Bachelor's Thesis in Biochemistry and Molecular Biology

THE POLYGENIC NATURE OF ANOREXIA NERVOSA: ASSESSMENT OF GENETIC RISK, HERITABILITY AND CLINICAL HETEROGENEITY THROUGH POLYGENIC RISK SCORES

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This thesis marks the end of an academic chapter, but it also weaves together many invisible threads, moments of doubt, joy, silence and surrender. I've often felt that words lose their meaning in my mind and dissolve before I can speak them. So instead, I write.

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ABSTRACT

Background: Anorexia nervosa (AN) is a complex psychiatric disorder with high mortality and a multifactorial etiology involving genetic, psychological, and metabolic components. Genome-wide association studies (GWAS) have confirmed its polygenic architecture. However, the contribution of polygenic risk scores (PRS) to AN risk and clinical variability remains underexplored.

Objective: To investigate the role of polygenic risk in AN by evaluating associations between PRSs and diagnosis, intergenerational transmission, and clinical features of the disorder. Functional analyses were performed to explore the biological pathways underlying these associations.

Methods: A total of 463 participants were included: 184 AN patients, 147 healthy controls, and 66 parent–child trios. Genomic data underwent quality control, imputation, and PRS calculation using PRS-CS. Thirty-one PRSs were selected from traits across four domains: mental health, personality, cognition/occupational performance, and metabolism. Logistic regression and polygenic Transmission Disequilibrium Test (pTDT) were used to assess associations with diagnosis and inheritance. Associations between PRSs and clinical variables (e.g., BMI, compulsive exercise, depression) were tested. Enrichment analyses identified biological processes shared across significant PRSs.

Results: AN patients had significantly higher PRS for loneliness (FDR p = 0.039) and neuroticism (FDR p = 0.043). Birthweight PRS was over-transmitted in trios (FDR p = 0.027), suggesting inherited risk. Within the AN group, several PRSs were nominally associated with clinical outcomes, including extraversion (depression, anxiety), openness (compulsive exercise, hospitalizations), and metabolic traits (fasting insulin and birthweight with hospitalizations), among others. Shared biological processes enriched across PRSs included mainly neurodevelopmental processes.

Conclusions: This study confirms the contribution of polygenic risk to AN diagnosis, heritability, and clinical heterogeneity. Personality- and metabolism-related PRSs, often overlooked in AN research, appear to influence disease expression. Enrichment analyses indicate shared neurodevelopmental and cellular pathways underlying polygenic risk. These findings support the integration of genetic risk profiling into future predictive and personalized strategies for AN.

Keywords: anorexia nervosa, polygenic risk score (PRS), psychiatric genetics, clinical heterogeneity, genome-wide association study (GWAS), transmission disequilibrium, enrichment analysis

ABBREVIATIONS

2hGlu: 2-hour glucose

ADHD: attention-deficit/hyperactivity disorder

AN: anorexia nervosa

ANX: anxiety

ASD: autism spectrum disorder

BD: bipolar disorder

BMI: body mass index

CP: cognitive performance

EA: educational attainment

ED: eating disorder

FDR: false discovery rate

GO: gene ontology

GWAS: genome-wide association study

HPA: hypothalamic–pituitary–adrenal (axis)

IFC: insulin fold change

IQ: intelligence quotient

LD: linkage disequilibrium

MAF: minor allele frequency

MDD: major depressive disorder

MDS: multidimensional scaling

Occatt: occupational attainment

OCD: obsessive-compulsive disorder

PCA: principal component analysis

pTDT: polygenic transmission disequilibrium test

PRS: polygenic risk score

PROI: proinsulin

QC: quality control

SNP: single nucleotide polymorphism

STAIC: state-trait anxiety inventory for children

SZ: schizophrenia

T2D: type 2 diabetes

VCF: variant call format

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1. INTRODUCTION

Eating disorders (ED) are psychiatric conditions marked by persistent disturbances in eating behaviors, as well as distressing thoughts and emotions related to food, body weight, and shape (Treasure et al., 2020). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), outlines diagnostic criteria for several feeding and EDs, including anorexia nervosa (AN), bulimia nervosa, binge-eating disorder, avoidant/restrictive food intake disorder, pica, and rumination disorder (American Psychiatric Association, 2013).

Among these, AN is characterized by a severe restriction of energy intake, an intense fear of gaining weight, and a distorted perception of one's body weight or shape (American Psychiatric Association, 2013). This disorder often results in significantly low body weight relative to what is expected for age, sex, and developmental stage.

1.1 Epidemiology: Prevalence and Mortality

AN disproportionately affects adolescents and young adults, with lifetime prevalence rates of about 0.1% to 4% in females and up to 0.3% in males (van Eeden et al., 2021). Incidence peaks between ages 15-19, with mortality rates as high as 5%, primarily from cardiac complications, electrolyte imbalances, and suicide (Cost et al., 2020; Puckett et al., 2021). Notably, suicide accounts for approximately 20% of these deaths (Cost et al., 2020). Furthermore, AN has the highest standardized mortality ratios (SMRs) among all psychiatric disorders, with a reported SMR of 5.21 (Krug et al., 2025).

1.*2 Clinical features of Anorexia Nervosa*

1.2.1 Subtypes

Two main subtypes of AN are reported: restricting type and binge-eating/purging type. The restrictive subtype is characterized by dieting, fasting and/or excessive exercise, resulting in weight loss. In the latter subtype, the individuals engage in binge eating or purging behavior through vomiting or the use of laxatives, diuretics or enemas (American Psychiatric Association, 2013). These subtypes often present overlapping symptoms and can transition over time, making diagnosis and treatment complex (American Psychiatric Association, 2013; Yao et al., 2021).

1.2.2 Comorbid diagnoses

A comorbidity is defined as a condition that co-occurs with the main diagnosis. For AN, identifying such comorbidities is crucial because of the impact that they can have on the severity

of the symptoms (Hambleton et al., 2022). For instance, one study points to a prevalence where 87.3% of individuals with AN met the criteria for at least one additional lifetime psychiatric disorder (Udo & Grilo, 2019). The most prevalent psychiatric comorbidities include anxiety disorders (ANX, 60%) (Hambleton et al., 2022), major depressive disorder (MDD, 50-75%) (Zhang et al., 2021), personality disorders (PD, 27%) (Laczkovics et al., 2023), suicidal ideation (SI, 20-43%) (Smith et al., 2018) and obsessive-compulsive disorder (OCD, 19%) (Mandelli et al., 2020), among others (Hambleton et al., 2022).

1.2.3 Personality traits

Patients with AN present distinct personality traits, including perfectionism, cognitive rigidity (inflexibility), neuroticism, and obsessionality. Among these, perfectionism is particularly prominent. AN patients often set unrealistically high standards for themselves and are overly self-critical when these standards are not met (Longo et al., 2024). This trait is closely linked to the severity of ED psychopathology and is associated with both restrictive eating behaviors and increased psychiatric comorbidities, including anxiety, depressive symptoms and obsessive tendencies. Furthermore, high levels of perfectionism in AN have been associated with lower self-directedness and cooperativeness, as well as an anxious temperament (Hambleton et al., 2022).

Cognitive rigidity, or poor cognitive flexibility, is another core feature. It manifests as an overreliance on rules and routines and resistance to change. This rigidity contributes to the chronic and persistent nature of restrictive eating and other maladaptive behaviors in AN (Rodgers et al., 2023). Neuroticism, characterized by increased emotional instability and negative affect, is also consistently observed in individuals with AN and is considered both a risk factor and a diagnostic marker for the disorder (Zhang et al., 2024). Obsessionality, including concerns about food, weight, and body image, are particularly prominent in the restricting subtype of AN and are often accompanied by obsessive-compulsive personality traits (Hambleton et al., 2022; Longo et al., 2024).

These personality features are not only associated with the onset and maintenance of AN but may also influence the course and prognosis of the illness, with higher levels of perfectionism and rigidity predicting poorer outcomes (Johansson et al., 2022; Zhang et al., 2024).

1.3 Etiology of AN

Despite the uncertainty of the disease's etiology, there is evidence involving disturbances in appetite-regulating and energy homeostasis pathways (Misra & Klibanski, 2014). Additionally, several studies have established a neurological and genetic predisposition and several life events that might cause dysregulations of the hypothalamic-pituitary-adrenal (HPA) axis (C. Bulik et al., 2015; Haines, 2023). These disturbances can be further exacerbated by environmental factors and psychological conditions. Therefore, AN is thought to have a multifactorial etiology, involving biological, social, genetic and psychological factors (**Figure 1**) (Mayo-Martínez et al., 2021).

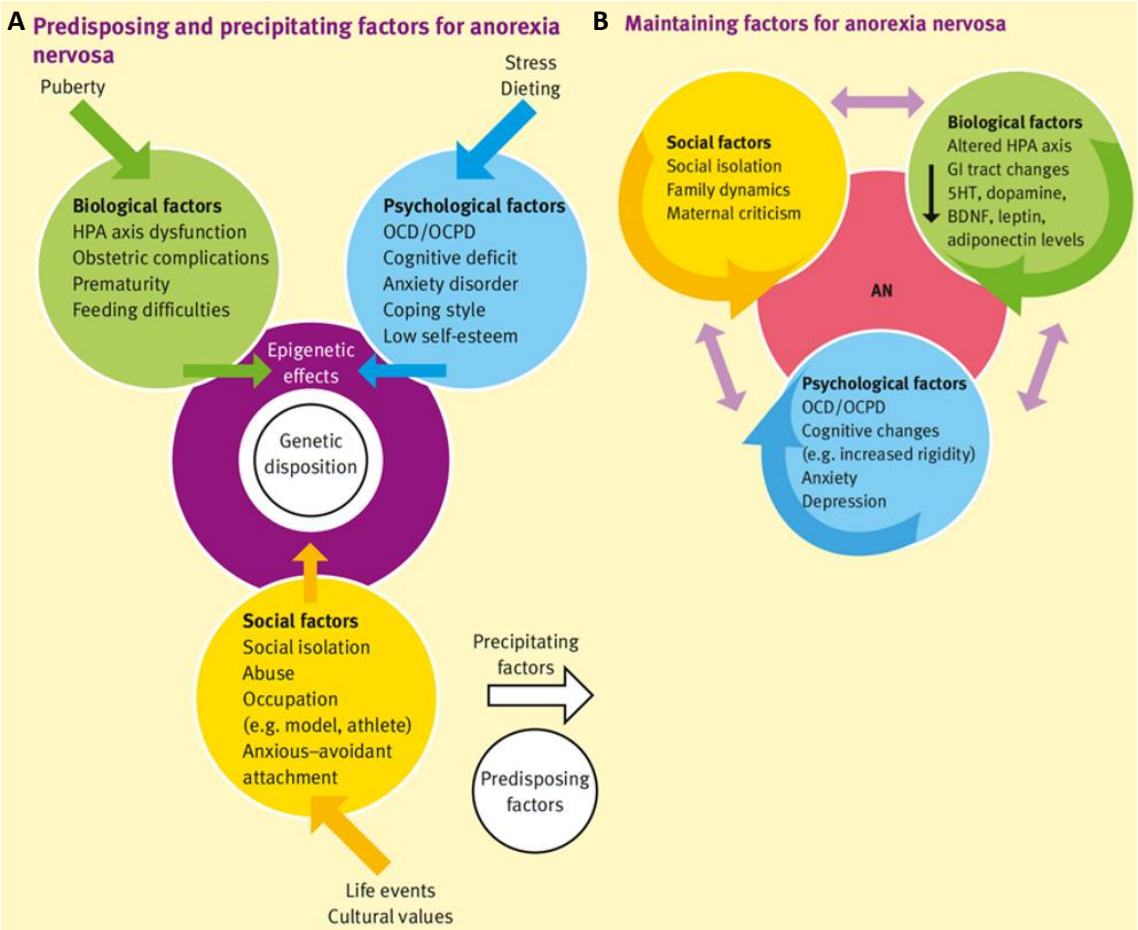


Figure 1. Multifactorial model of anorexia nervosa (AN) illustrating predisposing, precipitating, and maintaining factors. *The development and persistence of AN is influenced by an interplay of genetic, biological, psychological, and social factors. (A) Predisposing and precipitating factors, which include genetic disposition and are influenced by biological, psychological and social factors. These factors are triggered by life events such as puberty, stress, or dieting. (B) Maintaining factors, which contribute to the chronicity of the disorder, include continued disturbances in biological systems, psychological traits, and social context. Abbreviations: 5HT, serotonin; AN, anorexia nervosa; BDNF, brain-derived neurotrophic factor; GI, gastrointestinal; HPA, hypothalamic–pituitary–adrenal; OCD, obsessive–compulsive disorder; OCPD, obsessive–compulsive personality disorder. Adapted from (Woerwag-Mehta & Treasure, 2008)*

1.3.1 Biologic alterations

As a result of prolonged fasting and malnutrition, patients with AN often exhibit a range of metabolic alterations, particularly in endocrine and neurobiological systems (Cost et al., 2020; Mayo-Martínez et al., 2021). Hypercortisolemia is a consistent finding, reflecting chronic HPA axis activation. Although initially considered as an adaptive response to starvation, promoting gluconeogenesis and fat mobilization, persistent cortisol elevation contributes to muscle wasting, bone loss, and exacerbation of mood and anxiety symptoms (Cost et al., 2020; Misra & Klibanski, 2014).

Hypogonadotropic hypogonadism is also common. This condition involves low secretion of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). As a result, the ovaries produce less estradiol, and the testes produce less testosterone. In turn, these hormonal changes impair reproductive function (Boutari et al., 2020). Additionally, hypothyroidism is often observed due to impaired conversion of thyroxine (T4) to triiodothyronine (T3), leading to reduced metabolic rate (Haines, 2023).

Other significant metabolic alterations include those related to glucose metabolism and insulin sensitivity. Patients frequently exhibit reduced postprandial glucose and insulin responses to meals, reflecting a blunted endocrine response to feeding and chronic undernutrition (Heruc et al., 2018). Continuous glucose monitoring shows that individuals with AN often experience chronic, prolonged mild hypoglycemia, despite normal fasting glucose, with increased frequency and duration of hypoglycemic episodes throughout the day and night (Germain et al., 2023). This is accompanied by increased insulin sensitivity due to chronic energy restriction, such that even small amounts of insulin can cause pronounced reductions in blood glucose, contributing to unstable glycemic control (Misra & Klibanski, 2014).

These endocrine and metabolic disruptions are initially adaptive, supporting survival during starvation, but become maladaptive and contribute to the maintenance and complications of the disorder when prolonged (Misra & Klibanski, 2014).

In addition, several neurotransmitter pathways are impaired, particularly those involving serotonin (5-HT) and dopamine. In AN, 5-HT synthesis is reduced because of the lower availability of its precursor, tryptophan. This contributes to anxiety, dysphoric mood, and cognitive rigidity, partly via increased 5-HT_1A receptor activity. Elevated cortisol further alters serotonergic signaling in AN. Similar cortisol-serotonin dysregulation is observed in depression

and anxiety disorders, where chronic stress leads to long-term serotonergic imbalance (Ismaylova et al., 2025).

Dopaminergic activity, via D2 receptors, is also disrupted. Dieting and over-exercise can trigger dopamine release in reward areas of the brain, making weight loss feel rewarding. Over time, this reward response may become compulsive, similar to addiction (Södersten et al., 2016).

Overall, these neurochemical changes overlap with those seen in mood, anxiety, and OCD, which are frequently comorbid with AN (Haines, 2023; Plana et al., 2019). Genetic studies further support this overlap, implicating variants in genes such as Dopamine Receptor D2 (*DRD2*), involved in dopaminergic signaling and reward processing; Brain-Derived Neurotrophic Factor (*BDNF*), which plays a role in synaptic plasticity, learning, and mood regulation; and Melanocortin 4 Receptor (*MC4R*), an important regulator of energy homeostasis and appetite control (Paolacci et al., 2020). Together, these interactions help explain how AN bridges metabolic and psychiatric domains.

1.4 Genetic contributions to AN

As previously discussed, AN presentation is complex as it encompasses psychological and personality traits, and metabolic alterations. Furthermore, AN has a substantial genetic contribution that has become increasingly evident over recent decades. Twin and family studies estimate the heritability of AN to be between 48% and 74%, suggesting that nearly three-quarters of disease risk can be attributed to genetic variation (C. Bulik et al., 2015).

1.4.1 Study approaches for assessment of genetic liability to AN

Initial research into the genetic basis of AN primarily focused on candidate gene studies. However, most of these studies failed to replicate in larger cohorts and often yielded inconsistent or skewed findings (C. Bulik et al., 2015). Despite these limitations, these results were informative about the complex genetics involved in AN (C. M. Bulik et al., 2022).

In contrast, genome-wide association studies (GWAS) test thousands to millions of genetic variants simultaneously across the entire genome, with single-nucleotide polymorphisms (SNPs) being the most commonly studied variants (Uffelmann et al., 2021). GWAS have established that AN is a polygenic disorder, meaning that many genetic variants contribute a small amount to the overall risk (Duncan, Yilmaz, Gaspar, Walters, Bulik, et al., 2017; Watson et al., 2019).

Furthermore, these GWAS have identified multiple genes associated with AN involving both metabolic and psychiatric traits. Among the genes found, *CADM1* has been highlighted for its

role in energy and lipid metabolism regulation (Watson et al., 2019). Other genes are related to neurotransmission and synaptic plasticity, such as the previously mentioned *DRD2* and *BDNF* (Paolacci et al., 2020; Watson et al., 2019).

These findings have led to a reconceptualization of AN as a metabo-psychiatric disorder, where disruptions in appetite regulation, mood, and reward processing may all stem from shared genetic architecture (C. M. Bulik et al., 2022; Watson et al., 2019).

Given the polygenic nature of AN, interpreting GWAS results and understanding how multiple genetic variants jointly contribute to disease risk remains a challenge. To address this, polygenic risk scores (PRSs) have been developed as a method to quantify an individual's genetic liability for a complex trait like AN.

1.5 Polygenic Risk Score

A PRS is a numerical value that estimates an individual's predisposition to a specific trait or disorder by aggregating the effects of many genetic variants (Choi et al., 2020). It is calculated by summing the number of risk alleles carried by an individual, each weighted by its effect size derived from GWAS data (Choi et al., 2020; Wray et al., 2021).

PRSs are built upon GWAS findings, which identify SNPs significantly associated with the trait or disease in question by correlating allele frequencies with phenotypic data across large samples (Marees et al., 2018; Tam et al., 2019).

1.5.1 Technical considerations for PRS construction

To construct a PRS, several technical considerations must be taken into account, including data input, genotype imputation, quality control, and method selection for PRS construction. A summary of the typical PRS construction workflow is illustrated in **Figure 2**.

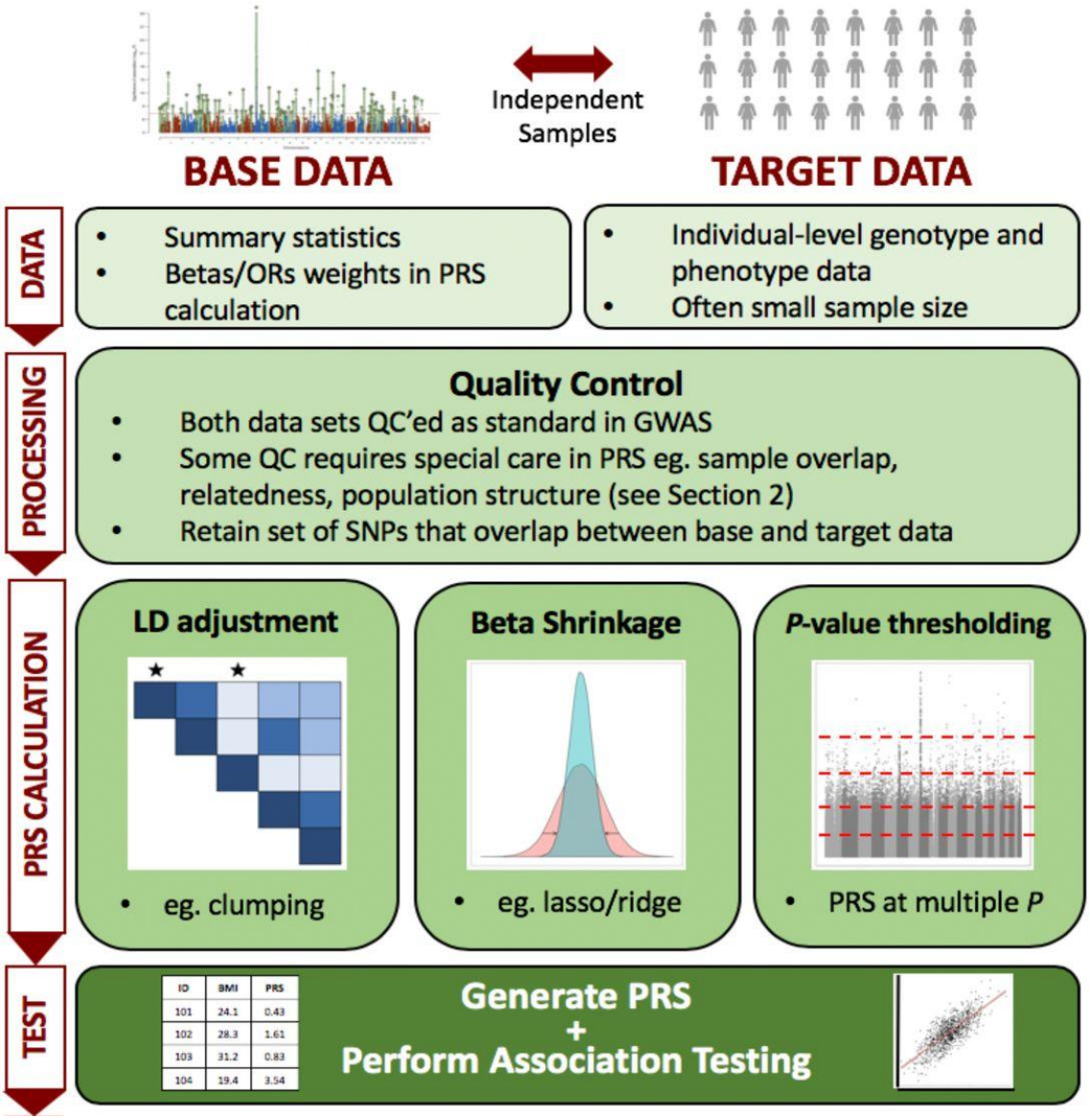


Figure 2. Overview of the polygenic risk score (PRS) analysis pipeline. *Key steps involved in generating and testing PRS using independent base and target data sets. Base data typically consists of genome-wide association study (GWAS) summary statistics, including effect size estimates. Target data consists of individual-level genotype and phenotype information, often with smaller sample sizes. After both data sets undergo standard quality control (QC), PRS calculation can be made following several strategies: LD adjustment, beta shrinkage, and p-value thresholding across a range of significance levels. Finally, PRS are computed and used in association testing to assess their relationship with the phenotype of interest. Abbreviations: GWAS, genome-wide association study; LD, linkage disequilibrium; OR: odds ratio; PRS, polygenic risk score; SNP, single nucleotide polymorphism; QC, quality control. Adapted from Choi et al., (2020)*

a) Data Requirements

Constructing a PRS requires two primary types of data: GWAS summary statistics and individual-level genotype data from the target sample. GWAS summary statistics provide information such

as SNP identifiers, effect alleles, effect sizes (e.g. odds ratios or beta values), and p-values. These values represent how strongly each genetic variant is associated with a particular trait in a large, external population (Uffelmann et al., 2021). The target dataset consists of genotype data for individuals in the study cohort, which must first undergo quality control (Choi et al., 2020).

b) Imputation

Genotype imputation is a statistical method used to predict missing genetic variants in study samples. In the context of PRS construction, imputation essentially "fills in" untyped SNPs using information from a densely genotyped reference panel (Marchini & Howie, 2010).

The process begins with phasing the observed genotype data. This involves determining the specific sequence of alleles on each chromosome for each individual. Then, the phased genotype data is modelled by comparing it to a reference panel (Blackburn et al., 2020). This is based on the linkage disequilibrium (LD) principle, which reflects the non-random association of alleles at nearby loci. Generally, SNPs located nearby in the genome tend to be inherited together (Blackburn et al., 2020; Marchini & Howie, 2010). To summarize, this correlation uses the LD principle to predict missing genotypes.

c) Quality control

Quality control (QC) is an important preliminary step in the construction of PRS, as it ensures that only high-quality, reliable genetic data is included in the analysis. Several filtering criteria are applied both at the genetic variant and individual levels (Anderson et al., 2010; Marees et al., 2018).

For SNPs, filters are applied to minimize technical artifacts and reduce noise (Anderson et al., 2010). Variants with a low minor allele frequency (MAF) are typically excluded, as rare alleles can compromise statistical power and may reflect population-specific artifacts rather than true genetic associations. SNPs with high rates of missing genotype data are also removed, since incomplete data can introduce bias and reduce the reliability of the analyses made. Hardy-Weinberg equilibrium (HWE) tests are used to assess whether the observed genotype frequencies align with expected genetic distributions in the population; significant deviations from HWE may indicate genotyping errors or population stratification (Choi et al., 2020; Marees et al., 2018).

Additional QC filters include heterozygosity outliers, which can signal sample contamination or inbreeding, and imputation quality scores (INFO) to assess the confidence of inferred genotypes for SNPs that have not been directly genotyped (Anderson et al., 2010; Marees et al., 2018). SNPs with low INFO are typically excluded to maintain the integrity of the dataset. Finally, duplicated SNP identifiers are removed to prevent redundancy and guarantee unambiguous mapping in PRS computation (Anderson et al., 2010).

In parallel, QC at the individual level addresses potential errors and inconsistencies related to the study participants. One key step is verifying concordance between reported and genetically inferred sex; discrepancies may indicate mislabeling or sample mix-ups. Individuals with excessive genotype missingness are excluded, as poor data quality in even a single sample can affect the overall analysis. Relatedness checks are also essential as the inclusion of closely related individuals (e.g., siblings or parent-offspring pairs) can violate assumptions of sample independence and skew allele frequency estimates (Zheng et al., 2012). Removing one individual from each related pair helps maintain the statistical validity of the dataset.

These QC measures, both at the SNP and individual level, are essential in studies of complex traits such as AN, where genetic signals are subtle and dispersed across several loci (Bang et al., 2023; Marees et al., 2018).

Once genotype data has been imputed and subjected to robust quality control, it is ready for use in polygenic scoring methods, which vary in their statistical complexity and assumptions.

1.5.2 Methods for calculating PRSs

There are different methods to calculate PRSs, depending on how SNPs are selected and weighed. A widely used traditional approach is Clumping and Thresholding (C+T), which involves two steps: first, selecting independent SNPs by removing those in high LD, and second, applying a p-value threshold to include only SNPs significantly associated with the trait (Ma & Zhou, 2021). Although easy to implement using tools like PLINK, this method is limited by the arbitrary choice of thresholds and the loss of information from excluded SNPs .

More recent Bayesian methods, such as PRS-CS (Polygenic Risk Score-Continuous Shrinkage), surpass traditional approaches using genome-wide SNP data and accounting for LD through an external reference panel (Choi et al., 2020). Rather than selecting a subset of variants, the PRS-CS method estimates the effect sizes of all SNPs using continuous shrinkage priors. This statistical technique applies a flexible penalty that shrinks small or noisy effect estimates toward zero while

preserving stronger signals (Choi et al., 2020; Ma & Zhou, 2021). This reduces overfitting and improves predictive accuracy. PRS-CS has been shown to outperform the C+T method, especially for complex, highly polygenic traits such as AN. For this reason, it is often preferred. Once the SNP effect sizes are estimated, the individual PRS is calculated as a weighted sum of the number of risk alleles carried at each SNP:

$$PRS_i = \sum_{j=1}^{m} G_{ij} * \beta_j$$

Where β_j is the effect size of SNP *j* and G_{ij} is the genotype of individual *i* at that SNP. This is coded as 0, 1 or 2 based on how many risk alleles they carry. The resulting scores are then scaled to allow for comparison across individuals and PRS.

1.5.3 Applications of Polygenic Risk Scores in Anorexia Nervosa

PRSs are useful for quantifying the heritable component of AN, helping to clarify how common genetic variants contribute to disease onset, intergenerational transmission, and clinical severity. By aggregating the effects of many small-risk alleles, PRSs can differentiate genetic liability between affected and unaffected individuals in case-control studies and reveal patterns of over-transmission from parents to children in family-based designs. One such method is the polygenic Transmission Disequilibrium Test (pTDT), which compares the PRS of the affected offspring to the expected score based on the average of their parents. This provides information into whether genetic risk is passed on more than expected by chance.

Beyond risk stratification, PRSs can also be employed to determine how genetic predispositions relate to clinical characteristics, such as symptom severity, comorbidity, or treatment outcomes. Therefore, PRSs can be used to advance in the understanding of the genetic architecture and heterogeneity.

Together, these advances show that PRSs can provide new information on both disease risk and severity. The present work aims to leverage PRS analyses, including both case-control comparisons and pTDT, to assess the heritable component of AN and explore how this genetic liability may relate to intergenerational transmission and variation in clinical severity.

2. HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

AN is a disorder with both psychiatric and metabolic components, influenced by a polygenic architecture. This study is guided by four interconnected hypotheses:

1. PRSs derived from psychiatric, personality, cognitive, and metabolic domains contribute to the genetic liability of AN.

2. PRSs associated with AN-related traits are over-transmitted from parents to affected offspring, supporting a heritable polygenic basis for the disorder.

3. The polygenic burden contributes to clinical heterogeneity within the AN population. Variation in PRS profiles among individuals with AN correlates with differences in clinical features, including disease severity, compulsive behaviors, hospitalizations, and comorbid psychiatric conditions.

4. Polygenic scores associated with AN and its clinical features converge on shared biological processes. Genes mapped from trait-associated SNPs within significant PRS will be enriched for specific and shared functional pathways, particularly those involved in neurobiological, psychological, or metabolic regulation.

2.2 Objectives

The primary objective of this thesis is to investigate the role of polygenic risk in AN. Specifically, this study aims to:

1. Evaluate the association between PRSs and AN diagnosis by comparing genetic scores between affected individuals and healthy controls across a range of psychiatric, personality, cognitive, and metabolic traits.

2. Assess intergenerational transmission of polygenic risk using the pTDT in a trio-based sample, to determine whether specific genetic liabilities are over-transmitted to affected offspring.

3. Explore the relationship between PRSs and clinical variability within the AN group, evaluating associations between polygenic scores and a range of clinical outcomes, including body mass index (BMI), anxiety, depression, compulsive exercise, and hospitalization.

4. Conduct functional enrichment analysis on significant PRSs to identify overrepresented biological pathways and processes that may help explain the molecular mechanisms driving AN and its phenotypic diversity.

2.3 Final Outcome Goal

The final goal of this project is to identify polygenic markers and underlying biological pathways that contribute to the development and clinical expression of AN. By integrating genetic risk profiling with clinical and functional data, this research aims to improve understanding of AN's pathophysiology and support the future development of predictive models, stratified interventions, and personalized treatment strategies for individuals at risk.

3. MATERIALS AND METHODS

3.1 Study Design and Participants

This project examined the genetic liability to AN using a PRS calculation approach that integrated both a case-control design and a family-based trio analysis using the polygenic Transmission Disequilibrium Test (pTDT) to assess the hereditary nature of the disorder (**Figure 3**).

3.1.1 Case-Control Sample

This subsample included 184 adolescents with AN and 147 healthy controls, recruited from previous genetic studies conducted at the Department of Child and Adolescent Psychiatry and Psychology, Hospital Clínic de Barcelona (Mas et al., 2013; Plana et al., 2019). All patients met DSM-IV (American Psychiatric Association, 2000) diagnostic criteria for AN, and diagnoses were confirmed through structured clinical interviews assessing developmental history and psychopathology. Exclusion criteria included intellectual disability, neurological disorders, and non-European ancestry.

Controls were recruited from schools in the same geographical area, matched to cases by age and years of education, and screened for lifetime and current psychiatric disorders using the Spanish version (Ulloa et al., 2006) of the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997). Affected and control participants were included only if they provided blood samples, passed genetic quality control, and had complete sociodemographic data.

3.1.2 Trio Sample

A subset of cases was included in the family-based trio analysis to perform the polygenic Transmission Disequilibrium Test (pTDT). This sample comprised individuals diagnosed with AN and their biological parents, forming complete trios (proband, mother, and father). The pTDT was used to assess the non-random transmission of polygenic risk from parents to affected offspring, providing information on the hereditary nature of AN. The final trio sample comprised 66 complete trios, selected based on the availability of genotyping data and quality control filters.

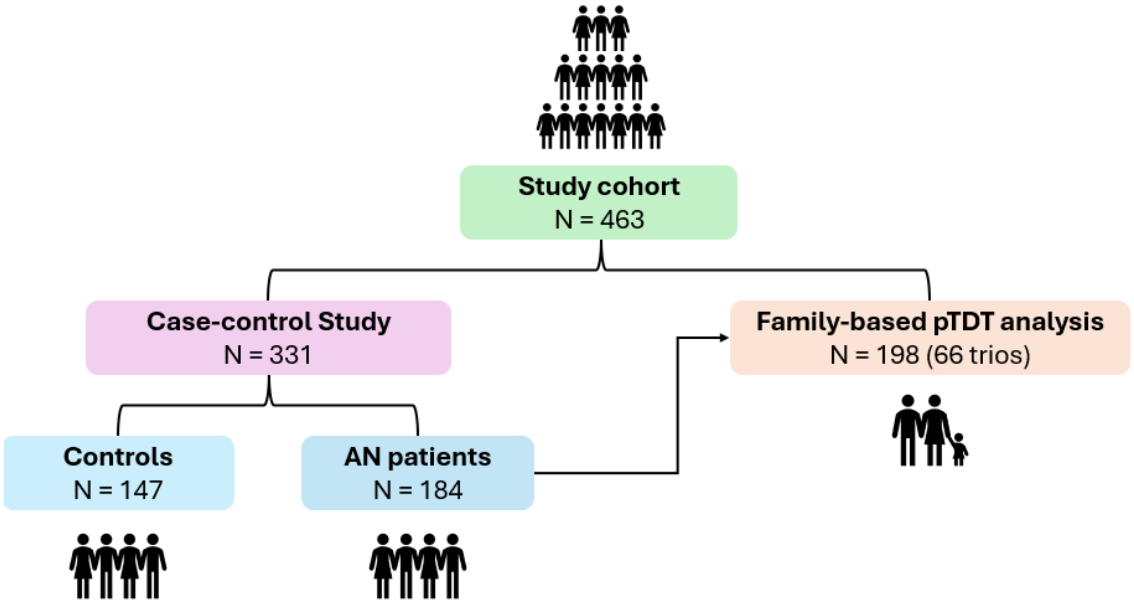


Figure 3. Overview of study cohort and subgroup composition. *The total study cohort consisted of 463 individuals, including patients with anorexia nervosa (AN), healthy controls, and parents of some AN cases. The case-control study subgroup (n = 331) included 184 AN patients and 147 healthy controls. The family-based Polygenic Transmission Disequilibrium Test (pTDT) analysis subgroup comprised 198 individuals (66 trios), each consisting of an AN proband and both biological parents. The value of n indicates the number of participants in each group.*

All participants self-identified as of European ancestry to minimize population stratification relative to the GWAS reference populations. Additional clinical data was collected using structured interviews and validated questionnaires. These included the Eating Attitudes Test-40 (EAT-40) (Garner & Garfinkel, 1979), which measures disordered eating behaviors and attitudes, and the State-Trait Anxiety Inventory for Children (STAIC) (Spielberger et al., 2012). STAIC evaluates anxiety in children and adolescents across two dimensions: state anxiety (transient emotional responses to specific situations) and trait anxiety (a general tendency to experience anxiety). It consists of two separate 20-item subscales, each scored from 20 to 60, with higher scores indicating more severe anxiety. Furthermore, scores can be expressed as percentiles. This approach is used to contextualize an individual's score relative to normative data for age, sex, and population (Spielberger et al., 2012).

Clinical data collected included: age of onset of AN, lowest BMI during illness, duration of illness, amenorrhea duration and type, family history of eating disorders, presence of comorbid psychiatric diagnoses, and severe depressive symptoms. Additional measures included whether the patient had been admitted to an inpatient unit, the number of hospitalizations, presence of compulsive exercise behaviors, and any history of suicide attempts.

All study procedures were approved by the Ethics Committee of Hospital Clínic de Barcelona. Written informed consent was obtained from all parents, and verbal assent was given by all underage participants, following a detailed explanation of the study.

3.2 Sample collection and Genotyping

Blood samples were collected in K2EDTA BD Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ, USA), stored at −20 °C, and sent to the laboratory for processing. Genomic DNA was extracted using the MagNA Pure LC DNA Isolation Kit – Large Volume with the MagNA Pure LC 2.0 Instrument (Roche Diagnostics GmbH, Mannheim, Germany). DNA concentration and purity were assessed via spectrophotometry using a NanoDrop ND-1000 (Thermo Fisher Scientific, Wilmington, DE, USA). A total of 2.5 µg of genomic DNA per participant was submitted to the Spanish National Genotyping Centre (CeGen) for genotyping using the Axiom™ Spain Biobank Array (developed at the University of Santiago de Compostela, Spain).

3.3 PRS calculation

To compute PRS, publicly available GWAS summary statistics retrieved from GWAS repositories such as the Psychiatric Genomics Consortium (PGC) or GWAS Catalog were used. In total, GWAS data for 31 traits were selected and grouped into four domains: mental health (including psychopathologies and endophenotypes), personality traits, cognitive and occupational performance, and metabolic phenotypes. Details of the selected phenotypes are provided in **Supplementary Table 1**.

A complete overview of the PRS computation workflow, including all preprocessing, imputation, quality controls, and scoring steps, is illustrated in **Supplementary Figure 1**.

3.3.1 Genotyping Data Processing

Raw genotyping data underwent a series of preprocessing and quality control steps to ensure accuracy and consistency before imputation and downstream analyses. Variant Call Format (.vcf) files were first converted into PLINK binary files (.bed, .bim, .fam), which encode genotype calls, variant information, and sample metadata, respectively. These formats are essential for both quality control and later steps such as PRS construction.

Pre-imputation quality control included standard filtering criteria at the SNP level. Variants with low MAF (< 0.01), deviation from HWE ($p < 1\times10^{-6}$), or high missingness (>10%) were removed.

3.3.2 Imputation

After quality control, the genotype data was organized by chromosome into Variant Call Format files (.vcf.gz), which are commonly used for storing genetic variation data. These files were submitted to the Michigan Imputation Server (Das et al., 2016), an established platform for genotype imputation, which infers untyped genetic variants based on reference data.

Imputation was performed using the server's standard pipeline, which uses Minimac4, a widely used algorithm for large-scale genotype imputation. As the reference panel, the Haplotype Reference Consortium (HRC) panel, version r1.1 (2016), was used (McCarthy et al., 2016). It contains high-quality haplotypes from thousands of individuals and is aligned to the GRCh37/hg19 human genome build.

Before imputation, the genotypes were phased using the Eagle v2.4 algorithm (Loh et al., 2016), which was also run on the Michigan Imputation Server. Phasing is the process of estimating the arrangement of alleles on each chromosome and helps improve imputation accuracy by identifying which variants are inherited together.

Following imputation, variant identifiers, which were initially recorded as genomic coordinates, were converted to standard reference SNP IDs (rsIDs) using publicly available annotation files. This step helps with downstream analysis and interpretation of the imputed variants.

3.3.3 Post-imputation Quality Control and Sample Filtering

Further genetic quality control was performed using PLINK v1.07 (Purcell et al., 2007). SNPs were retained if they met the previously described criteria and had a genotype call rate > 99% and an imputation INFO score > 0.8. Additionally, SNP pruning was conducted with a window/step size of 200/50 kb and $r^2 > 0.25$ to reduce linkage disequilibrium and avoid redundancy in genetic data.

This was followed by a sample-level QC, which included heterozygosity and relatedness checks. Individuals with genotype missingness > 1%, outlier heterozygosity (±3 standard deviations from the sample mean), mismatches between reported and genetically inferred sex, and relatedness above the π-hat threshold of 0.125, corresponding to relatedness closer than third-degree relatives, were excluded. Furthermore, only individuals of self-reported and confirmed European ancestry were retained to match the ancestry of the reference GWAS and the imputation panel.

3.3.4 Polygenic Risk Score Construction

PRS were calculated using the PRS-CS (Polygenic Risk Scores - Continuous Shrinkage) method (Ge et al., 2019), a Bayesian regression framework that applies continuous shrinkage priors to GWAS effect sizes. This method accounts for LD using an external reference panel, improving prediction accuracy and interpretability of PRS estimates (Ge et al., 2019). The European ancestry LD reference panel derived from the UK Biobank (Bycroft et al., 2018) was used for this analysis. All PRS-CS analyses were conducted using default parameter settings.

The resulting SNP weights were applied to individual-level imputed genotype data using PLINK to obtain PRS for each participant. Before statistical analysis, the PRSs were standardized within the total sample using the scale() function in R, which centers the scores by subtracting the sample mean and scales them by the sample standard deviation (z-score standardization).

3.4 Enrichment Analysis

PRSs that showed nominally significant associations with AN in the case-control analysis, pTDT, or clinical severity analyses were selected for downstream enrichment analysis. This aimed to extract biologically meaningful information by identifying functional pathways and biological processes associated with each PRS.

To perform the enrichment analysis, the list of SNPs included in each selected PRS was first extracted. These SNPs were then mapped to protein-coding genes using the MAGMA tool, with a gene annotation window of ±5 kilobases from the transcription start and end sites. This window size defines the upstream and downstream region considered when assigning SNPs to genes. Only SNPs with a p-value below the cut-off of 0.05 in the summary statistics of the corresponding GWAS were included in the analysis.

The resulting gene lists were then analyzed using the ClueGO plugin (Bindea et al., 2009) within the Cytoscape platform (Shannon et al., 2003). ClueGO integrates Gene Ontology (GO) annotations to identify significantly enriched biological processes among the input gene sets. GO terms were filtered to include those of intermediate specificity (tree levels 5–10) and required a minimum representation threshold based on both the number and proportion of genes per term. Functional similarity between GO terms was assessed using the Kappa score to cluster related terms into coherent functional groups.

The complete set of parameters used for the ClueGO analysis is summarized in **Table 1**. These settings were selected to provide a balance between statistical stringency and biological interpretability while minimizing redundancy among closely related GO terms.

Table 1. ClueGO parameters

ClueGO parameters	
Ontologies/Pathways	GO Biological Processes
Adjusted p-value threshold	< 0.05 (Bonferroni correction)
GO tree interval	Levels 5-10
GO Term/Pathway Selection (#/% Genes)	≥ 3 genes (≥ 20%)
Kappa Score	≥ 0.4

GO Gene Ontology

In addition to identifying enriched GO terms for each PRS individually, the analysis also examined shared GO terms across different PRS and across trait domains (mental health, personality, cognitive/occupational, and metabolic). This comparative approach allowed the identification of common biological pathways. Overlaps were visualized using Venn diagrams and further summarized with semantic clustering (ReViGO) to reduce redundancy and enhance biological interpretability (Supek et al., 2011).

3.5 Statistical Analysis

All statistical analyses were performed using R version 4.5.0 (R Core Team, 2025). Data visualization was conducted using the ggplot2 R package and additional tools from the tidyverse ecosystem. The overall statistical analysis included descriptive statistics, association testing for the case-control sample, and the application of the polygenic Transmission Disequilibrium Test (pTDT) for the trio subsample. Additionally, PRS scores were compared within the case group to explore whether differences in polygenic burden could help explain variability in the clinical phenotype. Results from the enrichment analysis were plotted using the VennDiagram R package and the ReViGO website.

3.5.1 Descriptive statistics

Sociodemographic and clinical characteristics were summarized using means and standard deviations for continuous variables (e.g., age) and percentages for categorical variables (e.g., sex). Group comparisons between individuals with AN and healthy controls were conducted using independent-sample Student's t-tests for continuous variables and chi-squared tests for categorical variables.

3.5.2 Genetic Architecture of Polygenic Risk Scores

To investigate the genetic relationships among the 31 PRSs studied, a pairwise Pearson correlation matrix was computed, and a principal component analysis (PCA) was performed. The correlation matrix was used to quantify shared genetic variance between traits and to visualize domain-specific clustering patterns. It was plotted using the corrplot R package. PCA was then applied to reduce dimensionality and further explore how traits grouped based on their shared polygenic architecture.

3.5.3 Genetic liability to anorexia nervosa

a) Case-control Study

Associations between PRSs and AN diagnosis were evaluated through logistic regression models. Each polygenic score was analyzed independently as a standardized continuous predictor. The dependent variable was case-control status. All models were adjusted for age, sex, and the first 10 principal components derived from a genetic PCA to control for population stratification.

The PCA was performed on sample genotype data using the SNPRelate R package (Zheng et al., 2012), applying LD pruning ($r^2 < 0.2$) to account for inference of ancestry-related components. In addition, a multidimensional scaling (MDS) analysis was conducted to assess population structure and detect ancestry outliers. MDS was performed using PLINK based on pruned SNPs from the HapMap3 reference panel. The resulting MDS coordinates were visualized using the calibrate R package.

Logistic regression was implemented using the glm() function in R, with a binomial distribution and logit link. Significance was defined as $p < 0.05$, and correction for multiple comparisons was applied using the false discovery rate (FDR).

b) Family-Based Transmission of Polygenic Risk: pTDT Analysis

The pTDT was applied to the trio subsample to evaluate whether affected offspring inherit polygenic scores that significantly deviate from the mid-parent expectation, as would be predicted under Mendelian inheritance in the absence of selection or bias. For each trio, the deviation from expected transmission was calculated as:

$$pTDT\ deviation = PRS_{child} - \frac{(PRS_{mother} + PRS_{father})}{2}$$

This deviation was computed for each polygenic score of interest. The mean deviation across all trios was tested against zero using a two-tailed one-sample Student's t-test, as previously described (Huang et al., 2024; Weiner et al., 2017). The t-statistic was calculated according to the formula:

$$t_{pTDT} = \frac{mean(pTDT\ deviation)}{\frac{s.d.(pTDT\ deviation)}{\sqrt{n}}}$$

Where *n* denotes the number of trios included in the analysis (N = 66) and *s.d* the standard deviation. A significant positive deviation indicates overtransmission of polygenic liability from parents to affected offspring, while a negative deviation suggests undertransmission. All pTDT analyses were conducted under the assumption of normality in the deviation distribution. Statistical significance was defined at $p < 0.05$ and correction for multiple comparisons was applied using FDR.

3.5.4 PRS and Clinical Phenotypes in AN

To explore whether differences in polygenic burden contribute to heterogeneity in clinical presentation among individuals with AN, additional analyses were conducted within the case group.

Associations between individual PRSs and clinical variables were tested using regression models appropriate to each outcome type. Continuous clinical variables (e.g., lowest BMI, STAIC trait and state) were analyzed using linear regression, while binary variables (e.g., presence of severe depression, history of suicide attempts, compulsive exercise) were assessed using logistic regression.

For each association, the PRS was entered as the independent variable, and the clinical feature as the dependent variable. Where applicable, models were adjusted for age and sex and the first 10 PCA components. Statistical significance was set at $p < 0.05$, and FDR correction was applied to account for multiple testing across traits.

Post-hoc pairwise comparisons were conducted for variables with more than two categories, such as the number of hospitalizations, to identify specific group differences.

4. RESULTS

4.1 Descriptive statistics of the study cohort

The demographic characteristics of the study population are shown in **Table 2**. The groups differed in gender distribution, with a higher proportion of females in the AN group. Additionally, the mean age was lower in the AN group than in controls.

Table 2. Demographic Characteristics of the Study Population

Feature	AN patients (N = 184)	Controls (N = 147)	Statistical test
Gender, N (%)			
Female	176 (95.7%)	96 (65.3%)	χ^2 = 49.3235 p = 2.17e-12
Male	8 (4.3%)	51 (34.7%)	
Age (mean ± SD)	13.45 ± 1.62	16.55 ± 1.7	t = -14.1448 p = 4.46e-32

AN anorexia nervosa; *SD* standard deviation

Clinical characteristics of the AN cohort are detailed in **Table 3**. Physical features included an adolescent age of onset and a low average BMI, while the average duration of illness was just over 10 months. Menstrual function was also recorded, with most patients reporting secondary amenorrhea.

In terms of family and psychiatric history, 17.8% of the sample reported a family history of ED. Psychiatric comorbidities were present in 35.0% of patients, with severe depression affecting 39.6%. Additionally, patients showed high anxiety levels, with mean STAIC-State and STAIC-Trait percentile scores of 56.25 and 59.08, respectively.

Clinical history reflected high healthcare utilization, as 73.3% of patients had been admitted to inpatient units, with an average of 1.88 hospitalizations per individual. Furthermore, risk-related behaviors were prevalent, with 64.9% of patients engaging in compulsive exercise and 17.9% reporting suicide attempts.

Several of these clinical features were selected for later analysis.

Table 3. Clinical Characteristics of Anorexia Nervosa Patients

Feature	AN patients	Sample Available (N)
Age of onset (mean ± SD)	13.45 ± 1.62	93
Lowest BMI (mean ± SD)	16.26 ± 1.66	176
Duration of illness, months (mean ± SD)	10.18 ± 8.68	160
Amenorrhea duration, months (mean ± SD)	10.61 ± 9.56	113

Feature	AN patients	Sample Available (N)
Amenorrhea type, N (%)		
Primary	23 (12.8%)	
Secondary	142 (78.9%)	180
Male	8 (4.4%)	
No amenorrhea	7 (3.9%)	
Family history of ED, N (%)	32 (17.8%)	180
Comorbid diagnoses, N (%)	63 (35.0%)	180
Severe depression, N (%)	59 (39.6%)	149
STAIC-State (mean ± SD)	56.25 ± 30.17	145
STAIC-Trait (mean ± SD)	59.08 ± 26.85	146
Admitted to inpatient unit, N (%)	132 (73.3%)	180
Number of hospitalizations (mean ± SD)	1.88 ± 2.32	180
Compulsive exercise, N (%)	111 (64.9%)	171
Suicide attempts, N (%)	24 (17.9%)	134

AN anorexia nervosa; *BMI* body mass index; *ED* eating disorder; *SD* standard deviation; *STAIC* State-Trait Anxiety Inventory for Children

4.2 Genetic Data Processing and Quality Control Summary

4.2.1 Case-Control Sample

The case-control dataset initially included 354 individuals and 606,944 SNPs. After quality control, 331 individuals (184 AN cases, 147 controls) were retained. Exclusions were due to genotype missingness >1% (n = 3), heterozygosity outliers (n = 8), relatedness (π-hat > 0.125, n = 8), and sex mismatches (n = 4). SNP-level filtering (MAF < 0.01, HWE $p < 1\times10^{-6}$, missingness >10%) was applied prior to imputation. Post-imputation, variants with INFO < 0.8 or call rate < 99% were excluded, resulting in 5,921,446 SNPs. A final round of filtering to the imputed data (MAF < 0.01, HWE $p < 1\times10^{-6}$, missingness >10%) yielded 4,620,620 high-quality variants for analysis.

4.2.2 Trio Sample

The trio dataset began with 216 individuals and 693,051 SNPs. After individual-level QC, 198 individuals (66 complete trios) remained. Exclusions were due to heterozygosity outliers (n = 5), relatedness (n = 8), and incomplete trios (n = 5). SNP filtering followed the same criteria as for the case-control sample. Imputation and post-imputation filtering (INFO > 0.8, call rate > 99%) resulted in 5,577,405 SNPs, with 4,580,759 retained after final QC.

4.3 Population Stratification Analysis

To evaluate and account for potential population stratification in the genetic data, PCA and MDS were performed on genome-wide SNP data. These methods were used to detect underlying population structure that could confound subsequent association analyses.

PCA identified continuous axes of genetic variation, with the first two principal components (PC1 and PC2) accounting for 0.45% and 0.40% of the total variance, respectively. Participants clustered as a genetically homogeneous group, with no clear separation by ancestry or case-control status.

Similarly, the MDS plot (**Figure 4**), based on pairwise genetic distances, confirmed the absence of population stratification. Individuals distributed uniformly without discernible clusters or stratified groupings. The study sample overlapped with reference populations of European ancestry, particularly the Utah Residents with Northern and Western European Ancestry (CEU) and Toscani in Italy (TSI) samples from the HapMap3 panel.

Given the subtle variance captured by the leading components, the first ten principal components were included as covariates in subsequent logistic regression models to adjust for any residual stratification effects.

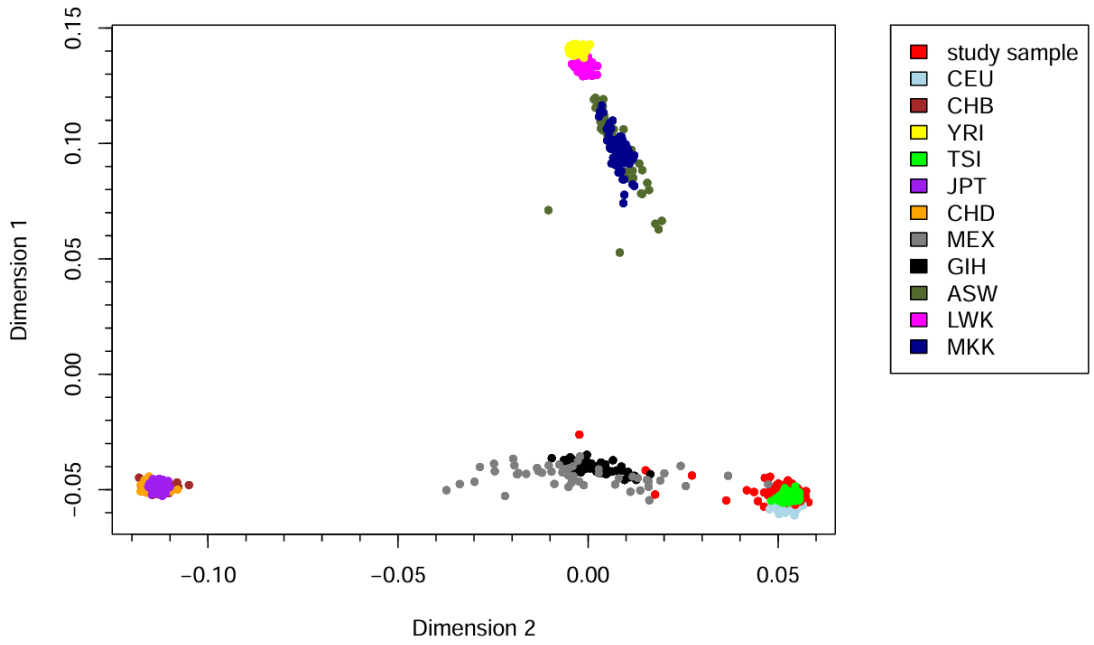


Figure 4. MDS plot overlap between the study sample and the International HapMap project. *ASW: African Ancestry in Southwest USA; CEU: Utah residents with Northern and Western European ancestry (from the CEPH collection); CHB: Han Chinese in Beijing, China; CHD: Chinese in Metropolitan Denver, Colorado (USA); GIH: Gujarati Indians in Houston, Texas (USA); JPT: Japanese in Tokyo, Japan; LWK: Luhya*

in Webuye, Kenya; MEX: Mexican Ancestry in Los Angeles, California (USA); MKK: Maasai in Kinyawa, Kenya; TSI: Toscani in Italy; YRI: Yoruba in Ibadan, Nigeria.

4.4 Genetic Architecture and Domain Clustering of PRSs

To investigate patterns of genetic overlap between PRSs, several analyses were conducted to examine correlations both within and across the four studied domains: cognitive and occupational performance, mental health, metabolic phenotypes and personality traits.

4.4.1 Pearson Correlation Matrix of PRSs

The Pearson correlation matrix highlights strong genetic clustering within each of the four main domains (**Figure 5**). Educational and occupational performance traits, such as educational attainment, intelligence quotient, and occupational attainment, showed significant positive correlations, reflecting shared genetic influences. In the mental health domain, significant positive correlations were seen among schizophrenia (SZ), bipolar disorder (BD), major depressive disorder (MDD), and obsessive-compulsive disorder (OCD). In contrast, other psychiatric traits like attention-deficit/hyperactivity disorder (ADHD) and insomnia showed more modest or variable associations. Metabolic traits, including BMI, type 2 diabetes (T2D), and 2-hour glucose (2hGlu), were also positively correlated, indicating shared genetic factors within this domain. Personality traits, including the Big Five (agreeableness, conscientiousness, extraversion, openness and neuroticism) and loneliness, generally showed weaker genetic correlations overall. However, neuroticism and loneliness were notably and significantly correlated with each other, and both also presented significant genetic links with several mental health traits.

Interestingly, AN did not show any significant genetic correlations with other traits in this analysis.

Overall, the matrix showed that correlations were generally stronger within domains than between them. This supports the idea of genetic independence across these trait domains.

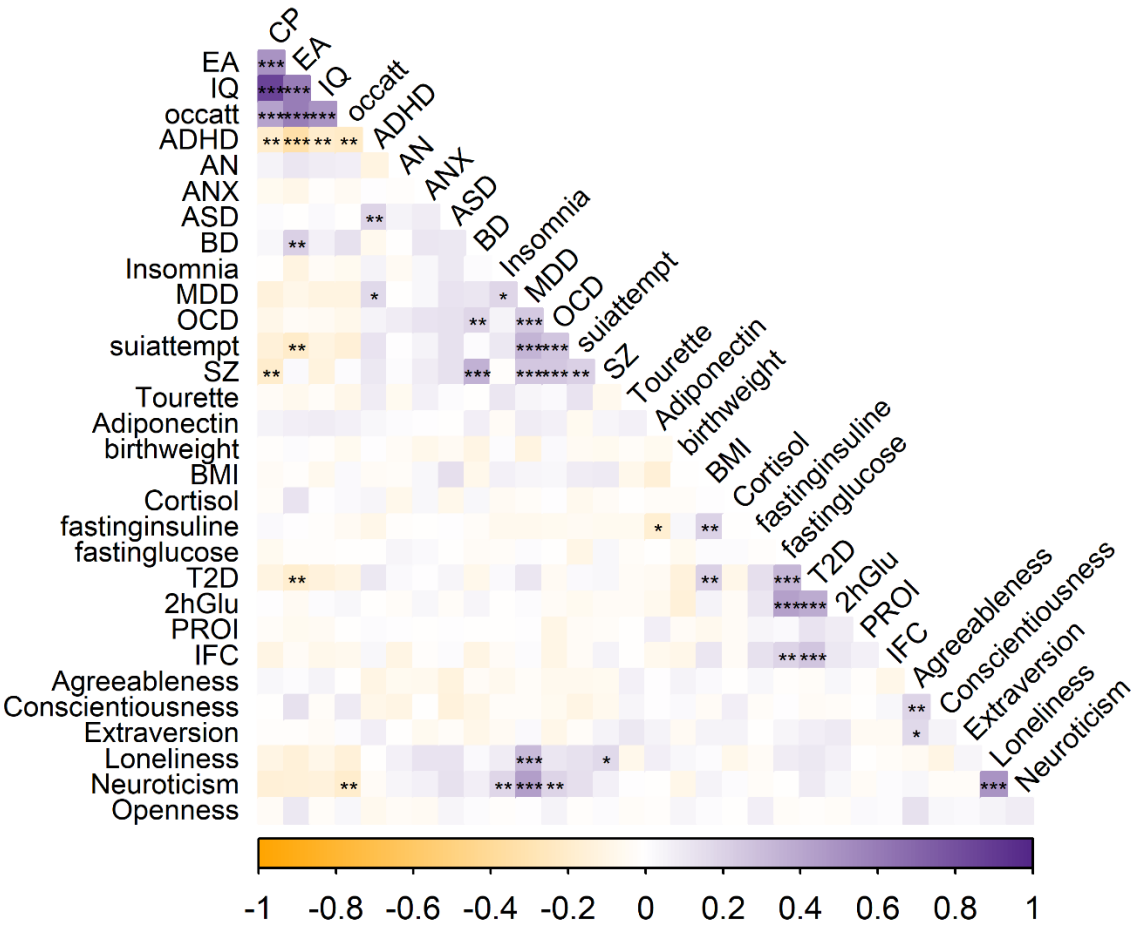


Figure 5. Pearson correlations between polygenic risk scores (PRSs) across domains. *The heatmap displays Pearson correlation coefficients between pairs of PRSs, grouped by domain: educational and occupational performance, mental health (including psychiatric disorders and endophenotypes), metabolic, and personality traits. The color scale represents the strength and direction of the correlation, ranging from negative (orange) to positive (purple). Statistical significance is indicated by * p < 0.05; ** p < 0.01; *** p < 0.001. All P-values were FDR-corrected for multiple comparisons. Trait abbreviations: 2hGlu: 2-hour glucose; ADHD: attention-deficit/hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety; ASD: autism spectrum disorder; BD: bipolar disorder; BMI: body mass index; EA: educational attainment; IFC: insulin fold change; IQ: intelligence quotient; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; occatt: occupational attainment; PROI: proinsulin; suiattempt: suicide attempt; SZ: schizophrenia.*

4.4.2 PRS PCA

The PCA results further confirmed the domain-specific clustering patterns observed in the correlation matrix (**Figure 6**). Traits related to cognitive and occupational performance separated clearly from other domains along the first principal component, showing relative genetic independence. Similarly, metabolic traits formed a distinct cluster, consistent with their internal correlations and minimal overlap with other domains in the correlation matrix. In contrast, mental health and personality traits exhibited greater overlap in the PCA space, reflecting moderate genetic correlations, particularly between neuroticism, loneliness, and certain mental health traits like MDD.

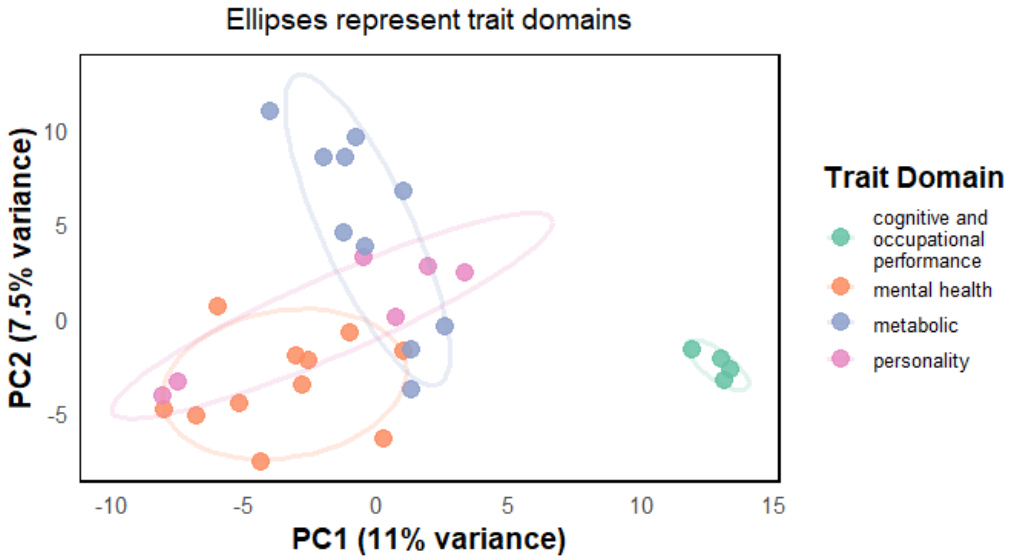


Figure 6. Principal Component Analysis plot of polygenic risk scores (PRSs), colored by domain*: green for cognitive and occupational performance, orange for mental health, blue for metabolic, and pink for personality. Ellipses in corresponding colors represent the spread of each domain. Cognitive and occupational performance traits form a distinct cluster, while mental health and personality traits show greater overlap, reflecting the genetic relationships observed in the correlation matrix.*

4.5 Case-Control Association Study

Results for associations between selected PRSs and AN diagnosis are shown in **Figure 7**. As seen in the heatmap, individuals with AN displayed higher mean PRS values for several traits, especially within the personality and mental health domains. The most notable differences were observed for neuroticism and loneliness, followed by other traits such as insomnia, OCD, and the PRS for AN itself.

In contrast, healthy controls showed relatively higher mean PRSs for traits such as agreeableness, insulin fold change after oral glucose (IFC), and ADHD.

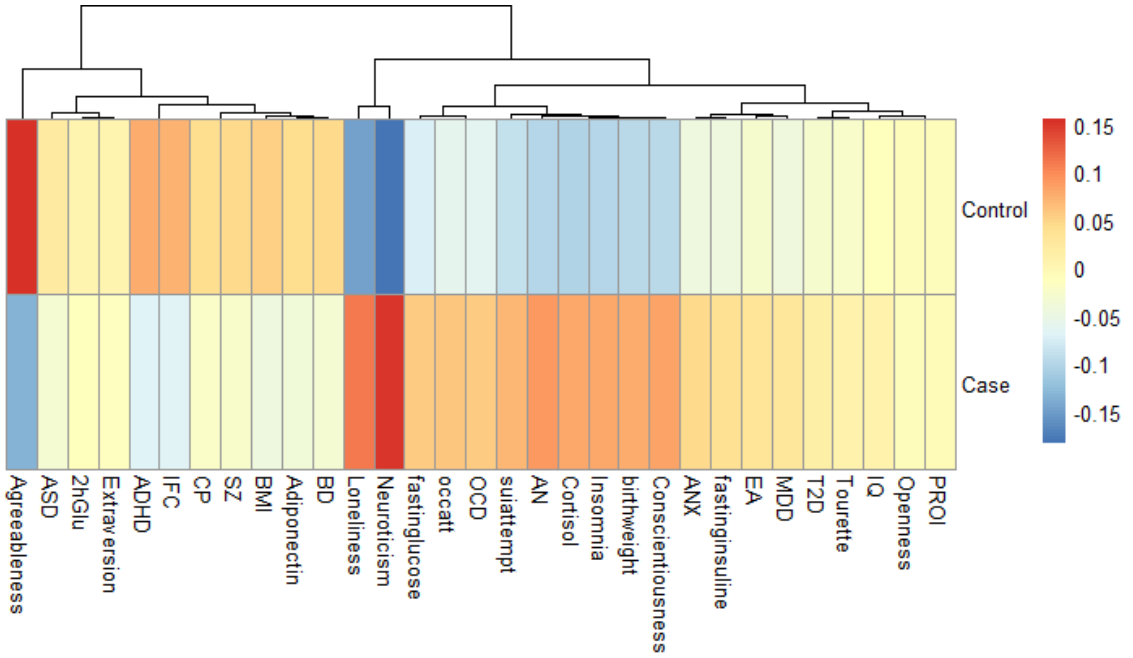


Figure 7. Heatmap of mean standardized polygenic risk scores (PRSs) across anorexia nervosa (AN) cases and healthy controls. *Each cell displays the average z-scored PRS for a given trait in each group, with color gradients ranging from blue (lower mean scores) to red (higher mean scores). The control group is represented at the top and the AN group at the bottom. Trait abbreviations: 2hGlu: 2-hour glucose; ADHD: attention-deficit/hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety; ASD: autism spectrum disorder; BD: bipolar disorder; BMI: body mass index; EA: educational attainment; IFC: insulin fold change; IQ: intelligence quotient; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; occatt: occupational attainment; PROI: proinsulin; suiattempt: suicide attempt; SZ: schizophrenia.*

Four traits showed significant links with case-control status before multiple testing correction: IFC, insomnia, loneliness, and neuroticism. As illustrated in **Figure 8**, cases had significantly higher PRS scores compared to controls in insomnia, loneliness, and neuroticism. Conversely, individuals with AN had significantly lower PRS scores for IFC, suggesting a potential link between decreased genetic liability for insulin response and disease status.

Following FDR correction, neuroticism (FDR p = 0.066) and loneliness (FDR p = 0.081) were close to significance but did not reach the adjusted threshold. Insomnia (FDR p = 0.319) and IFC (FDR p = 0.319) were not significant after correction.

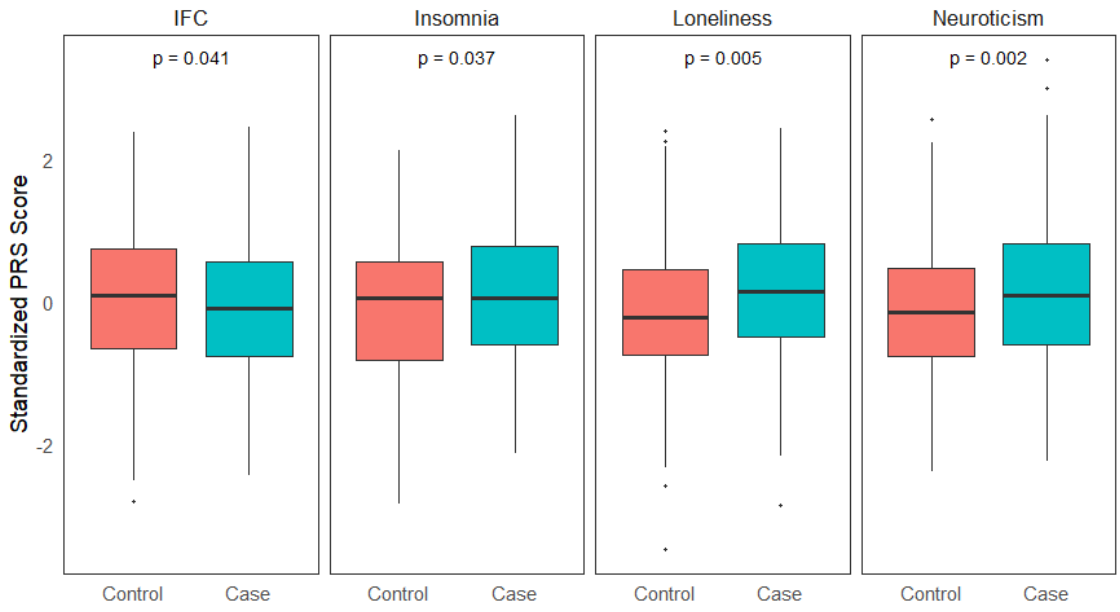


Figure 8. Distribution of standardized polygenic risk scores (PRSs) by anorexia nervosa (AN) case-control status for insulin fold change (IFC), insomnia, loneliness, and neuroticism. *Nominal p-values are shown. After FDR correction, neuroticism (FDR = 0.066) and loneliness (FDR = 0.081) were close to significance; IFC and insomnia were not significant (FDR = 0.319).*

Given the higher prevalence of AN among females, a secondary analysis was conducted by restricting the sample to female participants. The direction and magnitude of associations between PRS and case-control status were broadly consistent with those observed in the full sample. The female-only analysis replicated previously identified associations. Additionally, new nominal associations were observed in this female-only subset: lower PRS for agreeableness ($p = 0.026$) and higher PRS for birthweight ($p = 0.043$), cortisol levels ($p = 0.043$), and suicide attempt ($p = 0.026$) were associated with increased odds of AN (**Figure 9**).

Following FDR correction, only loneliness (FDR = 0.039) and neuroticism (FDR = 0.043) remained statistically significant. IFC (FDR = 0.13), insomnia (FDR = 0.17), and the additional traits identified in the female-only analysis (agreeableness, birthweight, cortisol, and suicide attempt; all FDR $p \geq 0.16$) did not reach significance after correction. These results strengthen the evidence for a genetic contribution of personality traits, particularly loneliness and neuroticism, to AN risk.

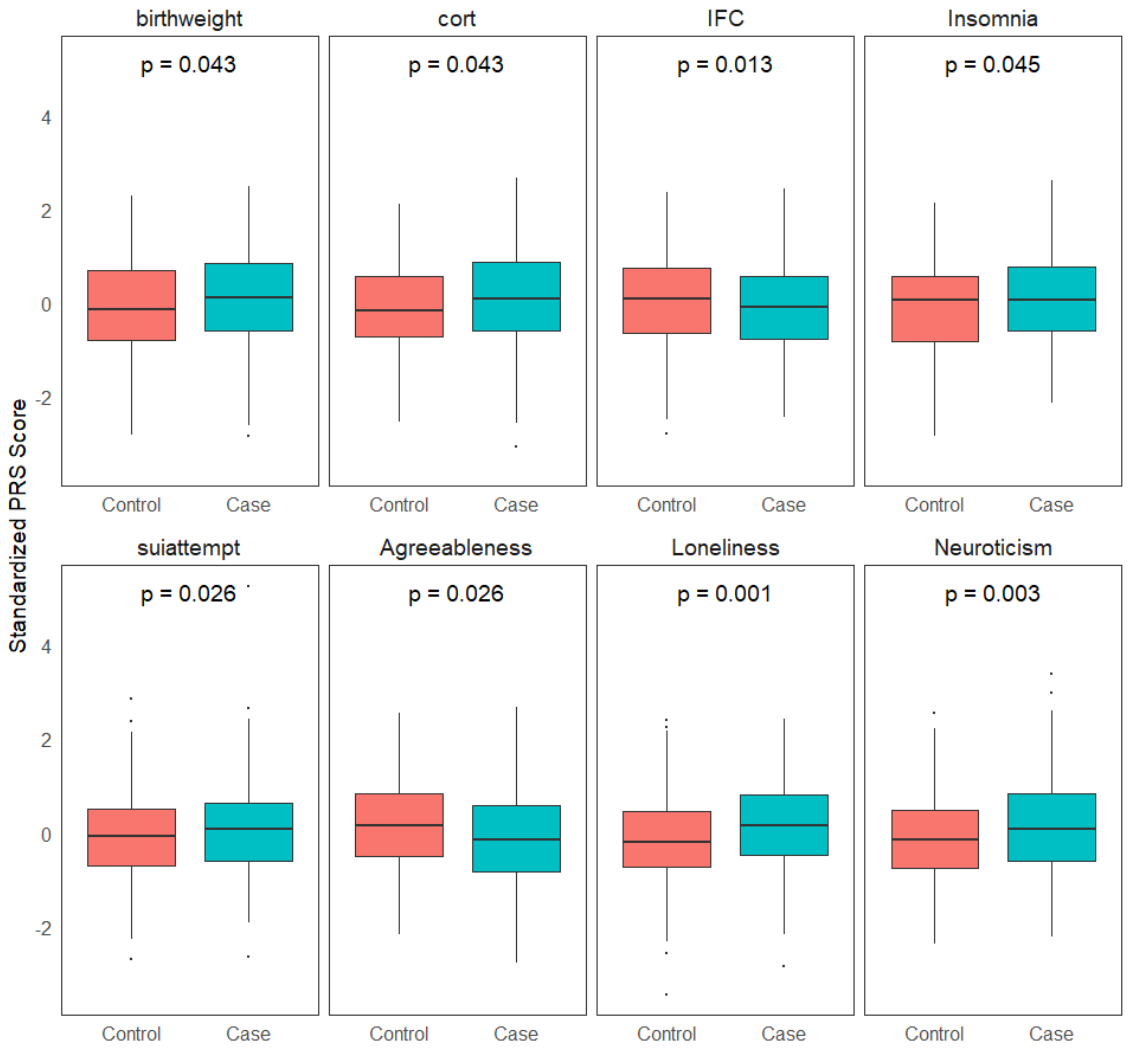


Figure 9. Distribution of standardized polygenic risk scores (PRSs) by anorexia nervosa (AN) in the female-only case-control analysis*. Boxplots show PRS values for: agreeableness, birthweight, cortisol (cort), insulin fold change (IFC), insomnia, loneliness, neuroticism, and suicide attempt (suiattempt). After FDR correction, only loneliness (FDR = 0.039) and neuroticism (FDR = 0.043) remained statistically significant.*

4.6 Family-Based Analysis: Polygenic Transmission Disequilibrium Test (pTDT)

To further explore the hereditary component of AN, pTDT was applied. Among the 31 traits assessed, two polygenic scores showed significant over-transmission: occupational attainment and birthweight (**Figure 10A** and **10C**). In the full trio sample, birthweight PRS showed robust over-transmission (p = 0.0007), while occupational attainment PRS also showed a moderate but significant effect (p = 0.0162). Following FDR correction, the birthweight PRS remained significant (FDR = 0.023), whereas the occupational attainment PRS did not (FDR = 0.251).

Given the potential for confounding due to parental history of ED, a sensitivity analysis was performed excluding trios in which either parent reported a history of any ED diagnosis. Notably,

while this exclusion criterion may omit trios affected by ED subtypes other than AN, it ensures a more conservative estimation of inherited risk. The over-transmission of PRS for both birthweight (p = 0.0004) and occupational attainment (p = 0.045) remained significant in this filtered subset.

To account for multiple testing, FDR correction was applied across all traits in the subsample. After adjustment, the over-transmission of birthweight PRS remained statistically significant (FDR = 0.027), whereas the occupational attainment PRS did not retain significance (FDR = 0.842).

No other PRS across domains showed significant deviation from the expected transmission pattern. However, the pTDT for AN was close to significance (p = 0.062). The complete pTDT results, organized by domain, are visualized in **Figure 10** panels A–D.

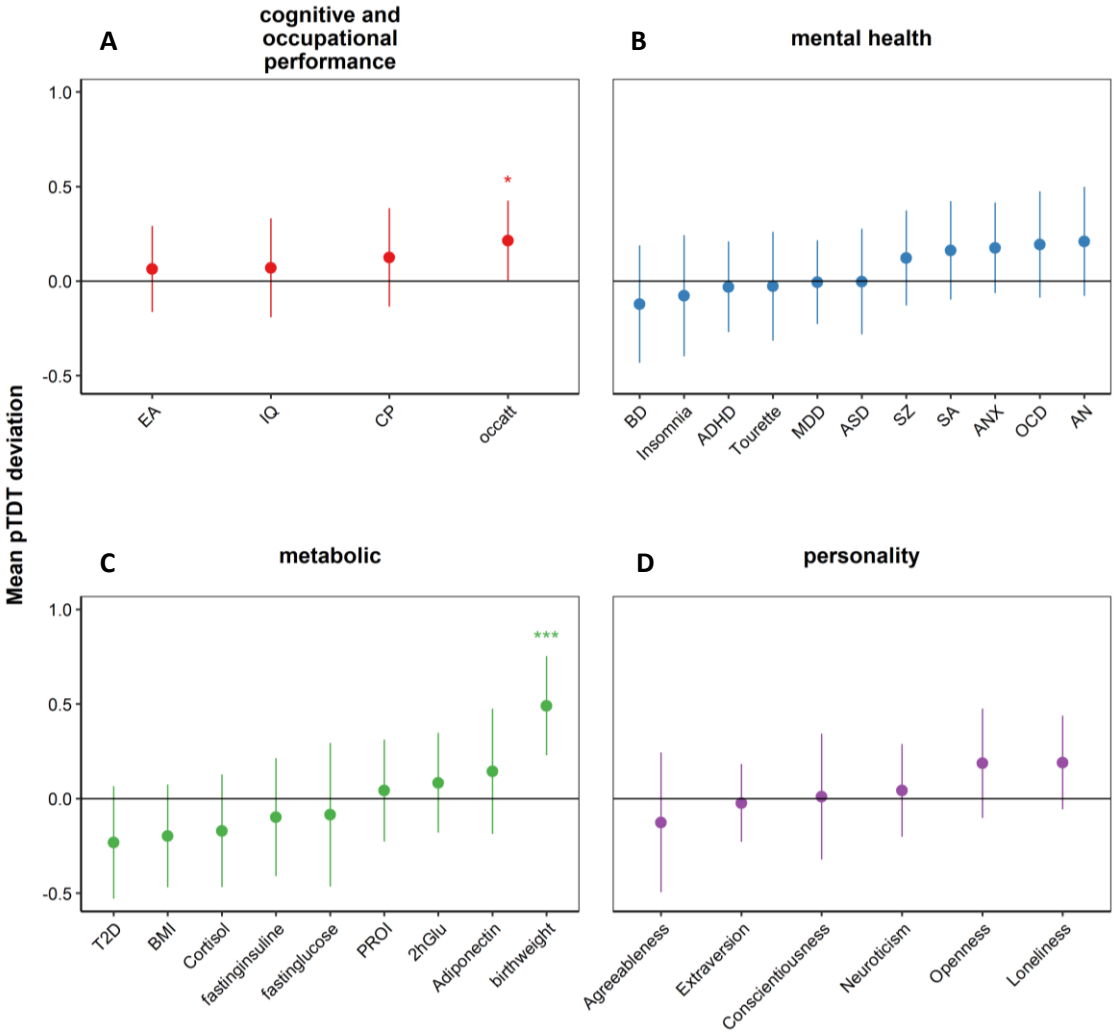


Figure 10. Polygenic transmission disequilibrium test (pTDT) analysis of polygenic risk scores (PRS) by domain. *Each subplot displays mean pTDT deviation, representing the average difference between the offspring PRS and the mid-parent PRS, for traits grouped into four domains: (A) cognitive and occupational performance, (B) mental health, (C) metabolic, and (D) personality. Error bars indicate 95% confidence intervals. Asterisks denote nominal statistical significance (* p < 0.05, *** p < 0.001). Trait abbreviations:*

2hGlu: 2-hour glucose; ADHD: attention-deficit/hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety; ASD: autism spectrum disorder; BD: bipolar disorder; BMI: body mass index; EA: educational attainment; IFC: insulin fold change; IQ: intelligence quotient; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; occatt: occupational attainment; PROI: proinsulin; suiattempt: suicide attempt; SZ: schizophrenia.

4.7 Clinical Features of Anorexia Nervosa

Here, the association between PRSs and clinical variability in AN was examined. These analyses aimed to identify genetic influences on specific phenotypic features beyond case-control status.

4.7.1 Body Mass Index

Analysis of lowest BMI as a continuous variable identified a nominally significant association with the neuroticism PRS (p = 0.007, FDR = 0.219) (**Figure 11**). This suggests a possible link between genetic liability for neuroticism and lesser weight loss during illness, although the result did not survive multiple testing correction.

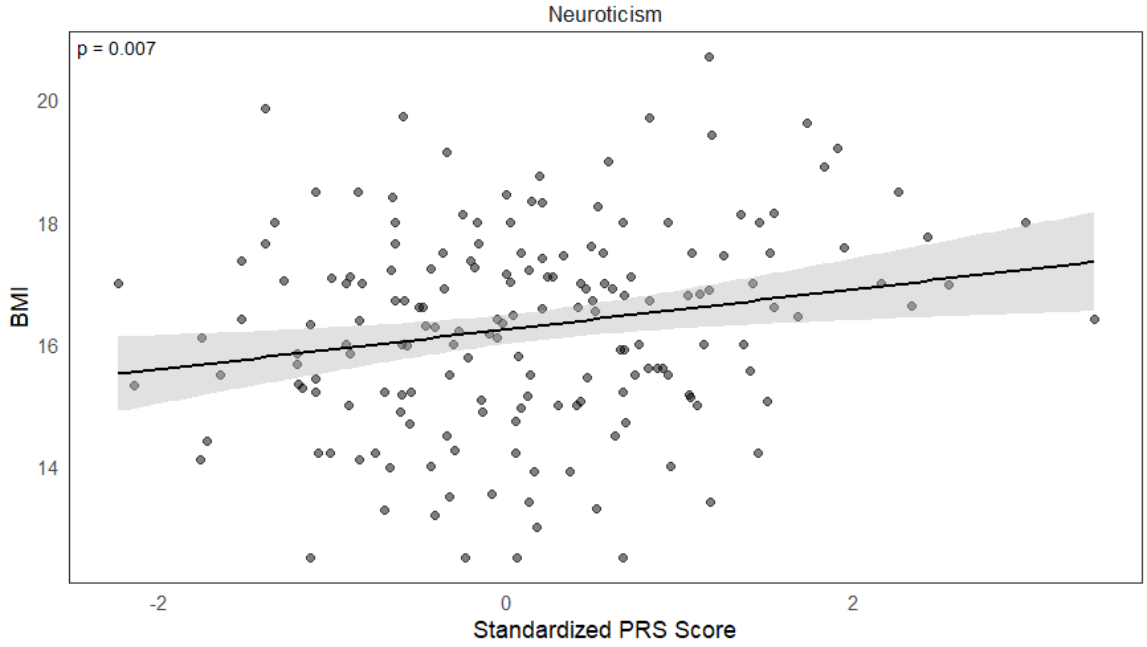


Figure 11. Scatter plots between standardized Polygenic Risk Score (PRS) for neuroticism and Body Mass Index (BMI). *The plot includes a linear regression line with 95% confidence interval (gray band). The association did not remain significant after FDR correction (FDR = 0.219).*

4.7.2 Severe depression

In patients with AN, two PRSs were nominally associated with the presence of comorbid MDD. The AN patients with severe depression had significantly lower PRS for extraversion (p = 0.036,

FDR = 0.521) and higher PRS for proinsulin (p = 0.023, FDR = 0.521) (**Figure 12**). However, neither association remained statistically significant after FDR correction.

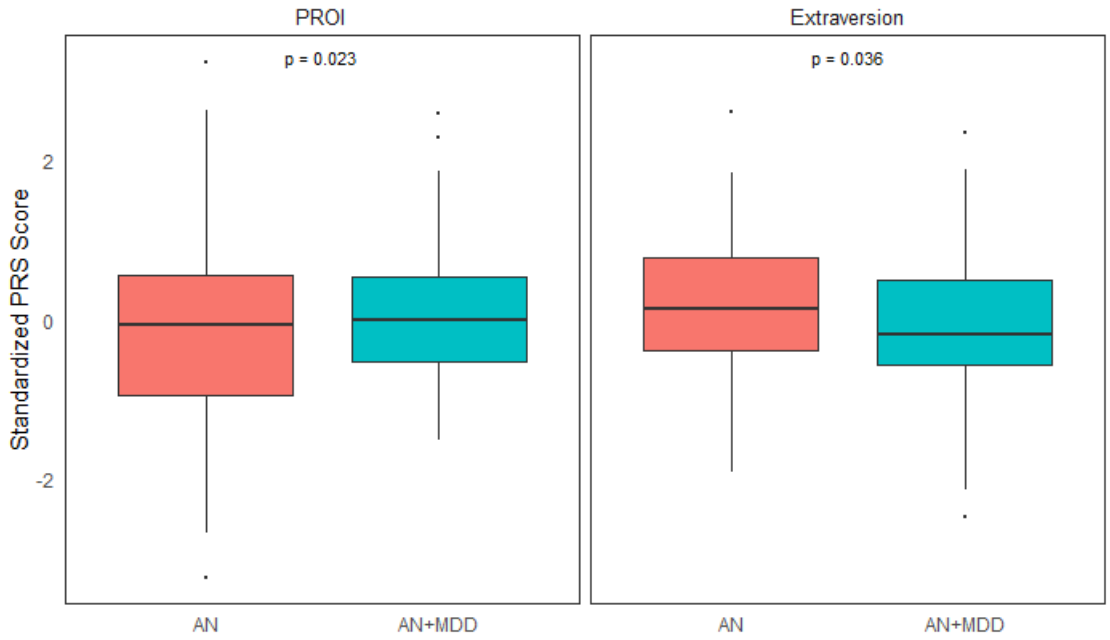


Figure 12. Distribution of standardized polygenic risk score (PRS) differences between anorexia nervosa (AN) patients with and without comorbid severe depression (MDD). *Box plots show PRS for proinsulin (PROI) and extraversion. Neither association remained statistically significant after FDR correction (FDR = 0.521 for both comparisons).*

4.7.3 Anxiety Symptoms

Trait and state anxiety were assessed using percentile scores derived from the STAIC scale. Nominal associations were observed between several PRSs and anxiety percentiles. For STAIC-state, the occupational attainment PRS was nominally associated (p = 0.049, FDR = 0.804) (**Figure 13A**). For STAIC-trait, nominal associations were identified with the MDD PRS (p = 0.034, FDR = 0.387) (**Figure 13B**) and the extraversion PRS (p = 0.023, FDR = 0.387) (**Figure 13C**). None of these associations remained significant after FDR correction.

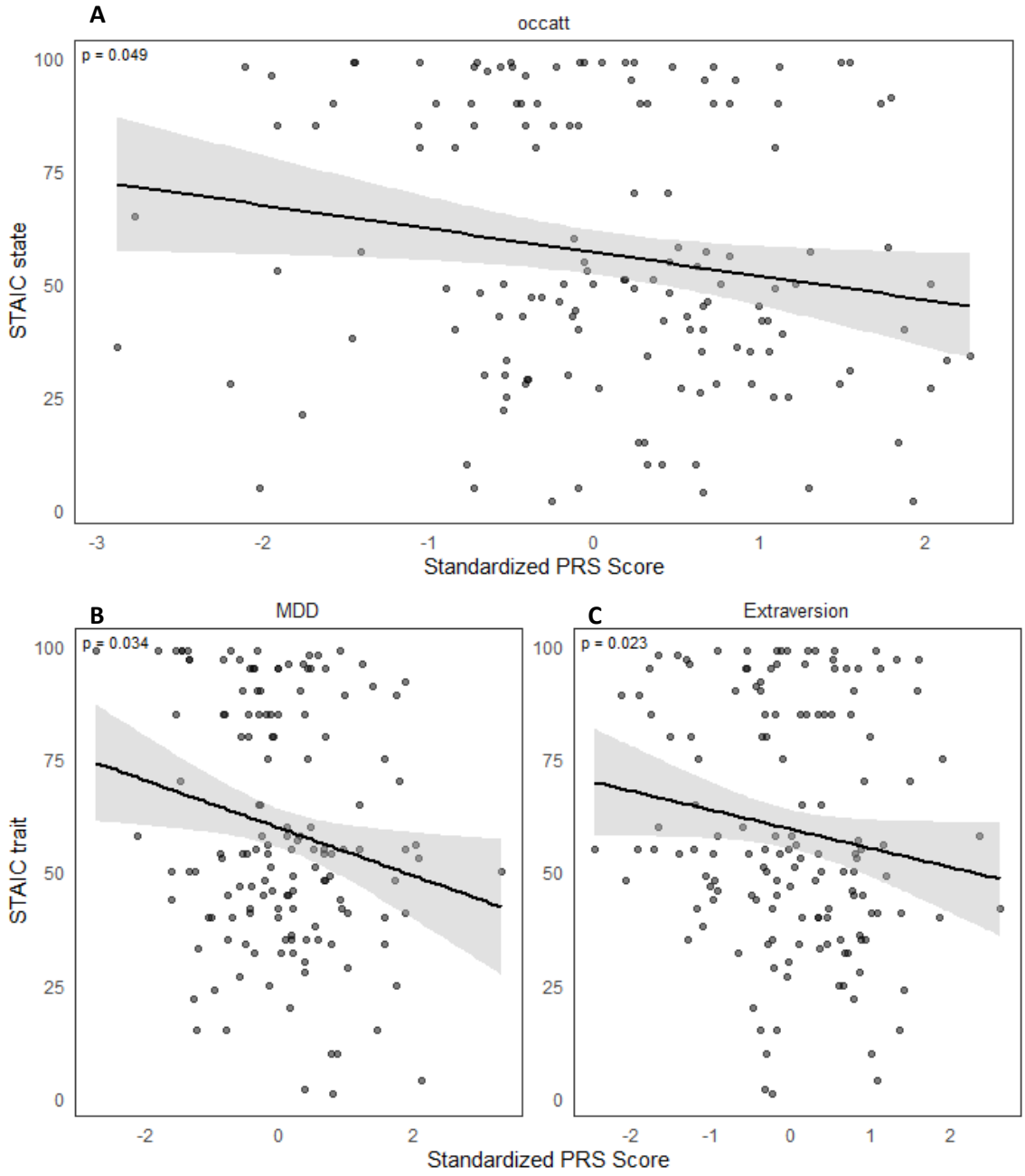


Figure 13. Scatter plots between standardized Polygenic Risk Score (PRS) and State-Trait Anxiety Inventory for Children (STAIC) anxiety percentiles. *(A) Occupational attainment PRS was nominally associated with STAIC-State anxiety. (B) Major depressive disorder (MDD) and (C) Extraversion PRSs were nominally associated with STAIC-Trait anxiety. Each plot includes a linear regression line with 95% confidence interval (gray band). None of the associations remained significant after FDR correction.*

4.7.4 Compulsive exercise

Five PRS showed nominal associations with compulsive exercise: cortisol, 2-hour glucose (2hGlu), OCD, extraversion and openness (all $p < 0.04$). However, none passed FDR correction (all FDR = 0.233), indicating limited evidence of polygenic contribution to this phenotype (**Figure 14**).

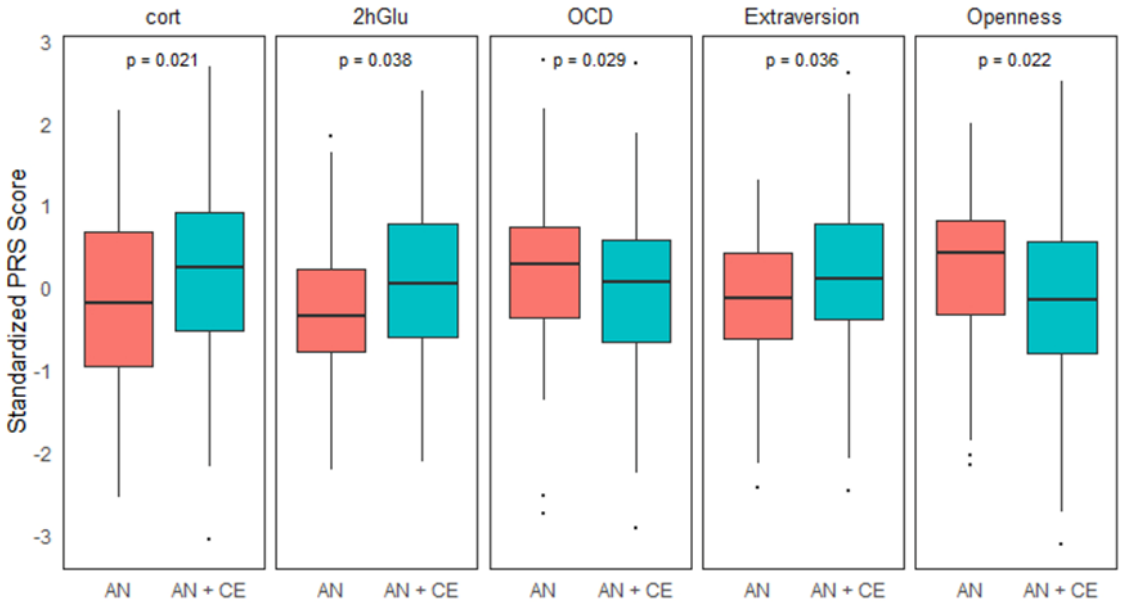


Figure 14. Distribution of standardized polygenic risk score (PRS) differences between anorexia nervosa (AN) patients and AN patients engaging in compulsive exercise (CE). *Box plots show PRS for cortisol (cort), 2-hour glucose (2hGlu), obsessive-compulsive disorder (OCD), extraversion and openness. After FDR correction, none of the associations remained statistically significant (FDR = 0.233).*

4.7.5 Number of hospitalizations

Nominal associations were observed between PRS and the number of hospitalizations. Individuals with more than one hospitalization exhibited higher PRS for birthweight (p = 0.018, FDR = 0.245) and fasting insulin (p = 0.008, FDR = 0.240), and lower scores for openness (p = 0.024, FDR = 0.245) (**Figure 15**).

Post-hoc pairwise comparisons showed that the fasting insulin PRS was significantly higher in individuals with more than one hospitalization compared to those with none (p = 0.022), and also higher compared to those with a single hospitalization (p = 0.008). Birthweight PRS showed a trend toward higher values in the >1 hospitalization group versus the no-hospitalization group (p = 0.052). For openness, PRS scores were lower in the group with more than one hospitalization compared to those with none (p = 0.053). None of these associations remained statistically significant after FDR correction.

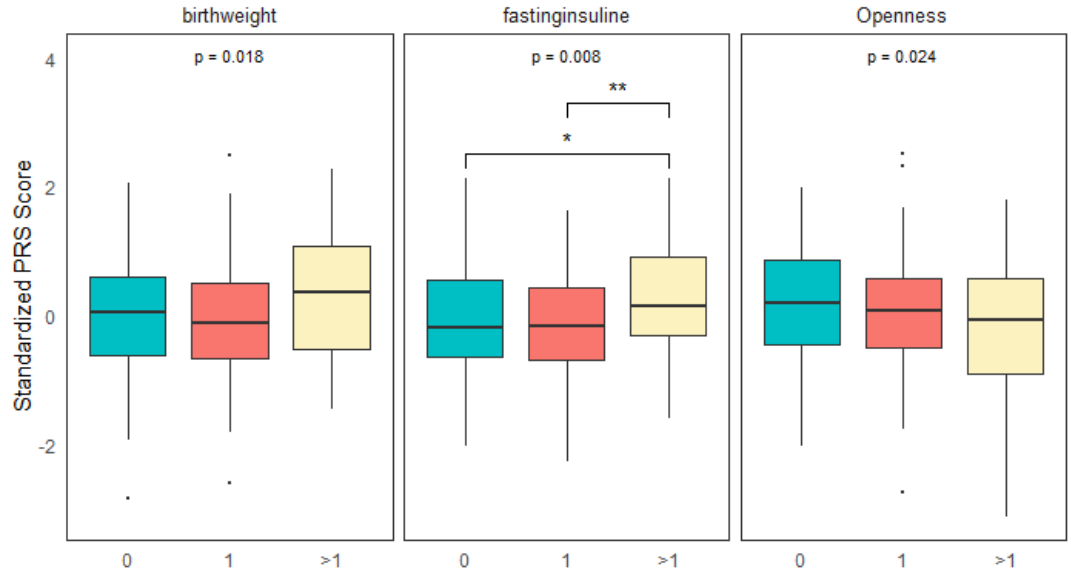


Figure 15. Polygenic risk score (PRS) differences across hospitalization frequency groups in anorexia nervosa (AN) patients. *Box plots showing standardized PRS for birthweight, fasting insulin, and openness across three hospitalization count groups: 0, 1, and >1. Overall p-values from linear models are displayed above each panel. For fasting insulin, post-hoc pairwise comparisons using estimated marginal means revealed significant differences between specific groups: * p < 0.05 and ** p < 0.01.*

4.7.6 Suicide attempt

Several PRSs were nominally associated with suicide attempt history, including those for anxiety (p = 0.028), BD (p = 0.024), IFC (p = 0.012), and suicide attempt PRS itself (p = 0.031) (**Figure 16**). These associations were not FDR-significant (FDR > 0.230).

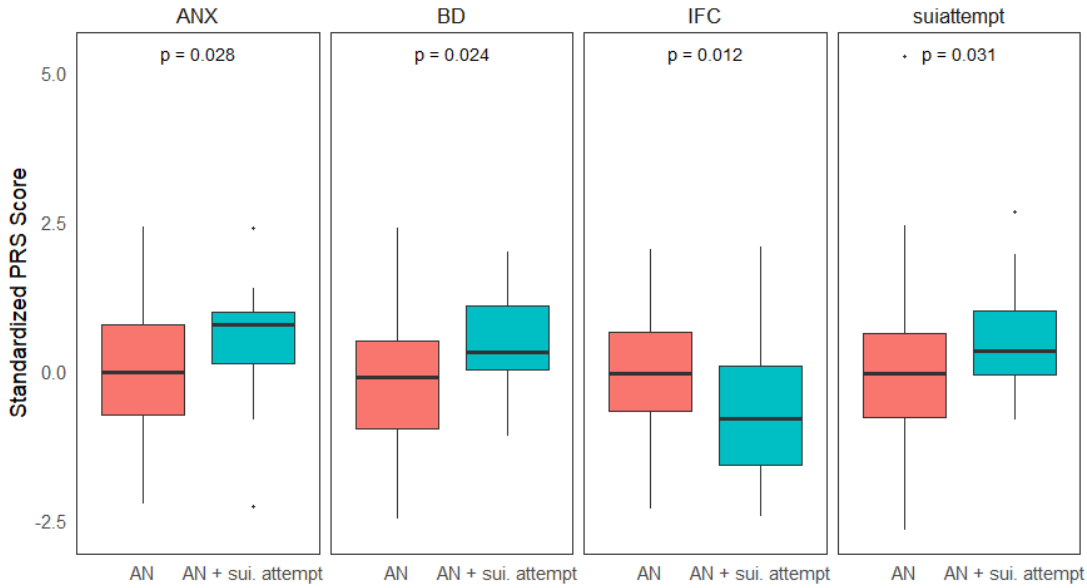


Figure 16. Distribution of standardized polygenic risk score (PRS) differences between anorexia nervosa (AN) patients and AN patients who attempted to commit suicide. *Box plots show PRS for anxiety (ANX), bipolar disorder (BD), insulin fold change (IFC) and suicide attempt (suiattempt). After FDR correction, none of the associations remained statistically significant (FDR > 0.230).*

4.8 PRS enrichment for biological processes

To identify the underlying biological mechanisms and provide functional interpretation of the results obtained in the association analysis, an enrichment analysis was performed on genes mapped from PRSs showing nominal significance.

To explore whether the associated PRSs across the different domains share similar biological processes, a Venn diagram was used to show the overlap of enriched GO terms identified by ClueGO across the four PRS domains: mental health, personality, metabolic, and cognitive and occupational performance (**Figure 17**).

A total of 88 GO terms were common to all four domains, pointing to a shared biological basis. These represented approximately 31% of the GO terms in the metabolic domain, 30% in personality, 40% in mental health, and over 81% in the cognitive and occupational performance domain. Beyond this core, the metabolic domain stood out for having the most unique terms, with 101 GO terms not shared with any other group, representing nearly 36% of its total. In contrast, the personality and mental health domains exhibited the highest pairwise overlap, sharing 53 GO terms, which corresponded to 18% and 24% of their respective GO terms. This suggests closer biological links between traits in these two domains.

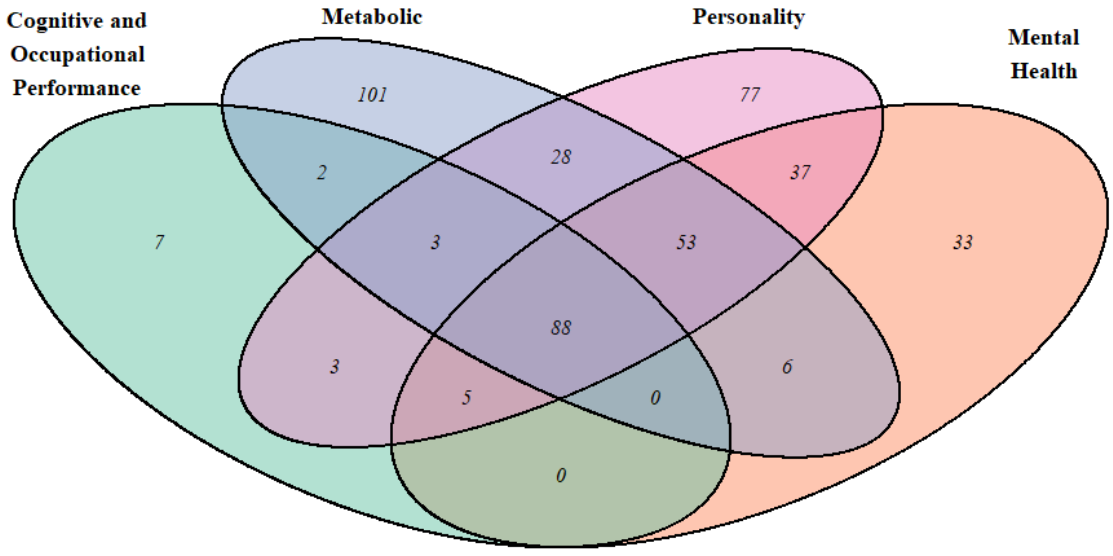


Figure 17. Venn diagram showing the number of enriched Gene Ontology (GO) terms overlapping between polygenic risk score (PRS) domains.

To identify shared biological processes across traits, GO terms enriched in at least 75% of the 18 significant PRSs identified in previous analyses were examined. The most frequent terms were

mainly related to nervous system development and function, including neuron development, synaptic transmission, and axon and dendrite growth (**Figure 18**).

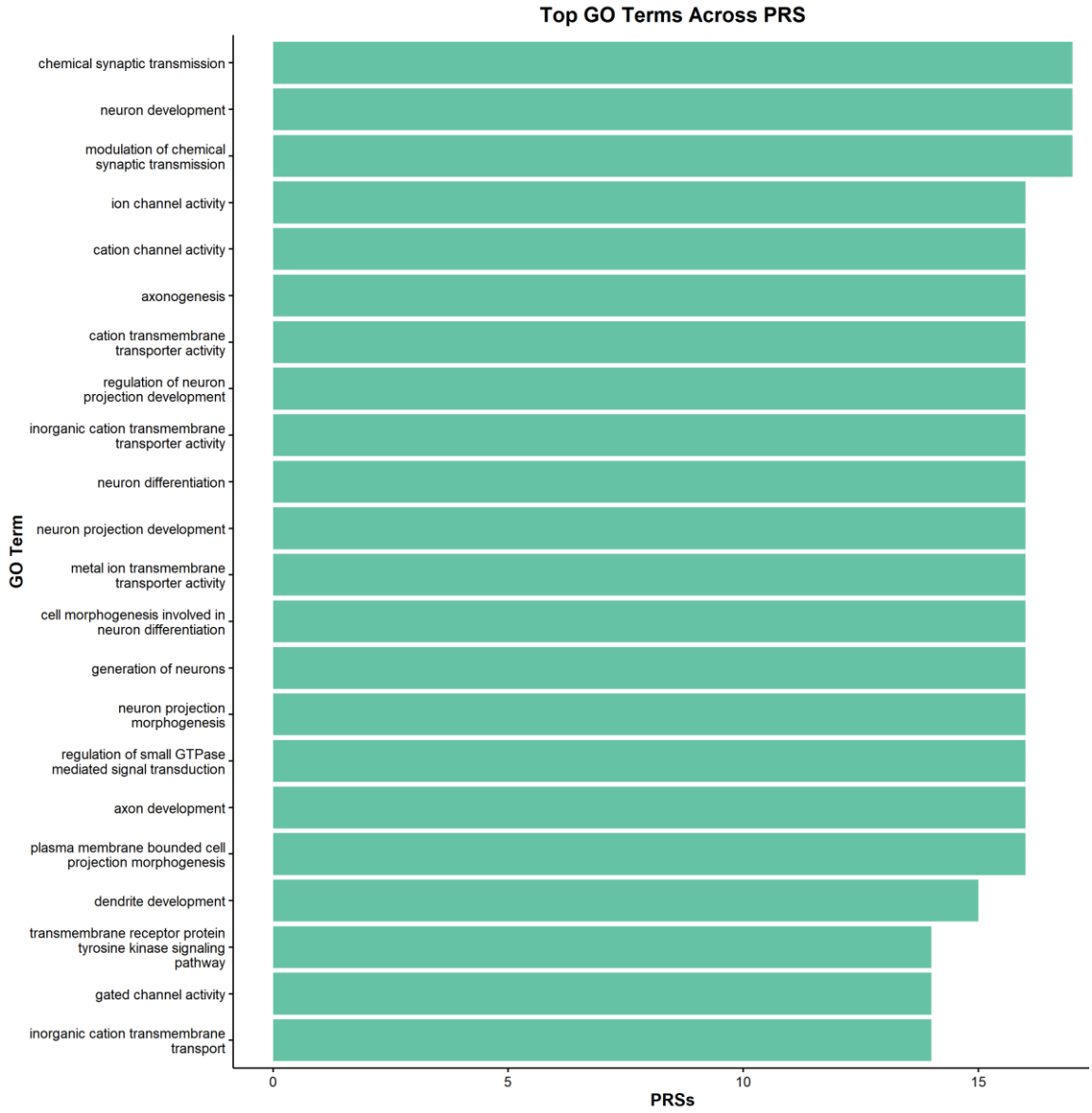


Figure 18. Shared Gene Ontology (GO) terms across polygenic risk scores (PRSs). *Bar plot showing the number of PRSs (out of 18) in which each GO term was found to be significantly enriched. Only GO terms enriched in at least 75% of the PRSs (i.e., in ≥14) are shown.*

To further explore the biological meaning of the GO terms shared across the four PRS domains, a ReViGO analysis was conducted to reduce redundancy and group similar terms. The resulting clusters revealed that approximately half of the enriched terms were related to neural and cellular organization or communication. These included processes such as synaptic signaling, neuron projection development, cytoskeleton organization, and signal transduction. Therefore, pointing to processes rooted in brain and cellular structure and function (**Figure 19**).

Figure 19. Tree map visualizing semantically clustered Gene Ontology (GO) biological processes enriched in polygenic risk scores (PRSs) across all four domains by ReViGO. *Cluster size corresponds to the frequency and significance of the terms. Approximately half of the enriched terms were related to neural and cellular organization or communication.*

5. DISCUSSION

Polygenic risk scores estimate an individual's genetic predisposition to a specific trait or phenotype by aggregating the effects of many common genetic variants. In recent years, GWAS have identified several SNPs associated with various psychiatric disorders, including AN, enabling the construction of PRSs as potential screening tools. When combined with clinical and environmental data, these scores can help identify individuals at elevated risk, supporting early intervention and tailored prevention strategies (Merner et al., 2024). Here, we evaluated how PRSs from several domains (personality traits, mental health, metabolic and cognitive and occupational performance traits) capture part of the genetic risk associated with AN, both in its heritability and clinical outcome (severity). To our knowledge, some of the PRSs used, particularly those related to metabolic and personality traits, have not been previously explored in the context of AN, thereby providing novel information about the disease. Additionally, we examined the correlation between the different PRSs and performed a gene set enrichment analysis to explore the biological processes involved in the polygenic nature of AN.

The most prominent associations were found within the personality domain, with higher PRS for loneliness and neuroticism in AN patients in the case-control study. These traits share a strong genetic correlation, observed both in our findings and previous literature (Abdellaoui et al., 2019). This indicates a tendency to experience negative emotions and being more prone to worry, self-doubt and emotional instability. Previous studies also reported significant genetic overlap between AN and neuroticism, reinforcing neuroticism's link to AN (Bang et al., 2023). Additionally, neuroticism PRS was also associated with clinical outcomes. There was a positive correlation between higher BMI and neuroticism, concurring with clinical studies that found this same interaction (Sutin & Terracciano, 2016). Interestingly, it mentioned that patients with high neuroticism were more focused on exercise and were more self-conscious about their appearance and weight. These genetic and behavioral predispositions may increase emotional vulnerability, particularly when weight loss goals are unmet, reinforcing cycles of disordered eating and severe AN symptoms.

Among other personality traits, several PRS were nominally associated with heritability and clinical severity of AN, including agreeableness, openness to experience and extraversion. For instance, when restricting the case-control study to only female participants, the agreeableness PRS reached statistical significance and was lower in AN patients. Although, to our knowledge, this genetic association has not been previously reported for AN, previous studies report a

negative genetic correlation between agreeableness and depression, anxiety and irritability (Gupta et al., 2024).

Openness reflects cognitive flexibility and willingness to engage with new experiences (de Moor et al., 2012). A lower PRS for openness suggests a genetically driven tendency towards rigidity, routine and resistance to change. This especially aligns with the cognitive rigidity commonly seen in AN (Rodgers et al., 2023) and could indicate more severe, chronic or treatment-resistant forms of AN. In our study, lower PRS for openness to experience was associated with higher levels of compulsive exercise and a greater number of hospitalizations. Compulsive exercise might indicate rigid adherence to routines, while multiple hospitalizations suggest a more chronic disease and difficulty adapting to therapeutic interventions. To sum up, a lower openness PRS likely reflects greater cognitive and behavioural rigidity, stronger adherence to maladaptive routines and reduced engagement in treatment.

For extraversion, lower PRS was associated with comorbid MDD and higher trait anxiety in individuals with AN. These associations align with previous genetic findings showing negative genetic correlations between extraversion and internalizing disorders such as depression and anxiety (Gupta et al., 2024). This pattern likely reflects a genetic predisposition toward social withdrawal, low positive affect, and emotional inhibition. In contrast, higher extraversion PRS was observed in patients engaging in compulsive exercise, potentially reflecting increased goal orientation, energy, or perfectionistic traits, as previously suggested (Bills et al., 2025). Overall, lower extraversion PRS appears to reflect a vulnerability to comorbidities such as depression and anxiety, while higher scores may relate to more active or driven behavioural profiles within AN.

Overall, these findings highlight the importance of personality-related genetic predispositions in shaping both the onset and clinical trajectory of AN. Traits such as high neuroticism and low openness may contribute to emotional vulnerability, cognitive rigidity, and behavioral patterns that sustain disordered eating. Moreover, the associations between extraversion, compulsive exercise, and comorbid depression suggest that distinct personality profiles may influence symptom expression and comorbidity risk.

In the mental health domain, endophenotypes such as insomnia and suicide attempts showed nominal associations with AN risk. A higher insomnia PRS was linked to increased odds of AN, suggesting that genetic liability to insomnia may contribute to susceptibility. This complements findings where the reverse direction was tested, showing that genetic liability to AN was associated with the insomnia phenotype (Wilcox et al., 2024). Together, these complementary findings might suggest a potential bidirectional or shared genetic basis between insomnia and

AN. For suicide attempt PRS, associations were observed with both case status and history of suicide attempts, aligning with known genetic overlap between AN and suicidality (Hambleton et al., 2022; Thornton et al., 2016).

The mental health domain also includes psychopathologies, which include the AN PRS itself. Although we did not find any significant associations between the AN PRS and clinical variables, other psychopathology PRS were associated with clinical severity, but not with AN risk itself. Specifically, higher PRS for ANX and BD were associated with a history of suicide attempts, and the MDD PRS was associated with greater anxiety severity. This supports the idea that comorbid diagnoses in AN are associated with increased severity and poorer clinical outcomes (Hambleton et al., 2022). These findings align with previous studies which support that the PRS for MDD is higher in individuals with anxiety, particularly in those with comorbid depression and anxiety, reflecting a shared genetic liability between these disorders (Coombes et al., 2023; Kendler et al., 2022). Moreover, PRS for ANX and BD are consistently higher in individuals with a history of suicide attempts, as shown in multiple studies across psychiatric populations (Fujikane et al., 2024; Mullins et al., 2022; Otsuka et al., 2023). While AN-specific evidence is limited, genetic correlation studies reveal substantial overlap between AN, MDD, anxiety, and BD (Bang et al., 2023; Yilmaz et al., 2023). This suggests that similar polygenic mechanisms may contribute to comorbidities and clinical severity, including suicide risk.

However, some results did not align with expectations. OCD PRS was significantly lower in AN patients with compulsive exercise, despite previous genetic research suggesting shared liability between AN and OCD for this behavior. A recent study proposed that compulsive exercise may reflect overlapping genetic risk for both disorders (Yilmaz et al., 2023). Our findings may differ due to limited power and should be interpreted with caution, as most of the presented associations were only nominally significant.

In the metabolic domain, consistent associations were observed across analyses. Notably, the birthweight PRS was significantly over-transmitted from parents to affected individuals and nominally higher in AN cases, particularly females. Moreover, higher birthweight PRS was associated with a higher number of hospitalizations. Interestingly, our findings appear to diverge from several epidemiological reports. Studies have shown that low birth weight (<2500 g) is modestly associated with increased risk for AN (Chatwin et al., 2023), particularly among males, while higher birth weight (>4500 g) is linked to a reduced risk (Papini et al., 2024). Although these findings suggest that reduced fetal growth may contribute to AN vulnerability, the genetic association we observe with higher birth weight PRS challenges a purely phenotypic

interpretation. It is important to recognize that PRS reflects genetic propensity, not the actual birth weight recorded at birth. A fetus with a genetically higher birth weight potential may still be born small due to maternal malnutrition, placental insufficiency, or other environmental stressors. It is also worth noting that individual birthweight data was unavailable and thus birth weight PRS and birth weight could not be tested for correlation. Additionally, few studies have explored the genetic link between birthweight and mental health; one found associations with ADHD, suicide attempts, post-traumatic stress disorder, and cognitive outcomes, but not with any other psychopathology (ASD, BP, OCD, MDD, or SZ) (Orri et al., 2021). Therefore, further research is needed to clarify the role of birthweight genetics in AN and related psychopathologies.

Further, we identified several associations between polygenic scores related to insulin and cortisol regulation and both the risk and severity of AN. Traits linked to increased insulin sensitivity, such as lower IFC PRS, were associated with AN diagnosis. In contrast, polygenic scores indicating insulin resistance, such as higher fasting insulin, proinsulin, and 2-hour glucose PRS, were associated with markers of illness severity, including comorbid depression, compulsive exercise, and increased hospitalizations. Additionally, higher cortisol PRS predicted both the onset and severity of AN. Although the relationship between AN and cortisol has been well established at the phenotypic level, with multiple studies confirming that patients with AN (Haines, 2023; Misra & Klibanski, 2014), no studies have addressed the shared genetic factors between the two.

These findings suggest that while insulin sensitivity may predispose to AN, insulin resistance and altered stress physiology could contribute to its chronicity and severity. This dual pattern partially mirrors previous genetic studies, which revealed both positive and negative genetic correlations between insulin-related traits and psychiatric disorders depending on the biological pathways involved (Adams et al., 2021; Fanelli et al., 2022). However, other population-based studies, found limited evidence for metabolic PRS associations with disordered eating symptoms, indicating that these genetic relationships may be context-dependent or specific to clinical populations (Abdulkadir et al., 2022). Altogether, our results highlight the need for further studies to clarify the causal nature and directionality of these metabolic influences in AN.

Collectively, these results support the hypothesis of metabolic contributions to AN etiology, particularly involving glucose homeostasis, HPA axis, and early growth genetics.

Finally, within the cognitive and occupational performance domain, occupational attainment was over-transmitted in the pTDT and was associated with lower levels of anxiety, as measured by

the STAIC state scale. These findings may reflect traits commonly observed in individuals with AN, such as perfectionism and obsessionality (Longo et al., 2024), potentially characterizing a subset of patients as high-achievers. Lam et al. (2022) identified genomic "meta-loci" showing local genetic correlations between cognitive traits and psychopathology. In particular, one meta-locus (CTP-3) showed a negative genetic correlation between cognitive performance and AN, suggesting that higher cognitive performance in this region may be protective for AN. However, the cognitive trait examined in that study (task performance) differs from our occupational attainment phenotype, and it remains uncertain whether this correlation would hold across traits. Further research is needed to clarify the role of cognitive and occupational performance traits in AN risk. Interestingly, the CTP-3 meta-locus is enriched for genes involved in carbohydrate and lipid metabolism, including the insulin receptor gene (*INSR*), supporting the conceptualization of AN as partly a metabolic disorder (Lam et al., 2022). This aligns with our findings implicating glucose and insulin traits, suggesting convergence between cognitive and metabolic factors in this potential AN subtype.

Overall, enrichment analysis revealed that significant PRS across domains converge on shared biological processes especially related to neural development, synaptic signaling, and cytoskeleton organization. This pattern suggests that, despite originating from diverse trait domains, many genetic risk variants influence AN through shared neurobiological pathways. Previous studies support this interpretation, showing that genes associated with AN are enriched in biological functions central to brain development and synaptic communication (Johnson et al., 2023). In parallel, other studies highlight the role of neurotrophic factors such as BDNF, which not only regulate neuronal growth and plasticity but also contribute to metabolic processes like appetite control and energy balance (Cao et al., 2024). Together, these findings indicate that AN risk involves both neural and metabolic systems, further supporting the reconceptualization of AN as a metabo-psychiatric disorder (Cao et al., 2024; Johnson et al., 2023).

5.1 Strengths and limitations

This study presents several strengths. First, it integrates both case-control and family-based designs, providing complementary information into the genetic architecture of AN. By combining PRS-based case-control analyses with the pTDT, we were able to evaluate not only group-level associations but also patterns of intergenerational transmission, thereby enhancing the robustness of our findings. Additionally, we assessed a broad range of phenotypes across psychiatric, personality, metabolic, and cognitive domains, allowing for a rich characterization of polygenic influences on AN.

The use of a female-only sub-analysis was another strength, given the well-established epidemiological predominance of AN among females. Restricting the sample to female participants improved statistical power and revealed additional significant associations that were not detected in the full sample. Encouragingly, all PRSs that were significant in the full sample remained significant in the female-only analysis, suggesting that the overall trends in genetic risk remain consistent across sex-stratified models.

Despite these strengths, several limitations must be acknowledged. One of the primary limitations is the underrepresentation of male participants, which limited our ability to evaluate sex-specific effects and replicate findings in the male subgroup. While the female-only analysis provided new information, excluding males entirely from the interpretation constrains the generalizability of our findings to the full spectrum of individuals affected by AN. Future studies with larger and more balanced samples are needed to clarify potential sex differences in genetic architecture.

Second, although the PRS associations with clinical features such as BMI, compulsive exercise, and hospitalization provide some leads, none of these associations survived correction for multiple testing. This limits the current utility of PRS for clinically actionable stratification of AN severity or subtypes. Larger samples and multivariate modeling approaches may eventually allow for the development of composite PRS-based classifiers with greater predictive power.

Additionally, this study was conducted in individuals of European ancestry and employed the HRC r1.1 2016 reference panel for genotype imputation, which is optimized for this population. While this alignment enhances imputation accuracy and internal validity, it limits the external generalizability of the findings to more diverse populations. Most publicly available GWAS used for PRS construction also derive from predominantly European cohorts, which further compounds the issue of ancestral bias (Fatumo et al., 2022). As a result, polygenic scores generated in this study may not perform equally well in non-European populations. Addressing this disparity will require greater inclusion of diverse ancestry groups in future GWAS, such as those supported by initiatives like TOPMed (Taliun et al., 2021), H3Africa (Matovu et al., 2014), and the China Kadoorie Biobank (Z. Chen et al., 2011).

Another limitation relates to the variability in GWAS discovery sample sizes across traits, which affects the predictive power of each PRS. For example, traits with larger and better-powered GWAS, such as birthweight (Warrington et al., 2019), are likely to yield stronger associations simply due to increased statistical resolution. This imbalance may confound comparisons across domains and obscure true biological relevance for less-powered traits.

Finally, although PRSs help explain the genetic liability, their clinical application remains limited. PRSs currently explain only a small proportion of the variance in most psychiatric disorders, including AN. Their predictive accuracy is insufficient for reliable risk prediction or individual-level prognosis, particularly given the complex interplay between genetic, environmental, and psychosocial factors (Merner et al., 2024; Murray et al., 2021).

In summary, while this study contributes to our understanding of the polygenic nature of anorexia nervosa, it also highlights the need for more powerful, diverse, and integrative approaches. Future work should focus on increasing sample sizes, improving diversity, and including multivariate and longitudinal designs to increase the clinical relevance of polygenic risk profiling in eating disorders.

In conclusion, our findings suggest that personality, mental health, metabolic, and cognitive PRS each contribute to the polygenic architecture of AN. While some associations were only nominally significant, key traits like neuroticism, loneliness, and birthweight showed robust signals across multiple analyses. These results highlight the multifaceted genetics of AN and support further integration of polygenic profiling in understanding and stratifying ED risk.

6. CONCLUSIONS

This thesis explored the polygenic architecture of AN by analyzing the contribution of PRS from mental health, personality, cognitive, and metabolic domains to disease risk, heritability, and clinical heterogeneity. The study was structured around both base-control and family-based designs, following a multi-level approach to genetic risk in AN. The main conclusions are:

- PRS from mental health (insomnia, suicide attempt), personality (agreeableness, loneliness, neuroticism), and metabolic (birthweight, cortisol, IFC) domains have a significant influence on the disease's onset in females. Particularly, insomnia, IFC, loneliness, and neuroticism are identified as contributors to overall disease liability, supporting the utility of PRS in identifying genetic risk factors for AN.

- Birthweight and occupational attainment PRS are over-transmitted from parents to affected offspring, indicating a heritable component of AN and suggesting preferential transmission of specific polygenic risk.

- Clinical heterogeneity in AN is partly explained by PRS variation across personality, mental health, and metabolic domains, linking genetic profiles to symptom expression and disease severity.

- Functional enrichment analysis indicates that PRS associated with AN diagnosis, heritability, or severity converge on biological processes related to neurodevelopmental pathways. This suggests that common biological pathways influence both disease risk and clinical expression.

Taken together, these results provide new evidence that the genetic liability to AN is multifactorial and involves a mix of mental health, personality, cognitive, and metabolic factors. This thesis demonstrates that PRS can be useful tools for quantifying genetic risk and understanding clinical diversity in AN.

7. REFERENCES

Abdellaoui, A., Chen, H., Willemsen, G., Ehli, E. A., Davies, G. E., Verweij, K. J. H., Nivard, M. G., de Geus, E. J. C., Boomsma, D. I., & Cacioppo, J. T. (2019). Associations between loneliness and personality are mostly driven by a genetic association with Neuroticism. *Journal of Personality*, *87*(2), 386–397. https://doi.org/10.1111/jopy.12397

Abdulkadir, M., Hübel, C., Herle, M., Loos, R. J. F., Breen, G., Bulik, C. M., & Micali, N. (2022). Eating disorder symptoms and their associations with anthropometric and psychiatric polygenic scores. *European Eating Disorders Review*, *30*(3), 221–236. https://doi.org/10.1002/erv.2889

Adams, D. M., Reay, W. R., Geaghan, M. P., & Cairns, M. J. (2021). Investigation of glycaemic traits in psychiatric disorders using Mendelian randomisation revealed a causal relationship with anorexia nervosa. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *46*(6), 1093–1102. https://doi.org/10.1038/s41386-020-00847-w

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.). American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Anderson, C. A., Pettersson, F. H., Clarke, G. M., Cardon, L. R., Morris, A. P., & Zondervan, K. T. (2010). Data quality control in genetic case-control association studies. *Nature Protocols*, *5*(9), 1564. https://doi.org/10.1038/NPROT.2010.116

Bang, L., Bahrami, S., Hindley, G., Smeland, O. B., Rødevand, L., Jaholkowski, P. P., Shadrin, A., Connell, K. S. O., Frei, O., Lin, A., Rahman, Z., Cheng, W., Parker, N., Fan, C. C., Dale, A. M., Djurovic, S., Bulik, C. M., & Andreassen, O. A. (2023). Genome-wide analysis of anorexia nervosa and major psychiatric disorders and related traits reveals genetic overlap and identifies novel risk loci for anorexia nervosa. *Translational Psychiatry*, *13*(1). https://doi.org/10.1038/S41398-023-02585-1

Bills, E., Muir, S. R., Stackpole, R., & Egan, S. J. (2025). Perfectionism and compulsive exercise: a systematic review and preliminary meta-analysis. *Eating and Weight Disorders : EWD*, *30*(1), 5. https://doi.org/10.1007/s40519-024-01704-1

Bindea, G., Mlecnik, B., Hackl, H., Charoentong, P., Tosolini, M., Kirilovsky, A., Fridman, W.-H., Pagès, F., Trajanoski, Z., & Galon, J. (2009). ClueGO: a Cytoscape plug-in to decipher functionally grouped gene ontology and pathway annotation networks. *Bioinformatics*, *25*(8), 1091–1093. https://doi.org/10.1093/bioinformatics/btp101

Blackburn, A. N., Blondell, L., Kos, M. Z., Blackburn, N. B., Peralta, J. M., Peter, •, Stevens, T., Lehman, D. M., Blangero, J., & Göring, H. H. H. (2020). Genotype phasing in pedigrees using whole-genome sequence data. *European Journal of Human Genetics*, *28*, 790–803. https://doi.org/10.1038/s41431-020-0574-3

Boutari, C., Pappas, P. D., Mintziori, G., Nigdelis, M. P., Athanasiadis, L., Goulis, D. G., & Mantzoros, C. S. (2020). The effect of underweight on female and male reproduction. *Metabolism: Clinical and Experimental*, *107*, 154229. https://doi.org/10.1016/j.metabol.2020.154229

Broadaway, K. A., Yin, X., Williamson, A., Parsons, V. A., Wilson, E. P., Moxley, A. H., Vadlamudi, S., Varshney, A., Jackson, A. U., Ahuja, V., Bornstein, S. R., Corbin, L. J., Delgado, G. E., Dwivedi, O. P., Fernandes Silva, L., Frayling, T. M., Grallert, H., Gustafsson, S., Hakaste, L., … Mohlke, K. L. (2023). Loci for insulin processing and secretion provide insight into type 2 diabetes risk. *The American Journal of Human Genetics*, *110*(2), 284–299. https://doi.org/10.1016/j.ajhg.2023.01.002

Bulik, C. M., Coleman, J. R. I., Hardaway, J. A., Breithaupt, L., Watson, H. J., Bryant, C. D., & Breen, G. (2022). Genetics and neurobiology of eating disorders. *Nature Neuroscience*, *25*(5), 543–554. https://doi.org/10.1038/s41593-022-01071-z

Bulik, C., Yilmaz, Z., & HArdaway, A. (2015). Genetics and epigenetics of eating disorders. *Advances in Genomics and Genetics*, 131. https://doi.org/10.2147/AGG.S55776

Bycroft, C., Freeman, C., Petkova, D., Band, G., Elliott, L. T., Sharp, K., Motyer, A., Vukcevic, D., Delaneau, O., O'Connell, J., Cortes, A., Welsh, S., Young, A., Effingham, M., McVean, G., Leslie, S., Allen, N., Donnelly, P., & Marchini, J. (2018). The UK Biobank resource with deep phenotyping and genomic data. *Nature 2018 562:7726*, *562*(7726), 203–209. https://doi.org/10.1038/s41586-018-0579-z

Cao, J., Gorwood, P., Ramoz, N., & Viltart, O. (2024). The Role of Central and Peripheral Brain-Derived Neurotrophic Factor (BDNF) as a Biomarker of Anorexia Nervosa Reconceptualized as a Metabo-Psychiatric Disorder. *Nutrients*, *16*(16). https://doi.org/10.3390/nu16162617

Chatwin, H., Holde, K., Yilmaz, Z., Larsen, J. T., Albiñana, C., Vilhjálmsson, B. J., Mortensen, P. B., Thornton, L. M., Bulik, C. M., & Petersen, L. V. (2023). Risk factors for anorexia nervosa: A population-based investigation of sex differences in polygenic risk and early life exposures. *International Journal of Eating Disorders*, *56*(9), 1703–1716. https://doi.org/10.1002/eat.23997

Chen, Y., Lu, T., Pettersson-Kymmer, U., Stewart, I. D., Butler-Laporte, G., Nakanishi, T., Cerani, A., Liang, K. Y. H., Yoshiji, S., Willett, J. D. S., Su, C. Y., Raina, P., Greenwood, C. M. T., Farjoun, Y., Forgetta, V., Langenberg, C., Zhou, S., Ohlsson, C., & Richards, J. B. (2023). Genomic atlas of the plasma metabolome prioritizes metabolites implicated in human diseases. *Nature Genetics 2023 55:1*, *55*(1), 44–53. https://doi.org/10.1038/s41588-022-01270-1

Chen, Z., Chen, J., Collins, R., Guo, Y., Peto, R., Wu, F., & Li, L. (2011). China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. *International Journal of Epidemiology*, *40*(6), 1652–1666. https://doi.org/10.1093/ije/dyr120

Choi, S. W., Mak, T. S. H., & O'Reilly, P. F. (2020). Tutorial: a guide to performing polygenic risk score analyses. In *Nature Protocols* (Vol. 15, Issue 9, pp. 2759–2772). Nature Research. https://doi.org/10.1038/s41596-020-0353-1

Coombes, B. J., Landi, I., Choi, K. W., Singh, K., Fennessy, B., Jenkins, G. D., Batzler, A., Pendegraft, R., Nunez, N. A., Gao, Y. N., Ryu, E., Wickramaratne, P., Weissman, M. M., Regeneron Genetics Center, Pathak, J., Mann, J. J., Smoller, J. W., Davis, L. K., Olfson, M., … Biernacka, J. M. (2023). The genetic contribution to the comorbidity of depression and anxiety: a multi-site electronic health records study of almost 178 000 people. *Psychological Medicine*, *53*(15), 7368–7374. https://doi.org/10.1017/S0033291723000983

Cost, J., Krantz, M. J., & Mehler, P. S. (2020). Medical complications of anorexia nervosa. *Cleveland Clinic Journal of Medicine*, *87*(6), 361–366. https://doi.org/10.3949/CCJM.87A.19084

Das, S., Forer, L., Schönherr, S., Sidore, C., Locke, A. E., Kwong, A., Vrieze, S. I., Chew, E. Y., Levy, S., McGue, M., Schlessinger, D., Stambolian, D., Loh, P. R., Iacono, W. G., Swaroop, A., Scott, L. J., Cucca, F., Kronenberg, F., Boehnke, M., … Fuchsberger, C. (2016). Next-generation genotype imputation service and methods. *Nature Genetics*, *48*(10), 1284–1287. https://doi.org/10.1038/NG.3656

Davies, G., Lam, M., Harris, S. E., Trampush, J. W., Luciano, M., Hill, W. D., Hagenaars, S. P., Ritchie, S. J., Marioni, R. E., Fawns-Ritchie, C., Liewald, D. C. M., Okely, J. A., Ahola-Olli, A. V., Barnes, C. L. K., Bertram, L., Bis, J. C., Burdick, K. E., Christoforou, A., Derosse, P., … Deary, I. J. (2018). Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. *Nature Communications 2018 9:1*, *9*(1), 1–16. https://doi.org/10.1038/s41467-018-04362-x

Day, F. R., Ong, K. K., & Perry, J. R. B. (2018). Elucidating the genetic basis of social interaction and isolation. *Nature Communications 2018 9:1*, *9*(1), 1–6. https://doi.org/10.1038/s41467-018-04930-1

de Moor, M. H. M., Costa, P. T., Terracciano, A., Krueger, R. F., de Geus, E. J. C., Toshiko, T., Penninx, B. W. J. H., Esko, T., Madden, P. A. F., Derringer, J., Amin, N., Willemsen, G., Hottenga, J.-J., Distel, M. A., Uda, M., Sanna, S., Spinhoven, P., Hartman, C. A., Sullivan, P., … Boomsma, D. I. (2012). Meta-analysis of genome-wide association studies for personality. *Molecular Psychiatry*, *17*(3), 337–349. https://doi.org/10.1038/mp.2010.128

Demontis, D., Walters, G. B., Athanasiadis, G., Walters, R., Therrien, K., Nielsen, T. T., Farajzadeh, L., Voloudakis, G., Bendl, J., Zeng, B., Zhang, W., Grove, J., Als, T. D., Duan, J., Satterstrom, F. K., Bybjerg-Grauholm, J., Bækved-Hansen, M., Gudmundsson, O. O., Magnusson, S. H., … Børglum, A. D. (2023). Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nature Genetics 2023 55:2*, *55*(2), 198–208. https://doi.org/10.1038/s41588-022-01285-8

Docherty, A. R., Mullins, N., Ashley-Koch, A. E., Qin, X., Coleman, J. R. I., Shabalin, A., Kang, J. E., Murnyak, B., Wendt, F., Adams, M., Campos, A. I., DiBlasi, E., Fullerton, J. M., Kranzler, H. R., Bakian, A. V., Monson, E. T., Rentería, M. E., Walss-Bass, C., Andreassen, O. A., …

Ruderfer, D. M. (2023). GWAS Meta-Analysis of Suicide Attempt: Identification of 12 Genome-Wide Significant Loci and Implication of Genetic Risks for Specific Health Factors. *American Journal of Psychiatry*, *180*(10), 723–738. https://doi.org/10.1176/appi.ajp.21121266

Duncan, L., Yilmaz, Z., Gaspar, H., Walters, R., Goldstein, J., Anttila, V., Bulik-Sullivan, B., Ripke, S., Eating Disorders Working Group of the Psychiatric Genomics Consortium, Thornton, L., Hinney, A., Daly, M., Sullivan, P. F., Zeggini, E., Breen, G., & Bulik, C. M. (2017). Significant Locus and Metabolic Genetic Correlations Revealed in Genome-Wide Association Study of Anorexia Nervosa. *The American Journal of Psychiatry*, *174*(9), 850–858. https://doi.org/10.1176/appi.ajp.2017.16121402

Duncan, L., Yilmaz, Z., Gaspar, H., Walters, R., Goldstein, J., Anttila, V., Bulik-Sullivan, B., Ripke, S., Thornton, L., Hinney, A., Daly, M. J., Sullivan, P. F., Zeggini, E., Breen, G., Bulik, C. M., Duncan, L., Yilmaz, Z., Gaspar, H., Goldstein, J., … Bulik, C. M. (2017). Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. *American Journal of Psychiatry*, *174*(9), 850–858. https://doi.org/10.1176/APPI.AJP.2017.16121402

Fanelli, G., Franke, B., De Witte, W., Ruisch, I. H., Haavik, J., van Gils, V., Jansen, W. J., Vos, S. J. B., Lind, L., Buitelaar, J. K., Banaschewski, T., Dalsgaard, S., Serretti, A., Mota, N. R., Poelmans, G., & Bralten, J. (2022). Insulinopathies of the brain? Genetic overlap between somatic insulin-related and neuropsychiatric disorders. *Translational Psychiatry*, *12*(1), 59. https://doi.org/10.1038/s41398-022-01817-0

Fatumo, S., Chikowore, T., Choudhury, A., Ayub, M., Martin, A. R., & Kuchenbaecker, K. (2022). Diversity in Genomic Studies: A Roadmap to Address the Imbalance. *Nature Medicine*, *28*(2), 243. https://doi.org/10.1038/S41591-021-01672-4

Fujikane, D., Ohi, K., Kuramitsu, A., Takai, K., Muto, Y., Sugiyama, S., & Shioiri, T. (2024). Genetic correlations between suicide attempts and psychiatric and intermediate phenotypes adjusting for mental disorders. *Psychological Medicine*, *54*(3), 488–494. https://doi.org/10.1017/S0033291723002015

Garner, D. M., & Garfinkel, P. E. (1979). The Eating Attitudes Test: an index of the symptoms of anorexia nervosa. *Psychological Medicine*, *9*(2), 273–279. https://doi.org/10.1017/s0033291700030762

Ge, T., Chen, C. Y., Ni, Y., Feng, Y. C. A., & Smoller, J. W. (2019). Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nature Communications 2019 10:1*, *10*(1), 1–10. https://doi.org/10.1038/s41467-019-09718-5

Germain, N., Genteuil, C. D., Belleton, G., Da Silva, T. L., Exbrayat, C., Degas, F., Hammour, A., Gay, A., Ravey, B., Massoubre, C., & Galusca, B. (2023). Continuous glucose monitoring assessment in patients suffering from anorexia nervosa reveals chronic prolonged mild hypoglycemia all over the nycthemeron. *European Eating Disorders Review : The Journal of the Eating Disorders Association*, *31*(3), 402–412. https://doi.org/10.1002/erv.2963

Grove, J., Ripke, S., Als, T. D., Mattheisen, M., Walters, R. K., Won, H., Pallesen, J., Agerbo, E., Andreassen, O. A., Anney, R., Awashti, S., Belliveau, R., Bettella, F., Buxbaum, J. D., Bybjerg-Grauholm, J., Bækvad-Hansen, M., Cerrato, F., Chambert, K., Christensen, J. H., … Børglum, A. D. (2019). Identification of common genetic risk variants for autism spectrum disorder. *Nature Genetics*, *51*(3), 431–444. https://doi.org/10.1038/s41588-019-0344-8

Gupta, P., Galimberti, M., Liu, Y., Beck, S., Wingo, A., Wingo, T., Adhikari, K., Kranzler, H. R., Stein, M. B., Gelernter, J., & Levey, D. F. (2024). A genome-wide investigation into the underlying genetic architecture of personality traits and overlap with psychopathology. *Nature Human Behaviour*, *8*(11). https://doi.org/10.1038/s41562-024-01951-3

Haines, M. S. (2023). Endocrine complications of anorexia nervosa. *Journal of Eating Disorders*, *11*(1), 24. https://doi.org/10.1186/s40337-023-00744-9

Hambleton, A., Pepin, G., Le, A., Maloney, D., Aouad, P., Barakat, S., Boakes, R., Brennan, L., Bryant, E., Byrne, S., Caldwell, B., Calvert, S., Carroll, B., Castle, D., Caterson, I., Chelius, B., Chiem, L., Clarke, S., Conti, J., … Maguire, S. (2022). Psychiatric and medical comorbidities of eating disorders: findings from a rapid review of the literature. *Journal of Eating Disorders*, *10*(1). https://doi.org/10.1186/S40337-022-00654-2

Heruc, G. A., Little, T. J., Kohn, M. R., Madden, S., Clarke, S. D., Horowitz, M., & Feinle-Bisset, C. (2018). Effects of starvation and short-term refeeding on gastric emptying and postprandial blood glucose regulation in adolescent girls with anorexia nervosa. *American Journal of Physiology. Endocrinology and Metabolism*, *315*(4), E565–E573. https://doi.org/10.1152/ajpendo.00149.2018

Howard, D. M., Adams, M. J., Clarke, T. K., Hafferty, J. D., Gibson, J., Shirali, M., Coleman, J. R. I., Hagenaars, S. P., Ward, J., Wigmore, E. M., Alloza, C., Shen, X., Barbu, M. C., Xu, E. Y., Whalley, H. C., Marioni, R. E., Porteous, D. J., Davies, G., Deary, I. J., … McIntosh, A. M. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience 2019 22:3*, *22*(3), 343–352. https://doi.org/10.1038/s41593-018-0326-7

Huang, Q. Q., Wigdor, E. M., Malawsky, D. S., Campbell, P., Samocha, K. E., Chundru, V. K., Danecek, P., Lindsay, S., Marchant, T., Koko, M., Amanat, S., Bonfanti, D., Sheridan, E., Radford, E. J., Barrett, J. C., Wright, C. F., Firth, H. V., Warrier, V., Strudwick Young, A., … Martin, H. C. (2024). Examining the role of common variants in rare neurodevelopmental conditions. *Nature*, *636*(8042), 404–411. https://doi.org/10.1038/s41586-024-08217-y

International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS). (2018). Revealing the complex genetic architecture of obsessive–compulsive disorder using meta-analysis. *Molecular Psychiatry*, *23*(5), 1181–1188. https://doi.org/10.1038/mp.2017.154

Ismaylova, E., Nemoda, Z., & Booij, L. (2025). Brain serotonin, oxytocin, and their interaction: Relevance for eating disorders. *Journal of Psychopharmacology*, *39*(3), 187–200. https://doi.org/10.1177/02698811241309617

Jansen, P. R., Watanabe, K., Stringer, S., Skene, N., Bryois, J., Hammerschlag, A. R., de Leeuw, C. A., Benjamins, J. S., Muñoz-Manchado, A. B., Nagel, M., Savage, J. E., Tiemeier, H., White, T., 23andMe Research Team, Tung, J. Y., Hinds, D. A., Vacic, V., Wang, X., Sullivan, P. F., … Posthuma, D. (2019). Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. *Nature Genetics*, *51*(3), 394–403. https://doi.org/10.1038/s41588-018-0333-3

Johansson, T., Birgegård, A., Zhang, R., Bergen, S. E., Landén, M., Petersen, L. V., Bulik, C. M., & Hübel, C. (2022). Polygenic association with severity and long-term outcome in eating disorder cases. *Translational Psychiatry*, *12*(1), 61. https://doi.org/10.1038/s41398-022-01831-2

Johnson, J. S., Cote, A. C., Dobbyn, A., Sloofman, L. G., Xu, J., Cotter, L., Charney, A. W., Birgegård, A., Jordan, J., Kennedy, M., Landén, M., Maguire, S. L., Martin, N. G., Mortensen, P. B., Thornton, L. M., Bulik, C. M., & Huckins, L. M. (2023). Mapping anorexia nervosa genes to clinical phenotypes. *Psychological Medicine*, *53*(6), 2619–2633. https://doi.org/10.1017/S0033291721004554

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(7), 980–988. https://doi.org/10.1097/00004583-199707000-00021

Kendler, K. S., Ohlsson, H., Sundquist, J., & Sundquist, K. (2022). Risk for Mood, Anxiety, and Psychotic Disorders in Individuals at High and Low Genetic Liability for Bipolar Disorder and Major Depression. *JAMA Psychiatry*, *79*(11), 1102–1109. https://doi.org/10.1001/jamapsychiatry.2022.2873

Ko, H., Kim, S., Kim, K., Jung, S.-H., Shim, I., Cha, S., Lee, H., Kim, B., Yoon, J., Ha, T. H., Kwak, S., Kang, J. M., Lee, J.-Y., Kim, J., Park, W.-Y., Nho, K., Kim, D. K., Myung, W., & Won, H.-H. (2022). Genome-wide association study of occupational attainment as a proxy for cognitive reserve. *Brain : A Journal of Neurology*, *145*(4), 1436–1448. https://doi.org/10.1093/brain/awab351

Krug, I., Liu, S., Portingale, J., Croce, S., Dar, B., Obleada, K., Satheesh, V., Wong, M., & Fuller-Tyszkiewicz, M. (2025). A meta-analysis of mortality rates in eating disorders: An update of the literature from 2010 to 2024. *Clinical Psychology Review*, *116*, 102547. https://doi.org/10.1016/j.cpr.2025.102547

Laczkovics, C., Czernin, K., Carlitscheck, J., Zeiler, M., Schlund, P., Wunram, H. L., Lehmkuhl, G., & Krischer, M. (2023). Personality Disorder in Adolescent Patients with Anorexia Nervosa. *Psychopathology*, *56*(4), 268–275. https://doi.org/10.1159/000527555

Lagou, V., Jiang, L., Ulrich, A., Zudina, L., González, K. S. G., Balkhiyarova, Z., Faggian, A., Maina, J. G., Chen, S., Todorov, P. V, Sharapov, S., David, A., Marullo, L., Mägi, R., Rujan, R.-M., Ahlqvist, E., Thorleifsson, G., Gao, H., Evangelou, E., … Meta-Analysis of Glucose and Insulin-Related Traits Consortium (MAGIC). (2023). GWAS of random glucose in 476,326 individuals

provide insights into diabetes pathophysiology, complications and treatment stratification. *Nature Genetics*, *55*(9), 1448–1461. https://doi.org/10.1038/s41588-023-01462-3

Lam, M., Chen, C.-Y., Hill, W. D., Xia, C., Tian, R., Levey, D. F., Gelernter, J., Stein, M. B., Hatoum, A. S., Huang, H., Malhotra, A. K., Runz, H., Ge, T., & Lencz, T. (2022). Collective genomic segments with differential pleiotropic patterns between cognitive dimensions and psychopathology. *Nature Communications*, *13*(1), 6868. https://doi.org/10.1038/s41467-022-34418-y

Lee, J. J., Wedow, R., Okbay, A., Kong, E., Maghzian, O., Zacher, M., Nguyen-Viet, T. A., Bowers, P., Sidorenko, J., Karlsson Linnér, R., Fontana, M. A., Kundu, T., Lee, C., Li, H., Li, R., Royer, R., Timshel, P. N., Walters, R. K., Willoughby, E. A., … Cesarini, D. (2018). Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nature Genetics*, *50*(8), 1112–1121. https://doi.org/10.1038/s41588-018-0147-3

Loh, P.-R., Danecek, P., Palamara, P. F., Fuchsberger, C., A Reshef, Y., K Finucane, H., Schoenherr, S., Forer, L., McCarthy, S., Abecasis, G. R., Durbin, R., & L Price, A. (2016). Reference-based phasing using the Haplotype Reference Consortium panel. *Nature Genetics*, *48*(11), 1443–1448. https://doi.org/10.1038/ng.3679

Longo, P., Bevione, F., Amodeo, L., Martini, M., Panero, M., & Abbate-Daga, G. (2024). Perfectionism in anorexia nervosa: Associations with clinical picture and personality traits. *Clinical Psychology & Psychotherapy*, *31*(1). https://doi.org/10.1002/cpp.2931

Ma, Y., & Zhou, X. (2021). Genetic prediction of complex traits with polygenic scores: a statistical review. *Trends in Genetics*, *37*(11), 995–1011. https://doi.org/10.1016/j.tig.2021.06.004

Mandelli, L., Draghetti, S., Albert, U., De Ronchi, D., & Atti, A.-R. (2020). Rates of comorbid obsessive-compulsive disorder in eating disorders: A meta-analysis of the literature. *Journal of Affective Disorders*, *277*, 927–939. https://doi.org/10.1016/j.jad.2020.09.003

Marchini, J., & Howie, B. (2010). Genotype imputation for genome-wide association studies. *Nature Reviews Genetics*, *11*(7), 499–511. https://doi.org/10.1038/nrg2796

Marees, A. T., de Kluiver, H., Stringer, S., Vorspan, F., Curis, E., Marie-Claire, C., & Derks, E. M. (2018). A tutorial on conducting genome-wide association studies: Quality control and statistical analysis. *International Journal of Methods in Psychiatric Research*, *27*(2). https://doi.org/10.1002/mpr.1608

Mas, S., Plana, M. T., Castro-Fornieles, J., Gassó, P., Lafuente, A., Moreno, E., Martinez, E., Milà, M., & Lazaro, L. (2013). Common genetic background in anorexia nervosa and obsessive compulsive disorder: Preliminary results from an association study. *Journal of Psychiatric Research*, *47*(6), 747–754. https://doi.org/10.1016/j.jpsychires.2012.12.015

Matovu, E., Bucheton, B., Chisi, J., Enyaru, J., Hertz-Fowler, C., Koffi, M., Macleod, A., Mumba, D., Sidibe, I., Simo, G., Simuunza, M., Mayosi, B., Ramesar, R., Mulder, N., Ogendo, S., Mocumbi, A. O., Hugo-Hamman, C., Ogah, O., El Sayed, A., … Rotimi, C. (2014). Enabling the

genomic revolution in Africa. *Science*, *344*(6190), 1346–1348. https://doi.org/10.1126/science.1251546

Mayo-Martínez, L., Rupérez, F. J., Martos-Moreno, G. Á., Graell, M., Barbas, C., Argente, J., & García, A. (2021). Unveiling Metabolic Phenotype Alterations in Anorexia Nervosa through Metabolomics. *Nutrients*, *13*(12), 4249. https://doi.org/10.3390/nu13124249

McCarthy, S., Das, S., Kretzschmar, W., Delaneau, O., Wood, A. R., Teumer, A., Kang, H. M., Fuchsberger, C., Danecek, P., Sharp, K., Luo, Y., Sidore, C., Kwong, A., Timpson, N., Koskinen, S., Vrieze, S., Scott, L. J., Zhang, H., Mahajan, A., … Marchini, J. (2016). A reference panel of 64,976 haplotypes for genotype imputation. *Nature Genetics*, *48*(10), 1279–1283. https://doi.org/10.1038/ng.3643

Merner, A. R., Trotter, P. M., Ginn, L. A., Bach, J., Freedberg, K. J., Soda, T., Storch, E. A., Pereira, S., & Lázaro-Muñoz, G. (2024). Psychiatric polygenic risk scores: Experience, hope for utility, and concerns among child and adolescent psychiatrists. *Psychiatry Research*, *339*, 116080. https://doi.org/10.1016/j.psychres.2024.116080

Misra, M., & Klibanski, A. (2014). Endocrine consequences of anorexia nervosa. *The Lancet. Diabetes & Endocrinology*, *2*(7), 581–592. https://doi.org/10.1016/S2213-8587(13)70180-3

Mullins, N., Forstner, A. J., O'Connell, K. S., Coombes, B., Coleman, J. R. I., Qiao, Z., Als, T. D., Bigdeli, T. B., Børte, S., Bryois, J., Charney, A. W., Drange, O. K., Gandal, M. J., Hagenaars, S. P., Ikeda, M., Kamitaki, N., Kim, M., Krebs, K., Panagiotaropoulou, G., … Andreassen, O. A. (2021). Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nature Genetics*, *53*(6), 817–829. https://doi.org/10.1038/s41588-021-00857-4

Mullins, N., Kang, J., Campos, A. I., Coleman, J. R. I., Edwards, A. C., Galfalvy, H., Levey, D. F., Lori, A., Shabalin, A., Starnawska, A., Su, M.-H., Watson, H. J., Adams, M., Awasthi, S., Gandal, M., Hafferty, J. D., Hishimoto, A., Kim, M., Okazaki, S., … Striker, R. (2022). Dissecting the Shared Genetic Architecture of Suicide Attempt, Psychiatric Disorders, and Known Risk Factors. *Biological Psychiatry*, *91*(3), 313–327. https://doi.org/10.1016/j.biopsych.2021.05.029

Murray, G. K., Lin, T., Austin, J., McGrath, J. J., Hickie, I. B., & Wray, N. R. (2021). Could Polygenic Risk Scores Be Useful in Psychiatry? *JAMA Psychiatry*, *78*(2), 210. https://doi.org/10.1001/jamapsychiatry.2020.3042

Nagel, M., Jansen, P. R., Stringer, S., Watanabe, K., de Leeuw, C. A., Bryois, J., Savage, J. E., Hammerschlag, A. R., Skene, N. G., Muñoz-Manchado, A. B., 23andMe Research Team, White, T., Tiemeier, H., Linnarsson, S., Hjerling-Leffler, J., Polderman, T. J. C., Sullivan, P. F., van der Sluis, S., & Posthuma, D. (2018). Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nature Genetics*, *50*(7), 920–927. https://doi.org/10.1038/s41588-018-0151-7

Orri, M., Pingault, J.-B., Turecki, G., Nuyt, A.-M., Tremblay, R. E., Côté, S. M., & Geoffroy, M.-C. (2021). Contribution of birth weight to mental health, cognitive and socioeconomic outcomes: two-sample Mendelian randomisation. *The British Journal of Psychiatry : The Journal of Mental Science*, *219*(3), 507–514. https://doi.org/10.1192/bjp.2021.15

Otowa, T., Hek, K., Lee, M., Byrne, E. M., Mirza, S. S., Nivard, M. G., Bigdeli, T., Aggen, S. H., Adkins, D., Wolen, A., Fanous, A., Keller, M. C., Castelao, E., Kutalik, Z., Van der Auwera, S., Homuth, G., Nauck, M., Teumer, A., Milaneschi, Y., … Hettema, J. M. (2016). Meta-analysis of genome-wide association studies of anxiety disorders. *Molecular Psychiatry*, *21*(10), 1391–1399. https://doi.org/10.1038/mp.2015.197

Otsuka, I., Galfalvy, H., Guo, J., Akiyama, M., Rujescu, D., Turecki, G., Hishimoto, A., & Mann, J. J. (2023). Mapping the genetic architecture of suicide attempt and suicide death using polygenic risk scores for clinically-related psychiatric disorders and traits. *Psychological Medicine*, *53*(6), 2689–2697. https://doi.org/10.1017/S0033291721004700

Paolacci, S., Kiani, A. K., Manara, E., Beccari, T., Ceccarini, M. R., Stuppia, L., Chiurazzi, P., Dalla Ragione, L., & Bertelli, M. (2020). Genetic contributions to the etiology of anorexia nervosa: New perspectives in molecular diagnosis and treatment. *Molecular Genetics & Genomic Medicine*, *8*(7), e1244. https://doi.org/10.1002/mgg3.1244

Papini, N. M., Presseller, E., Bulik, C. M., Holde, K., Larsen, J. T., Thornton, L. M., Albiñana, C., Vilhjálmsson, B. J., Mortensen, P. B., Yilmaz, Z., & Petersen, L. V. (2024). Interplay of polygenic liability with birth-related, somatic, and psychosocial factors in anorexia nervosa risk: a nationwide study. *Psychological Medicine*, *54*(9), 2073–2086. https://doi.org/10.1017/S0033291724000175

Plana, M. T., Torres, T., Rodríguez, N., Boloc, D., Gassó, P., Moreno, E., Lafuente, A., Castro-Fornieles, J., Mas, S., & Lazaro, L. (2019). Genetic variability in the serotoninergic system and age of onset in anorexia nervosa and obsessive-compulsive disorder. *Psychiatry Research*, *271*, 554–558. https://doi.org/10.1016/j.psychres.2018.12.019

Puckett, L., Grayeb, D., Khatri, V., Cass, K., & Mehler, P. (2021). A comprehensive review of complications and new findings associated with anorexia nervosa. *Journal of Clinical Medicine*, *10*(12). https://doi.org/10.3390/JCM10122555

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A. R., Bender, D., Maller, J., Sklar, P., De Bakker, P. I. W., Daly, M. J., & Sham, P. C. (2007). PLINK: a tool set for whole-genome association and population-based linkage analyses. *American Journal of Human Genetics*, *81*(3), 559–575. https://doi.org/10.1086/519795

R Core Team. (2025). *R: A Language and Environment for Statistical Computing*. https://www.R-project.org/

Rodgers, R. F., Smith, K., & Murray, S. B. (2023). Cognitive rigidity and restrictive eating disorders: Delineating the impact of low weight, low fat, weight suppression, acute negative energy balance, and chronic restriction. *The International Journal of Eating Disorders*, *56*(7), 1323–1328. https://doi.org/10.1002/eat.23937

Sarsani, V., Brotman, S. M., Xianyong, Y., Fernandes Silva, L., Laakso, M., & Spracklen, C. N. (2024). A cross-ancestry genome-wide meta-analysis, fine-mapping, and gene prioritization approach to characterize the genetic architecture of adiponectin. *HGG Advances*, *5*(1), 100252. https://doi.org/10.1016/j.xhgg.2023.100252

Savage, J. E., Jansen, P. R., Stringer, S., Watanabe, K., Bryois, J., de Leeuw, C. A., Nagel, M., Awasthi, S., Barr, P. B., Coleman, J. R. I., Grasby, K. L., Hammerschlag, A. R., Kaminski, J. A., Karlsson, R., Krapohl, E., Lam, M., Nygaard, M., Reynolds, C. A., Trampush, J. W., … Posthuma, D. (2018). Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nature Genetics*, *50*(7), 912–919. https://doi.org/10.1038/s41588-018-0152-6

Shannon, P., Markiel, A., Ozier, O., Baliga, N. S., Wang, J. T., Ramage, D., Amin, N., Schwikowski, B., & Ideker, T. (2003). Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Research*, *13*(11), 2498–2504. https://doi.org/10.1101/gr.1239303

Smith, A. R., Zuromski, K. L., & Dodd, D. R. (2018). Eating disorders and suicidality: what we know, what we don't know, and suggestions for future research. *Current Opinion in Psychology*, *22*, 63–67. https://doi.org/10.1016/j.copsyc.2017.08.023

Södersten, P., Bergh, C., Leon, M., & Zandian, M. (2016). Dopamine and anorexia nervosa. *Neuroscience and Biobehavioral Reviews*, *60*, 26–30. https://doi.org/10.1016/j.neubiorev.2015.11.003

Spielberger, C. D., Edwards, C. D., Montouri, J., & Lushene, R. (2012). State-Trait Anxiety Inventory for Children. In *PsycTESTS Dataset*. https://doi.org/10.1037/t06497-000

Supek, F., Bošnjak, M., Škunca, N., & Šmuc, T. (2011). REVIGO summarizes and visualizes long lists of gene ontology terms. *PloS One*, *6*(7), e21800. https://doi.org/10.1371/journal.pone.0021800

Sutin, A. R., & Terracciano, A. (2016). Personality traits and body mass index: Modifiers and mechanisms. *Psychology & Health*, *31*(3), 259–275. https://doi.org/10.1080/08870446.2015.1082561

Suzuki, K., Hatzikotoulas, K., Southam, L., Taylor, H. J., Yin, X., Lorenz, K. M., Mandla, R., Huerta-Chagoya, A., Melloni, G. E. M., Kanoni, S., Rayner, N. W., Bocher, O., Arruda, A. L., Sonehara, K., Namba, S., Lee, S. S. K., Preuss, M. H., Petty, L. E., Schroeder, P., … Zeggini, E. (2024). Genetic drivers of heterogeneity in type 2 diabetes pathophysiology. *Nature 2024 627:8003*, *627*(8003), 347–357. https://doi.org/10.1038/s41586-024-07019-6

Taliun, D., Harris, D. N., Kessler, M. D., Carlson, J., Szpiech, Z. A., Torres, R., Taliun, S. A. G., Corvelo, A., Gogarten, S. M., Kang, H. M., Pitsillides, A. N., LeFaive, J., Lee, S. been, Tian, X., Browning, B. L., Das, S., Emde, A. K., Clarke, W. E., Loesch, D. P., … Abecasis, G. R. (2021). Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. *Nature 2021 590:7845*, *590*(7845), 290–299. https://doi.org/10.1038/s41586-021-03205-y

Tam, V., Patel, N., Turcotte, M., Bossé, Y., Paré, G., & Meyre, D. (2019). Benefits and limitations of genome-wide association studies. *Nature Reviews Genetics*, *20*(8), 467–484. https://doi.org/10.1038/s41576-019-0127-1

Thornton, L. M., Welch, E., Munn-Chernoff, M. A., Lichtenstein, P., & Bulik, C. M. (2016). Anorexia Nervosa, Major Depression, and Suicide Attempts: Shared Genetic Factors. *Suicide and Life-Threatening Behavior*, *46*(5), 525–534. https://doi.org/10.1111/sltb.12235

Treasure, J., Duarte, T. A., & Schmidt, U. (2020). Eating disorders. *The Lancet*, *395*(10227), 899–911. https://doi.org/10.1016/S0140-6736(20)30059-3

Trubetskoy, V., Pardiñas, A. F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T. B., Bryois, J., Chen, C.-Y., Dennison, C. A., Hall, L. S., Lam, M., Watanabe, K., Frei, O., Ge, T., Harwood, J. C., Koopmans, F., Magnusson, S., Richards, A. L., Sidorenko, J., … van Os, J. (2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature*, *604*(7906), 502–508. https://doi.org/10.1038/s41586-022-04434-5

Udo, T., & Grilo, C. M. (2019). Psychiatric and medical correlates of DSM-5 eating disorders in a nationally representative sample of adults in the United States. *International Journal of Eating Disorders*, *52*(1), 42–50. https://doi.org/10.1002/eat.23004

Uffelmann, E., Huang, Q. Q., Munung, N. S., de Vries, J., Okada, Y., Martin, A. R., Martin, H. C., Lappalainen, T., & Posthuma, D. (2021). Genome-wide association studies. *Nature Reviews Methods Primers*, *1*(1). https://doi.org/10.1038/S43586-021-00056-9

Ulloa, R. E., Ortiz, S., Higuera, F., Nogales, I., Fresán, A., Apiquian, R., Cortés, J., Arechavaleta, B., Foulliux, C., Martínez, P., Hernández, L., Domínguez, E., & de la Peña, F. (2006). Interrater reliability of the Spanish version of Schedule for Affective Disorders and Schizophrenia for SchoolAge Children-Present and Lifetime version (K-SADS-PL). *Actas Espanolas de Psiquiatria*, *34*(1), 36–40. http://www.ncbi.nlm.nih.gov/pubmed/16525903

van Eeden, A. E., van Hoeken, D., & Hoek, H. W. (2021). Incidence, prevalence and mortality of anorexia nervosa and bulimia nervosa. *Current Opinion in Psychiatry*, *34*(6), 515–524. https://doi.org/10.1097/YCO.0000000000000739

Warrington, N. M., Beaumont, R. N., Horikoshi, M., Day, F. R., Helgeland, Ø., Laurin, C., Bacelis, J., Peng, S., Hao, K., Feenstra, B., Wood, A. R., Mahajan, A., Tyrrell, J., Robertson, N. R., Rayner, N. W., Qiao, Z., Moen, G.-H., Vaudel, M., Marsit, C. J., … Freathy, R. M. (2019). Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors. *Nature Genetics*, *51*(5), 804–814. https://doi.org/10.1038/s41588-019-0403-1

Watson, H. J., Yilmaz, Z., Thornton, L. M., Hübel, C., Coleman, J. R. I., Gaspar, H. A., Bryois, J., Hinney, A., Leppä, V. M., Mattheisen, M., Medland, S. E., Ripke, S., Yao, S., Giusti-Rodríguez, P., Hanscombe, K. B., Purves, K. L., Adan, R. A. H., Alfredsson, L., Ando, T., … Bulik, C. M. (2019). Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nature Genetics*, *51*(8), 1207–1214. https://doi.org/10.1038/s41588-019-0439-2

Weiner, D. J., Wigdor, E. M., Ripke, S., Walters, R. K., Kosmicki, J. A., Grove, J., Samocha, K. E., Goldstein, J. I., Okbay, A., Bybjerg-Grauholm, J., Werge, T., Hougaard, D. M., Taylor, J., Skuse, D., Devlin, B., Anney, R., Sanders, S. J., Bishop, S., Mortensen, P. B., … Arking, D. E. (2017). Polygenic transmission disequilibrium confirms that common and rare variation act additively to create risk for autism spectrum disorders. *Nature Genetics*, *49*(7), 978–985. https://doi.org/10.1038/ng.3863

Wilcox, H., Paz, V., Saxena, R., Winkelman, J. W., Garfield, V., & Dashti, H. S. (2024). The Role of Circadian Rhythms and Sleep in Anorexia Nervosa. *JAMA Network Open*, *7*(1), e2350358. https://doi.org/10.1001/jamanetworkopen.2023.50358

Willems, S. M., Ng, N. H. J., Fernandez, J., Fine, R. S., Wheeler, E., Wessel, J., Kitajima, H., Marenne, G., Sim, X., Yaghootkar, H., Wang, S., Chen, S., Chen, Y., Chen, Y.-D. I., Grarup, N., Li-Gao, R., Varga, T. V., Asimit, J. L., Feng, S., … Barroso, I. (2023). Large-scale exome array summary statistics resources for glycemic traits to aid effector gene prioritization. *Wellcome Open Research*, *8*, 483. https://doi.org/10.12688/wellcomeopenres.18754.1

Williamson, A., Norris, D. M., Yin, X., Broadaway, K. A., Moxley, A. H., Vadlamudi, S., Wilson, E. P., Jackson, A. U., Ahuja, V., Andersen, M. K., Arzumanyan, Z., Bonnycastle, L. L., Bornstein, S. R., Bretschneider, M. P., Buchanan, T. A., Chang, Y. C., Chuang, L. M., Chung, R. H., Clausen, T. D., … Langenberg, C. (2023). Genome-wide association study and functional characterization identifies candidate genes for insulin-stimulated glucose uptake. *Nature Genetics 2023 55:6*, *55*(6), 973–983. https://doi.org/10.1038/s41588-023-01408-9

Woerwag-Mehta, S., & Treasure, J. (2008). Causes of anorexia nervosa. *Psychiatry*, *7*(4), 147–151. https://doi.org/10.1016/j.mppsy.2008.02.010

Wray, N. R., Lin, T., Austin, J., McGrath, J. J., Hickie, I. B., Murray, G. K., & Visscher, P. M. (2021). From Basic Science to Clinical Application of Polygenic Risk Scores. *JAMA Psychiatry*, *78*(1), 101. https://doi.org/10.1001/jamapsychiatry.2020.3049

Yao, S., Larsson, H., Norring, C., Birgegård, A., Lichtenstein, P., D'Onofrio, B. M., Almqvist, C., Thornton, L. M., Bulik, C. M., & Kuja-Halkola, R. (2021). Genetic and environmental contributions to diagnostic fluctuation in anorexia nervosa and bulimia nervosa. *Psychological Medicine*, *51*(1), 62–69. https://doi.org/10.1017/S0033291719002976

Yengo, L., Sidorenko, J., Kemper, K. E., Zheng, Z., Wood, A. R., Weedon, M. N., Frayling, T. M., Hirschhorn, J., Yang, J., & Visscher, P. M. (2018). Meta-analysis of genome-wide association studies for height and body mass index in ∼700000 individuals of European ancestry. *Human Molecular Genetics*, *27*(20), 3641–3649. https://doi.org/10.1093/hmg/ddy271

Yilmaz, Z., Schaumberg, K., Halvorsen, M., Goodman, E. L., Brosof, L. C., Crowley, J. J., Mathews, C. A., Mattheisen, M., Breen, G., Bulik, C. M., Micali, N., & Zerwas, S. C. (2023). Predicting eating disorder and anxiety symptoms using disorder-specific and transdiagnostic polygenic scores for anorexia nervosa and obsessive-compulsive disorder. *Psychological Medicine*, *53*(7), 3021–3035. https://doi.org/10.1017/S0033291721005079

Yu, D., Sul, J. H., Tsetsos, F., Nawaz, M. S., Huang, A. Y., Zelaya, I., Illmann, C., Osiecki, L., Darrow, S. M., Hirschtritt, M. E., Greenberg, E., Muller-Vahl, K. R., Stuhrmann, M., Dion, Y., Rouleau, G., Aschauer, H., Stamenkovic, M., Schlögelhofer, M., Sandor, P., … Tourette Association of America International Consortium for Genetics, the Gilles de la Tourette GWAS Replication Initiative, the Tourette International Collaborative Genetics Study, and the Psychiatric Genomics Consortium Tourette Syndrome Working Group. (2019). Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies. *The American Journal of Psychiatry*, *176*(3), 217–227. https://doi.org/10.1176/appi.ajp.2018.18070857

Zhang, Z., Robinson, L., Campbell, I., Irish, M., Bobou, M., Winterer, J., Zhang, Y., King, S., Vaidya, N., Broulidakis, M. J., van Noort, B. M., Stringaris, A., Banaschewski, T., Bokde, A. L. W., Brühl, R., Fröhner, J. H., Grigis, A., Garavan, H., Gowland, P., … Desrivières, S. (2024). Distinct personality profiles associated with disease risk and diagnostic status in eating disorders. *Journal of Affective Disorders*, *360*, 146–155. https://doi.org/10.1016/j.jad.2024.05.132

Zhang, Z., Robinson, L., Jia, T., Quinlan, E. B., Tay, N., Chu, C., Barker, E. D., Banaschewski, T., Barker, G. J., Bokde, A. L. W., Flor, H., Grigis, A., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Martinot, J.-L., Stringaris, A., Penttilä, J., … Desrivières, S. (2021). Development of Disordered Eating Behaviors and Comorbid Depressive Symptoms in Adolescence: Neural and Psychopathological Predictors. *Biological Psychiatry*, *90*(12), 853–862. https://doi.org/10.1016/j.biopsych.2020.06.003

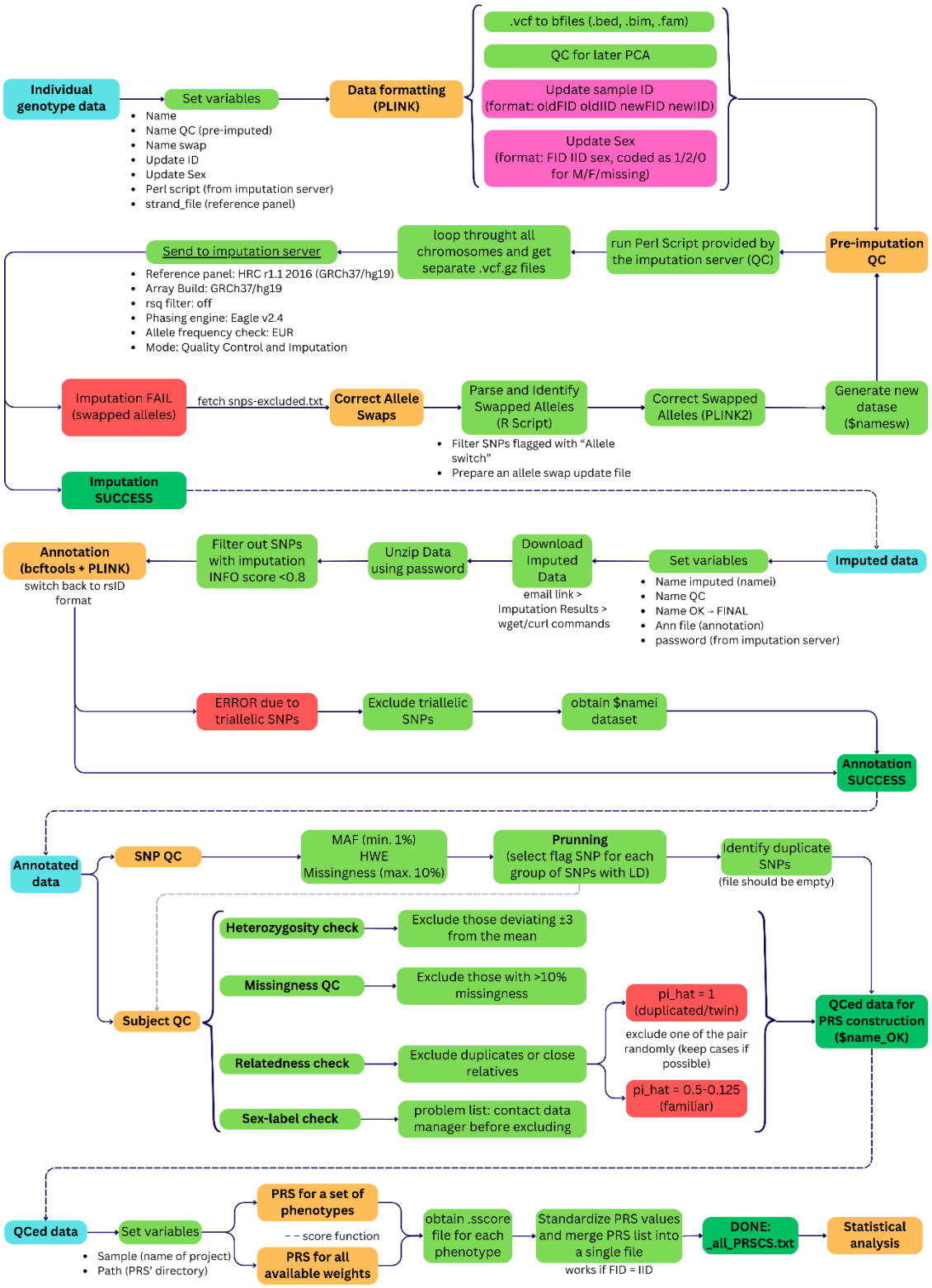
Zheng, X., Levine, D., Shen, J., Gogarten, S. M., Laurie, C., & Weir, B. S. (2012). A high-performance computing toolset for relatedness and principal component analysis of SNP data. *Bioinformatics (Oxford, England)*, *28*(24), 3326–3328. https://doi.org/10.1093/bioinformatics/bts606

8. SUPPLEMENTARY MATERIALS

Supplementary Table 1. Overview of genome-wide association studies (GWAS) used for polygenic risk score (PRS) analyses, grouped by domain. *For each trait, the effective sample size (Neff) and reference GWAS are indicated.*

DOMAIN	TRAIT	Neff	Reference GWAS
cognitive and occupational performance	CP	257,841	(Davies et al., 2018)
	EA	1,131,881	(Lee et al., 2018)
	IQ	269,867	(Savage et al., 2018)
	OA	248,847	(Ko et al., 2022)
mental health	ADHD	42,350	(Demontis et al., 2023)
	AN	11,279	(Duncan et al., 2017)
	ANX	11,437	(Otowa et al., 2016)
	ASD	43,392	(Grove et al., 2019)
	BD	14,536	(Mullins et al., 2021)
	Insomnia	302,494	(Jansen et al., 2019)
	MDD	412,673	(Howard et al., 2019)
	OCD	7,138	(IOCDF-GC et al., 2018)
	SA	125,977	(Docherty et al., 2023)
	SZ	108,605	(Trubetskoy et al., 2022)
	Tourette	12,427	(Yu et al., 2019)
metabolic	2hGlu	57,878	(Lagou et al., 2023)
	Adiponectin	38,609	(Sarsani et al., 2024)
	Birthweight	298,142	(Warrington et al., 2019)
	BMI	694,694	(Yengo et al., 2018)
	Cortisol	34,491	(Y. Chen et al., 2023)
	Fasting insulin	151,013	(Willems et al., 2023)
	Fasting glucose	200,622	(Willems et al., 2023)
	IFC	55,172	(Williamson et al., 2023)
	PROI	45,861	(Broadaway et al., 2023)
	T2D	586,265	(Suzuki et al., 2024)
personality	Agreeableness	17,375	(de Moor et al., 2012)
	Conscientiousness	17,375	(de Moor et al., 2012)
	Extraversion	17,375	(de Moor et al., 2012)
	Loneliness	452,302	(Day et al., 2018)
	Neuroticism	390,278	(Nagel et al., 2018)
	Openness	17,375	(de Moor et al., 2012)

2hGlu = 2-hour glucose, ADHD = attention-deficit/hyperactivity disorder, AN = anorexia nervosa, ANX = anxiety, ASD = autism spectrum disorder, BD = bipolar disorder, BMI = body mass index, CP = cognitive performance, EA = educational attainment, IFC = insulin following challenge, IOCDF-GC = International Obsessive Compulsive Disorder Foundation Genetics Collaborative IQ = intelligence quotient, MDD = major depressive disorder, OA = occupational attainment, OCD = obsessive-compulsive disorder, PROI = proinsulin, SA = suicide attempt, SZ = schizophrenia, T2D = type 2 diabetes



Supplementary Figure 1. Schematic overview of the complete pipeline for generating polygenic risk scores (PRSs) from individual-level genotype data. *The workflow begins with raw genotype data processing and quality control (QC), followed by imputation using a reference panel. Post-imputation, additional QC steps and annotation are performed, including SNP and sample filtering, heterozygosity, and relatedness checks. The final stage involves calculating PRS for multiple phenotypes. Key decision points, potential errors, and corrective actions are highlighted to ensure data integrity throughout the process.*