A behavioral-genetic investigation of bulimia nervosa and its relationship with alcohol use disorder

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ABSTRACT

Bulimia nervosa (BN) and alcohol use disorder (AUD) frequently co-occur and may share genetic factors; however, the nature of their association is not fully understood. We assessed the extent to which the same genetic and environmental factors contribute to liability to BN and AUD. A bivariate structural equation model using a Cholesky decomposition was fit to data from 7241 women who participated in the Swedish Twin study of Adults: Genes and Environment. The proportion of variance accounted for by genetic and environmental factors for BN and AUD and the genetic and environmental correlations between these disorders were estimated. In the best-fitting model, the heritability estimates were 0.55 (95% CI: 0.37; 0.70) for BN and 0.62 (95% CI: 0.54; 0.70) for AUD. Unique environmental factors accounted for the remainder of variance for BN. The genetic correlation between BN and AUD was 0.23 (95% CI: 0.01; 0.44), and the correlation between the unique environmental factors for the two disorders was 0.35 (95% CI: 0.08; 0.61), suggesting moderate overlap in these factors. The findings from this investigation provide additional support that some of the same genetic factors may influence liability to both BN and AUD.

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1. Introduction

Bulimia nervosa (BN) and alcohol use disorder (AUD; alcohol abuse/dependence) frequently co-occur (Bulik, 1987; Garfinkel et al., 1995; Bulik et al., 1997; Lilenfeld et al., 1998; Herzog et al., 1999; Dansky et al., 2000; Wade et al., 2004; Pereyra et al., 2010; Root et al., 2010). Estimates of the lifetime prevalence of AUD in women with BN have ranged from approximately 9% (Pyle et al., 1981) to 49% (Bulik, 1987), with the majority of investigations reporting between 20% and 25% (Mitchell et al.,1985; Holderness et al., 1994; Bulik et al., 2004; Baker et al., 2010; Root et al., 2010). Yet, the nature of this association is incompletely understood.

One compelling hypothesis is that BN and AUD may share a familial diathesis. Results from family studies have been inconsistent (Bulik, 1987; Kassett et al., 1989; Lilenfeld et al., 1997). For example, although studies uniformly reported that BN and

AUD co-occurred in families, Lilenfeld et al. (1997) found that only BN probands with AUD had higher rates of AUD in family members, suggesting possible independent transmission of the disorders. One limitation of family studies is that they are unable to disaggregate genetic and common environmental effects. Twin studies, in contrast, allow the variance in liability to be partitioned into additive genetic (A; the cumulative impact of several genes of small to moderate effect), common environmental (C; environmental effects that increase similarity in twins and result from etiological factors to which both members of a twin pair are exposed regardless of zygosity such as childhood socioeconomic status), and unique environmental factors (E; factors that make twins dissimilar; the E term also includes measurement error). Bivariate models can extend that paradigm to determine the extent to which these factors contribute to the liability of both disorders.

Two investigations using twin methodology have examined the genetic and environmental association between BN and AUD (Kendler et al., 1995; Baker et al., 2010). Kendler et al. (1995) applied multivariate pathway models to lifetime history of six major psychiatric disorders including BN and alcoholism. In the best-fitting model, a large proportion of the genetic liability to

alcoholism was attributable to genetic factors that did not influence liability to the other five disorders; however, there was evidence of some overlap in genetic liability between BN and alcoholism (6%, as reported by Slane et al., 2012).

In a second investigation using the same population-based sample from the Virginia Twin Registry (Kendler and Prescott, 2006), which included additional data from subsequent occasions of measurement, Baker et al. (2010) examined the genetic association between BN symptom count (i.e., a positive score was given for each BN symptom) and AUD. Using a bivariate approach, they reported a genetic correlation of 0.53 (95% confidence interval (CI): 0.30; 0.80) in the best-fitting model, suggesting moderate overlap in genetic factors contributing to BN and AUD. However, the broad CI indicates a lack of statistical power to assess the strength of the association.

Another recent investigation (Slane et al., 2012) examined the nature of the association between individual bulimic behaviors (i.e., binge eating and the use of inappropriate compensatory behaviors such as self-induced vomiting or laxative use) and problematic alcohol use in a small sample ($n=292$) of female twins from the Michigan State University Twin Registry (Klump and Burt, 2006). Parameter estimates for the best-fitting models indicated some overlap in genetic factors contributing to the liability of problematic alcohol use and binge eating (genetic correlation=0.31 (95% CI: 0.09; 0.53)) and also of problematic alcohol use and compensatory behaviors (genetic correlation=0.61 (95% CI: 0.34; 1.00)). These results provide additional evidence that some of the same genetic factors influence both bulimic behaviors and problematic alcohol use. However, the sample in this investigation was small, which might have decreased power and resulted in less precise estimates.

Thus, the results of these studies taken together suggest that BN and AUD may have shared genetic factors; however, additional large population-based twin studies of different samples are necessary to replicate and further elucidate the nature of this association. The purpose of this investigation was to evaluate the extent to which the same genetic and environmental factors contribute to the liability to both BN and AUD using a large population-based sample of twins from Sweden.

2. Method

2.1. Participants

Participants were from the Swedish Twin study of Adults: Genes and Environment (STAGE), which is a subsample of the Swedish Twin Registry (STR; http://ki.se/ki/jsp/polopoly.jsp?d=9610&l=en). STAGE is a population-based prospective sample of Swedish twins born in 1959–1985. In 2005, twins aged 20–47 were asked about demographic characteristics, health, and life-style habits using web-based surveys with a telephone survey option. Over 25,000 individuals from a total sample of 43,000 participated (response rate=59.6%). A more detailed description of the study design can be found elsewhere (Lichtenstein et al., 2006; Furberg et al., 2008). STAGE was approved by the Regional Ethics Committee at Karolinska Institutet and by the Biomedical Institutional Review Board at the University of North Carolina at Chapel Hill. All participants provided informed consent through the web-based interview or the telephone interview.

Our final sample for twin modeling included 4238 monozygotic (MZ) women and 3003 dizygotic (DZ) women from same sex pairs: 1816 MZ and 1275 DZ pairs with complete data, 281 MZ and 209 DZ pairs with incomplete data, and 44 MZ and 35 DZ individuals without cotwin information. The mean age was 33.0 years (S.D.=7.6).

2.2. Zygosity

Zygosity was assigned using responses from the following questions: (Q1) during childhood, were you and your twin partner as alike as 'two peas in a pod' or no more alike than siblings in general? and (Q2) How often did strangers have difficulty distinguishing between you and your twin partner when you were children? If both members of a twin pair responded 'alike as two peas in a pod' for Q1 and 'almost always' or 'often' for Q2, they were classified as MZ. If both twins responded 'not alike' for Q1 and 'seldom', 'almost never' or 'never' for Q2, they were classified as DZ. All other twins were classified as 'not determined.' This algorithm was validated using a panel of 47 single nucleotide polymorphisms (SNPs) in 198 randomly chosen twin pairs (Lichtenstein et al., 2002). Ninety-five percent ($n=188$) were correctly classified.

2.3. Measures

Information about lifetime eating disorders was collected using an assessment based on the Structured Clinical Interview (SCID) for Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV; First et al., 1997), which assesses major Axis I psychiatric diagnoses according to DSM-IV (American Psychiatric Association, 2000) diagnostic criteria. The reliability and validity of the SCID have been well-demonstrated, although estimates have varied across studies (for review see First and Gibbon, 2004). The lifetime prevalence of BN in this sample was 1.18% for women, which is somewhat lower than estimates from other population-based samples (Wade et al., 2006; Hudson et al., 2007; Baker et al., 2010). To increase statistical power, we used a broader definition for BN. This decision was made based on increasing evidence that a binge eating frequency of approximately four times a month, rather than the current twice a week frequency criterion for BN, is the most empirically validated threshold (Sullivan et al., 1998; Trace et al., 2012). Further, a frequency criterion of four times per month has been suggested for DSM-5 (Wilson and Sysko, 2009) and is an anticipated modification. In addition, previous research using this sample showed that the heritability point estimates for the DSM-IV (American Psychiatric Association, 2000) definition of BN ($a^2=0.62$; 95% CI: 0.40, 0.75) and a broader definition ($a^2=0.61$; 95% CI: 0.46; 0.73) were approximately the same (Bulik et al., 2010). Therefore, BN was considered present if the participant: (1) responded yes to having had eating binges when they ate what most people would regard as an unusually large amount of food in a short period of time with at least slight loss of control; (2) indicated that s/he engaged in vomiting, exercised more than 2 h per day, fasted, or used laxatives, diuretics, diet pills, or other methods during the same time that s/he was binge eating; (3) reported that binge eating occurred at least four times a month for at least 3 months; and (4) endorsed that weight or shape are moderately important things, important things, or the most important things that affect how she feel about herself. Participants were coded positive for BN if all criteria were present, negative for BN if only some criteria were met, and 'missing' if a diagnosis could not be made.

Lifetime alcohol abuse and dependence were also evaluated using an assessment based on the SCID for DSM-IV (First et al., 1997). This instrument assesses major Axis I psychiatric diagnoses according to DSM-IV (American Psychiatric Association, 2000) diagnostic criteria. All abuse and dependence criteria were assessed. If the participant met criteria for either abuse or dependence, she was coded positive for AUD. Participants were coded as missing if enough criteria were missing that a diagnosis could not be made. All others were coded as not meeting criteria for AUD.

2.4. Statistical analyses

2.4.1. Rationale

Biometric twin modeling is used in genetic epidemiology research to estimate the proportion of variance that genetic and environmental factors contribute to the liability to a latent phenotype. Specifically, these models assess the contribution of (1) additive genetic factors (heritability, a^2); (2) common environmental factors (c^2); and (3) unique environmental factors and measurement error (e^2) to the liability to a phenotype such that the total variance is the sum of $a^2+c^2+e^2$. Thus, by evaluating this 'ACE' model, the proportion of variance in liability to a disorder that is due to these genetic and environmental factors can be estimated. By comparing within-twin, cross-trait tetrachoric correlations for MZ twins with those for DZ twins, initial information regarding the genetic and environmental influences on liability to each of the two traits (BN and AUD) individually can be estimated. A similar comparison of the cross-twin, cross-trait tetrachoric correlations provides information on the shared liability between the traits (genetic and environmental correlations). This is because MZ twins share approximately 100% of their segregating genes and DZ twins share on average 50%. Thus, a larger within-twin, cross-trait correlation for MZ twins compared with DZ twins indicates that genetic factors influence the latent phenotype. Likewise, a larger cross-twin, cross-trait correlation for MZ twins compared with DZ twins indicates that genetic factors contribute to the phenotypic association of the traits. The presence of shared environmental factors is evident when the cross-twin, cross-trait correlation for MZ twins is not greater than twice that of the DZ twins. Under the equal environment assumption (EEA), common environmental influences are assumed to contribute equally to the correlation between members of MZ pairs and DZ pairs (Neale and Cardon, 1992).

2.4.2. Current study

A bivariate structural equation model using Cholesky's decomposition was fitted using the raw data option in Mx (Neale et al., 2001) statistical software to estimate a^2, c^2, and e^2 for BN and AUD and to estimate correlations indicating the proportion of variance the two traits share due to genetic (r_a), common environmental (r_c), and unique environmental (r_e) factors. For example, a genetic correlation estimated to be 1.00 indicates 100% overlap in the genetic factors influencing liability to the two traits. The raw data option in Mx (Neale et al., 2001) considers data to be missing at random: listwise deletion is not applied. Thus, if data for one twin in a pair are missing, information from the other twin is still retained. If data are missing at random, unbiased estimates should be obtained (Little and Rubin, 1987). The full model, which estimates