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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, R. Walters, Z. Yilmaz, L. Thornton, J. Baker, J. Coleman, C. Hübel, J. Kaprio, H. Edenberg, C. Bulik, and A. Agrawal assisted with interpretation of findings. H. Kranzler, J. Gelernter, and H. Zhou facilitated access to and interpretation of MVP summary statistics for AUD. 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.

Competing Financial Interests

The authors report the following potential competing interests. O. Andreassen received a speaker's honorarium from Lundbeck. G. Breen received grant funding and consultancy fees in preclinical genetics from Eli Lilly, consultancy fees from Otsuka and has received honoraria from Illumina. C. Bulik served on Shire Scientific Advisory Boards; she receives author royalties from Pearson. D. Degortes served as a speaker and on advisory boards, and has received consultancy fees for participation in research from various pharmaceutical industry companies including: AstraZeneca, Boehringer, Bristol Myers Squibb, Eli Lilly, Genesis Pharma, GlaxoSmithKline, Janssen, Lundbeck, Organon, Sanofi, UniPharma, and Wyeth; he has received unrestricted grants from Lilly and AstraZeneca as director of the Sleep Research Unit of Eginition Hospital (National and Kapodistrian University of Athens, Greece). J. 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Neale is a member of the scientific advisory board for Deep Genomics and has consulted for Camp4 Therapeutics Corporation, Merck & Co., and Avanir Pharmaceuticals, Inc. A. Agrawal previously received peer-reviewed funding and travel reimbursement from ABMRF for unrelated research. All other authors have no conflicts of interest to disclose.

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

A full list of authors and affiliations appears at the end of the article.

Abstract

Eating disorders and substance use disorders frequently co-occur. Twin studies reveal shared genetic risk between eating disorders and substance use, with the strongest associations between symptoms of bulimia nervosa (BN) and problem alcohol use, mainly abuse and dependence (twin-based genetic correlation [r_g]=0.23–0.53). Analytic advances facilitate the computation of genetic correlations using summary statistics from existing genome-wide association studies (GWAS). We investigated shared genetic risk between eating disorder and substance use and disorder phenotypes using GWAS data. Four eating disorder phenotypes (anorexia nervosa [AN], AN *with* binge-eating, AN *without* binge-eating, and a BN 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. Total 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, smoking cessation, and cigarettes per day) and AN *without* binge-eating (r_{gs}=−0.19 to −0.23; qs<0.04). The observed patterns of association between different eating disorder and substance use-related phenotypes highlights the potentially complex and substance-specific relationships between these behaviors associated with significant public health burden.

Keywords

comorbidity; eating disorders; genetic correlation; genome-wide association; linkage disequilibrium score regression; substance use disorders

A well-established phenotypic association exists 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 (BN) and binge-eating disorder (BED) than individuals with anorexia nervosa (AN) or healthy controls (Gadalla and Piran, 2007, Root *et al.*, 2010). Similarly, individuals with BN or BED are at increased risk for smoking, nicotine dependence (ND) (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, ND, 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 dependence) and across a variety of substances (i.e., alcohol, nicotine, and cannabis). It is crucial to elucidate shared etiological mechanisms for these associations 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 BN symptoms, including binge eating, and problem alcohol use (Munn-Chernoff and Baker, 2016), with a genetic correlation (twin-based r_g) ranging from 0.23 to 0.53 (Baker *et al.*, 2010, Baker *et al.*, 2017, Munn-Chernoff *et al.*, 2013, Munn-Chernoff *et al.*, 2015, Slane *et al.*, 2012, Trace *et al.*, 2013). Although there has been less focus on the genetic associations between BN symptoms and regular smoking and BN symptoms and illicit drug use disorder, twin-based r_gs of 0.35 and approximately 0.38, respectively, have been reported (Baker *et al.*, 2007, Baker *et al.*, 2010). A paucity of information exists regarding whether less problematic aspects of substance use exhibit a significant r_g with eating disorder phenotypes. Genetic factors influencing this comorbidity may only come into play 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, which typically yield large sample sizes (i.e., in the tens to hundreds of thousands). One such method is linkage disequilibrium score regression (LDSC; Bulik-Sullivan *et al.*, 2015a, Bulik-Sullivan *et al.*, 2015b), which 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, meaning that independent studies that assess only one phenotype can be jointly examined.

Thus, the aim of the current study was to estimate SNP-based 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. This study examines shared SNP-based genetic risk between eating disorder and multiple substance use-related phenotypes (i.e., alcohol, nicotine, and cannabis), using robust data from twin studies to shape our expectations. First, we hypothesize that the strongest SNP-based r_g will be between eating disorder phenotypes that have binge eating as a core symptom and alcohol use phenotypes (Munn-Chernoff and Baker, 2016). Second, we hypothesize that for binge-eating-related phenotypes, the SNP-based r_g will be lowest when examining typical alcohol consumption and highest when assessing AUD (Munn-Chernoff and Baker, 2016). Because we have less information from twin studies about genetic associations between eating disorders and smoking and cannabis use-related phenotypes, we do not forward any hypotheses for these substances. Findings from this study could yield important information about this clinically challenging pattern of comorbidity (Gregorowski *et al.*, 2013), ultimately suggesting biologically informed prevention efforts and improved treatments for patients presenting with these dual diagnoses.

Method

Participants

We included summary statistics from two existing GWAS of eating disorder phenotypes where particiants were primarily of European ancestry (Wade *et al.*, 2013, Watson *et al.*, in press) and six existing GWAS of substance use-related phenotypes using data only from individuals of European ancestry (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 BN factor score derived from the Eating Disorder Examination (EDE; Fairburn and Cooper, 1993). The EDE is a well-established, structured clinical interview used to determine eating disorder diagnoses. We did not examine BN or BED diagnoses because there are currently no published GWAS of either disorder; thus, the EDE-BN factor score represents the closest to a GWAS of BN available. Substance use-related phenotypes ranged from typical use (e.g., drinks per week, smoking initiation, and cannabis initiation) to abuse/dependence (i.e., AUD, ND, and cannabis use disorder [CUD]). 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 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 phenotype 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 between distributions 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 (FDR; 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_gs existed, using the jackknife procedure implemented through LDSC (Bulik-Sullivan *et al.*, 2015b).

For significant r_gs detected in LDSC where both the individual eating disorder and substance use-related phenotypes each had ~10 or more significant GWAS SNPs (Zhu *et al.*, 2018), bidirectional Mendelian randomization (MR) analyses (Smith and Ebrahim, 2003) were conducted using Generalised Summary-data-based Mendelian Randomisation (GSMR; Zhu *et al.*, 2018) to preliminarily investigate potentially causal relationships between liability to these phenotypes. As GSMR requires a reference sample with individual genotypes to account for LD, we used the 1000 Genomes Phase 3 European ancestries sample as our reference panel (1000 Genomes Project Consortium *et al.*, 2015). SNPs with evidence of horizontal pleiotropy were excluded (using the HEIDI-Outlier method; default p-value threshold=0.01). We only included genome-wide significant SNPs (p<5x10^{-8}) as possible instruments, and SNPs were clumped to ensure independence (i.e., amongst a set of genome-wide significant SNPs correlated at r^2>0.05 within a 1-Mb window, only the SNP with the lowest p-value was retained). As MR analyses are sensitive to sample overlap, we scanned the published papers to determine which samples were included in the discovery GWAS, and any known samples in common across the two discovery GWAS were excluded from the eating disorder GWAS and summary statistics were regenerated for MR analyses.

Results

The overall SNP-based heritability for the eating disorder phenotypes ranged from 0.1992 to 0.3911, whereas the corresponding heritabilities for the substance use-related phenotypes ranged from 0.0273 to 0.3548 (Supplemental Table 1). Figure 1 and Supplemental Table 1 show the 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 was not significantly genetically correlated with cigarettes per day or ND. For the remainder of the 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 −0.0252 (standard error [SE]=0.007; AN and cannabis initiation) to 0.0113 (SE=0.0072; AN and CUD), 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_gs were observed for alcohol use- and cannabis use-related phenotypes. First, the r_g was significiant 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 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_gs 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). No significant association between the BN factor, 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 also increase the risk for cannabis initiation. However, cannabis initiation was not significantly correlated with the BN factor (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 CUD (r_gs=−0.08–0.23; SEs=0.01; qs<0.57). Post-hoc analyses revealed significant differences in the r_gs for AN and cannabis initiation versus AN and CUD (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 CUD.

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 ND 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_gs comparing AN diagnosis and AN *without* binge-eating with each of the three non-diagnostic smoking traits all differed significantly from each other (z-scores ranged from −3.22 to −2.11; p-values<0.04).

Because the AN GWAS and cannabis initiation GWAS each identified eight significant loci (Pasman *et al.*, 2018, Watson *et al.*, in press), and the two studies comprising the AUD sample identified 10 significant loci (Kranzler *et al.*, 2019, Walters *et al.*, 2018), we also conducted exploratory follow-up MR analyses for AN-AUD and AN-cannabis initiation to examine whether there might be evidence of a causal relationship, given their significant r_g. We used summary statistics from a subset of the AN GWAS that did not include the UK Biobank cohort for the AN-cannabis initiation analysis, as this cohort overlapped with the cannabis initiation sample (AN subset without the UK Biobank cohort, N_{cases}=16,224,

[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.

$N_{controls}$=52,460). We did not obtain an estimate for the cannabis inititiation to AN direction of effect because only four SNPs were available after clumping, all of which were excluded for potential pleiotropy by the HEIDI-outlier analysis. There was no evidence of a causal relationship for any comparison (p>0.05; see Supplemental Table 2).

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 dependence. We found specific patterns of association between the two diagnostic categories for eating disorders, suggesting that differences between AN and BN, and between AN subtypes, with substance use-related phenotypes 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 r_g between problem alcohol use (i.e., AUD) and AN diagnosis. Second, we estimated positive r_gs 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 are influencing these traits in the same direction. Second, negative genetic correlations emerged between the three smoking phenotypes from the GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN) cohort and AN *without* binge-eating, but not with the other three eating disorder phenotypes. These negative genetic correlations indicate that some of the loci influencing the liability to these eating disorder and smoking phenotypes are shared, but are affecting the liability to these traits in opposite directions. Indeed, genetic correlations 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 genetic correlation between eating disorder phenotypes with binge eating as a key symptom and AUD would emerge. In line with these hypotheses, we found a signifant 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 association between AN and alcohol use-related phenotypes, and previous studies (Walters *et al.*, 2018, Watson *et al.*, in press) using LDSC have not reported significant r_gs 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.

Intriguingly, although we did not detect a significant r_g for AN *with* binge-eating or the BN factor score 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* BE (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 diagosis is heterogenous even within subytpes. Thus, 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 (Kaye *et al.*, 2013, 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 (Jonas and Gold, 1988, Stancil *et al.*, in press). Thus, our findings highlight the importance of expanding GWAS to include BN 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 the 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 BMI, 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). 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 BMI. Nonetheless, the preliminary MR analyses did not provide persuasive support for causal relationships, in either direction, between genetic liability to cannabis initiation and AN. The small number of SNPs used as instruments, due to the low number of independent genome-wide significant loci and exclusion of overlapping SNPs that were not ambiguous and palindromic, may have significantly limited power to make causal inferences. Nonetheless, in the absence of strong causal evidence, several hypotheses regarding the negative genetic correlation between cannabis initiation and AN are possible.

Finally, the significant negative r_gs between three smoking phenotypes—smoking initiation, current smoking, and cigarettes per day—and AN *without* binge-eating are intriguing, suggesting that increased genetic liability to AN *without* binge-eating is associated with decreased genetic liability to multiple smoking behaviors. 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 genetic correlation. Although not significant, a negative genetic correlation between smoking and AN has been reported (Bulik-Sullivan *et al.*, 2015a, Watson *et al.*, in press). Notably, our study includes individuals from these earlier reports and extends findings by including larger sample sizes for both AN and smoking phenotypes. Even though it is not evident from the existing literature that these opposing directions of effect directly relate to a shared predisposition versus a causal process, there is speculative support for loci related to nicotine addiction that might also influence decreased liability to food intake (Mineur *et al.*, 2011). Unfortunately, there are no twin studies of AN or AN-like traits and smoking with which to compare findings. Such speculations should be reviewed as one of several possible mechanisms that link smoking to AN, as AN is a complex multi-faceted disorder that extends well-beyond reduced food intake.

Another explanation for the negative genetic association is that it is due to a third, underlying variable influencing both AN *without* binge-eating and smoking. In the largest GWAS of smoking phenotypes, positive genetic correlations were 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 (Duncan *et al.*, 2017, Watson *et al.*, in press). Thus, the patterns of r_gs 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_gs between smoking and BMI, as well as AN and BMI, could reflect underlying disinhibitory pathways, as variants associated with BMI 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 it, substance use disorders relate to 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). Genetic liability to alcohol use has also been correlated with liability to psychiatric traits (e.g., major depression) in opposite directions depending on level of involvement (Kranzler *et al.*, 2019). However, we did not find similar elevations in r_gs when

contrasting ever smoking and ND, nor comparing cannabis initiation to CUD. It is possible that the lack of genetic overlap between AN and ND, as well as AN and CUD, 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. Still, there are several other explanations for this divergence in findings. 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 CUD than cannabis initiation. In addition to the considerably smaller sample size of the CUD 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 CUD. 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 to date, 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 publically 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 BN factor score and CUD GWAS were relatively small compared with the other GWAS, resulting in large standard errors and low power. Second, we were unable to uniformally examine sex differences in these r_gs. 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). Finally, SNP coverage was limited in the earlier GWAS of the BN 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 (PGC) are continuously adding samples and releasing data freezes with incrementally larger sample sizes, while collecting information on multiple substances (e.g., opioids). Thus, in coming years, the statistical power is expected to increase for AN (including the *with* and *without* binge-eating subtypes), BN, and BED, as well as AUD, ND, and CUD, from within and outside the PGC. 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 underlying etiology between eating disorder and substance use-related phenotypes is 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 highlights the uniqueness and complexity of their shared etiology. Additional research using contemporary genomic methods such as cross-disorder association studies could identify the specific loci contributing to this comorbidity. Once loci are identified, additional research that combines polygenic risk scores with measured environmental constructs could enhance the prediction, prevention, and treatment of co-occurring eating disorder and substance use-related traits.

Supplementary Material

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

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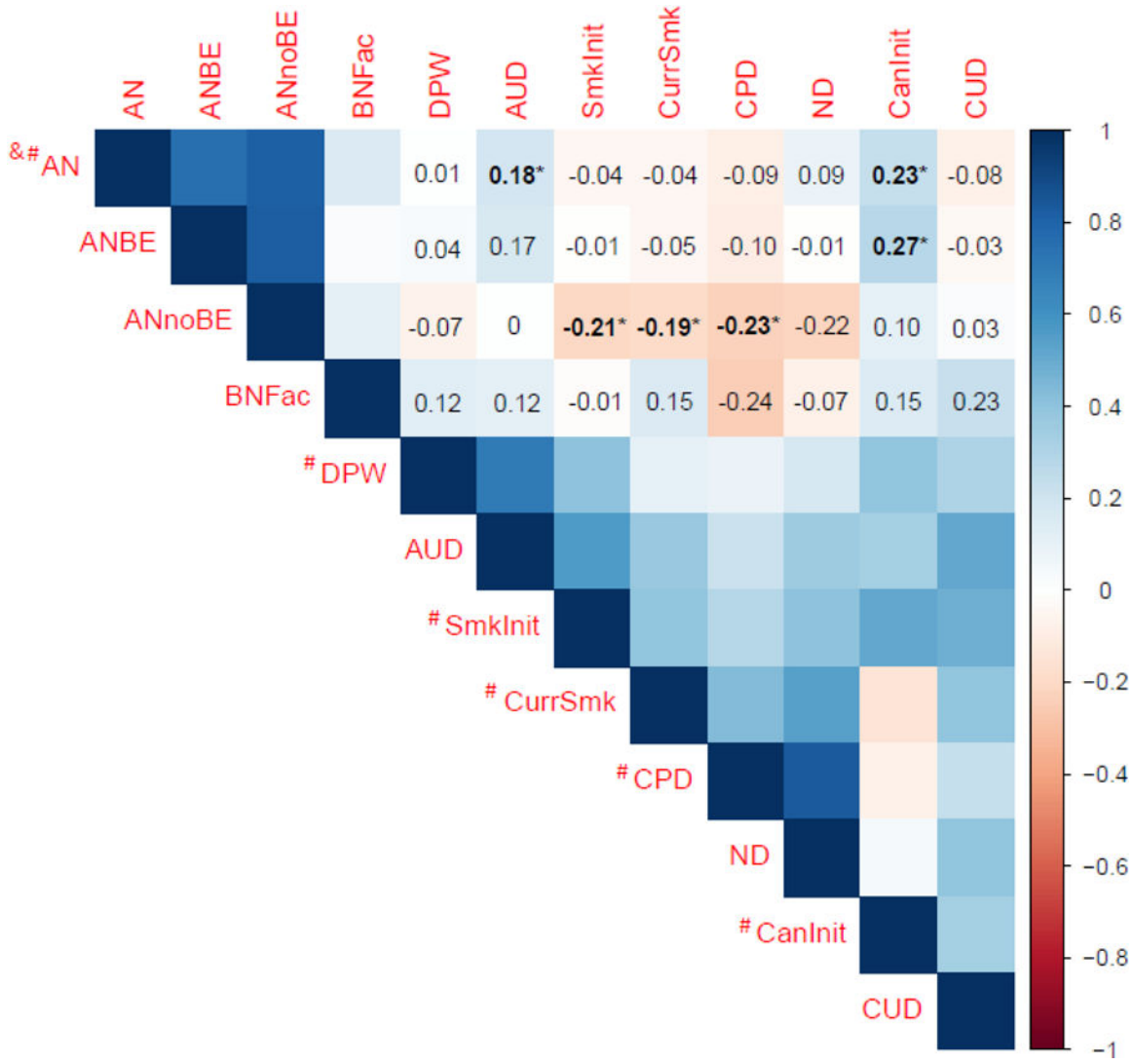

Figure 1. Genetic correlations between eating disorder subtypes and substance use-related phenotypes.

AN=anorexia nervosa; ANBE=anorexia nervosa *with* binge-eating; ANnoBE=anorexia nervosa *without* binge-eating; BNFac=bulimia nervosa factor score; DPW=drinks per week; AUD=alcohol use disorder; SmkInit=smoking initiation; CurrSmk=current smoking; CPD=cigarettes per day; ND=nicotine dependence; CanInit=cannabis initiation; CUD=cannabis use disorder. # indicates known or potential sample overlap with UK Biobank; & indicates known sample overlap with iPSYCH. Bolded and * values denote significant genetic correlations after correcting for multiple comparisons using False Discovery Rate (*n* tests=66; $q<0.05$).

Table 1.

Eating disorder-related phenotype descriptions.

Phenotype	Definitions
Anorexia nervosa (AN)[a]	Diagnostic criteria included: 1. BMI 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 *with* 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 *without* 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: 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

Note:

[a]A 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.

[b]The 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.

[c]Bulimia 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.

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
Eating Disorder Phenotype					
Watson et al. (in press)	PGC-ED	1. Anorexia nervosa 2. Anorexia nervosa *with* binge-eating 3. Anorexia nervosa *without* binge-eating	DSM-III-R, DSM-IV, ICD-8, ICD-9, ICD-10, or self-reported anorexia nervosa	16,992 / 55,525 2,381 / 10,249 2,262 / 10,254	8,219,102 8,982,440 8,671,192
Wade et al. (2013)	Australian Twin Registry	Bulimia nervosa factor	Eating Disorder Examination	151 / 2,291	6,150,213
Substance Use-Related Phenotype					
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 * 2. Smoking initiation 3. Current smoking [a] 4. Cigarettes per day *	Average number of drinks each week Ever vs. never regular smoker Current vs. former smokers Average number of cigarettes smoked per day	537,349 311,629 / 321,173 92,573 / 220,248 263,954	11,916,707 11,733,344 12,197,133 12,003,613
Hancock et al. (2017)	14 consortia	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.

[a]In 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.