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The Heritability of Eating Disorders: Methods and Current Findings

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Abstract

Family, twin, and adoption studies of anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), and the proposed purging disorder presentation (PD) have consistently demonstrated that genetic factors contribute to the variance in liability to eating disorders. In addition, endophenotypes and component phenotypes of eating disorders have been evaluated and provide further insight regarding genetic factors influencing eating disorders and eating disorder diagnostic criteria. Many of these phenotypes have demonstrated substantial heritability. This chapter reviews biometrical genetic methods and current findings from family and twin studies that investigate the role of genes and environment in the etiology of eating disorders. We review the methodology used to estimate heritability, the results of these studies, and discuss the implications of this research for the basic conceptualization of eating disorders and the future value of twin modeling in the molecular genetic era.

Knowledge of genetic influences on liability to eating disorders has grown rapidly over the past three decades. Indeed, numerous family, twin, and genetic studies have indicated that genetic effects contribute to the variance in liability to eating disorders including anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), and the proposed purging disorder presentation (PD). The consistency of these findings and their implications for prevention and treatment programs compel professionals who treat individuals with these conditions to become familiar with genetic epidemiological research relevant to their clinical work.

This chapter reviews biometrical genetic methods and current findings from family and twin studies that investigate the role of genes and environment in the etiology of eating disorders. In addition, we discuss the implications of this research for the basic conceptualization of eating disorders and the future value of twin modeling in the molecular genetic era.

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9.1 Genetic Epidemiology Methods: Family, Twin Studies and Adoption Studies

The threshold eating disorders, AN and BN, and the proposed syndromes of BED and PD are complex and often chronic illnesses. Estimates of the general population lifetime prevalence for these disorders range from approximately 0.5% for AN to 3% for BED in adult women [19, 23, 32], with lower prevalence in males [14, 23, 79]. Although the etiology of these conditions is generally as assumed to be biopsychosocial in nature; the following sections focus on genetic factors influencing liability to these disorders.

9.1.1 Family Studies

Family studies assess the lifetime risk that a relative of an individual with a disorder will develop the condition themselves in comparison to either: 1) the general risk of that disorder in the population or 2) the risk of the disorder in families of comparable individuals without the disorder. A statistically increased lifetime risk of, for example, AN in biological relatives of probands with AN, demonstrates the trait aggregates in families. However, this increased risk is not sufficient to prove that genes influence the disorder because the resemblance among family members could be due to either genetic or environmental factors shared within families (e.g., socio-cultural factors such as an over-emphasis on appearance) or, more likely, some combination of the two.

The familial nature of AN is well established. There is a significantly greater lifetime prevalence of AN or subthreshold eating disorders in first-degree relatives of probands (3%–12%) compared with relatives of controls (0%–4%) [16, 42, 61–63]. Specifically, relatives of probands with AN are 11.3 times more likely to have AN than relatives of controls [60].

Most research [27, 60] has found an increased incidence of BN in relatives of BN probands, with rare exception [24]. The morbid risk of BN in first-degree relatives of probands with the disorder is estimated to be between 4.4 [60] and 9.6 [27] times greater than in controls.

BED also occurs more frequently in family members of individuals with BED than in control families [2, 13, 22, 25]. Family studies report odds ratios between 1.9 and 2.2 for the risk of BED in a relative of a proband with BED compared with relatives of controls [13, 22, 26, 41].

PD has recently been proposed as independent, unique eating disorder presentation [28, 45]. Diagnostic criteria include recurrent purging episodes for the purposes of weight control in the absence of binge eating. To date, no family studies of purging disorder have been published. However, two population based studies found that between 1.1 and 5.3% of women met criteria for a lifetime diagnosis of PD [11, 67].

In addition, family studies indicate that the prevalence of both threshold and subthreshold AN and BN are elevated in relatives of AN and of BN probands compared with relatives of controls [16, 24, 42, 56, 60, 62, 78]. This suggests that 1) eating disorders are expressed in families as a broad spectrum of eating-related pathology and, 2) some liability factors are shared among the different eating disorder types.

9.1.2 Twin Studies

Twin studies are a useful tool to differentiate the effects of genes and the environment on behavioral characteristics and liability to psychopathology and illness [29]. Identical twins (i.e., monozygotic or MZ twins), for most intents and purposes, have identical DNA and thus the same genetic variants at all genes, neglecting stochastic errors in DNA replication

during development such as copy number variation [4]. Assuming stochastic error and gene by environment interaction are negligible, phenotypic differences observed between MZ twins can be attributed to environmental factors [49]. Similarities between twins could be either the result of genes, environmental influences coming from life experiences that twins share (“common environment”), or, in all probability, some combination of the two. Like full siblings, dizygotic or fraternal twins (DZ) share, on average, half of their genes. However, because DZ twins, like MZ twins, share an intrauterine environment and experience many events at the same age (e.g., starting school), common environmental influences are, in theory, similar in both kinds of twins. Certainly, there are many ways in which the MZ twin environment could be more similar than the DZ twin environment. One assumption of twin studies, the equal environment assumption, posits that the environment of MZ twins is no more similar than the environment of DZ twins on dimensions of etiological relevance to the trait under study [54]. However, at this time, there is scant evidence for violations of this equal environments assumption that would increase the similarity for eating disorder liability in MZ twins relative to that for DZ twins [5, 36]. Thus, differences in concordance rates of MZ versus DZ twins inform understanding of the relative contribution of genes and environment.

Standard twin models use concordance rates of MZ and DZ twins to assess the degree to which additive genetic effects (A), shared environmental effects (C), and/or unique environmental effects (E) contribute to the liability to a particular disorder. The objective of the model is to decompose the observed variance in liability to the disorder (V) in the population into these sources of variability: $V = a^2 + c^2 + e^2$, where a^2 is the proportion of variance due to A, also called heritability [12], c^2 is the proportion due to C, and e^2 is the proportion due to E [48].

If genetic factors were to act additively, it should be evident in the contrast of MZ to DZ correlations. For example, if a trait were entirely due to additive genetic effects, then MZ twins would be perfectly correlated because they share 100% of their genes, and the DZ correlation would be 0.50 because they share, on average, 50% of their genes [12]. The effect of common environment contributes equally to the similarity of both MZ and DZ pairs. Thus, if the MZ and DZ correlations for a trait were equal, then any positive correlation of the trait values must be due to common environment. Genetic influences are incompatible with equal correlations in MZ and DZ twins. A mix of environmental and genetic effects is inferred if the MZ correlation is greater than the DZ correlation, but less than twice as large. Unique environment refers to environmental influences to which only one member of a twin pair is exposed (e.g., participating in sports emphasizing thinness) and also incorporates measurement error. Unique environmental effects decrease the correlations of both MZ and DZ twin pairs.

The first, systematic, clinically-ascertained twin study of AN found that MZ twins had higher concordance rates than DZ twins [20, 21, 65]. Reanalysis of these data indicate that additive genetic effects accounted for 88% of the liability to AN, unique environmental effects account for the remainder, and shared environmental effects are absent [7].

Population-based twin studies substantiate the above results. Wade et al. [70] reported an estimated heritability of approximately 58% for AN, with the remaining variance accounted for by unique environmental factors. However, the broad confidence intervals for heritability do not exclude the possibility of common environmental influences contributing to the liability of AN. Similarly, several other studies estimated heritability for narrow and broad definitions of AN. Estimates ranged from 28% to 58% [6, 10, 40]. However, Klump et al. [38] reported a heritability estimate of 74% (95% CI: 35%, 95%) for AN syndrome in 17-

year-old female twins. The remaining variance in the latter studies was best attributed to unique rather than shared environmental factors.

Population-based studies of BN lend further support to the substantial role of additive genetic effects to the liability to eating disorders [5, 10, 30, 40, 71] and have yielded heritability estimates between 54 and 83%. However, as in the studies on AN, the confidence intervals around these heritability estimates are wide. These wide confidence intervals are likely due to the low statistical power of these studies and suggest that the influence of shared environmental effects on the liability to BN cannot be completely disregarded. To address this limitation, researchers have applied a measurement model to population-based twin data to boost power. By incorporating multiple waves of measurement, this method has the added benefit of increasing diagnostic reliability. Two studies that have used this approach have yielded heritability estimates for latent liability to BN of 83% (95% CI: 49%, 100%) [5] and 59% (95% CI: 36%, 60%) [71].

Twin studies of BED have reported heritability estimates ranging from 41% to 57% for varying definitions of this disorder [25, 51]. Currently, there are no published twin reports on the heritability of PD.

9.1.3 Adoption Studies

Adoption studies, while increasingly rare, allow the contributions of genetic and environmental effects to be distinguished and have greater power than twin studies to detect shared environmental influences. Because biological relatives have only genes in common with the adopted individual and adoptive relatives have only shared environment in common with the adopted individual, the relative influence of genetic and shared environmental factors can be estimated by comparing the incidence of a disorder or the similarity of a trait in biological relatives to adoptive relatives.

To date, only one adoption study on eating disorder pathology has been conducted [39]. Participants were biological and adopted female sibling pairs. Given the low prevalence of both AN and BN, disordered eating symptoms rather than the diagnoses themselves were explored. Heritability estimates from biometrical modeling ranged from 59% to 82%, which provide convergent evidence for the ever-increasing body of twin studies.

In aggregate, family, twin and adoption studies provide compelling evidence that genetic factors contribute to the etiology of eating disorders and some of these factors appear to be shared across the various types of eating disorders.

9.2 Eating Disorder Endophenotypes and Component Phenotypes

One strategy to enhance statistical power challenged by relatively low population prevalence of eating disorders has been to examine genetic influences putative endophenotypes or component phenotypes of eating disorders. Endophenotypes are considered to be measureable biological markers for a disease which are associated with the illness in the general population, are observable regardless of whether the illness is active, are observed in unaffected family members of probands at a higher rate than in the general population, and are heritable [8, 17]. Identification of endophenotypes, which are more proximal to the genotype than the disorder [8], can facilitate the refinement of diagnostic criteria. Specifically endophenotype identification can clarify which traits are most highly heritable, and thereby most reflective of reflecting underlying biological, neurocognitive or psychological processes. This, in turn, might aid in identifying genes which contribute to the liability of a disorder because the endophenotypes are theoretically less complex and influenced by a smaller number of genes [8].

Bulik et al. [8] identified a number of potential endophenotypes and component phenotypes for eating disorders. Some are disorder specific, and others are behaviors, attitudes and temperament characteristics associated with eating disorders. The following sections review those constructs that have been shown to be heritable.

9.2.1 DSM Criteria

An item factor approach has been applied to examine genetic and environmental contributions to the criteria for AN [44], BN [Mazzeo, 2009 #7296, and BED [46] in twins. The advantages to this model are: 1) the association between the latent trait (i.e. the specific eating disorder diagnosis) and each of the symptoms is estimated via the factor scores, 2) the relative contributions of genetic, shared environmental and unique environmental factors to liability to overall diagnosis are estimated, and 3) heritability and contribution of shared and unique environmental factors are estimated for each measured symptom (i.e., item). Thus, this model can facilitate the identification of endophenotypes by clarifying which specific criteria are both most strongly related to the overall diagnosis (as indicated by the factor loadings), and are most heritable.

Mazzeo et al. [44] used the item-factor approach to investigate AN within a population-based twin sample. Estimates of total heritability for several of the items assessed (i.e., whether participants had ever lost a lot of weight, whether friends and relatives had said they were too thin, whether weight affected how they felt about themselves at lowest weight, and lowest body mass index (BMI)), ranged between 29% and 34%. Heritability estimates for items related to weight concern at time of low weight were lower (ranging from 18% to 23%). Amenorrhea had a heritability estimate of 16% and was most strongly influenced by unshared environment. Results from the item factor model provided additional information: factor loadings indicating how strongly the symptoms were related to AN. Surprisingly, low BMI had the weakest association with AN. This was likely influenced by the structure of the survey, in which only individuals who met certain gateway criteria were asked the remaining questions. Symptoms most strongly associated with AN were losing a lot of weight, people saying you looked too thin, and the items related to weight concern.

These results inform future research on AN endophenotypes. Specifically, based on these results, it appears that a criterion such as amenorrhea, which did not load highly on the latent AN factor, and also had a low heritability estimate, may not be the most promising endophenotype for this diagnosis. However, endophenotypes or liability indices worthy of further examination would be those with the higher heritability estimates that are also associated to the greatest degree with AN: including intentional and extreme weight loss (as measured by items assessing whether participants had lost a lot of weight and whether others had noted they looked much too thin).

Finally, it should be noted that the use of gateway items in this study presents challenges to the identification of endophenotypes. Although this survey technique is a useful and appropriate strategy for reducing participant burden in large-scale epidemiological studies, it is important to recognize that the heritability of the AN criteria were only evaluated among the subset of the sample with a low lifetime BMI. It is possible that genetic and environmental factors operate differently within individuals who are already at a low BMI, compared to the general population.

Similarly, an item factor model was applied to twin data to estimate the heritability of BN criteria and to determine how strongly each symptom was associated with BN [43]. Items assessing inappropriate compensatory behaviors had heritability estimates ranging from 35% to 53%. Of these items, vomiting and laxative use were most highly associated with BN, although all items had reasonably high loadings on the overall latent construct (i.e., the BN

diagnosis). For the binge eating items examined, both loss of control and frequency had the greatest association with BN and had the highest heritability estimates (39% and 41%, respectively). The influence of weight and shape on self evaluation had the lowest factor loading and lowest heritability of the 11 symptoms examined. These results indicate that the symptoms are differentially heritable and confirm the centrality of binge eating and purging to the syndrome of BN.

Finally, Mitchell et al. [46] applied the item-factor model to BED in a population-based twin sample. Factor loadings for each criterion on the latent construct were high, suggesting that the individual items are relevant to an underlying, unidimensional diagnosis. Further, heritability estimates for the individual items were relatively similar, ranging from 29% to 43%. These results vary somewhat from those obtained in the item-factor analyses of AN and BN described previously [Mazzeo, 2009 #7212; [43], which identified greater variability in estimates of A, C and E across component diagnostic criteria.

It should be noted that, in all three of these item-factor studies [43, 44, 46], unique environmental factors accounted for the greatest proportion of variance at the item/criterion level. As noted previously, this component of variance includes both measurement error and unique environmental experiences. Thus, refinement of eating disorder assessment (including improvements in the questions asked, based on diagnostic revisions) should help differentiate whether specific symptoms are truly influenced more strongly by unique life events (e.g., appearance-oriented activities to which only one member of a twin pair is exposed) or whether an item's psychometric properties are attenuating heritability estimates.

9.2.2 Disordered Eating Behaviors

In addition to examining the genetic and environmental influences on threshold and subthreshold eating disorders, numerous studies have investigated eating disorder attitudes and related behaviors, including intentional weight loss, eating restraint, binge eating, and purging. This approach is appropriate as there is considerable interest in these behaviors as factors influencing the development and maintenance of eating disorders.

Restrained eating has gained a great deal of attention within the eating disorders field, as this behavior is hypothesized to trigger the development of eating pathology [50], a theory supported by longitudinal data [34, 57]. However, the measurement of restraint has proven challenging, and there is extensive and long-standing controversy about this construct and its assessment (e.g., [18, 58, 59, 74, 75, 77]. Nonetheless, restraint remains a focus of research, and could represent an important endophenotype, given its temporal relation to the development of disordered eating.

Results regarding the heritability of restraint are mixed. One study conducted with twins from the University of Washington Twin Registry found that, the heritability of restrained eating (measured by the Revised Restraint Scale) was 43%, adjusting for both sex and BMI [55]. These results differ from those obtained in an earlier study [47] in which an alternate measure of restraint, the Three Factor Eating Questionnaire (TFEQ), was used. Specifically, in this investigation restraint was not significantly influenced by additive genetic factors, but rather, were associated with shared ($c^2=.31$, $CI=.04-.42$) and specific ($e^2=.69$, $CI=.58-.80$), environmental factors. Similar results were obtained for the TFEQ Susceptibility to Hunger subscale. Scores on the TFEQ Disinhibition subscale, in contrast, (which assesses the tendency to eat or overeat in response to contextual cues) were significantly influenced by additive genetic factors ($a^2=.45$, $CI=.32-.57$); common environment did not contribute to variance in scores on this subscale. The disparate results of these two studies highlight the potential influence of psychometric issues in the derivation of heritability estimates.

Intentional weight loss (IWL) is a related eating symptom that has been the focus of behavioral genetic research. Results of these studies have been much more consistent than those investigating restraint. For example, Keski-Rahkonen et al. [33] obtained a heritability estimate of 38% for men and 66% for females. Similarly, Wade et al. [73] obtained a heritability estimate of .61 for IWL in their bivariate analysis of genetic and environmental factors influencing this construct and overeating. Wade et al. also reported a heritability estimate of 45% for overeating, and the genetic correlation between these two behaviors was .61, indicating that they share a number of genetic factors and are not completely independent behaviors.

A larger body of research has examined the heritability of binge eating [9, 52, 64, 72]. In one of the earliest of these studies [64], a bivariate analysis of objective binge eating and self-induced vomiting yielded substantial heritability estimates for both behaviors (46% and 72%, respectively). The genetic correlation between the two traits was .74; this high correlation suggests that these behaviors are significantly influenced by shared genetic factors. Similar results were obtained in a subsequent study by Bulik et al. [9], in which the heritability of binge eating was estimated at 49%. Further, the genetic correlation between this behavior and obesity was .34 indicating only a modest overlap of genetic factors.

The relation between binge eating and self-induced vomiting was evaluated in a bivariate model by Wade et al. [72]. Although these authors also found a substantial genetic correlation between the behaviors, the estimates for heritability were considerably lower than those obtained by Sullivan et al. [64] for both binge eating and vomiting: 17% and 8% respectively. These differences in heritability estimates across studies could be due to the assessment of different populations or to the use of frequency criteria in one study but not the other.

Night eating has more recently become a focus of scientific inquiry. Root et al. [52] estimated heritability for binge eating and night eating separately for males and females. For males, the estimates were 74% and 44%, respectively. For females, the estimates were 70% and 35%, respectively, with a genetic correlation of .66.

In sum, although some investigations have reported relatively high heritability estimates for specific eating disorder behaviors (e.g., self-induced vomiting, binge eating), there is considerable variability in these estimates across studies. These differences are likely attributable the definition of the constructs used and the format used to assess them. For example, as noted previously, many large-scale epidemiological surveys have used gateway items to assess eating disorders as part of a study of multiple psychiatric disorders [44]. In contrast, other studies have used measures such as the Eating Disorders Examination (EDE; e.g., [72], which is administered to all participants, without the use of gateway criteria. Further, specific symptoms, such as binge eating, have been defined as occurring with loss of control [52] and without this component.[9, 64] These differences underscore the importance of clearly defining the behavior of interest, and using the most reliable and valid forms of measurement available for their assessment.

9.2.3 Eating Disorder Attitudes and Temperament

Similarities in temperament and attitudes among women with eating disorders have long been noted among clinicians working with this population [3]. These similarities include a relentless drive for thinness, body dissatisfaction, perfectionism, obsessionality and sensitivity to reward and punishment. Given that these constructs have been found to exist both before eating disorder onset, e.g. [66], and persist following recovery in many patients, e.g. [35], they represent potential endophenotypes of interest.

Drive for thinness and body dissatisfaction are perhaps the most proximal risks factor for eating disorders and among the most frequently studied in the area of behavior genetics. One of the earliest of these studies [21] examined the Eating Disorder Inventory (EDI) [15] and reported a heritability estimate of “near 1.0” for the Drive-for-Thinness scale, although the standard errors were large. Two other studies also investigated the constructs measured by the EDI in twins and reported heritability estimates ranging from 28–52% for the subscales, with the remainder of the variance being attributed to unique environmental effects [53, 76]. Baker et al. [1] and Keski-Rahkonen et al. [31] examined heritability of EDI sub-scales in males and females separately. Both studies found that genetic factors contributed more to the variance of both Drive-for-Thinness and Body Dissatisfaction in females (51%–61% and 57%–59%, respectively) as compared with males (heritability estimates of 20% – 40% [1] and 0% [31]). Klump et al. [37] examined EDI sub-scales in two samples of adolescent twins, aged 11 and 17. For the younger cohort, both additive genetic effects and common environment effects were found to significantly contribute to most sub-scales. However, the contribution of additive genetic effects outweighs the contribution of common environmental effects in the older cohort. Overall, these results, suggest that heritability estimates are gender and age specific.

Studies from the Australian Twin Registry examined measures of dietary restraint and concern about eating, weight and shape from the EDE [68]. Heritability estimates for the total EDE score were 62% (95% CI: 21–71%). Individual variation of three of the EDE subscale measures was also best explained by a model which included only additive genetic and unique environmental effects (no shared environmental effects), with heritability estimates ranging from 32–62%. The exception was the Weight Concern measure, best explained by a model containing shared and unique environmental effects only (no additive genetic effects). Further, in a study by Wilksch and Wade [76], the heritability of importance of weight and shape was assessed. The heritability estimate of the importance of weight and shape was low: 15% of the variance observed in this measure was accounted for by genetic factors. Yet, Wade and Bulik [69] obtained a heritability estimate of 25% for weight and shape concerns.

Temperament, specifically, perfectionism, sensitivity to reward, sensitivity to punishment, and obsessionality have been studied in relation to shape and weight concerns [69, 76]. The temperament measures had heritability estimates ranging from 27% to 71%. The perfectionism measures and weight and shape concerns shared about 10% of their genetic factors, indicating that different genes influence these constructs. In contrast, sensitivity to punishment and weight and shape concerns had a genetic correlation of .52. Although these temperament measures do not share a considerable proportion of genetic influences with the eating disorders weight and shape criterion, they have demonstrated substantial heritability and are prevalent in the eating disorders population and, thus, deserve further study.

In summary, genetic effects certainly contribute to the liability of eating disorders. Using endophenotypes to identify genes implicated in the etiology of eating disorders could open up new areas of exploration of biological pathways that lead to dysregulated eating, appetite, and weight regulation, as well as anxiety, obsessionality, and core eating disorder symptoms, such as drive for thinness. Such avenues may provide refinements in diagnosis by using objective biological measures, which could ultimately inform prevention and treatment strategies.

9.3 The Value of Family and Twin Studies in the Molecular Genetic Era

Family and twin studies of eating disorders are valuable methods to evaluate the magnitude of genetic effects on the liability to eating disorders. Further, these approaches have been

employed to identify and refine endophenotypes and component phenotypes. This research has implications for molecular genetic studies: the focus on endophenotypes can increase the size of the population available for study and, perhaps more importantly, phenotypes identified in twin studies with consistently higher heritabilities can be used for sample selection for molecular genetic studies to potentially yield a more genetically homogenous population. This approach, theoretically, may enhance our ability to identify loci associated with the phenotypes and ultimately delineate underlying biological mechanisms that influence risk for and maintenance of disordered eating behavior. In addition, advances in molecular genetics may open new avenues for exploring environmental risk factors as well as gene x environment interactions and correlations. As our library of replicated genes expands for eating disorders, we will be able to further explore gene x environment interplay in large well-characterized twin samples.

Abbreviations

A	additive genetic effects
a²	proportion of variance due to additive genetic effects
AN	anorexia nervosa
BED	binge eating disorder
BMI	body mass index
BN	bulimia nervosa
C	shared environmental effects
c²	proportion of variance due to shared environmental effects
CI	95% confidence interval
DZ	dizygotic
E	unique environmental effects
e²	proportion of variance due to unique environmental effects
EDE	Eating Disorders Examination
EDI	Eating Disorder Inventory
IWL	intentional weight loss
MZ	monozygotic
PD	purging disorder
TFEQ	Three Factor Eating Questionnaire
V	variance is liability to a disorder

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