Predicting eating disorder and anxiety symptoms using disorder-specific and transdiagnostic polygenic scores for anorexia nervosa and obsessive-compulsive disorder

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Original Article

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Abstract

Background. Clinical, epidemiological, and genetic findings support an overlap between eating disorders, obsessive-compulsive disorder (OCD), and anxiety symptoms. However, little research has examined the role of genetics in the expression of underlying phenotypes. We investigated whether the anorexia nervosa (AN), OCD, or AN/OCD transdiagnostic polygenic scores (PGS) predict eating disorder, OCD, and anxiety symptoms in a large developmental cohort in a sex-specific manner.

Methods. Using summary statistics from Psychiatric Genomics Consortium AN and OCD genome-wide association studies, we conducted an AN/OCD transdiagnostic genome-wide association meta-analysis. We then calculated AN, OCD, and AN/OCD PGS in participants from the Avon Longitudinal Study of Parents and Children to predict eating disorder, OCD, and anxiety symptoms, stratified by sex (combined N = 3212–5369 per phenotype).

Results. The PGS prediction of eating disorder, OCD, and anxiety phenotypes differed between sexes, although effect sizes were small. AN and AN/OCD PGS played a more prominent role in predicting eating disorder and anxiety risk than OCD PGS, especially in girls. AN/OCD PGS provided a small boost over AN PGS in the prediction of some anxiety symptoms. All three PGS predicted higher compulsive exercise across different developmental time-points [β = 0.03 (s.e. = 0.01) for AN and AN/OCD PGS at age 14; β = 0.05 (s.e. = 0.02) for OCD PGS at age 16] in girls.

Conclusions. Compulsive exercise may have a transdiagnostic genetic etiology, and AN genetic risk may play a role in the presence of anxiety symptoms. Converging with prior twin literature, our results also suggest that some of the contribution of genetic risk may be sex-specific.

Introduction

Eating disorders and obsessive-compulsive disorder (OCD) are serious psychiatric conditions with high social, psychological, and physical impact (American Psychiatric Association, 2013;
Clinical, epidemiological, and genetic findings support an overlap between eating disorders and anxiety disorders, particularly anorexia nervosa (AN), and OCD (Anttila et al., 2018; Cederlof et al., 2015; du Toit, van Kradenburg, Niehaus, & Stein, 2001; Godart, Flament, Perdereau, & Jeammet, 2002; Kaye, Bulik, Thornton, Barbarich, & Masters, 2004; Lilenfeld et al., 1998; Meier et al., 2015; Rubenstein, Pigott, L’Heureux, Hill, & Murphy, 1992; Strober, Freeman, Lampert, & Diamond, 2007; Swinburne & Touyz, 2007; Watson et al., 2019; Yilmaz et al., 2020). While research on eating disorders and OCD comorbidity has primarily focused on diagnoses, many symptoms and behaviors are common to both diagnoses, spanning diagnostic categories, and their presence often precedes disorder onset (Nolen-Hoeksema & Watkins, 2011; Stice, 2016). Little research has examined these associations – or symptom phenotypes – in a developmental context. Premorbid OCD symptoms and anxiety disorders or symptoms are common in patients with AN (Cederlof et al., 2015; Schaumberg et al., 2019). Childhood anxiety may precede eating disorder symptoms and AN in adolescence (Schaumberg et al., 2019), and shared genetic and environmental influences play a role in anxiety and disordered eating symptoms (Silberg & Bulik, 2005). Though no longer classified as an anxiety disorder (American Psychiatric Association, 2013), OCD is highly comorbid with anxiety disorders and includes anxiety symptoms, especially in children (Anagnostopoulos et al., 2016). An improved understanding of the overlap among eating disorders, OCD, and intermediate phenotypes such as anxiety symptoms could aid in conceptualizing mechanisms and processes contributing to the clinical and genetic overlap among these disorders. Additionally, symptom dimensions may transition over development, shifting from childhood obsessive-compulsive symptoms to adolescent eating disorders (Anderluh, Tchanturia, Rabe-Hesketh, & Treasure, 2003; Micali et al., 2011) and vice versa. Thus, shared and unique risk factors may contribute to the symptoms of OCD and eating disorders across development.

Genome-wide association studies (GWAS) of AN (Watson et al., 2019) and OCD (International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) & OCD Collaborative Genetics Association Studies (OCGAS), 2018) have provided important insights into the highly polygenic architecture of these disorders and their positive genetic correlation (Watson et al., 2019). Application of polygenic scores (PGS) – the weighted sum of common risk variants per individual – examine the genetic architecture of complex traits using evidence for association from variants below the stringent threshold for genome-wide significance (Wray et al., 2014). The use of PGS has been validated across psychiatric diagnoses and symptom-level measures (Axelrud et al., 2018; Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013; Lee et al., 2013; Mistry, Harrison, Smith, Escott-Price, & Zammit, 2018; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Ripke et al., 2013, 2014), demonstrating that genetic variants associated with risk are often shared across diagnostic categories (Mistry et al., 2018). Moreover, transdiagnostic PGS (determined by either AN or OCD case status) of genetically correlated disorders may enhance predictive power for either disorder (Maier et al., 2015).

Sex differences in the prevalence and presentation of eating disorders, anxiety disorders, and OCD warrant sex-specific examination of risk factors. While the majority of AN cases are female (Hudson, Hiripi, Pope, & Kessler, 2007; Swanson, Crow, Le Grange, Swendsen, & Merikangas, 2011), AN in males often has an earlier age of onset and is likely to be more severe (El Ghoch, Calugi, Milanese, Bazzani, & Dalle Grave, 2017; Kinasz, Accurso, Kass, & Le Grange, 2016; Voderholzer et al., 2019). Similarly, the lifetime prevalence of eating disorders is much higher in females than males (Hudson et al., 2007; Swanson et al., 2011), possibly with the exception of subthreshold binge eating (Hudson et al., 2007). Furthermore, the twin literature has reported differences in the heritability estimates for disordered eating in boys and girls (Klump et al., 2012). The lifetime prevalence of anxiety disorders is up to 60% higher in women than in men (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). In the case of OCD, childhood onset is more common among males and adolescent onset is more common among females (Ruscio, Stein, Chiu, & Kessler, 2010). Importantly, sex differences in the presentation of symptoms such as restraint and weight and shape concern in eating disorders (Kinasz et al., 2016) and contamination/cleaning and sexual/religious symptoms in OCD (Torresan et al., 2013) have also been reported. Given these discrepancies, we could expect: (a) notable sex differences in the role of genetic risk and eating disorders, OCD, and anxiety symptom phenotypes; and (b) that genetic risk may be more impactful and predictive for boys, especially in the case of eating disorders.

This study examined whether the AN, OCD, or AN/OCD PGS predicts eating disorders, OCD, and anxiety symptom dimensions or diagnoses using a developmental framework in male and female participants from a population-based cohort. Our main hypothesis was that AN/OCD PGS would demonstrate better statistical power than AN or OCD PGS, and the transdiagnostic PGS would evidence the most benefit compared with single-trait PGS when predicting intermediate phenotypes shared across the two disorders, such as generalized anxiety or worrying. We also hypothesized that symptom dimensions specific to each disorder would be predicted by disorder-specific PGS (e.g., thin ideal internalization by AN, or symmetry/checking behavior by OCD). Importantly, in light of the differences in lifetime prevalence and/or age of onset of eating disorders, OCD, and anxiety disorders between sexes, we hypothesized that there would be sex-specific differences in the prediction of AN, OCD, and AN/OCD PGS, and high AN genetic risk would play a larger role in predicting eating disorder symptoms in boys than girls.

Methods
Participants
The Avon Longitudinal Study of Parents and Children (ALSPAC) is a longitudinal, population-based study of women and their children (Boyd et al., 2013). All pregnant women living in Avon, United Kingdom who were expected to deliver between 1 April 1991 and 31 December 1992 were invited to participate. Children from 14,541 pregnancies were enrolled, 13,988 of whom were alive at one year. An additional 713 children were enrolled at or after age 7 (Boyd et al., 2013). The study website contains details of all the data that are available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/). Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Briefly, informed consent for the use of data collected via questionnaires and clinics was
obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. Mothers provided written consent for the participation of their children, and children were invited to give assent whenever it was appropriate. Study participants have the right to withdraw their consent for elements of the study or from the study entirely at any time. Full details of the ALSPAC consent procedures are available on the study website (http://www.bristol.ac.uk/alspac/researchers/research-ethics/).

For genetic analyses, we used post-quality control (QC) dosage files for 7977 unrelated participants (Martin, Hamshere, Stergioulis, O’Donovan, & Thapar, 2014; Paternoster et al., 2012), 7779 of whom passed additional QC performed as a part of this study (3787 girls and 3992 boys; see online Supplementary Information). The final number of participants with genotype and at least one phenotype information was 3270 girls and 3297 boys.

**Measures**

Table 1 provides a list of all measures, assessment timepoints, and methods of administration. Measures assessing psychopathology at younger ages (before age 14) were primarily assessed via parent-report. Those assessing psychopathology during adolescence (age 14 or older) were primarily assessed via self-report.

Eating disorder symptoms for the previous year were evaluated at ages 14 and 16 using questions adapted from the Youth Risk Behavior Surveillance System Questionnaire (Kann et al., 1996), validated in a population-based study of adolescents (Field, Taylor, Celio, & Colditz, 2004). Binge-eating, purging, fasting, and compulsive exercise were characterized and categorized as described previously (Micali, Daniel, Ploubidis, & De Stavola, 2018; Micali et al., 2015) (online Supplementary Information). Eating disorder diagnoses at ages 14 and 16 were derived using DSM-5 criteria (American Psychiatric Association, 2013) as detailed in a previous publication by our group (Schaumberg et al., 2019). Eating disorder cognitions, including body image distortion, emotional eating, external eating, body dissatisfaction, thin ideal internalization, dietary restraint, weight concern, and shape concern, were assessed by validated, age-appropriate self-report measurements (online Supplementary Information).

OCD and anxiety symptoms at age 7, 10, 13, and 15 were collected using the Development and Wellbeing Assessment (DAWBA; online Supplementary Information) (Goodman, Ford, Richards, Gatward, & Meltzer, 2000; Goodman, Heiervang, Collishaw, & Goodman, 2011). Probabilities of anxiety disorder diagnoses at ages 7 (specific phobia and separation anxiety), 10 (OCD), 13 (OCD, social phobia, and generalized anxiety disorder), and 15 (generalized anxiety disorder) were determined using computer-generated DAWBA band variables (Goodman et al., 2011), which assign the probability of the participant meeting DSM-IV criteria for an anxiety disorder. We defined likely cases as those where likelihood of case status based on response pattern was ≥50%. We also defined five latent OCD or anxiety factors for ages 10 and 13: (1) OCD-symmetry; (2) OCD-dirt/germs; (3) physical anxiety; (4) worrying; and (5) social phobia (Schaumberg et al., 2019) (online Supplementary Information).

**Data analysis**

We calculated AN, OCD, and AN/OCD PGS to predict 27 eating disorder, six OCD, and 11 anxiety phenotypes in the ALSPAC target sample using PRS-CS (Ge, Chen, Ni, Feng, & Smoller, 2019). AN PGS was constructed using the Anorexia Nervosa Genetics Initiative & Psychiatric Genomics Consortium (PGC) Eating Disorder Working Group Freeze 2 AN GWAS (Watson et al., 2019), and OCD PGS was calculated using the Freeze 1 PGC OCD GWAS [International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) & OCD Collaborative Genetics Association Studies (OCGAS), 2018]. The AN/OCD summary statistics file was obtained from a GWAS meta-analysis of the AN and OCD datasets (see online Supplementary Information, Table S1, and Fig. S1). All of the discovery samples and the ALSPAC target sample included in our analysis were of European ancestry, determined using genomic ancestry principal components through comparison with a European ancestry (CEU) reference panel. We examined how well each of the eating disorder, OCD, and anxiety symptom phenotypes were predicted by: (1) AN; (2) OCD; and (3) AN/OCD PGS in girls and boys separately to elucidate whether sex-specific differences existed. Additional results for the combined sample with and without sex as a covariate are summarized in online Supplementary Tables S3 and S4. Due to insufficient power, only binary phenotypes with ≥50 cases are reported.

**Results**

**Eating disorder symptom phenotypes and diagnoses**

In girls, AN PGS predicted eating disorders not otherwise specified/purging eating disorder at age 14 [β = 0.1130 (0.0552), p = 0.041], presence of a threshold or subthreshold eating disorder at age 14 [β = 0.1214 (0.0498), p = 0.015], and compulsive exercise at age 14 [β = 0.0336 (0.0143), p = 0.019] (Table 2). OCD PGS predicted thin ideal internalization at age 14 [β = 0.1264 (0.0487), p = 0.010] and compulsive exercise at age 16 [β = 0.0535 (0.0240), p = 0.025]. AN/OCD PGS predicted pressure to lose weight at age 14 [β = 0.0839 (0.0423), p = 0.047], the presence of a threshold or subthreshold eating disorder at age 14 [β = 0.1146 (0.0493), p = 0.020], fasting at age 14 [β = 0.0148 (0.0064), p = 0.020], and compulsive exercise at age 14 [β = 0.0287 (0.0142), p = 0.043].

In boys, emotional eating at age 14 was predicted by AN PGS [β = 0.2583 (0.1096), p = 0.019] as well as AN/OCD PGS [β = 0.2371 (0.1109), p = 0.033] (Table 3). None of the eating disorder phenotypes were predicted by OCD PGS in boys.

**OCD and anxiety symptom phenotypes and diagnoses**

In girls, AN PGS predicted a higher score for OCD latent factor dirt/germs at age 13 [β = 0.0281 (0.0129), p = 0.030] and an increased likelihood of separation anxiety at age 7 [β = 0.4342 (0.1246), p = 0.001] (Table 2). AN/OCD PGS predicted an increased likelihood of separation anxiety [β = 0.4868 (0.1246), p < 0.001] as well as higher scores for latent factors OCD dirt/germs [β = 0.0277 (0.0128), p = 0.031], worrying [β = 0.0334 (0.0164), p = 0.042], and social phobia at age 13 [β = 0.0367 (0.0155), p = 0.018], OCD PGS did not predict any of the OCD or anxiety phenotypes.

In boys, AN PGS predicted a higher score for latent factor worrying at age 10 [β = 0.0292 (0.0133), p = 0.028] but a lower score for OCD latent factor dirt/germs at age 13 [β = −0.0297 (0.0132), p = 0.025] (Table 3). AN/OCD PGS also negatively predicted OCD latent factor dirt/germs at age 13 [β = −0.0300 (0.0133), p = 0.025], whereas OCD PGS predicted a lower score for latent factor social phobia at age 10 [β = −0.0254 (0.0125), p = 0.042].
In this exploratory study, we were able to predict eating disorder, OCD, and anxiety phenotypes using AN, OCD, and AN/OCD PGS in girls and boys separately during different developmental points in a large population sample. The majority of phenotypes predicted by AN PGS were also predicted by AN/OCD PGS (e.g. emotional eating at age 14 in boys; separating anxiety at age 7 in girls). However, this overlap was not 100% (e.g. latent factor worrying at age 10 in boys predicted by AN and not AN/OCD PGS), and none of the phenotypes predicted by OCD PGS were also predicted by AN/OCD PGS, suggesting that the genetic risk associated with some phenotypes may be more OCD-specific than being based on a transdiagnostic common factor. Notably, there were no phenotypes predicted separately by both AN and OCD PGS. Considering the notably smaller sample size of the OCD GWAS compared to the AN GWAS (2688 v. 16992 cases), OCD PGS is likely to be underpowered, and some phenotypes associated with a higher genetic load for OCD may be predicted by the AN/OCD PGS. There were also phenotypes only predicted by the transdiagnostic PGS (e.g. thin ideal internalization at age 14 in girls), further demonstrating the likely boost in statistical power for both AN and OCD with the use of the transdiagnostic genotype.

Compulsive exercise was the only intermediate phenotype that was positively predicted by more than one disorder-specific PGS in girls, suggesting it may be a key intermediate phenotype that, although commonly associated with eating disorders, is influenced by genetic risk for both AN and OCD. Together with evidence for shared genetic risk between a broad AN phenotype and OCD, these findings highlight the importance of considering a transdiagnostic approach in genetic studies of eating disorders and anxiety disorders.

### Table 1. Eating disorder, obsessive-compulsive disorder, and anxiety diagnostic and symptom-based constructs

| Age(s) | Construct | Scale | Report |
|--------|-----------|-------|--------|
| 10     | Body image distortion | Stunkard Figure Rating Scale | Self |
| 14     | Fear of weight gain | Youth Risk Behavior Surveillance System Questionnaire | Self |
|        | Pressure to lose weight | Perceived Sociocultural Pressure Scale | Self |
|        | Restraint | Dutch Eating Behavior Questionnaire | Self |
|        | Emotional eating | | |
|        | External eating | | |
|        | Thin-ideal internalization | Ideal-Body Stereotype Scale-Revised | Self |
|        | Body dissatisfaction | Satisfaction and Dissatisfaction With Body Parts Scale | Self |
|        | Weight and shape concern | McKnight Risk Factor Survey | Self |
| 14 and 16 | Anorexia nervosa | Youth Risk Behavior Surveillance System Questionnaire | Self |
|          | Bulimia nervosa or subthreshold bulimia nervosa | | |
|          | Binge-eating disorder or subthreshold binge-eating disorder | | |
|          | Eating disorders not otherwise specified or purging disorder | | |
|          | Any threshold/subthreshold eating disorder | | |
|          | Fasting | | |
|          | Purging | | |
|          | Binge eating | | |
|          | Compulsive exercise | | |
| 10 and 13 | Obsessive-compulsive disorder | Development and Wellbeing Assessment | Parent |
|          | Obsessive-compulsive disorder latent factor symmetry | | |
|          | Obsessive-compulsive disorder latent factor dirt/germs | | |
| Anxiety | 7 | Separation anxiety | Development and Wellbeing Assessment | Parent |
| 10 and 13 | Social phobia | Development and Wellbeing Assessment | Parent |
|          | Latent factor physical anxiety | | |
|          | Latent factor worrying | | |
|          | Latent factor social phobia | | |
| 13 | Generalized anxiety disorder | Development and Wellbeing Assessment | Parent |
| 15 | | Development and Wellbeing Assessment | Self |
Table 2. Prediction of eating disorder, obsessive-compulsive disorder, and anxiety symptom dimensions and diagnoses using polygenic scores in girls

| Phenotype                                      | Sample size | PGS     | $\beta$   | s.e.     | Test statistic $b$ | $P$   |
|------------------------------------------------|-------------|---------|-----------|-----------|-------------------|-------|
| **Eating disorder symptom dimensions and diagnoses** |             |         |           |           |                   |       |
| Body image distortion at age 10                | 2512        | AN      | $-0.0039$ | $0.0138$  | $-0.283$          | 0.777 |
|                                                |             | OCD     | $0.0078$  | $0.0133$  | $0.587$           | 0.557 |
|                                                |             | AN/OCD  | $-0.0052$ | $0.0137$  | $-0.381$          | 0.703 |
| Fear of weight gain at age 14                   | 2277        | AN      | $0.0200$  | $0.0164$  | $1.222$           | 0.222 |
|                                                |             | OCD     | $0.0099$  | $0.0159$  | $0.624$           | 0.533 |
|                                                |             | AN/OCD  | $0.0242$  | $0.0162$  | $1.489$           | 0.137 |
| Pressure to lose weight at age 14               | 2263        | AN      | $0.0813$  | $0.0428$  | $1.900$           | 0.057 |
|                                                |             | OCD     | $0.0201$  | $0.0414$  | $0.486$           | 0.627 |
|                                                |             | AN/OCD  | $0.0839$  | $0.0423$  | $1.984$           | **0.047** |
| Restraint at age 14                             | 2257        | AN      | $0.0478$  | $0.0269$  | $1.774$           | 0.076 |
|                                                |             | OCD     | $0.0091$  | $0.0259$  | $0.350$           | 0.726 |
|                                                |             | AN/OCD  | $0.0501$  | $0.0267$  | $1.880$           | 0.060 |
| Emotional eating at age 14                      | 2167        | AN      | $-0.0006$ | $-0.1294$ | $0.005$           | 0.996 |
|                                                |             | OCD     | $0.0361$  | $0.1248$  | $0.289$           | 0.772 |
|                                                |             | AN/OCD  | $-0.0447$ | $0.1279$  | $-0.349$          | 0.727 |
| External eating at age 14                       | 2068        | AN      | $0.0621$  | $0.0732$  | $0.849$           | 0.396 |
|                                                |             | OCD     | $0.0003$  | $0.0709$  | $0.004$           | 0.990 |
|                                                |             | AN/OCD  | $0.0322$  | $0.0726$  | $0.444$           | 0.657 |
| Thin ideal internalization at age 14            | 2283        | AN      | $0.0755$  | $0.0505$  | $1.495$           | 0.135 |
|                                                |             | OCD     | $0.1264$  | $0.0487$  | $2.593$           | **0.010** |
|                                                |             | AN/OCD  | $0.0796$  | $0.0500$  | $1.592$           | 0.112 |
| Body dissatisfaction at age 14                  | 2297        | AN      | $0.2948$  | $0.1677$  | $1.758$           | 0.079 |
|                                                |             | OCD     | $0.2531$  | $0.1620$  | $1.562$           | 0.118 |
|                                                |             | AN/OCD  | $0.2899$  | $0.1661$  | $1.745$           | 0.081 |
| Weight and shape concern at age 14              | 2299        | AN      | $0.0331$  | $0.0417$  | $0.794$           | 0.428 |
|                                                |             | OCD     | $0.0392$  | $0.0404$  | $0.970$           | 0.332 |
|                                                |             | AN/OCD  | $0.0481$  | $0.0413$  | $1.164$           | 0.245 |
| AN at age 14                                    | 78 cases, 2242 controls | AN | $0.1734$  | $0.1180$  | $1.470$           | 0.142 |
|                                                |             | OCD     | $0.0624$  | $0.1136$  | $0.550$           | 0.583 |
|                                                |             | AN/OCD  | $0.1845$  | $0.1167$  | $1.582$           | 0.114 |
| Bulimia nervosa or subthreshold bulimia nervosa at age 14* | 44 cases, 2276 controls | AN | $-$       | $-$       | $-$               | $-$   |
|                                                |             | OCD     | $-$       | $-$       | $-$               | $-$   |
|                                                |             | AN/OCD  | $-$       | $-$       | $-$               | $-$   |
| Binge-eating disorder or subthreshold binge-eating disorder at age 14* | 17 cases, 2303 controls | AN | $-$       | $-$       | $-$               | $-$   |
|                                                |             | OCD     | $-$       | $-$       | $-$               | $-$   |
|                                                |             | AN/OCD  | $-$       | $-$       | $-$               | $-$   |
| Eating disorders not otherwise specified or purging disorder at age 14* | 419 cases, 1901 controls | AN | $0.1130$  | $0.0552$  | $2.045$           | **0.041** |
|                                                |             | OCD     | $-0.0157$ | $0.0534$  | $-0.294$          | 0.769 |
|                                                |             | AN/OCD  | $0.1026$  | $0.0546$  | $1.878$           | 0.060 |
| Any threshold/subthreshold eating disorder at age 14* | 558 cases, 1762 controls | AN | $0.1214$  | $0.0498$  | $2.439$           | **0.015** |
|                                                |             | OCD     | $-0.0003$ | $0.0480$  | $-0.007$          | 0.994 |

(Continued)
Table 2. (Continued.)

| Phenotype                                      | Sample size | PGS          | β     | s.e.    | Test statistic | P     |
|-----------------------------------------------|-------------|--------------|-------|---------|----------------|-------|
| AN/OCD                                        |             | AN/OCD      | 0.1146| 0.0493  | 2.327          | 0.020*|
| Fasting at age 14                             | 2074        | AN/OCD      | 0.0122| 0.0064  | 1.897          | 0.058 |
| Purging at age 14                              | 2278        | AN/OCD      | −0.0031| 0.0062  | −0.497         | 0.619 |
| Binge eating at age 14                         | 2289        | AN/OCD      | 0.0148| 0.0064  | 2.327          | 0.020*|
| Compulsive exercise at age 14                  | 2240        | AN/OCD      | 0.0336| 0.0143  | 2.349          | 0.019*|
| AN at age 16<sup>c</sup>                        | 56 cases, 2035 controls | AN/OCD      | −0.0151| 0.1370  | −0.110         | 0.912 |
| Bulimia nervosa at age 16<sup>c</sup>          | 121 cases, 1970 controls | AN/OCD      | 0.0785| 0.1333  | 0.589          | 0.556 |
| Binge-eating disorder at age 16<sup>c,d</sup>  | 48 cases, 2043 controls | AN/OCD      | 0.0390| 0.1351  | −0.288         | 0.773 |
| Eating disorders not otherwise specified or purging disorder at age 16<sup>c</sup> | 843 cases, 1248 controls | AN/OCD      | 0.0455| 0.0450  | 1.012          | 0.312 |
| Any threshold/subthreshold eating disorder at age 16<sup>c</sup> | 1068 cases, 1023 controls | AN/OCD      | 0.0415| 0.0440  | 0.329          | 0.742 |
| Fasting at age 16                              | 1972        | AN/OCD      | −0.0040| 0.0180  | −0.220         | 0.826 |
| Purging at age 16                              | 1990        | AN/OCD      | 0.0133| 0.0140  | 0.954          | 0.340 |
| Binge eating at age 16                         | 1715        | AN/OCD      | 0.0169| 0.0183  | 0.923          | 0.356 |
| Compulsive exercise at age 16                  | 1840        | AN/OCD      | 0.0262| 0.0248  | 1.058          | 0.290 |
| OCD at age 10<sup>c,d</sup>                    | <5 cases    | AN/OCD      | 0.0179| 0.0245  | 0.731          | 0.465 |

Obsessive-compulsive disorder symptom dimensions and diagnosis

(Continued)
Table 2. (Continued.)

| Phenotype                                                                 | Sample size | PGS     | β      | s.e. | Test statistic | P    |
|----------------------------------------------------------------------------|-------------|---------|--------|------|----------------|------|
| OCD                                                                       | 2590        | AN      | 0.0037 | 0.0094 | 0.397          | 0.691|
| AN/OCD                                                                   |             | OCD     | 0.0106 | 0.0090 | 1.173          | 0.241|
| OCD latent factor – symmetry, checking at age 10                         | 2590        | AN      | −0.0002 | 0.0083 | −0.027         | 0.979|
| AN/OCD                                                                   |             | OCD     | 0.0127 | 0.0080 | 1.585          | 0.113|
| OCD latent factor – dirt/germs at age 10                                 | 2590        | AN      | −0.0010 | 0.0083 | −0.110         | 0.913|
| OCD at age 13\textsuperscript{c,d}                                      | <5 cases    | AN      | –      | –     | –              | –    |
| OCD                                                                      |             | AN/OCD  | –      | –     | –              | –    |
| OCD latent factor – symmetry, checking at age 13                         | 2421        | AN      | −0.0208 | 0.0151 | −1.381         | 0.167|
| AN/OCD                                                                   |             | OCD     | 0.0183 | 0.0147 | 1.246          | 0.213|
| OCD latent factor – dirt/germs at age 13                                 | 2421        | AN      | 0.0281 | 0.0129 | 2.175          | 0.030*|
| AN/OCD                                                                   |             | OCD     | −0.0157 | 0.0126 | −1.248         | 0.212|
| Anxiety symptom dimensions and diagnoses                                 |             | AN/OCD  | 0.0277 | 0.0128 | 2.160          | 0.031*|
| Separation anxiety at age 7\textsuperscript{c}                           | 68 cases, 2544 controls | AN      | 0.4342 | 0.1246 | 3.485          | 0.001*|
| OCD                                                                      |             | AN/OCD  | 0.4868 | 0.1246 | 3.906          | <0.001*|
| Specific phobia at age 7\textsuperscript{c}                             | 53 cases, 2564 controls | AN      | 0.2390 | 0.1406 | 1.699          | 0.089|
| OCD                                                                      |             | AN/OCD  | 0.2519 | 0.1400 | 1.799          | 0.072|
| Latent factor – physical anxiety at 10                                    | 2590        | AN      | 0.0287 | 0.0147 | 1.953          | 0.051|
| OCD                                                                      |             | AN/OCD  | 0.0150 | 0.0142 | 1.056          | 0.291|
| Latent factor – worrying at age 10                                       | 2590        | AN      | 0.0078 | 0.0148 | 0.526          | 0.599|
| OCD                                                                      |             | AN/OCD  | 0.0065 | 0.0143 | 0.450          | 0.652|
| Latent factor – social phobia at 10                                      | 2590        | AN      | 0.0114 | 0.0119 | 0.958          | 0.338|
| OCD                                                                      |             | AN/OCD  | 0.0131 | 0.0115 | 1.139          | 0.255|
| Social phobia at age 13\textsuperscript{c,d}                             | 30 cases, 2396 controls | AN      | –      | –     | –              | –    |
| OCD                                                                      |             | AN/OCD  | –      | –     | –              | –    |
| Generalized anxiety disorder at age 13                                    | 100 cases, 2317 controls | AN      | 0.1078 | 0.1040 | 1.036          | 0.300|
| OCD                                                                      |             | AN/OCD  | 0.1597 | 0.1019 | 1.567          | 0.117|
| Latent factor – physical anxiety at age 13                                 | 2421        | AN      | −0.0012 | 0.0132 | −0.092         | 0.927|
| OCD                                                                      |             | AN/OCD  | 0.0042 | 0.0129 | 0.325          | 0.746|
| Latent factor – physical anxiety at age 13                                 | 2421        | AN      | −0.0032 | 0.0131 | −0.241         | 0.810|

(Continued)
general propensity for physical activity (Watson et al., 2019), this finding suggests that genetic factors may be particularly relevant to understanding the development of compulsive exercise in eating disorders. Compulsive exercise encompasses many of the hallmark symptoms of AN (e.g. weight and shape concern) and OCD (e.g. compulsive behavior) (Davis & Kaptein, 2006). Furthermore, comorbid OCD symptoms are especially pronounced in the subpopulation of AN patients with compulsive exercise (Blachnio et al., 2016; Davis & Claridge, 1998; Davis & Kaptein, 2006; Davis, Katzman, & Kirsh, 1999; Naylor, Mountford, & Brown, 2006), which has significant clinical relevance since the presence of compulsive exercise in AN is an established predictor of treatment outcomes, including higher pathology at discharge from inpatient treatment (Dalle Grave, Calugi, & Marchesini, 2008), relapse (Carter, Blackmore, Sutandar-Pinnock, & Woodside, 2004), and greater energy requirements for weight gain (Kaye, Gwirtsman, Obarzanek, & George, 1988). Treatments for this symptom are currently lacking, and our preliminary results point to the need for additional investigation of the habitual and compulsive nature of exercise behavior in girls, which may lead to targeted intervention development for this symptom that derives from a modern biobehavioral understanding of both eating disorders and OCD. It is not clear why this association was not present in boys, but one potential explanation is the lack of statistical power (0.52 in boys vs. 0 in girls) (Klump et al., 2012), suggesting that AN genetic load could manifest itself earlier in boys, which is not what we observed in our study. Except for body image distortion at age 10, all eating disorder phenotypic data were collected at age 14 onward, so we cannot rule out the possibility that AN PGS may predict eating disorder phenotypes in boys at an earlier age than we have data available for. Another possible explanation is that the risk for disordered eating in boys could be attributed to a higher genetic load for other eating disorders – for which currently no large GWAS results exist – or other phenotypes independent of AN. Additionally, PGS is designed to account for common genetic variation, therefore genetic risk for eating disorders in males could be potentially driven by other types of variation such as copy number variants, rare variants, epigenetic factors, or other genetic mechanisms that PGS does a poor job of capturing.

Genetic prediction of anxiety symptoms and diagnoses also showed notable differences in boys and girls. For instance, AN PGS predicted separation anxiety at age 7 in girls and increased worrying at age 10 in boys. Epidemiological studies show over a 10-fold increase in AN risk among girls with separation anxiety disorder (Bulik, Sullivan, Fear, & Joyce, 1997), and a twin-based study reported a shared genetic effect influencing liability to AN, separation anxiety, and childhood overanxious disorder (which is very similar to generalized anxiety disorder in adults) during different stages of development (Silberg & Bulik, 2005), supporting our findings about the presence of a shared genetic pathway between anxiety and AN. We unexpectedly observed that lower OCD-specific genetic risk predicted lower scores on the latent factor indexing social phobia at age 13 in boys. While anxiety symptoms are common in patients with OCD, OCD is distinct from anxiety disorders phenotypes – in fact it is now a separate diagnostic chapter in DSM – and our results suggest

| Phenotype                              | Sample size | PGS     | β       | s.e.   | Test statistic | P      |
|----------------------------------------|-------------|---------|---------|--------|---------------|--------|
| Latent factor – worrying at age 13     | 2421        | AN      | 0.0303  | 0.0165 | 1.832         | 0.067  |
|                                        |             | OCD     | 0.0019  | 0.0161 | 0.116         | 0.908  |
|                                        |             | AN/OCD  | 0.0334  | 0.0164 | 2.035         | 0.042  |
| Latent factor – social phobia at age 13| 2421        | AN      | 0.0306  | 0.0156 | 1.961         | 0.050  |
|                                        |             | OCD     | 0.0032  | 0.0152 | 0.209         | 0.834  |
|                                        |             | AN/OCD  | 0.0367  | 0.0155 | 2.374         | 0.018  |
| Generalized anxiety disorder at age 15  | 154 cases, 1899 controls | AN      | 0.1188  | 0.0858 | 1.385         | 0.166  |
|                                        |             | OCD     | 0.0656  | 0.0835 | 0.786         | 0.432  |
|                                        |             | AN/OCD  | 0.0895  | 0.0850 | 1.054         | 0.292  |

Abbreviations: PGS, polygenic score; β, standardized beta regression coefficient; s.e., standard error; AN, anorexia nervosa; OCD, obsessive-compulsive disorder; AN/OCD, anorexia nervosa/obsessive-compulsive transdiagnostic phenotype.

*Genomic principal components 1-5 were used as covariates to account for population stratification.

*We report t-values for continuous phenotypes and z-values for binary phenotypes.

*Binary phenotype.

Due to insufficient statistical power, any binary measure with less than 50 cases is not included in the final analysis.

(Also bolded) Statistically significant at p < 0.05.
### Table 3. Prediction of eating disorder, obsessive-compulsive disorder, and anxiety symptom dimensions and diagnoses using polygenic scores in boys*

| Phenotype                                                | Sample size | PGS          | β   | s.s.    | Test statisticb | pb  |
|----------------------------------------------------------|-------------|--------------|-----|---------|-----------------|-----|
| **Eating disorder symptom dimensions and diagnoses**     |             |              |     |         |                 |     |
| Body image distortion at age 10                         | 2246        | AN           | 0.0059 | 0.0136  | 0.430           | 0.667 |
|                                                          |             | OCD          | −0.0260 | 0.0137  | −1.898          | 0.058 |
|                                                          |             | AN/OCD       | 0.0103 | 0.0138  | 0.746           | 0.456 |
| Fear of weight gain at age 14                            | 1850        | AN           | 0.0073 | 0.0113  | 0.643           | 0.520 |
|                                                          |             | OCD          | −0.0010 | 0.0114  | −0.090          | 0.928 |
|                                                          |             | AN/OCD       | 0.0123 | 0.0115  | 1.073           | 0.283 |
| Pressure to lose weight at age 14                         | 1853        | AN           | 0.0490 | 0.0324  | 1.512           | 0.131 |
|                                                          |             | OCD          | −0.0260 | 0.0137  | −1.898          | 0.058 |
|                                                          |             | AN/OCD       | 0.0103 | 0.0138  | 0.746           | 0.456 |
| Restraint at age 14                                       | 1817        | AN           | 0.0221 | 0.0206  | 1.070           | 0.285 |
|                                                          |             | OCD          | −0.0054 | 0.0208  | −0.260          | 0.795 |
|                                                          |             | AN/OCD       | 0.0193 | 0.0209  | 0.923           | 0.356 |
| Emotional eating at age 14                                | 1760        | AN           | 0.2583 | 0.1096  | 2.357           | 0.019*|
|                                                          |             | OCD          | −0.0289 | 0.1110  | −0.260          | 0.795 |
|                                                          |             | AN/OCD       | 0.2371 | 0.1109  | 2.139           | 0.033*|
| External eating at age 14                                 | 1540        | AN           | 0.0720 | 0.0866  | 0.832           | 0.406 |
|                                                          |             | OCD          | 0.1174 | 0.0885  | 1.327           | 0.185 |
|                                                          |             | AN/OCD       | 0.0562 | 0.0871  | 0.645           | 0.519 |
| Thin ideal internalization at age 14                      | 1770        | AN           | 0.0792 | 0.0707  | 1.121           | 0.262 |
|                                                          |             | OCD          | 0.0002 | 0.0708  | 0.002           | 0.998 |
|                                                          |             | AN/OCD       | 0.0847 | 0.0715  | 1.184           | 0.237 |
| Body dissatisfaction at age 14                            | 1872        | AN           | 0.2237 | 0.1620  | 1.381           | 0.168 |
|                                                          |             | OCD          | −0.0538 | 0.1633  | −0.330          | 0.742 |
|                                                          |             | AN/OCD       | 0.2364 | 0.1637  | 1.444           | 0.149 |
| Weight and shape concern at age 14                        | 1865        | AN           | 0.0366 | 0.0338  | 1.083           | 0.279 |
|                                                          |             | OCD          | −0.0323 | 0.0340  | −0.951          | 0.342 |
|                                                          |             | AN/OCD       | 0.0305 | 0.0342  | 0.892           | 0.372 |
| AN at age 14c,d                                          | 28 cases, 1887 controls | AN | – | – | – |
|                                                          |             | OCD          | – | – | – |
|                                                          |             | AN/OCD       | – | – | – |
| Bulimia nervosa or subthreshold bulimia nervosa at age 14c,d | 19 cases, 1896 controls | AN | – | – | – |
|                                                          |             | OCD          | – | – | – |
|                                                          |             | AN/OCD       | – | – | – |
| Binge-eating disorder or subthreshold binge-eating disorder at age 14c,d | 8 cases, 1907 controls | AN | – | – | – |
|                                                          |             | OCD          | – | – | – |
|                                                          |             | AN/OCD       | – | – | – |
| Eating disorders not otherwise specified or purging disorder at age 14c | 174 cases, 1741 controls | AN | 0.1147 | 0.0808  | 1.421           | 0.155 |
|                                                          |             | OCD          | 0.0455 | 0.0805  | 0.566           | 0.572 |
|                                                          |             | AN/OCD       | 0.1395 | 0.0817  | 1.707           | 0.088 |
| Any threshold/subthreshold eating disorder at age 14c     | 229 cases, 1686 controls | AN | 0.1107 | 0.0715  | 1.548           | 0.122 |
|                                                          |             | OCD          | −0.0200 | 0.0712  | −0.279          | 0.780 |

(Continued)
Table 3. (Continued.)

| Phenotype                                      | Sample size | PGS       | β        | s.e.   | Test statistic b | p     |
|------------------------------------------------|-------------|-----------|----------|--------|------------------|-------|
| AN/OCD                                         |             | 0.1151    | 0.0723   | 1.591  | 0.112            |       |
| Fasting at age 14                              | 1858        | AN        | −0.0009  | 0.0036 | −0.243           | 0.808 |
| OCD                                            |             | 0.0020    | 0.0036   | 0.561  | 0.575            |       |
| AN/OCD                                         |             | 0.0007    | 0.0036   | 0.183  | 0.855            |       |
| Purging at age 14                              | 1854        | AN        | −0.0030  | 0.0034 | −0.878           | 0.380 |
| OCD                                            |             | −0.0011   | 0.0034   | −0.326 | 0.744            |       |
| AN/OCD                                         |             | −0.0007   | 0.0035   | −0.188 | 0.851            |       |
| Binge eating at age 14                         | 1878        | AN        | 0.0080   | 0.0083 | 0.963            | 0.336 |
| OCD                                            |             | 0.0111    | 0.0083   | 0.133  | 0.894            |       |
| AN/OCD                                         |             | 0.0099    | 0.0084   | 1.185  | 0.236            |       |
| Compulsive exercise at age 14                  | 1787        | AN        | 0.0155   | 0.0132 | 1.176            | 0.240 |
| OCD                                            |             | 0.0164    | 0.0133   | 1.230  | 0.219            |       |
| AN/OCD                                         |             | 0.0168    | 0.0134   | 1.257  | 0.209            |       |
| AN at age 16                                   | 15 cases, 1476 controls | AN | –        | –      | –               | –     |
| OCD                                            |             | –         | –        | –      | –               | –     |
| AN/OCD                                         |             | –         | –        | –      | –               | –     |
| Bulimia nervosa at age 16                       | 25 cases, 1466 controls | AN | –        | –      | –               | –     |
| OCD                                            |             | –         | –        | –      | –               | –     |
| AN/OCD                                         |             | –         | –        | –      | –               | –     |
| Binge-eating disorder at age 16                 | 10 cases, 1481 controls | AN | –        | –      | –               | –     |
| OCD                                            |             | –         | –        | –      | –               | –     |
| AN/OCD                                         |             | –         | –        | –      | –               | –     |
| Eating disorders not otherwise specified or purging disorder at age 16 | 236 cases, 1255 controls | AN | 0.0317   | 0.0712 | 0.445           | 0.656 |
| OCD                                            |             | 0.0926    | 0.0719   | 1.287  | 0.198            |       |
| AN/OCD                                         |             | 0.0121    | 0.0721   | 0.167  | 0.867            |       |
| Any threshold/subthreshold eating disorder at age 16 | 286 cases, 1205 controls | AN | 0.0402   | 0.0660 | 0.609           | 0.543 |
| OCD                                            |             | 0.0618    | 0.0667   | 0.928  | 0.354            |       |
| AN/OCD                                         |             | 0.0338    | 0.0669   | 0.504  | 0.614            |       |
| Fasting at age 16                              | 1407        | AN        | 0.0010   | 0.0084 | 0.114           | 0.909 |
| OCD                                            |             | −0.0010   | 0.0084   | −0.113 | 0.910            |       |
| AN/OCD                                         |             | −0.0021   | 0.0085   | −0.248 | 0.804            |       |
| Purging at age 16                              | 1412        | AN        | 0.0024   | 0.0047 | 0.505           | 0.614 |
| OCD                                            |             | 0.0073    | 0.0046   | 1.582  | 0.114            |       |
| AN/OCD                                         |             | 0.0025    | 0.0047   | 0.529  | 0.597            |       |
| Binge eating at age 16                         | 1214        | AN        | 0.0132   | 0.0128 | 1.033           | 0.302 |
| OCD                                            |             | −0.0171   | 0.0129   | −1.325 | 0.185            |       |
| AN/OCD                                         |             | 0.0223    | 0.0129   | 1.723  | 0.085            |       |
| Compulsive exercise at age 16                  | 1346        | AN        | 0.0169   | 0.0197 | 0.860           | 0.390 |
| OCD                                            |             | 0.0152    | 0.0195   | 0.782  | 0.435            |       |
| AN/OCD                                         |             | 0.0124    | 0.0199   | 0.620  | 0.535            |       |

Obsessive-compulsive disorder symptom dimensions and diagnosis

| OCD at age 10c,d                               | 15 cases, 2610 controls | AN | –        | –      | –               | –     |

(Continued)
Table 3. (Continued.)

| Phenotype | Sample size | PGS | β | s.e. | Test statisticb | p       |
|-----------|-------------|-----|----|------|----------------|---------|
| OCD       | –           | –   | –  | –    | –              | –       |
| AN/OCD    | –           | –   | –  | –    | –              | –       |
| OCD latent factor – symmetry, checking at age 10 | 2607 | AN | 0.0187 | 0.0104 | 1.794 | 0.073 |
|           | OCD        | –0.0073 | 0.0105 | –0.699 | 0.484 |
|           | AN/OCD    | 0.0193 | 0.0105 | 1.830 | 0.067 |
| OCD latent factor – dirt/germs at age 10 | 2607 | AN | 0.0157 | 0.0087 | 1.798 | 0.072 |
|           | OCD        | –0.0014 | 0.0088 | –0.155 | 0.877 |
|           | AN/OCD    | 0.0160 | 0.0089 | 1.804 | 0.071 |
| OCD at age 13c,d | 6 cases, 2419 controls | AN | – | – | – | – |
| OCD       | –           | –   | –  | –    | –              | –       |
| AN/OCD    | –           | –   | –  | –    | –              | –       |
| OCD latent factor – symmetry, checking at age 13 | 2411 | AN | 0.0139 | 0.0144 | 0.961 | 0.337 |
|           | OCD        | –0.0183 | 0.0145 | –1.262 | 0.207 |
|           | AN/OCD    | 0.0154 | 0.0145 | 1.062 | 0.288 |
| OCD latent factor – dirt/germs at age 13 | 2411 | AN | –0.0297 | 0.0132 | –2.243 | 0.025* |
|           | OCD        | –0.0177 | 0.0133 | –1.327 | 0.185 |
|           | AN/OCD    | –0.0300 | 0.0133 | –2.246 | 0.025* |
| Anxiety symptom dimensions and diagnoses | | | | | | |
| Separation anxiety at age 7c | 80 cases, 2670 controls | AN | 0.0521 | 0.1152 | 0.452 | 0.651 |
| OCD       | –0.0697 | 0.1127 | –0.619 | 0.536 |
| AN/OCD    | 0.0571 | 0.1163 | 0.491 | 0.624 |
| Specific phobia at age 7c | 51 cases, 2701 controls | AN | 0.1224 | 0.1430 | 0.856 | 0.392 |
| OCD       | –0.0699 | 0.1407 | –0.497 | 0.619 |
| AN/OCD    | 0.1510 | 0.1444 | 1.046 | 0.296 |
| Latent factor – physical anxiety at age 10 | 2607 | AN | 0.0181 | 0.0143 | 1.264 | 0.206 |
| OCD       | –0.0147 | 0.0145 | –1.020 | 0.308 |
| AN/OCD    | 0.0111 | 0.0145 | 0.763 | 0.445 |
| Latent factor – worrying at age 10 | 2607 | AN | 0.0292 | 0.0133 | 2.197 | 0.028* |
| OCD       | 0.0057 | 0.0134 | 0.424 | 0.671 |
| AN/OCD    | 0.0171 | 0.0134 | 1.274 | 0.203 |
| Latent factor – social phobia at age 10 | 2607 | AN | 0.0117 | 0.0124 | 0.947 | 0.344 |
| OCD       | –0.0254 | 0.0125 | –2.037 | 0.042* |
| AN/OCD    | 0.0061 | 0.0125 | 0.486 | 0.627 |
| Social phobia at age 13c | 25 cases, 2399 controls | AN | – | – | – | – |
| OCD       | –           | –   | –  | –    | –              | –       |
| AN/OCD    | –           | –   | –  | –    | –              | –       |
| Generalized anxiety disorder at age 13c | 54 cases, 2370 controls | AN | 0.1184 | 0.1376 | 0.861 | 0.390 |
| OCD       | 0.1169 | 0.1389 | 0.841 | 0.400 |
| AN/OCD    | 0.1658 | 0.1386 | 1.196 | 0.232 |
| Latent factor – physical anxiety at age 13 | 2411 | AN | –0.0118 | 0.0140 | –0.838 | 0.402 |
| OCD       | –0.0052 | 0.0141 | –0.371 | 0.710 |
| AN/OCD    | –0.0091 | 0.0141 | –0.643 | 0.520 |

(Continued)
that OCD may be distinct from anxiety disorders at a genetic level, especially for men. Replication of these associations is required to better understand the nature of these relationships and the importance of potential sex differences in the biological pathways associated with anxiety risk.

Notably, significant PGS predictions did not always fall cleanly in accordance with hypothesized disorder-specific symptom phenotypes, especially in the case of anxiety phenotypes. For instance, AN – but not OCD – PGS predicted higher scores for OCD-dirt/germs and worrying during different developmental timepoints in girls. While contamination fears are often associated with OCD, they are not unique to OCD and have a cross-disorder component. In fact, it is not uncommon for individuals with AN to present with food-related contamination fears (Drummond & Kolb, 2008). In our previous ALSPAC study, we found that the latent factor worrying significantly predicts eating disorder symptoms at ages 14 and 16 as well as AN diagnosis at age 16 (Schaumberg et al., 2019). This may suggest that uncontrolled worrying may be an underlying early symptom of AN and disordered eating that precedes the manifestation of an eating disorder.

Our study has notable strengths that merit consideration. This is the first study to use AN, OCD, or AN/OCD PGS to predict eating disorder and anxiety intermediate phenotypes in a large population sample through a developmental perspective and also to examine how genetic risk may manifest differently in boys and girls. We augmented the diagnostic approach by including intermediate phenotypes measured continuously to capture the full range of these underlying traits in the general population. Furthermore, studying these associations in the general population allows a finer understanding of intermediate phenotypes and broader psychopathology as treatment-seeking individuals might have notable differences from the general population (e.g. increased comorbid psychopathology).

Limitations of our study include reliance on self- or parent-report symptoms instead of clinical diagnoses, phenotype data being available for only a subset of participants with the potential for response bias, and potential Type 2 error due to lack of statistical power for PGS in the prediction of genetic risk. The effect sizes observed were relatively small, and due to the exploratory nature of our study with the aim of elucidating sex differences using transdiagnostic prediction and symptom-level data, we did not correct for multiple testing with the hopes of generating potential hypotheses for future work. Of note, few participants met diagnostic criteria for AN, bulimia nervosa, or binge-eating disorder, whereas we had better statistical power for the non-specific eating disorder statuses (especially in girls), which likely explains why PGS did not predict AN diagnoses in either sex and none of the eating disorder diagnoses in boys. Similarly, a high probability (50% or higher) for anxiety disorder diagnoses was uncommon despite our attempt to increase power through dichotomizing these items, and even with dichotomizing, we did not have enough cases to include OCD diagnosis in our outcomes. Additionally, we did not address the presence of comorbid psychiatric diagnoses, therefore we cannot account for the role of comorbidities or the genetic risk associated with these additional diagnoses. However, as comorbidity is the norm and not the exception, our results are likely to capture associations that are more likely to be present in clinical and population settings, as pure forms of eating disorders and OCD are not common. With the exception of body image distortion at age 10, all eating disorder data were collected at age 14 onward, therefore we were unable to examine the potential association between PGS and eating behavior in early childhood. From a genetic perspective, whether all of the eating disorder-related symptom phenotypes examined as a part of our study actually fall on an etiological continuum with AN is not clear (Dinkler et al., 2021). Finally, the AN PGS was constructed using a much larger GWAS than the OCD GWAS, which may have translated to OCD PGS being more heavily skewed by AN PGS than OCD PGS. Taken together, results of our study provide preliminary support for utilizing the high positive genetic correlation between AN and OCD (Watson et al., 2019), leading to a small boost in predictive power through the use of a transdiagnostic PGS.

### Table 3. (Continued.)

| Phenotype                              | Sample size | PGS  | β     | s.e.  | Test statistic<sup>b</sup> | p   |
|----------------------------------------|-------------|------|-------|------|-----------------------------|-----|
| Latent factor – worrying at age 13     | 2411        | AN   | 0.0012| 0.0153| 0.077                       | 0.939|
|                                        |             | OCD  | 0.0017| 0.0154| 0.109                       | 0.914|
|                                        |             | AN/OCD|−0.0022|0.0154|−0.143                      | 0.886|
| Latent factor – social phobia at age 13| 2411        | AN   | 0.0200| 0.0147| 1.364                       | 0.173|
|                                        |             | OCD  | −0.0023|0.0148|−0.154                      | 0.877|
|                                        |             | AN/OCD|0.0078|0.0148|0.527                       | 0.598|
| Generalized anxiety disorder at age 15<sup>c</sup> | 42 cases, 1813 controls | AN   | –     | –     | –                           | –   |
|                                        |             | OCD  | –     | –     | –                           | –   |
|                                        |             | AN/OCD|–     |–     |–                           | –   |

Abbreviations: PGS, polygenic score; β, standardized beta regression coefficient; s.e., standard error; AN, anorexia nervosa; OCD, obsessive-compulsive disorder; AN/OCD, anorexia nervosa/obsessive-compulsive transdiagnostic phenotype.

<sup>a</sup>Genomic principal components 1-5 were used as covariates to account for population stratification.

<sup>b</sup>T-values for continuous phenotypes and z-values for binary phenotypes.

<sup>c</sup>Binary phenotype.

<sup>d</sup>Due to insufficient statistical power, any binary measure with less than 50 cases is not included in the final analysis.

<sup>e</sup>(also bolded) Statistically significant at p < 0.05.
anticipate this statistical boost to become more notable as AN and (especially) OCD GWAS sample sizes continue to increase. Furthermore, our findings also point to differences in the manifestation of genetic risk for eating disorder and anxiety symptoms in boys and girls. Genetic risk associated with AN may be a stronger predictor of eating disorder symptoms earlier in development, whereas OCD genetic risk—albeit limited based on current GWAS data—may increase in effect across adolescence. Another significant observation was that compulsive exercise may be an intermediate phenotype or clinical manifestation of shared genetic risk factors for both AN and OCD. Compulsive exercise might be a distinct AN subphenotype, and clinical research should continue to explore habitual and compulsive processes associated with this symptom. Finally, this study opens up new avenues for a clearer understanding of biology of behaviors and intermediate phenotypes in eating disorders.

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Author contributions. ZY was responsible for genetic study design, quality control of genotype data, genetic analyses, and manuscript preparation. KS, EIL, and LCB were responsible for study design, quality control and preparation of phenotype data, statistical analysis of phenotype data, and manuscript preparation. MH was responsible for carrying out the transdiagnostic AN/OCD GWAS. JJC, MM, CAM, and GB were responsible for genetic study design, oversight of genetic analyses, and manuscript preparation. CMB oversaw and participated in the development of the research question, study design, and manuscript preparation. NM and SCZ were responsible for the development of the research question and provided oversight for all aspects of the study.

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Conflict of interest. CAM has received funding for a book contract with W.W. Norton, Inc., serves as a co-chair of the Tourette Association of America scientific advisory board, is a member of the International OCD Foundation scientific and clinical advisory board, as well as a member of the steering committee for the Family Foundation for OCD Research. GB received grant funding and consultancy fees in preclinical genetics from Eli Lilly, consultancy fees from Otsuka, and has received honoraria from Illumina. CMB has received grant support and served on Shire Scientific Advisory Board, is a consultant for Idorsia, and receives author royalties from Pearson. All other authors have no conflicts of interest to disclose.

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