Genetic Epidemiology, Endophenotypes, and Eating Disorder Classification

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ABSTRACT

Objective: To explore how genetic epidemiology has informed the identification of endophenotypes and how endophenotypes may inform future classification of eating disorders.

Method: Literature review and synthesis.

Results: Although a number of endo- and subphenotypes have been suggested for eating disorders, few reach the rigorous definitions developed for candidate endophenotypes.

Conclusion: Further study of endophenotypes and subphenotypes for eating disorders may assist with developing a more homogenous classification system that more closely reflects underlying biological mechanisms, and provides a clearer focus for the development of coherent models and treatments. © 2007 by Wiley Periodicals, Inc.

Keywords: endophenotypes; subphenotypes; genetic epidemiology; eating disorders; anorexia nervosa; bulimia nervosa; binge eating; obsessionality

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Introduction

Anorexia nervosa (AN), bulimia nervosa (BN), and eating disorders not otherwise specified (EDNOS) are potentially devastating illnesses. The current tripartite classification system represents a series of cumulative historical accidents which, rather than optimizing and incorporating extant empirical observations, perpetuates clinical opinion and the biases inherent therein. In part, this reflects the uncomfortable truth that sufficient data of the appropriate type do not exist to inform the diagnostic criteria for eating disorders fully, yet certain troubling facts underscore the importance of critically evaluating and revising our diagnostic approach to eating disorders.

We address how genetic (family, twin, and molecular) and related biological research can inform future renditions of the DSM criteria for eating disorders by introducing the concept of endo- and subphenotypes and address how their identification can assist with developing a scaffold upon which to refine and rebuild our diagnostic criteria. We then take a "within disorder" approach to explore how these studies can inform the extant criteria for AN and BN followed by a "cross-disorder" approach to explore what these studies can tell us about endophenotypes that cross diagnostic boundaries that may inform future diagnostic criteria. Finally, we address directions for future research.

Our bias is that refinements of the diagnostic criteria for eating disorders could be more richly informed by biology. Our current diagnostic criteria are heterogeneous—Reichborn et al.[1] noted considerable within-diagnosis heterogeneity in symptom origin, with some criteria reflecting observable, measurable, and heritable features and others which are unobservable, difficult to measure, and more influenced by environmental factors which require complicated inferences about intentions and cognitions of the patient. Whereas gene–environment interplay is essential to understand the

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development of psychiatric disorders, and environmental main effects cannot be ignored, we argue that core diagnostic criteria should be observable, measurable and, if possible, reflect underlying biological processes.

Can Endophenotypes Inform Diagnostic Criteria?

The concept of endophenotype was identified in 1973[2] and has been resurrected with modern genetic approaches. Endophenotypes are measurable components unseen by the unaided eye along the pathway between disease and distal genotype. An endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature.[3] Endophenotypes are heritable, cosegregate with a psychiatric illness in the general population, are state-independent, (i.e., manifest in the individual whether or not illness is active), and are found in nonaffected family members at a higher rate than in the general population.[3–5] Other enhancements of the definition of endophenotype include being linked to the causal process, involved in plausible biological mechanisms, predictive of the disorder probabilistically, and lying closer to the site of the primary causative agent.[4,6–9] The term subphenotype has also been used to identify more homogeneous subgroups of complex syndromes (e.g. early onset depression or BN with self-induced vomiting). Although not as clearly defined as endophenotypes, they are commonly employed as a means to reduce the heterogeneity inherent in sampling based on a diagnostic category or syndrome. An example of the hierarchy would be: the phenotype of schizophrenia; the subphenotype of individuals with schizophrenia who report auditory hallucinations; the endophenotype of P50 event-related potential suppression.

While the ostensible advantage of endo- and subphenotypes is that they are hypothesized to involve fewer genes that would simplify the detection of contributing genetic loci, the reported genetic effect sizes for endophenotypes have not proven to be unanimously significantly larger than those observed for the phenotypes they underlie.[4] However several significant advantages emerge from the identification of endophenotypes, including deconstruction of complex disorders[10] that could theoretically assist in developing a more biologically based and homogenous classification system for eating disorders.[11] Refining endophenotypes for eating disorders may assist with identifying core, genetically influenced traits that inform the underlying scaffolding around which the diagnostic criteria for eating disorders should be constructed. Thus many fields of psychiatry have embraced research on endophenotypes, however, only four references were located in eating disorder field.[12–15] Table 1 presents candidate endo- and subphenotypes for eating disorders and evaluates them across the definitional dimensions presented above. Although the designation of endo- or subphenotype is not always clear, we have attempted to evaluate each candidate for endophenotype status based on extant data.

Within Disorder Perspective

Anorexia Nervosa

Criterion A. The hallmark feature of AN is maintenance of low body weight, yet aside from body weight itself, we have little evidence regarding underlying biological mechanisms that initiate or maintain this symptom. Twin studies have shown that BMI is heritable[16] and hundreds of genes have been reported to influence BMI and/or obesity.[17] Much less is known about the low end of the BMI continuum, and it is unclear whether what we do know about biology of low BMI applies to the low weight seen in AN.

Concerns with the phrasing of Criterion A (i.e., particularly the term "refusal") and the appropriateness of the 85% weight cutoff have been dealt with extensively elsewhere.[18] We focus on BMI per se. Premorbid weights of individuals with AN span the BMI spectrum, although very high BMIs may be underrepresented.[19] Even after recovery, BMIs are lower than expected[20–23]; in part due to reduced body fat.[24] Although few adequately designed studies have been conducted, the BMIs of family members of individuals with AN do not appear to be lower than relatives of those without AN.[25,26] Hebebrand et al.[18] noted that the low weight maintained in AN defies observations about the body's tendency to defend its set point. This fundamental dysregulation sets AN apart from healthy low weight.

Low weight in AN differs from healthy underweight in many ways. First, in over 400 male and female students with a BMI below 85% average body weight, most individuals were healthy[27,28] (Hebebrand et al., unpublished data) and tracking

TABLE 1. Summary of data addressing whether psychological, physical, and biological traits represent endophenotypes or subphenotypes for eating disorders

	Endophenotype Criteria							
Trait	Measurable	Heritable	Cosegregates with Illness	State Independent	Observed in Unaffected Family Members	Biologically Plausible Causal Mechanism	ENDO?	SUB?
Perfectionism	+	Moderate	++	+++	+	UNKNOWN	UNKNOWN	++
Obsessionality	+	Moderate	+++	+++	+	+	+	
Drive for thinness	+	Moderate	+++	++	+?	+	UNKNOWN	+++
Anxiety	+	Moderate	+++	++	+	+	+	
Negative emotionality	+	Moderate	+++	++	+	+	+	
Decreased food intake	+	Moderate-Large	+++	+	UNKNOWN	+++	UNKNOWN	+++
Low body weight (dysregulation of body weight)	+++	Moderate-Large	+++	+	UNKNOWN	UNKNOWN	UNKNOWN	+++
Increased physical activity	+	Moderate-Large	+++	+	UNKNOWN	UNKNOWN	UNKNOWN	+++
Cognitive set shifting	++	Moderate-Large	++	+	+	+++	++	
Binge eating	+	Moderate	+++	No	UNKNOWN	+	NO	+++
Self-induced vomiting	+	Moderate-Large	+++	No	UNKNOWN	UNKNOWN	NO	+++
Impulsivity	++	Moderate	++	++	+	+	+	
Undue influence of weight or shape	+	Small	+++	++	UNKNOWN	No		

AN = anorexia nervosa; ANR = restricting type AN; BN = bulimia nervosa; ANBP = binge/purge type AN; ENDO = endophenotype; SUB = subphenotype; UNKNOWN = no studies have examined the issue or existing data are inconclusive. Plus marks (+) denote the strength of data supporting each criterion. For example, for the "Measurable" column, a single plus (+) denotes that only self-report measures were used to assess the trait. A double plus mark (++) indicates that observer ratings or neuropsychological data were used to assess the trait. A triple plus mark (+++) indicates that the trait can be measured objectively by an outside observer (e.g., body weight) or can be assessed with a biological assay or marker (e.g., 5HT transporter activity). For the remaining criteria columns, the plus marks indicate the strength of the data supporting the criterion in terms of the number of studies reporting positive findings (i.e., + = few studies; ++ = more studies; +++ = many studies). For the ENDO? and SUB? column, the plus marks indicate the extent to which the trait satisfies the criteria for an endophenotype or subphenotype (+ = some evidence that criteria are supported; ++ = moderate evidence; +++ = strong evidence). Traits exhibiting the strongest evidence in support of their categorization as endophenotypes are noted in bolded and outlined text.

of BMI in adulthood[29] implies that many lean young adults will remain so over time. These individuals can also expect a longer life span than those with higher body weight.[30] Second, intentional weight loss is not common among students with a BMI $\leq$ 85% average body weight, in contrast, $\sim$25–33% of such underweight individuals repeatedly attempt to gain weight and are unhappy with their thinness (Hebebrand et al., unpublished data). Moreover, the presence of constitutional thinness in women and men has been shown to be associated with decreased rather than increased odds of having disordered eating behaviors and attitudes.[31–33] Third, the "risk" of thinness was elevated in the relatives of constitutionally thin individuals (Hebebrand et al., unpublished data). In contrast, two studies have reported relatives of AN probands to be at no greater risk of thinness (Hebebrand et al., unpublished data),[25] while another found cotwins of twins with AN were at significantly higher risk for current low BMI.[34] However, if subthreshold forms of AN are accounted for, cotwins of twins with AN do not appear to differ in BMI from women from the general population.[26] Fourth, serum leptin levels also differentiate between constitutionally lean females and those with AN.[27,28] Fifth, initially at least, weight loss in AN is usually voluntary, and although intentional weight loss is moderately heritable, the majority of genetic factors affecting BMI are different from those affecting intentional weight loss.[35]

Molecular genetic studies that incorporated relevant covariates into linkage analyses have included the related construct of minimum BMI, a variable that more closely approximates the core phenotype of AN as it indexes the extreme low BMI values reached as the body experiences a complete failure to regulate weight. For minimum BMI achieved during the illness, families showed highly concordant and extreme values rendering the variable appropriate for covariate-based linkage analyses.[36] Incorporation of this variable enabled identification of a suggestive signal for lifetime minimum BMI at 4q13.1 in the AN cohort and one significant [4q21.1] and three suggestive [3p23, 10p13, 5p15.3] signals in the BN cohort.[37] These findings could highlight specific factors that influence the anomalous dysregulation of body weight in AN.

In sum, twin studies have explicated factors associated with intentional weight loss and constitutional thinness, but they have not honed in on the grossly abnormal weight dysregulation associated with the maintenance of unusually low body weight in AN. Serum leptin appears to distinguish between constitutional thinness and AN, and mini-

mum BMI provides valuable information to hone linkage signals for AN. Although not nearly definitive, these findings collectively support the importance of continuing to refine and explore factors associated with low body weight as core subphenotype for AN.

Criterion B. Fear of fatness or fear of weight gain has been considered to be a key feature of AN, yet family, twin and genetic studies have little to say about the underlying biology of the symptom. Hebebrand et al.[18] underscore the lack of reliability and validity of this criterion, difficulty with measurement, absence in non-Western cultures,[38,39] failure to reflect the biology of AN,[40,41] and fluctuations over the course of AN.[42,43] Thus, this criterion is best conceptualized as an environmental feature relevant to understanding maintenance factors for AN, for predicting clinical course, and for understanding cultural manifestations,[44] but not a candidate endophenotype reflective of a core underlying biological process.

Criterion C. This composite criterion clusters three distinct and possibly unrelated processes—all difficult to measure and lacking a plausible biological explanation: disturbance in experiencing one's body weight or shape, denial of the seriousness of the current low body weight, or undue influence of body weight or shape on self-evaluation. Although sometimes confused with body dissatisfaction, undue influence of weight and shape has a specific meaning solely relating to the degree that self-evaluation is influenced by weight or shape relative to other factors in the person's life (e.g., work, specific skills, relationships).

Twin studies have not found consistent genetic contributions to undue influence of weight and shape: in a Norwegian study,[1] this trait was best explained by models incorporating only common and unique environment, without any genetic effects. However, a recent study[15] which defined the criterion for undue influence of either weight or shape as a combined phenotype, did find a small contribution of additive genetic variance of 25% (95% CI: 14–36%). Compared with unaffected women, this combined phenotype remained significantly elevated in women recovered from an eating disorder, representing either scarring effects of illness or a predisposing and persistent trait. Thus, the degree to which "undue influence" meets the requirements for an endophenotype is largely unknown.

A second issue with the "undue influence" is the extent to which it reflects a "normative discontent" amongst women in much of the developed world. It is conceivable that whereas the content of the concerns may be environmentally mediated, the cognitive-affective component of this feature may be heritable. Alternatively, these psychological features may best be considered to reflect the cultural context in which the core biological features of eating disorders emerge. If one adopts the position that gene environment interaction may be operative in eating disorders, then these more culturally embedded features may serve as environmental triggers for underlying genetic predisposition. As such they become less attractive as core phenotypes for eating disorders and may best be considered as contextual rather than diagnostic features.

Criterion D. Although some aspects of menstruation have been studied in the context of twin research (e.g. timing of puberty[45]), no family or twin studies have addressed the familiality or heritability of amenorrhea. It is difficult to conceptualize amenorrhea as a unique diagnostic criterion for AN, when on the most basic biological level, the curtailment of energy intake (for any reason) compromises normal reproductive function and results in amenorrhea.[46,47] Given that amenorrhea cannot be assessed in males, in pre-menarcheal girls and in females using hormonal contraceptives, one alternative to current criterion is a diagnostic requirement of somatic symptoms indicating adaptation to semi-starvation (e.g., hypothermia, bradycardia, hypotension, lanugo hair and/or amenorrhea). Together with criterion A this would imply that the underweight is of such a degree as to have led to physiological alterations of the organism, thus entailing a clear distinction between healthy leanness and disorder-inherent thinness. This broader novel criterion would be age independent, applicable to both sexes,[18] and likely to be heritable to some degree.

Bulimia Nervosa

Criterion A. The symptom of binge-eating has received considerable support as a subphenotype of BN. Dismantling BN into its component behaviors of objective binge eating and self-induced vomiting, Sullivan et al.[48] estimated the heritability of binge eating to be 49% (95% CI: 32–63%), which concurred with other reported estimates (41%[49] to 82%[50] controlling measurement error). Genetic risk factors for binge eating and BN may be largely similar, whereas nonshared environment may be important in influencing the risk for developing BN once binge eating is initiated.[51] In sum, binge-eating represents a heritable, somewhat measurable candidate behavioral subphenotype for BN.

Criterion B. This criterion lumps several compensatory behaviors: self-induced vomiting; use of laxatives, diuretics, enemas, or other medications; excessive exercise, and fasting. Whether these behaviors share an underlying mechanism is unclear. Intriguingly Sullivan et al.[48] revealed substantial genetic effects on self-induced vomiting ($a^2 = 72$; 95% CI: 55–88) suggesting that it is strongly heritable and perhaps more reliably measured than binge eating which has shown at best moderate reliability,[52] perhaps due to the lack of clarity of the "out of control" sub-criterion. In the absence of clear data on other forms of purging and physical activity in BN, it is premature to determine whether these behaviors meaningfully cluster as one criterion.

Criterion C. To determine whether the twice per week threshold is meaningful for binge eating and whether a meaningful threshold exists for self-induced vomiting in a genetically informative sample, Sullivan et al.[48] chose the a priori principal validator of risk to cotwin. For the different thresholds of binge eating, the risk ratio peaked at four binges per month or once per week. For vomiting thresholds, the risk ratio increased with greater thresholds—as vomiting increased so did risk to the co-twin. Their results did not support the current thresholds for binge eating and vomiting in the DSM-IV BN criteria. Family and twin studies have not addressed the 3-month duration criterion. Although additional confirmation is required, these data suggest that the most appropriate threshold would be one binge per week.

Criterion D. To address this criterion, we refer to the discussion above under Criterion C for anorexia nervosa.

Cross-Disorder Perspective

In addition to exploring what we know about the extant criteria, we must also consider whether genetic research supports the inclusion of additional optional or obligatory symptoms into future diagnostic schemes. To achieve this, we take a "cross-disorder" approach and explore what endophenotypes might exist that cross the boundaries between currently conceptualized disorders. This approach is consistent with some observations including a latent profile analysis that suggested, from a general population perspective, there is no meaningful differentiation between clinically significant eating disorders, including EDNOS[33] and with unpublished data which show AN and BN spectrum disorders share 50% of their genetic risk factors (Wade, Treloar, Heath, Martin, unpublished manuscript). It is also noteworthy that this approach may identify trans-diagnostic endophenotypes that may identify meaningful biological bridges between entire classes of psychiatric illnesses (e.g. anorexia nervosa and autism spectrum disorders[53]). Within this framework, four areas emerge as worthy of further investigation as possible cross-diagnostic endophenotypes, outlined in Table 1. These include increased physical activity, dimensions of temperament (obsessionality, impulsivity and negative emotionality), dimensions reflecting weight concern (including drive for thinness), and impaired set shifting. As well as meeting the criteria for an endophenotype, the utility of each must be further judged with respect to whether they are unique to eating disorders as opposed to other psychiatric disorders.

Physical Activity

Increased physical activity observed in a subgroup of individuals with eating disorders (primarily AN) during the course of the illness raises the question of whether subtyping on the basis of hyperactivity is meaningful. Animal models of "anorexia based activity" exist[54] and both rodent and human studies indicate that hypoleptinemia is associated with hyperactivity and motor restlessness.[55,56] In food restricted rats, exogenous leptin suppresses the development of semi-starvation induced hyperactivity[57]; in AN patients leptin levels are inversely correlated with motor restlessness.[58] The optional inclusion of symptoms of elevated activity would allow reference to a biologically based phenomenon, which appears rather specific to AN. Less is known about hyperactivity in BN and EDNOS. This feature may mainly be found in those BN patients with low body weight (or low body fat) which, as in AN, could reflect hypoleptinemia.

Temperament

Temperament and personality indicators, whilst heritable and cosegregating with illness, may share some problems with non-behavioral measures including being influenced by many genes rather than few. A number of temperaments are worthy of consideration as inclusions in future diagnostic criteria, including those that have been shown to remain elevated after recovery, or elevated in unaffected family members, namely high harm avoidance, low self-directedness and cooperativeness,[59] obsessive-compulsive personality disorder (OCPD) and obsessive compulsive spectrum disorders,[60,61] perfectionism and ineffectiveness, and lower levels of interoceptive awareness[62] and self-directedness.[63,64]

Negative emotionality should also be considered given longitudinal evidence that this temperamental trait prospectively predicts disordered eating symptoms[65,66] and exhibits shared genetic variance with these characteristics.[67] Anxiety or depression precede the onset of bulimic symptoms,[68] and parental depression also predicts development of an eating disorder in children.[69] Family studies suggest that these heritable disorders are important in increasing risk for eating disorders.[61,70,71] There is evidence for shared genetic vulnerability between AN and depression[72] and anxiety.[73] Further, such shared genetic vulnerability exists between BN and depression, as well as BN and a range of anxiety disorders including phobia, panic disorder, and GAD.[74,75] Cluster B personality disorders are elevated among BN probands,[60] and Wade et al.[75] found that risk for BN in one sibling was associated with risk for higher levels of novelty seeking and psychoactive substance use (a possible behavioral marker for novelty seeking) in the other sibling when the other sibling was male.

In sum, obsessionality and forms of anxiety show promise as diagnostically meaningful endophenotypes for both AN and BN. Perfectionism may show diagnostic utility due to sharing some degree of genetic risk factors with obsessionality.[15] Impulsivity or indicators of novelty seeking may be a useful diagnostic endophenotype for eating disorders that are characterized by binge eating. Negative emotionality, whilst not a diagnostic endophenotype specific to eating disorders, may be a necessary but not sufficient inclusion to diagnostic criteria, especially as an indicator of the clinical severity of eating disorders.[33] Clearly, additional research using family designs and robust outcome variables is required to understand the relation between personality and eating disorders.[76]

Cognitive Features

Various cognitive features predict the onset of disordered eating, including weight concern and drive for thinness, composite measures of dietary restraint, body dissatisfaction, feeling fat, importance of weight and fear of weight gain.[77–79] A composite measure of weight concern was elevated in women with AN compared to controls, as was dietary restraint for women who had either lifetime AN or BN.[33] Consistent with evidence supporting this variable as an endophenotype, a follow-up study of 108 infants at 8 years of age showed that maternal restraint predicted worries about being too fat in girls but not boys.[80] However, the composite measure of weight concern has been found to be influenced by environmental variance only,[81] while other studies suggest that measures of body dissatisfaction, weight preoccupation and drive for thinness are influenced by genetic factors in older adolescent female twins.[82–84] Interestingly, shared genetic variance between negative emotionality and both body dissatisfaction and weight preoccupation were limited.[67] Drive for thinness is associated with potentially biologically plausible mechanisms, where elevated levels are associated with carriers of the deletion polymorphism of the serotonin transporter promoter 5-HTTLPR[85] and has been a valuable covariate in linkage analyses.[86] In women recovered from bulimia-type AN, [^{18}F]altanserin binding potential and drive for thinness were negatively correlated in several cortical regions, suggesting that altered 5-HT neuronal system activity persisted.[87]

Given that different measures have been used to capture these cognitive features, further work is required to increase the reliability and validity of these measures before conclusions can be drawn about their potential status as an eating disorder endophenotype, including the degree to which they are influenced by genetic factors.

In sum, measures of weight concern have shown promise in predicting onset and persistence of cross-diagnostic eating disorder behaviors. However, twin studies suggest that these measures suffer from some degree of inconsistency in relation to genetic risk factors. Drive for thinness, a construct that captures the composite nature of weight concern including body dissatisfaction, dieting, and importance of weight, does show promise as a biologically plausible endophenotype across eating disorders.

Set-Shifting

Of particular intuitive appeal as a candidate for an endophenotype are tests of cognitive processes, given their measurable nature. Of interest in relation to eating disorders are measures of executive functioning, responsible for the supervision of such cognitive processes as setting goals, planning and organizing. One indication of executive functioning is set-shifting ability, has been examined specifically with respect to AN. Set shifting involves the ability to move back and forth between tasks, operations or sets, and impaired ability in this area is postulated to contribute to rigid and obsessional behavior. It is moderately heritable,[88,89] deficits are present in women with AN[90–92] and BN,[93] and are observed in both women with AN and women with high levels of obsessionality who have no eating disorder history compared to controls.[94] Importantly, these set-shifting deficits persist after recovery from AN.[95] In addition, sisters of

women with AN exhibit significantly impaired set shifting compared to controls,[12] comparable to that of their siblings with AN. Further appeal with respect to this measure of cognitive function as a potential endophenotype is its association with the dopaminergic system.[96]

In sum, whilst measures of cognitive function show much promise as endophenotypes for eating disorders, much remains unknown, especially with respect to functioning in BN. Of consideration is the degree to which set shifting is specific to eating disorders, as such impairment has also been noted in bipolar disorder[97] and schizophrenia.[98] Other measures of cognitive function may provide some degree of specificity for eating disorders, and further research is required to discover and validate endophenotypes in this area of executive function. Constructs of theoretical interest to eating disorders and which show some degree of heritability include response inhibition (Willcutt et al., unpublished data)[88] and contingencies (Willcutt et al., unpublished data).[99]

Where To From Here?

Our review indicates that the pursuit of clarification of endophenotypes and subphenotypes for eating disorders may be a fruitful approach for clarifying diagnostic criteria that more closely reflect underlying biological mechanisms. The eating disorders field has fallen somewhat behind in psychiatry in these pursuits and would be served well by a concerted research effort in this area. Our hope is that this paper will represent a "call to arms" for twin and genetic researchers to utilize our powerful methodology to better identify endophenotypes that may assist with refining core DSM criteria for eating disorders. Over thirty years ago, Robins and Guze[100] cited family aggregation as one of the criteria for validation of diagnostic criteria. Genetic and biological data were viewed on equal footing with the phenomenology, course, and outcome data needed to establish a disorder as an independent diagnostic entity. Acknowledging that familial aggregation has limitations as a validator of psychiatric illness,[101] and recognizing the importance of nature-nurture interplay in the final phenotypic expression of disease, we believe that in order to "carve nature at its joints," we must put the "nature" back into our diagnostic conceptualizations of eating disorders.

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References

1. Reichborn-Kjennerud T, Bulik C, Kendler K, Roysamb E, Tambs K, Harris J, et al. Influence of weight on self-evaluation: A population-based study of gender differences. Int J Eat Disord 2004;35:123–132.
2. Gottesman I, Shields J. Genetic theorizing and schizophrenia. Br J Psychiatry 1973;122:15–30.
3. Gottesman I, Gould T. The endophenotype concept in psychiatry: Etymology and strategic intentions. Am J Psychiatry 2003;160:636–645.
4. Flint J, Munafo M. The endophenotype concept in psychiatric genetics. Psychol Med 2007;37:163–180.
5. Hasler G, Drevets W, Gould T, Gottesman I, Manji H. Toward constructing an endophenotype strategy for bipolar disorders. Biol Psychiatry 2006;60:93–105.
6. Lavori P, Krause-Steinrauf H, Brophy M, Buxbaum J, Cockroft J, Cox D, et al. Principles, organization, and operation of a DNA bank for clinical trials: A Department of Veterans Affairs Cooperative Study. Control Clin Trials 2002;23:222–239.
7. Tsuang M, Faraone S, Lyons M. Identification of the phenotype in psychiatric genetics. Eur Arch Psychiatry Clin Neurosci 1993;243:131–142.
8. Castellanos F, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. Nat Rev Neurosci 2002;3:617–628.
9. Almasy L, Blangero J. Endophenotypes as quantitative risk factors for psychiatric disease: Rationale and study design. Am J Med Genet 2001;105:42–44.
10. Braff DL, Freedman R, Schork NJ, Gottesman II. Deconstructing schizophrenia: An overview of the use of endophenotypes in order to understand a complex disorder. Schizophr Bull 2007;33:21–32.
11. Berrettini W. Genetic bases for endophenotypes in psychiatric disorders. Dialog Clin Neurosci 2005;7:95–101.
12. Holliday J, Tchanturia K, Landau S, Collier D, Treasure J. Is impaired set-shifting an endophenotype of anorexia nervosa? Am J Psychiatry 2005;162:2269–2275.
13. Steiger H, Gauvin L, Joober R, Israel M, Kin N, Ng Y, et al. Intrafamilial correspondences on platelet [superscript 3H-] paroxetine-binding indices in bulimic probands and their unaffected first-degree relatives. Neuropsychopharmacology 2006;31:1785–1792.
14. Shroff H, Reba L, Thornton LM, Tozzi F, Klump KL, Berrettini WH, et al. Features associated with excessive exercise in women with eating disorders. Int J Eat Disord 2006;39:454–461.
15. Wade T, Bulik C. Shared genetic and environmental risk factors between undue influence of body shape and weight on self evaluation and dimensions of perfectionism. Psychol Med 2007;37:635–644.
16. Maes H, Neale M, Eaves L. Genetic and environmental factors in body mass index. Behav Genet 1997;27:325–351.
17. Rankinen T, Zuberi A, Chagnon YC, Weisnagel SJ, Argyropoulos G, Walts B, et al. The human obesity gene map: The 2005 update. Obesity (Silver Spring) 2006;14:529–644.
18. Hebebrand J, Casper R, Treasure J, Schweiger U. The need to revise the diagnostic criteria for anorexia nervosa. J Neural Transm 2004;111:827–840.
19. Coners H, Remschmidt H, Hebebrand J. The relationship between premorbid body weight, weight loss, and weight at

referral in adolescent patients with anorexia nervosa. Int J Eat Disord 1999;26:171–178.
20. Hebebrand J, Himmelmann G, Herzog W, Herpertz-Dahlmann B, Steinhausen H, Amstein M, et al. Prediction of low body weight at long-term follow-up in acute anorexia nervosa by low body weight at referral. Am J Psychiatry 1997;154:566–569.
21. Sullivan PF, Bulik CM, Fear JL, Pickering A. Outcome of anorexia nervosa. Am J Psychiatry 1998;155:939–946.
22. Steinhausen H. The outcome of anorexia nervosa in the 20th century. Am J Psychiatry 2002;159:1284–1293.
23. Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2006;61:348–358.
24. Frey J, Hebebrand J, Muller B, Ziegler A, Blum WF, Remschmidt H, et al. Reduced body fat in long-term followed-up female patients with anorexia nervosa. J Psychiatr Res 2000;34:83–88.
25. Halmi KA, Struss A, Goldberg SC. An investigation of weights in the parents of anorexia nervosa patients. J Nerv Ment Dis 1978;166:358–361.
26. Keski-Rahkonen A, Hoek H, Susser E, Linna M, Sihvola E, Raevuori A, et al. Epidemiology and course of anorexia nervosa in the community. Am J Psychiatry, in press.
27. von Prittwitz S, Blum W, Ziegler A, Scharmann S, Remschmidt H, Hebebrand J. Restrained eating is associated with low leptin levels in underweight females. Mol Psychiatry 1997;2:420–422.
28. Köpp W, Blum W, von Prittwitz S, Ziegler A, Lubbert H, Emons G, et al. Low leptin levels predict amenorrhea in underweight and eating disordered females. Mol Psychiatry 1997;2:335–340.
29. Casey V, Dwyer J, Coleman K, Valadian I. Body mass index from childhood to middle age: A 50-y follow-up. Am J Clin Nutr 1992;56:14–18.
30. Manson J, Willett W, Stampfer M, Colditz G, Hunter D, Hankinson S, et al. Body weight and mortality among women. N Engl J Med 1995;333:677–685.
31. Slof R, Mazzeo S, Bulik C. Characteristics of women with persistent thinness. Obes Res 2003;11:971–977.
32. Mazzeo SE, Slof RM, Tozzi F, Kendler KS, Bulik CM. Characteristics of men with persistent thinness. Obes Res 2004;12:1367–1369.
33. Wade T, Crosby R, Martin N. Use of latent profile analysis to identify eating disorder phenotypes in an adult Australian twin cohort. Arch Gen Psychiatry 2006;63:1377–1384.
34. Walters EE, Kendler KS. Anorexia nervosa and anorexic-like syndromes in a population-based female twin sample. Am J Psychiatry 1995;152:64–71.
35. Keski-Rahkonen A, Neale BM, Bulik CM, Pietilainen KH, Rose RJ, Kaprio J, et al. Intentional weight loss in young adults: Sex-specific genetic and environmental effects. Obes Res 2005;13:745–753.
36. Bulik C, Bacanu S, Klump K, Fichter M, Halmi K, Keel P, et al. Selection of eating disorders phenotypes for linkage analysis. Am J Med Genet B Neuropsychiatr Genet 2005;139:81–87.
37. Bacanu S, Bulik C, Klump K, Fichter M, Halmi K, Keel P, et al. Linkage analysis of anorexia and bulimia nervosa cohorts using selected behavioral phenotypes as quantitative traits or covariates. Am J Med Genet B Neuropsychiatr Genet 2005;139: 61–68.
38. Ngai E, Lee S, Lee A. The variability of phenomenology in anorexia nervosa. Acta Psychiatr Scand 2000;102:314–317.
39. Lee S, Lee A, Ngai E, Lee D, Wing Y. Rationales for food refusal in Chinese patients with Anorexia Nervosa. Int J Eat Disord 2001;29:224–229.
40. Treasure J, Campbell I. The case for biology in the aetiology of anorexia nervosa. Psychol Med 1994;24:3–8.
41. Casper R. Behavioural activation and lack of concern, core symptoms of anorexia nervosa? Int J Eat Disord 1998;24:381–393.
42. Strober M, Freeman R, Morrell W. Atypical anorexia nervosa: Separation from typical cases in course and outcome in a long-term prospective study. Int J Eat Disord 1999;25:135–142.
43. Ramacciotti C, Dell'Osso L, Paoli R, Ciapparelli A, Coli E, Kaplan A, et al. Characteristics of eating disorder patients without a drive for thinness. Int J Eat Disord 2002;32:206–212.
44. Keel P, Klump K. Are eating disorders culture-bound syndromes? Implications for conceptualizing their etiology. Psychol Bull 2003;129:747–769.
45. Eaves L, Silberg J, Foley D, Bulik C, Maes H, Erkanli A, et al. Genetic and environmental influences on the relative timing of pubertal change. Twin Res 2004;7:471–481.
46. Chehab F. Leptin as a regulator of adipose mass and reproduction. Trends Pharmacol Sci 2000;21:309–314.
47. Frisch R. Fatness and fertility. Sci Am 1988;258:88–95.
48. Sullivan PF, Bulik CM, Kendler KS. The genetic epidemiology of binging and vomiting. Br J Psychiatry 1998;173:75–79.
49. Reichborn-Kjennerud T, Bulik C, Kendler K, Maes H, Roysamb E, Tambs K, et al. Gender differences in binge-eating: A population-based twin study. Acta Psychiatr Scand 2003;108:196–202.
50. Bulik C, Sullivan P, Kendler K. Heritability of binge-eating and broadly defined bulimia nervosa. Biol Psychiatry 1998;44: 1210–1218.
51. Wade TD, Bulik CM, Sullivan PF, Neale MC, Kendler KS. The relation between risk factors for binge eating and bulimia nervosa: A population-based female twin study. Health Psychol 2000;19:115–123.
52. Wade T, Bulik C, Kendler K. Reliability of bulimia nervosa and major depression. Br J Psychiatry 2000;177:72–76.
53. Zucker N, Pelphrey K, Bulik C, Losh M, Piven J. Anorexia nervosa and autism spectrum disorders: Guided inquiry into social cognitive endophenotypes. Submitted.
54. Kas MJ, Van Elburg AA, Van Engeland H, Adan RA. Refinement of behavioural traits in animals for the genetic dissection of eating disorders. Eur J Pharmacol 2003;480:13–20.
55. Hebebrand J, Exner C, Hebebrand K, Holtkamp C, Casper R, Remschmidt H, et al. Hyperactivity in patients with anorexia nervosa and in semistarved rats: Evidence for a pivotal role of hypoleptinemia. Physiol Behav 2003;79:25–37.
56. Hebebrand J, Muller T, Holtkamp K, Herpertz-Dahlmann B. The role of leptin in anorexia nervosa: Clinical implications. Mol Psychiatry 2007;12:23–35.
57. Exner C, Hebebrand J, Remschmidt H, Wewetzer C, Ziegler A, Herpertz S, et al. Leptin suppresses semi-starvation induced hyperactivity in rats: implications for anorexia nervosa. Mol Psychiatry 2000;5:476–481.
58. Holtkamp K, Herpertz-Dahlmann B, Hebebrand K, Mika C, Kratzsch J, Hebebrand J. Physical activity and restlessness correlate with leptin levels in patients with adolescent anorexia nervosa. Biol Psychiatry 2006;60:311–313.
59. Klump K, Strober M, Bulik C, Thornton L, Johnson C, Devlin B, et al. Personality characteristics of women before and after recovery from an eating disorder. Psychol Med 2004;34:1407–1418.
60. Lilenfeld L, Kaye W, Greeno C, Merikangas K, Plotnikov K, Pollice C, et al. A controlled family study of restricting anorexia and bulimia nervosa: Comorbidity in probands and disorders in first-degree relatives. Arch Gen Psychiatry 1998;55:603–610.
61. Bellodi L, Cavallini M, Bertelli S, Chiapparino D, Riboldi C, Smeraldi E. Morbidity risk for obsessive-compulsive spectrum disorders in first-degree relatives of patients with eating disorders. Am J Psychiatry 2001;158:563–569.
62. Woodside DB, Bulik CM, Halmi KA, Fichter MM, Kaplan A, Berrettini WH, et al. Personality, perfectionism, and attitudes toward eating in parents of individuals with eating disorders. Int J Eat Disord 2002;31:290–299.
63. Fassino S, Svrakic D, Abbate-Daga G, Leombruni P, Amianto F, Stanic S, et al. Anorectic family dynamics: Temperament and character data. Compr Psychiatry 2002;43:114–120.

64. Fassino S, Amianto F, Daga G, Leombruni P, Garzaro l, Levi M, et al. Bulimic family dynamics: Role of parents' personality—A controlled study with the temperament and character inventory. Compr Psychiatry 2003;44:70–77.
65. Leon G, Fulkerson J, Perry C, Cudeck R. Personality and behavioral vulnerabilities associated with risk status for eating disorders in adolescent girls. J Abnorm Psychol 1993;102:438–444.
66. Leon G, Fulkerson J, Perry C, Keel P, Klump K. Four-year prospective evaluation of risk factors for disordered eating and assessment of psychopathology in adolescent girls and boys. J Youth Adol 1999;28:181–196.
67. Klump KL, McGue M, Iacono WG. Genetic relationships between personality and eating attitudes and behaviors. J Abnorm Psychol 2002;111:380–389.
68. Zaider T, Johnson J, Cockell S. Psychiatric disorders associated with the onset and persistence of bulimia nervosa and binge eating disorder during adolescence. J Youth Adol 2002;31:319–329.
69. Moorhead D, Stashwick C, Reinherz H, Giaconia R, Striegel-Moore R, Paradis A. Child and adolescent predictors for eating disorders in a community population of young adult women. Int J Eat Disord 2003;33:1–9.
70. Gershon E, Schreiber J, Hamovit J, Dibble E, Kaye W, Nurnberger J, et al. Clinical findings in patients with anorexia nervosa and affective illness in their relatives. Am J Psychiatry 1984;141:1419–1422.
71. Hudson J, Mangweth B, Pope H, De Col C, Hausmann A, Gutweniger S, et al. Family study of affective spectrum disorder. Arch Gen Psychiatry 2003;60:170–177.
72. Wade TD, Bulik CM, Neale M, Kendler KS. Anorexia nervosa and major depression: Shared genetic and environmental risk factors. Am J Psychiatry 2000;157:469–471.
73. Keel P, Klump K, Miller K, McGue M, Iacono W. Shared transmission of eating disorders and anxiety disorders. Int J Eat Disord 2005;38:99–105.
74. Kendler KS, Walters EE, Neale MC, Kessler RC, Heath AC, Eaves LJ. The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression and alcoholism. Arch Gen Psychiatry 1995;52:374–383.
75. Wade T, Bulik C, Prescott C, Kendler K. Sex influences on shared risk factors for bulimia nervosa and other psychiatric disorders. Arch Gen Psychiatry 2004;61:251–256.
76. Lilenfeld LR, Wonderlich S, Riso LP, Crosby R, Mitchell J. Eating disorders and personality: A methodological and empirical review. Clin Psychol Rev 2006;26:299–320.
77. Killen J, Taylor C, Hayward C, Haydel K, Wilson D, Hammer L, et al. Weight concerns influence the development of eating disorders: A 4-year prospective study. J Consult Clin Psychol 1996;64:936–940.
78. McKnight Investigators. Risk factors for the onset of eating disorders in adolescent girls: Results of the McKnight longitudinal risk factor study. Am J Psychiatry 2003;160:248–254.
79. Joiner T, Heatherton T, Keel P. Ten-year stability and predictive validity of five bulimia-related indicators. Am J Psychiatry 1997;154:1133–1138.
80. Jacobi C, Agras W, Hammer L. Predicting children's reported eating disturbances at 8 years of age. J Acad Child Adol Psychiatry 2001;40:364–372.
81. Wade T, Martin N, Tiggemann M. Genetic and environmental risk factors for the weight and shape concerns characteristic of bulimia nervosa. Psychol Med 1998;28:761–771.
82. Klump KL, McGue M, Iacono WG. Age differences in genetic and environmental influences on eating attitudes and behaviors in preadolescent and adolescent female twins. J Abnorm Psychol 2000;109:239–251.
83. Keski-Rahkonen A, Bulik CM, Neale BM, Rose RJ, Rissanen A, Kaprio J. Body dissatisfaction and drive for thinness in young adult twins. Int J Eat Disord 2005;37:188–199.
84. Rutherford J, McGuffin P, Katz R, Murray R. Genetic influences on eating attitudes in a normal female twin population. Psychol Med 1993;23:425–436.
85. Frieling H, Romer K, Wilhelm J, Hillemacher T, Kornhuber J, de Zwaan M, et al. Association of catecholamine-O-methyltransferase and 5-HTTLPR genotype with eating disorder-related behavior and attitudes in females with eating disorders. Psychiatric Genet 2006;16:205–208.
86. Devlin B, Bacanu S, Klump K, Bulik C, Fichter M, Halmi K, et al. Linkage analysis of anorexia nervosa incorporating behavioral covariates. Hum Mol Genet 2002;11:689–696.
87. Bailer U, Price J, Meltzer C, Mathis C, Frank G, Weissfeld L, et al. Altered 5-HT-sub(2A) receptor binding after recovery from bulimia-type anorexia nervosa: Relationships to harm avoidance and drive for thinness. Neuropsychopharmacology 2004;29:1143–1155.
88. Friedman N, Miyake A, Corley R, Young S, DeFries J, Hewitt J. Not all executive functions are related to intelligence. Psychol Sci 2006;17:172–179.
89. Campana A, Macciardi F, Gambini O, Scarone S. The Wisconsin Card Sorting Test performance in normal subjects: A twin study. Neuropsychobiol 1996;34:14–17.
90. Tchanturia K, Serpell L, Troop N, Treasure J. Perceptual illusions in eating disorders: Rigid and fluctuating styles. J Behav Ther Exp Psychiatry 2001;32:107–115.
91. Tchanturia K, Morris RG, Anderluh MB, Collier DA, Nikolaou V, Treasure J. Set shifting in anorexia nervosa: An examination before and after weight gain, in full recovery and relationship to childhood and adult OCPD traits. J Psychiatr Res 2004;38:545–552.
92. Steinglass J, Walsh B, Stern Y. Set shifting deficit in anorexia nervosa. J Int Neuropsychol Soc 2006;12:431–435.
93. Ferraro F, Wonderlich S, Jocic Z. Performance variability as a new theoretical mechanism regarding eating disorders and cognitive processing. J Clin Psychol 1997;53:117–121.
94. Wilsdon A, Wade T. Executive functioning in anorexia nervosa: Exploration of the role of obsessionality, depression and starvation. J Psychiatric Res 2006;40:746–754.
95. Tchanturia K, Morris RG, Surguladze S, Treasure J. An examination of perceptual and cognitive set shifting tasks in acute anorexia nervosa and following recovery. Eat Weight Disord 2002;7:312–315.
96. Avila C, Barros A, Ortet G, Parcet M, Ibanez M. Set-shifting and sensitivity to reward: A possible dopamine mechanism for explaining disinhibitory disorders. Cog Emot 2003;17:951–959.
97. Robinson L, Thompson J, Gallagher P, Goswami U, Young A, Ferrier I, et al. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. J Affect Disord 2006;93:105–115.
98. Snitz B, Macdonald A, Carter C. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes. Schizophr Bull 2006;32:179–194.
99. Kuntsi J, Rijsdijk F, Ronald A, Asherson P, Plomin R. Genetic influences on the stability of attention-deficit/hyperactivity disorder symptoms from early to middle childhood. Biol Psychiatry 2005;57:647–654.
100. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: Its application to schizophrenia. Am J Psychiatry 1970;126:107–111.
101. Kendler K. Reflections on the relationship between psychiatric genetics and psychiatric nosology. Am J Psychiatry 2006;163:1138–1146.