

Genetic architecture of eating disorder risk and specific symptoms in the general adult population

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Abstract

Eating disorders (EDs) affect 2%–5% of the population, while subclinical symptoms are more prevalent. Previous diagnosis-based genome-wide association studies (GWASs) identified risk variants, but the genetic architecture of ED symptoms in the general population remains unclear. Using the five-item SCOFF screening tool, we conducted six GWASs in the Estonian Biobank (EstBB; N = 212,000): one for higher ED risk and one for each SCOFF item. We estimated genetic correlations with 59 external phenotypes, evaluated polygenic risk scores (PRSs) for uncontrolled eating in an independent subsample, and performed phenome-wide association studies (PheWAS) linking genetic risk to medical diagnoses. We found 14 independent genome-wide significant SNPs associated with increased ED risk and cognitive-behavioral symptoms like *loss of control* and *food dominates*, with SNP heritability ranging from 2% to 8%. Notably, variants in *FTO* and *MC4R* were linked to both *higher ED risk* and *cognitive-behavioral symptoms*, while *ROBO2* and *TMEM18* correlated with *higher ED risk* and *loss of control*, highlighting appetite regulation pathways. Cognitive-behavioral symptoms exhibited moderate-to-strong genetic correlations with anthropometric, psychiatric, lifestyle, personality, and somatic traits. PheWASs identified associations between PRSs of ED symptoms and medical conditions (28, 27, and 24 significant associations for *higher ED risk*, *loss of control*, and *food dominates*, respectively), mainly cardiometabolic. All PRSs predicted uncontrolled eating in the independent subsample. Our findings suggest genetic liability and health burden related to ED symptoms in the general population are predominantly driven by cognitive-behavioral than weight-compensatory symptoms. Symptom-based approach could complement current diagnosis-based methods and lead towards improved intervention and prevention.

Introduction

Eating disorders (EDs) are complex psychiatric conditions associated with significant somatic comorbidity, psychological distress, and elevated premature mortality^{1,2}. While clinical diagnoses such as anorexia nervosa and bulimia nervosa are scarce, disordered eating behaviors and attitudes – including restrictive eating, preoccupation with body weight and shape, and loss of control over eating are more prevalent in the general population and exist along a spectrum of severity³. Understanding the underlying mechanisms of these symptoms in the broader population is essential for improving early identification and intervention strategies to prevent deterioration and adverse health consequences.

Previous studies have consistently demonstrated that EDs are moderately to highly heritable, with estimates ranging from 20% for SNP-based to 80% for twin-based heritability while also depending on the phenotype definition and study population^{4,5}. Moreover, recent genome-wide association studies (GWAS) have begun to uncover common genetic variants associated with clinical EDs^{6–8}. However, less is known about the genetic architecture of eating disorder symptoms as they manifest in the general population – outside clinical thresholds – where they may contribute to subclinical impairment and, without timely interventions, lead to severe health consequences. So far, the ED GWASs have primarily

focused on anorexia nervosa due to its high mortality rate ^{6,8,9}. Although recently the first two genome-wide association studies of binge-eating behavior and binge-eating disorder were conducted ^{10,11}. However, researchers are increasingly shifting their focus toward a symptom-level approach to better capture the complex nature of EDs and to improve the detection of individuals at risk of developing EDs ^{12,13}. A better understanding of such pheno- and genotypic complexity of ED symptoms would benefit clinical approaches for EDs.

To facilitate population-level screening and early detection of disordered eating, brief self-report instruments such as the SCOFF (**S**ick, **C**ontrol, **O**ne stone, **F**at, **F**ood) questionnaire have been widely used ^{14,15}. SCOFF is a five-item screening tool designed to identify individuals with high risk for EDs based on the core symptoms, including self-induced vomiting, loss of control over eating, excessive concern with body weight, and food domination. While it is primarily used in clinical settings to detect individuals requiring further assessment, the SCOFF also captures meaningful variation in ED symptoms among non-clinical populations ¹⁶.

We conducted a genome-wide analysis of SCOFF-based higher ED risk and individual ED symptoms in the general population using data from the large-scale Estonian Biobank (EstBB). Our objectives were to (1) identify genetic variants associated with higher ED risk and specific symptoms; (2) quantify heritability and shared genetic architecture with other psychiatric, lifestyle, anthropometric, somatic and personality traits; (3) evaluate polygenic prediction of eating behavior in an independent subsample; and (4) map medical diagnostic profiles associated with genetic liability to ED risk and its symptoms based on 20 years of electronic health records.

Methods

Study design and sample

The Estonian Biobank (EstBB) is a population-based biobank covering approximately 20% of the adult population in Estonia (N ~ 212,000) ¹⁷. All EstBB participants with informed consent provided blood samples for genome-wide genotyping and filled out a questionnaire on demographic and lifestyle factors. The biobank is linked to national electronic health records (EHR), including the Health Insurance Fund's (HIF) database, containing information on all diagnoses and medication prescriptions covering years 2004–2025.

SCOFF questionnaire and eating disorder symptoms

A large questionnaire-based data collection “Wellbeing and mental health” (Mental Health online Survey, MHoS) was conducted in EstBB during spring 2021 to specifically assess symptoms of common psychiatric problems, risk- and protective factors and psychiatric medication use, and side effects (n = 86,244; response rate 47%) ¹⁸. ED symptoms were assessed using the modified Estonian version of the SCOFF instrument, which is a validated five-item assessment tool to identify individuals with higher risk

for EDs^{14,15}. The modification included converting units from pounds to kilograms and displaying items in a different order. The questionnaire items were presented in the following order: (1) Would you say that food dominates your life (*food dominates*); (2) Do you worry that you have lost control over how much you eat (*lost control*); (3) Have you recently lost more than 6 kg in a 3-month period (*lost > 6 kg*); (4) Do you believe yourself to be fat when others say you are too thin (*feel fat*); (5) Do you make yourself sick because you feel uncomfortably full (*make yourself sick*). A sum-score ranging from 0 to 5 was generated by scoring each of the five questions as no = 0/yes = 1, whereas a sum-score ≥ 2 indicates higher eating disorder risk (*higher ED risk*)¹⁴. Individuals with missing data (n = 2,575 (~ 3%)) or with answer 'prefer not to answer' were excluded from the analysis. From here on, we refer to three symptoms as cognitive-behavioral symptoms (*higher ED risk, lost control, and food dominates*) and three symptoms as weight-compensatory symptoms (*lost > 6 kg, feel fat, make yourself sick*).

Characteristics of SCOFF-based eating disorders risk groups

To characterize and compare the *higher ED risk* (sum-score ≥ 2) and *lower ED risk* (sum-score < 2) groups, we included variables age, sex, body mass index (BMI), smoking habits, educational attainment (EA) and International Classification of Diseases version 10 (ICD-10) diagnosis codes. BMI was calculated from self-reported weight (kg) divided by height² (kg/m²), both collected as part of the MHoS. Weight and height data in MHoS were missing for 1,871 individuals; where missing value was replaced with the last BMI measure available prior to MHoS. Education and lifestyle variables were obtained from the questionnaire. For the analysis EA was coded as 0 = no university degree; 1 = university degree. Lifetime smoking status was coded as 0 = never; 1 = ever. From ICD-10 codes, we included EDs F50 and specified subcodes: F50.0 to F50.1 (*anorexia nervosa*), F50.2 to F50.3 (*bulimia nervosa*), F50.8 to F50.9 (other/unspecified EDs). Besides, we included common comorbidities for EDs as F20 (schizophrenia), F31 (bipolar disorder), F32 and F33 (depressive episodes and recurrent depressive disorder), F90 (attention-deficit/hyperactivity disorder; ADHD), F10 (alcohol use disorders; AUDs), F40 to F42 (anxiety disorders), E66 (obesity), I20 to I25 (ischemic heart diseases), I10 (primary hypertension), E11 (type 2 diabetes; T2D). To compare *higher ED risk* with *lower ED risk* group, we applied a chi-square test for two categorical variables, ANOVA for comparisons with more than two categories, and an independent samples t-test for continuous variables with a normal distribution.

Genome-wide association analysis

All EstBB participants are genotyped using the Global Screening Arrays and imputed using an Estonian-specific reference panel¹⁹. Detailed quality control (QC) steps of genetic data are in Supplementary Info. All GWASs included approximately 8.5 million SNPs after applying the standard QC filters (INFO 0.8, MAF > 0.01). We conducted six GWASs: one for the *higher ED risk*, followed by a GWAS for each symptom separately. We ran GWASs using REGENIE software v4.0²⁰, adjusting for age at questionnaire completion, sex, and 10 genetic principal components (PCs) to account for population structure. We did not adjust the GWASs for BMI to prevent spurious associations and overadjustment, as BMI could be a collider between SNPs and ED risk²¹.

To assess BMI-related genetic effects, we ran sensitivity GWASs in two groups: 1) underweight/normal ($\text{BMI} \leq 24.99 \text{ kg/m}^2$), 2) overweight/obese ($\geq 25.0 \text{ kg/m}^2$). To examine sex differences, we performed sex-specific GWASs.

SNP-based heritability and genetic correlations

We used Linkage Disequilibrium Score Regression (LDSC) software version 1.0.1 to estimate SNP-heritability (h^2_{snp}) of the *higher ED risk* and each ED symptom separately. First, we estimated pairwise genetic correlations (r_g) between *higher ED risk* and individual symptoms, applying Bonferroni correction across all pairwise comparisons ($0.05/15 = 3.33 \times 10^{-3}$). Second, we examined cross-trait pairwise r_g with 59 anthropometric, psychiatric, lifestyle, socioeconomic, personality, and somatic traits^{22,23}, applying Bonferroni correction ($0.05/59 = 8.47 \times 10^{-4}$). For cross-trait genetic correlations, we used publicly available GWAS summary statistics. LD score analyses employed the HapMap3 reference panel and European LD scores (excluding the HLA region) from 1000 Genomes Phase 3.

Functional annotation and gene mapping

We used FUMA GWAS platform v1.7.0 (<http://fuma.ctglab.nl/>) to annotate and map GWAS results to genes²⁴. We defined genome-wide significant SNPs ($p < 5 \times 10^{-8}$) independent at $r^2 < 0.6$ as independent significant SNPs (IndSigSNPs), with lead SNPs selected at $r^2 < 0.1$. We used the European 1000 Genomes Phase 3 reference panel (excluding the MHC region). We merged IndSigSNPs within 250 kb into one genomic locus. SNPs in LD with IndSigSNPs ($r^2 \geq 0.6$, ≤ 10 kilobase window, minor allele frequency $\geq 1\%$) were considered candidate SNPs. We queried the FUMA GWAS Catalog (version 2022-11-29) to identify top three reported associations and used Open Targets Genetics (<https://genetics.opentargets.org/>) to prioritize genes via variant-to-gene model²⁵ and locus-to-gene models²⁶. Gene functions were further supported using Mouse Genome Informatics²⁷.

Out of sample prediction of uncontrolled eating

Polygenic risk scores

We calculated polygenic risk scores (PRSs) based on six main GWASs summary statistics: 1) higher ED risk = PRS_{HigherEDrisk}; 2) make yourself sick = PRS_{MakeSick}; 3) lost control = PRS_{ControlLoss}; 4) lost > 6 kg = PRS_{WtLoss6kg}; 5) feel fat = PRS_{FeelFat}; 6) food dominates = PRS_{FoodDominates}. For PRS analyses, we used PRS-CS-auto, a Bayesian regression framework to infer the posterior effect sizes of SNPs from six GWAS summary statistics and an external linkage disequilibrium reference panel²⁸. SNPs with $\text{MAF} < 0.01$ and $\text{INFO} < 0.8$ were excluded, leaving ~ 8 million SNPs for each PRS. Allele scoring was performed with PLINK 2.0²⁹. PRSs were standardized within the whole EstBB before analysis with a mean of zero and each unit representing one standard deviation.

Polygenic risk scores associations

We tested PRS_{HigherEDrisk} and PRSs for each ED symptom in an independent EstBB subsample (n = 11,218). This subsample consisted of participants from a personality survey (n = 78,102), who had responded to the item '*when starting to eat, I have difficulties to stop*' (uncontrolled eating)³⁰, excluding MHoS participants and their relatives ($\pi\text{-hat} \geq 0.25$). We applied ordinal logistic regression with uncontrolled eating (six-point Likert scale: completely, rather, quite incorrect; quite, rather, completely correct) as an outcome and standardized PRS, age, sex and 10 first PCs as predictors.

Phenome-wide association studies

To examine medical conditions associated with genetic liability for six ED symptoms, we conducted a phenome-wide association study (PheWAS) linking each standardized PRS to ICD-10 diagnoses recorded in EHR over 20 years (2004–2023)³¹. The final PheWAS sample excluded MHoS participants and their relatives ($\pi\text{-hat} \geq 0.25$). For each PRS, we applied 1278 logistic regressions with individual ICD-10 codes as outcomes and the standardized PRS as the predictor, adjusting for year of birth, sex and the first 10 PCs. We excluded the ICD-10 codes with < 50 cases to protect participants' anonymity and avoid spurious findings. To adjust for the large number of tests, we applied Bonferroni correction to reduce the risk of false positive results ($p = 0.05/1278 = 3.91 \times 10^{-5}$). ICD-10 codes were obtained via linking EstBB to the Estonian HIF and other national health registries.

Results

Overview of the eating disorder risk sample

Our study comprises six GWASs, but here we focus on the primary *higher ED risk* GWAS sample (n = 78,697) EstBB participants with pheno- and genotypic data (Fig. 1). Predominantly, there were significant differences in the characteristics of *higher* and *lower ED risk* groups (Table 1). The higher risk group was, on average, younger (45.1 vs 48.6, SD = 14.5 for both), included more females (79.0% vs 67.5%), many more obese individuals (35.8% vs 15.7%), slightly more smokers (25.3% vs 22.1%) and fewer university graduates (53.7% vs 57.3%). Psychiatric diagnoses were mainly significantly more prevalent in the higher risk group. The largest difference occurred for *bulimia nervosa* (ICD-10 codes: F50.2 + F50.3), where the difference between risk groups was more than 11-fold (1.1% vs 0.1%), followed by 7-fold difference in other and unspecified ED group (0.7% vs 0.1%) and by more than 5.75-fold difference in any ED diagnosis (F50*) (2.3% vs 0.4%). Similarly, the between-group differences for somatic diagnoses were the largest for obesity (E66), which was 2.8 times more prevalent among higher risk compared to lower risk group. For the rest of the psychiatric comorbidities such as depression, ADHD, alcohol related and anxiety disorders, reaction to severe stress, and for somatic comorbidities as primary hypertension and T2D, group differences persisted, with the higher risk group showing 0.5 to 2.0 times greater prevalence. Except for bipolar disease and schizophrenia, where the risk was comparable in both risk groups and for ischemic heart diseases (ICD-10 codes: I20 to I25), the risk was lower for the higher risk group.

Table 1
Descriptives for eating disorders risk GWAS sample (n = 79,545).

Total	Lower ED risk	Higher ED risk	p-value
	58,499 (74.3%)	20,198 (25.7%)	
Mean age ± SD	48.6 ± 14.5	45.1 ± 14.5	$< 2.2 \times 10^{-16}$
Sex, n (female %)	39,467 (67.5%)	15,964 (79.0%)	$< 2.2 \times 10^{-16}$
BMI cat., n (%)			
underweight	1,071 (1.8%)	174 (0.9%)	$< 2.2 \times 10^{-16}$
normal	28,679 (49.0%)	6,248 (30.9%)	
overweight	19,558 (33.5%)	6,544 (32.4%)	
obese	9,191 (15.7%)	7,232 (35.8%)	
Ever smoking, n (%)			
yes	12,919 (22.0%)	5,107 (25.3%)	$< 2.2 \times 10^{-16}$
no	45,187 (77.3%)	14,957 (74.0%)	
missing	393 (0.7%)	134 (0.7%)	
Education			
no university degree	24,716 (42.3%)	9,245 (45.8%)	$< 2.2 \times 10^{-16}$
university degree	33,524 (57.3%)	10,839 (53.7%)	
missing	259 (0.4%)	114 (0.5%)	
Any eating disorders	235 (0.4%)	456 (2.3%)	$< 2.2 \times 10^{-16}$
anorexia nervosa	80 (0.1%)	105 (0.5%)	$< 6.7 \times 10^{-16}$
bulimia nervosa	53 (0.1%)	232 (1.1%)	$< 2.2 \times 10^{-16}$
other ED or subtype unspecified	80 (0.1%)	136 (0.7%)	$< 2.2 \times 10^{-16}$
Schizophrenia	117 (0.2%)	43 (0.2%)	0.795
Bipolar disorder	80 (0.1%)	40 (0.2%)	0.069
Depression	7,113 (12.1%)	3,367 (16.7%)	$< 2.2 \times 10^{-16}$
ADHD	141 (0.2%)	79 (0.4%)	< 0.001

Total	Lower ED risk	Higher ED risk	p-value
	58,499 (74.3%)	20,198 (25.7%)	
Alcohol use disorders	1,189 (2.0%)	473 (2.3%)	< 0.01
Anxiety	10,374 (17.7%)	4646 (23.0%)	< 2.2×10^{-16}
Obesity	2,046 (3.5%)	1,971 (9.8%)	< 2.2×10^{-16}
Ischemic heart diseases	5,828 (10.0%)	1,740 (8.6%)	< 2.3×10^{-08}
Primary hypertension	14,963 (25.6%)	5,676 (28.1%)	< 2.2×10^{-12}
Type 2 diabetes	2,357 (4.0%)	1,136 (5.6%)	< 2.2×10^{-16}

Genome-wide association studies and annotation of identified signals

We performed six GWASs: one for *higher ED risk* and one for each ED symptom (Fig. 2). We identified 14 independent genome-wide significant SNPs across three GWASs - *higher ED risk*, *lost control* and *food dominates*, with ten lead SNP all in intronic regions. FUMA mapping prioritized most genes for *lost control* (8 genes), followed by *higher ED risk* (4 genes), and *food dominates* (2 genes).

Lead SNPs from these three GWASs mapped to *FTO* and *MC4R*, genes linked to weight-related traits. Prioritized genes included *ROBO2* for *higher ED risk* and *lost control*, and five genes as *GPR61*, *GSTM1*, *TMEM18*, *NRN1*, *FAIM2* for *lost control*. According to FUMA GWAS catalogue (version 2022-11-29) these SNPs are mainly associated with increased BMI, T2D or adiposity (Supplementary Table S2). However, our query in the Mouse Genome Informatics database confirmed that disruptions in several of these prioritized genes were related to distorted eating patterns, like *GPR61* and *TMEM18*-knockout mice have demonstrated increased food intake, while *GPR61* disruption was also linked to polyphagia. The *ROBO2* gene has mouse evidence of abnormal sensory capabilities. *GSTM1*, *NRN1* and *FAIM2* were linked to glucose levels, body size and kidney abnormalities, respectively. We did not detect GWAS significant signals for the remaining three symptoms (e.g. *lost > 6kg*, *feel fat* and *make yourself sick*).

Sex-stratified GWAS and genetic correlation analysis

We conducted sex-stratified GWASs (Supplementary Figs. 2–3, Tables 3–6) and estimated genetic correlations (Supplementary Table 4), which ranged from 0.92 to 1.07, indicating largely shared genetics. Results resembled main analyses, with significant loci identified on the same chromosomes for *higher ED risk*, *lost control*, and *food dominates* in both sexes (Supplementary Tables 5–6). Male-specific deviations included an additional locus on chromosome 13 (*BIVM*, *ERCC5*) for *lost control* and a hit on chromosome 6 (*KIFC1*), likely near the HLA region. In females, *lost control* showed a significant signal on chromosome 6 prioritizing *ADGBR3*.

BMI-stratified GWAS and genetic correlation analysis

To avoid collider bias with BMI, GWASs were not adjusted for BMI but conducted separately in two BMI groups: underweight/normal (< 25 kg/m²) and overweight/obese (≥ 25 kg/m²) (Supplementary Figures S4–S5, Supplementary Table 7). Genetic correlations between groups were high ($r_g=0.85–1.07$) (Supplementary Table 8). However, significant associations appeared only in the overweight/obese group with signals on chromosome 16 (*FTO* gene) for *higher ED risk*, *lost control*, and *food dominates* (Supplementary Table 9).

SNP-based heritability and genetic correlations between ED symptoms

We estimated the SNP-based heritability (h^2_{SNP}) for *higher ED risk* and five SCOFF items using LDSC software. The observed scale h^2_{SNP} ranged from 2% to 8%, highest for *higher ED risk* and *lost control* (both $h^2_{SNP}=8\%$), followed by *food dominates* (7%), *make yourself sick* (5%), *feel fat* (3%), and lowest for *lost > 6 kg* (2%) (Fig. 3, Supplementary Table 10). We estimated genetic correlations (r_g) among ED symptoms, revealing substantial shared genetic influences, with most remaining significant after multiple correction. A near-perfect r_g between *higher ED risk* and *lost control* ($r_g=1.00$, 95% CIs: 0.97 – 1.04), and strong correlations between *higher ED risk* and *food dominates* ($r_g=0.89$, 95% CIs: 0.83 – 0.96), as well as *lost control* and *food dominates* ($r_g=0.89$, 95% CIs: 0.78 – 0.95) (Fig. 3, Supplementary Table 11). Also, phenotypically *higher ED risk* was mainly driven by positive answers to *lost control* and *food dominates* (Supplementary Table 12). Most other correlations were moderate-to-strong (0.47–0.76), while some pairs (e.g., *make yourself sick* with two others) showed weak, non-significant correlations.

Genetic correlations with other traits

We aimed to examine shared genetic links between *higher ED risk*, five ED symptoms, and various anthropometric, psychiatric, lifestyle, socioeconomic, personality, and somatic traits. Significant genetic overlap was found between *higher ED risk* and 28 traits, with similar patterns for key symptoms *lost control* (27 traits) and *food dominates* (24 traits) out of 59 tested (Fig. 4, Supplementary Tables 13 – 18). Cognitive-behavioral symptoms showed strong positive correlations with anthropometric traits—especially waist circumference, BMI, and waist-hip ratio—with the highest correlation ($r_g = 0.73$, 95% CIs: 0.62 – 0.84) between *higher ED risk* and waist circumference. Psychiatric traits like ADHD, alcohol use disorder, insomnia, MDD, and PTSD had moderate positive correlations ($r_g=0.21 – 0.56$) across all three symptoms, while *food dominates* uniquely correlated with alcohol dependence. Subjective well-being correlated negatively with *higher ED risk* and *lost control*. Lifestyle and socioeconomic factors such as smoking and screen time were positively linked, whereas sleepiness and education showed negative associations. Personality traits including neuroticism and irritability also correlated positively. Somatic traits revealed positive links with cardiometabolic conditions and asthma. Weight-compensatory symptoms had fewer and less consistent associations compared to cognitive-behavioral symptoms. Numerous significant moderate-to-strong correlations underlined wide shared genetics of ED symptoms and other traits.

SCOFF-based polygenic score performance in an independent EstBB subsample

We tested six SCOFF-based polygenic risk scores (PRSs) for association with uncontrolled eating in an independent EstBB sample (Figure 5). The strongest effect was observed for the PRS_{ControlLoss}, where one standard deviation increase raised the odds of moving up one Likert category for uncontrolled eating by nearly 20% (OR=1.18; 95%CI: 1.13–1.23), followed by PRS_{HigherEDrisk} (OR = 1.15) and PRS_{FoodDom} (OR = 1.10). Other PRSs showed weaker yet significant associations. These findings confirm that ED-related PRSs are linked to uncontrolled eating, supporting our GWAS findings.

Medical profiles of SCOFF-based polygenic risk scores

We conducted six PheWASs in an independent EstBB subsample (n=71,594) to test associations between standardized SCOFF-based PRSs and 1,278 ICD-10 diagnoses derived from EHRs in EstBB (Figure 6, Supplementary Tables 19–24). After multiple-testing correction, PRS_{HigherEDrisk} showed the broadest range of significant associations (28 diagnoses), followed by PRS_{ControlLoss} (27), and PRS_{FoodDom} (24), whereas PRS_{WtLoss6kg}, PRS_{FeelFat} and PRS_{MakeSick} were associated with fewer outcomes (5–10 diagnoses).

Across all PRSs, the strongest association was observed with obesity (ICD-10: E66). One standard deviation increase in PRS_{HigherEDrisk} and PRS_{ControlLoss} was associated with 1.29-fold higher risk of obesity (95% CIs: 1.27–1.31), and with 1.23-fold higher risk for PRS_{FoodDom} (95% CIs: 1.21–1.25). Notably, even PRSs of weight-compensatory symptoms showed their strongest association with obesity. PRS_{HigherEDrisk} was additionally associated with several cardiometabolic conditions, including T2D (OR = 1.19, 95% CI: 1.16–1.22), hypertensive heart disease (OR = 1.12, 95% CI: 1.10–1.14), gout (OR = 1.17, 95% CI: 1.14–1.20), and knee osteoarthritis (OR = 1.11, 95% CI: 1.09–1.13). The top four strongest association patterns for PRS_{ControlLoss} and PRS_{FoodDom} were the same as for PRS_{HigherEDrisk}, while for PRS_{ControlLoss} primary hypertension (OR = 1.09) and for PRS_{FoodDom} (OR = 1.10) cholelithiasis showed the fifth strongest association instead.

Discussion

We present the first genome-wide association studies of self-reported eating disorder (ED) risk and five ED symptoms in a population-based sample of adults, measured by the validated SCOFF screening questionnaire for EDs^{14,15}. We identified 14 genome-wide significant SNPs across 11 loci in three main GWASs of *higher ED risk* and symptoms *lost control* and *food dominates*. The item-level analysis revealed that the genetic signals were mainly driven by cognitive-behavioral symptoms and not by the weight-compensatory symptoms of EDs. Similarly, out-of-sample SCOFF-based PRS analysis showed an

association with uncontrolled eating in an independent sample. Additionally, genetic correlation analysis suggested that the *higher ED risk* and items *lost control*, and *food dominates* have moderate-to-strong genetic overlap with several anthropometric, psychiatric, lifestyle and socioeconomic, personality, and somatic traits. In parallel, PheWAS analyses revealed significant associations between ED symptoms on health in the general population, particularly on cardiometabolic and endocrine conditions in *higher ED risk*, *lost control* and *food dominates* groups.

Overall, out of the six ED phenotypes investigated, *higher ED risk* and the symptoms *lost control* and *food dominates* showed the strongest genetic and phenotypic links. Although the *higher ED risk* was largely driven by positive answers to these two items, the very strong pairwise genetic correlation between *food dominates* and *lost control* themselves, indicates that the *higher ED risk* and these two items' high correlations could still be explained by naturally largely shared genetic components. These three symptoms appear to represent rather key features of bulimia nervosa and binge eating³². We did not detect any significant genetic signal for the remaining three ED symptoms: *make yourself sick*, *lost > 6 kg in three months* and *feel fat*, which mainly capture the weight-compensatory symptoms. The h^2_{SNP} estimates were lower for these symptoms, potentially indicating lower contribution of common genetic variants for these symptoms. Identifying genetic variants for weight-compensatory symptoms may need larger sample sizes, achievable through large-scale collaborative efforts with genomic and symptom-level data. Therefore, we will mainly focus on discussing cognitive-behavioral symptoms.

GWAS findings and gene prioritization

In our main six genome-wide association studies, the number of detected significant genetic risk loci ranged from two to seven. The highest number of loci was found for *lost control* – 8 loci. This is comparable to the first meta-GWAS of binge-eating behavior, where 6 loci were found¹¹. For three cognitive-behavioral symptoms, common prioritized genes were *FTO* and *MC4R* genes, whereas for *higher ED risk* and *lost control* also the *ROBO2* gene. The first two genes are well-known for obesity-related and/or metabolic traits, such as BMI^{33,34} but have been reported to directly track binge eating too^{10,35}.

Beyond shared genes in the three GWAS studies, several genes like *GSTM1*, *GPR61*, *TMEM18*, *ROBO2*, *NRN1*, and *FAIM2* were specifically linked to the *lost control*. Interpreting these findings within the current post-GWAS landscape of EDs is challenging, as large-scale GWASs have predominantly focused on anorexia nervosa^{6,8}. To date, only two well-powered binge-eating GWASs exist, each using different phenotype definitions. Termorshuizen et al. found genome-wide associations for binge-eating on chromosomes 1, 3, 12, 16, and 18, aligning with our *lost control* chromosomes. Despite using a machine-learning-derived binge-eating phenotype within the Million Veteran Program, Burstein et al. also identified genome-wide significant associations on chromosome 6, like in our *lost control* finding.

One of the most interesting common findings for the *higher ED risk* and *lost control* was *ROBO2* gene on chromosome 3. Notably, *ROBO2* mutations in mouse models have been associated with abnormal

sensory processing²⁷. This aligns with evidence that individuals with EDs often show impaired interoceptive awareness (e.g., hunger, fullness) and heightened exteroceptive sensitivity to food-related cues such as taste, smell, or texture^{36–38}.

The role of BMI in eating disorders

There is no clear consensus on BMI's role in GWAS studies of EDs. While low BMI defines anorexia nervosa, its role in bulimia and binge-eating is complex due to genetic overlap and complex causal links. Some studies, like Burstein et al., adjust for BMI to remove its effect, while others, including ours and Termorshuizen et al. main GWAS, did not. We considered BMI as a potential collider rather than a confounder. However, in addition to the main GWAS without BMI adjustment, Termorshuizen et al. conducted also BMI-subtracted GWAS, which showed that most ED genetic signals are independent of BMI, with only 12% of binge-eating's genetic variance linked to BMI, while the remaining 88% attributable to the non-BMI factor¹⁰. Furthermore, Micali and colleagues showed that the association between *FTO* and binge-eating was independent of BMI among adolescents³⁵. Yet, another study suggested a causal bidirectional relationship between ED symptoms and BMI³⁹. Our BMI-stratified analysis found stronger genetic associations in the overweight/obese group, with no significant hits in the underweight/normal group. This may reflect modifying effect of lifestyle factors such as physical activity or stress and emotions⁴⁰ or that those with higher BMI already struggle with their weight and they are more prone to report ED symptoms.

Despite this, genetic correlations between BMI groups were high, indicating most genetic influences on ED symptoms are shared across BMI levels.

Genetic overlap with psychiatric, somatic and sociodemographic factors

Our genetic correlation analysis of *higher ED risk* and symptoms *lost control* and *food dominates* match known ED comorbidities. We found shared genetic links with body traits like waist circumference and BMI, psychiatric traits including depression, loneliness, ADHD, PTSD, and substance use disorders, lifestyle factors such as smoking, leisure screen time and sedentary behavior, and somatic diseases as T2D, metabolic syndrome, hypertension and asthma and personality traits such as neuroticism and irritability. Negative correlations appeared with sleepiness, education, sedentary work, and age at menarche. Similarly, Termorshuizen et al. reported negative correlation with age at menarche and a non-significant positive link with education for binge-eating¹⁰

Our PheWAS results confirm that higher genetic risk for ED and its specific symptoms, represented by PRSs, are linked to extensive comorbidities both phenotypically and genetically, suggesting pleiotropic genetic effects. We found the strongest associations between polygenic scores for cognitive-behavioural symptoms (PRS_{HigherEDrisk}, PRS_{ControlLoss} and PRS_{FoodDom}) and obesity diagnosis based on ICD-10 code. Surprisingly, similarly strongest and positive association with obesity appeared for the remaining three symptoms PRSs (PRS_{WtLoss6kg}, PRS_{FeelFat} and PRS_{MakeSick}). For cognitive-behavioral

symptoms, the top five strongest associations were shown with diseases belonging to four disease groups (e.g. endocrine, nutritional and metabolic, hypertensive, arthropathies, and cholelithiasis), which are also well-known comorbidities of obesity⁴¹. In line with comorbidities detected on a phenotypic level for EDs, we confirmed the shared genetics for *higher ED risk* and somatic conditions such as cardiovascular disease, T2D and hypertension^{4,42}. Also, strong association between PRSs for cognitive-behavioral symptoms and arthropathies could possibly be explained by already significantly higher BMI and 2.8-fold higher prevalence of obesity in higher ED risk group, which already on their own are associated with higher levels of inflammation leading to increased burden to joints⁴¹. One possible explanation for strong association with cholelithiasis might be that disordered eating habits in individuals with higher ED risk lead to changes in gastrointestinal physiology resulting in higher chances of gallstone formation^{42,43}, although such associations would require further investigation. According to previous research on phenotypic level, psychiatric comorbidities as depression, anxiety disorders, and substance use disorders are also common among individuals with eating disorders². We could not detect such an association on a PheWAS level, which may indicate that the mental outcomes of individuals with *high ED risk* might remain undetected by the medical system. Psychiatric disorders are characterized by a very broad range and severity of symptoms, therefore it might often be more challenging to reach a diagnosis compared to physical health problems. Similarly to our PheWAS analysis, testing six SCOFF-based PRSs in an independent sample in association with uncontrolled eating behavior, showed promising results with the strongest association between PRS_{-HigherEDrisk} and uncontrolled eating. Such ED symptom-based PRSs are the first ones in the ED field and are an important foundation to initiate a symptom-based approach.

Strengths and limitations

Most ED genetic studies focus on diagnosed ED without the possibility to investigate the genetics of specific ED symptoms. Our item-level approach allows us to take a more granular approach to disentangle the genetic signals underlying the general ED risk and each specific symptom. In addition, because EDs, especially related to cognitive-behavioral symptoms, often remain undiagnosed, the self-reported screening instrument approach taken in our study provides the opportunity to investigate the underlying genetics of disordered eating behavior among individuals in the general population, where ED diagnosis is scarce. Majority of individuals have not been diagnosed with an ED, nevertheless their health and wellbeing are severely impacted by their ED symptoms. Our data demonstrates a large gap between individuals with higher ED risk (25.7%) and those with ED diagnosis (approximately 1% in the whole sample and 2.3% among *higher ED risk* group), indicating that by only focusing on diagnosed cases, we are potentially missing a considerable proportion of individuals with disordered eating behavior. Besides, conducting only studies based on criteria of having diagnosis would restrict us to the most severe cases and would leave out individuals at risk, where the implementation of prevention strategies could be beneficial.

Since the SCOFF questionnaire was originally developed as a brief screening instrument for primary care settings¹⁴, it lacks phenotyping depth to reliably differentiate between the risks of distinct EDs. While our results generally provide validation for the SCOFF instrument in capturing individuals with higher ED risk in a population-based sample, more thorough phenotyping would allow us to explore the causes and consequences of various ED-related phenotypes. The SCOFF instrument contains only five items and does not capture some ED domains, such as the avoidant restrictive food intake disorder.

In addition, we have initiated a symptom-based approach framework based on a European biobank, however including a more diverse set of ancestries in future studies would allow us to generalize our findings to reduce existing health disparities.

In conclusion, using a brief screening instrument in the Estonian Biobank, we detected genetic effects on ED itself and specific ED symptoms in the general population, particularly cognitive-behavioral symptoms. The identified genetic signal was associated with significant health issues in an independent sample, highlighting substantial pleiotropy and warranting more clinical attention to ED symptoms in the general population. A symptom-informed genetic framework for ED risk complements diagnosis-based approaches and motivates a move toward dimensional phenotyping that can better map phenotypic heterogeneity. This work enhances our understanding of the biological basis and health impact of a diverse set of disordered eating behaviors in the general population and paves the way for early intervention efforts to prevent impairing health consequences.

Declarations

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Conflicts of interest

No competing interests to declare.

Author contributions

K.P., T.S., K.L. designed the study; K.P. performed data analyses; K.K. performed one set of sub-analyses, K. P. and K. L. drafted the manuscript; K.P. and K.L. T. L. and R. M. advised on the sub-analyses. K. P. and K. L. interpreted the results and revised the manuscript; all authors read and approved the submitted paper.

Data Availability

The genotypic and phenotypic data from EstBB are available under restricted access (application process described at <https://genomics.ut.ee/en/content/estonian-biobank#dataaccess>) and can be obtained with the permission of the Estonian Committee on Bioethics and Human Research.

Ethics statement

The activities of the EstBB are regulated by the Human Genes Research Act, which was adopted in 2000 specifically for the operations of the EstBB. Individual level data analysis in the EstBB was carried out under ethical approval [21.03.2026 1.1–12/770] from the Estonian Committee on Bioethics and Human Research (Estonian Ministry of Social Affairs), using data according to release application ["6–7/GI/12089"] from the Estonian Biobank.

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Figures

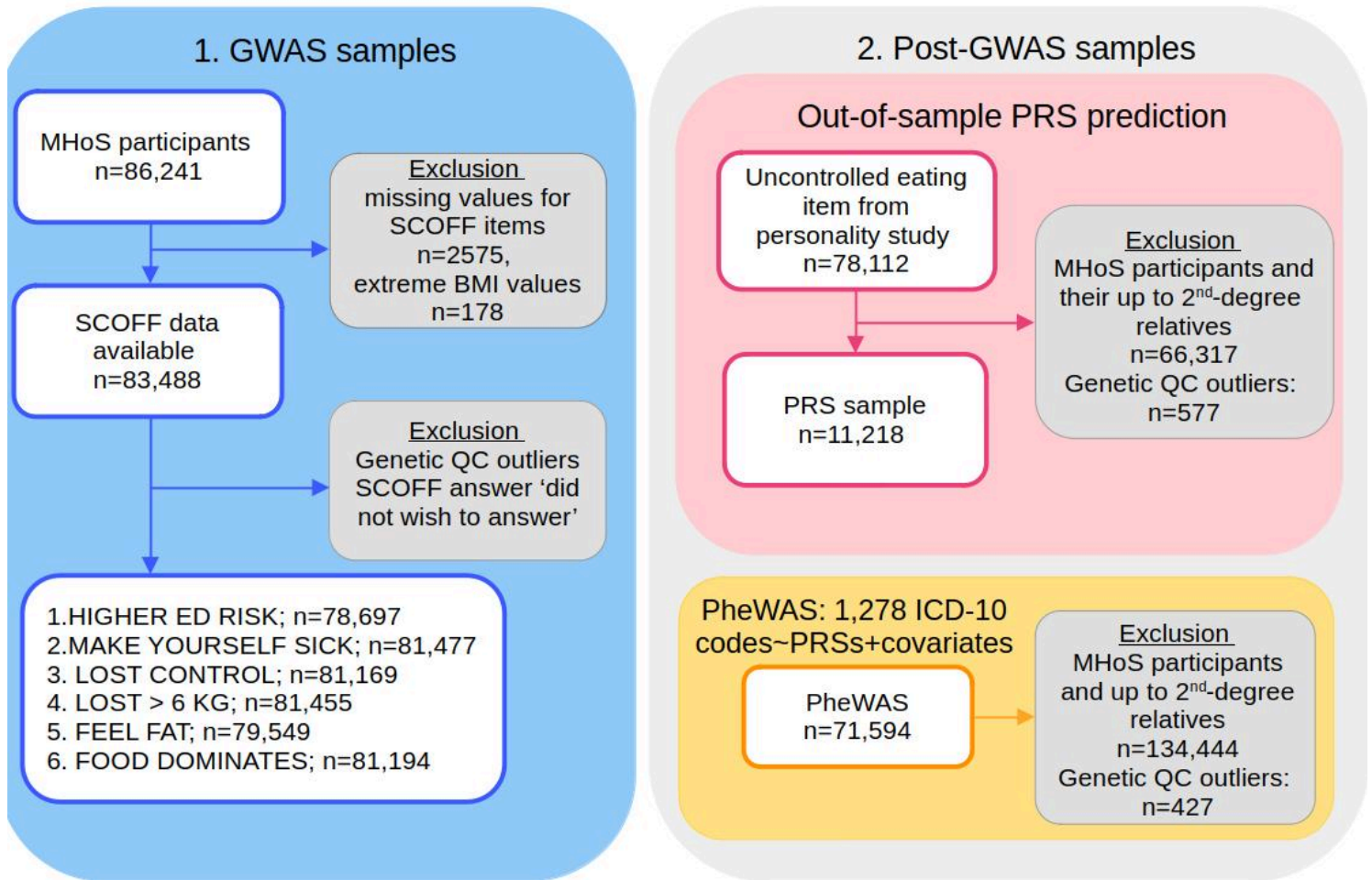


Figure 1

Study flowchart: sample selection and conducted analyses.

Abbreviations used: GWAS –genome-wide association study, MHoS – Mental Health Online Survey, SCOFF –screening tool for eating disorders, BMI – body mass index, QC –quality control, PheWAS – phenome-wide association study, PRS –polygenic risk score. Note: n=86,241 (3 individuals less than in the original study due to participants drop-out).

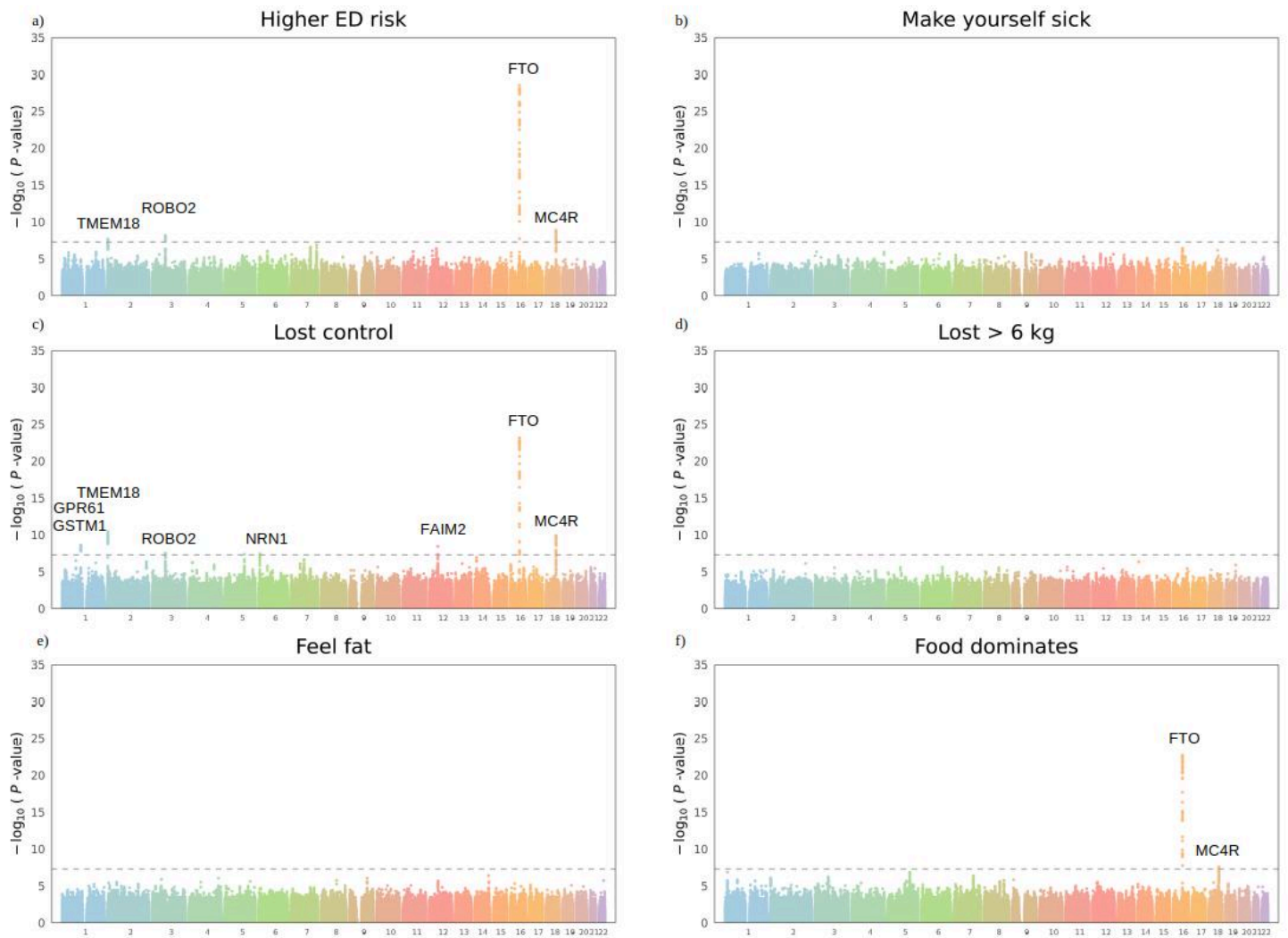


Figure 2

Manhattan plots for higher ED risk and for each ED symptom based on the SCOFF questionnaire. On x-axis there are chromosomes 1 to 22, y-axis shows $-\log_{10}(\text{p-value})$ for the association of genetic variants detected in GWAS. The grey dashed line is a genome-wide significance threshold of $p < 5 \times 10^{-8}$. For each lead SNP in genetic risk loci, the prioritized genes are marked. GWAS sample sizes are marked in Supplementary Table 1 and QQ-plots in Supplementary Figure 1.

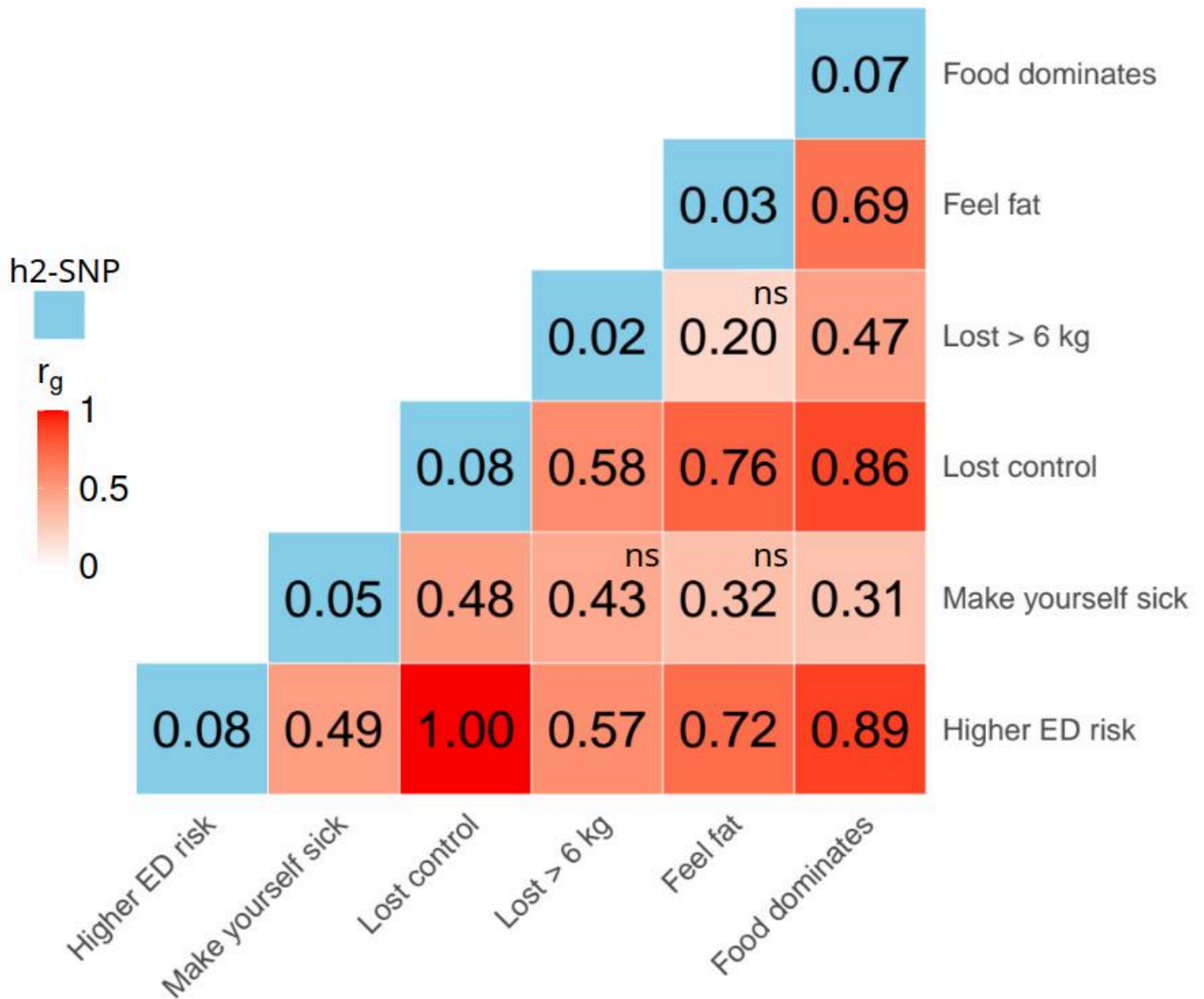


Figure 3

Observed-scale SNP-based heritabilities and genetic correlations between higher ED risk and ED symptoms based on SCOFF questionnaire. Light blue color marks SNP-based heritability (h^2_{SNP}) and red color marks genetic correlation (r_g). On x- (left to right) and y-axis (bottom to top) are marked higher ED risk and five ED symptoms. Ns marks non-significant genetic correlation after multiple correction (0.05/15).

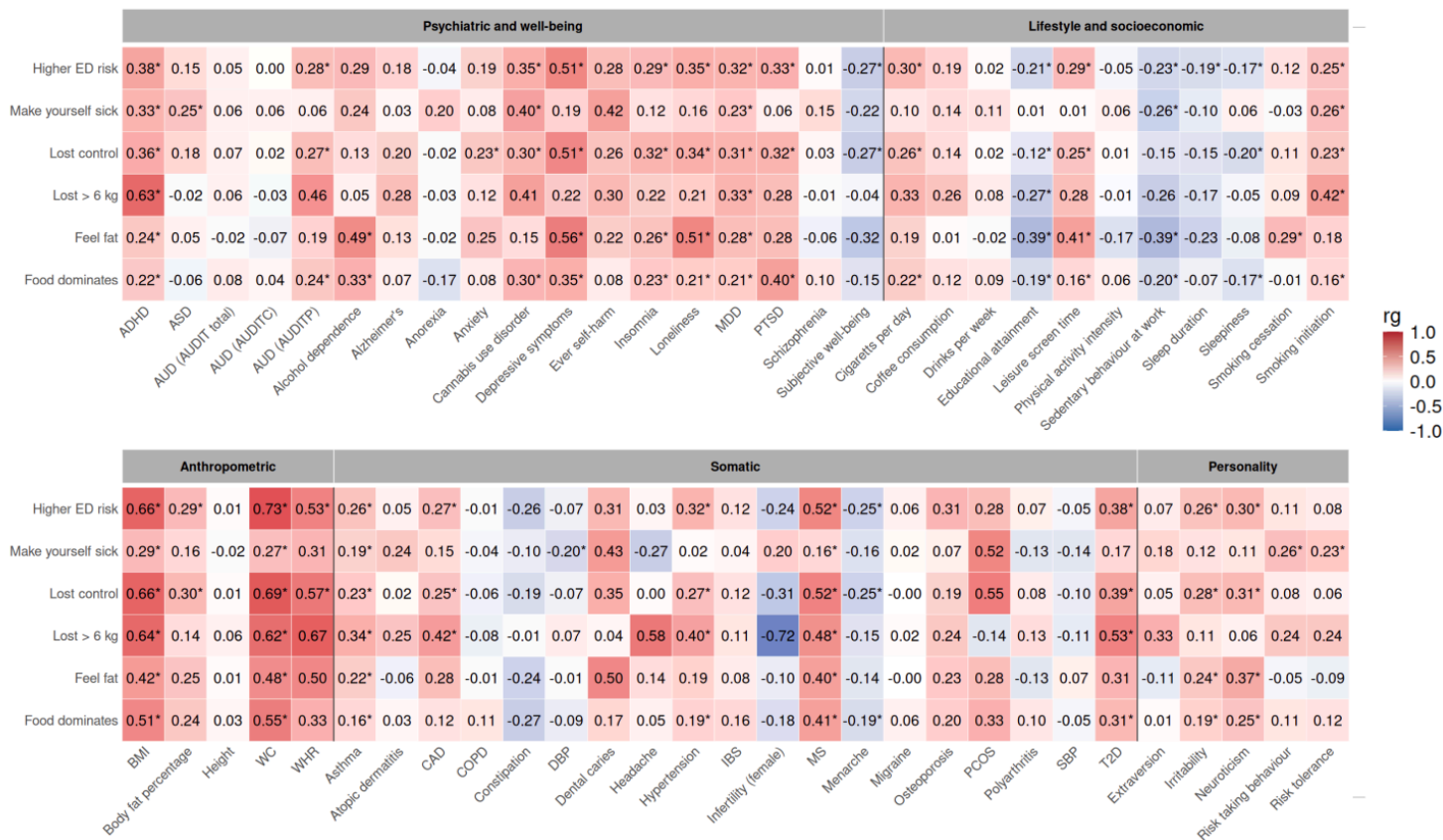


Figure 4

Genetic correlations of higher ED risk and five ED symptoms with other traits and diseases. X-axis shows other traits; y-axis shows higher ED risk and five ED symptoms based on SCOFF questionnaire. The heatmap colors represent genetic correlation strength (blue for negative and red for positive correlation) and numerically are marked genetic correlation estimates (r_g). R_g estimates reaching above multiple testing correction threshold (0.05/59) are marked with asterisk (*).

Abbreviations: AUD – alcohol use disorder, ADHD – attention-deficit hyperactivity disorder, ASD – autism spectrum disorder, MDD – major depressive disorder, PTSD – post-traumatic stress disorder, BMI – body mass index, WC – waist circumference, WHR – waist-hip ratio, COPD – chronic obstructive pulmonary disease, CAD – coronary artery disease, DBP – diastolic blood pressure, IBS – irritable bowel syndrome, PCOS – polycystic ovary syndrome, SBP – systolic blood pressure, T2D – type 2 diabetes.

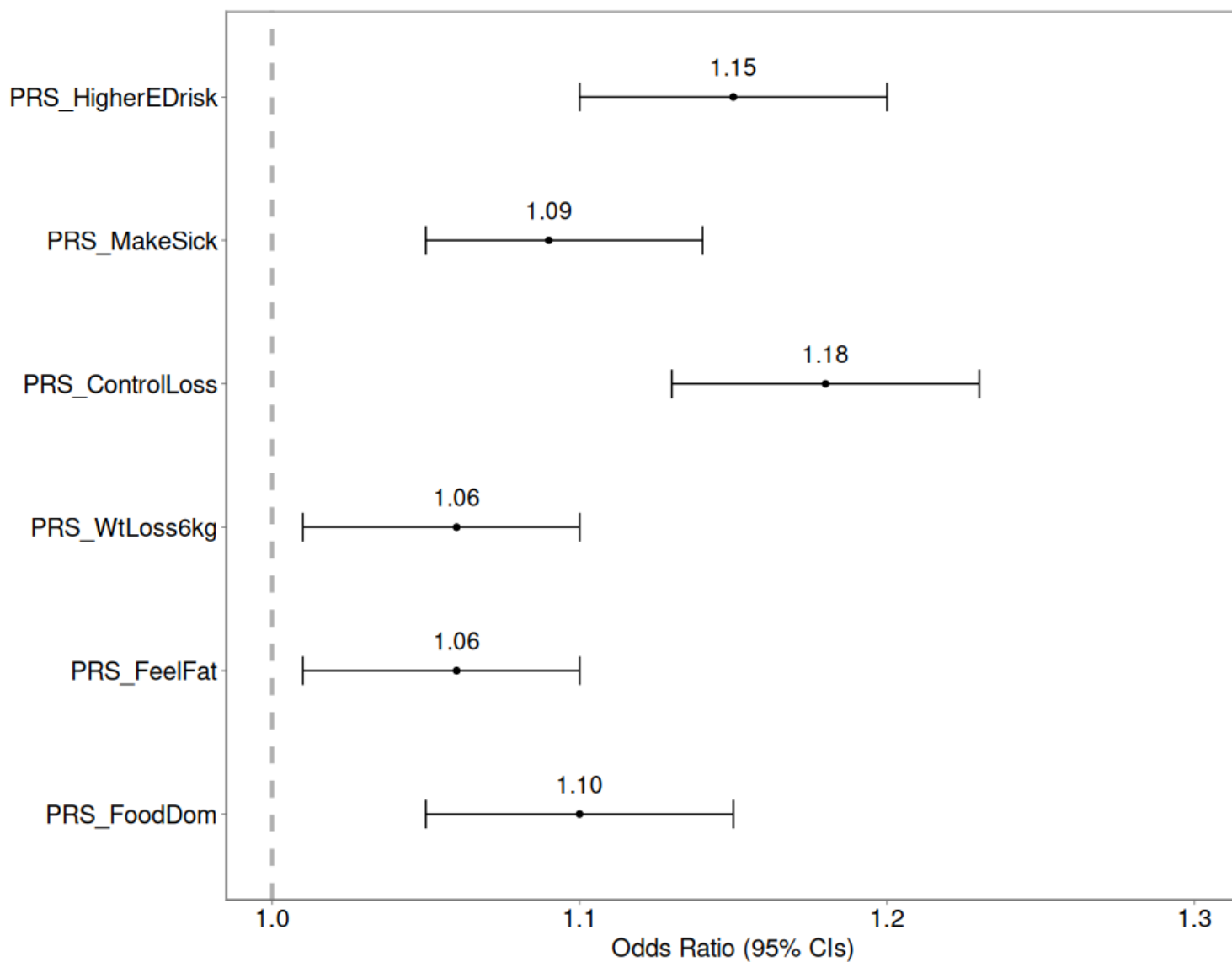


Figure 5

Polygenic risk scores prediction of item responses to “when starting to eat, I have difficulties to stop” in an independent EstBB sub-sample (n=11,218). The response options were on a 6-point Likert scale with categories ranging from completely incorrect to completely correct. The x-axis marks the odds ratios (marked with dot) with horizontal whiskers corresponding to 95% confidence intervals (95% CIs) and the y-axis standardized PRSs calculated based on corresponding GWAS summary statistics.

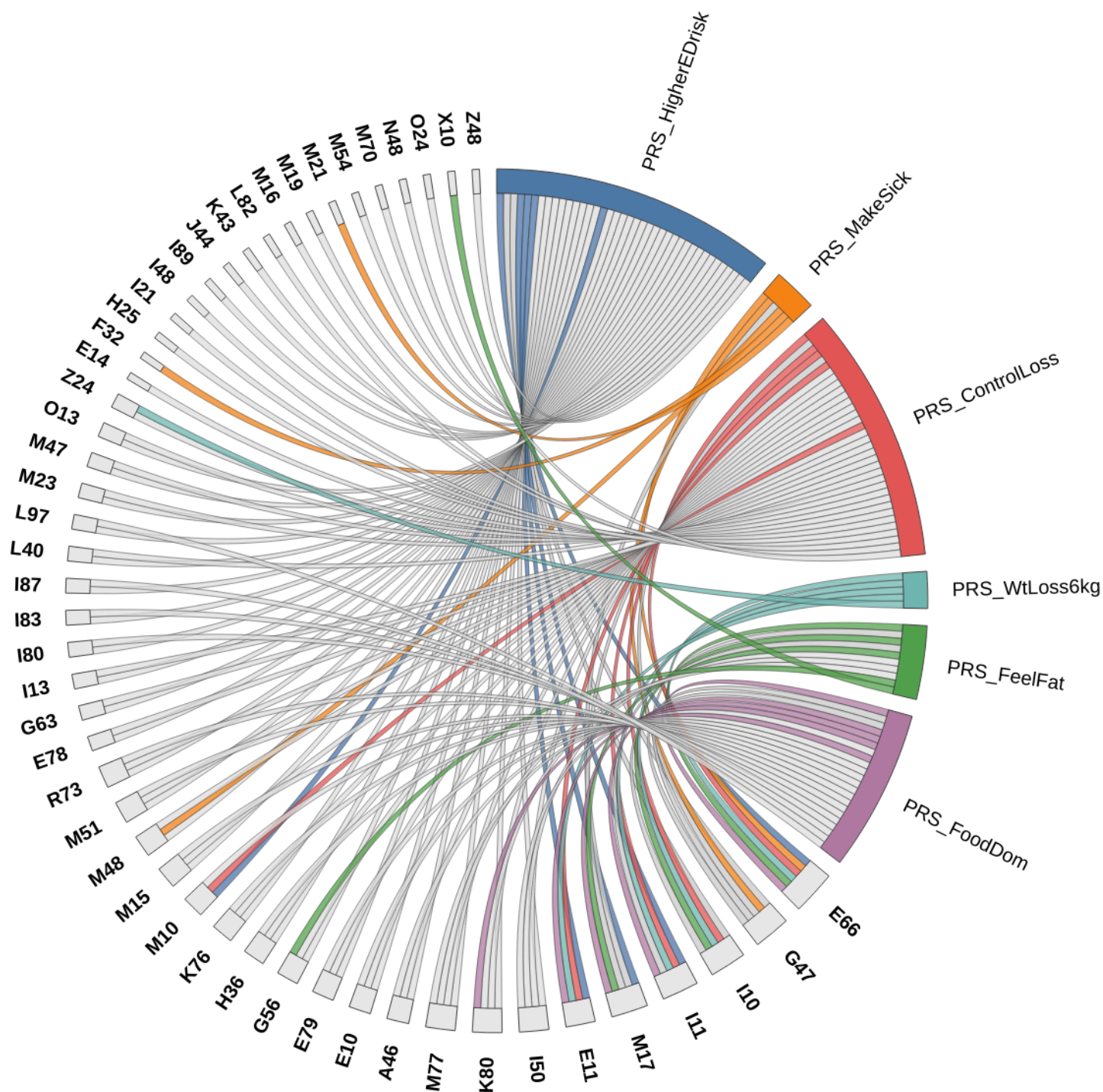


Figure 6

Interactive Chord Diagram of phenome-wide association studies between each eating disorder PRSs and ICD-10 codes. On the left side of the outer ring are marked ICD-10 codes, which showed significant association ($0.05/1,278$) with at least one of the standardized PRS. On the right side are marked six polygenic risk scores for eating disorder symptoms. Html: <https://interactive-phewas.netlify.app/chord-diagram>

Supplementary Files

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