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The Genetic Epidemiology of Purging Disorder, Anorexia Nervosa, and Obsessive Compulsive Personality Disorder

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THE GENETIC EPIDEMIOLOGY OF PURGING DISORDER, ANOREXIA NERVOSA, AND OBSESSIVE COMPULSIVE PERSONALITY DISORDER

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

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Dedication

To Helen, Mark, Mimi, and Theresa for whom I am forever grateful

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List of Acronyms
(in alphabetical order)

1. A…….....additive genetic effects
2. AIC……..... .Akaike's Information Criteria
3. AN…….....anorexia nervosa
4. AN-R…….....anorexia nervosa restricting subtype
5. AN-BP…….....anorexia nervosa binge purge subtype
6. APA…….....…….American Psychiatric Association
7. BDNF…….…….....brain derived neurotrophic factor
8. BED…….....…….binge eating disorder
9. BMI…….…….…….....body mass index
10. BN…….…….....……...bulimia nervosa
11. BULIT-R……...…….....…Bulimia Test-Revised
12. C…….....……...common environmental effects
13. CI…….…….....……confidence interval
14. CNV…….....……...…..…copy number variation
15. CP…….…….....……..……common pathway
16. DSM…….....……Diagnostic and Statistical Manual of Mental Disorders
17. DTR…….....……Danish Twin Registry
18. DZ…….....……..…dizygotic
19. EDI…….....….....Eating Disorder Inventory
20. EDNOS…….....……eating disorder not otherwise specified
21. E…….....…..unique environmental effects/error
22. EI…….…….....……Eating Inventory
23. F-MPS…….....……Frost Multidimensional Perfectionism Scale
24. GAN…….....……Genetics of Anorexia Nervosa
25. GWAS……...…….....…..…genome wide association studies
26. H-MPS……...….....…Hewitt Multidimensional Perfectionism Scale
27. HTR2A…….....…….serotonin 2A receptor
28. ICD…….....……..…International Classification of Disease
29. IP…….....…….independent pathway
30. IRB…….....…….institutional review board
31. IRT…….....……item response theory
32. LOD…….....…….….logarithm of the odds
33. MLS……..….....nonparametric multipoint maximum LOD scores
34. MTFS…….....……..…Minnesota Twin Family Study
35. MZ…….....……...…….monozygotic
36. NIMH…….....……...…… National Institute of Mental Health
37. OCD…….....……..…...…obsessive compulsive disorder
38. OCPD…….....……...…..obsessive compulsive personality disorder
39. OCS…….....…….obsessive compulsive symptoms
40. PD…….....……...…….….purging disorder
41. NIPHTP……....…Norwegian Institute of Public Mental Health Twin Panel
42. NOS……...…..….....….not otherwise specified
43. NPL……...…....….nonparametric linkage

44. NTP……..…….……...……..…Norwegian Twin Panel
45. SAS……..……..Statistical Analysis System software
46. SCID……..…….StructuredClinical Interview
47. SEM……...…structural equation modeling
48. SNP……..……..…...…single nucleotide polymorphism
49. SPSS…….…Statistical Package for the Social Sciences
50. STR……...……..Swedish Twin Registry
51. TFEQ……....……....Three Factor Eating Questionnaire
52. TMT……....……...……..…Trail Making Test
53. VTR……....……...Virginia Twin Registry
54. WCST……....…….…..Wisconsin Card Sorting Task
55. WHO……....……...…World Health Organization
56. 5-HIAA……....…….……5-hydroxyindolacetic acid
57. 5-HT……....……serotonin
58. 5-HTIAA…….....……5-Hydroxyindoleacetic acid

Abstract

THE GENETIC EPIDEMIOLOGY OF PURGING DISORDER, ANOREXIA NERVOSA, AND OBSESSIVE COMPULSIVE PERSONALITY DISORDER

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Although a variety of factors influence the development of eating disorders, genetic factors contribute notably to their etiology. Understanding genetic factors associated with eating disorders is important, as they can influence how these disorders are recognized, researched, and treated. This dissertation included two studies addressing important questions within the fields of eating disorders and genetics; specifically, Study 1 addressed the prevalence and heritability of purging and purging disorder in a population-based sample of female twins from the United States; and Study 2 investigated the nature of the co-morbidity between anorexia nervosa and obsessive compulsive personality disorder in a population-based sample of female twins from Norway. Twin methodology was applied for both studies. Univariate analyses, a bivariate Cholesky decomposition, and an item-factor modeling approach were used. Results from Study 1 revealed estimates of 3.0%, 3.4%, 3.7%, and 11.5% for self-induced vomiting, laxative and diuretic abuse, and excessive exercise.

Laxative abuse was more strongly influenced by common environmental effects, while liability to excessive exercise was more strongly influenced by common genetic factors. Due to insufficient data, an item-factor model of purging disorder did not yield conclusive results. In Study 2, the phenotypic correlation between anorexia nervosa and obsessive compulsive personality disorder was 0.08. A bivariate Cholesky decomposition revealed that an AE-AEr_e model best fit the data, indicating that additive genetic effects moderately contribute to both anorexia nervosa and obsessive compulsive personality disorder individually but that these genetic influences are not shared between the two disorders. In addition, this model suggests that the slight overlap in liability between the two disorders is entirely accounted for by unique environmental effects and error. These results provide preliminary findings on important topics within the field of eating disorders and genetics research. Further study of the heritability of purging and purging disorder, as well as the nature of the co-morbidity between anorexia nervosa and obsessive compulsive personality disorder, is needed in large population-based samples. Better understanding the etiology of disordered eating and frequently co-occurring diagnoses, both at the diagnosis and symptom level, might have the potential to inform classification and treatment.

The Genetic Epidemiology of Purging Disorder, Anorexia Nervosa, and Obsessive Compulsive Personality Disorder

Chapter One: Eating Disorder Classification Etiology and Genetic Epidemiology

Over the last 25 years, research on eating disorders has increased exponentially (e.g., Lacey & Crisp, 1980; Lowenkopf & Wallach, 1986; Muir, Wertheim, & Paxton, 1999; Taylor, Barr, & Luce, 2006; Williams, Goodie, & Motsinger, 2008; Walsh, 2009; Woznica, 1990). Nonetheless, enhanced treatment and prevention approaches are urgently needed as anorexia nervosa (AN), bulimia nervosa (BN), and eating disorders not otherwise specified (EDNOS) are a significant cause of morbidity and mortality (Crow et al., 2009; Harris & Barraclough, 1994; Mitchell & Crow, 2006). Although a variety of factors are involved in the development of eating disorders, studies suggest that genetics substantially influence their etiology (Bulik, Sullivan, Wade, & Kendler, 2000; Lilenfeld et al., 1998; Slof-Op't Landt et al., 2005; Strober, Freeman, Lampert, Diamond & Kaye, 2000). Understanding genetic factors associated with eating disorders is important, as they can influence how these disorders are recognized, researched, and treated. This study investigated the genetic epidemiology of eating disorders using twin methodology. Specifically, this study addressed 1) the prevalence and heritability of purging behavior and purging disorder (PD) in a population-based sample of female twins from the United States; and, 2) the extent of overlap between genetic and environmental factors that contribute to the liability to AN and obsessive compulsive personality disorder (OCPD) in a population-based sample of female twins from Norway. The following sections present a general discussion of eating disorder diagnosis, classification, etiology, and genetic epidemiology, followed by a detailed

description of the individual studies proposed.

Classification of Eating Disorders

According to the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition; *DSM-IV*; American Psychiatric Association [APA], 1994) the two major eating disorders are AN and BN. EDNOS is another major diagnostic category for individuals with "disorders of eating that do not fit the criteria for any specific eating disorder" (APA, 1994, p.594). AN is typically characterized by extreme weight loss, fear of fat, and a loss of menstruation (Gucciardi, Cleasun, Ahmad & Stewert, 2004) and has the highest mortality rate of all psychiatric disorders (Birmingham, Su, Hlynsky, Goldner & Gao, 2005; Sullivan, 1995). BN involves repeated binges followed by compensatory behaviors such as self-induced vomiting, laxative abuse, or extreme exercise (Kaye, Gendall, & Strober, 1998). Most individuals with BN are of average body weight but display great concern for their weight and shape (Advoat & Kutlesic, 1995). The EDNOS category is used for individuals who meet some, but not all, of the diagnostic criteria for AN or BN. EDNOS is discussed further in the next section.

Problems in Classification

The current classification system for eating disorders is suboptimal (e.g. Bulik et al., 2007; Chavez & Insel, 2007; Clinton & Norring, 2005; Striegel-Moore & Wonderlich, 2007; Thomas et al., 2009; Wade, 2007; Walsh & Sysko, 2009). With the publication of *DSM-V* slated for 2012, criticism of the current classification system has been a research focus(Walsh, 2009).

Clinton and Norring (2005) argue that the *DSM-IV* diagnostic criteria (APA, 1994) are based largely on clinical opinion and consensus rather than empirical data. One criticism of the *DSM-IV* (APA) is that the eating disorder diagnostic categories might not be mutually

exclusive (Franko, Wonderlich, Little & Herzog, 2004; Palmer, 2003). For example, individuals often report cross-diagnosis movement from one eating disorder to another (Fairburn & Harrison, 2003; Fairburn, Cooper, & Shafran, 2003; Nielson & Palmer, 2003; Milos, Spindler, Schnyder & Fairburn, 2005; Tozzi et al., 2005). Indeed, when BN was first described by Gerald Russell (1979), he characterized it as an "ominous variant" of AN because many of his patients with BN had histories of AN. Empirical data support this clinical observation; between 8% and 62% of individuals initially diagnosed with AN develop bulimic symptoms during the course of their illness (Bulik, Sullivan, Fear, & Pickering, 1997; Eckert, Halmi, Marchi, Grove & Crosby, 1995; Eddy et al., 2002; Strober, Freeman & Morrell, 1997; Tozzi et al., 2005). Although AN and BN are conceptualized as distinct diagnoses, most agree that these two categories represent only a small component of the eating disorder continuum (Keel, Haedt, & Edler, 2005).

EDNOS is an example of the "Not Otherwise Specified (NOS)"category in the *DSM-IV* (APA, 1994). The NOS categories of the *DSM* were created to include atypical presentations of disorders encountered in clinical practice (Fairburn & Bohn, 2005). According to the *DSM*, the NOS diagnoses are intended to "indicate a category within a class of disorders that is residual to the specific categories in that class…" (APA, 1980, p.32; 1987, p. 23).

Yet, the prevalence of EDNOS is greater than the combined prevalence of AN and BN in clinical samples (Dalle Grave & Calugi, 2008; Rocket, Kaplan, & Olmsted, 2007; Ricca, Mannuci, Mezzani, Bernardo, Zucchi, et al, 2001; Turner & Bryant Waugh, 2004; Williamson, Gleaves, & Salvin, 1992). Studies suggest that up to between 50% and 70% of patients presenting with eating disorder psychopathology meet criteria for EDNOS (Ricca et

al., Turner et al., 2004). Four separate studies of outpatient adult eating disorder samples found that EDNOS was the most common diagnosis, with an average weighted prevalence of 60% (Martin, Williamson, & Thaw, 2000; Ricca et al., 2001; Turner & Bryant-Waugh, 2004). In addition, Turner and Bryant-Waugh reported that only 33% of individuals seeking treatment in their study met criteria for AN or BN. Thus, clinically significant eating disorders incorporate a broader range of symptomatology than that accounted for by the standard AN and BN diagnoses (Wade, Bergin, Tiggemann, Bulik & Fairburn, 2006; Wade, 2007).

Further, the severity of pathology and psychosocial impairment is comparable between individuals with EDNOS, AN, and BN (Fairburn & Bohn, 2005; Keel, Gravener, Joiner, & Haedt, 2009). Clinical descriptions of EDNOS are consistent in stating that most cases have features similar to AN and BN (Crow, Agras, Halmi, Mitchell & Kraemer, 2002; Waller, 1993; Walsh & Garner, 1997). Three studies (Fairburn et al., 2007; Ricca et al., 2001; Turner & Bryant-Waugh, 2004) using the Eating Disorder Examination (EDE; Fairburn & Cooper, 1993) found that individuals with EDNOS presented with significant cognitive symptomatology related to eating, shape, and weight, suggesting that these "partial" syndromes are clinically significant. In addition, in the study by Turner and Bryant-Waugh, individuals with EDNOS scored similarly to individuals with AN and BN on several EDE items, again suggesting comparable clinical impairment among EDNOS, AN, and BN. Fairburn and Bohn's work offered further support for this finding and noted that the similarity extends to the severity of associated psychological features, course of illness, and degree of psychosocial impairment.

Although there are many studies of the course, outcome, and treatment of AN and BN, few have investigated EDNOS (Fairburn & Bohn, 2005). This might be due to the fact that, across psychiatric nosology, NOS diagnoses are not commonly studied (Pincus, Wakefield Davis, & McQueen, 1999). Fairburn and Bohn report that NOS diagnoses are not regarded as a priority among grant-giving organizations. This is a significant concern, as the course of EDNOS is chronic, and is associated with significant distress and psychosocial impairment (Herzog, Hopkins, & Burns, 1993). The dearth of research regarding EDNOS has a direct impact on patient care (Herzog et al.; Martin et al., 2000) as the majority of individuals who suffer from eating disorders manifest symptoms consistent with an EDNOS diagnosis. In light of this, grant funding agencies such as the National Institutes of Health have recently made NOS research a priority (Chavez & Insel, 2007). There has been a recent surge in publications of EDNOS (e.g., Keel et al., 2009; Thomas et al., 2009; Stice, Marti, Shaw, & Jaconis, 2009; Walsh & Sysko, 2009), which is important as the etiology of this diagnosis remains largely unclear.

Risk Factors in the Development of Eating Disorders

Current studies have suggested that eating disorders are caused by a variety of factors, including sociocultural (e.g. Becker & Hamburg; 1996; Garner, Garfinkel, Schwartz, & Thompson, 1980; Polivy & Herman, 1985; Striegel-Moore & Bulik, 2007), familial (e.g., Biederman et al., 1985; Grigoroui-Serbanescu, Magureanu, Milea, Dorbrescu & Marinescu, 2003; Strober et al., 2000), and genetic influences (e.g., Bulik et al., 2007; Slof-Op't Landt et al., 2005; Askevold & Heiberg, 1979; Holland, Hall, Murray, Russel & Crisp, 1984; Garner, 1993). Sociocultural factors include the media's idealization of the thin body ideal, and peer pressures to achieve an unrealistically thin body type (Levine & Harrison, 2004; Irving,

1990). Sociocultural models of disordered eating (Polivy & Herman, 1985; Striegel-Moore, Silberstein, & Rodin, 1986) suggest that the perception of a discrepancy between the self and the thin ideal leads to psychological discomfort. In turn, a desire to ameliorate this discomfort might lead to eating disordered behavior. For example, in some women, restrained eating could lead to overeating, which might exacerbate body image concerns and lead to further restraint and or purging (Polivy & Herman; Striegel-Moore et al.). There is strong evidence for the involvement of cultural factors in eating disorders. Striegel-Moore and Bulik report that cultural models of eating disorders are supported by the following: (a) the high percentage of female cases of disordered eating; (b) the increase in incidence of eating disorders in women coinciding with the decreasing body-weight ideal for women; (c) cross-cultural studies and reported higher incidence of eating disorders in cultures which emphasize thinness; and (d) the significant association between thin ideal internalization and disordered eating.

However, although a large percentage of females pursue a thinness through diet or exercise, only an estimated 1.7% - 2.5% manifest threshold eating disorders (APA, 1994). Thus, while sociocultural factors appear to play a significant role in the development of eating disorders in some individuals (Becker et al., 1999), the relatively low prevalence of eating disorders among women exposed to the same culture, suggests that other factors have an important influence as well (Haworth-Hoeppner, 2000; Tester & Gleaves, 2005). Consequently, additional factors have been proposed to amplify or diminish eating disorder risks associated with exposure to the Western thin body ideal (Striegel-Moore et al., 1986).

In particular, other environmental factors, including parental and peer behaviors contribute significantly to the development of eating pathology (Eten & Golan, 2009;

Twamley & Davis, 1999). For example, Twamley and Davis reported that low family pressures to control weight moderated the relation between exposure to thin norms and internalization of these messages. In addition, other environmental variables including social pressure amplify or mitigate the risk of eating disorders (Striegel-Moore et al., 1986). For example, individuals exposed to peer teasing might be more likely to develop disordered eating (Thompson, Coovert, Richards, Johnson & Cattarin, 1995; Thompson & Heinberg, 1993). Similarly, individuals from higher social classes might be more prone to develop disordered eating as they presumably have more time, attention and resources available to focus on the achievement of cultural beauty ideals (Striegel-Moore & Bulik). Although these factors might influence the etiology of eating disorders, they are likely not solely responsible for their development (Bulik, 2005; Striegel-Moore & Bulik). Personality traits such as perfectionism as well as social anxiety, elevated weight, and high impulsivity might also contribute. These sociocultural and environmental factors likely combine with genetic influences (Strober et al., 2000) to contribute to the development of disordered eating as described in the next section.

Genetic Factors and Eating Disorders

Controlled Family Studies

Family studies are typically a first step in examining whether a particular disorder or trait is familial (Pinheiro, et al., 2006). To date, all but one family study of AN and BN (Logue, Crowe, & Bean; 1989) have reported increased rates of eating disorders in relatives of affected individuals (e.g. Biederman et al., 1985; Grigoroui-Serbanescu et al., 2003; Halmi et al., 1991; Hudson et al., 1987; Kassett et al., 1989; Lilenfeld et al., 1998; Stern et al., 1992;

Strober et al., 2000; Strober, Freeman, Lampert, Diamond & Kaye, 2001; Strober et al., 1986).

An investigation by Strober et al. (2000) examined lifetime prevalence of AN and BN in first-degree relatives of probands with these disorders according to the *DSM-IV-TR* (APA, 2000) criteria. Prevalence values were obtained via in-person structured clinical and family history interviews with relatives of 152 patients with restrictive AN, 171 patients with BN, and 181 healthy controls. For full syndrome AN, the risks for developing AN were 11.4 and 12.1 in female relatives of AN and BN probands, respectively. Corresponding risks for developing BN were 3.5 and 3.7 for female relatives of AN and BN probands, respectively. When partial syndrome eating disorders were considered, the relative risks fell by one-half in each group. Similarly, Lilenfeld et al. (1998) examined familial aggregation in first degree relatives of patients with eating disorders and found that relatives of affected individuals have approximately a ten-fold greater lifetime risk of subthreshold forms of eating disorders compared to relatives of unaffected individuals.

The cross-transmission of eating disorders in families suggests a familial diathesis or vulnerability to AN and BN. Unfortunately, family studies are not the best method for determining the specific genetic and environmental components of transmission. Twin studies, on the other hand, are able to provide more information regarding etiology.

Twin Studies

Twin studies allow researchers to examine familial components of disordered eating by comparing trait similarities among monozygotic (MZ) and dizygotic (DZ) twins (Bulik, 2005). MZ twinning occurs during the first 2 weeks of gestation, after the first mitosis, yielding two embryos that are, for the most part, genetically identical. It should be noted,

however, that recent research on copy number variation (CNV) has found differences in MZ twins, suggesting some evidence for mosaicism of genetic makeup (Bruder et al., 2008). Although more research is needed regarding these potential MZ CNV differences, it is generally assumed that MZ twins share 100% of their genetic makeup. Thus, twin studies are based on the premise that differences between MZ twins can be attributed to environmental factors (Plomin, DeFries, McClearn, & Rutter, 1997). DZ twinning results from the fertilization of two ova by different spermatozoa. On average, DZ twins share half of their genetic information. Therefore, differences in DZ twins can result from both genetic and environmental effects. Twin studies can be a powerful tool for detecting heritability and quantifying the contribution of genetic and environmental factors to a trait (Hinney, Friedel, Remschmidt & Hebebrand, 2004).

The comparison of MZ and DZ twins allows partitioning of the variance in susceptibility for eating disorders into additive genetic, shared environmental, and unique environmental effects (Plomin, DeFries, & McClearn, 1990). Additive genetic effects (a^2) are the cumulative effects of many genes, each of which contributes a small to moderate effect on the development of disordered eating (Bulik, 2005; Kendler et al., 1991; Plomin et al.). Because MZ twins share 100% and DZ twins share 50% of their genes on average, genetic effects are believed to be operative when MZ twin correlations are approximately twice the DZ twin correlations. Shared environmental factors (c^2) reflect the common influences in the environment to which both twins are exposed regardless of zygosity. These factors are inferred when MZ and DZ correlations are approximately equal or when the DZ correlation is larger than half the MZ twin correlation. Lastly, unique environmental factors (e^2) include the environmental influences to which only one member of a twin pair was exposed (as well

as measurement error). These influences are identified when MZ twin correlations are less than 1.00 or when MZ and DZ twin pairs are not significantly correlated on the variables of interest (Plomin, et al.).

In summary, twin studies enable the exploration of the genetic determinants of specific phenotypes (e.g., eating disorder symptoms). This information can be used to evaluate the contribution to liability of the genotype being measured and to partition out the environmental factors related to eating disorders (Slof-Op't Landt et al., 2005). Twin studies offer a particularly powerful method for examining the extent to which eating disorders, and their component symptoms, are genetically determined.

Twin Studies and the Heritability of Eating Disorders

anorexia nervosa. The first heritability investigations of eating disorders in twins were clinical case reports and studies of clinically ascertained twins (Askevold & Heiberg, 1979; Fichter & Noegel, 1990; Holland et al., 1984; Holland, Scottie & Treasure, 1988; Hsu, Chesler, & Santhouse, 1990; Nowlin, 1983; Treasure & Holland, 1995). The criteria applied to AN and BN were not consistent across these studies. Nonetheless, these studies almost universally found that the concordance rates of MZ twins were greater than those of DZ twins for both AN and BN. Bulik et al. (2000) fit a full ACE model (estimating a^2, c^2, and e^2) from these clinically ascertained data. Because the sample sizes for each study alone were too small to analyze, they were combined prior to running the model. Assuming a population prevalence of AN of 0.75%, they found that 88% (95% Confidence Interval [CI]: 33, 97) of the variance was due to a^2, with the remaining variance 12% (95% CI: 0, 59) due to e^2, suggesting that genetic factors account for the majority of the variance in the etiology of AN (Bulik et al.).

There are currently six different population-based twin registries that have assessed eating disorders: the Danish Twin Registry (DTR; Korgegaard, Hoerder, Joergensen, Gillberg & Kyvik, 2001), the Minnesota Twin Family Study (MTFS; Klump, Miller, Keel, McGue & Iacono, 2001), the Virginia Twin Registry (VTR; Bulik, Sullivan, & Kendler, 1998; Kendler et al., 1991; Kendler et al., 1995; Wade, Bulik, Neale & Kendler, 2000; Walters & Kendler, 1995; Walters et al., 1992), the Swedish Twin Registry (STR; Bulik et al., 2006), the Norwegian Twin Panel (NTP; Mazzeo et al., 2008), and the Australian Twin Registry (Wade, Martin, & Tiggemann, 1999).

Due to low prevalence, broader phenotypes for eating disorders were used to boost statistical power in the DTR (Kortegaard et al., 2001), the MTFS (Klump et al., 2001), and the VTR (Bulik et al., 1998; Kendler et al., 1991; Kendler et al., 1995; Wade et al., 2000; Walters & Kendler, 1995; Walters et al., 1992). The DTR included both broad and narrow phenotypes for AN. Heritability estimates were 48% (95% CI: 27, 65) and 52% (95% CI: 38, 65), respectively (Kortegaard et al.). Wade et al. derived heritability estimates for AN from the VTR. Their study included 2,163 women (597 monozygotic and 433 dizygotic). For the best fitting AE model, AN was estimated to have a heritability of 58% (95% CI: 32, 84). It should be noted that the 95% CI's are wide and thus, the estimates imprecise. The authors emphasized that it is important to consider the full model in addition to the best fitting model and concluded that they are unable to rule out a contribution of shared environment due to the wide confidence intervals.

In the MTFS, Klump et al. (2001), examined heritability in clinically ascertained twin pairs with AN. Diagnoses were determined using the Eating Disorders Structured Clinical Interview, which is based on the Structured Clinical Interview of *DSM-III-R* (Spitzer et al.,

1987) and was modified to fit *DSM-IV* (APA, 1994) AN criteria. In addition, a 30-item version of the Eating Disorder Inventory (EDI, Gardner, Olmsted, & Polivy, 1983) was used to validate diagnoses. Similar to Wade et al. (2000) and Bulik et al. (2000), they found that in the best fitting model, 76% (95% CI: 35, 95) of the variance in this disorder was due to a^2, with 24% (95% CI: 5, 65) of the variance due to e^2. Klump and colleagues concluded that future longitudinal studies are needed to examine additional factors, including developmental differences in genetic and environmental effects.

Studies using the STR (Bulik et al., 2006), and the NTR (Mazzeo et al., 2008) examined the prevalence of the narrowly-defined *DSM-IV-TR* (APA, 2000) AN diagnosis. Bulik et al. derived heritability estimates for AN in the STR and reported parameter estimates of 56% (95% CI: 0, 87) for a^2, 5% (95% CI: 0, 64) for c^2, and 38% (95% CI: 13, 84) for e^2. In contrast, Mazzeo et al. found that in a sample of 448 MZ and 263 DZ twins from the NTR, the overall heritability estimate was moderate with parameter estimates of 22% (95% CI: 0, 50) for a^2, 14% (95% CI: 0, 44) for c^2, and 64% (95% CI: 49, 79) for e^2. The overall heritability of AN was lower in the NTR than the overall heritability in the STR (Bulik et al.), as well as in other studies using a broad definition of AN (e.g. Klump et al., 2001; Kortegaard et al., 2001; Wade et al., 2000). However, the estimate from the NTR was within the confidence interval obtained by Bulik et al. Although there are some discrepancies in estimates across studies, these studies uniformly suggest that AN is familial and that the greatest contribution of variance to susceptibility comes from a^2. Studies of BN have yielded similar findings, as will be reviewed in the following section.

bulimia nervosa. Several studies have examined genetic and environmental contributions to BN liability. As previously described with AN, Bulik et al. (2000) combined

data from clinical case reports and fit a full ACE model from three clinical case series of twins (Fitcher & Noegel, 1990; Hsu et al., 1990; Treasure & Holland, 1989). Assuming a population prevalence of 2.5% for BN, a^2 was found to account for 47% (95% CI: 0, 66) of the variance with 30% (95% CI: 0, 56) due to shared environmental effects, and 23% (95% CI: 9, 44) due to c^2, suggesting that additive genetic effects account for the majority of the variance in liability to BN.

In addition, both univariate and bivariate twin analyses of BN (Bulik et al., 1998; Kortegaard et al, 2001; Kendler et al., 1991; Walters et al., 1992) have demonstrated high heritability estimates ranging from 50% (Walters et al.) to 70% (Bulik et al.). For example, heritability of BN was investigated in two univariate analyses using different waves of data from the VTR (Bulik et al.; Kendler et al.). The first investigation found that 54% (95% CI: 0, 77) of the variance in BN was due to a^2, 1% (95% CI: 0, 65) to c^2, and 46% (95% CI: 23, 77) to e^2 (Kendler et al.). Results of the second study indicated that 51% (95% CI: 0, 86) of the variance was due a^2, 0% (95% CI: 0, 68) to c^2, and 49% (95% CI: 14, 100) to e^2 (Bulik et al.). Although there are some inconsistencies between the point estimates for a^2, the 95% confidence intervals for these estimates are overlapping and thus, reasonably consistent. However, it should be noted that the confidence intervals for the estimates in all studies are fairly large, and frequently include zero, suggesting that they may not be non-significant. Larger sample sizes are necessary to refine parameter estimates and narrow confidence intervals. Nonetheless, these studies uniformly suggest that additive genetic effects account for the largest proportion of variance in susceptibility to BN.

It is important to note that although both AN and BN have been found to be strongly influenced by genetic factors, recent research also suggests that specific symptoms within

distinct diagnostic categories might be differentially heritable (Neale, Mazzeo, & Bulik, 2003; Wade et al., 1998). Several recent studies have identified differences in contributions of genetic and environmental factors to specific eating disorder symptoms (Neale et al.; Reichborn-Kjennerud et al., 2004; Wade, Martin, & Tiggemann, 1998; Wade & Bulik, 2007). For example, one study by Wade et al. (1998), estimated genetic and environmental risk factors for BN using a biometrical model fitting approach. The undue influence of body weight on self-concept was more strongly associated with environmental rather than genetic factors (Wade et al., 1998; Wade & Bulik, 2007), suggesting that environment influences the relation between body weight and dissatisfaction with self. Similar results were obtained in a study by Reichborn- Kjennerud et al. (2004), who found that the undue influence of weight on self-evaluation was accounted for by both shared and unshared environmental factors and that additive genetic effects did not contribute significantly to variance in this symptom among either men or women.

Another study by Neale, Mazzeo, et al. (2003) found that scores on the restraint scale (a measure of dieting behavior) of the Eating Inventory (EI; Stunkard & Messick, 1988) were more strongly associated with environmental than genetic factors, suggesting that dieting is a learned behavior. In contrast, disinhibited eating, or one's tendency to eat or overeat in response to contextual cues, was more strongly associated with additive genetic than environmental effects, suggesting that biology might primarily influence liability to this specific symptom.

Most recently, Mazzeo et al. (2008) found that AN symptoms were differentially heritable. Specifically, they found that heritability estimates for weight loss items were moderate (a^2 estimates ranged from 0.31 (95% CI: 0, 0.49) to 0.33 (95% CI: 0.16, 0.45),

while additive genetic effects contributed little to the variance in amenorrhea, which was most strongly influenced by unshared environment (a^2 = 0.16 (95% CI: 0, 0.5); e^2 = 0.71 (95% CI: 0.41, 0.95). Overall, these results highlight the importance of examining disordered eating at the symptom, rather than at the diagnostic level. As Striegel-Moore & Bulik (2007) stated, "A *DSM-IV* diagnostic category…might actually represent an occasionally co-occurring yet etiologically diverse mixture of genetically and environmentally influenced symptoms" (p. 91). Assessing eating disorders at the symptom level will allow for refinement of phenotypes due to clarification of sources of variation for specific components of eating disorder symptomatology (Bulik, 2005). This work could ultimately facilitate improvements in treatment specificity and prevention. Twin studies are an important first step in suggesting that eating disorders involve a strong genetic component. However, they are unable to provide information regarding the relationships between eating disorders and specific genes. To identify these relations molecular genetic studies are needed.

Molecular Genetic Studies

Over the past several decades, important advancements in the study of molecular genetics have occurred. Two types of molecular genetics approaches, linkage studies and association studies, have been used to better understand the genetic etiology of eating disorders (reviewed in Bulik et al., 2007 and Pinheiro, Sullivan, Bacaltchuck, Prado-Lima & Bulik, 2006). Recently genome wide association studies (GWAS) have also been employed (Nakabayashi et al., 2009). The large majority of studies that have clearly identified direct links between genes and disease have investigated uncommon diseases with a classical Mendelian inheritance pattern. However, the majority of human diseases, including psychiatric disorders, have complex etiologies. One-to-one relationships between phenotypes

and genotypes are far more difficult to identify in cases of complex disorders. Nonetheless, exciting initial findings regarding the molecular genetics of eating disorders have been reported. The findings of these investigations are briefly reviewed in the following sections.

Linkage Studies

Linkage studies are conducted to determine if there is a relation between a phenotype and specific regions of a genome. In linkage analyses, the segregation of alleles in families is used to identify chromosomal regions that might contain genetic variation associated with risk (Slagboom & Meulenbelt, 2002), narrowing the entire genome substantially (to base pairs or a limited number of chromosomes). Linkage studies are a broad method for searching the human genome. They don't require an priori hypothesis but necessitate large multiplex families (Allison, Heo, Schork, Wong, & Elston, 1998; Cardon & Bell, 2001; Sham, 1998).

Several linkage studies for AN have been previously published (Bulik et al., 2007; Devlin et al., 2002; Grice et al., 2002; Kaye et al., 2008). The majority of this research has been conducted through the Price Foundation (Bulik et al., 2003; Devlin et al.; Grice et al.; Kaye et al., 2004; Kaye, Lilenfeld et al., 2000), a private, European-based foundation, which supports multicenter international collaboration to promote understanding of genetic liability to AN. Kaye and Lilenfeld et al. describe the methodology for the first linkage study of AN, involving 192 families. In order to meet inclusion criteria for the study, the proband was required to meet lifetime *DSM-IV* (APA, 1994) criteria for AN minus criterion D (amenorrhea) with fulfillment of AN criteria within three years of ascertainment. The proband was also required to have at least one affected first through fourth degree relative who met lifetime *DSM-IV* (APA, 1994) criteria for AN, BN, or EDNOS. Blood for DNA

analysis was collected from all probands, affected family members, as well as from the biological parents of these individuals when possible (Kaye et al., 2000).

In the total sample of AN-affected relative pairs, none of the linkage peaks had a nonparametric linkage (NPL) above 1.80. Analyses performed in the restrictive subtype of AN yielded a peak at 1p33-36 (NPL score = 3.03) and a peak at 4q12-14 (NPD score = 2.44; Bergen et al., 2003; Grice et al., 2002). In addition, a quantative trait locus analysis (QTL) was performed with obsessionality and drive for thinness (Devlin et al., 2002), which demonstrated three suggestive links on chromosomes 1q31 (logarithm of the odds [LOD] score = 3.46 for drive for obesessionality and drive for thinness combined), 2p11 (LOD score = 2.22 for obsessionality), and 13q13 (LOD score = 2.5 for drive for thinness).

Following up on the Price Foundation research, Kaye et al., 2008, in collaboration with the Genetics of Anorexia Nervosa (GAN) collaborative study through funding by the National Institute of Mental Health (NIMH), initiated additional research examining the molecular genetics of AN. The GAN collaboration includes 11 clinical and data analytical sites and has an overarching goal of detecting and localizing genetic variation that increases susceptibility to AN.

The initial part of the GAN sample consists of 200 families, comprising 200 probands and 232 affected relatives. The majority of the relatives have some form of AN (approximately 95%). In a paper published in 2008, the authors report that the next step for the GAN collaboration is to analyze the first 200 families for linkage. These researchers also plan to complete the recruitment of approximately 400 families and to perform linkage analyses on the complete cohort. The results of this study, in combination with the findings from the Price Foundation Studies, are an important first step in refining regions of the

genome involved in susceptibility for AN.

Only one known linkage study investigating BN has been published (Kaye et al., 2004, in conjunction with Bulik, Devlin, Bacanu, Thornton, Klump et al., 2003). In this study, BN probands were required to have a lifetime diagnosis of BN according to *DSM-IV* criteria (APA, 1994). Relatives were required to have a *DSM-IV* (APA) diagnosis of an eating disorder (AN, BN, or EDNOS). In total, 365 relative pairs were recruited and DNA was recruited from biological parents when possible (Kaye et al., 2004).

Three regions of linkage were found on chromosome 10p13 (nonparametic muiltipoint maximum LOD score [MLS] = 2.92), chromosome 10p14 (MLS = 2.70) and 14q22-23 (MLS = 1.97). Additional linkage analyses were also performed on a subset of 133 families, in which at least two affected individuals reported regular vomiting. This phenotype was chosen because self-induced vomiting has been found to be substantially heritable (Sullivan et al., 1998) and because vomiting has been associated with reliable reporting of BN (Wade, Bulik, & Kendler, 2000). Although no additional regions of linkage were found, the linkage peak on chromosome 10p13 increased (LOD score = 3.39). Next, the use of genetic association studies to examine the relationship between candidate genes located under linkage peaks and the phenotype of interest will be reviewed.

Case-Control Association Studies

Until recently, genetic association studies have largely focused on candidate genes for eating disorders. In these studies, the allele or genotype frequencies, single nucleotide polymporhisms (SNP), at markers are compared between control subjects and affected individuals (Slagboom & Meulenbelt, 2002). The current literature examining the associations between candidate genes and eating disorders has primarily focused on genes

encoding proteins involved in the regulation of feeding and body composition, as well as genes involved in neurotransmitter pathways believed to regulate affect and behavior. Association studies of AN and BN have largely implicated serotonergic genes, dopaminergic genes, neropeptides, and other candidate genes.

The serotonin pathway has been the focus of much research in eating disorders. Serotonin is involved in a variety of regulatory functions, including body weight regulation and eating behavior. Both animal and human studies have found that indirect and direct serotonin agonists, which act to increase serotonin at the neurosynaptic cleft, decrease food intake (Lucki, 1998; Simansky, 1996). Interestingly, in long-term weight-recovered individuals with AN or BN, elevated levels of 5-hydroxyindolacetic acid (5-HIAA), a serotonin metabolite, have been found in cerebral spinal fluid (Kaye et al., 1998; Kaye et al., 1991), suggesting potential abnormalities within the serotonin system. Additionally, serotonin has been implicated in perfectionism and obsessionality, which are frequent personality traits of individuals with eating disorders (Hinney, 2000).

Various linkage and association studies in eating disorders implicate the serotonin system (Di Bella, Catalono, Cavallini, Riboldi & Bellodi, 2000; Bergen, van den Bree, Yeager, Welch, & Ganjei, 2003; Hu, 2003; Matsushita, 2004; Brown, Bujac, Mann, Stubbins, & Blundell, 2007). Within this system, the serotonin 2A receptor gene (*HTR2A*) as been the most frequently investigated. *HTR2A* is regulated by estrogen (Fink & Sumner, 1996), which has also been implicated in disordered eating. Interestingly, individuals recovered from AN and BN have been found to have reduced *HTR2A* receptor binding, compared to control participants (Frank et al., 2002; Kaye et al., 2001), suggesting that alterations of this gene may be involved in susceptibility to eating disorders. Several studies

have focused on the G-1438A polymorphism in the promoter region of the *HTR2A* gene and found that women with eating disorders are more likely to have an A allele (Ricca et al., 2004). Additional studies have also focused on the serotonin receptor *1D* gene and reported that serotonin *1D* polymorphisms were associated with AN and AN restricting subtype (AN-R; Bergen et al.; Brown et al.). Although these initial studies have provided interesting findings, many studies investigating the involvement of the serotergnic pathway in disordered eating have been underpowered. Replication studies with larger samples are needed to better understand the role of the serotonergic pathway.

Abnormalities in the dopaminergic system also have been hypothesized to be involved in disordered eating. Specifically, many symptoms of disordered eating, including weight loss, hyperactivity, distortion of body-image, and obsessive-compulsive behavior have all been linked to dopamine (Kaye, Strober, & Jimerson, 2004). An association study by Gabrovesk et al. (2004) examined the catechol-O-methyltrasnferace, an enzyme that catabolizes brain chatecholmaine neurotrasmitters such as dopamine and norepinephrine (Axelrod & Tomchick, 1958). Results of this investigation suggested no association between the rs4680 polymorphism and AN.

Bergen et al. (2005) tested several polymorphisms of the *D2* receptor gene for association with AN. For purging-type AN, association was reported for the rs1800947 and the rs6278 polymorphisms in a case-control design. The transmission disequilibrium test suggested preferential transmission for the rs6277 and rs1799732 polymorphisms. Although these results regarding the dopaminergic system, and in particular the *D2* gene, are initially exciting, replication in large independent samples is needed.

Research has also suggested that the opioid receptor delta-1 (Brown et al., 2007) as

well another candidate pathway including brain derived neurotrophic factor (*BDNF*), which modulates neurotransmitter activity, might be involved in eating disorder pathology. Specifically, Brown et al. found that three SNPS in *OPRD1* were associated with restricting and binge-purge AN. Several studies have also reported that polymorphisms of the *BDNF* gene (located on chromosome 1) might be involved in eating disorders (Friedel et al., 2005; Koizumi et al., 2004; and Ribasés et al., 2003; 2004). Variants of the *BDNF* gene have also been found to be associated with obsessive-compulsive disorder (Hall, Dhilla, Charalambous, Gogos, & Karayiorgou, 2003), which often occur co-morbidly with AN (Godart, Flament, Perdereau, & Jaemmet, 2002).

For the most part, genetic association studies have not provided definitive conclusions and have been criticized for being underpowered (Bulik et al., 2007). Positive findings for genes *HTR1D*, *OPRD1*, and *BDNF* have been found in multiple studies with large sample sizes, suggesting some promising directions for future research. Until recently, association studies of eating disorders have been limited to candidate gene approaches (Kas, Kaye, Mathes & Bulik, 2009; Nakabayashi et al., 2009). However, with the completion of the Human Genome Project (International Human Genome Sequencing Consortium; 2004) and progress by the HapMap Project (International HapMap Consortium, 2007) the amount of information available on genetic markers has increased exponentially, including SNPs and microsatellite markers (MS). Statistical analyses and genotyping platforms for GWAS have developed as a result, greatly expanding genetics research and showing superior results to the linkage analysis and candidate gene approach.

A recent investigation by Nakabayashi et al. (2009), as part of the Japanese Genetic Research Group, conducted a genome-wide case-control association study using 23 465

polymorphic microsatellite markers to identify genomic regions that might be implicated in susceptibility to AN. This is the first known GWAS performed in eating disorders. Ten novel loci related to AN were identified by the MS marker-based GWAS system. Subsequently, SNP based association studies were conducted for seven of the 10 loci to further narrow down genomic regions involved in susceptibility to AN. A total of 456 unrelated Japanese females with eating disorders participated in this study. Of those, 218 had a diagnosis of AN-R and 113 had a diagnosis of AN binge/purge subtype (AN-BP), according to the *DSM-IV* (APA, 1994). A total of 872 Japanese healthy controls participated. In the SNP based fine mapping, two loci, 1q41 and 11q22 remained significantly associated with AN. Neither loci showed a significant positive association with BN. The association analysis of the MS-SNP detected a significant association of the A-4-g-t halotype, comprising four SNP/MS markers (rs6590474, D11SO268i, rs737582 and rs7947224), on the 11q22 locus with AN. Although this study is important in successfully mapping genetic association with AN to at least two genomic regions, its authors note that additional adequately powered studies using case/control populations are needed.

Over the past 15 years perspectives of the etiology of eating disorders have been revolutionized by advancements in genetics and technology. Molecular studies such as linkage, association, and recently GWAS have begun to shed light on the genetic susceptibility to eating disorders. These studies, in combination with twin studies, which are the focus of this project, may lead to increased understanding of the interaction between genes and environment in liability to disordered eating.

Purpose

The purpose of this dissertation was to examine two important questions within the

field of eating disorders and genetics using twin methodology. The two projects presented address concerns in the literature regarding diagnosis, treatment, and prevention; specifically, 1) the heritability of purging and purging disorder in a population-based sample of female twins and 2) genetic and environmental contributions to anorexia nervosa and obsessive compulsive personality disorder. Relevant background literature and methodology for these projects will be discussed.

Chapter Two: The Heritability of Purging and Purging Disorder in a Population-Based Sample of Female Twins

Eating disorders are among the most debilitating and lethal of psychiatric illnesses (Gucciardi et al., 2004). Recent research suggests that specific eating disorder symptoms might be differentially heritable (Neale et al., 2003; Mazzeo et al., 2008; Wade et al., 1998). The varying contributions of genes and environment to symptoms within a single diagnostic entity suggests that focusing on the symptom, rather than the diagnostic level, could clarify the etiology of disordered eating and inform treatment and prevention.

Purging, which can include self-induced vomiting, laxative use, or diuretic use, is one eating disorder symptom which has been found to be highly heritable (Beumont, Kopec-Schrader & Touyz, 1995; Sullivan, Bulik & Kendler, 1998; Wade et al., 2006). In addition, excessive exercise is a related problematic weight control behavior frequently used to counterbalance caloric intake (Mond & Calogero, 2009; Mond, Myers, Crosby, Hay & Mitchell, 2008). Although purging is associated with physical and psychological morbidity, only one study has examined the heritability of purging as a distinct phenotype and no studies have examined the genetic epidemiology of excessive exercise in a population based sample (Sullivan et al.). Recently, a new eating disorder presentation, purging disorder (PD) has been proposed (Keel et al., 2005; Mehler, Crews & Weiner, 2004). PD is defined as recurrent purging in the absence of binge eating and can have severe medical consequences including death (Keel et al., 2005; Mehler et al.). In addition, research suggests that women with current (Keel et al.) or lifetime (Wade et al.) PD report greater depression, anxiety, comorbid Axis I and Axis II disorders, and suicidal ideation, compared to women with no eating disorder histories of eating disorders. To date, only two studies have examined the

prevalence of PD in a large, population-based sample (Favaro, Ferrara, & Santonastaso, 2003; Wade et al.) and no extant research has investigated the heritability of this proposed disorder. Understanding genetic and environmental factors associated with purging, excessive exercise, and PD might influence how eating disorders are recognized, researched and treated.

Thus, the goals of this study were to: 1) assess the prevalence of purging behaviors, excessive exercise, and PD in a population-based sample of female twins, and 2) to estimate genetic and environmental contributions to purging behaviors, excessive exercise, and PD in this sample.

The Heritability of Purging and Purging Disorder

Purging is a common symptom of disordered eating that includes self-induced vomiting, laxative, and diuretic abuse (Beumont et al., 1995). The VTR, a rich dataset that has been used to explore the genetic basis of a wide variety of psychiatric conditions (Kendler & Prescott, 1998), has generated prevalence and heritability estimates of self-induced vomiting at 4.8% and 70%, respectively (Sullivan et al., 1998). To date, little research has examined the prevalence or heritability of other forms of purging including abuse of laxatives and diuretics. However, like self-induced vomiting, these purging behaviors pose serious health risks.

For example, laxative and diuretic abuse have been associated with renal and electrolyte abnormalities, serious medical complications of the gastrointestinal and endocrine systems, and oral and cardiovascular complications (Mehler et al., 2004). In addition, although it is classified as a nonpurging symptom of BN, excessive exercise is a dangerous weight control behavior often used to compensate for binge eating (Mond, Hay, Rodgers &

Owen, 2006). Excessive exercise has been associated with musculoskeletal injuries due to overuse and exercise-induced amenorrhea, both of which can have long term physical consequences (Hays, 1999). Excessive exercise has also been linked to decreased quality of life after controlling for levels of eating disorder psychopathology, suggesting that this behavior has an independent and negative effect on quality of life for individuals with eating disorders (Mond & Calogero, 2009; Mond et al., 2006; Mond et al., 2008). Thus, greater understanding of the genetic and environmental determinants of purging and excessive exercise could promote targeted prevention and treatment of these behaviors, which are associated with negative health and psychological consequences. The current study focused on purging symptoms, excessive exercise and PD.

Because it is a newly proposed diagnostic entity, PD currently falls in the EDNOS category. PD involves recurrent purging for the purpose of weight or shape control in the absence of objectively large binge episodes in normal-weight individuals. This behavior can result in extreme physical and psychological consequences (Keel et al., 2005; Mehler et al., 2004; Wade et al., 2006) and has only recently gained scientific attention (Haedt & Keel, 2010; Keel, Mayer & Harden-Fischer, 2001; Keel & Striegel-Moore, 2009; Keel et al., 2005, 2008; Binford & le Grange, 2005; Mond et al., 2006; Wade et al., 2006; Wade, 2007). To date, only two studies have examined the prevalence of PD in a large, population-based sample (Wade et al., 2006; Favaro et al., 2003) and no extant research has investigated the heritability of this proposed disorder. In studies by Wade et al. and Favaro et al., PD was found to affect 1.1-5.3% of women in their lifetimes, compared with 1.9-2.0% for AN, and 2.9-4.6% for BN. These findings indicate that PD is not an obscure presentation, but rather is as prevalent as AN and BN. It is notable that these prevalence estimates for PD exclude

women with lifetime histories of other *DSM-IV* (APA, 1994) eating disorders. Thus, these women would typically be excluded from most studies investigating the epidemiology, etiology, and treatment of eating disorders. Nonetheless, concerns have been raised about the utility of PD as a diagnosis, as will be reviewed in the following section.

Concerns Regarding the PD as a Potential Diagnostic Category

There has been controversy regarding whether PD can be fully differentiated from BN, as suggested by the name "subjective bulimia nervosa" (Keel et al., 2001). However, Keel and colleagues (Haedt & Keel, 2010; Keel & Streigel-Moore, 2009; Keel et al., 2001, 2005) found significant differences between individuals with BN and those with PD, suggesting that they are distinct diagnostic entities. For example, compared to women with PD, women with BN engaged in twice the frequency of binge eating and purging episodes. Women with BN also had higher scores on the Bulimia Test-Revised (BULIT-R) than women with PD. In addition, women with BN reported significantly greater impulsivity than individuals with PD (Keel et al., 2001). Lastly, women with BN reported greater disinhibition around food and more hunger than women with PD (Keel et al., 2005). These results were stable at a six-month follow-up period, indicating the potential long-term differences in severity between PD and BN.

PD, as part of the residual category of EDNOS, might not be as serious and worthy of clinical attention as AN and BN (Keel et al., 2005). A 2005 study by Keel et al. evaluated the clinical significance of PD among normal-weight individuals by comparing three groups of women: (a) women with *DSM-IV* (APA, 1994) BN-purging subtype, (b) women with PD (who would have met criteria for BN-purging subtype except for objectively large binge episodes), and (c) non-eating disordered controls. Compared to controls, women with PD

were significantly impaired on measures of eating pathology, general psychopathology, and impulsiveness/personality disorders. Similar to previous findings (Keel et al., 2001), individuals with PD did not differ significantly from individuals with BN on measures of eating disorder severity, body image disturbance, or dietary restraint. Results of this study suggest that PD is comparable to BN in terms of psychological and physiological risk factors.

A recent study by Fink, Smith, Gordon, Holm-Denoma, and Joiner (2008) reported similar findings. This study compared 294 ethnically diverse undergraduate women diagnosed with different types of eating disorders including AN, BN, binge eating disorder (BED), and PD, as well as control participants. Similar to Keel et al. (2001; 2005), they found that PD is a distinct and valid eating disorder diagnostic category. Specifically, they reported that women with PD displayed similar levels of drive for thinness as women with AN, and similar levels of purging ideation to women with BN. Individuals with BN had significantly higher anxiety levels than those with PD. However, individuals with PD displayed levels of impulsivity that were significantly higher than those of individuals with AN. Finally, they found that women with any eating disorder diagnosis were more likely to have a comorbid Axis I diagnosis than women without an eating disorder diagnosis. The authors note that one important limitation of this study was the low prevalence of eating disorders in the sample. Nonetheless, it is important to note that, although exploratory, this study replicated the findings of Keel et al. (2005), and thus provides additional support for the conceptualization of PD as a distinct diagnosis.

In 2007, a meta-analysis by Keel examined 14 studies, including 10 samples which included individuals with PD. Across studies, individuals with PD were characterized by clinically significant elevations in eating pathology associated with impairments in

psychosocial functioning, distress, and increased risk for death, pain, or disability, again supporting previous findings suggesting that PD is as severe as AN and BN (Fink et al., 2008; Keel et al., 2005)

Despite these findings, there is ongoing debate regarding the validity and clinical utility of the PD diagnosis at a diagnostic level (Keel & Striegel-Moore, 2009). Moreover, one limitation of previous studies is that PD has primarily been assessed at the diagnostic level. As noted previously in Chapter One, symptom level assessment is particularly important in studies of heritability, as genes and environment might influence individual symptoms differentially (Neale et al., 2005; Neale, Mazzeo, et al., 2003; Mazzeo et al., 2008; Wade et al., 1998). Better understanding sources of variance for specific components of PD could improve and inform eating disorder classification and treatment.

Purpose

The purpose of this study was to examine the prevalence and heritability of purging behaviors, excessive exercise and PD using multivariate twin modeling. Estimates of the degree to which susceptibility to a trait or disorder is more strongly due to genetic or environmental factors can be determined using MZ/DZ twin correlations (Neale & Cardon, 1992). However, biometric model fitting, in which the contributions of all three types of influence (i.e., additive genetic or A, common environmental or C, and unique environmental or E) are examined simultaneously, is necessary to estimate the magnitude of these effects (Neale & Cardon; Klump, Wonderlich, Lehoux, Lilenfeld & Bulik, 2002). Structural equation modeling (SEM) is one method that is useful for testing complex multivariate theoretical hypotheses (Bollen, 1989; Fassinger, 1987) and can be applied to twin data.

Specifically, SEM, a statistical technique used to assess relations among both manifest and latent variables (Martens, 2005), was used in this study. SEM is particularly useful because it allows researchers to model latent variables, or underlying theoretical constructs. Instead of relying on one variable to serve as a proxy for the construct, each latent variable is represented by several measured indicator variables (MacCallum, 1995; Martens, 2005). This reduces measurement error and allows for a more thorough assessment of complex latent variables. In addition, SEM can be used to calculate the reliability of measurement instruments as well as the estimated latent variables (Kenny, 1979). This makes SEM distinct among statistical techniques based on the general linear model, in which measurement error is present but is not accounted for and might bias results (Bollen, 1989). Additionally, SEM is particularly appropriate for testing multivariate relations. Specifically, in SEM, single constructs can be both a predictor of some construct and predicted by another construct.

The extension of SEM to twin data involves using multiple groups and applying constraints, which allows for a statistically and scientifically rigorous test of a priori hypotheses. Parameter estimates and their confidence intervals allow determination of the best estimate available from the data and provide information regarding the accuracy of the parameter estimate (Neale, Booker, Xie, & Maes, 2003). SEM can be used to determine the statistical model which best fits the data. Specifically, results of these models provide estimates of the proportion of variance in a trait due to each of these three factors (genetic, common environmental, and unique environmental). With this information, heritability of a disorder can be calculated.

Method

Participants

European American female twins recruited from the Mid-Atlantic Twin Registry (MATR) were included in this study. These respondents were all European American because, at the time of data collection, sample sizes of minority twin pairs in the MATR were too small to provide statistical power to obtain reliable estimates for low prevalence variables.

Beginning in late 1999, questionnaires were mailed to all MATR participants who had previously participated in psychiatric diagnostic interviews (Kendler, et al., 1992). All variables in the current study were derived from the items included in a self-report questionnaire. The questionnaire focused on issues related to religiosity, eating, and weight. Some attempts were made to contact by phone non-responding twins whose co-twin had responded; however, follow-ups with non-responders were unable to be completed due to limited resources. No new data were collected for the purpose of this study.

Recruitment and Informed Consent Procedures

Informed consent procedures were conducted in accordance with the Institutional Review Board (IRB) at Virginia Commonwealth University. Participants signed a waiver of written documentation of informed consent for this protocol acknowledging that they were informed about the purpose, description, potential risks or discomforts, benefits, cost of participation, payment for participation, confidentiality, and withdrawal procedures associated with the study.

Measures

In the 1999 Virginia Twin Survey, self-report measures of eating and weight behavior include items from the Three-Factor Eating Questionnaire (TFEQ; Stunkard & Messick, 1985), the Body Dissatisfaction and Drive for Thinness subscales of the EDI (Garner, Olmsted, & Polivy, 1983), and ratings of body size in childhood, adolescence and adulthood. Eating disorder diagnostic items included in the questionnaire were written according to the Structured Clinical Interview for DSM Diagnoses-Axis 1 (SCID-I; First, Spitzer, Gibbon & Williams, 1997). These items included detailed symptom level assessments of AN, BN, and BED. Participants first responded to a question asking if they had ever had eating binges. Individuals who endorsed this item completed subsequent questions regarding BN and BED criteria. All participants responded to a question asking what behaviors they had engaged in to control their shape and weight as well as the influence of weight and shape on their self-evaluation.

The criteria for purging subtypes are outlined in the 4th edition of the *DSM-IV-TR* (APA, 2000). Self-induced vomiting, laxative abuse, diuretic abuse, and excessive exercise were examined in the current study. PD is defined by Keel et al. (2005) as a disorder in which *DSM-IV-TR* (APA) criteria for BN-purging subtype are met except for the absence of objectively large binge episodes. In the current study, diagnostic algorithms for purging and PD were constructed from self-report items assessing behavioral characteristics associated with purging and PD (see Table 1)

Table 1

Criteria Used to Categorize Participants as Having Purging Behaviors or PD.

Criteria for Purging:

1. In response to the question, "During your most extreme efforts to control your shape and weight, how often did you do the following:"
   a) make yourself vomit b) laxatives c) diuretics (water pills) d) exercise more than 2 hours per day

   Individuals WITH purging must answer: "every day", nearly every day", or "a few days a week" to at least one of the a-c items
   Individuals WITHOUT purging will have answered: "once a week", "less than once a week", "once", or "never" to all a-c items
   * a, b, c, and d will each be an item in the purging behavior box in Figure 1.

Criteria for Purging Disorder:

1. In response to the question "Have you ever had eating binges when you ate what most people would regard as an unusually large amount of food in a short period of time?"

   Individuals WITH PD answered "no"
   Individuals WITHOUT PD answered "yes"
   *****Item 1.1 and 2.1 in Figure 2

2. In response to the question, "During your most extreme efforts to control your shape and weight, how often did you do the following:"
   a) make yourself vomit b) laxatives c) diuretics (water pills) d.) exercise more than 2 hours per day

   Individuals WITH PD answered: "every day", nearly every day", or "a few days a week" to at least one of the a-d items
   Individuals WITHOUT PD answered: "once a week", "less than once a week", "once", or "never" to all a-d items
   *Item 1.2, 1.3, 1.4, 1.5, 2.2, 2.3. 2.4, 2.5, in Figure 2

2. In response to the question, "Choose which statement that best describes you?"

   Individuals WITH PD answered, "Weight or shape is the most important thing that affects how I feel about myself" or "Weight or shape plays a major part in how I feel about myself"
   Individuals WITHOUT PD answered, "Weight or shape plays a moderate part in how I feel about myself", "weight or shape plays a small part in how I feel about myself", or "weight or shape is not at all important to how I feel about myself"
   *Items 1.6 and 2.6 in Figure 2

Statistical Analyses

Descriptive analyses were conducted using the Statistical Package for the Social Sciences (SPSS, 2005) and Statistical Analysis System software (SAS Institute Inc., 2006). All modeling analyses examining genetic and environmental contributions to purging and PD were conducted using Mx (Neale, Booker, et al., 2003), which is a combination of a matrix algebra interpreter and a numerical optimizer. This program utilizes many built-in fit functions to enable structural equation modeling and other types of statistical modeling of data, and is particularly useful for modeling twin data to partition the variance of a given phenotype into additive genetic (A), common environmental (C), and unique environmental (E) influences. It was proposed that univariate ACE modeling would be used to partition the variance of purging behaviors (self-induced vomiting laxative abuse, diuretic abuse) and excessive exercise (see Figure 1) into influences due to these three factors. These models also estimate expected correlations for MZ and DZ twins and provide information regarding how well the model fits the data. Model assumptions are that correlations for genetic effects between twins are 1.0 for MZs and 0.5 for DZs and that environmental influences are perfectly correlated for both MZ and DZ twin pairs. Unique environmental and error variance are assumed to be uncorrelated (Neale, Eaves, & Kendler, 1994).

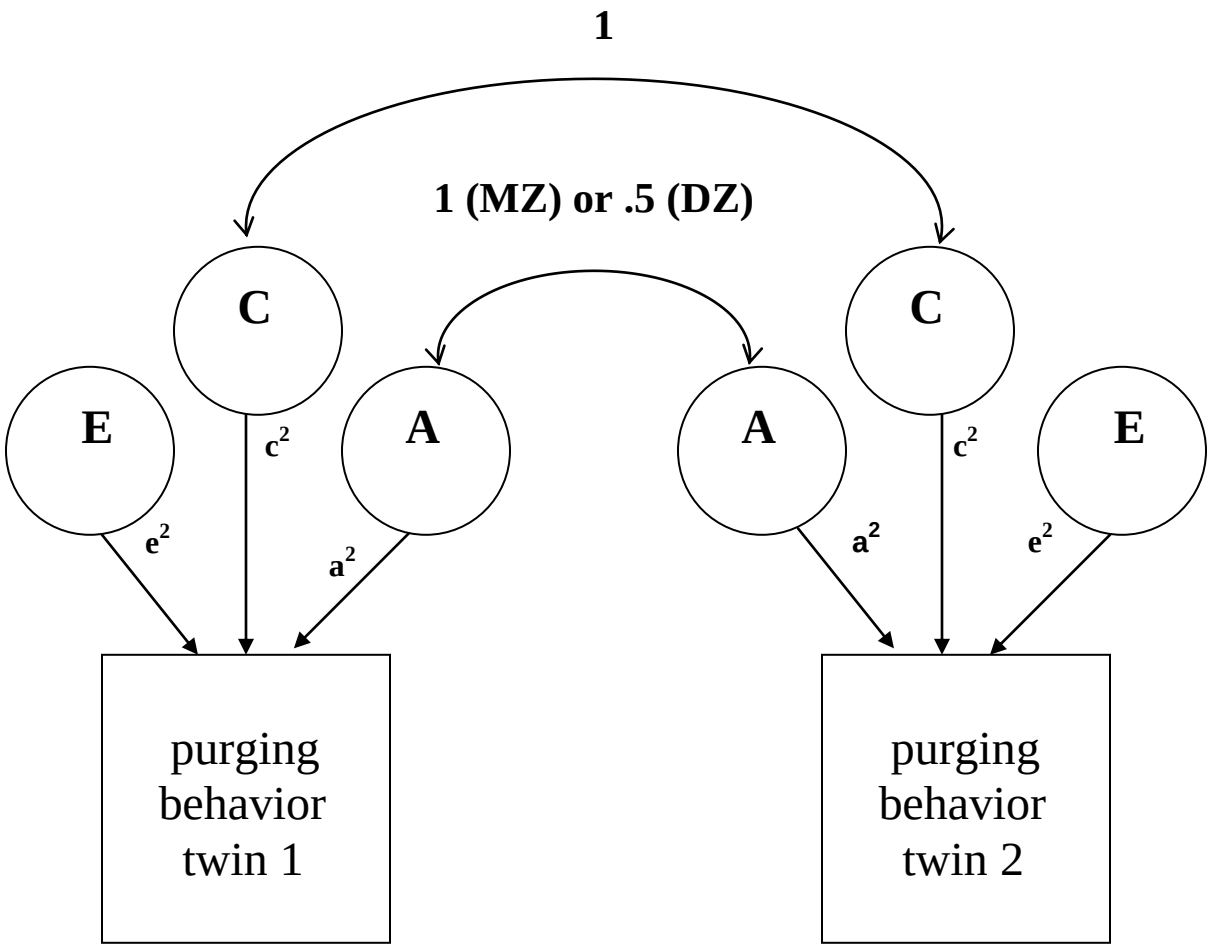

Figure 1. Univariate ACE Model. It was proposed that this model would be analyzed for each of the purging items/behaviors (self-induced vomiting, laxative abuse, diuretic abuse, and excessive exercise) to partition the variance into influences due to A (additive genetic), C (shared environmental), and E (unique environmental). Assumptions of this model are that correlations for genetic effects between twins are 1.0 for MZs and 0.5 for DZs. Unique environmental and error variance are assumed to be uncorrelated.

Univariate ACE models are based on structural equation modeling (SEM), a well-known analytic technique that can be applied to twin data. Traditional SEM techniques are used to estimate relations between observed (measured) variables and latent (unmeasured) variables as well as relations among latent variables. With SEM, parameter estimates and their confidence intervals can be estimated, allowing for determination of the best estimate of a parameter available from the data and also providing insight into the accuracy with which the parameter is known (Neale, Booker, et al., 2003). In the case of the ACE model, the latent variables are the genetic, common environmental, and unique environmental contributions to the variance of the measured phenotype. The parameters of interest in these models are the paths representing the influences of A, C, and E on the phenotype; confidence intervals are also obtained for these estimates. Lastly, SEM allows for the determination of which model best fits the data. After obtaining initial estimates of A, C, and E, submodels are fit to the data. These include AE (dropping C, or the c^2 path in Figure 1), CE (dropping A or the a^2 path in Figure 1), and E only (dropping both A and C in Figure 1). The fit of these submodels is determined using the chi-square test statistic and Akaike's Information Criteria (AIC, Akaike, 1987). A significant chi-square result indicates that the model should be rejected. In cases where the chi-square statistic indicates that all models fit adequately, the chi-square difference test and AIC values are used to compare the fit of the models.

It was proposed that the heritability of PD (see Figure 2) would be assessed using an item-factor modeling approach (Neale, Aggen, Maes, Kubarych & Schmitt, 2006). This method is a latent trait model that is formally equivalent to a two-parameter normal item response. The model estimates a "location" on the factor liability score for each diagnostic criterion. This is the point on the liability scale where there is .5 probability of endorsing the

criterion. The model also estimates the portion of variance unique to each PD criterion not accounted for by the common factor. This procedure applies the common factor model to multivariate binary or ordinal data, such that the likelihood of item data is computed conditional on the latent trait. Marginal maximum likelihood (MML) estimation computes the likelihood of item data conditional on the latent trait by integrating over the latent trait. This method utilizes finite mixture distribution, which is specified for points on the latent trait. Gaussian quadrature weights are assigned to these different points along the distribution of the latent factor. To compute the overall likelihood, these individual weighted likelihoods are summed. In this model, which draws on Item Response Theory (IRT), items assessing PD are used as indicators of the latent trait, PD. As with IRT, factor loadings relating the item to the latent trait represent the item's discrimination (i.e. the item's ability distinguish between individuals at different levels of the latent factor). Similar to the univariate ACE model, the variance of the latent trait is partitioned into A, C, and E influences (see Figure 2). In addition to obtaining information about the genetic and environmental contributions to the latent trait PD, heritability estimates, and confidence intervals for these estimates, can be obtained for each individual item.

These estimates can provide information about which symptoms of PD are more strongly influenced by genetic or environmental factors. Further, the residual variance (i.e., that not due to the latent factor) of each item can be partitioned into A, C, and E as well. Submodels assessing whether A and C contribute significantly to the variance in PD can be tested as described previously for univariate ACE models.

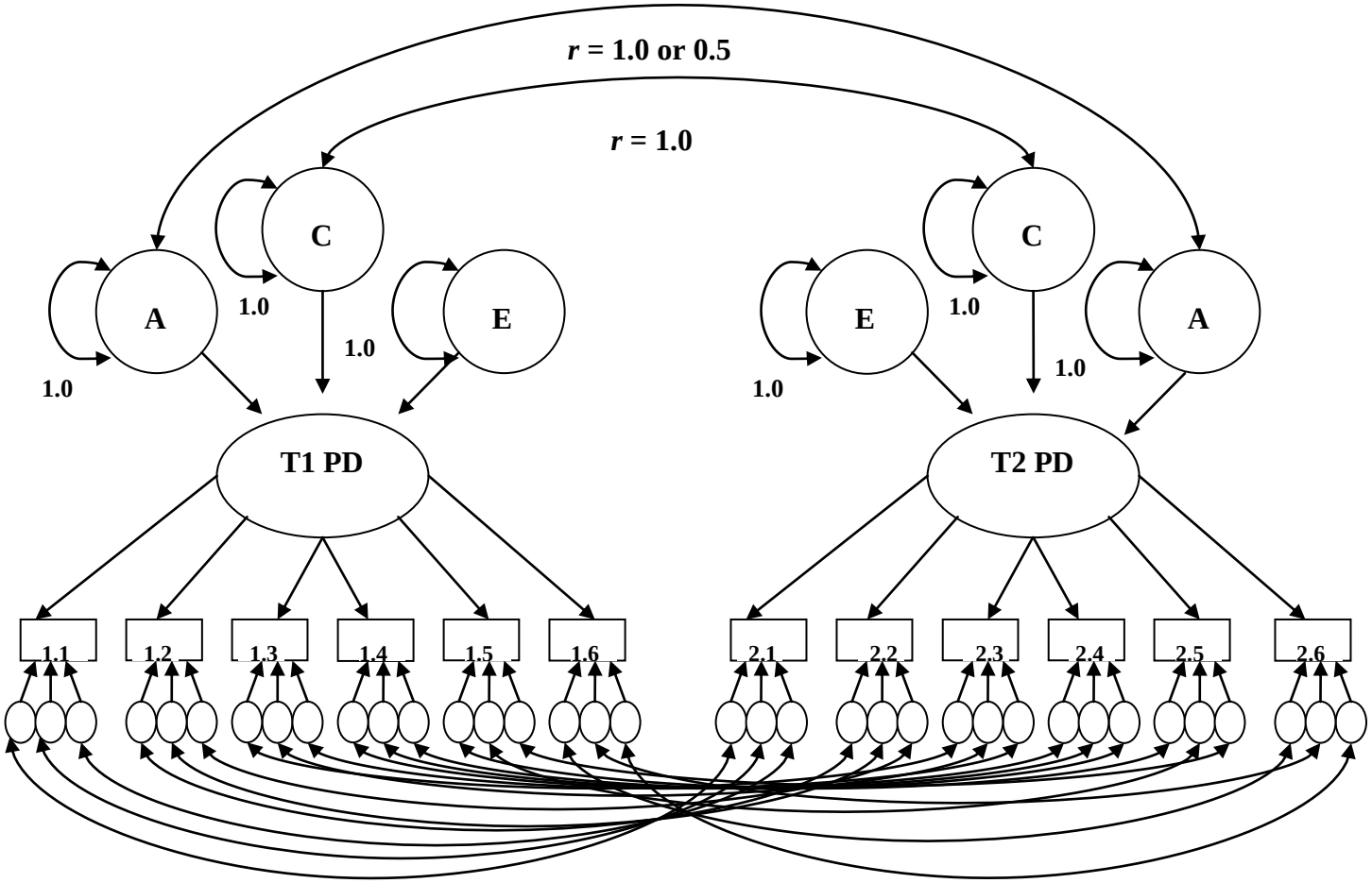

Figure 2. Item level analysis of PD using an item-factor approach. Items (represented by square boxes) are listed in Table 2.

Results

Descriptive Analyses

The sample consisted of 1022 female-female twins (246 complete MZ pairs, 122 MZ singletons, 158 complete DZ pairs, and 92 DZ singletons). There was one pair of unknown zygosity, which was removed from the data set. Participants' ages ranged from 23 to 58 years (M = 38.08; SD = 7.67).

Prevalence of Purging Symptoms

As previously described (see Table 1), purging symptoms were assessed at the ordinal level, according to the frequency of the behavior; 0 = "never", 1 = "once", 2 = "less than once a week", 3 = "once a week", 4 = "a few days a week", 5 = "nearly everyday", and 6 = "every day." The frequencies of the scores for each purging symptom are reported in Table 2.

Next, each ordinal purging symptom item was recoded to be binary (yes/no). Individuals receiving a score of 4, 5, or 6, were considered meeting criteria for the purging behavior and those receiving a score of 0, 1, or 2 were considered subthreshold. Descriptive statistics indicated that 31 (3.0%), 35 (3.4%), 38 (3.7%) and 121 (11.8%) individuals reported self-induced vomiting, laxative use, diuretic use, and excessive exercise, respectively. In total, 178 individuals (17.41 %) endorsed at least one of the four purging behaviors. The rates of different purging methods and their combinations are reported in Table 3.

Table 2

Frequency of Scores for Purging Symptoms.

Score	Self- Induced Vomiting (%)	Laxatives (%)	Diuretics (%)	Excessive Exercise (%)
0	916 (89.60)	860 (84.60)	851 (83.27)	758 (74.17)
1	27 (2.64)	41 (4.01)	48 (4.70)	23 (2.25)
2	12 (1.17)	41 (4.01)	43 (4.21)	56 (5.48)
3	7 (0.68)	14 (1.37)	11 (1.08)	31 (3.03)
4	14 (1.37)	19 (1.86)	17 (1.66)	73 (7.41)
5	7 (0.68)	11 (1.08)	12 (1.17)	33 (3.23)
6	10 (0.98)	5 (0.49)	9 (0.88)	15 (1.47)
Missing	29 (2.84)	31 (3.03)	31 (3.03)	33 (3.23)

Table 3

Rates of Different Purging Methods and Their Combinations.

		N	%
1	self-induced vomiting	15	1.47
2	laxative abuse	14	1.37
3	diuretic abuse	17	1.67
4	excessive exercise	96	9.39
5	self-induced vomiting and laxative abuse	3	0.29
6	self-induced vomiting and diuretic abuse	1	0.10
7	self-induced vomiting and excessive exercise	7	0.68
8	laxative and diuretic abuse	6	0.59
9	laxative abuse and excessive exercise	3	0.29
10	diuretic abuse and excessive exercise	6	0.59
11	self-induced vomiting, laxatives abuse, and diuretic abuse	1	0.10
12	self-induced vomiting, laxatives abuse, and excessive exercise	2	0.20
13	self-induced vomiting, diuretic abuse, and excessive exercise	1	0.10
14	laxatives abuse, diuretic abuse, and excessive exercise	5	0.49
15	self-induced vomiting, laxative abuse, diuretic abuse, and excessive exercise	1	0.10

Twin Modeling

Considerations Regarding These Modeling Analyses. Purging symptoms were assessed at the binary level. It should be noted that the following analyses of purging behaviors involved a small sample size (which reduced the statistical power), and the purging behaviors (self-induced vomiting and diuretic abuse) were endorsed on a relatively infrequent basis. In addition, the heritability of several of the purging symptoms could not be assessed due to insufficient data. Table 4 presents a summary of the model fit statistics as well as the parameter estimates resulting from the univariate model-fitting for laxative abuse and excessive exercise. As previously stated, in cases where the chi-square test statistic indicated that all models adequately fit the data, the AIC value was used to determine the best fitting model. However, it is recommended that AIC values be interpreted with consideration of both the twin correlations and estimates from the full model, particularly in studies where power is known to be low (Sullivan & Eaves, 2002). Given the relatively low power of this study, current results should be viewed as preliminary. Larger population-based samples are needed to make definitive conclusions regarding the specific nature of the liability to these phenotypes.

Univariate Twin Analyses

self-induced vomiting. The tetrachoric twin correlations for MZ and DZ twin pairs were 0.68 (95% CI: 0.29, 0.90) and -0.84 (95% CI: -0.99, -0.77). There were three concordant MZ twin pairs and zero concordant DZ twin pairs. Due to insufficient data (i.e., specifically the absence of any concordant DZ pairs), twin analyses were not conducted.

laxative abuse. The tetrachoric twin correlations for MZ and DZ twin pairs were 0.53 (95% CI: 0.05, 0.83) and 0.80 (95% CI: 0.32, 0.97), respectively. There were two concordant

MZ twin pairs and two concordant DZ twin pairs. Parameter estimates for the ACE model of laxative abuse indicated that 0% (95% CI = 0, 73.14) of the variance in the latent trait was influenced by additive genetic effects, 64.70% (95% CI = 0, 85.53) by common environmental factors, and 35.30% (95% CI =14.39, 68.60) by unique environmental factors and error. Comparing reduced models indicated that the fit of the CE model was not significantly different from that of the full ACE model ($\Delta\chi^2(1) = 0.00$, $p > .05$). Additionally, the fit of the AE model was not significantly different from the full ACE model ($\Delta\chi^2(1) = 3.33$, $p > .05$). However, the fit of the E model was significantly worse than that of the full model, ($\Delta\chi^2(2) = 12.73$, $p < .01$), suggesting evidence of familial aggregation in liability to this phenotype. According to the AIC values, the CE model provided the best fit to the data, suggesting that common environmental factors influence liability to laxative abuse (see Table 4).

diuretic abuse. The tetrachoric twin correlations for MZ and DZ twin pairs were 0.50 (95% CI: 0.03, 0.81) and -0.87 (95% CI: -0.98, 0.53). There were two concordant MZ twin pairs and zero concordant DZ twin pairs. Due to insufficient data (i.e., specifically the absence of any concordant DZ pairs), twin analyses were not conducted.

excessive exercise. The tetrachoric twin correlations were 0.48 (95% CI: 0.21, 0.70) and 0.22 (95% CI: -0.21, 0.58) for MZ and DZ's, respectively. There were ten concordant MZ twin pairs and three concordant DZ twin pairs. Parameter estimates for the ACE model of excessive exercise indicate that 48.64% (95% CI = 0, 69.60) of the variance in the latent trait is influenced by additive genetic effects, 0% (95% CI = 0, 56.90) by common environmental factors, and 51.36% (95% CI = 30.40, 78.23) by unique environmental factors and error. Submodel comparisons indicated that the fit of the CE model was not significant

from that of the ACE model ($\Delta\chi^2(1) = 1.23$, $p > .05$). The fit of the AE model was also not significantly different from the fit of the ACE model ($\Delta\chi^2(1) = 0.00$, $p > .05$). However, the fit of the E model was significantly worse than that of the full model ($\Delta\chi^2(2) = 12.68$, $p < .01$), suggesting evidence of familial aggregation in liability to this phenotype. According to the AIC values, the AE model provided the best fit to the data, indicating that additive genetic factors influence in liability to excessive exercise (see Table 4). However, as previously stated, the full ACE model should also be considered given the relatively low power of the analysis.

Table 4

Parameter Estimates and Fit Statistics for Univariate Models of Laxative Abuse and Excessive Exercise.

	a^2 95% CI	c^2 95% CI	e^2 95% CI	-2lnL	df	$\Delta\chi 2$(df)	AIC
Laxative Abuse							
ACE	0.00 (0 – 0 .73)	0.65 (0.0 – 0.86)	0.35 (0.14 – 0.69)	289.21	985	---	-1680.79
AE	0.63 (0.25 – 0.86)	---	0 .37 (0.14 – 0.76)	292.54	986	3.33(1)	-1679.46.
CE*	**---**	**0.65 (0.31 – 0.86)**	**0 .35 (0.14 – 0.69)**	**289.21**	**986**	**0.00(1)**	**-1682.79**
E	---	---	1.00 (1.00 – 1.00)	301.95	987	12.73(2)	-1672.10
Excessive Exercise							
ACE	0.49 (0.0 – 0.70)	0 (0.0 – 0.57)	0 .51 (0.30 – 0.78)	720.73	983	---	-1245.27
AE*	**0.49 (0.23 – 0.70)**	**---**	**0 .51 (0.30 – 0.77)**	**720.73**	**984**	**0.00(1)**	**-1247.27**
CE	---	0.40 (0.17 – 0.60)	0.60 (0.40 – 0.83)	722.00	984	1.27(1)	-1246.00
E	---	---	1.00 (-1.00 – 1.00)	733.41	985	12.68(2)	-1236.59

Note. A = additive genetic effects. C = common environmental effects. E = unique environmental effects and error. * denotes best fitting model.

Prevalence and Heritability of Purging Disorder

To assess the prevalence and heritability of PD, from individuals meeting criteria for a broad diagnosis of AN (*n* = 28, 2.73 %) were removed from all subsequent analyses evaluating PD at the diagnostic level. Of the individuals meeting criteria for AN, 15 endorsed

The remaining sample included 994 individuals. To receive a diagnosis of PD, individuals had to endorse the following three criteria (see Table 5): absence of binge eating, presence of at least one purging behavior (at threshold level; see Table 1), and undue influence of weight and shape on self evaluation. In this sample, 800 (80.7%) individuals endorsed an absence of binge eating, 163 (16.4%) individuals endorsed engaging in at least one purging behavior, and 372 (37.46%) individuals endorsed the undue influence of weight and shape on self evaluation. Out of 993 individuals, 42 (4.2%) met all three criteria for PD.

Twin Modeling

As proposed, the heritability of PD was assessed using an item-factor modeling approach (Neale et al., 2006). All purging symptoms and undue influence were entered as ordinal variables to maximize statistical power. Results of this analysis suggested that 99% of the variance in liability to PD was due to additive genetic effects, 1% due to unique environmental effects and error, and 0% due to common environmental factors. Results did not substantially differ when the variables were entered as ordinal or binary. These estimates are extremely unlikely and, upon inspection of the data, these extreme estimates were deemed a result of sparse data, rather than true liability to the phenotype Cross-twin cross-trait concordance values were zero for many of the cells in the DZ sample; resulting in very low polychoric correlations (see Table 6). Although the item-factor model is designed to

maximize statistical power in low prevalence phenotypes, this sample appears to be prohibitively small.

Table 5.

Number of Individuals Meeting Each Purging Disorder Criterion.

Criterion	Interview question	Number of participants meeting criterion
1. Absence of binge eating		**n = 800**
2. Purging Behavior	All items assessing criteria 2 began with the stem: "During your most extreme efforts to control your weight and shape, how often you did the following:	
	a. make yourself vomit (n=29) b. laxatives (n= 30) c. diuretics (n=36) e. exercise more than 2 hours per day (n=113)	
	Meets criteria 2 (endorse at least one of a-e)	**n = 163**
3. Undue influence of weight and shape on self-evaluation		**n = 372**
Met full criteria for PD		**n = 42**
Individuals missing one or more criterion		**n = 261**

Table 6

Polychoric Correlations for Purging Disorder Items.

Item	1	2	3	4	5	6	7	8	9	10	11	12
T1Vomiting (1)		0.68	0.64	0.62	0.41	-0.51	-0.98	0.28	0.14	0.11	0.34	0.02
T1Laxatives (2)	0.59		0.66	0.58	0.26	-0.49	0.03	0.21	-0.01	0.20	0.00	-0.13
T1Diuretics (3)	0.45	0.72		0.43	0.07	-0.33	-0.06	0.19	-0.01	-0.09	-0.03	0.04
T1Extreme Exercise (4)	0.28	0.48	0.54		0.22	-0.21	-0.20	-0.20	-0.31	0.18	-0.28	0.20
T1 Undue Influence (5)	0.47	0.46	0.21	0.10		-0.35	-0.05	0.23	0.03	-0.07	0.20	-0.09
T1 Absence of Binge eating (6)	-0.42	-0.60	-0.35	-0.26	-0.31		0.17	-0.04	-0.04	0.05	0.06	0.33
T2Vomiting (7)	0.72	0.48	0.32	0.12	0.41	-0.34		0.06	0.31	0.11	0.28	-0.53
T2 Laxatives (8)	0.60	0.56	0.44	0.17	0.25	-0.27	0.71		0.47	0.18	0.28	-0.59
T2 Diuretics (9)	0.30	0.37	0.50	0.24	0.10	-0.24	0.40	0.51		0.16	0.35	-0.34
T2 Excessive Exercise (10)	0.04	0.33	0.50	0.50	0.23	-0.22	0.37	0.39	0.45		0.35	0.01
T2 Undue Influence (11)	0.43	0.45	0.23	-0.03	0.37	-0.25	0.52	0.40	0.19	0.17		-0.24
T2Absence of Binge Eating(12)	-0.66	-0.48	-0.30	-0.17	-0.30	0.50	-0.69	-0.48	-0.31	-0.21	-0.37	

Note. MZ twins are below the diagonal. DZ twins are above the diagonal.1 = twin1 vomiting. 2 = twin1 laxatives. 3 = twin1 diuretics. 4 = twin1 excessive exercise. 5 = twin1 undue influence of weight and shape on self evaluation. 6 = twin1 absence of binge eating. 7 = twin2 vomiting. 8 = twin2 laxatives. 9 = twin2 diuretics. 10 = twin2 excessive exercise 11 = twin2 undue influence. 12 = twin2 absence of binge eating.

Additional Analyses

Univariate Analysis of Purging Disorder

Given the inconclusive results yielded by the item-factor modeling analysis, a univariate approach was applied. PD was entered as a binary variable and the tetrachoric correlations for PD for MZ and DZ twins were -0.87 (95% CI: -0.99, 0.49) and 0.32 (95% CI: -0.27, 0.77). There were zero concordant MZ pairs and one concordant DZ pair. Due to insufficient data, twin analyses were not conducted.

Discussion

The Prevalence of Purging Behaviors and Excessive Exercise

The data revealed prevalence estimates of 3.0%, 3.4%, 3.7% and 11.5% for self-induced vomiting, laxatives and diuretic abuse, and excessive exercise, respectively. A previous population-based study using participants from a different wave of the MATR, conducted by Sullivan et al. (1998), generated a prevalence estimate for self-induced vomiting of 4.8%. These results suggest that self-induced vomiting is not an an unual means of controlling weight but rather, appears to affect approximately 3.0% to 4.8% of the female population. Although studies have investigated the prevalence of purging behaviors in college and community based samples (Berg, Frazier & Sherr, 2009; Mond et al., 2006), no other known studies have examined the prevalence or heritability of laxative and diuretic abuse and excessive exercise in a population-based sample. Researchers have noted the necessity of research in this area (Mond & Calogero, 2009), underscoring the importance of the present investigation.

Excessive exercise was endorsed at a much greater frequency than the other purging behaviors in this sample. Similar discrepancies in frequency of excessive exercise relative to

other purging behaviors have also been found in college (Berg et al., 2009) and community based samples (Mond et al., 2006). There may be several reasons for this finding. First, people form favorable impressions of individuals who eat healthfully and exercise regularly (Chaiken, Pliner, 1987; Fries & Croyle, 1993; Hodgins, 1992; Martin & Leary, 2001), viewing them as more physically attractive and as possessing more positive personality characteristicszes (Martin & Leary, 2001). Thus, excessive exercise appears to be less stigmatized than other eating disorder behaviors and as a result, individuals may be more willing to report engaging in this behavior. In addition, individuals tend to overestimate the frequency and severity of physical exercise (Klesges, Eck, Mellon, Fulliton, Somes et al., 1989; Sallis & Saelens, 2000), which may further explain the relatively high endorsement of excessive exercise in the study.

Future investigations on the genetic epidemiology of excessive exercise should include a more comprehensive assessment of the phenotype that specifically address whether excessive exercise behaviors are related to disordered eating. One limitation of this study was that excessive exercise was assessed by one binary item asking participants if they exercised two hours a day “everyday”, “nearly every day”, “a few days a week”, “less than once a week”, “once a week”, or “never.” Future investigations should consider assessing for other symptoms associated with this phenotype including the extent to which exercise is intended to influence weight or shape, the degree to which guilt is experienced when exercise is postponed, and whether exercise is undertaken during injury. An assessment of this nature would likely temper any over-endorsement of this behavior.

The Heritability of Purging Behaviors and Excessive Exercise

This is the first known investigation to examine the heritability of multiple purging behaviors in a population-based sample. One limitation of this study was low statistical power, resulting from infrequent endorsement of the purging behaviors. Due to a lack of concordant twin pairs, heritability estimates for self-induced vomiting and diuretic abuse could not be determined. Heritability estimates were calculated for laxative abuse and excessive exercise. However, the results of these analyses should be viewed cautiously as they are based on sparsely endorsed data. Given this caveat, we report evidence of familial aggregation in liability to laxative abuse and excessive exercise. Further, laxative abuse was more strongly influenced by common environmental factors, while excessive exercise was more influenced by additive genetic factors. These findings provide additional support for the hypothesis that specific eating disorder symptoms might be differentially heritable (Neale, Mazzeo, et al., 2003; Mazzeo et al., 2008; Wade et al., 1998).

Although the data are sparse and should be interpreted cautiously, these preliminary findings are nonetheless interesting. There are several possible hypotheses regarding why excessive exercise may be more strongly influenced by additive genetic factors, while laxative abuse may be more strongly influenced by common environmental factors. For example, research has suggested that exercise has important health benefits (Adamu et al., 2006). Thus, it is possible that propensity for excessive exercise might be potentially adaptive, explaining why this trait might be more strongly influenced by additive genetic factors. Laxatives, on the other hand, have been created by modern technology; abuse of these substances posits no health benefit or evolutionary advantage. Thus, it makes sense that liability to this behavior might be more influenced by common environmental factors.

Although these hypotheses are interesting, future investigations in larger population-based samples are needed to acquire more accurate estimates of the heritability of purging behaviors and excessive exercise.

The Prevalence of Purging Disorder

This study is one of very few investigations to estimate the prevalence of PD in a population based sample. Previous population-based studies have reported prevalence estimates ranging between 1.1% to 5.6% (Favaro et al., 2003; Wade et al., 2006). In this sample, PD was found to affect 4.2% of the population over the lifetime, which falls within the range identified by Favaro et al. and Wade et al..

The Heritability of Purging Disorder

This study also examined the heritability of PD using an item-factor model (Neale et al., 2006), which provides information about the genetic and environmental contributions to the latent trait as well as to each individual item. Although the item-factor model is designed to maximize statistical power in low prevalence phenotypes, the sample was prohibitively small and reasonable estimates could not be determined. Next, a univariate model for PD was also applied but again, the data were too sparse to provide meaningful estimates. Future investigations should examine the heritability of PD at the item level using larger population-based samples.

Directions for Future Research on Purging Disorder

In addition to replicating the results of the current study, future research should investigate several other aspects of PD. One direction for future research on PD is to determine a consistent operationalized definition of the proposed disorder. A current limitation of extant investigations is that no set definition for PD has been consistently used

(Haedt & Keel, 2010). For example, some studies have defined the disorder broadly, including purging and nonpurging compensatory behaviors (e.g., Machado, Machdo, Gonclaves, & Hoek, 2007; Spoor, Stice, Burton, & Bohon, 2007), while others have restricted PD to individuals who engage in self-induced vomiting or who abuse laxatives and diuretics (e.g., Favaro et al., 2003; Keel et al., 2005). In addition, the minimum frequency of purging behaviors has not been consistently defined across studies (Binford & le Grange; Machado et al.); rather it has ranged from once per week to no specified time frame. Discrepancies in defining central features of PD have made comparison of results across studies difficult.

Haedt and Keel (2010), examine the pros and cons of various definitions for PD. They discuss the merit of including more broad subtypes of purging such as diet pills, fasting, and excessive exercise, as opposed to staying with stringent criteria for purging, which would only include self-induced vomiting, laxative, and diuretic use. The authors note the importance of determining a definition that is not too narrow, resulting in large numbers of individuals falling in the EDNOS category. On the contrary, they also note that overly inclusive diagnoses are inherently problematic because they increase diagnostic heterogeneity by overpathologizing normal behavior. The authors compared four definitions of PD that varied on two dimensions: group of compensatory behaviors and minimum frequency of behavior. Findings of this study suggest that an optimum definition of PD might include purging in the form of self-induced vomiting, laxative abuse, or diuretic abuse occurring at a frequency of at least once a week. Future investigations should continue to refine a standard definition for PD.

Limitations

There are several limitations to the design and analysis of this study that warrant mention. First, twins might not be representative of the general population. Twins differ from singletons on a number of parameters including shorter gestation, a higher probability of low birth weight, birth complications, and greater prenatal mortality (Naeye, Tafari, Judge & Marboe, 1978). However, psychiatric studies have found that twins have similar risks as singletons for disordered eating (Kendler et al., 1991). In addition, generalizability is also supported by the similar prevalence of eating disorders in twins and singletons (Bushnell, Wells, Hornblow, Oakley-Browne & Joyce, 1990; Kendler et al.). Lastly, previous studies with this sample have found that the demographics of participants are comparable to those in other twin studies (Mazzeo, Aggen, Anderson, Tozzi & Bulik, 2003).

Another limitation is that because this study includes European American women exclusively, findings will not generalize to individuals from other racial/ethnic groups. The sample was originally limited to European American twins because sample sizes of minority twins were too small to provide statistical power to obtain reliable estimates for low prevalence variables. Since the data included in this research plan were collected, the sample has expanded to include twins from Virginia, North Carolina, and South Carolina. This expanded dataset is more representative of the ethnic diversity in those three states; however, the data required for these analyses are not yet available in this expanded sample. Future research should examine the heritability of purging and PD in diverse samples.

In addition, there might be measurement issues regarding the assessment of PD. This survey does not include the duration of purging (in months), which is necessary to determine the presence of PD according to the criteria proposed by Keel et al.(2001). However, these

data were collected before the advent of PD and assess all other criteria. As previously mentioned, determining consistent criteria for PD is a current priority (Haedt & Keel, 2010).

Lastly, using a cross-sectional design does not provide information about whether genetic factors influence purging subtypes at different points in the lifespantime. However, no other known studies have investigated liability to laxative abuse and excessive exercise. Thus, these results provide preliminary information that might lay the groundwork for future longitudinal investigations.

There are also many strengths of this study. Treatment and prevention efforts for disordered eating can be informed by a careful analysis of causal factors, including genetic influences both at the diagnostic and symptom level. In addition, determining the prevalence of specific symptoms of disordered eating in a population-based sample is important in order to best prioritize and target treatment and prevention efforts. This study is unique in generating a population-based prevalence estimate of purging behaviors and PD. It is also the first study to examine the heritability of laxative abuse and excessive exercise in a population-based sample.

Chapter Three: Genetic and Environmental Contributions to Anorexia Nervosa and Obsessive Compulsive Personality Disorder

As previously described, AN is a significant public health concern that is strongly familial and heritable (Lilenfeld et al., 1998; Slof-Op't Landt et al., 1995; Strober, et al., 1997; 2000). Obsessive compulsive diagnoses, including obsessive compulsive disorder (OCD) and OCPD, are also significant health concerns that have been found to be strongly influenced by genetic factors (Grados & Wilcox, 2007; Jonnal, Gardner, Prescott, & Kendler, 2000; Voyiaziakis et al., 2009). Previous studies have identified evidence of an association between obsessive compulsive disorder and AN (Halmi et al., 2005; Strober, Freeman, Lampert, & Diamond, 2007; Solyom, Freeman, & Miles, 1982), and it has been proposed that both might fall within the obsessive compulsive spectrum (Hollander, 1993). Disorders hypothesized to belong to the obsessive compulsive spectrum share similarities with OCD, such as symptoms, course of illness, treatment response, familial loading and presumed etiology (Hollander, 1993; Hollander, Kim, Braun, Simeon, & Zanar, 2009; McElroy, Phillips & Keck, 2004). Although much research has focused on the relation between AN and OCD, few studies have examined the association between AN and OCPD. Researchers have suggested that AN might be more closely related to OCPD than OCD, as both AN and OCPD involve trait related behavior (Casper, 1990). For example, AN is characterized by the traits of perfectionism and inflexibility (Dubois, 1949; Halmi et al., 2005; King, 1963; Lilenfeld, Wonderlich, Riso, Crosby & Mitchell, 2006), which are also prominent symptoms of OCPD.

Many individuals with eating disorders have comorbid OCPD, although estimates of comorbidity have varied widely (i.e., from 3% to 60%; Herzog et al., 1992; Piran, Lerner,

Garfinkel, Kenedy, & Brouilette, 1998; Wonderlich, Swift, Slotnick, & Goodman, 1990). This large variance in comorbidity estimates might be due to issues of measurement, which will be discussed in more detail later in a subsequent section of this paper. Higher comorbidity rates have been reported in individuals with AN than in controls (Lilenfeld et al., 1998; Strober et al., 2007). In addition, family studies have reported a higher prevalence of OCPD in relatives of individuals with AN compared to relatives of individuals without AN (Lilenfeld et al.; Strober et al.). Despite these associations, the nature of the relation between AN and OCPD is not well understood.

The purpose of this study is to explore the etiology of the comorbidity between AN and OCPD in a population-based sample of female twins. Previous research has not investigated the extent to which genetic and environmental factors influencing liability to these two syndromes are shared. AN was discussed in Chapter One. In this chapter, obsessive compulsive diagnoses and their proposed etiologies will be broadly reviewed, followed by a discussion of comorbidity within the obsessive compulsive spectrum and the hypothesized nature of the association between AN and OCPD.

OCD and OCPD

Obsessive compulsive diagnoses are very distressing, chronic, and costly (Dupont, Ric, Shiraki, & Rowland, 1995; Lopez & Murray, 1998). There are two obsessive compulsive diagnoses in the *DSM-IV-TR* (APA, 2000), OCD, which is an Axis I disorder and OCPD, which is an Axis II disorder (APA). Both OCD and OCPD are characterized by obsessive compulsive symptoms (OCS), including preoccupation with orderliness, rigidity, and perfectionism. In addition, OCS can occur at a subthreshold level that is less disruptive or distressing to the individual (Jonnal et al., 2000). According to the *DSM-IV-TR* (APA),

OCPD is represented by, “a pattern of preoccupation with orderliness, perfectionism, and mental and interpersonal control, at the expense of flexibility, openness, and efficiency “ (p. 672-673). These characteristics must be evident by early adulthood and present in a variety of contexts. The prevalence of OCPD in community and population based samples has been estimated to be between 0.9% and 3% (Karno, Golding, Sorenson, & Burnam, 1988; Samuels et al., 2002; Torgersen, Kringlen, & Cramer, 2001). OCD, on the other hand, is marked by the presence of recurrent obsessions or compulsions that are severe enough to be time consuming, or cause significant distress or impairment. Obsessions include thoughts, ideas, or images, which result in anxiety or distress and are experienced as intrusive and inappropriate. Compulsions are defined as repetitive behavior, mental acts, or rituals that function to prevent anxiety or distress (APA, 2000). OCD is thought to affect 2% to 3% of the population (Karno, Golding, Sorenson, & Burnam, 1988). The primary difference between OCPD and OCD is that the former is centered on traits (e.g. perfectionism) while the latter emphasizes behaviors (e.g., obsession and compulsions). There is an ongoing debate regarding the relation between OCPD and OCD, which will be briefly reviewed in the next section.

The Relation between OCD and OCPD

Over the past 25 years, there has been considerable interest in the relation between OCPD and OCD and many studies have examined their comorbidity (e..g. Black 1974; Rasmussen & Tsuang, 1986; McGlashan et al., 2000). For example, early investigations reported low rates (0-6%) of OCPD in individuals with OCD (Black; Rasmussen & Tsuang; Tyrer, Casey & Gall, 1983). These studies, however, used the *DSM-III* (APA, 1980) criteria

for OCPD, which is very stringent and requires four out of five OCPD criteria to be present for diagnosis.

More recent editions of the *DSM* (APA, 1987, 1994, 2000) have reported higher rates of comorbidity between the two disorders. Studies using the *DSM-III-R* (APA, 1987), which only required five out of nine OCPD criteria to be present for diagnosis, found that up to 30% of individuals with OCD had comorbid OCPD (Diaferia et al., 1997). A more recent study by McGlashan and colleagues (2000) using the *DSM-IV* (APA, 1994) criteria, found that 20.9% of individuals diagnosed with OCPD met criteria for OCD. In contrast, between 0.9% and 3% of individuals in the general population meet criteria for OCPD (Karno et al., 1988 Samuels et al., 2002; Torgersen, Kringlen, & Cramer, 2001), suggesting that individuals with OCPD have a greater propensity for OCD. Although precise estimates of OCPD in individuals with OCD have varied by sample populations and assessment materials, overall results suggest that OCPD occurs with greater frequency in individuals with OCD than in the general population (Diaferia et al., 1997). Yet, while there appears to be potential overlap between OCD and OCPD, the factors influencing this relation are not entirely clear. Investigations of the etiology of the symptoms underlying these disorders might help explain the comorbidity between OCPD and OCD.

Etiology of OCD and OCPD

OCPD and OCD, like other psychiatric disorders, are thought to be influenced by both environmental and genetic factors. Although research in the last few decades has expanded, the etiological factors involved in the development and maintenance of these disorders are not fully understood (Cromer, Schmidt, & Murphy, 2007).

One hypothesis is that obsessive compulsive spectrum disorders are the consequence of adverse environmental influences. A recent study by Cromer et al. (2007) found a significant association between traumatic life events and OCD, suggesting that environmental influences might play an important role in the development of the disorder. Additional studies have found that parents of children with OCD suffer from poorer mental health than parents of healthy children (Derisley et al., 2005). Further, OCD patients report having parents who were overprotective or emotionally neglectful more often than healthy controls (Cavedo & Parker, 1994). Obsessive compulsive symptoms (OCS) can also originate during stressful life events and significant stressors can lead to relapse in symptoms (Metzner, 1963; Marks, 1987). For example, a study of veterans of the Vietnam War found that among those with high-war-zone experience, OCD prevalence was 5.2%. Similarly, Solomon et al. (1991) found elevated scores on measures of obsessive compulsive symptoms in Israeli combat veterans compared to controls.

Yet, although environmental influences are involved in the development and maintenance of OCS, other research suggests that OCS are highly heritable (Calvo et al., 2009; Wiessman et al., 2005). Research exploring the genetic components of OCPD and OCD has included both family and twin studies.

Family and Twin Studies of Obsessive Compulsive Diagnoses: Evidence for Genetic Vulnerability

Liability to obsessive compulsive behaviors is strongly influenced by genetic factors (Hudziak et al., 2004; Pauls, 2008; van Grootheest, Cath, Beekman & Boomsma, 2005). Numerous studies suggest that genetics are significantly involved in the development of OCD. For example, direct-interview family studies have found the incidence of OCD to be

3.4 to 10.1% in first-degree relatives of individuals with the disorder, which is substantially higher than the incidence in the general population (Bellodi, Sciuto, Diaferia, Ronchi & Smeraldi, 1992; Pauls, Alsobrook, Goodman Rasumssen, & Leckman, 1995; Sciuto, Pasquale & Bellodi, 1995). However, only one study to date has investigated genetic contributions to OCPD. Reichborn-Kjennerud et al. (2006) applied a single-factor independent pathway multivariate model to the number of endorsed criteria for avoidant personality disorder, dependent personality disorder, and OCPD. The authors concluded that an AE model best fit the data. Within this AE multivariate model, 27% of the variance in OCPD was attributable to additive genetic effects. Although this suggests that OCPD is moderately heritable, this is the only extant study of the heritability of OCPD and thus, is a starting point for further investigation.

Research has also suggested that genetic factors strongly influence the liability to OCS (Carey & Gottesman, 1981; Jonnal et al., 2000; Skre, Onstad, Torgersen, Lygren & Kringlen, 1993; van Grootheest et al., 2008). Several studies have found higher concordance rates for OCS in MZ than DZ twins (Carey & Gottesman; Skre et al.). One study (Clifford, Murray & Fulker, 1984), which included a sample of 419 MZ and DZ twin pairs, reported that the heritability of OCS was estimated at 47%. In a more recent investigation by Jonnal et al. (2000), a sample of 1,054 female twins from the VTR was used to estimate heritability of OCS. A principal components analysis suggested that two factors corresponded roughly to obsessions and compulsions. The best fitting model yielded heritability estimates of 33% and 26% for obsessions and compulsions, respectively, suggesting moderate heritability. Most recently, van Grootheest et al. (2009) investigated the contribution of genetic and environmental factors to OCS in 5893 MZ and DZ twins and 1304 siblings from the

population-based Netherlands Twin Registry. They found that OCS demonstrated moderate heritability in both men and women. Thirty-nine percent and 50% of the variance in OCS, in men and women respectively, was accounted for by common genetic factors. The rest of the variance was attributable to common environmental factors. In a second study, van Grootheest, Hottenga, Beekman et al. investigated the stability of OCS in MZ and DZ in the same sample across four time points from 1991 to 1997. Stability of OCS was analyzed as a function of genetic and environmental components. They found that approximately 40% of the stability in OCS was explained by genetic factors and the remaining variance was explained by common environmental and unique environmental factors. Interestingly, genetic correlations across time were high, varying between 0.61 and 0.90 across the four time points, suggesting that stability of OCS was predominantly due to stable genetic factors. In the following section, research investigating the obsessive compulsive spectrum of disorders will be reviewed and its implications for the current study of comorbidity between AN and OCPD will be discussed.

Anorexia Nervosa as an Obsessive Compulsive Spectrum Disorder

Disorders are hypothesized to belong to the obsessive compulsive spectrum based on their similarities they share with OCD, including symptoms, course of illness, treatment response, familial loading, and presumed etiology (Hollander, 1993; McElroy et al., 1994). As noted above, researchers have hypothesized that AN should be considered a disorder on the obsessive compulsive spectrum (Hollander). This hypothesis is based in part on research indicating that the prevalence of comorbid AN and OCD is between 10% and 60% (see review in Godart, Flament, Perdereau, & Jaemmet, 2002). In addition, a review by Rothberg (1988) of 11 major investigations of comorbidity in AN found that OCS were the second

most frequent symptoms reported after depression. Similarly, Solyom et al. (1982) found that after excluding food and body-related obsessions, individuals with AN displayed high trait scores on OCS.

OCPD also falls within the obsessive compulsive spectrum (Fineberg, Sharma, Sivakumaran, Sahakian, & Chamberlain, 2007). As previously described, OCD and OCPD are frequently comorbid (Diafera et al., 1997; Karno et al., 1988; McGlashan et al., 2000). Although much research has focused on the relation between AN and OCD, few studies have examined the association between AN and OCPD. Nonetheless, some authors (Casper, 1990; Lilenfeld et al., 2006) have suggested that AN might be more closely related to OCPD than OCD. This hypothesis is based on the fact that, in addition to disordered eating behaviors, individuals with AN often manifest personality traits (Casper) such as perfectionism, rigidity, and inflexibility, which are characteristic of OCPD (DuBois, 1949; Lilenfeld et al.). A diagnosis of OCD, on the other hand, is more strongly characterized by obsessive compulsive behaviors, such as hand-washing, repeated checking, etc., which are less commonly found among individuals with AN.

Comorbidity of AN and OCPD

The prevalence of OCPD among individuals with eating disorders is reported to be between 3% and 60% (Herzog et al., 1992; Piran et al., 1988; Wonderlich et al., 1990), with higher prevalence reported for individuals with AN than BN (Lilenfeld et al., 1998). This broad range in comorbidity estimates is likely due to differences in the approaches used to measure OCPD (Arntz, 1999). An early study by Piran et al. investigated the prevalence of personality disorders, including OCPD, in 68 adult women with AN. Individuals with both AN-R (n=30) and AN-BP (n=38) were included in the study. *DSM-III-R* (APA, 1987)

diagnoses for personality disorders were used and were independently derived by two clinicians (Piran et al.). Participants were given the Diagnostic Interview for Borderlines (Gunderson & Kolb, 1978), the Minnesota Multiphasic Personality Inventory (Dahlostrom, Welsh, & Dahlstrom, 1975), and the Childhood Events Questionnaire (Barnes, Ennis & Trachtenberg, 1985). Results suggested that 3.3% and 2.6% of patients with AN-R and AN-BP met criteria for OCPD, respectively. The authors noted potential limitations of their study including methodological issues in the classification of personality disorders and small sample size.

In a similar study, Wonderlich et al. (1990) assessed the prevalence of personality disorders in 20 individuals with either AN-R (n = 10) and AN-BP (n = 10). Participants were patients at the University of Wisconsin Eating Disorders Program. Personality disorders were assessed using Structured Clinical Interview for DSM Diagnoses-Axis -II (SCID-II; Spitzer & Williams, 1986). To assess inter-rater reliability of the SCID-II diagnoses, an independent rater listened to 30% of the audio taped interviews collected by the first author. Complete agreement for personality disorder diagnoses was achieved for 12 of the 14 interviews. Disagreements were discussed and resolved by the interviewers. Results suggested that 60% of AN-R patients and 0% of AN-BP patients met criteria for OCPD. Limitations of this study include its very small sample size, lack of a control group, and rater disagreement. In addition, the authors noted that the assessment was conducted when AN-R was acute. Thus, the severity of AN-R might have had a transient effect on the severity of OCPD.

A 1992 study by Herzog et al. investigated the prevalence of personality disorders in 31 women ages 31 – 65 with AN using the SCID-II (Spitzer & Williams, 1986). This study was conducted as part of a longitudinal outcome study of eating disorders at Massachusetts

General Hospital. They found that 10% of patients with AN-R had concurrent OCPD. However, it should be noted that the extremely small sample size is a limitation of this study.

Similarly, Halmi et al. (2005) examined the prevalence of OCPD among participants with restricting AN (n = 75) and AN-BP (n = 275) as part of the International Price Foundation Genetic Study (see Kaye et al., 2004 for full details regarding methodology). AN diagnoses were assessed using the Structured Inventory of AN and BN symptoms (Fichter, Herpertz, Quadflieg & Herpertz-Dahlmann, 1998) and with Module H of the SCID-I (First et al., 1997). OCPD was assessed with the SCID-II (First et al., 1997). They found that 15% of individuals with AN-R and 12% of individuals with AN-BP met diagnostic criteria for OCPD. Strengths of this study included a relatively large sample size. Regarding limitations, the authors noted that the sample was composed of families in which more than one member had an eating disorder and thus, these "higher density" families might differ from those families with sporadic cases.

A more recent study (Strober et al., 2007) investigated the relation between AN and anxiety disorders, including OCPD, through the use of a case-control family study design. Women between the ages of 18 and 28, recruited from a specialty treatment setting, and at least one first degree relative were included in the study. Results indicated that 55 of the 152 individuals with AN-R (36.2%) met criteria for OCPD. In addition, the prevalence of OCPD in relatives of women with AN-R was three times that of controls (20.7% vs. 7.0%). The authors noted several limitations to this study including that AN probands were recruited from a specialty treatment setting, which might limit external validity.

Overall, these studies suggest that AN and OCPD are frequently co-morbid. Although there is variation in the comorbidity estimates found across studies, this range is likely at

least partially attributable to the use of different measures of AN and, in particular, OCPD. Personality disorders by nature are difficult to diagnose and have undergone significant revisions over the last 20 years (Arntz, 1999). Future studies, incorporating new research, should continue to investigate the comorbidity between AN and OCPD.

The Nature of the Relation between AN and OCPD

Sixty years ago, Du Bois (1949) suggested that what we now refer to as AN should be diagnosed as 'compulsion neurosis with cachexia' suggesting the inherent symptom overlap between AN and OC diagnoses. Individuals with AN report severe restriction of food intake, an obsessive pursuit of thinnes s, body preoccupation, and rumination regarding intake. Compulsive calorie counting and excessive exercise are also frequent symptoms of AN. Researchers have become interested in the relation between AN and OCS because personality characteristics associated with AN include rigidity, ritualism, perfectionism, and meticulousness (Matsunga, Iwaski, Yamagami, & Kaye, 1999).

One hypothesis regarding the relation between AN and OCPD is that both disorders might be the neurobiological result of biological processes, namely starvation (Keys et al., 1950). A second hypothesis contends that an obsessional personality or traits predate or co-occur with AN, suggesting that they share common etiopathogenic roots that fall within the same obsessive-compulsive spectrum, and are characterized by perfectionism, deficits in executive functioning, and neurobiological abnormalities. The following sections review the evidence for both of these hypotheses.

Starvation Secondary to AN Might Result in OCPD

Research has suggested that starvation secondary to AN can result in OCPD, but the two disorders are nonetheless distinct. Thornton and Russell (1997) argue that there are

several inherent problems with the assumption that individuals with AN manifest obsessive characteristics premorbidly. Specifically, these authors report that, in contrast to individuals receiving inpatient treatment for AN, individuals receiving outpatient treatment do not demonstrate increased obsessionality (Fahey, 1991). Thus, OCPD symptoms could be associated with greater AN severity or might be confounded by low body weight. Indeed, low serotonin levels, a result of starvation, are common among both individuals with AN and those with OCS (Kaye, Gwirtsman, George, & Ebert, 1991).

Data from the Minnesota studies of human starvation (Keys et al., 1950) are consistent with the hypotheses that obsessionality in patients with eating disorders is a result of weight loss and that OCPD symptoms might be secondary to AN. In this study, 32 males developed features typical of both AN and OCPD secondary to study-induced starvation. Although the generalizability of these findings is limited, due to the small (and exclusively male) sample, this study provides preliminary evidence that an obsessional pre-morbid personality is not required for the development of OCS secondary to starvation.

AN and OCPD, Implications for a Common Etiology

The association between AN and OCPD might also be accounted for by common etiopathogenic roots that underlie the obsessive-compulsive spectrum. Thus, these disorders might reflect common psychological (Karwautz et al., 2001), neurobiological (Enoch, et al., 1998), or genetic (Tchanturia et al., 2003) elements. Kaye et al. (2004) suggest that "childhood anxiety represents one important genetically mediated pathway towards the development of anorexia nervosa…" and that as a result, obsessive compulsive symptoms likely predate development of disordered eating.

Pre pre-morbid obsessional traits have be found in individuals with AN (Dally, 1969; Kay & Leigh, 1954; King, 1963; Morgan & Russell, 1975; Norris, 1979). A 2003 study by Anderluh et al. retrospectively examined childhood traits believed to reflect obsessive compulsive personality in 44 women with AN. They found that childhood obsessive compulsive personality features were highly predictive of AN.

In a study by Råstam (1992), researchers performed a blind, systematic chart review of pre-morbid personality functioning in 51 Swedish adolescents with AN as a means of identifying personality functioning prior to AN onset. They found that individuals with AN histories displayed significantly more features of OCPD than matched controls (35% vs. 4%). In addition, almost 60% of individuals with AN reported having compulsive personality traits even though they were not diagnosed with OCPD (compared with 18% in the control group). Of those who previously suffered from OCPD, four developed OCD during the course of AN, compared to zero in the control group. However, it is unknown whether the adolescents had eating disorder symptoms at the time of the chart notes. The authors conclude that approximately 35% of AN cases reviewed noted severe OCPD prior to the onset of AN and that another 25% noted perfectionistic and obsessional features not meeting the diagnostic criteria for OCPD.

perfectionism. Perfectionism, a predominant characteristic among both individuals with AN and OCPD (Bastiani et al., 1995; Bulik et al., 2003; Halmi et al., 2000; Kim, Heo, Kang, & Treasure, 2009; Serpell, Livingstone, Neiderman, & Lask, 2002), can be a debilitating psychological problem (Pacht, 1984). Hollender (1978, p. 384) describes perfectionism as "the practice of demanding oneself or other a higher quality of performance than is required by the situation." Perfectionist qualities include "setting unrealistic standards

and striving to attain those standards, selective attention to and over-generalization of failure, stringent self-evaluations, and a tendency to engage in all-or-none thinking whereby total success or total failure exist as outcomes" (Hewitt & Flett, 1991, p. 460). Perfectionism is a pre-morbid risk factor for AN (Fairburn et al., 1999; Karwautz et al., 2001) and persists after recovery from AN (Matsunaga et al., 2000; Strinivasagasm et al., 1995). Further, mothers of individuals with eating disorders display higher levels of perfectionism (Woodside et al., 2002).

Three important studies have investigated the role of perfectionism in AN (Bastiani et al., 1995; Halmi et al., 2005; Srivasagam et al., 1995). The Bastiani et al. study investigated different dimensions of perfectionism in patients with AN (n = 11), individuals with a history of AN who had experienced weight restoration within the prior four weeks (n = 8), and healthy controls (n=10). The aim of this study was to characterize perfectionism in AN and to determine if perfectionist characteristics persist after nutritional restoration. Participants completed the EDI (Garner et al., 1983), a 64-item, self-report questionnaire that measures behavioral and cognitive characteristics of AN. The EDI contains eight subscales, one of which assesses perfectionism. The Perfectionism subscale emphasizes personal standard setting and parental expectation and is comprised of six items. Participants also completed the 35-item Frost Multidimensional Perfectionism Scale (F-MPS; Frost, Marten, Lahart, & Rosenblate, 1990), which identifies the following five dimensions of perfectionism: Concern Over Mistakes, Personal Standards, Parental Expectations, Doubts About Actions, and Organization, Order, and Precision. Lastly, all individuals were given the Hewitt Multidimensional Perfectionism Scale (H-MPS; Hewitt & Flett, 1991), a 45-item self-

report measure, which assesses Self-Oriented, Other-Oriented, and Socially Prescribed Perfectionism.

Significant differences were found among groups for all subscales of the F-MPS, except Parental Expectations (Bastiani et al., 1995). Post-hoc analyses revealed that individuals with current AN and weight restored individuals with a history of AN scored similarly on all subscales of the F-MPS. However, individuals with current AN scored significantly higher than control women on all subscales except Parental Expectations. Interestingly, recovered individuals scored higher than controls on Concern Over Mistakes and on Organization, Order, and Precision. On the H-MPS (Hewitt & Flett, 1991), significant differences were found among groups for the subscales for Self-Oriented Perfectionism and Socially Prescribed Perfectionism. Post-hoc analyses revealed that individuals with AN and recovered individuals scored similarly on all subscales of the H-MPS. Individuals with AN scored significantly higher than controls on Self-Oriented and Socially Prescribed Perfectionism and recovered individuals scored higher than controls on Self-Oriented Perfectionism only. On the EDI, significant differences were found among the three groups. Specifically, recovered individuals and individuals with AN had similar scores on all subscales. Individuals with AN scored significantly higher than control individuals on all subscales. Recovered individuals scored higher than control women only on the Perfectionism and Drive for Thinness subscales.

Thus, Bastiani et al.'s study (1995) yielded several important findings relevant to the current investigation. First, scores on both the F-MPS and H-MPS support the hypothesis that patients with current AN are perfectionistic. In addition, these findings suggest that individuals with AN experience perfectionism as self-imposed, and not as a reaction to the

expectations of others. Second, results suggest that perfectionism persists after weight restoration. These findings should be replicated with a sample that experienced weight restoration for a longer duration.

In a related study, Srinvasagam et al. (1995) investigated whether perfectionist and obsessive behaviors persist after recovery from AN. They compared 20 individuals who had recovered from AN (i.e., maintained normal weight for at least a year) with 16 healthy women on the EDI (Garner, Olmsted, & Polivy, 1983), the F-MPS (Frost et al., 1990), and the Yale-Brown Obsessive Compulsive Scale (Goodman et al., 1989). Of the individuals with AN, 11 had been diagnosed with AN-R and nine with AN-BP. The AN-R and AN-BP groups scored similarly on all three inventories and thus, due to the small sample size, were combined and compared with the control group. Individuals recovered from AN obtained significantly higher scores on the EDI Perfectionism Subscale and on overall perfectionism, as measured by the F-MPS, than controls. Recovered individuals also scored higher on the Yale-Brown Obsessive Compulsive Scale, which suggests that they have symptoms of OCD, including specific concern with symmetry and exactness, which persist beyond weight restoration. The authors concluded that weight loss appears to exaggerate the intensity of concerns related to perfectionism but the concerns themselves, characterized as an obsessive need for exactness and perfectionism, remain independent of changes in weight. The authors suggested that these behaviors might be traits related to an underlying biological vulnerability to AN.

A 2005 study by Halmi et al. looked specifically at the relations among perfectionism, eating disorders, OCPD, and OCD in a sample of 607 individuals with diagnoses of AN and/ or BN. Participants completed measures assessing perfectionism,

OCPD, and OCD. Lifetime AN and BN were assessed using the SIAB (Fichter et al., 1998). Module H of the SCID-I was also used. Lifetime OCD and OCPD were assessed using the SCID-I (First et al., 1997) and perfectionism was measured using the F-MPS (Frost et al., 1990). One limitation of this study is that it examined individuals with AN and BN together and thus, provides no information regarding the relation between OCS and specific eating disorder diagnoses.

Halmi et al. (2005) found that the Concern Over Mistakes and Doubts About Actions subscales of the F-MPS best discriminated between individuals with and without at least one obsessive-compulsive diagnosis in addition to either AN or BN. However, both of these subscales were found to be better indicators of OCPD than OCD. The Personal Standards subscale of the F-MPS was associated with OCPD, while the Parental Expectation subscale was more strongly associated with OCD. Based on these findings, the authors concluded that perfectionism appears to be more closely associated with OCPD features than OCD in individuals with AN and BN. In addition, Halmi et al. concluded that dimensions of perfectionism, including concern over mistakes and other features of OCPD, might represent an important phenotype placing an individual at greater risk for developing AN, These results provide justification for further examining the influence of genetic and environmental factors on the comorbidity between AN and OCPD (Westen & Harnden-Fischer, 2001).

Investigations of genetic influences on perfectionism are also relevant to the current study. For example, Tozzi et al. (2004) examined the structure and heritability of perfectionism using female-female twin pairs (n=1022) who completed items from the F-MPS (Frost et al., 1990). Three of the original F-MPS subscales were included: Personal Standards, Doubts About Actions, and Concern Over Mistakes. Independent pathway (IP)

and common pathway (CP) models were used to investigate the extent to which genetic and environmental factors influenced the three domains of perfectionism. The authors found that MZ correlations were consistently higher than DZ twin correlations for all three subscales. The multivariate IP model provided a better fit to the data than the more parsimonious CP model, suggesting that the pattern of familial resemblance is not well characterized by a unidimensional perfectionism factor. Based on the IP model, there was evidence that Personal Standards and Concern Over Mistakes share some common genetic effects and that Doubts About Actions and Concern Over Mistakes share some common environmental factors. The authors reported that Concern Over Mistakes appeared to be the driving component of the construct because it was highly correlated with both Parental Expectations and Doubts About Actions. They concluded that Concern Over Mistakes is a very good measure of the latent factor of perfectionism, with Parental Expectations and Doubts About Actions serving as proxy indicators of Concern Over Mistakes. In other words, Concern Over Mistakes represents the core of perfectionism, a construct which Doubts About Actions and Parental Expectations measure less precisely.

It is important to consider the limitations of this study, which was conducted with an exclusively European-American sample and thus, might not be applicable to other ethnic groups. In addition, the results of this investigation are limited by behavioral domains assessed by the F-MPS subscales used. However, this study was conducted with a large, population-based and genetically informative sample. Further, its results provide important information regarding the construct of perfectionism. Future research should continue to explore the nature of the perfection phenotype by examining how different dimensions of this construct are related to the comorbidity between AN and OCPD.

executive functioning. Various deficits in executive functioning have been noted in the eating disorder literature (Kemps, Tiggemann, Marshall, 2005; Southgate, 2005; Cooper & Fairburn, 2002; Fassino et al., 2002; Greet et al., 1996; Tchanturia et al., 2004; Zastrow et al., 2009). For example, individuals with AN score lower on executive functioning tasks than controls (Lena, Fiocco, & Leyenaar, 2004). Fassion et al. (2002) and Koba et al. (2002) found that individuals with AN had significantly more errors on the Wisconsin Card Sorting Task (WCST, Berg, 1948), a test of frontal lobe functioning implicated in executive functioning. In addition, Tchanturia et al. (2004) found that individuals with AN performed significantly worse than controls on multiple tests of mental flexibility, another indicator of executive functioning.

Set shifting, or the ability to move back and forth between multiple tasks, or mental sets (Miyake et al., 2000), is a major component of executive functioning. Set shifting ability is essential for cognitive-behavioral flexibility, allowing an individual to adapt his or her behavior to meet the changing demands of the environment. Problems in set-shifting might manifest in a variety of forms of cognitive inflexibility (e.g. concrete or rigid approaches to problem solving) or response inflexibility (e.g. perseverative or stereotyped behavior; Roberts, Tchanturia, Stahl, Southgate & Treasure, 2007). Deficits in set-shifting have also been associated with OCD (Fontenelle, Marques, Engelhardt, & Versiani, 2001). Recent research has suggested that set shifting difficulties might be related to the development of disordered eating (Southgate et al., 2005; Tchanturia et al., 2005; Steinglass & Walsh, 2006; Zastrow et al., 2009).

For example, individuals with AN have also been shown to perform poorly on set shifting tasks compared to control individuals. A 2007 systematic review and meta-analysis

(Roberts, Tchanturia, Stahal, Southgate, & Treasure) examined set-shifting in eating disorders. Fifteen papers that administered at least one of six neuropsychological set-shifting tasks including, the Trail Making Test (TMT; Reitan, 1958; Kravariti et al., 2003), the WCST (Berg, 1948), the Brixton Task (Burgess & Shalice, 1997), the Haptic Illusion (Uznadze, 1966; Tchanturia, Serpell, Troop & Treasure, 2002), the CatBat Task (Eliava, 1964), and the set shifting subset of the Cambridge Neuropsychological Tests Automated Battery (CANTAB; Downes et al., 1989) to individuals with eating disorders were reviewed. A consistent deficit was found across diagnoses, state of illness, and the set-shifting measures. The size of the pooled effect varied between tasks, from small (TMT), to medium (WCST and CatBat task), to large (Haptic Illusion). Although this study employed a limited amount of data from recovered/weight-restored subgroups of individuals with AN, preliminary results suggest that deficits in set shifting, particularly as measured by the TMT (Reitan), the Haptic Illusion (Uzande; Tchanturia et al.), and the CatBat (Eliava), remain following weight restoration and might represent biological vulnerability to AN (Roberts et al., 2007).

A 2004 study by Tchanturia et al. examined whether sub-optimal set shifting was state or trait related by examining set shifting in patients with current or past AN, and the association of these deficits with obsessive compulsive behaviors and traits. The authors compared set-shifting abilities in female individuals with current AN (AN-R, $n = 20$; AN-BP, $n = 14$) prior to receiving treatment, individuals with past AN in long-term recovery ($n = 18$, stable body mass for minimum of a year, regular menses for a year, and no psychotropic medication for a year), and healthy controls ($n = 36$). Participants were given a battery of neuropsychological tests assessing various facets of set shifting and executive functioning. A

computerized version of the TMT (Reitan, 1958; Kravariti et al., 2003) assessed rapid simple alternation between mental sets; the Brixton Test (Burgess & Shallice, 1997), the Set Flexibility Picture Test (Surguladze, 1995) and the Cat Bat Test (Eliava, 1964) were used to assess problem solving and set shifting. The Uznadze Illusion Task (Uznadze, 1966) was used to assess perceptual set-shifting. Lastly, the Verbal Fluency Test (Lezak, 1995) assessed cognitive retrieval and flexibility in cognitive search options. In addition, a semi-structured interview evaluated OCPD traits in childhood and adulthood.

Results indicated that scores of individuals with current AN-R or AN-BP on several set shifting tasks (e.g. including the TMT and the Brixton Illusion) were significantly lower than those of the recovered and control groups. Individuals recovered from AN had significantly more illusions on the Uznadze Illusion Task (Uzandze, 1966) and made more errors on the Set Flexibility Picture Test, relative to the control group. Overall, the individuals recovered from AN obtained scores that were between individuals with current AN and healthy controls, suggesting that nutritional status might play some role but is not entirely responsible for the mental inflexibility associated with AN.

Across studies, findings suggest that executive functioning deficits might be related to an underlying biological vulnerability to AN. Research suggests that the neurobiological deficits found among individuals AN might mirror the behavioral and personality characteristics, such as rigidity and inflexibility observed within this diagnostic group (see reviews by Braun & Chouinard, 1992; Lauer, 2002).

neurobiological evidence. Neurobiological similarities between AN and OCPD also suggests an underlying biological relation (Enoch et al., 1998; Jarry & Vaccarino, 1996). Several hypotheses have been proposed regarding the nature of this neurobiological link.

Neurodevelopment models of eating disorders emphasize the possible effects of in utero and postnatal factors (Connan, Campbell, Katzman, Lightman, & Treasure, 2003), such as *BDNF*, which is involved in neuronal proliferation, differentiation and survival during development (Lindsay et al., 1994; Lindvall et al., 2004; Thorenen, 1995), and is expressed in hypothalamic nuclei associated with eating behaviors (Rios et al., 2001). A polymorphism in *BDNF* (Val66Met; rs6265) has been associated with AN (Ribasés et al., 2003, 2004, 2005; Koizumi et al., 2004, 2006; Hashimoto et al., 2005). For example, Ribasés et al. (2003) identified an association between the AN and the Met66 variant within the *BDNF* gene. In addition, serum *BDNF* concentrations in AN patients were lower than in healthy controls (Nakazato et al., 2003, 2006; Monteleone et al., 2004, 2005). Further, these differences persisted following weight restoration (Nakazato et al., 2006).

A recent study (Nakazota et al., 2008) examined *BDNF* levels and set shifting abilities in women with acute AN (AN group), individuals recovered from AN (ANRec group), and healthy controls (HC group). Dimensional measures of psychopathology were used, including lowest and highest lifetime body mass index (BMI), the Eating Disorder Examination Questionnaire (EDE-Q; Fairburn & Beglin, 1994), the Mausley Obsessive-Compulsive Inventory (Hodgson & Rachman, 1977) and the Hospital Anxiety and Depression Scale (Zigmond & Smith, 1983). *BDNF* was measured using an Emax Immunoassay System kit (Promega, Madison, WI, USA) and the WCST (Berg, 1948) was given to assess set shifting ability. Serum *BDNF* concentrations in the AN group were significantly lower than in the HC group and the ANRec group, suggesting that decreased serum *BDNF* might be at least partially related to low weight status. Further, the AN group made significantly more errors on the WCST compared to the control group. Scores of the

ANRec group were between those who were currently ill and healthy controls but these deficits were not significant. There was no significant correlation between serum *BDNF* concentrations and WCST performance. The authors note several limitations of this study. First, 62% of individuals in the AN group were receiving inpatient treatment at the time of testing, whereas none of the individuals who had recovered from AN had a history of hospitalization. Thus, it is possible that these two groups were substantively different with respect to AN severity. This study also involved a small sample and used cross-sectional design, which did not allow researchers to determine if set-shifting difficulties were state or trait related. Lastly, no genetic data were collected and thus, researchers could not establish whether serum *BDNF* concentrations were associated with AN-related polymorphisms in the *BDNF* gene. Future longitudinal, genetically informed studies, using individuals with similar severity levels of eating pathology should examine whether there is an association between serum *BDNF* concentration and neuropsychological traits.

Hypothalamic serotonin (5-HT) dysfunction is another neurobiological factor implicated in both eating and obsessive compulsive disorders (Enoch et al., 1998); 5-HT metabolites, receptor-polymorphisms, and pharmaceuticals have all provided evidence for the involvement of 5-HT in these disorders. A review by Jarry and Vaccarino (1996) suggests that both neurochemical and behavioral expressions of AN and obsessive compulsive spectrum disorders occur on a continuum with constrained behavior of an avoidant quality and high levels of 5-HT on one end, and disinhibited approach behavior and low levels of 5-HT on the other. Increased levels of 5-hydroxyindoleacetic acid (5-HIAA), an important 5-HT metabolite, are found in individuals with obsessive compulsive disorders involving avoidance behavior (Insel et al., 1985; Kreis, Farrow, & Ross, 1991) and in

restricting AN (Kaye, Ebert, Raleigh, & Lake, 1984; Kaye et al., 1988). In addition, these abnormalities are evident after weight restoration in individuals with AN, suggesting that 5-HT dysfunction might be trait (Collier et al., 1997) rather than state related (e.g., secondary to starvation).

Prior studies have shown an association of a 5-HT_{2a}-receptor polymorphism, -1438G/A, with AN (Collier et al., 1997). The exact function of the 5-HT_{2a} receptor is unknown but it is thought to play a role in both eating behaviors and anxiety (Kaye, Weltzin, Hsu, & Bulik, 1991). 5-HT_{2a} is a G-protein coupled receptor that controls signal transduction by activating phospholipase C. It is unknown whether the G and A variant alleles are different functionally. However, if they do have different functional roles, the variation in the promoter might alter transcription, thereby potentially altering the number of 5-HT_{2a} receptors or their function (Enoch et al., 1998), which might affect eating behavior and anxiety.

A 1998 study by Enoch et al. failed to find evidence of an association between 5-HT polymorphisms and BN. These researchers genotyped three independent sets of unrelated people for the -1438G/A 5-HT polymorphism (AN n = 88, BN n = 59, control n = 357, OCD n = 62). Two sets were from the United States (US) and one set was from Italy. They found that the A variant of the -1438G/A allele was more common in US individuals with AN. However, US individuals with BN did not significantly differ from controls. This finding was replicated in Italian patients with eating disorders, who demonstrated the same trend in allele patterns. Finally, there was a significant increase in the A variant of the -1438A/G allele in patients with OCD. These findings suggest that the 5-HT2A – 1438A/G promoter

polymorphism, or a closely linked variant, might contribute to behaviors, such as perfectionism and obsessionality, frequently seen in both AN and OCPD.

The involvement of 5-HT in both AN and obsessive compulsive spectrum disorders is also supported by the use of selective serotonin reuptake inhibitors (SSRIs) in their treatment (Kasper, Fuger, & Moller, 1992; Mayer & Walsh, 1998). Serotonergic agonists show positive effects in treating OCS (Goodman et al., 1989; Griest, Jefferson, Kobak, Katzelnick & Serlin, 1995; Jenicke, Buttolph, Baer, Riccardi, & Holland, 1989). Fewer investigations have examined the effectiveness of SSRI's in treating AN; however, in the small number of available studies (Ferguson, LaVia, Crossan & Kaye, 1999; Holtkamp et al., 2005; Kaye et al., 1993; Rosenblum & Forman, 2003; Walsh et al., 2006; VaSwani, Linda & Ramesh, 2003; Walsh, Kaplan, Attia, et al., 2006), results were mixed. Nonetheless, there is some evidence to suggest that SSRI's might facilitate recovery from AN (Kaye et al.).

In exploring the nature of the comorbidity between AN and OCPD, the majority of research suggests that they share common etiopathogenic roots and that starvation secondary to AN does not cause OCS, but instead, exacerbates them. This is supported by research on perfectionism, executive functioning, and neurobiology which implicate genetic factors in the comorbidity of these disorders. However, more research is needed exploring the genetic and environmental etiopathogenic roots between AN and OCPD.

Purpose and Proposal

The purpose of this study was to examine the nature of the comorbidity between AN and OCPD. Prior investigations have suggested that there is an association between AN and OCPD. However, no studies have examined the extent to which genetic and environmental factors influencing liability to these two disorders are shared. Estimates of the degree to

which susceptibility to comorbid disorders is more strongly due to genetic or environmental factors can be determined using MZ/DZ twin correlations (Neale et al., 1994). However, biometric model fitting, in which the contributions of all three types of influences are examined simultaneously, is necessary to estimate the magnitude of these effects. SEM, as described in Chapter Two, is one useful method for testing complex multivariate theoretical hypotheses (Bollen, 1989; Fassinger, 1987) and can be applied to twin data. This research could provide new information regarding the etiology of the comorbidity of these two disorders.

Method

Participants

Participants were from the Norwegian Institute of Public Health Twin Panel (NIPHTP). Twins in the NIPHTP are found through the Norwegian Medical Birth Registry, established January 1, 1967, which receives mandatory notification of all births. Two questionnaire studies have been previously conducted in this sample: the first wave in 1992 on twins born between 1967 and 1974 and the second wave in 1998 on twins born 1967-1979. A total of 12,000 twins received the second wave questionnaire and 8,045 responded after one reminder (63% response rate). The NIPHTP has been described in detail elsewhere (Harris, Magnus, & Tambs, 2002; Kendler, Aggen, Tambs & Reichborn-Kjennerud, 2006).

Data for analysis were derived from an interview study for Axis I and Axis II psychiatric disorders that began in 1999. Participants were recruited from the 3,153 complete pairs who, in the second wave questionnaire, agreed to participate in an interview study. An additional 68 pairs were drawn directly from the NIPHTP. Of the 3,221 eligible pairs, 0.8% were unwilling or unable to participate, and in 16.2% of pairs, only one twin agreed to the

interview. After two attempts to contact, 38.2% did not respond. In total, 50.5% of the eligible female-female twin pairs participated.

Zygosity was determined based on questionnaire methodology using discriminant analysis. In 2006, Harris et al. updated these classifications using results from a subset of twins for whom zygosity was established from genetic markers and found that 97.5% of the sample was originally classified correctly. In addition, in all but 385 twin pairs, zygosity was determined by molecular methods based on the genotyping of 24 microsatellite markers. A study using the same sample (Reichborn-Kjennerud et al., 2007) estimated that misclassification rate was 0.7%, which is unlikely to bias results (Neale, 2003).

Assessments

Axis I diagnoses were assessed using the Norwegian version of the computerized Composite International Diagnostic Interview (CIDI: Wittchen & Pfister, 1997). The CIDI is a comprehensive structured diagnostic interview, which assesses DSM-IV Axis I disorders (APA, 1994) and International Classification of Diseases-10th edition (ICD-10) diagnoses. The CIDI was developed by the WHO and the former US Alcohol, Drug Abuse and Mental Health Administration. It manifests good test-retest and inter-rater reliability (Wittchen, 1994; Wittchen, Lachner, Wunderlich & Pfister, 1998). Previous studies have used both the pencil and computerized version of the CIDI in Norway (Kringlen, Torgersen & Cramer, 2001; Landheim, Bakken, & Vaglum, 2003).

A Norwegian version of the Structured Interview for DSM-IV (APA, 1994) Personality Disorders (SIDP-IV; Pfohl, Blum, & Zimmerman, 1995) was used to assess personality disorders. This instrument was originally developed in 1983, and has been used in a number of studies in different countries, including Norway (Helgeland, Kjelsberg, &

Torgersen, 2005; Torgersen, Kringlen & Cramer, 2001). This measure includes non-pejorative questions organized into topical sections rather than by disorders. This format increases the likelihood that useful information from related questions will be taken into account when rating associated criteria within that section. It also allows for a more natural flow of the interview. The SIDP-IV uses a '5-year rule', meaning that behaviors, cognitions, and feelings predominating for most of the past five years are considered representative of the individual's long-term personality functioning. In a sample of Norwegian men and women, this measure was found to have good inter-rater reliability and internal consistency (Cronbach's alpha = .90; Reichborn-Kjennerud et al., 2007).

Interviewers for this study were predominantly psychology students in the final part of their studies (equivalent to US students in the final two years of a clinical psychology doctoral program) and experienced psychiatric nurses. Interviewers were trained by the World Health Organization (WHO) and were closely supervised. Each twin in a pair was interviewed by different interviewers. Most interviews were conducted in-person. However, 231 (8.3%) were done via telephone due to practical constraints. Approval was received from the Norwegian Data Inspectorate and Regional Ethical Committee, and written informed consent was obtained from all participants after complete description of the study.

Statistical Analysis

It was anticipated that the prevalence of AN and OCPD would be low in this sample due to their relatively low population prevalence (APA, 1994; Samuels et al., 2002; Torgersen, et al., 2001). Thus, a dimensional approach was used (Widiger & Samuel, 2005), in which ordinal variables based on the number of criteria endorsed for AN (out of 9 criteria) and OCPD (out of 8 criteria) were constructed. The number of subthreshold criteria ($\geq$1) was

summed, assuming that the liability for each trait is continuous and normally distributed (i.e., that the classification of 0-1 represents different degrees of severity). This approach was used as it optimizes statistical power.

Ordinal Variable Construction for AN

In the current study, eating disorder items were based on *DSM-IV* (APA, 1994) and ICD-10 (World Health Organization, 1991). Participants were first asked if they had ever lost a lot of weight (≥15 lb) either by dieting or without meaning to (item 1). Second, they were asked if friends or relatives had ever said that they were much too thin or 'looked like a skeleton' (item 2). If participants endorsed neither of these items, they skipped to the next section of the interview, and their data were coded as missing for the subsequent eating disorder questions. Third, participants were asked the lowest weight they attained after the age of 14 and their height at that time (item 3). If their reported lowest weight was not less than 125 lb, they skipped to the next section of the interview. Participants who endorsed at least one of the first two items as well as the low weight criterion were subsequently asked questions regarding their fears about regaining weight (at the time of low weight; item 4), whether they considered themselves (item 5) or parts of their bodies (item 6) fat at this time, whether weight impacted their self-evaluation (item 7), whether others told them that their low weight was a hazard to their health (item 8) and whether they missed menstrual periods during this time (i.e. amenorrhea; item 9). Responses to these items, except for weight and height, were binary (yes/no).

BMI was calculated based on responses to the question regarding lowest weight since age of 14 and height at that time (item 3). This variable was subsequently dichotomized for data analysis; a score of 1 indicated a BMI ≤18.50. A score of 0 indicated a BMI ≥18.50. All

nine dichotomized AN items were summed to obtain an ordinal composite score between 0 and 9 on AN for each participant.

Ordinal Variable Construction for OCPD

The SIDP-IV included items assessing criteria for *DSM-IV* (APA, 1994) OCPD items. The specific *DSM-IV* criterion associated with each question was rated using the following scoring guidelines: 0 = not present or limited to rare isolated examples, 1 = subthreshold (some evidence of the trait, but not sufficiently pervasive to consider the criterion present), 2 = present (criterion is clearly present for most of the past 5 years, i.e. present at least 50% of the time), 3 = strongly present. As noted in Table 7, multiple items were used to evaluate each of the following: preoccupation with details, rules, lists, order, organization, etc (criterion A), perfectionism that interferes with task completion (criterion B), excessive devotion to work (criterion C), over-conscientious, scrupulous, and inflexible about morality, ethics, and values (criterion D), unable to discard worn-out or worthless objects without sentimental value (criterion E), reluctant to delegate tasks (criterion F), miserly spending towards self and others (criterion G), and rigidity and stubbornness (criterion H).

Table 7

OCPD Items for Each Criterion.

***DSM-IV* Criterion A: Is Preoccupied with details rules lists, order, organization or schedules to the extent that the major point of the activity is lost.**

- When you're working on something do you often spend so much time on small details that you lose site of the main point?
- Do you often spend so much time getting organized, that you have trouble getting a task done?
- Has anyone ever told you that you spend too much time making lists and schedules of what you need to do? Do you think you do?

***DSM-IV* Criterion B: Shows perfectionism that interferes with task completion**

- Would people describe you as perfectionist?
- Do you think you are a perfectionist? (if yes, the next question was asked)
- How often do your high standards keep you from getting projects completed on time?

***DSM-IV* Criterion C: Is excessively devoted to work and productivity to the exclusion of leisure activities and friendships.**

- Would you call yourself a workaholic?
- Have others complained about how much time you spend working?
- Has your devotion to work left you with little time for family activities, friendships, or entertainment?

***DSM-IV* Criterion D: Is over conscientious, scrupulous, and inflexible about matters of morality, ethics or values (not accounted for by cultural or religious identification)**

- Are you stricter about moral and ethical values than most people you know?
- Have other people complained that you're too strict about moral issues (if yes) what did they complain about?
- How often do you worry that you've done something immoral or unethical?

***DSM-IV* Criterion E: Is unable to discard worn-out or worthless objects even when they have no sentimental value.**

- Some people find it impossible to throw anything away, even when it's old and worn out. Does this sound like you?
- What kinds of things do you keep? Why do you keep them?
- Do others complain or tease you about the things you save?

***DSM-IV* Criterion F: Is reluctant to delegate tasks or to work with others unless they submit to exactly his or her way of doing things.**

- Do you end up doing a lot of jobs yourself because no one else will do it exactly the way you want it done?
- Do you often take over other people's responsibilities to make sure you get things done right? (if yes) examples?

***DSM-IV* Criterion G: Adopts miserly spending style toward both self and others; money is viewed as something to be hoarded for future catastrophes.**

- After you pay your bills, what kinds of things do you like to spend money on?
- Are you slow to spend money on yourself?
- Are you slow to spend money on others?
- Some people worry so much about terrible things happening in the future, that they hold on to all their money. Does this sound like you? (if yes) Tell me about that.

***DSM-IV* Criterion H: Shows rigidity and stubbornness.**

- Would other people describe you as being stubborn or set in your ways? (if yes) What makes them say that? Do you agree?

Each OCPD variable was recoded to be binary (yes/no for each symptom). In order to optimize statistical power, the number of subthreshold criteria endorsed (≥1), as opposed threshold criteria (≥2) was used as the cut-off for dichotomizing the items. This is also consistent with previous research by Reichborn-Kjennerud et al. (2007). The eight dichotomized items were summed to yield an ordinal composite score between 0 and 8 for each participant.

Analysis

Mx (Neale, Booker, et al., 2003) was used for all twin modeling analyses. Univariate models were first conducted to examine variance components of AN and OCPD separately, yielding two sets of estimates of a^2, c^2, and e^2 (Kendler, 1993; Neale & Cardon, 1992). A bivariate Cholesky decomposition was performed, which yielded estimates of the genetic, common environmental, and unique environmental influences on the covariance between the two phenotypes (see Figure 3); 95% confidence intervals for each of these parameters were calculated (Neale & Miller, 1997). Three distinct independent correlations, corresponding to the degree of overlap between a^2, c^2, and e^2 for the first trait and a^2, c^2 and e^2 for the second trait (r^a, r^c, and r^e in Figure 3), were then calculated. The fit of the full ACE model was then compared to that of nested sub-models. Chi-square analyses and AIC values (Akaike, 1987) were used to assess the optimal combination of goodness of fit and parsimony of the various models. To be considered good fitting, models should have a nonsignificant chi-square value *(p* > .05). In addition, smaller AIC (as x2 — *2df)* vales indicate better fit. The best fitting and most parsimonious model was retained.

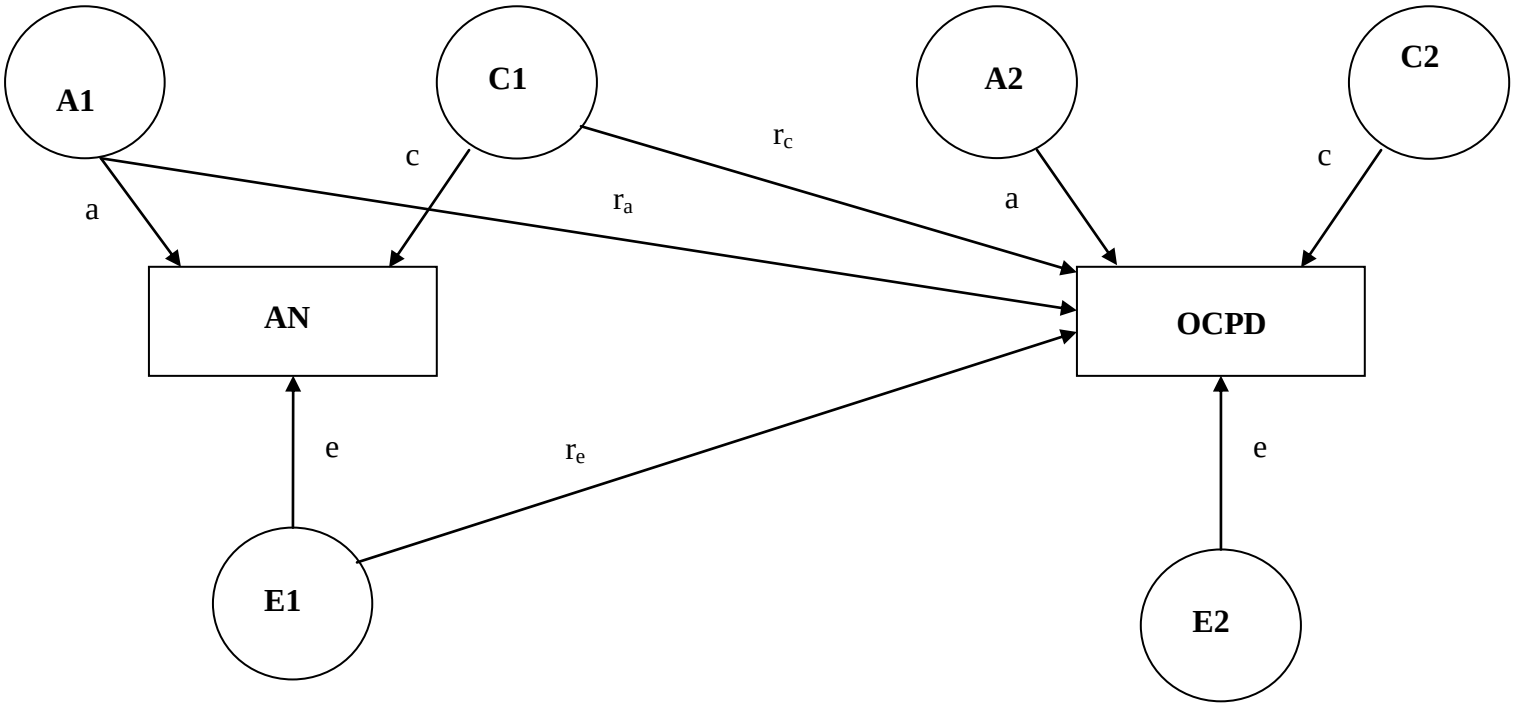

Figure 3. Bivariate Cholesky decomposition for AN and OCPD.

Results

Descriptive Statistics

The final sample consisted of 1,430 females twins: MZ (448 complete pairs and 4 singletons) and DZ (263 complete pairs and 4 singletons) twins. Participants' ages ranged from 19.0 to 36.0 (M = 28.19, SD = 3.89). Descriptive statistics indicated that 1.9% and 2.3% of the sample met criteria for *DSM-IV-R* (APA, 2000) lifetime diagnosis of AN and OCPD, respectively.

Anorexia Nervosa

For the 11 items assessing AN, 550 participants endorsed item 1 and 470 endorsed item 2 (see Table 8); in total, 765 participants endorsed either item 1 or 2 and thus, were asked to report the lowest weight they attained after the age of 14. A total of 662 participants reported a weight of less than 125 lbs and thus, met criteria to continue the questionnaire. Participants who endorsed either item 1 or 2 and who met the low weight criterion (< 125 lbs) were asked additional questions assessing specific symptoms of AN during the time they were at their lowest weight. Specifically, 311, 168, 87, 115, 231, 132, and 73 participants endorsed items 3, 4, 5, 6, 7, 8, and 9, respectively (see Table 8). The AN composite score summaries are listed in Table 9.

Table 8

Anorexia Nervosa Item Numbers, Corresponding Interview Questions, and Scoring.

Item no.	Interview question	Number of participants endorsing the item
1[a]	Have you ever lost a lot of weight, that is > 15lb, either by dieting or without meaning to (not by having a baby or operation)?	550
2[a]	Did relatives or friends ever say you were much too thin or looked like a skeleton?	470
3 BMI[b]	What is the lowest weight you ever dropped to/ Had after age 14 (for women, was the weight < 125 lb)? How tall were you then? BMI ≤18.5	311
4	At that time, when your weight was at its lowest Or other people said that you were too thin, were you afraid that you'd regain the weight?	168
Items 5 – 8 being with the stem: "When your weight was at its lowest or other people said you were too thin…"		
5	…did you still think you were too fat?	87
6	…did you still think some parts of your body were too fat?	115
7	…did your weight affect how you felt about yourself?	231
8	…did others tell you that your weight was a hazard to your health?	132
9	Did you ever miss three menstrual periods in a row around the time that you were losing weight/had low weight?	73

BMI, body mass index.

[a] If participants endorsed neither item 1 nor item 2, they skipped to the next section of the interview.

[b] If participants endorsed either item 1 or 2 but did not report a low weight < 125 lbs, they skipped to the next section of the interview.

Obsessive Compulsive Personality Disorder

Frequencies of the possible OCPD composite scores are reported in Table 9; the number of participants endorsing each item is presented in Table 10. There were no skip patterns in the interview questions; thus all participants answered each of the eight items. Due to low OCPD prevalence, and based on a previous study by Reichborn-Kjennerud et al. (2007) using the same sample, the upper three categories for the total composite score were collapsed, resulting in seven categories (0 – 6).

Table 9

Anorexia Nervosa and Obsessive Compulsive Personality Disorder Item Composite Score Frequency.

	AN	OCPD
Composite Score	Number of participants obtaining score	Number of participants obtaining score
0	52	360
1	112	334
2	115	296
3	61	230
4	43	107
5	22	70
6	25	22*
7	22	6*
8	13	2*
Missing**	965	3

Note: * indicates that these categories were combined. ** participants were scored as missing if they responded "no" to either of the gateway items for AN because they would not have been asked the additional AN items.

Table 10

Obsessive Compulsive Personality Disorder Item Numbers, Corresponding DSM-IV Criteria, and Participant Endorsement.

Item no.	*DSM-IV* criteria	Number of participants meeting criteria
1	Is preoccupied with details rules lists, order, organization or schedules to the extent that the major point of the activity is lost	178
2	Shows perfectionism that interferes with task completion	384
3	Is excessively devoted to work and productivity to the exclusion of leisure activities and friendships	326
4	Is over conscientious, scrupulous, and inflexible about matters of morality, ethics or values (not accounted for by cultural or religious identification)	240
5	Is unable to discard worn-out or worthless objects even when they have no sentimental value	254
6	Is reluctant to delegate tasks or to work with others unless they submit to exactly his or her way of doing things	460
7	Adopts miserly spending style toward both self and others; money is viewed as something to be hoarded for future catastrophes.	130
8	Shows rigidity and stubbornness	601

Twin Analyses

Biometric Genetic Models. Prior to conducting all modeling analyses, within-twin and cross-twin polychoric correlations for AN and OCPD were examined (see Table 11). Polychoric correlations were calculated using the liability threshold model, which assumes that the liability for a certain trait (i.e., AN or OCPD) is normally or approximately distributed within the population, and that only individuals exceeding a certain threshold of liability will express the trait. As shown in Table 11, within-twin pair correlations for each disorder were higher in MZ than DZ twins. These estimates provide some preliminary evidence for a genetic component to the development of AN and OCPD (as the MZ twin correlation is greater than twice the DZ correlation). However, it should be noted that the confidence intervals for the correlations are wide for both AN and OCPD. Thus, these findings require replication before making definitive interpretations regarding liability to these disorders.

The within-twin correlations for AN and OCPD indicated that AN is associated with OCPD but that the magnitude of this correlation is small with wide confidence intervals including zero for DZ twins. The cross-twin cross-trait correlations were similar for MZ and DZ twins, with overlapping confidence intervals, suggesting that the association between AN and OCPD in not largely explained by genetic factors.

Table 11

Polychoric Correlations (95% confidence interval) for MZ and DZ Twins.

	Twin One		**Twin Two**	
	AN	OCPD	AN	OCPD
Twin One				
AN	1	0.12 (-0.10-0.33)	0.08 (-0.30-0.42)	-0.05 (0.30-0.19)
OCPD	0.02 (-0.15-0.19)	1	-0.05 (-0.27-0.19)	0.12 (-0.02-0.24)
Twin Two				
AN	0.25 (-0.03-0.48)	0.03 (-0.15-0.21)	1	0.03 (-0.2-0.27)
OCPD	-0.03 (-0.20-0.14)	0.25 (0.15-0.34)	0.13 (0.01 – 0.26)	1

Note: MZ twin correlations are below the diagonal and DZ twin correlations are above the diagonal. AN = anorexia nervosa. OCPD = obsessive compulsive personality disorder.

Considerations Regarding These Modeling Analyses

It should be noted that in the following analyses of AN and OCPD, the phenotypes of interest were endorsed on a relatively infrequent basis. Given the relatively low power of this study, current results should be viewed as preliminary. Larger population-based samples are needed to make definitive conclusions regarding the specific nature of the individual and shared liability to these phenotypes.

Univariate Analyses

Anorexia nervosa. Table 12 presents a summary of model fit statistics as well as parameter estimates for the univariate model of AN. Parameter estimates for the unconstrained ACE model indicate that 18% (95% CI = 0, 47) of the variance in this latent trait was influenced by additive genetic effects, 6% (95% CI = 0, 37) by common environmental factors, and 76% (95% CI = 53, 99) by unique environmental factors and error.

Comparing reduced models indicated that the fit of the CE model was not significantly different from that of the ACE model ($\Delta\chi^2(1) = 0.59$, $p > .05$). The fit of the AE model was also not significantly different from the full model ($\Delta\chi^2(1) = 0.09$, $p > .05$). Further, the fit of the E model was not significantly different form the full model ($\Delta\chi^2(2) = 3.08$, $p > .05$). According to the AIC values, the AE model provided the best fit to the data, indicating that additive genetic and nonshared environmental factors most strongly influence liability to excessive exercise. However, given the small sample size, low phenotypic prevalence of AN, and the wide confidence intervals for the parameter estimates, results from the full model should also be considered (Sullivan & Eaves, 2002).

Obsessive Compulsive Personality Disorder. Results of the univariate model of OCPD are also presented in Table 12. Parameter estimates for the ACE model indicated that 13% (95% CI = 0, 29) of the variance in the latent trait was influenced by additive genetic effects, 12% (95% CI = 0, 24) by common environmental factors, and 75% (95% CI = 67, 85) by unique environmental factors and error. Submodel comparisons indicated that the fit of the CE model was not significantly different from that of the ACE model ($\Delta\chi^2(1) = 2.6$, $p > .05$). The fit of the AE model was also not significantly different from that of the full model ($\Delta\chi^2(1) = 0.08$, $p > .05$). However, the fit of the E model was significantly worse than that of the full model, ($\Delta\chi^2(2) = 27.01$, $p < .01$), suggesting evidence of familial aggregation in liability to this phenotype. Due to insufficient data, it cannot be determined whether additive genetic effects, common environmental effects, or both are responsible for the origin of OCPD. However, the CI for E did not include 1.0, indicating that unique environmental influences do not alone explain the etiology of OCPD. According to the AIC values, the full ACE model provided the best fit to the data.

Table 12

Parameter Estimates and Fit Statistics for Univariate Models of AN and OCPD.

	a^2 95% CI	c^2 95% CI	e^2 95% CI	-2lnL	df	Δ χ2(df)	AIC
anorexia nervosa							
ACE	0.18 (0.0 – 0.47)	0.06 (0.0 – 0.37)	0 .76 (0.53 – 1.00)	1747.84	419	---	909.84
AE*	**0.24 (0.0 – 0.47)**	**---**	**0 .75 (0.53 – 1.00)**	**1747.94**	**420**	**0.10(1)**	**907.94**
CE	---	0.18 (0.00 – 0.38)	0 .82 (0.62 – 1.00)	1748.84	420	0.59(1)	908.43
E	---	---	1.00 (-1.00 – 1.00)	1705.91	421	3.07(2)	908.91
obsessive compulsive personality disorder							
ACE*	**0.13 (0.0 – 0.29)**	**0.12 (0.00 – 0.24)**	**0 .75 (0.66 – 0.85)**	**4893.11**	**1400**	**---**	**2093.11**
AE	0.25 (0.15 – 0.34)	---	0 .75 (0.67 – 0.85)	4896.21	1401	3.09(1)	2094.21
CE	---	0.20 (0.12 – 0.28)	0.80 (0.72 – 0.88)	4895.72	1401	2.60(1)	2093.72
E	---	---	1.00 (-1.00 – 1.00)	4920.21	1402	27.10 (2)	2116.21

Note. A = additive genetic effects. C = common environmental effects. E = unique environmental effects and error. * denotes best fitting model.

Bivariate Twin Analyses

Bivariate twin modeling was used to quantify the sources of variation in liability to AN and OCPD. In this type of model, sources of variation are estimated for both AN and OCPD, yielding two sets of estimates of a^2, c^2, and e^2 (Kendler, 1993; Neale & Cardon, 1992). Three independent correlations corresponding to the degree of overlap between a^2, c^2, and e^2 for variable one and a^2, c^2, and e^2 and for variable two (r_a r_c r_e in Figure 3) were calculated. These correlations reflect the degree of covariation between the additive genetic factors, common environmental factors, and unique environmental factors, respectively, that influence liability to AN and OCPD. Mx was used to perform a bivariate Cholesky decomposition (Neale & Cardon, 1992); the input data were polychoric correlation matrices and the associated asymptotic weighted least squares matrices (Joreskog & Sorebom, 1993). Mx was also used to calculate the 95% confidence intervals for these parameters.

Results for the bivariate analyses of AN and OCPD are shown in Table 13 and Figures 4 and 5. In addition to the full model, nine sub-models were tested. Only one model (X) offered a significantly worse fit than the full model. In cases where the chi-square test statistic indicated that all models adequately fit the data, the AIC value was used to determine the best fitting model. The best-fitting and most parsimonious model was the AE-AEr_e (VII). In this model, the majority of the variance for both AN and OCPD is accounted for by nonshared environmental factors and error (76% and 74%, respectively), with the remaining variance accounted for by additive genetic effects. Figure 5 shows the path coefficients for the best fit model with 95% confidence intervals. The parameter estimates for the two different disorders can be calculated from the path coefficients. For AN, a^2 was 0.23 (0.48^2) and e^2 was 0.76 (0.87^2). For OCPD, a^2 was 0.26 (0.51) and e^2 was 0.74 (0.08^2+.0.86^2).

In the best fitting model, the nonshared environmental liabilities for AN and OCPD are very weakly correlated (r_e = 0.08; 95% CI: -0.03, 19), which suggests a very small overlap in the nonshared environmental liability to the two phenotypes. It should be noted that the confidence intervals on the r_e parameter estimate included zero, making definitive interpretation difficult. Models setting a correlation between additive genetic factors and common environmental factors of the two behaviors (i.e. r_a r_e) did not fit the data as well, suggesting that common genetic and environmental risk factors between the two phenotypes are largely absent. Due to the relatively small sample, low item endorsement and subsequent limited power, the full ACE-ACE r_a r_c r_e model (Figure 5) should be considered (Sullivan & Eaves, 2002). The path coefficients for the full model are shown in Figure 5.

Table 13

Bivariate Model Fit Statistics for AN and OCPD.

Model no.	Model	-2lnL	df	Δ χ2(df) *p*	AIC
I	ACE-ACE, r_a, r_c, r_e	6678.15	1858	----	2962.15
II	ACE-ACE, r_c, r_e	6678.16	1859	0.00(1) > 0.05	2960.16
III	ACE-ACE, r_a r_e	6678.17	1859	0.02(1) > 0.05	2960.17
IV	ACE-ACE r_e	6778.22	1860	0.07(2) > 0.05	2958.22
V	ACE-ACE	6680.37	1861	0.53 (3) > 0.05	2958.37
VI	AE-ACE r_e	6678.15	1861	0.07(3) > 0.05	2956.22
VII	**AE-AE r_e**	**6678.22**	**1862**	**0.02(4) > 0.05**	**2954.22**
VIII	AE- AE r_a r_e	6678.17	1861	0.02 (3) > 0.05	2956.17
IX	CE-CE r_c r_e	6681.93	1861	3.77(3) > 0.05	2990.84
X	E-E, r_e	6767.410	1877	29.81(6) < 0.05	3013.41

Note. AIC = Akiake's Information Criterion; -2lnL = -2 log likelihood, df = degrees of freedom; ACE = additive genetic, common environment, and unique environmental effects model; AE = additive genetic and unique environmental effects model; CE = common environmental effects model; E = unique environmental effects model.

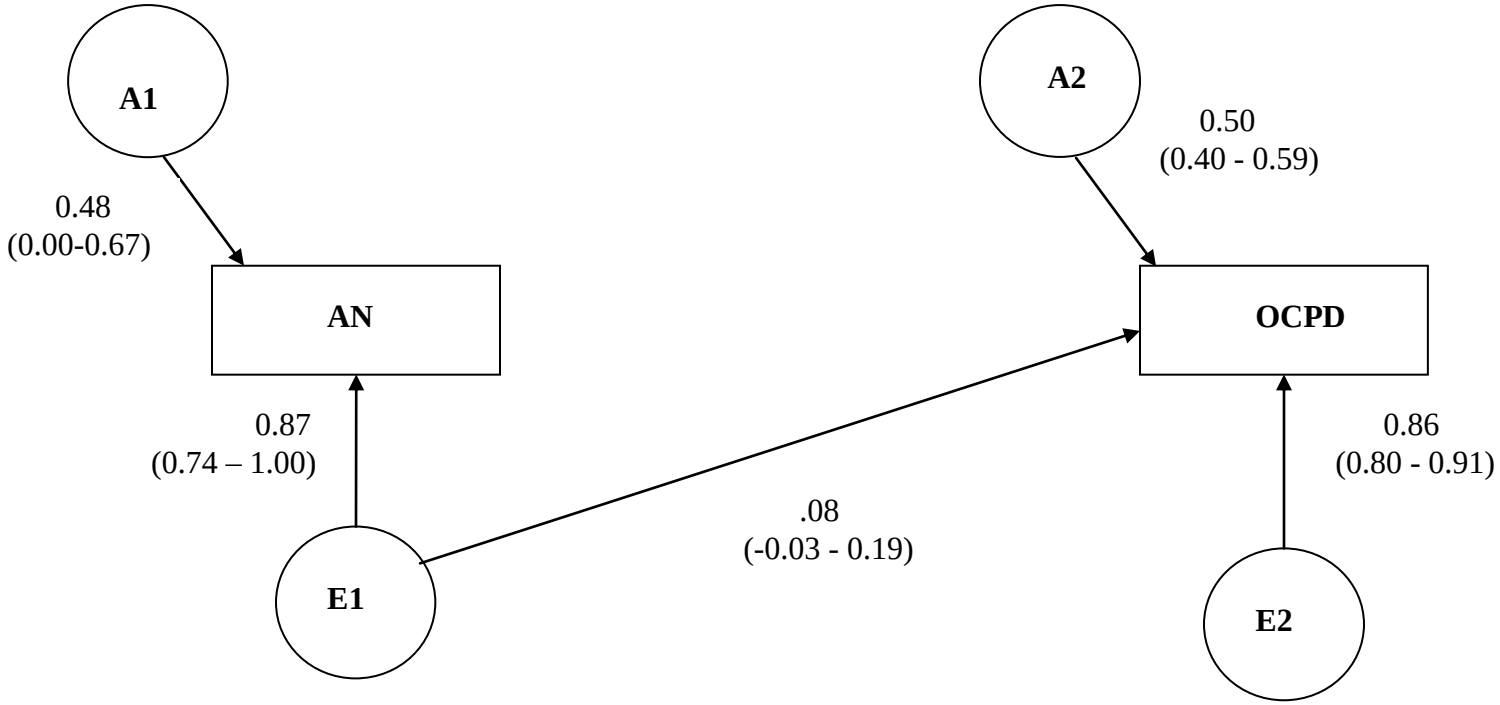

Figure 4. Best fit AE-AE r_e model (Model VII), Bivariate Cholesky, for AN and OCPD with path coefficients and 95% confidence intervals

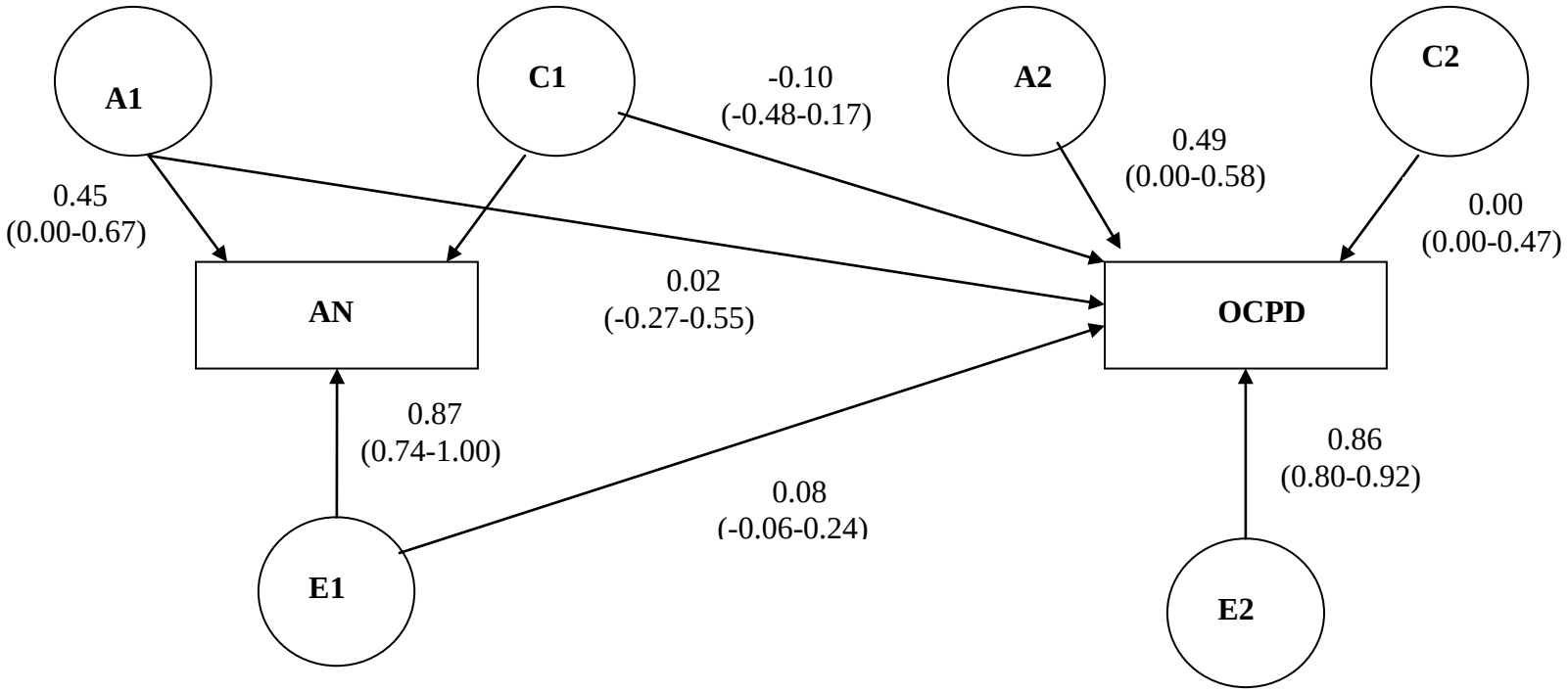

Figure 5. Full ACE-ACE r_a r_c r_e model (Model I), Bivariate Cholesky, for AN and OCPD with path coefficients and 95% confidence interval.

Additional Analyses

In the previous analyses the nature of the comorbidity between AN and OCPD was assessed using a dimensional approach, in which ordinal variables were based on the number of criteria endorsed for AN and OCPD. However, the relationship between these two variables was also investigated at a diagnostic level, according to *DSM-IV-TR* criteria (APA, 2000), using binary items for AN and OCPD. To meet diagnostic criteria for OCPD, individuals had to endorse at least four of the symptoms listed in Table 14, which is also consistent with the *DSM-IV-TR* (APA) criteria. Twenty-eight (2.0%) individuals met diagnostic criteria for AN and 33 individuals (2.3%) met criteria for OCPD. For AN, there was one concordant MZ pair and 0 concordant DZ pairs. There were no concordant MZ or DZ twin pairs for OCPD. Thus, due to sparse data, no univariate or bivariate modeling analyses were performed. Future analyses should investigate the co-morbidity of AN and OCPD at a diagnostic level in larger samples with more affected individuals.

Table 14

Criteria Used for AN Diagnosis.

Criteria/Item	Response to Meet Criteria
1a. What is the lowest weight you ever dropped to/ Had after age 14 (for women, was the weigh < 125 lb)?	1a. weight < 125lbs
1b. How tall were you then?	1b. BMI< 17.55
2. At that time, when your weight was at its lowest or other people said that you were too thin, were you afraid that you'd regain the weight?	2. yes
3. Items for criteria 3 began with the stem: "When your weight was at its lowest or other people said you were too thin…"	
3a …did you still think you were too fat?	
3b …did you still think some parts of your body were too fat?	
3c …did your weight affect how you felt about yourself?	
3d …did others tell you that your weight was a hazard to your health?	
	3. yes to one of 3a-3d
4. Did you ever miss three menstrual periods in a row around the time that you were losing weight/had low weight (or had your periods not begun by age 15)?	4. yes to either

Discussion

AN and OCPD are significant psychiatric health concerns (Lilenfeld et al., 1998; Dupont et al., 1995), which have been found to be strongly influenced by genetic factors (Hudziak et al., 2004; Pauls, 2008; Slof-Op't Landt et al., 1995). In addition, although estimates of co-morbidity between have varied widely, research has suggested that these disorders may be related through common etiopathogenic roots that underlie the obsessive-compulsive spectrum (Enoch et al., 1998; Kaye et al., 2004; Karwautz et al., 2001; Tchanturia et al., 2003). Thus, these disorders may reflect common psychological (Karwutz et al., 2001), neurobiological (Enoch et al., 1998), or genetic (Tchanturia et al., 2003) elements. The purpose of this investigation was to examine the nature of the comorbidity between AN and OCPD using biometric model fitting.

Univariate Analyses

Univariate analyses of AN revealed that an AE model best fit the data and that the heritability for this disorder was moderate (see Table 12). In this study, the heritability estimates for the full ACE are comparable to those found in a previous investigation by Mazzeo et al. (2007), which used the same sample. Employing an item-factor approach to assess the heritability of AN, Mazzeo et al. reported parameter estimates of 22% (95% CI: 0, 50) for a^2, 14% (95% CI: 0, 44) for c^2, and 64% (95% CI: 49, 79) for e^2. The estimates found in this study, as well as those found by Mazzeo et al., are lower than those obtained in a prior investigation examining the heritability of the full AN diagnosis (Bulik et al., 2006). They are also lower than those found in previous studies using broader definitions of AN (e.g. Wade et al., 2000; Klump et al., 2001; Koretegaard et al., 2001). Nonetheless, the estimates found in this study are within the confidence intervals found by Bulik et al. Inconsistencies in

heritability estimates across studies might be influenced by the use of different items and variable questionnaire formats (e.g., the presence or absence of gateway items). In addition, estimates of heritability are sample dependent and no one study can provide a definitive value regarding the heritability of AN. Thus, multiple studies, including this one, cumulatively inform knowledge regarding the genetic and environmental liability to AN.

This study is only the second known investigation to estimate the heritability of OCPD in a population based sample. Reichborn-Kjennerud et al. (2007) reported prevalence and heritability estimates of OCPD in a bivariate analysis of cluster C personality disorders. They found that the AE model best fit the data with a moderate heritability estimate of 0.26 (95% CI = 0.16, 0.30) and the remaining variance due to unique environmental factors. The current study used a subsample of the participants from the Reichborn-Kjennerud et al. study. Specifically, the Reichborn-Kjennerud study included both same and opposite sex twins and the present study only included female-female twins. Both the present study and the investigation by Reichborn-Kjennerud et al., used the number of subthreshold criteria (rather than the criteria at or above threshold) endorsed to create the dimensional OCPD variable.

Given that these two samples largely overlap and used identical definitions for OCPD, it is not surprising that similar heritability estimates were observed across investigations. In the present study, the AE univariate model also yielded a moderate heritability estimate of 0.25 (95% CI: 0.15, 0.34). The full ACE model, which was deemed the best fitting based on AIC values, yielded a lower heritability estimate (0.13; 95% CI: 0.0, 0.29) with the remaining variance attributable to C (0.12; 95% CI: 0.00, 0.24) and E (0.75; 95%CI: 0.66, 0.85). Overall, the findings of this study, in combination with those from Reichborn- Kjennerud et al. (2007), suggest a familial liability to OCPD, which may include

a moderate genetic component. These findings are consistent with previous research suggesting that genetic factors substantially contribute to obsessive compulsive symptoms (Cary & Grottesman, 1981; Jonnal et al., 2000; van Grootheest et al., 2008). The potential confound of assortative mating should also be considered when interpreting these results. Assortative matting occurs when individuals choose to mate with those who they resemble phenotypically (Crow & Felsenstein, 1968) and results in artificially inflated estimates of the shared environmental component and an underestimation of heritability. Assortative mating has been shown to take place with many other psychiatric disorders (Maes et al., 1998). Accounting for assortative mating requires additional data from the parents of probands, which was unavailable in this study. Thus, it is possible that assortative mating may have biased results, unduely inflating C and decreasing A. Additional studies examining the heritability of OCPD in large population-based samples are needed to replicate these findings.

Bivariate Analyses

Prior studies have suggested that there is an association between AN and OCPD (Herzog et al., 1992; Piran et al., 1988; Wonderlich et al., 1990). However, no other investigations have examined the extent to which genetic and environmental factors influencing liability to these two disorders are shared. This is the first known study to examine the nature of the comorbidity between AN and OCPD. For these data, an AE-AEr_e model fit best. These results indicated that additive genetic effects moderately contributed to both AN and OCPD individually, but that these genetic influences were not shared among the two disorders. Unique environmental effects and error accounted for the majority of the variance in both AN and OCPD. Surprisingly, this investigation found a very small

phenotypic correlation between AN and OCPD (0.08). This finding suggests that there is minimal overlap in the etiology of the two disorders, which was solely accounted for by unique environmental effects and error (r_e). These findings might represent the true nature of the relation between AN and OCPD; however, it is also possible that the very small phenotypic correlation may be due to low prevalence of these disorders in this relatively small sample. Although multiple attempts were made to maximize statistical power in this investigation (i.e. using a dimensional approach to creating variables, using subthreshold criteria for OCPD), one inherent difficulty in studying phenotypes with a low base rates is infrequent item endorsement, and subsequently low power. Although this study provides interesting preliminary information, larger population-based samples are needed to make definitive conclusions regarding the nature of the relation between AN and OCPD as well as the specific nature of any shared liability to these phenotypes.

Limitations

There were several limitations to this study that should be noted. First, measurement issues should be considered, particularly the use of gateway items for AN. Although the use of gateway items is useful for reducing participant burden, by definition, these items screen out the majority of the sample. Thus, heritability estimates of derived from studies using gateway items only assess this component of variance in individuals who have met these screening criteria. These individuals are likely to be substantively different from the total sample. The use of gateway items might also have lead to an underestimation of AN symptomatology, as AN symptoms are typically underreported by affected individuals (Wade, 2007). Thus, the cases of AN identified in this study might include more individuals with chronic or severe AN, rather than representing the full spectrum of this clinical

diagnosis. A second measurement limitation is that low weight participants were classified using a BMI of ⩽18.55. Thus, some individuals whose weight is in the low-average range might have been classified as underweight. However, because BMI is only one symptom of AN, this decision regarding BMI cut-offs mostly likely did not have a significant influence on the,bn results.

Another potential limitation is that, due to the low prevalence of individuals who meet diagnostic criteria for AN and OCPD, we examined dimensional representations of the *DSM-IV* (APA, 1994) diagnoses conceptualized as the number of criteria endorsed. As twin analysis are based on the liability threshold model (Falconer, 1965), it should have, in principle, made no difference if the variable studied was categorical or dimensional as long as the dimensional variable reflected the same underlying liability as the categorical diagnosis. However, it is important to consider the operational definition of the variables we used. Specifically, we were unable to examine the genetic and environmental contributions to AN and OCPD diagnoses due to insufficient data, a relied upon sum scores as the best alternative. However, sum scores have significant limitations, as was reviewed in Chapter Two (Neale et al., 2005). Future research on larger sample sizes or clinical populations is needed to examine genetic and environmental contributions to AN and OCPD diagnoses.

Another limitation of this study is that the twins in our sample were interviewed only once. Although we can demonstrate high inter-rater reliability in diagnoses, we can not estimate the test–retest reliability over time or the causal relations between these disorders. Previous studies have shown that the two-year test–retest reliability of OCPD is relatively low (McGlashan et al., 2000). In twin analyses, measurement errors are reflected in E, which implies that a reduction in reliability would result in attenuated heritability estimates.

Furthermore, analyses of sum scores might yield biased estimates of variance components of the latent trait. Thus, the analyses conducted might have been subject to these biases, which likely deflated the familial (A and C) and inflated the non-familial (E) components (Neale et al., 2005).

Another potential limitation of this study was the potentially confounding role of starvation on the severity of OCPD symptoms. As previously discussed, OCPD symptoms might be associated with greater AN severity due to decreased serotonin (Kaye et al., 1991). Thus, researchers have argued that OCPD symptoms might be secondary to AN. Because this study was cross-sectional, no hypotheses could be made about the temporal relation between AN and OCPD. Future studies should examine the associations between these variables using a longitudinal design.

In addition, because we used a sample of young Norwegian women, results from this investigation might not generalize well to other populations, including men or other ethnic groups. However, because of the extremely low prevalence of eating disorders, the likelihood of having a sample size large enough to have the power to conduct these analyses in minority populations is low. It is also possible that twins are different than singletons in their risk for either AN and OCPD. However, this question has been addressed in several studies, and results suggest that rates of psychopathology do not substantially differ between twins and singletons (Kendler, 1993).

Despite these limitations, this study has several strengths, including the use of a large population-based sample. In addition, this study was the first to investigate the nature of the comorbidity between AN and OCPD. Additional studies are needed in large population-based samples in order to clarify further the nature of the relation between the AN and OCPD

phenotypes. This research might have important implications for research and classification of eating disorders and diagnoses within the obsessive compulsive spectrum.

Conclusions

Over the last 25 years, research in the eating disorder filed has increased exponentially (e.g. Lacey & Crisp, Lowenkoph & Wallach, 1986; Miur et al., 1999; Taylor et al., 2006; Williams et al., 2008; Walsh, 2009). Important advances have been made in understanding the etiology of disordered eating, which suggest that genetics substantially influence etiology (Bulik et al., 2000; Lilenfeld et al., 1998, Slof-Op't Landt et al., 2005). Large population-based twin samples have allowed researchers to explore the genetic determinants of specific phenotypes including eating disorders (e.g. Bulik et al., 2006; Kortegaard et al., 2001; Klump et al., 2001; Mazzeo et al., 2008; Wade et al., 1999). In addition, advances in technology have facilitated research investigating the molecular genetics of disordered eating (Bulik et al., 2003; Devlin et al., 2002; Grice et al., 2002; Kaye et al., 2008; Nakabayashi et al., 2009).

The eating disorder classification system is currently in transition, with the anticipated release of the *DSM-V,* slated for 2012. Criticism of the current tripartite classification system has suggested that this system is suboptimal and based largely on clinical opinion and consensus rather than empirical data (e.g. Bulik et al., 2007; Chavez & Insel, 2007; Clinton & Noring, 2005). Advances in genetic epidemiological research are providing critical information that may impact future classifications of eating disorders. For example, in a 2007 article, Bulik et al. state that "Our basis is that refinements of the diagnostic criteria for eating disorders could be more richly informed by biology" (p.52). These authors further note that identifying core genetically influenced traits that underlie

diagnostic criteria for eating disorders could inform our understanding of these disorders. Research investigating new eating disorders presentations (such as PD, Keel et al.2004) and specific symptoms of eating disorders should also inform diagnosis and classification systems for these conditions (Mazzeo et al., 2007).

This dissertation attempted to address two "hot topics" in the area of eating disorders classification. Specifically, the first study assessed the prevalence and heritability of purging and PD, one of the newer eating disorder categories that is being considered for inclusion in *DSM-V* (Walsh, 2009). The second study addressed two diagnoses, which are thought to share core underlying traits (AN and OCPD). Although these investigations were limited by a number of factors, including sample size and low statistical power, their preliminary findings highlight the complexity of genetic epidemiological research and could pave the way for important future work in the field of disordered eating.

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APPENDIX A

Additional Analyses

1. Prevalence and heritability of purging disorder with diet pill use included as a purging behavior

2. Genetic and environmental contributions to anorexia nervosa and obsessive compulsive personality disorder at a diagnostic level.

Vita

Sara Elizabeth Trace was born on September 29, 1981 in Nashville, TN. She graduated from the Harpeth Hall School in Nashville, TN, in 2000. She received her Bachelor of Arts in Neuroscience from Bates College, Lewiston, Maine, in 2004 and her Masters of Science degree from Virginia Commonwealth University, Richmond, Virginia, in 2006. She completed her pre-doctoral clinical internship in the Department of Psychiatry at Yale University School of Medicine in 2009-1010. During her tenure as a graduate student she was funded on a T32 National Institute of Health training grant in t he department of Psychiatric and Behavioral Genetics. Subsequently, she was awarded the Ruth L. Kirschstein National Research Service Award (F31) for her project titled "The Heritability of Purging and Purging Disorder in a Sample of Female Twins." In addition, she has been awarded the department's Student Research Award as well as the annual award presented by the Health Division of APA's Counseling. In 2009, she was awarded an Academy of Eating Disorders young investigator's travel award. Sara will begin as a post-doctoral fellow in eating disorders in the Department of Psychiatry at the University of North Carolina at Chapel Hill in August 2010.