirrored the main analyses, with differences attributable to reduced sample size (Supplementary Results 4 and Supplementary Table 6).

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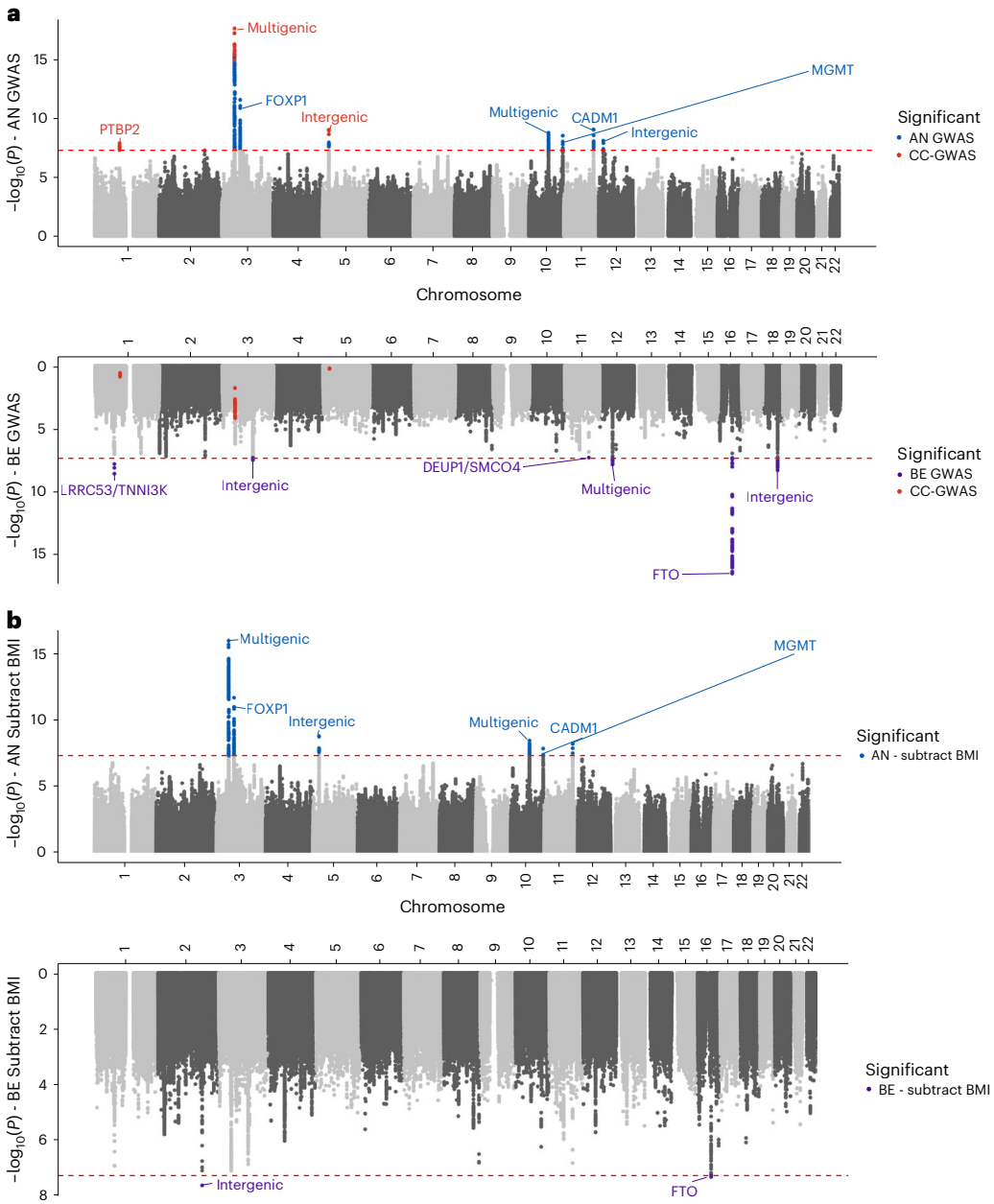


Fig. 1 | Miami plots of AN and BE-BROAD GWAS association analyses with and without the BMI component. a,**b**, Miami plots showing results from the AN (top; 24,223 cases, 1,243,971 controls) and BE-BROAD (bottom; 39,279 cases, 1,227,436 controls) meta-analyses. The dotted red line indicates the genome-wide significance threshold ($P \leq 5 \times 10^{-8}$). We performed association analyses using two-sided logistic regression (PLINK2, SAIGE or REGENIE, depending on study characteristics) followed by fixed-effects meta-analysis. Main GWAS analyses, with variants reaching genome-wide significance colored in blue if significant in the AN GWAS and in purple if significant in the BE-BROAD GWAS. Variants reaching genome-wide significance in the case–case GWAS of BE-BROAD versus AN are colored in red (**a**). GWAS-by-subtraction analyses, showing results from the non-BMI genetic component. Variants reaching genome-wide significance are colored in blue for the AN non-BMI component and in purple for the BE-BROAD non-BMI component (**b**).

Genetic relationship between eating phenotypes and other traits

We assessed the genetic similarity of BE-BROAD and AN via bivariate causal mixture modeling ('MiXeR'), via case–case GWAS and through examining their SNP-r_g with each other and with other traits[17,18]. The SNP-r_g between BE-BROAD and AN was 0.46 (SE of 0.04, $P = 3.44 \times 10^{-30}$), indicating moderate genetic overlap (Supplementary Table 7). Bivariate MiXeR yielded similar SNP-r_g (0.49, SE of 0.01) and indicated 2,654 overlapping causal variants (83% of all BE-BROAD causal variants) with highly concordant effects (95%; Fig. 2a). This was not distinguishable from the minimum plausible overlap given the genetic correlation observed—an overlap of >2,450 fully concordant causal variants (Supplementary Results 5 and Supplementary Table 8). Case–case GWAS uses genetic distance, the average squared difference in allele frequency at causal SNPs[17]. This was higher between individuals with AN and controls (0.46) and between case groups (0.40), than between individuals with BE-BROAD and controls (0.25, Fig. 2b). We identified case-divergent loci on chromosomes 1, 3 and 5, overlapping with loci from the AN GWAS (Fig. 1), suggesting that some loci differentiate AN from controls and from BE-BROAD.

We used LDSC to calculate pairwise SNP-r_g for BE-BROAD and AN with 225 psychiatric, personality, metabolic and anthropometric traits (Table 3 and Supplementary Table 9). We generally observed positive SNP-r_g of BE-BROAD with psychiatric and anthropometric

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Table 2 | Association statistics for genome-wide significant loci for BE-BROAD and AN

Phenotype	Locus	CHR	Locus start	Locus end	Lead SNP	*P* value	REF/ALT	OR	SE	ALT frequency cases	ALT frequency controls	INFO		Genes
BE-BROAD	1	1	74,977,295	75,014,362	rs7541513	2.65×10^{-9}	G/A	1.05	0.009	0.427	0.425	0.952	–	*LRRC53/TNNI3K*
	2	3	117,420,697	117,953,697	rs1456193	3.25×10^{-8}	T/C	1.06	0.011	0.808	0.802	0.996	–	Intergenic
	3	11	93,171,140	93,231,940	rs2925354	4.91×10^{-8}	G/A	0.93	0.013	0.107	0.112	0.995	–	*DEUP1/SMCO4*
	4	12	50,169,080	50,285,780	rs7953534	1.40×10^{-8}	G/A	1.05	0.009	0.351	0.333	0.985	–	Multigenic
	5	16	53,797,904	53,845,494	rs11642015	2.97×10^{-17}	C/T	1.07	0.009	0.429	0.417	1.000	–	*FTO*
	6	18	57,730,978	57,914,978	rs66723169	5.02×10^{-9}	C/A	1.06	0.010	0.254	0.209	0.995	–	Intergenic
AN	1	1	96,700,455	97,285,455	rs10747478	1.43×10^{-8}	T/G	0.94	0.011	0.570	0.587	0.998	Yes	*PTBP2*
	2	3	47,501,450	51,741,450	rs113519699	2.86×10^{-18}	A/C	1.18	0.019	0.102	0.087	0.997	Yes	Multigenic
	3	3	70,602,234	71,074,242	rs9310201	3.12×10^{-12}	A/T	1.08	0.011	0.427	0.408	0.982	Yes	*FOXP1*
	4	5	24,868,440	25,300,440	rs6872919	1.07×10^{-9}	A/C	1.07	0.011	0.570	0.532	0.997	Yes	Intergenic
	5	10	75,850,972	76,524,972	rs10740439	1.91×10^{-9}	C/T	0.93	0.012	0.711	0.716	0.994	No	Multigenic
	6	10	131,274,055	131,459,255	rs12762024	3.28×10^{-9}	G/C	1.07	0.011	0.447	0.455	0.995	Yes	*MGMT*
	7	11	114,997,256	115,284,956	rs6589488	9.80×10^{-9}	A/T	0.91	0.016	0.846	0.875	0.990	Yes	*CADM1*
	8	12	17,635,314	17,965,314	rs12817084	8.93×10^{-9}	T/C	1.10	0.011	0.115	0.117	0.991	No	Intergenic

Association analyses were performed using two-sided logistic regression (PLINK2, SAIGE or REGENIE depending on study characteristics); genome-wide significance was defined as $P<5\times10^{-8}$ with no additional multiple correction applied. Loci are numbered sequentially within analysis from chromosome 1 to chromosome X. Base pair start and end positions correspond to hg19. ORs are given relevant to the ALT allele. Genes are listed if at least one transcript in GENCODE version 47 lies at least partially within the locus, with more than three genes defined as multigenic. ALT, alternative (tested) allele; CHR, chromosome; INFO, imputation information metric; OR, odds ratio; REF, reference allele; SE, standard error; SNP, single-nucleotide polymorphism.

phenotypes, except for persistent thinness and pubertal growth, which were negative. No SNP-r_g between metabolic traits and BE-BROAD were significant except for BMI-adjusted fasting insulin. We validated and extended previously observed SNP-r_g patterns with AN[6]: positive SNP-r_g with psychiatric disorders, neuroticism, educational attainment and physical activity; negative SNP-r_g with metabolic and anthropometric traits (except for total cholesterol in high-density lipoprotein); and, notably, nonsignificant SNP-r_g with persistent thinness (Table 3 and Supplementary Table 9).

We tested for significant differences between the SNP-r_g of BE-BROAD and SNP-r_g of AN with other traits (Fig. 3, Supplementary Fig. 16 and Supplementary Table 10). Most psychiatric and behavioral phenotypes showed similar SNP-r_g with BE-BROAD and AN except attention deficit hyperactivity disorder (ADHD; higher with BE-BROAD, difference $P = 1.06\times10^{-7}$) and obsessive–compulsive disorder (higher with AN, $P = 4.79\times10^{-5}$). BE-BROAD, but not AN, was positively correlated with Alcohol Use Disorder Identification Test (AUDIT-P) problem items, four smoking-related phenotypes and general risk tolerance ($P \le 4.83\times10^{-7}$). AN, but not BE-BROAD, was negatively correlated with automobile speeding propensity ($P = 1.21\times10^{-4}$).

BE-BROAD and AN diverged in their associations with anthropometric and metabolic traits. For example, BE-BROAD was positively correlated, and AN negatively, with waist-to-hip ratio ($P = 2.05\times10^{-31}$). BE-BROAD showed a stronger pattern of SNP-r_g with certain sociodemographic traits ($P < 2\times10^{-4}$), displaying negative SNP-r_gs with age at menarche and age at first birth in females and positive SNP-r_gs with social deprivation and loneliness. AN showed no significant SNP-r_g with these traits but was more strongly positively associated than BE-BROAD with educational traits such as college/university completion.

As 18% of BE-BROAD cases had (known) AN (and 30% of AN cases met the criteria for BE-BROAD), BE-BROAD results may include AN-related effects (Supplementary Table 11). To test this, we repeated the BE-BROAD GWAS, excluding studies that focused on AN recruitment (Supplementary Results 6). The SNP-r_g between BE-BROAD and the reduced GWAS did not differ from unity (0.96, SE of 0.07) but SNP-r_gs with anthropometric traits were stronger in the reduced GWAS, suggesting that AN cases with BE may mask BE–anthropometric genetic associations (Supplementary Fig. 17 and Supplementary Table 12).

Role of BMI genetics

We applied GWAS-by-subtraction to assess the complex role of BMI in eating disorders by removing BMI-related genetic variance[19]. We modeled a factor shared between each eating phenotype and BMI and a non-BMI factor capturing the eating phenotype only. The shared factor explained 12% (SE of 2.7%) of genetic variance in BE-BROAD, leaving 88% (SE of 7.9%) accounted for by the non-BMI factor. In AN, the shared factor accounted for 10% (SE 1.4%) of genetic variance and the non-BMI factor, 90% (SE 5.5%). GWASs of the non-BMI factor for both phenotypes generally yielded larger *P* values for lead SNPs but consistent effect sizes (Fig. 1 and Supplementary Table 13). The non-BMI factors showed stable or slightly increased SNP-r_g with psychiatric disorders compared with the full GWASs, whereas SNP-r_g with anthropometric and metabolic traits were typically attenuated (Supplementary Fig. 18 and Supplementary Table 14).

Mendelian randomization analyses supported causal effects in both directions between a higher BMI risk and higher BE-BROAD/lower AN risk. The BE-BROAD non-BMI component was associated with a higher BMI, while the AN non-BMI component was not. Associations of BMI with both non-BMI components were inconsistent across methods (Supplementary Results 7 and Supplementary Table 15).

Genetically regulated gene expression

We used S-PrediXcan[20] to identify predicted genetically regulated gene expression associated with our phenotypes (Supplementary Fig. 19 and Supplementary Table 16). Within-tissue significant results are described in Supplementary Results 8. For BE-BROAD, two gene–tissue associations were experiment-wide significant (*PRKAR2A*–sigmoid colon and *KLHDC8B*–heart, atrial appendage; $P < 8.32\times10^{-8}$). In AN, 300 gene–tissue associations were experiment-wide significant ($P < 8.32\times10^{-8}$) across 29 unique genes, predominantly from the gene-dense locus on chromosome 3: 47–52 Mb.

We calculated cross-tissue-predicted genetically regulated gene expression using S-MultiXcan[21] to identify apparent tissue-specific associations that are better interpreted as cross-tissue (Supplementary Results 9, Supplementary Fig. 20 and Supplementary Table 17). Ten genes had significant ($P < 2.25\times10^{-6}$) cross-tissue expression in BE-BROAD, including four tissue-level associations (including *KLHDC8B*

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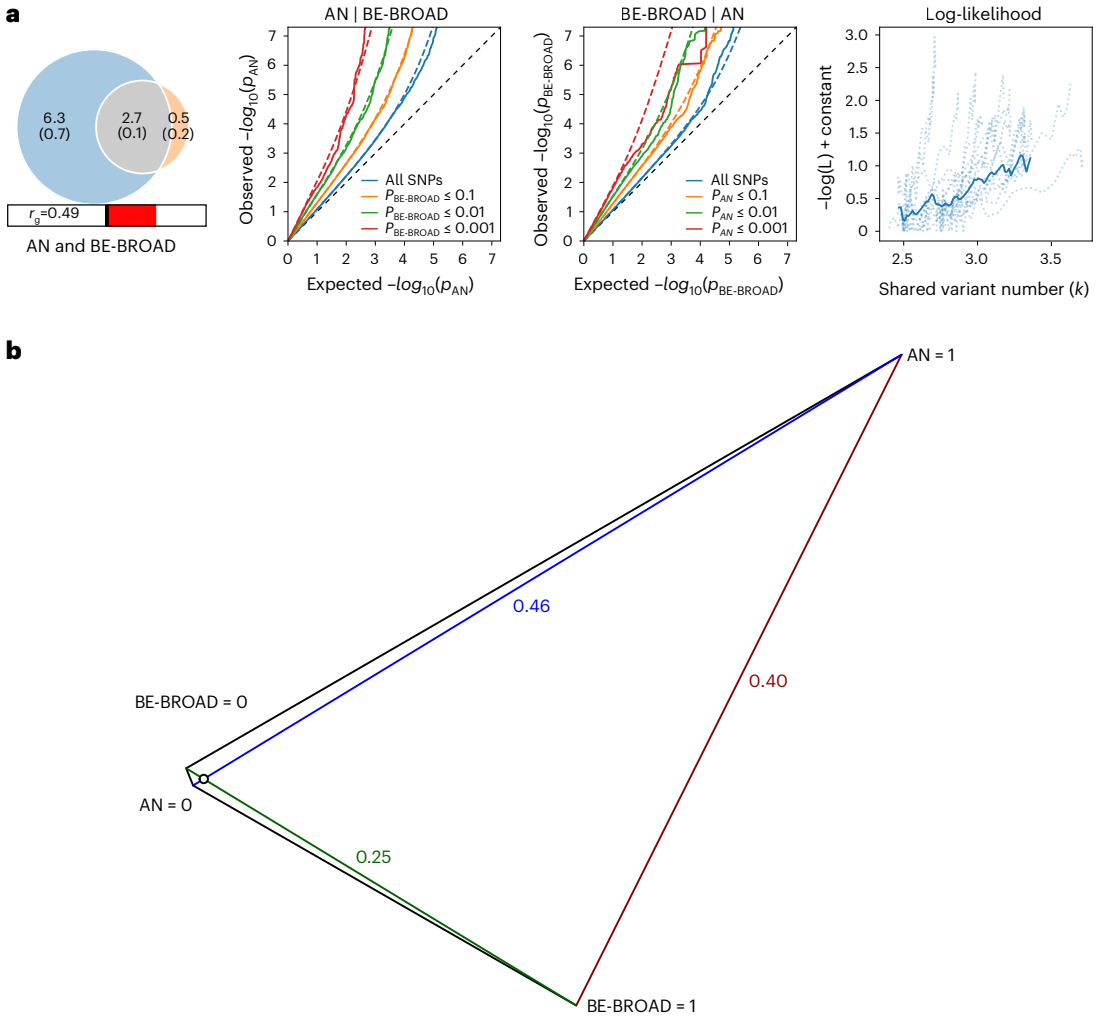


Fig. 2 | Estimates of genetic similarity between BE-BROAD and AN. a, Bivariate causal mixture modeling results from MiXeR (AN: 24,223 cases, 1,243,971 controls; BE-BROAD: 39,279 cases, 1,227,436 controls). Left: venn diagram showing overlap of putative causal variants in AN (blue) and BE-BROAD (orange), demonstrating high overlap (gray) and moderate genetic correlation (bar beneath). Middle: Q–Q plots of variant effects for AN conditional on BE-BROAD (left) and BE-BROAD conditional on AN (right), demonstrating enrichment for associations with each trait conditional on the other. Right: log-likelihood plot of model fit under differing models, from the minimal overlap model (leftmost) to the full overlap model (rightmost), showing that the best model fit (lowest *y* axis value) is not distinguishable from the minimal overlap. **b**, Genetic distance between cases and controls of BE-BROAD and AN estimated by case–case GWAS. The genetic distance is the square root of the average squared difference in allele frequency at causal SNPs.

but not *PRKAR2A*). A total of 43 genes showed significant cross-tissue expression in AN, including 23 tissue-level associations.

Gene-level associations

We conducted gene-wise (Supplementary Table 18), gene-set (Supplementary Table 19), drug-set (Supplementary Table 20) and drug-class analyses using MAGMA v1.10 (ref. 22) (Supplementary Table 21 and Supplementary Results 10). For BE-BROAD, we identified 22 Bonferroni-significant genes ($P < 2.59 \times 10^{-6}$), nine of which (43%) were linked to the gene-dense locus on chromosome 3: 47–52 Mb. *FTO* had the strongest association ($P = 2.8 \times 10^{-22}$). Gene-set, drug-set and drug-class analysis yielded no significant results. For AN, we identified 76 significant genes ($P < 2.58 \times 10^{-6}$), mostly (54/76, 71%) from chromosome 3: 47–52 Mb. Gene-set analysis implicated targets of RBFOX1-3 (RNA-binding proteins that regulate neuronal alternative splicing[23]) and mutation-constrained genes with a probability of loss-of-function intolerance (pLI) >0.9. No significant drug sets emerged, but antimigraine preparations as a class were significantly associated with AN, consistent with previous associations between AN and migraine polygenic risk scores (PRSs)[24].

Combined evidence from proximity and expression suggests greater functional relevance than proximity alone[25]. Restricting MAGMA gene-wise results to S-PrediXcan tissue-level significant genes prioritized 7 genes across four loci in BE-BROAD and 38 genes across eight loci in AN (Supplementary Table 22).

Tissue and cell-type analyses

We used stratified LDSC[26] to estimate h^2_{SNP} enrichment for BE-BROAD and AN among genes specifically expressed in GTEx human tissues (Supplementary Results 11, Supplementary Fig. 21 and Supplementary Table 23) and cell types from the Human Brain Atlas[27,28] (Supplementary Fig. 22 and Supplementary Table 24). After accounting for multiple testing, no associations were significant.

Polygenic prediction

In leave-one-study-out (LOO) PRS analyses, BE-BROAD PRSs were significantly associated with a higher risk of BE-BROAD (average liability-scale variance of 0.32%) and AN PRSs were significantly associated with a higher risk of AN (average liability-scale variance of 2.32%; Supplementary Results 12, Supplementary Fig. 23 and Supplementary Table 25).

Table 3 | A representative subset of significant genetic correlations (r_g) of BE-BROAD and AN with external traits

Trait	Category	PMID	r_g (AN)	SE (AN)	*P* value (AN)	r_g (BE)	SE (BE)	*P* value (BE)
BMI	Anthropometric	30239722	−0.31	0.020	**2.37×10^{-56}**	0.36	0.032	**1.94×10^{-28}**
Body fat percentage	Anthropometric	30593698	−0.35	0.028	**2.71×10^{-36}**	0.20	0.042	**2.65×10^{-6}**
Fat-free mass	Anthropometric	30593698	−0.15	0.022	**2.93×10^{-11}**	0.30	0.034	**6.92×10^{-19}**
Fat mass	Anthropometric	31852892	−0.32	0.023	**3.63×10^{-43}**	0.31	0.035	**1.36×10^{-18}**
Persistent thinness	Anthropometric	30677029	0.11	0.074	0.123	−0.46	0.110	**2.37×10^{-5}**
Pubertal growth (height difference, 8 years to adult)	Anthropometric	23449627	−0.03	0.053	0.606	−0.37	0.079	**3.08×10^{-6}**
Severe early-onset obesity	Anthropometric	30677029	−0.11	0.059	0.0587	0.48	0.080	**1.40×10^{-9}**
Waist–hip ratio	Anthropometric	30239722	−0.25	0.021	**1.72×10^{-34}**	0.19	0.034	**1.37×10^{-8}**
Waist–hip ratio (BMI-adjusted)	Anthropometric	30239722	−0.09	0.020	**9.33×10^{-6}**	−0.05	0.033	0.119
Fasting insulin (age- and sex-adjusted)	Metabolism	33402679	−0.30	0.048	**2.79×10^{-10}**	0.15	0.069	0.0292
Fasting insulin (BMI-adjusted)	Metabolism	34059833	−0.17	0.035	**9.62×10^{-7}**	−0.29	0.047	**6.29×10^{-10}**
HbA1c	Metabolism	28898252	−0.14	0.042	6.00×10^{-4}	−0.03	0.053	0.524
HbA1c (BMI-adjusted)	Metabolism	34059833	−0.16	0.034	**5.22×10^{-6}**	0.01	0.044	0.765
Type 2 diabetes	Metabolism	30297969	−0.18	0.024	**1.76×10^{-14}**	0.11	0.040	6.10×10^{-3}
ADHD	Psychiatric	36702997	0.07	0.029	0.0126	0.31	0.042	**2.20×10^{-13}**
Autism	Psychiatric	32747698	0.17	0.044	**1.00×10^{-4}**	0.29	0.057	**3.96×10^{-7}**
Bipolar disorder	Psychiatric	34002096	0.25	0.027	**3.80×10^{-21}**	0.23	0.035	**4.22×10^{-11}**
Insomnia	Psychiatric	30804565	0.10	0.033	2.90×10^{-3}	0.21	0.044	**2.02×10^{-6}**
MDD	Psychiatric	39814019	0.30	0.025	**1.04×10^{-33}**	0.39	0.031	**1.35×10^{-36}**
OCD	Psychiatric	28761083	0.48	0.069	**2.85×10^{-12}**	0.08	0.081	0.322
Probable anxiety diagnosis	Psychiatric	31748690	0.28	0.039	**1.42×10^{-12}**	0.32	0.060	**1.03×10^{-7}**
PTSD	Psychiatric	33510476	0.11	0.049	0.0274	0.24	0.062	**1.00×10^{-4}**
Schizophrenia	Psychiatric	35396580	0.24	0.021	**4.85×10^{-30}**	0.23	0.033	**7.04×10^{-12}**
General risk tolerance	Behavioral	30643258	0.00	0.028	0.991	0.21	0.040	**6.76×10^{-8}**
Loneliness	Behavioral	31518406	0.13	0.032	**4.96×10^{-5}**	0.37	0.044	**4.14×10^{-17}**
Physical activity	Behavioral	36071172	0.19	0.034	**5.87×10^{-8}**	0.09	0.046	0.0633
Educational attainment (years)	Sociodemographic	30038396	0.25	0.022	**1.25×10^{-29}**	0.04	0.030	0.142
AUDIT-P	Substance use	30336701	0.01	0.040	0.870	0.37	0.057	**7.00×10^{-11}**
Cannabis use disorder	Substance use	33096046	0.02	0.046	0.610	0.30	0.063	**2.78×10^{-6}**
Heavy smoker	Substance use	28166213	−0.04	0.039	0.255	0.30	0.048	**3.82×10^{-10}**
Lifetime cannabis use	Substance use	30150663	0.22	0.038	**8.48×10^{-9}**	0.32	0.051	**6.36×10^{-10}**

r_gs were calculated using two-sided LDSC, with Bonferroni correction applied for 225 traits tested ($P<2\times10^{4}$); bold values indicate r_g estimates surviving this threshold. Note: the full set of genetic correlations is presented in Supplementary Table 9. ADHD, attention deficit hyperactivity disorder; AUDIT-P, Alcohol Use Disorder Identification Test Problem items; MDD, major depressive disorder; OCD, obsessive–compulsive disorder; PMID, PubMed ID of GWAS for external trait; PTSD, post-traumatic stress disorder; r_g, single-nucleotide polymorphism-based genetic correlation; SE, standard error of the mean.

PRSs from the European ancestry AN GWAS were positively associated with a higher risk of AN in East Asian ancestry studies from Korea and Japan (odds ratio (OR) 1.36, 95% confidence interval (CI) 1.09–1.70, $P = 0.0066$), explaining 1.3% of the variance (assuming a population prevalence of 1.5%). In cross-sex analyses, PRSs from females were positively associated with risk in males (BE-BROAD: OR 1.06–1.20, AN: 1.07–1.41), but the results were not consistently significant across studies owing to variable power (Supplementary Results 12, Supplementary Fig. 24 and Supplementary Table 26). BE-BROAD and AN PRS were elevated in BE-BROAD only, AN-only and combined BE-BROAD and AN case groups compared with controls ($P \leq 0.019$). Both BE-BROAD groups typically had a significantly higher BE-BROAD PRS than the AN-only group, while both AN groups had a significantly higher AN PRS than the BE-BROAD only in one study but not in another (Supplementary Results 12, Supplementary Fig. 25 and Supplementary Table 27).

Discussion

In this BE GWAS, we implicate six genomic loci. These have been previously associated with smoking[29], risk-taking behavior[30] and age at menarche[31]. An overlap between BE and impulse-control behaviors was further observed in positive SNP-r_g with smoking, general risk tolerance and problematic alcohol use. Loss of control is a key component of BE, and impulse-control behaviors have been associated with binge-type eating disorders clinically[32–34]. Our findings imply that BE shares genetic underpinnings with psychiatric disorders and impulse-control behaviors.

Loci associated with BE-BROAD have also been implicated in anthropometric traits, including a BMI-related signal near *FTO*[35,36] that was not associated with AN or its subtypes. The *FTO* locus has been studied extensively, but the causal mechanism contributing to high BMI remains unclear[37]. Our results imply that the relationship between *FTO* and a high BMI could result partly from BE, consistent with previous

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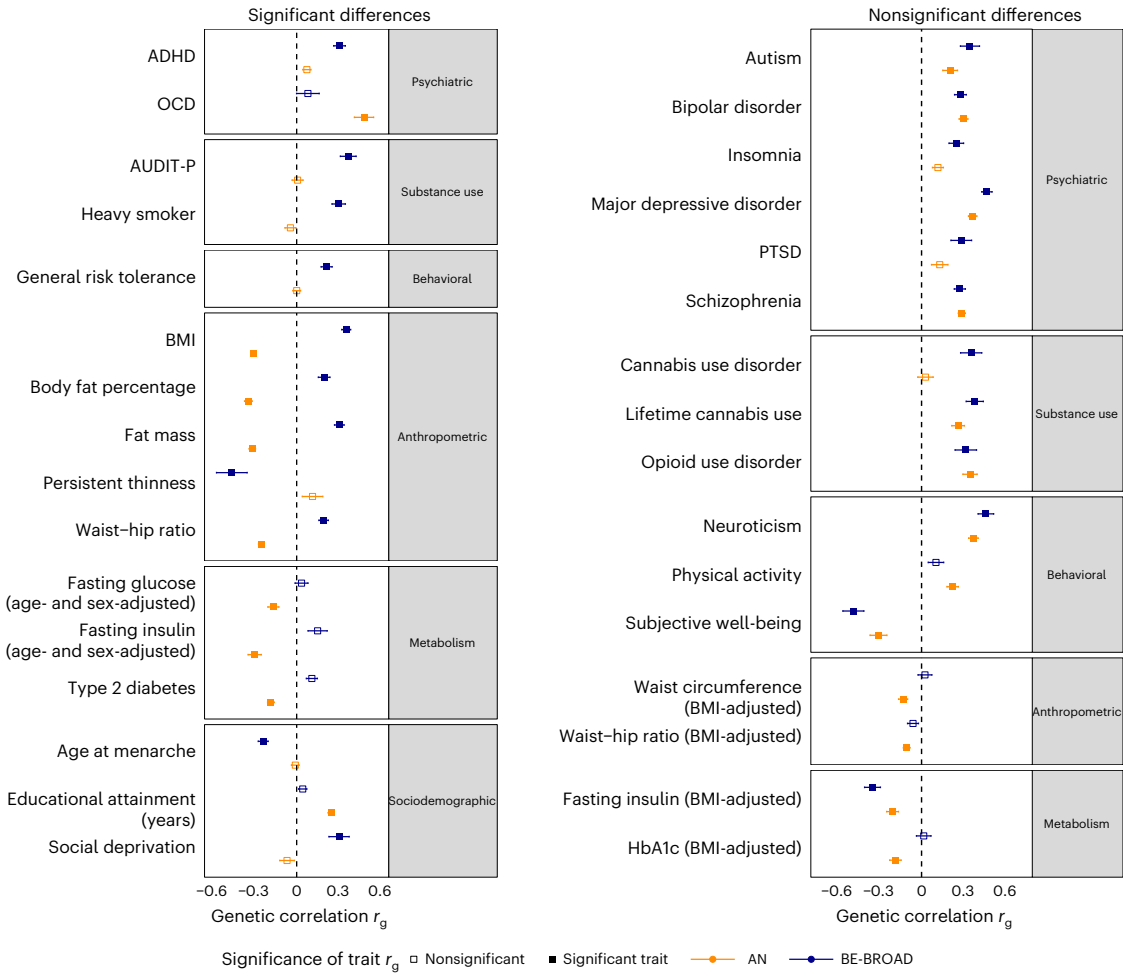


Fig. 3 | Genetic correlations (r_g) of selected external traits with BE-BROAD and AN. Point estimates represent r_gs as estimated by LDSC, with error bars indicating ±1 SE. Filled dots indicate traits with a significant r_g with BE-BROAD and/or AN after Bonferroni correction ($P < 2 \times 10^{-4}$, on the basis of 225 traits tested); open/unfilled dots indicate nonsignificant r_g estimates. Information about the summary statistics used in our analysis is presented in Supplementary Table 9. PGC, Psychiatric Genomics Consortium; FFM, fat-free mass. Left: genetic correlations differing significantly between BE-BROAD (39,279 cases, 1,227,436 controls) and AN (24,223 cases, 1,243,971 controls). Right: genetic correlations not differing between BE-BROAD and AN.

findings that BE was related to *FTO* independent of BMI and could mediate the pathway between *FTO* and a high BMI[38]. Genetic correlations of BE with anthropometric traits and impulse-control behaviors mirror clinical observations in individuals with BE and suggest that the relationship of BE to these traits and behaviors partly reflects pleiotropy rather than being purely environmental or a consequence of BE itself.

For AN, we validated six previously identified loci, identified two additional loci and identified one locus for AN-R. The four single-gene loci identified by Watson et al.[6] remained genome-wide significant, suggesting that genes located in these regions—*CADM1*, *MGMT*, *FOXP1*, *PTBP2*—may warrant further investigation in the etiology of AN[39]. The AN-R-identified locus narrowly missed genome-wide significance in AN ($P = 5.89 \times 10^{-8}$) and has previously been implicated in schizophrenia[40]. The locus contains several genes, but only *DLX1* was indicated by both proximity-based and expression-based gene mapping. The product of *DLX1* is differentially expressed in the brain and may be involved in several processes of neural development[41]. Further studies are needed to confirm that *DLX1* is implicated in AN-R, given the multigenic locus. Our gene-level results should be viewed cautiously, as greater power is needed to effectively fine-map associated loci and link causal variants to genes.

Despite increasing our effective sample size for AN by 64% since our previous freeze[6], we identified only two additional loci and two previously implicated loci were no longer significant. Several added studies were population based and used more lenient case criteria compared with previous clinical diagnoses and targeted AN-specific recruitment[42]. Consistent with this, AN PRSs typically captured less variance in AN in new studies (Supplementary Results 12 and Supplementary Table 25). Genetic signal becomes more heterogeneous as GWAS sample sizes increase[43,44], as our data reflect: although the lead AN-associated SNPs showed no evidence of heterogeneity (Supplementary Figs. 7–14), variant heterogeneity statistics (I^2) were higher in our AN GWAS than in that by Watson et al.[6] (Supplementary Results 13 and Supplementary Table 28). Nonetheless, our AN GWAS measured variants with greater precision (average variant SE of 0.0199 versus SE of 0.0255 in Watson et al.), indicating increased power despite increased heterogeneity (Supplementary Results 13).

Previously, we hypothesized that AN is a metabo-psychiatric disorder[6]—here, we investigated shared and distinct metabolic/anthropometric and psychiatric components across multiple eating disorder-related phenotypes. BE-BROAD shares genetic features with other psychiatric phenotypes, including significant SNP-r_g with psychiatric traits[6,7,24,45]. Notably, BE-BROAD showed no significant association with obsessive–compulsive disorder, whereas AN had a positive SNP-r_g. BE-BROAD was positively genetically correlated with ADHD, while AN showed no significant association; however, this may result from an underlying positive SNP-r_g between ADHD and the psychiatric

component of AN being nullified by negative SNP-r_g between ADHD and the component of AN shared with BMI.

We observed key differences for SNP-r_gs with nonpsychiatric traits. We validated our previous finding of significant SNP-r_gs between AN and metabolic-related traits[6] but not with BE-BROAD. BE-BROAD displayed a negative SNP-r_g with age at menarche, while AN showed no genetic overlap. Observational studies find that a later age of menarche is associated with AN[46,47]; however, disentangling this from the effects of starvation and a low BMI is difficult. In previous research, early-onset AN was negatively associated with age at menarche but typical-onset AN was not[48]. An earlier age at menarche is associated with impulsive traits, such as substance use and risky behavior[46], and with BMI[49]. Both impulsivity and BMI are often higher in those with BE[1,32,33].

Striking differences were observed in anthropometric traits: eating disorders and their component features share genetic factors with anthropometric traits but these effects act in opposite directions depending on the presentation. Significant SNP-r_gs between BE-BROAD and anthropometric traits were positive compared with the negative SNP-r_gs observed in AN, consistent with previous research[24,45]. To investigate this further, we assessed BE-BROAD and AN after subtracting the genetic component each shares with BMI. The BMI component accounted for 12% of the genetic variance of BE-BROAD and 10% of AN, despite a low BMI being central to AN diagnosis. The low variance explained by the BMI component argues that neither our AN nor BE-BROAD GWAS is BMI GWAS by proxy. This is further supported by the *FTO* locus association with BE-BROAD, which is observed in AN-ascertained studies where affected individuals are likely to have a lower BMI than unaffected individuals. Consistent with previous literature[50], we found no evidence for genetic overlap between persistent thinness and AN, indicating that the cognitive–behavioral component of AN distinguishes these low-BMI phenotypes genetically.

BMI is a blunt measure of body composition, with a partly behavioral etiology[26,51] and a complicated relationship with eating disorders. The negative SNP-r_g between AN and BMI may be driven by genetic enrichment for AN risk in females with a lower BMI, rather than a uniform linear relationship across BMI[52]. Both BE and AN are heterogeneous, and subtypes may have differing relationships with BMI. More sophisticated analyses with a wider range of body composition measurements and eating disorder presentations (including atypical AN in the normal- or high-BMI range) will improve understanding.

We present a GWAS of BE, a large-scale investigation of AN and AN subtypes and chromosome X analyses for all phenotypes. We extend eating disorder genetic research beyond AN alone and demonstrate that BE is a psychiatric phenotype with distinctive genetic relationships with external traits. Individuals with AN were as genetically distant from individuals with BE as they were from unaffected individuals, emphasizing the distinct nature of these eating disorder-related phenotypes. Nonetheless, we highlight the following limitations. We focused on individuals of European genetically inferred ancestry, limiting generalizability. The analysis of PRSs in two small East Asian studies used European prevalence estimates, potentially introducing bias. Differences in population structure, genetic architecture and environmental factors, such as a lower average BMI in East Asia[53], could influence cross-ancestry prediction of AN. Global populations need to be included in GWAS to strengthen genetic risk prediction and our understanding of eating disorders[13].

Given the known diagnostic crossover between eating disorders, cross-sectional studies cannot account for later symptom emergence; for example, an individual with AN-R could develop AN-BP[2]. It is not possible to fully mitigate this limitation. However, (1) many studies included individuals well beyond the typical age of diagnosis, making new diagnoses or diagnostic crossover less likely; (2) hidden diagnostic crossover probably contributes to false negatives and underestimation of differences between GWAS, rather than introducing false positives[54]; and (3) our previous work shows that extremely high rates of diagnostic contamination (a similar effect to hidden diagnostic crossover) are needed to affect locus discovery[55].

Despite our best efforts at harmonization, heterogeneity might exist within the phenotypes owing to factors such as distinct ascertainment methods. Ideally, a single approach such as clinic-based recruitment with structured diagnostic interviews would be used but is untenable given the need for large sample sizes. Also, our sample is mostly female and results may not generalize to those who are not female. Finally, although strongly associated with BE-BROAD and AN risk, PRSs remain weak predictors of BE-BROAD and AN status. Improving prediction accuracy will require combining PRSs with other risk factors.

We redress the historical focus on AN in genetic studies of eating disorders by identifying six genetic loci relating to BE-BROAD, validating six loci related to AN, reporting two additional loci and finding one locus related to AN-R. We demonstrate that BE is genetically related to other psychiatric phenotypes, with both shared and distinct patterns from AN, providing genetic substantiation of clinically observed comorbidity. The number of loci we implicate in BE-BROAD and AN is typical of early-phase GWAS studies[56], motivating GWAS meta-analyses of all eating disorders (AN, bulimia nervosa, BE disorder and avoidant/restrictive food intake disorder) and transdiagnostic behaviors (for example, BE and restriction) to drive variant discovery and further refine our understanding of shared and unique genetic features that distinguish presentations and inform a genetically informed nosology of eating disorders[12].

Methods

Ethics

This work is a secondary analysis of data from individual studies. We provide ethics and statements of informed consent (or exclusion from informed consent) and institutional review board approval for each study as a Supplementary Note. Data access information is presented in Supplementary Table 1.

Summary of studies

Details of the ascertainment and definition of cases and controls for each study are presented in Supplementary Table 1. Broadly, we identified cases and controls on the basis of clinical diagnoses, diagnostic algorithms and/or self-report questionnaires[42]. AN (and its subtypes) is a diagnostic phenotype, requiring case participants to meet clinical or research diagnostic definitions. BE-BROAD is a symptom phenotype: cases either explicitly endorsed BE as a symptom or had a diagnosis requiring BE (specifically bulimia nervosa or BE disorder; Table 1). The BE/purging subtype of AN can be diagnosed without BE and so is not sufficient for inclusion as a BE-BROAD case. Controls had no history of BE nor of an eating disorder, where possible. If this information was unavailable, unscreened controls were included assuming minimal misclassified individuals in the control groups, given that the collective lifetime prevalence of eating disorders is ~5%[16].

We included data from 14 previously analyzed[6] studies from the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED) and 13 additional studies (Supplementary Table 1). These data were restricted to individuals of European ancestry owing to few non-European ancestry studies being available at the time of analysis—we included two studies with individuals of East Asian ancestry for follow-up cross-ancestry PRS analyses. Details on genetic ancestry definition are provided in the Supplementary Methods.

Data from studies providing individual-level data ($n = 11$) were combined with studies that contributed summary statistics ($n = 16$; Supplementary Table 1). Detailed descriptions of each of the studies are provided in the Supplementary Note. We included data if the total number of cases for any phenotype before quality control was >100. If cases for an individual phenotype were <50, we excluded that phenotype from analyses.

Genotype quality control and imputation

Approaches to quality control and imputation differed between studies and are described in detail in the Supplementary Methods.

Association analyses

For case–control studies of unrelated individuals, we used PLINK2 to conduct logistic regression using a study-appropriate number of genomic principal components to account for ancestry (Supplementary Table 4). For studies with related individuals or unbalanced case–control ratios, we used SAIGE[57] or REGENIE[58]. Further details on study-specific aspects of association analysis are provided in the Supplementary Methods. All analyses were two-tailed. Post-GWAS processing and quality control is described in the Supplementary Methods.

Meta-analysis and quality control

Using the postimputation module of Ricopili[59], we performed inverse-variance weighted fixed-effect meta-analyses in METAL[60], including assessing variant heterogeneity as I^2 values (a comparison of variant heterogeneity between our AN GWAS and that of Watson et al.[6] is included in the Supplementary Methods). We included all variants but primarily report results for variants with an imputation INFO score >0.6 and a minor allele frequency (MAF) ≥0.01. We defined independent significant SNPs as those with a genome-wide significant P value ($P < 5 \times 10^{-8}$) that were independent ($r^2 < 0.6$) from each other. We defined significant genomic loci by merging linkage disequilibrium (LD) blocks of neighboring independent significant SNPs (<250 kb). We defined independent lead SNPs as independent significant SNPs independent of each other at $r^2 < 0.1$. We defined independently associated SNPs (conditional on lead SNPs) at each locus using a stepwise conditional analysis performed using the Genome-wide Complex Trait Analysis software conditional and joint association analysis tool (GCTA-COJO)[61], using one of our largest studies (usa2) as our LD reference.

Female-only analyses and female-to-male polygenic risk scoring

We conducted a supplementary female-only GWAS for BE-BROAD and AN and generated female-only PRS using PRS-CS, which we applied on male-only datasets with sufficient data (that is, n case and n control >100). For the BE-BROAD female-only meta-analysis, all studies except usa1 and biov were included, and alsp, moba and ukd2 were included as male-only target studies. For the AN female-only meta-analysis, all studies except itgr, spa1, ukd1 and net2 were included, and ipsy, fngn and ukb2 were included as male-only target studies.

SNP-based heritability and distinguishing polygenicity from other sources of inflation

We used LDSC[62] to estimate SNP-based heritability (h^2_{SNP}). These estimates were transformed to the liability scale, assuming population prevalences as follows: BE-BROAD 4.5%[14], BE-NARROW 3.5%[14], AN 1.5%[16], AN-R 0.8%[16,63] and AN-BP 0.7%[16,63]. For all analyses using LDSC, we applied an LD reference panel from the European subset of the 1000 Genomes Project (1kGP), restricted to SNPs present in the HapMap 3 panel[64]. For N, we calculated the sum of effective N across all studies and specified 0.5 for sample prevalence[65]. All LDSC analyses, including tests of the difference of h^2_{SNP} and SNP-r_g from 0 and from 1, were two-tailed tests of deviation from a chi-squared distribution with jack-knifed standard errors.

Test statistics from GWAS of a polygenic trait are expected to be inflated, but inflation may also be due to spurious SNP associations caused by population stratification and cryptic relatedness of study participants. We used statistics from LDSC[62] to determine the source of inflation. Although the LDSC intercept is commonly used to distinguish polygenicity from spuriously inflated statistics, we calculated the attenuation ratio statistic, defined as (LDSC intercept − 1)/(mean of association chi-squares statistics − 1), which may be a less biased metric compared with the LDSC intercept[15]. We included variants with MAF ≥0.01 and INFO ≥0.6.

Genetic relationship between traits

We used LDSC to calculate SNP-r_g with several aims. First, we assessed the genetic relationships among the five eating disorder-related phenotypes. Second, we calculated SNP-r_g between BE-BROAD/AN and 225 traits covering eight categories: (1) psychiatric trait or disorder, (2) substance use, (3) psychological/personality/behavioral, (4) anthropometric, (5) metabolism, (6) blood, (7) sociodemographic and (8) somatic trait or disease. We selected these traits from an internal catalog on the basis of their power (h^2_{SNP} Z-score >4)[66]. We tested whether SNP-r_g differed from zero and applied a Bonferroni-corrected P value threshold of 2.20×10^{-4} on the basis of 225 traits. For significant SNP-r_g with BE-BROAD and/or AN, we compared the SNP-r_g between BE-BROAD and AN using the LDSC block-jackknife procedure (Bonferroni-corrected P value threshold of 2.20×10^{-4})[67].

We used MiXeR v1.2.0 to conduct univariate and bivariate causal mixture modeling of BE-BROAD and AN, limited to autosomal variants with INFO ≥0.6 and MAF ≥0.01, and with the major histocompatibility complex (MHC) region (chromosome 6: 26–34 Mb) excluded[18]. MiXeR refines the interpretation of heritability and genetic correlation by extending LDSC, using GWAS summary statistics to model the number of causal variants underlying a trait (polygenicity) and the average contribution of each causal variant to heritability (discoverability). Bivariate MiXeR enables the number of shared causal variants between traits to be estimated and the extent to which they have the same direction of effect. We followed protocols and used LD reference files provided by the authors of MiXeR (https://github.com/precimed/mixer).

We used case–case GWAS (CC-GWAS) to test for allele frequency differences between BE-BROAD and AN cases (as opposed to traditional GWAS, which compares cases with controls)[17]. We included nonambiguous SNPs from HapMap 3 with INFO ≥0.6 and MAF ≥0.01. CC-GWAS calculates genetic distances between cases and controls of the two traits using equation (1),

$$\sqrt{m \times F_{ST,causal}}. \quad (1)$$

In equation (1), m is the number of independent causal variants and $F_{ST,causal}$ is the average normalized squared differences in allele frequencies based on liability-scale h^2_{SNP}, SNP-r_g and population prevalence. We assumed m = 10,000, consistent with psychiatric disorder polygenicity[17] and set the BE-BROAD population prevalence to 4.5% (range 0.1–10%) and AN to 1.5% (range 0.1–4.3%). We defined independent CC-GWAS loci with PLINK 1.9 (--clump-p1 5e-8 --clump-p2 5e-8 --clump-r2 0.1 --clump-kb 3000) and defined a genome-wide significant SNP if $P < 5 \times 10^{-8}$ in the CC-GWAS ordinary least squares test and $P < 10^{-4}$ in the CC-GWAS exact test.

Influence of BMI

We used GWAS-by-subtraction[19], an application of genomic structural equation modeling (genomic SEM)[68], in R v4.3.1 (ref. 69) to estimate the proportion of variance in BE-BROAD and AN independent of BMI (Supplementary Methods). Latent genomic SEM factors model shared genomic covariance across traits, making results less influenced by spurious biases than would conditioning on phenotypic traits in a GWAS[70]. We used GWAS summary statistics from BE-BROAD, AN and BMI[35].

We specified two latent variables as a function of BMI and (for example) BE-BROAD: a shared variable ('BMI') as 'BMI = ~NA × BE-BROAD + start(0.4) × BMI' and a non-BMI variable ('non-BMI') as 'non-BMI = ~NA × BE-BROAD' (Supplementary Fig. 26). In line with previous applications of GWAS-by-subtraction[19], we set latent variable

variance to 1 and covariance to 0 and constrained the model such that all (co)variance in BMI and BE-BROAD was captured by BMI and non-BMI. We used the diagonally weighted least squares estimator[68]. Additional computational settings are presented in Supplementary Table 30.

We regressed the two latent factors on individual SNPs, yielding a GWAS of the BMI and non-BMI factors. We used LDSC[62] to calculate SNP-r_g of the non-BMI factor with all traits identified in initial SNP-r_gs. As a sensitivity analysis, we restricted BE-BROAD to studies that were not ascertained for AN, reasoning that this might better capture BE behavior outside of AN. We applied the same GWAS-by-subtraction model on that selection of studies (Supplementary Table 11).

We also conducted two-sample Mendelian randomization analyses of BE-BROAD/AN with BMI, testing causal effects in both directions with two-tailed tests. We used SNPs in linkage equilibrium as genetic instruments, with $P < 5 \times 10^{-6}$ for BE-BROAD and AN and $P < 5 \times 10^{-9}$ for BMI. The instrument used for BMI was that suggested by the authors of the BMI GWAS[35]. We repeated analyses using the non-BMI factor GWAS of BE-BROAD and of AN. To test robustness to potential violations of the assumptions of Mendelian randomization, we conducted analyses using inverse-variance weighted analysis, MR-Egger, mode-based estimation and median-based estimation, implemented in R 4.3.2, using the packages TwoSampleMR, MendelianRandomisation and MR-PRESSO[69,71,72] (Supplementary Methods). We determined the strength of association of our genetic instruments using *F* statistics[73]. We used Cochran's *Q* statistic to test for instrument heterogeneity, with $P < 0.05$ indicating heterogeneity[74]. To investigate potential confounding via horizontal pleiotropy, we assessed the deviation of the MR-Egger intercept from 0 and performed a global bias test in MR-PRESSO. We excluded from the analysis SNPs identified by MR-PRESSO as pleiotropic. We ran further methods robust to heterogeneity, including the penalized weighted median estimator, the contamination mixture method and MR-Lasso[75]. We assessed results visually (Supplementary Methods).

Identification of gene–tissue associations with eating phenotypes

We used S-PrediXcan[20] to identify genetically regulated gene expression associated with our phenotypes. We tested the association of gene expression using available GTEx v8 MASHR[20,76,77] and CommonMind DLPFC[78,79] tissue models. MASHR-based PredictDB models use fine-mapping methods for selection of eQTLs included in the predictor models, improving prediction[20,76,77]. We included 45 GTEx v8 MASHR models, removing non-natural tissues (cell lines), tissues with $N < 100$ individuals (kidney cortex) and testis[80]. We performed liftover of our GWAS summary statistics to hg38, harmonization and imputation on the basis of recommended preprocessing by Barbeira et al.[78] using GWAS tools (https://github.com/hakyimlab/MetaXcan/wiki/Best-practices-for-integrating-GWAS-and-GTEX-v8-transcriptome-prediction-models and https://github.com/hakyimlab/summary-gwas-imputation/wiki/GWAS-Harmonization-And-Imputation). We tested whether imputed differences in genetically regulated gene expression between cases and controls differed from 0 as a two-tailed *Z* test. We used two different Bonferroni significance thresholds: an experiment-wide threshold, correcting for 600,382–602,744 tests performed across all tissues ($P < 0.05/\text{Tests}_{\text{Total}} = P < 8.32 \times 10^{-8}$), and a tissue-specific threshold, correcting for varying numbers of tests performed within each tissue ($P < 0.05/\text{Tests}_{\text{Tissue } x}$; Supplementary Table 16). We performed two-tailed exact binomial tests for tissue enrichment using binom.test() in R for associations at three different significance thresholds: experiment-wide significance ($P < 0.05/\text{Tests}_{\text{Total}}$), tissue-specific significance ($P < 0.05/\text{Tests}_{\text{Tissue } x}$) and nominally significance ($P < 0.05$).

S-MultiXcan measures the joint association of genetically regulated gene expression across tissues with a phenotype of interest using summary statistics, leveraging shared eQTLs across tissues[21]. Using our GTEx v8 MASHR S-PrediXcan results as input, we ran S-MultiXcan on each of our phenotypes for all genes ($N = 22{,}241$). S-MultiXcan returns the *P* value for association of multi-tissue gene expression with the trait of interest (S-MultiXcan *P*), along with best single-tissue *P* value, both from two-tailed tests. To account for potential false positive associations, we removed any significant S-MultiXcan associations where the single best tissue *P* value was $>1 \times 10^{-4}$ and Bonferroni-corrected for all genes tested ($P < 0.05/22{,}241 = 2.25 \times 10^{-6}$)[21].

Gene-wise and gene-set analysis, including drug-target and drug-class analyses

Following previous publications[81], we used MAGMA v1.10 (ref. 22) to test the association between each phenotype and the aggregate effect of SNPs mapped to protein-coding genes (gene analysis); groups of genes with shared functional, biological or other characteristics (gene-set analysis); sets of genes targeted by drugs (drug-set analysis) and signal enrichment within drug classes. We used SNPs with MAF ≥0.01 and INFO ≥0.6 present in ≥80% of the total sample and ≥50% of studies. We mapped SNPs to protein-coding genes, including variants 35-kb upstream and 10-kb downstream of hg19 gene positions from Ensembl release 75 (ref. 82). We obtained gene-wise *P* values with the multi-SNP-wise model (Supplementary Methods). We tested 19,332–19,418 ENSEMBL genes across the five phenotypes and applied a Bonferroni correction of $P < 2.60 \times 10^{-6}$. We used the 1kGP reference panel for estimating between-SNP LD.

For gene-set analyses, we applied a competitive analysis (one-tailed test; Supplementary Methods). We defined biological pathways on the basis of Gene Ontology and canonical pathways from MSigDB v6.1 and psychiatric pathways identified from literature. We tested 7,324–7,325 pathways across the five phenotypes and applied a Bonferroni correction of $P < 6.83 \times 10^{-6}$.

For drug-set analyses, we defined drug sets on the basis of drug targets from the Drug–Gene Interaction database DGIdb v4.2.0[83], the Psychoactive Drug Screening Database Ki DB[84], CheMBL v27[85], the Target Central Resource Database v6.7.0[86] and DSigDB v1.0[87], all downloaded in October 2020. We applied a competitive analysis and subsequently grouped the results on the basis of the Anatomical Therapeutic Chemical class of the respective drugs[88]. For drug-class analysis, we determined statistical significance from one-tailed Wilcoxon Mann–Whitney tests of the area under the receiver operating characteristic curve of ranked drug–gene sets (Supplementary Methods). We applied a Bonferroni correction of $P < 3.23 \times 10^{-5}$ (on the basis of 1,546–1,547 drug sets) for the drug-set analysis and $P < 3.08 \times 10^{-4}$ (on the basis of 162 drug classes) for the drug-class analysis to account for multiple testing.

Tissue and cell-type specific analyses

Tissue and cell-type specific analyses are described in the Supplementary Methods.

Polygenic prediction

We used PRS-CS[89] to generate PRS for BE-BROAD and AN. The inclusion of target studies for each phenotype was based on the effective sample size (N_{eff} half >1,000), study characteristics and availability of individual-level data (more detailed information provided in the Supplementary Methods). We generated LOO GWAS summary statistics, excluding each target study, and used these as the base data to calculate individual-level PRS in each target study. We included nonambiguous SNPs with INFO ≥0.6 and MAF ≥0.01. We used the 1kGP Phase 3 EUR LD reference panel and provided median sample size per LOO meta-analysis as input for PRS-CS. Posterior SNP effect size estimates from PRS-CS were combined across chromosomes to calculate individual PRS via PLINK (--score 2 4 6 sum)[90]. We standardized individual PRSs in R (version 4.3.2)[69]. We performed two-tailed logistic regression of BE-BROAD and AN PRS on BE-BROAD and AN, adjusting for study-specific genetic principal components. ORs reflected one

standard deviation increase in the PRS. We assessed the proportion of variance explained by the standardized PRS for each phenotype as the Nagelkerke's pseudo-R^2 of the full model minus that of the null model excluding the PRS[91], converted to the liability scale using population prevalences of BE-BROAD and AN as used for LDSC[92]. We also divided individuals into PRS deciles and assessed their relative risk of BE-BROAD and AN compared with the lowest PRS decile. We examined the sensitivity, specificity and precision of each PRS to predict BE-BROAD and AN status using the pROC[93] and pracma[94] packages in R, comparing the area under the receiver operating characteristic curve and under the precision recall curve of the full model against the null model.

We used female-only GWAS summary statistics as base data in PRS-CS[89] to assess whether female BE-BROAD PRS was associated with BE-BROAD risk in males in three studies (alsp, moba, ukd2, $N_{case_male_total}$ = 1,055, $N_{control_male_total}$ = 38,046). Parallel analysis of the association of female AN PRS with male AN risk was conducted in three studies (ukb2, fngn, ipsy, $N_{case_male_total}$ = 1,524, $N_{control_male_total}$ = 388,891).

We assessed whether BE-BROAD PRS and AN PRS differed across subgroups, including (1) those with BE-BROAD only, (2) those with both BE-BROAD and AN and (3) those with AN only. We selected aunz and sedk to assess individuals with both BE-BROAD and AN and to assess the AN only group. We selected ukb2 and ukd2 for assessing BE-BROAD and AN PRS levels in all subgroups (Supplementary Methods and Supplementary Table 1). We performed linear regression on each PRS for each subgroup compared with controls, adjusting for study-specific genetic principal components. We compared differences in BE-BROAD PRS and AN PRS between subgroups and controls and across different subgroups.

We applied AN PRS from our European genetic ancestry meta-analysis to two East Asian genetic ancestry studies (Japanese: N_{case} = 77, $N_{control}$ = 117, Korean: N_{case} = 75, $N_{control}$ = 109). Raw genetic data from both studies were merged, and pre-imputation quality control and imputation were conducted as for the European ancestry studies. We used the 1kGP Phase 3 EUR LD reference panel for PRS, which aligns with the ancestry of the base GWAS[89]. We used European AN prevalence estimates for liability scale conversion, as what sparse estimates exist from East Asia approximately align with estimates in countries with European genetic ancestry majorities[95].

Sensitivity analyses using down-sampled BE-BROAD data

A considerable portion (13%) of BE-BROAD cases were recruited through studies ascertained for AN. To understand the influence of AN on this BE-BROAD phenotype, we conducted an additional BE-BROAD meta-analysis excluding studies ascertained for AN (Supplementary Table 11). We calculated SNP-r_g to compare the genetic relationship of the 'not-ascertained-for-AN' BE-BROAD GWAS and the original BE-BROAD GWAS with traits significantly correlated with the original BE-BROAD GWAS or with the AN GWAS (hypothesizing that AN-related effects may mask or drive SNP-r_gs between such traits and the original BE-BROAD GWAS).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Data access is described in Supplementary Table 1. Available individual-level genotype data (except in countries where sharing of individual-level data is prohibited by national law) and summary statistics from individual studies used in this study are available to researchers via collaboration with study principal investigators (PIs) or (for a subset of studies) via a secondary analysis proposal to the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC) at https://pgc.unc.edu/for-researchers/data-access-committee/data-access-information/. Summary statistics of all GWAS meta-analyses reported in this work are available via Figshare and the PGC website, conditional on agreeing to terms and conditions of use, at https://pgc.unc.edu/for-researchers/download-results/.

Code availability

Code underlying this work are available via GitHub at https://github.com/psychiatric-genomics-consortium/PGC3_EAD_Public.

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Author contributions

Specific author contributions are listed in Supplementary Table 29. All authors made substantial contributions to the conception or design of the work, or to the acquisition, analysis or interpretation of data for the work, and critically reviewed the work for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests

S.J.-M. and F.F.-A. have received consultancy and speaker honoraria from Novo Nordisk. O.A. is a consultant to Precision Health and Cortechs.ai and has received speaker's honoraria from Lundbeck, Janssen, Lilly and Otsuka. J.K. is a member of the Scientific Advisory Board for Myriad Neuroscience. M.L. has received lecture honoraria from Lundbeck pharmaceuticals. Q.L. was an employee of Janssen Research & Development, LLC, when the work was completed and holds company equity. N.M. receives an honorarium as associate editor on the *European Eating Disorders Review*. D.R. served as consultant for Janssen; received honoraria from Boehringer-Ingelheim, Gerot Lannacher, Janssen and Pharmagenetix; received travel support from Angelini, Janssen and Schwabe; and served on advisory boards of AC Immune, Boehringer-Ingelheim, Roche and Rovi. P.S. is a shareholder in Neumora Therapeutics and serves on the advisory board. C.B. receives royalties from Pearson Education, Inc., and has served as a consultant for Orbimed. All other authors declare no competing interests.

Additional information

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection for this paper.
Data analysis	We used the following software in data analysis: PLINK1.9 (1.9b_6.17-x86_64); PLINK2 (various versions across sites, version 2.00a2.3_x86_64 used centrally); ReGENIE (various versions across sites); SAIGE (various versions used across sites); LiftOver (no versioning at time of writing); Python (various versions, primarily 2.7.18); BCFTools (1.10.2); HRC-1000G-check-bim (4.3.0, available from https://www.chg.ox.ac.uk/~wrayner/tools/); DENTIST (1.2.0); RICOPILI (2019, Oct); METAL (2011-03-25); GCTA-COJO (1.93.1); PRS-CS (1.1.0); LDSC (1.0.0); CC-GWAS (no versioning at time of writing); GenomicSEM (v0.0.5c); R (various versions); TwoSampleMR (0.6.8); MendelianRandomisation(0.10.0); MRPRESSO (1.0); S-PrediXcan/S-MultiXcan (0.6.11); MAGMA (1.10); MiXeR (1.2.0). Imputation was conducted on various platforms and to various reference panels, but primarily used the TopMED imputation server (https://imputation.biodatacatalyst.nhlbi.nih.gov/) imputing to TopMED freeze 8, using Eagle (2.4) for phasing and Minimac4 for imputation. Linking code between these different software was used but was not central to the research - this code will be made publicly available on GitHub after publication (https://github.com/psychiatric-genomics-consortium/PGC3_EAD_Public).

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All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
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Individual level genotype data (except in countries where sharing of individual level data is prohibited by national law) and summary statistics used in this study are available to bona fide researchers working in collaboration with a member of the Eating Disorders Working Group of the PGC via secondary analysis proposals (https://pgc.unc.edu/for-researchers/data-access-committee/data-access-information/).

Summary statistics from this work will be made available via Figshare and the PGC website on publication (https://pgc.unc.edu/for-researchers/download-results/).

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Our analyses include stratification by sex. As part of our genomic quality control measures, we align genetic sex (inferred through X-chromosome heterozygosity) with reported "sex" – this is inferred to mean sex assigned at birth (and in some cohorts this may be explicitly specified) but in some cases, reported sex may reflect gender or sexual identity and not sex assigned at birth. As such, it is possible that some trans individuals, or individuals whose gender and sexual identity do not otherwise align with their sex assigned at birth, may have been incorrectly identified as sample swap errors and excluded from analysis. However, this is difficult to rectify, especially in cohorts collected some time ago where recontact of participants is not possible. We do not refer to gender in our analyses. We conducted female-only GWAS, and used this to perform female-to-male polygenic score analysis. We did not conduct male-only GWAS as sample sizes were too small. Overall, our analysis includes 39,279 individuals reporting binge-eating behaviours and 1,227,436 comparison individuals, of whom 37,580 and 691,808 individuals respectively are female. Data was available on 1487 and 79,144 male individuals. For anorexia nervosa, we include 24,223 individuals with a history of anorexia nervosa and 1,243,971 comparison individuals, of which 21,898 and 694,722 individuals are female. Male data for the anorexia nervosa analyses was available for 718 and 353,303 individuals. Differences between sex stratified numbers and overall numbers reflect cohorts where stratified data were too small for inclusion.
Reporting on race, ethnicity, or other socially relevant groupings	Our analyses are mostly restricted to individuals from European ancestries. By this, we refer to homogeneous groupings of individuals on principal component axes derived from genome-wide genotype data, which reflect global human population structure. Given the locales from which we collected data, the majority grouping in most cohorts was comprised of participants who reported European ethnicities, and so we designate the participants in these groups as being of European ancestries. We recognise the Eurocentric predominance of data within genomics, and we are working to expand recruitment of participants to studies of eating disorder genetics to better reflect the global ancestry distribution. As an initial step, we include polygenic risk scoring analyses from our European ancestry GWAS into two cohorts from East Asian ancestries (defined parallel to the process described above).
Population characteristics	We do not consider population characteristics as covariates in our analyses as they were focused on discovering new variant-trait associations. The relationship between genetic and environmental factors in eating disorders is an important area of research, but the small effect sizes typical of common genetic effects on psychiatric traits necessitate the collection of very large sample sizes, which would be impaired by additionally requiring samples to have similarly-collected information on population characteristics. We anticipate that subsets of our underlying data will be used by future researchers to examine these more nuanced questions of gene-environment interplay.
Recruitment	Participants were recruited using a variety of different methods implemented across the different sites and cohorts. Broadly, we identified cases and controls based on clinical diagnoses, diagnostic algorithms, and/or self-report questionnaires. Most cohorts collected data from clinical eating disorder services - however, a substantial proportion of our anorexia nervosa analyses came from the ANGI project, which recruited participants via professional organisations such as the Academy for Eating Disorders, conventional media, social media, (press) conferences and support groups, and word-of-mouth. There are additionally large components of the study drawn from population cohorts like the MoBA cohort and the iPSYCH cohort, while other large components are drawn from population biobanks like UK Biobank, Estonian Biobank, and FinnGEN. Epidemiological biases likely affect each of our cohorts, although it is likely that some of these biases will not act consistently across cohorts. As such, these biases likely contribute to increasing the heterogeneity of our data, reducing precision, but will have less effect on biasing specific effect estimates.
Ethics oversight	Price Foundation Collaborative Group and Children's Hospital of Philadelphia (CHOP): Ethical approval was obtained by each of the individual study sites (Cornell University, University of California at Los Angeles, University of Pittsburgh, University of Toronto, University of London, and University of Munich.). For the CHOP controls, CHOP's Research Ethics Board approved the study, and informed consent was obtained from all participants or their parents. Anorexia Nervosa Genetics Initiative (ANGI): ANGI-Australia and New Zealand (ANGI-ANZ) and Queensland Skin Study (QSkin): For ANGI-ANZ, all participants provided informed consent. Ethical approval for the Australian arm of the study was obtained by the QIMR Berfhoger Human Research Ethics Committee; for New Zealand, this was provided by the Health and Disability Ethics Committee of the New Zealand Ministry of Health. For QSkin, ethical approval was obtained by the QIMR Berghofer Human Research Ethics Committee (QIMR-HEC approval P1309, P2034). ANGI-Denmark (ANGI-DK) and the The Lundbeck Foundation Initiative for

Integrative Psychiatric Research (iPSYCH): Participants from ANGI-DK and the iPSYCH study did not provide written informed consent, as an exemption from consent was provided by the Danish Scientific Ethics Committee (Videnskabsetisk Komité). This exemption was most recently approved in 2018. Additional Danish cases: All participants provided written informed consent before participating in the study. The study was approved by the Capital Region of Denmark's Committees on Health Research Ethics (De Videnskabsetiske Komiteer for Region Hovedstaden) (approval number H-KF-01-024/01). ANGI-United States of America (ANGI-US): ANGI-US was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill (IRB: 13-0081). All participants were broadly consented for research. ANGI-Sweden, LifeGENE and Binge-Eating Genetics Initiative (BEGIN): This project has been approved by the ethical review board in Sweden. The fundament of the ethical permit comes from ANGI Sweden (dnr 2013/112-31/2) which has later been amended to also include individuals with another diagnosis than AN (dnr 2014/1563) and to change the study name to BEGIN (dnr 2016/1852-32). For LifeGene, the Regional Ethical Review Board of Stockholm provided ethical approval, and all participants provided online consent. Australian Genetics of Depression Study: Ethics approval for all aspects of the project was obtained from the QIMR Berghofer Human Research Ethics Committee (P2118 & P3434). Avon Longitudinal Study of Parents and Children (ALSPAC): Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. The main caregiver initially provided consent for child participation, and from the age of 16 years, the offspring themselves have provided informed written consent. The Vanderbilt University biorepository (BioVU): The study was approved by the Vanderbilt University Medical Center Institutional Review Board (IRB #201609). The Estonian Biobank: The research project has obtained approval from the Estonian Council on Bioethics and Human Research (1.1-12/624). The Finnish Study of Genetics (FinnGEN): Written informed consent was obtained from all the study participants. For the Finnish Institute of Health and Welfare (THL)-driven FinnGen preparatory project and FinnGen project, all patients and control subjects had provided informed consent for biobank research, based on the Finnish Biobank Act. Alternatively, the North Karelia Project (FINRISK) and Health 2000 cohorts were based on study specific consents and later transferred to the THL Biobank after approval by Valvira, the National Supervisory Authority for Welfare and Health. Recruitment protocols followed the biobank protocols approved by Valvira. Data from the Eating Disorders Continuum (EDC) at the Douglas Mental Health University Institute in Montreal: In all cases, there was consent to participation in one or more of the original studies, as well as to sharing of DNA with other research groups for additional genetic studies. All aspects were approved by the Research Ethics Boards of the Douglas Mental Health University Institute or Montreal West Island Integrated University Health and Social Services Centre. Jannsen: The CAPSS220BED clinical study (ClinicalTrials.gov ID: NCT00210808) was conducted by Johnson & Johnson Pharmaceutical Research & Development, L.L.C., and was approved by the appropriate ethical review boards and followed the principles outlined in the Declaration of Helsinki for all human investigations. In addition, informed consent has been obtained from the study participants. The Norwegian Mother, Father and Child Cohort Study (MoBa): The establishment of MoBa and initial data collection was based on a licence from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics (20311). Utrecht Research Group Eating Disorders (URGE) cohort: Informed consent was obtained from all patients who provided DNA. The Biobank Ethics Committee of the University of Utrecht gave ethical approval for this work. UK Biobank: UK Biobank is registered as a Research Tissue Bank (North West - Haydock Research Ethics Committee, 21/NW/0157). All data and sample applications may use this ethical clearance to conduct their research. Separate Research Ethics Committee or other ethical clearance is not required. This research was conducted under application 82087 (PI: Jonathan Coleman). Charlotte's Helix: Charlotte's Helix participants were recruited using ethics approval provided by the Research Ethics Committee South Central Oxford C (15/SC/0388). The Genetic Links to Anxiety and Depression (GLAD) Study, and the National Institute for Health Research (NIHR) Bioresource: The GLAD Study was approved by the London - Fulham Research Ethics Committee on 21st August 2018 (REC reference: 18/LO/1218) following a full review by the committee. The NIHR BioResource has been approved as a Research Tissue Bank by the East of England - Cambridge Central Committee (REC reference: 17/EE/0025). Korean Study of Anorexia Nervosa: The study was approved by the Institutional Review Board of Inje University (INJE 2016-01-003-002). Genetics Consortium for Anorexia Nervosa: Each study site (Medical University of Vienna, Toronto General Hospital, Charles University, University of Helsinki, Institut National de la Santé et de la Recherche Médicale, University of Pittsburgh, University of North Carolina at Chapel Hill, Roseneck Hospital for Behavioral Medicine, University of Munich, Kings College London, Laureate Psychiatric Hospital, Weill Cornell Medical College, Sheppard Pratt Health System, Neuropsychiatric Research Institute Fargo, University of California at Los Angeles, University of Pennsylvania, University of Birmingham, University of Duisburg-Essen, GlaxoSmithKline Leeds, Athens University, Medical School, Padua/Verona/Treviso/Vicenza/ Portogruaro hospitals, University Medical Center Utrecht, Altrecht in Zeist, Poznan University of Medical Sciences, Center for Genomic Regulation Barcelona, Department of Psychiatry University Hospital of Bellvitge, Karolinska Institutet, McLean Hospital/Harvard Medical School, Vanderbilt University School of Medicine) obtained informed consent from all participants, as well as permission from local ethical committees.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Quantitative cross-sectional, observational, case-control study.
Research sample	Individuals reporting binge-eating behaviour and/or anorexia nervosa and comparison individuals. Recruited from multiple cohorts across the USA, Europe, and Australia, as well as additional cohorts from the Republic of Korea and Japan. Recruits are likely of various ages (not reported for all cohorts) and are predominantly female due to the higher prevalence of anorexia nervosa in women. The sample is not population representative, as it is in most cases deliberately over-recruited for eating disorders. The sample was designed to maximise available data for individuals with eating disorder phenotypes and genome-wide genotype data.
Sampling strategy	Sampling varied across cohorts, dependent on the original aim of the cohort. This analysis is secondary data analysis of pre-existing cohort data. No a priori effect size calculation was performed, as the intention of recruitment was to recruit all available individuals with eating disorder phenotypes and genome-wide genotype data. Post-recruitment effect size calculations were performed to indicate effect sizes that this study was powered to detect – these are not post hoc power calculations as they are not dependent on the observed statistics of the sample, only the sample size.
Data collection	Participants reported phenotypic data via self-report questionnaires, or phenotypes were gathered from medical records or interviews. Genotypic data was obtained by genome-wide genotyping using various microarrays.
Timing	The period of data collection varies by cohort.
Data exclusions	Data exclusions varied by cohort. In general, individuals were excluded if medical or psychiatric conditions were present that could have confounded a diagnosis of anorexia nervosa. Control individuals were generally screened for psychiatric illnesses, although this was not possible in all cohorts.
Non-participation	This was a cross-sectional study, and as such non-participation does not apply.
Randomization	Participants were not allocated into experimental groups.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks	This field has persisted incorrectly in the form – not applicable.
Novel plant genotypes	This field has persisted incorrectly in the form – not applicable.
Authentication	This field has persisted incorrectly in the form – not applicable.