

Shared Genetic Risk between Eating Disorder- and Substance-Use-Related Phenotypes: Evidence from Genome-Wide Association Studies

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Abstract

Eating disorders and substance use disorders frequently co-occur. Twin studies reveal shared genetic variance between liabilities to eating disorders and substance use, with the strongest associations between symptoms of bulimia nervosa and problem alcohol use (genetic correlation [r_g], twin-based=0.23-0.53). We estimated the genetic correlation between eating disorder and substance use and disorder phenotypes using data from genome-wide association studies (GWAS). Four eating disorder phenotypes (anorexia nervosa [AN], AN *with* binge-eating, AN *without* binge-eating, and a bulimia nervosa factor score), and eight substance-use-related phenotypes (drinks per week, alcohol use disorder [AUD], smoking initiation, current smoking, cigarettes per day, nicotine dependence, cannabis initiation, and cannabis use disorder) from eight studies were included. Significant genetic correlations were adjusted for variants associated with major depressive disorder and schizophrenia. Total study sample sizes per phenotype ranged from ~2,400 to ~537,000 individuals. We used linkage disequilibrium score regression to calculate single nucleotide polymorphism-based genetic correlations between eating disorder- and substance-use-related phenotypes. Significant positive genetic associations emerged between AUD and AN ($r_g=0.18$; false discovery rate $q=0.0006$), cannabis initiation and AN ($r_g=0.23$; $q<0.0001$), and cannabis initiation and AN *with* binge-eating ($r_g=0.27$; $q=0.0016$). Conversely, significant negative genetic correlations were observed between three non-diagnostic smoking phenotypes (smoking initiation, current smoking, and cigarettes per day) and AN *without* binge-eating ($r_{gs}=-0.19$ to -0.23 ; $qs<0.04$). The genetic correlation between AUD and AN was no longer significant after co-varying for major depressive disorder loci. The patterns of association between eating disorder- and substance-use-related phenotypes highlights the potentially complex and substance-specific relationships among these behaviors.

Eating and Substance Use

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Keywords: eating disorders; substance use; genetic correlation

For Review Only

Shared Genetic Risk between Eating Disorder- and Substance-Use-Related Phenotypes: Evidence from Genome-Wide Association Studies

Well-established phenotypic associations exist between eating disorder and substance use phenotypes, with evidence for specific relations between particular types of eating disorders and substance use disorders. The prevalence of an alcohol use disorder (AUD) is greater among individuals with bulimia nervosa and binge-eating disorder than individuals with anorexia nervosa (AN) or healthy controls (Gadalla and Piran, 2007, Root *et al.*, 2010). Similarly, individuals with bulimia nervosa or binge-eating disorder are at increased risk for smoking, nicotine dependence (Solmi *et al.*, 2016, Wiederman and Pryor, 1996), and cannabis use (Krug *et al.*, 2008, Wiederman and Pryor, 1996) compared with individuals with AN or healthy controls, though these results are not consistent (Root *et al.*, 2010). Importantly, women with the binge-eating/purging subtype of AN report a higher prevalence of AUD, smoking, nicotine dependence, and cannabis use than women with the restricting subtype of AN (Anzengruber *et al.*, 2006, Krug *et al.*, 2008, Root *et al.*, 2010). Thus, binge eating—a transdiagnostic symptom defined as eating a large amount of food in a short period of time while experiencing loss of control—may be a key component of the observed association.

However, prior research has only partially addressed whether binge eating is the critical eating disorder symptom in the comorbidity, especially across different milestones of substance use (i.e., initiation through substance use disorder) and across a variety of substances (i.e., alcohol, nicotine, and cannabis). Elucidating shared sources for these associations is crucial because of the increased morbidity and mortality associated with comorbid presentations (Duncan *et al.*, 2006, Franko *et al.*, 2013) and because improvements in one disorder may exacerbate (or weaken) symptoms of the other disorder (Center on Addiction and Substance

Abuse, 2003). Refining our understanding of these associations could improve prevention and treatment approaches for these debilitating disorders, their comorbidity, and their sequelae.

Accumulating findings from twin studies implicate shared genetic factors between eating disorder- and substance-use-related phenotypes. The strongest reported association is between bulimia nervosa symptoms (including binge eating) and problem alcohol use, with a genetic correlation (r_g) ranging from 0.23 to 0.53 (for a review, see Munn-Chernoff and Baker, 2016). Although there has been less focus on genetic associations between bulimia nervosa symptoms and regular smoking and bulimia nervosa symptoms and illicit drug use disorder, twin-based r_g s of 0.35 and approximately 0.38, respectively, have been reported (Baker *et al.*, 2007, Baker *et al.*, 2010). Limited information exists regarding whether less problematic aspects of substance use exhibit a significant r_g with eating disorder phenotypes. The impact of genetic factors influencing this comorbidity may significantly increase once an individual has progressed to problematic alcohol use, as genetic effects are more prominent in problem substance use, such as abuse and dependence, than with the initiation and general use of substances (Heath *et al.*, 1997, Rhee *et al.*, 2003, True *et al.*, 1997, van den Bree *et al.*, 1998). No study has comprehensively examined a range of eating disorder- and substance-use-related phenotypes to determine whether the r_g varies with different aspects of substance use and whether the r_g varies depending on the eating disorder and substance examined.

Recent advances in genomic methods allow for an assessment of r_g using existing genome-wide association study (GWAS) summary statistics. Unlike twin studies, these genome-wide methods allow for use of unrelated cases and controls, typically yielding sample sizes in the tens to hundreds of thousands. One such method, linkage disequilibrium score regression (LDSC; Bulik-Sullivan *et al.*, 2015a, Bulik-Sullivan *et al.*, 2015b), estimates single-nucleotide

polymorphism (SNP)-based heritability and r_g between phenotypes. Of particular relevance to low prevalence phenotypes, such as AN, estimation of SNP-based r_g does not require both phenotypes to be measured in the same individual; thus, independent studies assessing only one phenotype can be jointly examined.

The current study estimated SNP-based genetic correlations (r_{gs}) between eating disorder- and substance-use-related phenotypes based upon summary statistics from the largest published eating disorder GWAS and existing GWAS encompassing a range of substance-use-related phenotypes (i.e., alcohol, nicotine, and cannabis), using robust data from twin studies to shape our three hypotheses. First, we hypothesized that the strongest SNP-based r_g would be between eating disorder phenotypes that have binge eating as a core symptom and alcohol use phenotypes, rather than between eating disorder phenotypes and nicotine- and cannabis-use-related phenotypes (Munn-Chernoff and Baker, 2016). Second, we hypothesized that for binge-eating-related phenotypes, the SNP-based r_g would be higher when assessing AUD than typical alcohol consumption (Munn-Chernoff and Baker, 2016), since we expected that two problem behaviors are more likely to share genetic risk than a problem behavior (e.g., binge eating) and a normative pattern (e.g., alcohol consumption). Because we have less information from twin studies about genetic associations between liabilities to eating disorders and tobacco (nicotine) and cannabis use-related phenotypes, we do not forward specific hypotheses for these substances. Finally, prior studies document robust genetic associations for major depressive disorder and schizophrenia with both eating disorders and substance-use-related phenotypes (e.g., Kranzler *et al.*, 2019; Liu *et al.*, 2019; Watson *et al.*, 2019). We hypothesized that r_{gs} between eating disorders and substance use and disorder would be attenuated when accounting for variants associated with major depressive disorder and schizophrenia. Findings from this

study will yield important information about the role of genetics in this clinically challenging pattern of comorbidity (Gregorowski *et al.*, 2013).

Method

Participants

We included summary statistics from two existing GWAS of eating disorder phenotypes where participants were primarily of European ancestry (Wade *et al.*, 2013, Watson *et al.*, 2019) and data from individuals of European ancestry from six existing GWAS of substance-use-related phenotypes (Demontis *et al.*, 2019, Hancock *et al.*, 2017, Kranzler *et al.*, 2019, Liu *et al.*, 2019, Pasman *et al.*, 2018, Walters *et al.*, 2018). The eating disorder phenotypes (**Table 1**) included a diagnosis of AN (which was further parsed into AN *with* binge-eating or AN *without* binge-eating) and a bulimia nervosa factor score derived from the Eating Disorder Examination (Fairburn and Cooper, 1993), a well-established structured clinical interview for eating disorders. We did not examine bulimia nervosa or binge-eating disorder because there are currently no published GWAS for either disorder; thus, the bulimia nervosa factor score represents the closest to a GWAS of bulimia nervosa available. Substance-use-related phenotypes ranged from typical use (e.g., drinks per week, smoking initiation, and cannabis initiation) to substance use disorder (i.e., AUD, nicotine dependence, and cannabis use disorder). Sample sizes for the phenotypes ranged from 2,442 (bulimia nervosa factor score) to 537,349 (drinks per week) individuals. **Table 2** provides individual study details.

Statistical Analysis

We used LDSC (Bulik-Sullivan *et al.*, 2015a, Bulik-Sullivan *et al.*, 2015b) to evaluate SNP-based genetic correlations (r_g) between samples. This method uses the linkage disequilibrium (LD) structure of the genome to estimate the distribution of effect sizes for individual SNPs as a function of their LD score. Under a polygenic model, causal SNPs are likely to be overrepresented in higher LD score bins (i.e., including additional SNPs in high LD), such that associations with SNPs in these LD bins will make stronger contributions to the phenotypic variation under study. This polygenic distribution of effect sizes across LD score bins provides an estimate of SNP-based heritability, i.e., the proportion of phenotypic variance that is attributable to the aggregate effects of genome-wide SNPs. The correlation of effect sizes across LD bins between two phenotypes then provides an estimate of SNP-based r_g .

Genetic correlations range from -1 to +1, where the sign indicates that the same genetic factors are contributing to variation in the target traits in *opposite* or *same* directions, respectively. The LDSC intercept for the genetic covariance provides evidence about sample overlap across two traits. SNPs (MAF>0.01) found in the HapMap3 EUR population were used to calculate LD scores. We used the false discovery rate (Benjamini and Hochberg, 1995) to correct for multiple testing ($n=66$ tests; $q<0.05$). Finally, post-hoc analyses examined whether significant differences between two r_g s existed, using the jackknife procedure implemented through LDSC (Bulik-Sullivan *et al.*, 2015b).

We used GNOVA (Lu *et al.*, 2017a) to stratify significant r_g s between the eating disorder- and substance-use-related phenotypes into both tissue-specific (for seven broadly-defined tissue classes: brain, cardiovascular, epithelial, gastrointestinal, immune-related,

muscular, and “other”) and non-tissue-specific functional regions of the genome. GenoCanyon (Lu *et al.*, 2015) and GenoSkyline (Lu *et al.*, 2017b, Lu *et al.*, 2016) annotation methods, which integrate transcriptomic and epigenomic data from ENCODE (Encode Project Consortium, 2012) and Roadmap Epigenomics Project (Roadmap Epigenomics Consortium *et al.*, 2015), were used to define functional regions of the genome.

Finally, for significant r_{gs} detected in LDSC, multi-trait-based conditional and joint analysis using GWAS summary data (mtCOJO; Zhu *et al.*, 2018) was used to condition both input GWAS (e.g., AN and AUD) for variants associated with major depressive disorder (Wray *et al.*, 2018) at $p < 5 \times 10^{-7}$ and schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, 2014) at $p < 5 \times 10^{-8}$. Because fewer genome-wide significant SNPs were identified for major depressive disorder than schizophrenia, we chose a more lenient p -value threshold for major depressive disorder to capture a comparable number of SNPs. LDSC was used to compute r_{gs} using the resulting genome-wide summary statistics for each trait after separately adjusting for major depressive disorder or schizophrenia variants to examine whether conditioning on either disorder would affect the observed genetic relationships.

Results

The overall SNP-based heritability for the eating disorder phenotypes ranged from 0.20 to 0.39, whereas the corresponding heritabilities for the substance-use-related phenotypes ranged from 0.03 to 0.35 (Table S1). Figure 1 and Table S1 show the genetic correlations (r_{gs}) between all four eating disorder phenotypes and eight substance-use-related phenotypes. Broadly speaking, there were significant r_{gs} across substance-use-related phenotypes, ranging from 0.21 (AUD and cigarettes per day) to 0.70 (drinks per week and AUD). Cannabis initiation risk was

not significantly genetically correlated with cigarettes per day or nicotine dependence. For the remaining results, we focus on previously unexplored associations of interest in this study— correlations between eating disorder- and substance-use-related phenotypes. For these associations, the genetic covariance intercepts ranged from -0.03 (standard error [SE]=0.01; AN and cannabis initiation) to 0.01 (SE=0.01; AN and cannabis use disorder), indicating some sample overlap (or low-level confounding) existed (Yengo *et al.*, 2018), although the LDSC approach parses this overlap from the r_g estimation.

Significant positive r_g s were observed for alcohol- and cannabis-use-related phenotypes. First, the r_g was significant between AN and AUD ($r_g=0.18$; SE=0.05; $q=0.0006$), but not between AN and drinks per week ($r_g=0.01$; SE=0.03; $q=0.91$), suggesting that genetic factors that increase risk for AN also increase risk for AUD, but little evidence exists for shared genetic risk between AN and typical alcohol consumption. These two correlations significantly differed from each other (z-score=3.51, $p=0.0005$). Intriguingly, there was a significant difference in r_g s for AN and AUD versus AN *without* binge-eating and AUD (z-score=2.28, $p=0.02$), but not for AN and AUD versus AN *with* binge-eating and AUD (z-score=0.23, $p=0.82$). The genetic covariance estimates between AN and AUD were significant in both functional (corrected $\rho_g=0.01$; corrected $r=0.23$; corrected $q=0.007$) and non-functional categories (corrected $\rho_g=0.01$; corrected $r=0.19$; corrected $q=0.002$; **Table S2**), but not in any specific tissue type. No significant association between the bulimia nervosa factor score, which included items pertaining to both binge eating and compensatory behaviors, and either alcohol-use-related phenotype was observed.

Second, the significant r_g between AN and cannabis initiation was 0.23 (SE=0.04, $q<0.0001$) and the significant r_g between AN *with* binge-eating and cannabis initiation was 0.27

($SE=0.08$, $q=0.0017$), indicating that genetic factors that increase the risk for AN may also increase risk for cannabis initiation. However, cannabis initiation was not significantly correlated with the bulimia nervosa factor score ($r_g=0.15$, $SE=0.18$, $q=0.57$) or with AN *without* binge-eating ($r_g=0.10$, $SE=0.08$, $q=0.31$). No significant associations were observed between any eating disorder phenotype and cannabis use disorder (r_g s=-0.08-0.23; SE s=0.01; q s ≤ 0.57). Post-hoc analyses revealed significant differences in the r_g s for AN and cannabis initiation versus AN and cannabis use disorder (z -score=2.70, $p=0.01$). However, the r_g between AN *with* binge-eating and cannabis initiation, while significant, was statistically different from the r_g between AN *with* binge-eating and cannabis use disorder. The genetic covariance estimate between AN *with* binge-eating and cannabis initiation was significant in both functional (corrected $\rho_g=0.01$; corrected $r=0.60$; corrected $q<0.0001$) and non-functional categories (corrected $\rho_g=0.01$; corrected $r=0.30$; corrected $q=0.004$; **Table S3**), but not in any specific tissue type. The genetic covariance estimate between AN *without* binge-eating and cannabis initiation was only significant in non-functional categories (corrected $\rho_g=0.01$; corrected $r=0.27$; corrected $q=0.004$; **Table S4**).

Conversely, for smoking phenotypes, significant correlations were only observed for the AN *without* binge-eating subtype. Smoking initiation ($r_g=-0.21$, $SE=0.06$, $q=0.0006$), current smoking (referred to as smoking cessation in [Liu *et al.*, 2019])¹ ($r_g=-0.19$, $SE=0.08$, $q=0.03$), and cigarettes per day ($r_g=-0.23$, $SE=0.07$, $q=0.003$) were significantly and negatively associated with AN *without* binge-eating. Although the correlation between nicotine dependence and AN *without* binge-eating was in the same direction as the other smoking phenotypes, it was not significant ($r_g=-0.22$, $SE=0.12$, $q=0.14$). The r_g s for AN diagnosis and each of the three non-

¹ In Liu *et al.* (2019), the phenotype is noted as “smoking cessation”, where current smokers were coded as 2 and former smokers were coded as 1. Because the comparison group is “current smokers”, we have renamed this phenotype as “current smoking” for clarification and ease of interpretation across all smoking phenotypes.

diagnostic smoking traits versus AN *without* binge-eating and these same smoking traits all differed significantly from each other (z-scores ranged from -3.22 to -2.11; p -values ≤ 0.04). The genetic covariance estimate between AN *without* binge-eating and smoking initiation was only significant in the non-functional category (corrected $\rho_g = -0.01$; corrected $r = -0.17$; corrected $q = 0.007$; **Table S5**). For AN *without* binge-eating and current smoking, the genetic covariance estimate was significant in both functional (corrected $\rho_g = -0.01$; corrected $r = -0.32$; corrected $q = 0.01$) and non-functional categories (corrected $\rho_g = -0.01$; corrected $r = -0.21$; corrected $q = 0.03$; **Table S6**). Finally, the genetic covariance estimate between AN *without* binge-eating and cigarettes per day was only significant in the non-functional category (corrected $\rho_g = -0.02$; corrected $r = -0.35$; corrected $q = 0.003$; **Table S7**).

After conditioning the AN and AUD GWAS summary statistics for loci associated with major depressive disorder, the positive r_g between AN and AUD was attenuated ($r_g = 0.07$; $SE = 0.05$, $q = 0.125$; **Table S8**) and significantly lower than the unadjusted r_g (z-score = 2.48, $p = 0.01$). In contrast, after conditioning the AN *with* binge-eating and cannabis initiation GWAS for major depressive disorder, the resulting r_g was marginally smaller but remained significant after correction for multiple tests ($r_g = 0.21$, $SE = 0.08$, $q = 0.016$). After conditioning for the major depressive disorder GWAS, r_{gs} between AN *without* binge-eating and smoking initiation, current smoking, and cigarettes per day remained significant and modestly increased in magnitude ($r_{gs} = -0.27$ to -0.31 ; $SEs = 0.05$ to 0.09 ; $qs < 0.0009$). All r_{gs} remained significant after conditioning the AN and substance-use-related phenotypes for schizophrenia ($r_{gs} = -0.20$ to 0.27 ; $SEs = 0.04$ to 0.08 ; $qs < 0.03$; **Table S9**).

Discussion

Using existing GWAS data, we investigated genetic associations between liabilities to four eating disorder- and eight substance-use-related phenotypes spanning initiation and typical use to substance use disorder. We found differential patterns of association between AN with and without binge-eating and substance-use-related traits, which may point toward substance-specific genetic relationships. Additionally, there may be some degree of symptom overlap contributing to these associations.

Three main patterns emerged. First, in line with prior twin studies, we observed a positive genetic correlation (r_g) between problem alcohol use (i.e., AUD) and AN diagnosis. Second, we observed positive, significant r_g s between cannabis initiation and AN diagnosis, as well as cannabis initiation and the AN *with* binge-eating subtype. This is a novel finding not previously examined in twin research. The positive genetic associations suggest that some genetic loci may be influencing these traits in the same direction. Second, negative r_g s emerged between the three non-diagnostic smoking phenotypes and AN *without* binge-eating, but not with the other three eating disorder phenotypes. These negative r_g s indicate that some of the loci influencing liability to these eating disorder and smoking phenotypes might be shared, but are affecting the liability to these traits in opposite directions. Indeed, r_g s cannot identify specific loci or underlying mechanisms that contribute to the shared risk. Nevertheless, the results provide initial evidence for differential genetic associations between the liability to varying eating disorder- and substance-use-related phenotypes.

Based on findings from twin studies, we hypothesized that: 1) the strongest SNP-based r_g would be between eating disorder phenotypes that have binge eating as a core symptom and alcohol use phenotypes; and 2) a significant positive r_g between eating disorder phenotypes with

binge eating as a key symptom and AUD would emerge. In line with these hypotheses, we found a significant genetic association between AUD and AN diagnosis, but not between typical alcohol consumption (i.e., drinks per week) and AN. No twin study has examined genetic associations between AN and alcohol-use-related phenotypes, and previous studies (Walters *et al.*, 2018, Watson *et al.*, 2019) using LDSC have not reported significant r_g s between these traits. That we found a significant association most likely reflects the larger AN sample size in our study (from 3,495 cases and 10,982 controls to 16,992 cases and 55,525 controls), as well as combining two large existing GWAS of AUD, emphasizing the importance of increasing sample sizes for GWAS.

Importantly, the r_g s between the eating disorder- and substance-use-related phenotypes were robust to conditioning on schizophrenia loci. However, the r_g between AN and AUD was not robust to the adjustment for major depressive disorder-associated variants. Major depressive disorder is among the most prominent comorbidities in individuals with AN and AUD (American Psychological Association, 2013), and GWAS for both traits document strong r_g s between major depressive disorder and these disorders (Kranzler *et al.*, 2019; Walters *et al.*, 2019; Watson *et al.*, 2019). Our results indicate that the three disorders share genetic underpinnings. We cannot discount the possibility of a genetic relationship between AN and AUD that is distinct from major depressive disorder; however, much larger sample sizes may be required to detect such an association.

Intriguingly, although we did not detect a significant r_g for AN *with* binge-eating with AUD, the point estimate for the r_g between AUD and AN *with* binge eating was similar to that for AUD and AN diagnosis (0.17 vs. 0.18, respectively) and higher than AUD and AN *without* binge eating (0.01). Sample sizes for these AN subtypes were smaller than for AN diagnosis;

however, the two subtypes included approximately equal numbers of cases and controls. Indeed, binge eating was assessed in such a way that we were unable to tease apart purging behaviors, and AN diagnosis is heterogenous even within subtypes. Therefore, binge eating may be one plausible key component of the observed genetic association. For example, binge eating has been shown to activate brain reward circuitry in a similar manner to substances (e.g., Volkow *et al.*, 2013), and administration of naltrexone, an opioid antagonist approved by the U.S. Food and Drug Administration for the treatment of AUD (Kranzler and Soyka, 2018), has been shown to reduce the frequency of binge-eating episodes among individuals with an eating disorder (e.g., Stancil *et al.*, 2019). We did not detect a significant r_g with the bulimia nervosa factor score, although that GWAS was relatively underpowered. Thus, our findings highlight the importance of expanding GWAS to include bulimia nervosa and binge-eating disorder, where a core symptom of both disorders is binge eating, to elucidate whether binge eating is a critical eating disorder symptom in the comorbidity with AUD and to home in on relevant shared mechanisms.

The significant genetic associations between cannabis initiation and AN are novel, yet consistent with the negative genetic association between cannabis use and body mass index, and with observational (Pasman *et al.*, 2018) and experimental (Di Marzo and Matias, 2005, Volkow *et al.*, 2017) studies regarding the role of endocannabinoids in appetite regulation, energy expenditure, stress, and reward. One of the principal psychoactive agents of cannabis, delta-9-tetrahydrocannabinol (THC), a partial agonist of the endogenous cannabinoid 1 (CB1) receptor, is presumed to be orexigenic and may acutely increase appetite and food intake, contributing to its potential role as an appetite stimulant in patients with an anorexia or cachexia syndrome (Reuter and Martin, 2016) due to a disease (e.g., HIV, AIDS) or in response to treatment (e.g., chemotherapy). An antagonist of the CB1 receptor was previously tested as a highly promising

anti-obesity medication (Rimonabant, SR141716), which is particularly relevant since some genes may influence AN and obesity in opposite directions (Watson *et al.*, 2019). Further, the endocannabinoid anandamide has been shown to be elevated in individuals with acute AN (Monteleone and Maj, 2013), indicating disruption in food-related reward and eating behavior regulation. Animal and human studies have also provided initial evidence for the therapeutic effectiveness of cannabinoid agonists in treating eating disorders (Andries *et al.*, 2014, Avraham *et al.*, 2017). It is also likely that individuals with high genetic liability to AN are less likely to experiment with a substance that has a documented hyperphagia component. Thus, there is evidence of a complex biological relationship between cannabis use and eating disorders, as well as body mass index.

Finally, the significant negative r_g s between three tobacco-smoking phenotypes—smoking initiation, current smoking, and cigarettes per day—and AN *without* binge-eating are intriguing, suggesting that AN *without* binge-eating and tobacco-smoking behaviors are alternate expressions of shared mechanisms. Phenotypic studies are inconsistent about the association between the restricting subtype of AN and smoking. Some studies suggest that individuals with restricting AN have a higher prevalence of various smoking phenotypes than controls (Krug *et al.*, 2008), whereas other studies indicate no significant difference between the two groups (Anzengruber *et al.*, 2006). A recent meta-analysis did not find differences in the odds of lifetime smoking between individuals with AN and healthy controls (Solmi *et al.*, 2016), yet the authors did not assess differences by AN subtype. Individuals with AN may smoke as a way to control or lose weight (White, 2011), and temporary weight gain does occur with smoking cessation (Filozof *et al.*, 2004). However, a positive phenotypic correlation need not be accompanied by a r_g in the same direction (or genetic contributors to the phenotypic association at all). Still, there is

plausible support for the negative r_g . Although not significant, a negative r_g between smoking and AN has been reported (Bulik-Sullivan *et al.*, 2015a, Watson *et al.*, 2019). Notably, our study includes individuals from these earlier reports and extends findings by including larger sample sizes for both AN and smoking phenotypes. Unfortunately, there are no twin studies of AN or AN-like traits and smoking with which to compare findings.

One explanation for the negative genetic association is that it is due to a third, underlying variable influencing both AN *without* binge-eating and smoking. We tested for the potential role of variants associated with major depressive disorder and schizophrenia and found the r_g s to be robust to those adjustments. In the largest GWAS of smoking phenotypes, positive r_g s were also observed between smoking initiation and cigarettes per day with multiple cardiometabolic traits, including type 2 diabetes and fasting glucose (Liu *et al.*, 2019). These same metabolic traits were negatively genetically correlated with AN (Watson *et al.*, 2019). Thus, the patterns of r_g s might point to metabolic, rather than psychiatric, factors in influencing the apparent genetic association between smoking phenotypes and AN. However, the associations could also reflect adoption of unhealthy lifestyles that promote obesity and are correlated with smoking. In addition, the r_g s between smoking and body mass index, as well as AN and body mass index, may reflect underlying disinhibitory pathways, as variants associated with body mass index show enrichment in the central nervous system (Goodarzi, 2018). The current approach is not designed to disentangle these putative etiological mechanisms, but our findings do encourage careful study of the specific relationships between eating and substance use disorders.

Substance use and substance use disorders are partially distinct, and although excessive substance use is a necessary component of substance use disorders, the latter is associated with psychological and physiological impairment related to excess use and aspects of loss of control

over the behavior. Consistent with our findings for alcohol, accumulating evidence suggests that genetic liability to other psychiatric traits (e.g., schizophrenia) is strongly correlated with liability to substance use disorders (e.g., AUD) but not substance use (e.g., alcohol consumption; Kranzler *et al.*, 2019; Liu *et al.*, 2019; Walters *et al.*, 2018). Genetic liability to alcohol use has also been correlated with liabilities to psychiatric disorders (e.g., major depressive disorder) in opposite directions depending on level of involvement (Kranzler *et al.*, 2019). However, we did not find similar elevations in r_g s when contrasting ever smoking and nicotine dependence, nor comparing cannabis initiation to cannabis use disorder. It is possible that the lack of genetic overlap between AN and nicotine dependence, as well as AN and cannabis use disorder, is related to the relatively modest sample size of those discovery GWAS. A similar non-significant r_g was noted for AUD when the Walters *et al.*, 2018 alcohol dependence GWAS was used as the sole source of summary statistics for problem drinking in the current study. Several other explanations for this divergence in findings exist. For instance, for tobacco, the highly addictive nature of nicotine may result in convergence in genomic effects on earlier and later stages of smoking (i.e., a much larger proportion of those who ever smoke become dependent compared with the proportion of those who drink alcohol and develop AUD). For cannabis, given its lower addictive potential, we might have expected stronger associations with cannabis use disorder than with cannabis initiation. In addition to the considerably smaller sample size of the cannabis use disorder GWAS, the association with cannabis initiation could also be attributed to the small number of cohorts in that discovery GWAS that included individuals with a high likelihood of cannabis use disorder. It is also possible that the relationship between AN and cannabis use is distinct and that earlier, but not later stages of cannabis use are genetically related to liability to

AN. Future studies should consider the multi-stage nature of substance use and misuse when examining cross-trait correlations.

This is the largest and most comprehensive assessment of shared genetic risk between eating disorder- and substance-use-related phenotypes, using existing GWAS data from large cohorts (up to ~537,000 individuals per phenotype). We were able to separately assess approximate AN subtypes (i.e., *with* binge-eating vs. *without* binge-eating) to evaluate the extent to which binge eating, in the context of AN, may share genetic risk with substance-use-related phenotypes. Using these large datasets—many of which are publicly available—allows for the rapid development of scientific knowledge regarding the underlying etiology of psychiatric disorder and substance use comorbidity. Nevertheless, some limitations exist. First, sample sizes for the bulimia nervosa factor score and cannabis use disorder GWAS were relatively small compared with the other GWAS, resulting in large standard errors and low power. Second, we were unable to uniformly examine sex differences in these r_g s. Since the prevalence of eating disorders is higher in women than men, and the prevalence of substance use disorders is higher in men than women (American Psychiatric Association, 2013), it will be important to explore possible sex differences in genetic associations as the GWAS data become available. Notably, we previously did not find evidence for sex differences in the r_g between binge eating and problem alcohol use (Munn-Chernoff *et al.*, 2013). Third, even though we did not detect significant r_g s for all pairs of traits, it is possible that local genetic associations exist for some of these trait pairs. Such local correlations, for instance, in certain chromosomal regions but not others, particularly when in opposing directions (e.g., a positive local correlation at one chromosomal location and a negative local correlation at another) might dilute the overall r_g estimate. Although such a systematic evaluation of each pair of traits is beyond the scope of this

report, we did note some support for enrichment of the aggregated genetic covariance in both functional and non-functional genomic regions for several of the significant r_g s. Finally, SNP coverage was limited in the earlier GWAS of the bulimia nervosa factor score because that study used older genotyping platforms and imputation panels that included fewer SNPs than current imputation panels. The Eating Disorders and Substance Use Disorders Working Groups of the Psychiatric Genomics Consortium are continuously adding samples and releasing data freezes with incrementally larger sample sizes, while collecting information on multiple substances (e.g., opioids). In coming years, the statistical power is expected to increase for AN (including the *with* and *without* binge-eating subtypes), bulimia nervosa, and binge-eating disorder, as well as AUD, nicotine dependence, and cannabis use disorder, from within and outside the Psychiatric Genomics Consortium. This will allow for a more refined assessment of specific eating disorder symptoms, including binge eating, in relation to substance-use-related phenotypes.

In conclusion, findings from this study suggest that the shared sources of variation in liabilities to eating disorder- and substance-use-related phenotypes are not consistent across traits or levels of substance involvement, extending results from twin studies to a genome-wide SNP approach. Despite the typically high co-occurrence of alcohol, tobacco, and cannabis use, and their genetic overlap (Pasman *et al.*, 2018), the differential patterns seen between the eating disorder- and substance-use-related phenotypes highlight the uniqueness and complexity of their shared etiology. Potential clinical implications include watching for the emergence of symptoms of one disorder (e.g., AN) while being treated for the other behavior (e.g., alcohol use disorder), and understanding that, for example, women with AN who use nicotine may not be able to quit successfully both because they are afraid of gaining weight and they have high genetic susceptibility for smoking via the shared genetic risk between AN and smoking-related traits.

Additional research using contemporary genomic methods, such as cross-disorder association studies, could identify the specific loci contributing to this comorbidity. Future research that combines genome-wide data with measured environmental constructs, such as trauma (Center on Addiction and Substance Abuse, 2003), that may increase risk for this comorbidity could enhance the prediction, prevention, and treatment of co-occurring eating disorder- and substance-use-related traits.

For Review Only

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Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED)

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Substance Use Disorders Working Group of the Psychiatric Genomics Consortium (PGC-SUD)

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Data Access

This manuscript was a joint collaboration between the Eating Disorders and Substance Use Disorders Working Groups of the Psychiatric Genomics Consortium. These data can be found at <https://www.med.unc.edu/pgc/data-index/>. Additional datasets included in this study were obtained multiple ways. We received summary statistics directly from the first author of the primary GWAS manuscript for the bulimia nervosa factor score (Australian Twin Registry), alcohol use disorder (Million Veteran Program), nicotine dependence (multiple samples), and cannabis initiation (International Cannabis Consortium and UK Biobank). Summary statistics for drinks per week, smoking initiation, smoking cessation, and cigarettes per day (GSCAN) were downloaded from <https://conservancy.umn.edu/handle/11299/201564> on March 7, 2019. Summary statistics for cannabis use disorder (iPSYCH) were downloaded from <https://ipsych.dk/forskning/downloads/> on June 27, 2019.

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Authors Contribution

M. Munn-Chernoff, C. Bulik, and A. Agrawal were responsible for the study concept and design. M. Munn-Chernoff, E.C. Johnson, and Y.-L. Duan performed the statistical analyses, and J. Coleman, R. Walters, and Z. Yilmaz assisted with the data analysis. M. Munn-Chernoff, E.C. Johnson, Y.L. Duan, J. Coleman, L. Thornton, R. Walters, Z. Yilmaz, J. Baker, C. Hübel, J. Kaprio, H. Edenberg, C. Bulik, and A. Agrawal assisted with interpretation of findings. T. Wade facilitated access to and interpretation of the summary statistics for the bulimia nervosa factor score. H. Kranzler, J. Gelernter, and H. Zhou facilitated access to and interpretation of the Million Veteran Program summary statistics for AUD. D. Hancock facilitated access to and interpretation of the summary statistics for nicotine dependence. M. Munn-Chernoff, E.C. Johnson, L. Thornton, C. Bulik, and A. Agrawal drafted the manuscript. All remaining authors provided data for this study and consulted on the analytic plan. All authors critically reviewed the content and approved the final version for publication.

References

1000 Genomes Project Consortium, Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, Marchini JL, McCarthy S, McVean GA, Abecasis GR (2015). A global reference for human genetic variation. *Nature* 526:68-74.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: Author.

Andries A, Frystyk J, Flyvbjerg A, Stoving RK (2014). Dronabinol in severe, enduring anorexia nervosa: a randomized controlled trial. *Int J Eat Disord* 47:18-23.

Anzengruber D, Klump KL, Thornton L, Brandt H, Crawford S, Fichter MM, Halmi KA, Johnson C, Kaplan AS, LaVia M, Mitchell J, Strober M, Woodside DB, Rotondo A, Berrettini WH, Kaye WH, Bulik CM (2006). Smoking in eating disorders. *Eat Behav* 7:291-299.

Avraham Y, Paturski I, Magen I, Vorobiev L, Berry EM (2017). 2-Arachidonoylglycerol as a possible treatment for anorexia nervosa in animal model in mice. *Brain Res* 1670:185-190.

Baker JH, Mazzeo SE, Kendler KS (2007). Association between broadly defined bulimia nervosa and drug use disorders: Common genetic and environmental influences. *Int J Eat Disord* 40:673-678.

Baker JH, Mitchell KS, Neale MC, Kendler KS (2010). Eating disorder symptomatology and substance use disorders: Prevalence and shared risk in a population based twin sample. *Int J Eat Disord* 43:648-658.

Benjamini Y, Hochberg Y (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J Royal Statist Soc, Series B* 57:449-518.

Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, ReproGen Consortium, Psychiatric Genomics Consortium, Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium 3, Duncan L, Perry JR, Patterson N, Robinson EB, Daly MJ, Price AL, Neale BM (2015a). An atlas of genetic correlations across human diseases and traits. *Nat Genet* 47:1236-1241.

Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Patterson N, Daly MJ, Price AL, Neale BM (2015b). LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* 47:291-295.

Center on Addiction and Substance Abuse (2003). Food for thought: Substance abuse and eating disorders. Columbia University (ed). The National Center on Addiction and Substance Abuse at Columbia University: New York, NY. pp. 1-83.

Demontis D, Rajagopal VM, Thorgeirsson TE, Als TD, Grove J, Leppala K, Gudbjartsson DF, Pallesen J, Hjorthoj C, Reginsson GW, Tyrfingsson T, Runarsdottir V, Qvist P, Christensen JH, Bybjerg-Grauholm J, Baekvad-Hansen M, Huckins LM, Stahl EA, Timmermann A, Agerbo E, Hougaard DM, Werge T, Mors O, Mortensen PB, Nordentoft M, Daly MJ, Stefansson H, Stefansson K, Nyegaard M, Borglum AD (2019). Genome-wide association study implicates *CHRNA2* in cannabis use disorder. *Nat Neurosci* 22:1066-1074.

Di Marzo V, Matias I (2005). Endocannabinoid control of food intake and energy balance. *Nat Neurosci* 8:585-589.

Duncan AE, Neuman RJ, Kramer JR, Kuperman S, Hesselbrock VM, Bucholz KK (2006). Lifetime psychiatric comorbidity of alcohol dependence and bulimia nervosa in women. *Drug and Alcohol Dependence* 84:122-132.

Encode Project Consortium (2012). An integrated encyclopedia of DNA elements in the human genome. *Nature* 489:57-74.

Fairburn CG, Cooper Z (1993). The Eating Disorder Examination. In: *Binge Eating: Nature, Assessment and Treatment*. Fairburn CG, Wilson GT (eds). Guilford Press: New York. pp. 317-359.

Filozof C, Fernandez Pinilla MC, Fernandez-Cruz A (2004). Smoking cessation and weight gain. *Obes Rev* 5:95-103.

Franko DL, Keshaviah A, Eddy KT, Krishna M, Davis MC, Keel PK, Herzog DB (2013). A longitudinal investigation of mortality in anorexia nervosa and bulimia nervosa. *Am J Psychiatry* 170:917-925.

Gadalla T, Piran N (2007). Co-occurrence of eating disorders and alcohol use disorders in women: A meta analysis. *Arch Womens Ment Health* 10:133-140.

Goodarzi MO (2018). Genetics of obesity: What genetic association studies have taught us about the biology of obesity and its complications. *Lancet Diabetes Endocrinol* 6:223-236.

Gregorowski C, Seedat S, Jordaan GP (2013). A clinical approach to the assessment and management of co-morbid eating disorders and substance use disorders. *BMC Psychiatry* 13: 289.

Hancock DB, Guo Y, Reginsson GW, Gaddis NC, Lutz SM, Sherva R, Loukola A, Minica CC, Markunas CA, Han Y, Young KA, Gudbjartsson DF, Gu F, McNeil DW, Qaiser B, Glasheen C, Olson S, Landi MT, Madden PAF, Farrer LA, Vink J, Saccone NL, Neale MC, Kranzler HR, McKay J, Hung RJ, Amos CI, Marazita ML, Boomsma DI, Baker TB, Gelernter J, Kaprio J, Caporaso NE, Thorgeirsson TE, Hokanson JE, Bierut LJ, Stefansson K, Johnson EO (2017). Genome-wide association study across European and African American ancestries identifies a SNP in DNMT3B contributing to nicotine dependence. *Mol Psychiatry* 23:1-9.

Heath AC, Bucholz KK, Madden PA, Dinwiddie SH, Slutske WS, Bierut LJ, Statham DJ, Dunne MP, Whitfield JB, Martin NG (1997). Genetic and environmental contributions to alcohol dependence risk in a national twin sample: Consistency of findings in women and men. *Psychol Med* 27:1381-1396.

Kranzler HR, Soyka M (2018). Diagnosis and pharmacotherapy of alcohol use disorder: A review. *JAMA* 320:815-824.

Kranzler HR, Zhou H, Kember RL, Vickers Smith R, Justice AC, Damrauer S, Tsao PS, Klarin D, Baras A, Reid J, Overton J, Rader DJ, Cheng Z, Tate JP, Becker WC, Concato J, Xu K, Polimanti R, Zhao H, Gelernter J (2019). Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations. *Nat Commun* 10:1499.

Krug I, Treasure J, Anderluh M, Bellodi L, Cellini E, di BM, Granero R, Karwautz A, Nacmias B, Penelo E, Ricca V, Sorbi S, Tchanturia K, Wagner G, Collier D, Fernandez-Aranda F (2008). Present and lifetime comorbidity of tobacco, alcohol and drug use in eating disorders: A European multicenter study. *Drug Alcohol Depend* 97:169-179.

Liu M, Jiang Y, Wedow R, Li Y, Brazel DM, Chen F, Datta G, Davila-Velderrain J, McGuire D, Tian C, Zhan X, 23andMe Research Team, HUNT All-In Psychiatry, Choquet H, Docherty AR, Faul JD, Foerster JR, Fritsche LG, Gabrielsen ME, Gordon SD, Haessler J, Hottenga JJ, Huang H, Jang SK, Jansen PR, Ling Y, Magi R, Matoba N, McMahon G, Mulas A, Orru V, Palviainen

T, Pandit A, Reginsson GW, Skogholt AH, Smith JA, Taylor AE, Turman C, Willemsen G, Young H, Young KA, Zajac GJM, Zhao W, Zhou W, Bjornsdottir G, Boardman JD, Boehnke M, Boomsma DI, Chen C, Cucca F, Davies GE, Eaton CB, Ehringer MA, Esko T, Fiorillo E, Gillespie NA, Gudbjartsson DF, Haller T, Harris KM, Heath AC, Hewitt JK, Hickie IB, Hokanson JE, Hopper CJ, Hunter DJ, Iacono WG, Johnson EO, Kamatani Y, Kardia SLR, Keller MC, Kellis M, Kooperberg C, Kraft P, Krauter KS, Laakso M, Lind PA, Loukola A, Lutz SM, Madden PAF, Martin NG, McGue M, McQueen MB, Medland SE, Metspalu A, Mohlke KL, Nielsen JB, Okada Y, Peters U, Polderman TJC, Posthuma D, Reiner AP, Rice JP, Rimm E, Rose RJ, Runarsdottir V, Stallings MC, Stancakova A, Stefansson H, Thai KK, Tindle HA, Tyrfingsson T, Wall TL, Weir DR, Weisner C, Whitfield JB, Winsvold BS, Yin J, Zuccolo L, Bierut LJ, Hveem K, Lee JJ, Munafo MR, Saccone NL, Willer CJ, Cornelis MC, David SP, Hinds DA, Jorgenson E, Kaprio J, Stitzel JA, Stefansson K, Thorgeirsson TE, Abecasis G, Liu DJ, Vrieze S (2019). Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet* 51:237-244.

Lu Q, Hu Y, Sun J, Cheng Y, Cheung KH, Zhao H (2015). A statistical framework to predict functional non-coding regions in the human genome through integrated analysis of annotation data. *Sci Rep* 5:10576.

Lu Q, Li B, Ou D, Erlendsdottir M, Powles RL, Jiang T, Hu Y, Chang D, Jin C, Dai W, He Q, Liu Z, Mukherjee S, Crane PK, Zhao H (2017a). A powerful approach to estimating annotation-stratified genetic covariance via GWAS summary statistics. *Am J Hum Genet* 101:939-964.

Lu Q, Powles RL, Abdallah S, Ou D, Wang Q, Hu Y, Lu Y, Liu W, Li B, Mukherjee S, Crane PK, Zhao H (2017b). Systematic tissue-specific functional annotation of the human genome highlights immune-related DNA elements for late-onset Alzheimer's disease. *PLoS Genet* 13:e1006933.

Lu Q, Powles RL, Wang Q, He BJ, Zhao H (2016). Integrative tissue-specific functional annotations in the human genome provide novel insights on many complex traits and improve signal prioritization in genome wide association studies. *PLoS Genet* 12:e1005947.

Monteleone P, Maj M (2013). Dysfunctions of leptin, ghrelin, BDNF and endocannabinoids in eating disorders: beyond the homeostatic control of food intake. *Psychoneuroendocrinology* 38:312-30.

Munn-Chernoff MA, Baker JH (2016). A primer on the genetics of comorbid eating disorders and substance use disorders. *Eur Eat Disord Rev* 24:91-100.

Munn-Chernoff MA, Duncan AE, Grant JD, Wade TD, Agrawal A, Bucholz KK, Madden PAF, Martin NG, Heath AC (2013). A twin study of the association between alcohol dependence, binge eating, and compensatory behaviors. *J Stud Alcohol Drugs* 74:664-673.

Pasman JA, Verweij KJH, Gerring Z, Stringer S, Sanchez-Roige S, Treur JL, Abdellaoui A, Nivard MG, Baselmans BML, Ong JS, Ip HF, van der Zee MD, Bartels M, Day FR, Fontanillas P, Elson SL, 23andMe Research Team, de Wit H, Davis LK, MacKillop J, Substance Use

Disorders Working Group of the Psychiatric Genomics Consortium, International Cannabis Consortium, Derringer JL, Branje SJT, Hartman CA, Heath AC, van Lier PAC, Madden PAF, Magi R, Meeus W, Montgomery GW, Oldehinkel AJ, Pausova Z, Ramos-Quiroga JA, Paus T, Ribases M, Kaprio J, Boks MPM, Bell JT, Spector TD, Gelernter J, Boomsma DI, Martin NG, MacGregor S, Perry JRB, Palmer AA, Posthuma D, Munafo MR, Gillespie NA, Derks EM, Vink JM (2018). GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. *Nat Neurosci* 21:1161-1170.

Reuter SE, Martin JH (2016). Pharmacokinetics of cannabis in cancer cachexia-anorexia syndrome. *Clin Pharmacokinet* 55:807-812.

Rhee SH, Hewitt JK, Young SE, Corley RP, Crowley TJ, Stallings MC (2003). Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Arch Gen Psychiatry* 60:1256-1264.

Roadmap Epigenomics Consortium, Kundaje A, Meuleman W, Ernst J, Bilenky M, Yen A, Heravi-Moussavi A, Kheradpour P, Zhang Z, Wang J, Ziller MJ, Amin V, Whitaker JW, Schultz MD, Ward LD, Sarkar A, Quon G, Sandstrom RS, Eaton ML, Wu YC, Pfenning AR, Wang X, Claussnitzer M, Liu Y, Coarfa C, Harris RA, Shores N, Epstein CB, Gjoneska E, Leung D, Xie W, Hawkins RD, Lister R, Hong C, Gascard P, Mungall AJ, Moore R, Chuah E, Tam A, Canfield TK, Hansen RS, Kaul R, Sabo PJ, Bansal MS, Carles A, Dixon JR, Farh KH, Feizi S, Karlic R, Kim AR, Kulkarni A, Li D, Lowdon R, Elliott G, Mercer TR, Neph SJ, Onuchic V, Polak P, Rajagopal N, Ray P, Sallari RC, Siebenthall KT, Sinnott-Armstrong NA, Stevens M,

Thurman RE, Wu J, Zhang B, Zhou X, Beaudet AE, Boyer LA, De Jager PL, Farnham PJ, Fisher SJ, Haussler D, Jones SJ, Li W, Marra MA, McManus MT, Sunyaev S, Thomson JA, Tlsty TD, Tsai LH, Wang W, Waterland RA, Zhang MQ, Chadwick LH, Bernstein BE, Costello JF, Ecker JR, Hirst M, Meissner A, Milosavljevic A, Ren B, Stamatoyannopoulos JA, Wang T, Kellis M (2015). Integrative analysis of 111 reference human epigenomes. *Nature* 518:317-330.

Root TL, Pisetsky EM, Thornton L, Lichtenstein P, Pedersen NL, Bulik CM (2010). Patterns of co-morbidity of eating disorders and substance use in Swedish females. *Psychol Med* 40:105-115.

Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511:421-427.

Solmi M, Veronese N, Sergi G, Luchini C, Favaro A, Santonastaso P, Vancampfort D, Correll C. U, Ussher M, Thapa-Chhetri N, Fornaro M, Stubbs B (2016). The association between smoking prevalence and eating disorders: A systematic review and meta-analysis. *Addiction* 111:1914-1922.

Stancil SL, Adelman W, Dietz A, Abdel-Rahman S (2019). Naltrexone reduces binge eating and purging in adolescents in an eating disorder program. *J Child Adolesc Psychopharmacol* 29:721-724.

True WR, Heath AC, Scherrer JF, Waterman B, Goldberg J, Lin N, Eisen SA, Lyons MJ, Tsuang MT (1997). Genetic and environmental contributions to smoking. *Addiction* 92:1277-1287.

van den Bree MB, Johnson EO, Neale MC, Pickens RW (1998). Genetic and environmental influences on drug use and abuse/dependence in male and female twins. *Drug Alcohol Depend* 52:231-241.

Volkow ND, Hampson AJ, Baler RD (2017). Don't worry, be happy: Endocannabinoids and cannabis at the intersection of stress and reward. *Annu Rev Pharmacol Toxicol* 57:285-308.

Volkow ND, Wang GJ, Tomasi D, Baler RD (2013). The addictive dimensionality of obesity. *Biol Psychiatry* 73:811-818.

Wade TD, Gordon S, Medland S, Bulik CM, Heath AC, Montgomery GW, Martin NG (2013). Genetic variants associated with disordered eating. *Int J Eat Disord* 46:594-608.

Walters RK, Polimanti R, Johnson EC, McClintick JN, Adams MJ, Adkins AE, Aliev F, Bacanu SA, Batzler A, Bertelsen S, Biernacka JM, Bigdeli TB, Chen LS, Clarke TK, Chou YL, Degenhardt F, Docherty AR, Edwards AC, Fontanillas P, Foo JC, Fox L, Frank J, Giegling I, Gordon S, Hack LM, Hartmann AM, Hartz SM, Heilmann-Heimbach S, Herms S, Hodgkinson C, Hoffmann P, Jan Hottenga J, Kennedy MA, Alanne-Kinnunen M, Konte B, Lahti J, Lahti-Pulkkinen M, Lai D, Ligthart L, Loukola A, Maher BS, Mbarek H, McIntosh AM, McQueen MB, Meyers JL, Milaneschi Y, Palviainen T, Pearson JF, Peterson RE, Ripatti S, Ryu E,

Saccone NL, Salvatore JE, Sanchez-Roige S, Schwandt M, Sherva R, Streit F, Strohmaier J, Thomas N, Wang JC, Webb BT, Wedow R, Wetherill L, Wills AG, 23andMe Research Team, Boardman JD, Chen D, Choi DS, Copeland WE, Culverhouse RC, Dahmen N, Degenhardt L, Domingue BW, Elson SL, Frye MA, Gabel W, Hayward C, Ising M, Keyes M, Kiefer F, Kramer J, Kuperman S, Lucae S, Lynskey MT, Maier W, Mann K, Mannisto S, Muller-Myhsok B, Murray AD, Nurnberger JI, Palotie A, Preuss U, Raikkonen K, Reynolds MD, Ridinger M, Scherbaum N, Schuckit MA, Soyka M, Treutlein J, Witt S, Wodarz N, Zill P, Adkins DE, Boden JM, Boomsma DI, Bierut LJ, Brown SA, Bucholz KK, Cichon S, Costello EJ, de Wit H, Diazgranados N, Dick DM, Eriksson JG, Farrer LA, Foroud TM, Gillespie NA, Goate AM, Goldman D, Grucza RA, Hancock DB, Harris KM, Heath AC, Hesselbrock V, Hewitt JK, Hopfer CJ, Horwood J, Iacono W, Johnson EO, Kaprio JA, Karpyak VM, Kendler KS, Kranzler HR, Krauter K, Lichtenstein P, Lind PA, McGue M, MacKillop J, Madden PAF, Maes HH, Magnusson P, Martin NG, Medland SE, Montgomery GW, Nelson EC, Nothen MM, Palmer AA, Pedersen NL, Penninx B, Porjesz B, Rice JP, Rietschel M, Riley BP, Rose R, Rujescu D, Shen PH, Silberg J, Stallings MC, Tarter RE, Vanyukov MM, Vrieze S, Wall TL, Whitfield JB, Zhao H, Neale BM, Gelernter J, Edenberg HJ, Agrawal A (2018). Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. *Nat Neurosci* 21:1656-1669.

Watson HJ, Yilmaz Z, Thornton LM, Hubel C, Coleman JRI, Gaspar HA, Bryois J, Hinney A, Leppa VM, Mattheisen M, Medland SE, Ripke S, Yao S, Giusti-Rodriguez P, Anorexia Nervosa Genetics Initiative, Hanscombe KB, Purves KL, Eating Disorders Working Group of the Psychiatric Genomics Consortium, Adan RAH, Alfredsson L, Ando T, Andreassen OA, Baker

JH, Berrettini WH, Boehm I, Boni C, Perica VB, Buehren K, Burghardt R, Cassina M, Cichon S, Clementi M, Cone RD, Courtet P, Crow S, Crowley JJ, Danner UN, Davis OSP, de Zwaan M, Dedoussis G, Degortes D, DeSocio JE, Dick DM, Dikeos D, Dina C, Dmitrzak-Weglarz M, Docampo E, Duncan LE, Egberts K, Ehrlich S, Escaramis G, Esko T, Estivill X, Farmer A, Favaro A, Fernandez-Aranda F, Fichter MM, Fischer K, Focker M, Foretova L, Forstner AJ, Forzan M, Franklin CS, Gallinger S, Giegling I, Giuranna J, Gonidakis F, Gorwood P, Mayora MG, Guillaume S, Guo Y, Hakonarson H, Hatzikotoulas K, Hauser J, Hebebrand J, Helder SG, Herms S, Herpertz-Dahlmann B, Herzog W, Huckins LM, Hudson JI, Imgart H, Inoko H, Janout V, Jimenez-Murcia S, Julia A, Kalsi G, Kaminska D, Kaprio J, Karhunen L, Karwautz A, Kas MJH, Kennedy JL, Keski-Rahkonen A, Kiezebrink K, Kim YR, Klareskog L, Klump KL, Knudsen GPS, La Via MC, Le Hellard S, Levitan RD, Li D, Lilienfeld L, Lin BD, Lissowska J, Luykx J, Magistretti PJ, Maj M, Mannik K, Marsal S, Marshall CR, Mattingsdal M, McDevitt S, McGuffin P, Metspalu A, Meulenbelt I, Micali N, Mitchell K, Monteleone AM, Monteleone P, Munn-Chernoff MA, Nacmias B, Navratilova M, Ntalla I, O'Toole JK, Ophoff RA, Padyukov L, Palotie A, Pantel J, Papezova H, Pinto D, Rabionet R, Raevuori A, Ramoz N, Reichborn-Kjennerud T, Ricca V, Ripatti S, Ritschel F, Roberts M, Rotondo A, Rujescu D, Rybakowski F, Santonastaso P, Scherag A, Scherer SW, Schmidt U, Schork NJ, Schosser A, Seitz J, Slachta L, Slagboom PE, Slof-Op 't Landt MCT, Slopian A, Sorbi S, Swiatkowska B, Szatkiewicz JP, Tachmazidou I, Tenconi E, Tortorella A, Tozzi F, Treasure J, Tsitsika A, Tyszkiewicz-Nwafor M, Tziouvas K, van Elburg AA, van Furth EF, Wagner G, Walton E, Widen E, Zeggini E, Zerwas S, Zipfel S, Bergen AW, Boden JM, Brandt H, Crawford S, Halmi KA, Horwood LJ, Johnson C, Kaplan AS, Kaye WH, Mitchell JE, Olsen CM, Pearson JF, Pedersen NL, Strober M, Werge T, Whiteman DC, Woodside DB, Stuber GD, Gordon S, Grove J, Henders AK, Jureus A,

Kirk KM, Larsen JT, Parker R, Petersen L, Jordan J, Kennedy M, Montgomery GW, Wade TD, Birgegard A, Lichtenstein P, Norring C, Landen M, Martin NG, Mortensen PB, Sullivan PF, Breen G, Bulik CM (2019). Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nat Genet* 51:1207-1214.

White MA (2011). Smoking for weight control and its associations with eating disorder symptomatology. *Compr Psychiatry* 53:403-407.

Wiederman MW, Pryor T (1996). Substance use among women with eating disorders. *Int J Eat Disord* 20:163-168.

Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, Adams MJ, Agerbo E, Air TM, Andlauer TMF, Bacanu SA, Baekvad-Hansen M, Beekman AFT, Bigdeli TB, Binder EB, Blackwood DRH, Bryois J, Buttenschon HN, Bybjerg-Grauholm J, Cai N, Castelao E, Christensen JH, Clarke TK, Coleman JIR, Colodro-Conde L, Couvy-Duchesne B, Craddock N, Crawford GE, Crowley CA, Dashti HS, Davies G, Deary IJ, Degenhardt F, Derks EM, Direk N, Dolan CV, Dunn EC, Eley TC, Eriksson N, Escott-Price V, Kiadeh FHF, Finucane HK, Forstner AJ, Frank J, Gaspar HA, Gill M, Giusti-Rodriguez P, Goes FS, Gordon SD, Grove J, Hall LS, Hannon E, Hansen CS, Hansen TF, Herms S, Hickie IB, Hoffmann P, Homuth G, Horn C, Hottenga JJ, Hougaard DM, Hu M, Hyde CL, Ising M, Jansen R, Jin F, Jorgenson E, Knowles JA, Kohane IS, Kraft J, Kretschmar WW, Krogh J, Kutalik Z, Lane JM, Li Y, Li Y, Lind PA, Liu X, Lu L, MacIntyre DJ, MacKinnon DF, Maier RM, Maier W, Marchini J, Mbarek H, McGrath P, McGuffin P, Medland SE, Mehta D, Middeldorp CM, Mihailov E, Milaneschi Y,

Milani L, Mill J, Mondimore FM, Montgomery GW, Mostafavi S, Mullins N, Nauck M, Ng B, Nivard MG, Nyholt DR, O'Reilly PF, Oskarsson H, Owen MJ, Painter JN, Pedersen CB, Pedersen MG, Peterson RE, Pettersson E, Peyrot WJ, Pistis G, Posthuma D, Purcell SM, Quiroz JA, Qvist P, Rice JP, Riley BP, Rivera M, Saeed Mirza S, Saxena R, Schoevers R, Schulte EC, Shen L, Shi J, Shyn SI, Sigurdsson E, Sinnamon GBC, Smit JH, Smith DJ, Stefansson H, Steinberg S, Stockmeier CA, Streit F, Strohmaier J, Tansey KE, Teismann H, Teumer A, Thompson W, Thomson PA, Thorgeirsson TE, Tian C, Traylor M, Treutlein J, Trubetsky V, Uitterlinden AG, Umbricht D, Van der Auwera S, van Hemert AM, Viktorin A, Visscher PM, Wang Y, Webb BT, Weinsheimer SM, Wellmann J, Willemsen G, Witt SH, Wu Y, Xi HS, Yang J, Zhang F; eQTLGen; 23andMe, Arolt V, Baune BT, Berger K, Boomsma DI, Cichon S, Dannlowski U, de Geus ECJ, DePaulo JR, Domenici E, Domschke K, Esko T, Grabe HJ, Hamilton SP, Hayward C, Heath AC, Hinds DA, Kendler KS, Kloiber S, Lewis G, Li QS, Lucae S, Madden PFA, Magnusson PK, Martin NG, McIntosh AM, Metspalu A, Mors O, Mortensen PB, Muller-Myhsok B, Nordentoft M, Nothen MM, O'Donovan MC, Paciga SA, Pedersen NL, Penninx B, Perlis RH, Porteous DJ, Potash JB, Preisig M, Rietschel M, Schaefer C, Schulze TG, Smoller JW, Stefansson K, Tiemeier H, Uher R, Volzke H, Weissman MM, Werge T, Winslow AR, Lewis CM, Levinson DF, Breen G, Borglum AD, Sullivan PF, & Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet* 50:668-681.

Yengo L, Yang J, Visscher PM (2018). Expectation of the intercept from bivariate LD score regression in the presence of population stratification. *bioRxiv*, <https://doi.org/10.1101/310565>.

Table 1. Eating disorder-related phenotype descriptions.

Phenotype	Definitions
Anorexia nervosa (AN) ^a	Diagnostic criteria included: <ol style="list-style-type: none"> 1. Body mass index less than minimally expected 2. Intense fear of gaining weight 3. Weight or shape disturbance, undue influence of weight or shape, or denial of the seriousness of the disorder
AN <i>with</i> binge-eating ^b	Individuals with AN who also engaged in binge eating episodes, defined as eating a large amount of food in a short period of time while having a sense of loss of control over the eating episode. The binge eating episodes must have occurred at least twice a week for three months.
AN <i>without</i> binge-eating ^b	Individuals with AN who did not engage in binge eating episodes.
Bulimia nervosa (BN) ^c factor	Derived from a factor analysis that included the following items: <ol style="list-style-type: none"> 1. Reporting self-induced vomiting to control body weight 2. Reporting suffering from or being treated for binge eating 3. Reporting suffering from or being treated for bulimia

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Note: ^aA fourth diagnostic criterion for AN includes amenorrhea. However, amenorrhea was excluded as a required criterion for cases in the Psychiatric Genomics Consortium datasets since it is no longer a diagnostic criterion in the DSM-5. ^bThe DSM and ICD include two subtypes of anorexia nervosa (AN)—a binge-eating/purging subtype and a restricting subtype. Although it would have been ideal to examine differences between the AN binge-eating/purging subtype and AN restricting subtype, this was not possible with current Psychiatric Genomics Consortium data. However, there was sufficient information about presence or absence of binge eating, which resulted in creating the AN *with* binge-eating and AN *without* binge-eating subtypes. ^cBulimia nervosa is defined as: 1) recurrent episodes of binge eating; 2) recurrent inappropriate compensatory behaviors (e.g., self-induced vomiting, laxative use) to prevent weight gain; 3) the binge eating and inappropriate compensatory behaviors occurring an average of twice a week for three months; 4) having undue influence of body weight and shape; and 5) disturbance not occurring during AN.

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Table 2. Details of samples included in analyses.

Study	Sample/Consortium	Phenotype(s)	Definition	Sample Size (cases / controls if binary)	Number of SNPs in summary statistics file
<i>Eating Disorder Phenotype</i>					
Watson et al. (2019)	PGC-ED	1. Anorexia nervosa	DSM-III-R, DSM-IV, ICD-8,	16,992 / 55,525	8,219,102
		2. Anorexia nervosa <i>with</i> binge-eating	ICD-9, ICD-10, or self-reported anorexia nervosa	2,381 / 10,249	8,982,440
		3. Anorexia nervosa <i>without</i> binge-eating		2,262 / 10,254	8,671,192
Wade et al. (2013)	Australian Twin Registry	Bulimia nervosa factor	Eating Disorder Examination	151 / 2,291	6,150,213
<i>Substance Use-Related Phenotype</i>					
Kranzler et al. (2019)	MVP	Alcohol use disorder	ICD-9 or ICD-10	34,658 / 167,346	6,895,251
Walters et al. (2018)	PGC-SUD	Alcohol dependence	DSM-IV	8,485 / 20,272	9,271,145
Liu et al. (2019)	GSCAN	1. Drinks per week*	Average number of drinks each week	537,349	11,916,707
		2. Smoking initiation	Ever vs. never regular smoker	311,629 / 321,173	11,733,344
		3. Current smoking ^a	Current vs. former smokers	92,573 / 220,248	12,197,133

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Table 2 (cont). Details of samples included in analyses.

Study	Sample/Consortium	Phenotype(s)	Definition	Sample Size (cases / controls if binary)	Number of SNPs in summary statistics file
		4. Cigarettes per day*	Average number of cigarettes smoked per day	263,954	12,003,613
Hancock et al. (2017)	14 samples	Nicotine dependence**	Mild (FTND score 0-3), Moderate (FTND score 4-6), or Severe (FTND score 7-10)	14,184 (Mild) 9,206 (Moderate) 5,287 (Severe)	10,622,668
Pasman et al. (2018)	ICC UK Biobank	Cannabis initiation	Lifetime cannabis use	43,380 / 118,702	11,733,371
Demontis et al. (2019)	iPSYCH	Cannabis use disorder	ICD-10	2,387 / 48,985	8,969,939

Note: SNPs=single nucleotide polymorphisms; PGC-ED=Eating Disorders Working Group of the Psychiatric Genomics Consortium; DSM=Diagnostic and Statistical Manual; ICD=International Classification of Diseases; PGC-SUD=Substance Use Disorders Working Group of the Psychiatric Genomics Consortium; MVP=Million Veteran Program; GSCAN=GWAS & Sequencing Consortium of Alcohol and Nicotine use; FTND=Fagerström Test of Nicotine Dependence; ICC=International Cannabis Consortium; iPSYCH=Lundbeck Foundation Initiative for Integrative Psychiatric Research. *Treated as a continuous phenotype. **Treated as an

ordinal phenotype. ^aIn Lui et al. (2019), the phenotype is labeled as “smoking cessation”. It was renamed as “current smoking” to reflect the coding scheme and for ease in comparing across all smoking phenotypes.

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