2009

DISORDERED EATING AND SUBSTANCE USE: A MULTIVARIATE LONGITUDINAL TWIN DESIGN

Jessica Baker
Virginia Commonwealth University

Follow this and additional works at: https://scholarscompass.vcu.edu/etd
Part of the Psychology Commons

© The Author

Downloaded from
https://scholarscompass.vcu.edu/etd/1853

This Dissertation is brought to you for free and open access by the Graduate School at VCU Scholars Compass. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of VCU Scholars Compass. For more information, please contact libcompass@vcu.edu.
DISORDERED EATING AND SUBSTANCE USE: A MULTIVARIATE LONGITUDINAL TWIN DESIGN

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

by

JESSICA H. BAKER
M.S., Virginia Commonwealth University, 2007
B.Sc., Michigan State University, 2003

Director: Kenneth Kendler, MD
Rachel Brown Banks Professor of Psychiatry, Department of Psychiatry

Co-Chair: Scott Vrana, PhD
Psychology Department Chair, Department of Psychology

Virginia Commonwealth University
Richmond, VA
May 2010
Acknowledgement

I wish to thank a number of people for helping me achieve the completion of this dissertation. First, I would like to acknowledge and thank my advisor and committee chair, Dr. Kenneth S. Kendler, for his advice, guidance, and mentoring throughout this project. I would also like to thank my co-chair Dr. Scott Vrana and committee members Dr.’s Suzanne Mazzeo, Dace Svikis, and Hermine Maes for their helpful comments and suggestions regarding this dissertation. In addition, I would like to thank Dr. Hermine Maes for her assistance and willingness to aid with any statistical questions. I also wish to thank Dr. Paul Lichtenstein for allowing me access to the data utilized. More personally, I would like to thank my friends for their support and helpful distractions during the completion of my dissertation.
Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acknowledgements</td>
<td>ii</td>
</tr>
<tr>
<td>List of Tables</td>
<td>xii</td>
</tr>
<tr>
<td>List of Figures</td>
<td>xiv</td>
</tr>
<tr>
<td>Chapter</td>
<td></td>
</tr>
<tr>
<td>1 Genetic Risk Factors for Disordered Eating in Adolescent Males and Females</td>
<td>3</td>
</tr>
<tr>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>Review of the Literature</td>
<td>4</td>
</tr>
<tr>
<td>Eating Disorders</td>
<td>4</td>
</tr>
<tr>
<td>Definition of Eating Disorders</td>
<td>4</td>
</tr>
<tr>
<td>Sex-differences in Eating Disorders</td>
<td>4</td>
</tr>
<tr>
<td>Genetic Risk for Eating Disorders</td>
<td>7</td>
</tr>
<tr>
<td>Sex-differences in the Genetic Risk for Eating Disorders</td>
<td>9</td>
</tr>
<tr>
<td>Structure of Eating Disorders</td>
<td>15</td>
</tr>
<tr>
<td>Study One Purpose Statement</td>
<td>15</td>
</tr>
<tr>
<td>2 Method</td>
<td>16</td>
</tr>
</tbody>
</table>
Participants

Measures

Eating Disorder Inventory-II

Statistical Analyses

Twin Methodology

Univariate Analyses

Sex-differences

Assumptions

Power

Twin Analyses

Univariate Model-fitting Analyses Examining Sex-differences

Multivariate Model-fitting Analyses

Results

Descriptive Statistics

Univariate Twin Analyses

Multivariate Twin Analyses
Specificity of Substance Use/Misuse .....................................................90
Developmental Trajectory ....................................................................92
Sex-differences .......................................................................................98
Study Limitations and Strengths ..........................................................100
Study Implications and Future Directions ............................................101

9 Examination of the Genetic Covariance Between Disordered Eating and Substance Use 104

Introduction ...........................................................................................104

Review of the Literature ........................................................................104

Eating Disorders and Substance Use/Misuse in Females .................104

Nicotine ..........................................................................................105

Alcohol ............................................................................................106

Illicit Drugs ......................................................................................106

Eating Disorders and Substance Use/Misuse in Males .....................108

Disordered Eating and Substance Use/Misuse ...............................109

Comorbidity Hypotheses .....................................................................110

Shared Etiology ..................................................................................110
List of Tables

Table 1: Twin Studies Examining Sex-differences in Disordered Eating ..................13
Table 2: Means, Standard Deviations and Intraclass Correlations for Disordered Eating.31
Table 3: Model-fitting Results from Univariate and Multivariate Twin Models. ..........34
Table 4: Parameter Estimates for Univariate Model of EDI Subscales .......................36
Table 5: Proportion of Variance Accounted for by Common and Specific Genetic and Environmental Factors in Females and Males from Multivariate Common Pathway Model ..................................................................................................................................41
Table 6: Frequency of Substance Use ....................................................................73
Table 7: Twin Correlations for Substance Use Across Waves ..................................75
Table 8: Results from Univariate Analyses of Substance Use Variables ..................77
Table 9: Model-fitting Results from Within wave Common and Independent Pathway Models ..................................................................................................................................................................77
Table 10: Estimates of and Sources for Additive Genetic Effects on Smoking, Alcohol, Intoxication, and Illicit Drug Use .................................................................................................................................83
Table 11: Estimates of and Sources for Shared Environmental Effects on Smoking, Alcohol, Intoxication, and Illicit Drug Use .................................................................86
Table 12: Estimates of and Sources for Unique Environmental Effects on Smoking, Alcohol, Intoxication, and Illicit Drug Use. .................................................................87

Table 13: Genetic and Environmental Effects on Common Factors in the Within Wave Common Pathway Models by Sex. ...............................................................88

Table 14: Mean Scores for EDI Subscales. .................................................................123

Table 15: Frequency of Subjects within Trichotomized EDI Subscales. ......................123

Table 16: Correlations Between EDI Subscales and Substance Use by Sex and Zygosity.127
List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1a</td>
<td>Independent pathway model</td>
<td>27</td>
</tr>
<tr>
<td>Figure 1b</td>
<td>Common pathway model</td>
<td>28</td>
</tr>
<tr>
<td>Figure 2</td>
<td>Genetic and environmental path estimates from multivariate common pathway</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>model including all five zygostiy groups</td>
<td></td>
</tr>
<tr>
<td>Figure 3</td>
<td>Genetic components of the full model fitted to self-report measures of nicotine,</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>alcohol intoxication, and illicit drug use at ages 13-14, 16-17, and 19-20.</td>
<td></td>
</tr>
<tr>
<td>Figure 4</td>
<td>Path estimates for multivariate longitudinal common pathway model</td>
<td>80</td>
</tr>
<tr>
<td>Figure 5</td>
<td>Path diagram of the decomposition of genetic and environmental covariance</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td>between disordered eating and substance use</td>
<td></td>
</tr>
<tr>
<td>Figure 6a</td>
<td>Bar graph of raw drive for thinness scores</td>
<td>124</td>
</tr>
<tr>
<td>Figure 6b</td>
<td>Bar graph of raw bulimia scores</td>
<td>125</td>
</tr>
<tr>
<td>Figure 6c</td>
<td>Bar graph of raw body dissatisfaction scores</td>
<td>126</td>
</tr>
<tr>
<td>Figure 7</td>
<td>Path diagram of the best-fitting model of the decomposition of genetic and</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>environmental covariance between disordered eating and substance use</td>
<td></td>
</tr>
</tbody>
</table>
Abstract

DISORDERED EATING AND SUBSTANCE USE: A MULTIVARIATE LONGITUDINAL TWIN DESIGN

By Jessica H. Baker, M.S.

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

Virginia Commonwealth University, 2009

Major Director: Kenneth S. Kendler
Director, Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry

Eating disorders and substance use disorders both exhibit a clear sex-difference in prevalence. Eating disorders are more common in females while substance use disorders are more common in males. Previous research has also established a strong association between these two disorders, especially within females. Much less research has
examined comorbidity in males. The etiology and reasons for these sex-differences and for the comorbidity of eating and substance use disorders remain unclear. The present report aimed to examine disordered eating (DE), substance use (SU), and their comorbidity further, in both sexes, using disorder eating attitudes and behaviors and substance use rather than diagnoses. DE was examined with the Drive for Thinness, Bulimia, and Body Dissatisfaction subscales of the Eating Disorder Inventory-II. Nicotine, alcohol, and illicit drug use was also assessed. Male and female twin pairs from The Swedish Twin study of CHild and Adolescent Development will be used which includes 1,480 twin pairs assessed at three age points; 13-14, 16-17, and 19-20. A twin design was utilized to examine important aspects of the genetic and environmental risk factors for DE, SU, and their comorbidity within three distinct studies. In Study I multivariate twin designs were used and revealed that an underlying common factor was responsible for the three facets of DE in both sexes at age 16-17. Sex-differences were exhibited within these genetic influences such that only 50% of the genetic risk for the DE factor is shared between the sexes. Total heritabilities for the three subscales were higher for females. In Study II a longitudinal, multivariate twin design was used and revealed that an underlying common factor was responsible for SU at all three assessment ages. In general, genetic effects became more substance specific, and common shared environmental effects decreased across the age groups. In Study III, the genetic and environmental covariance between the DE and SU common factors at age 16-17 was examined. The covariance between DE and SU was partly mediated through familial factors, and these factors impacted
covariance similarly in the sexes. Genetic and shared environmental factors each accounted for approximately 50% of covariance.
Introduction

Eating disorders and substance use disorders are associated with serious physical, psychological, and social impairments. Because of these impairments, it is pertinent that we learn as much as possible about the cause, treatment, and prevention of these disorders. Both of these disorders also have clear sex-differences in prevalence. Eating disorders are more common in females while substance use disorders are more common in males (American Psychiatric Association [APA], 2000). Research has also established a strong association between eating disorders and substance use disorders. These disorders frequency co-occur at rates higher than population base rates. Unfortunately, the etiology and reasons for the sex-differences and comorbidity of eating disorders and substance use disorders remains unclear.

Twin studies have identified genetic factors to contribute to the development of both eating disorders and substance use disorders (Agrawal & Lynskey, 2008; Bulik, Sullivan, Wade, & Kendler, 2000). Studies have also suggested possible sex-differences in the genetic risk factors for these disorders, which could explain the difference in prevalence’s between the sexes (Jang, Livesley, & Vernon, 1997; Keski-Rahkonen, Bulik et al., 2005). However, research examining sex-differences in the genetic risk factors for eating disorders and disordered eating are in its’ infancy. While more research has investigated these differences in substance use disorders, little has been conducted examining substance use and also utilizing adolescent samples.

The purpose of the present project is to further investigate the genetic risk factors for disordered eating and substance use utilizing an adolescent sample. The current
report includes three separate projects. First, there will be an examination of the genetic risk factors for three aspects of disordered eating (body dissatisfaction, bulimia, and drive for thinness) including an investigation of possible sex-differences in this genetic risk. The second project examines genetic risk factors for substance use across three separate time periods. There will also be an investigation of possible sex-differences in this genetic risk. Finally, the last project will be an examination of the comorbidity of disordered eating and substance use, examining for shared genetic risk factors and possible sex-differences in this shared genetic risk.
Chapter 1 Genetic Risk Factors for Disordered Eating in Adolescent Males and Females

Introduction

Eating disorders occur in approximately 0.5 to 3% of the population with more females than males being diagnosed (APA, 2000; Striegel-Moore, Garvin, Dohm, & Rosenheck, 1999). Previously, the female to male ratio of eating disorder diagnoses in nonclinical populations has been estimated at 10:1 (APA, 2000). However, recent research indicates a lower sex-difference in eating disorder risk, with a female to male ratio of 4:1 for anorexia nervosa (Woodside et al., 2001). New data also suggests that up to 25% of adults with eating disorders are male (Hudson, Hiripi, Pope, & Kessler, 2007).

This sex-difference in eating disorder risk has been attributed to both environmental and genetic factors including sociocultural pressures to be thin in females (Andersen & Holman, 1997; Ricciardelli & McCabe, 2004; Stice, 1994; Striegel-Moore, Silberstein, & Rodin, 1986) and reproductive hormones (Edler, Lipson, & Keel, 2006; Klump, Burt, Sisk, & Keel, 2007; Klump et al., 2005; Klump, Keel, Culbert, & Edler, 2008; Klump, Miller, Keel, McGue, & Iacono, 2001). Males may also have a higher threshold for exhibiting an eating disorder. For example, binge eating may be a more normative behavior in males, especially during adolescence. Males are also less likely to label the consumption of large quantities of food a “binge” and to report feeling out of control during consumption (Carlat & Camargo, 1991; Franco, Tamburino, Carroll, & Bernal, 1988; Katzman, Wolchik, & Braver, 1984; Lewinsohn, Seeley, Moerk, & Striegel-Moore, 2002).
Despite previous research, it is still unclear whether fewer males develop an eating disorder because they are exposed to less societal pressures to be thin or whether they have a biological protection against developing an eating disorder (Andersen, 1999). Thus, the objective of the current study is to examine the genetic and environmental influences on aspects of disordered eating in males and females to assess whether the same genetic risk factors are at play.

Review of the Literature

Eating Disorders

Definition of Eating Disorders

Eating disorders, including bulimia nervosa (BN), anorexia nervosa (AN), and eating disorder not otherwise specified (EDNOS), are characterized by aberrant eating and weight regulation behaviors and disturbances in attitudes about weight, body shape, and perceptions of body shape. Central to AN is an irrational fear of weight gain and an unwavering obsession with being thin. To obtain a diagnosis of AN, an individual must also only weigh less than 85% of their ideal body weight. BN is characterized by binge eating followed by compensatory behaviors (i.e. self-induced vomiting, laxative use, fasting) that are aimed at riding the body of the excess food (APA, 2000). EDNOS is an eating disorder diagnostic category for disorders of that that do not meet specific criteria for AN or BN and includes binge eating disorder (APA, 2000).

Sex-differences in the Eating Disorders

Until recently, the development of an eating disorder in males and differences between males and females with these disorders received little attention in the literature.
Most of the research that was conducted focused on individual cases or small clinical sample populations, combining afflicted males of all ages (Rosen, 2003). Currently, research has shifted to focus on larger community based samples of males to examine etiologic factors. In fact, this recent work has revealed some unsettling trends and has increased interest in male body image and eating disturbances. For example, a condition referred to as “reverse anorexia nervosa” or “muscle dysmorphia” has been described in males, in which muscular men perceive themselves as thin and underdeveloped (Pope, Gruber, Choi, Olivardia, & Phillips, 1997; Pope, Katz, & Hudson, 1993). The distorted body perceptions of males with muscle dysmorphia are strikingly analogous to females diagnosed with AN although they display a primary focus on exercise and a secondary focus on dieting (Pope et al., 1997).

Existing research also indicates that males and females with an eating disorder display more similarities than differences. In fact, research examining subjects with an eating disorder diagnosis indicates eating disorders in males are clinically analogous to those in females (Bosch-Bramon, Troop, & Treasure, 2000; Braun & Sunday, 1999; Carlat, Camargo, & Herzog, 1997; Eliot & Baker, 2001; Geist, Heinmaa, Katzman, & Stephens, 1999; Margo, 1987; Olivardia, Pope, Mangweth, & Hudson, 1995; Scott, 1986; Sharp, Clark, Dunan, Blackwood, & Shapiro, 1994; Sterling & Segal, 1985; Woodside et al., 2001). The clinical presentation and course, symptomatology, medical complications, and prognosis have all shown to be comparable (Rosen, 2003). However, males have a higher prevalence of over exercise and a lower prevalence of dieting and other
compensatory behaviors compared to females (Anderson & Bulik, 2004; Lewinsohn et al., 2002; Schneider & Agras, 1987; Sharp et al., 1994).

Similarities in males and females have also been revealed in the risk for eating disorders and disordered eating. Analogous to the aforementioned studies, these studies typically report similar patterns and risk (Croll, Neumark-Sztainer, Story, & Ireland, 2002; Keel, Klump, Leon, & Fulkerson, 1998; Kinzl, Mangweth, Traweger, & Biebl, 1997; Muise, Stein, & Arbess, 2003; Neumark-Sztainer & Hannan, 2000; Olivardia et al., 1995; Pope, Hudson, & Jonas, 1986; Slane, Burt, & Klump, 2007; Woodside et al., 2001). For example, body mass index, negative effect, and societal pressure to be thin have been shown to be associated with the development of disordered eating and eating disorders in both females (for review see Jacobi, Hayward, de Zwaan, Kraemer, & Agras, 2004) and males (for review see Ricciardelli & McCabe, 2004). However, similarities between males and females could also reflect a common sequelae of starvation and malnutrition rather than similarity in premorbid factors (Rosen, 2003).

Body dissatisfaction is often a central feature of eating disorders and research demonstrates an association between body dissatisfaction and disordered eating and eating disorders in males (Keel, Fulkerson, & Leon, 1997; Keel et al., 1998; Leon, Fulkerson, Perry, & Early-Zald, 1995; McCabe, Ricciardelli, & Finemore, 2002; Olivardia et al., 1995; Ricciardelli & McCabe, 2001, , 2004). However, the manifestation appears to be different. Males tend to be more dissatisfied with their bodies when they are underweight or overweight and most happy when they are average, compared to females who are happiest with their bodies when underweight (Cohane & Pope, 2001;
Presnell, Bearman, & Stice, 2004; Ricciardelli & McCabe, 2001). Despite this difference, body dissatisfaction has been shown to predict bulimic behavior in males regardless of whether the male desires a smaller or bigger (i.e. more muscular) body (Ricciardelli & McCabe, 2001). It is still unclear however, whether body dissatisfaction is a risk for an eating disorder or a prodromal symptom.

Finally, some important differences in risk for an eating disorder have also been found. Homosexuality appears to be exclusively associated with eating disorder development in males and premorbid obesity is also more frequently seen in males with an eating disorder (Bosch-Bramon et al., 2000; Carlat et al., 1997; Carlat & Camargo, 1991; Franco et al., 1988; Ricciardelli & McCabe, 2004; Russell & Keel, 2002; Schneider & Agras, 1987; Sharp et al., 1994).

Genetic Risk for Eating Disorders

Multiple studies have been conducted to examine whether familial factors impact on risk for the development of an eating disorder. This is typically examined through family, twin, and adoption studies. Family studies investigate whether eating disorders aggregate within families while adoption and twin studies can assess the degree to which the familial influences on eating disorders result from genetic or shared environmental factors. They studies can also estimate the relatives magnitude of these effects. To date, no adoption studies have been utilized.

Cumulative evidence from twin studies indicates a genetic influence on the pathogenesis of eating disorders in females (Bulik et al., 2000; Klump, Kaye, & Strober, 2001). Heritability estimates for AN have varied between 22% and 76% (Bulik et al.,
2006; Klump, Miller et al., 2001; Mazzeo et al., 2008; Wade, Bulik, & Kendler, 2000) while estimates for BN vary between 54% and 83% (Bulik, Sullivan, & Kendler, 1998; Bulik et al., 2000; Kendler et al., 1991; Kendler et al., 1995). Although these results have been somewhat inconsistent in the estimated heritabilities, it does appear both AN and BN have a genetic component (Fairburn, Cowen, & Harrison, 1999).

According to these same studies, unique environment (which reflects those experiences that make twins dissimilar) is more important than shared environment (which results from environmental experiences that make twins similar (Kendler & Prescott, 2006). However, given the wide estimates for confidence intervals for shared environment in these studies, we cannot eliminate it definitively as an influence on eating disorder development (Bulik et al., 2000).

Finally, one of the aforementioned twin studies deserves special attention because the authors conducted a twin measurement model which allows for the correction of measurement error (Bulik et al., 1998). This is accomplished by incorporating more than one measurement occasion into the standard twin model. Results indicate the magnitude of unique environment is lowered when unreliability of measurement is controlled for.

Further supporting the heritability of eating disorders, research indicates that disordered eating attitudes and behaviors also have a heritable component. Heritabilities for binge eating, self-induced vomiting, and dietary restraint are between 46% and 72% in females (Klump, Kaye et al., 2001; Klump, McGue, & Iacono, 2000; Neale, Mazzeo, & Bulik, 2003; Sullivan, Bulik, & Kendler, 1998). Specific eating attitudes and behaviors that have been shown to be important risk factors for the development of an
eating disorder in females are also influenced by genetic effects. For example, research has shown body dissatisfaction and weight preoccupation to precede the development of an eating disorder in females (Jacobi et al., 2004; Patton, 1988) and twin studies have found that 32% to 72% of the variance in body dissatisfaction, eating and weight concerns, and weight preoccupation can be attributed to genetic factors (Klump, Kaye et al., 2001; Klump, McGue et al., 2000; Wade, Martin, & Tiggemann, 1998; Wade, Wilkinson, & Ben-Tovim, 2003).

**Sex-differences in the Genetic Risk for Eating Disorders.** Extensive research has attempted to tease apart the contribution of psychological and social factors to sex-differences in risk for eating disorders. An alternate approach is to examine for the existence and nature of sex-differences in genetic risk. The manifestation and risk for eating disorders may be analogous in the sexes however; there may be a biological explanation as to why females are more susceptible. Using this approach we are able to assess whether the genetic factors influencing the development of an eating disorder in males and females are the same or at least partially distinct. Genetic studies of eating disorders in males are in their infancy, as are studies investigating possible genetic differences between the sexes for the risk of an eating disorder.

As seen in Table 1, we are aware of eight studies examining the heritability of disordered eating in males; seven of which include a female comparison group (Eiben, 2007; Keski-Rahkonen, Bulik et al., 2005; Keski-Rahkonen, Neale et al., 2005; Reichborn-Kjennerud et al., 2003; Reichborn-Kjennerud, Bulik, Kendler et al., 2004; Reichborn-Kjennerud, Bulik, Tambs, & Harris, 2004; Slane et al., 2007; Tholin,
Rasmussen, Tynelius, & Karlsson, 2005). While the results of these studies are somewhat discrepant, the most consistent finding is lower heritability estimates for males compared to females.

For example, two studies examined aspects of body dissatisfaction and drive for thinness and showed lower heritability estimates for males (Eiben, 2007; Keski-Rahkonen, Bulik et al., 2005). However, results are discrepant between these studies with regard to environmental factors. Results revealed by Eiben (2007) suggest genetic and shared environmental factors are important for males while results by Keski-Rahkonen and colleagues (2005a) suggest no genetic influence, only shared and unique environmental. Specifically, Eiben reports heritability estimates for body dissatisfaction at 37% and 58% and at 23% and 41% for drive for thinness in males and females, respectively. Lower heritabilities have also been exhibited for a measure of intentional weight loss in males (38% vs. 66%). However, no shared environmental factors were indicated for males (Keski-Rahkonen, Neale et al., 2005). Finally, examining aspects of cognitive restraint, emotional eating, and uncontrolled eating heritability estimates ranged from 45-60% in males while shared environment was not shown to contribute to eating behavior (Tholin et al., 2005). However, no female comparison group was utilized.

Inconsistencies could be because of two main factors. First, only two of the aforementioned studies utilize the same assessment instrument (Eiben, 2007; Keski-Rahkonen, Bulik et al., 2005), making comparisons across studies difficult. However, even these two studies show discrepant results. This may be because authors scored their
measures of disordered eating differently. The age of these samples also varies, ranging from adolescence to adulthood.

The abovementioned studies also have one major limitation: they fit twin models to male and female data separately and compared parameter estimates by inspection. This approach does not permit for a rigorous examination of quantitative or qualitative sex-differences because it does not utilize sex-limitation twin models. Quantitative effects answers the question as to whether genetic factors are more important for the etiology of disordered eating in males or females (Kendler & Prescott, 2006). While it is possible to fit quantitative models with only same-sex twin pairs, opposite-sex twin pairs are needed to examine for qualitative effects. Qualitative effects examine whether the same genes are involved in the etiology of disordered eating in the sexes (Kendler & Prescott, 2006).

Four studies have examined quantitative or qualitative sex-effects (Reichborn-Kjennerud et al., 2003; Reichborn-Kjennerud, Bulik, Kendler et al., 2004; Reichborn-Kjennerud, Bulik, Tambs et al., 2004; Slane et al., 2007). Two studies by Reichborn-Kjennerud and colleagues (2003; 2004) examined quantitative and qualitative sex-effects on binge eating. The first examination showed no quantitative effects (i.e. the magnitude of the genetic and environmental effects were the same in male and females). However, results indicated qualitative effects (Reichborn-Kjennerud et al., 2003). This suggests the genetic factors influencing binge eating are not entirely the same in both sexes. In the follow-up examination however, excluding those individuals who report compensatory behaviors, no quantitative or qualitative sex-differences were exhibited (Reichborn-Kjennerud, Bulik, Tambs et al., 2004). Similarly, Slane and colleagues (2007) reported
no quantitative sex-differences on the facets of weight preoccupation and binge eating. Quantitative effects were however, indicated for body dissatisfaction, with females having a higher heritability (Slane et al., 2007). Finally, one additional study revealed no quantitative or qualitative sex-effects on a measure of the influence of weight on self-evaluation (Reichborn-Kjennerud, Bulik, Kendler et al., 2004).

Taken together, results appear somewhat inconsistent. While most of the previous studies indicate lower heritability estimates for males compared to females, results in regard to environmental influences are discrepant. Some studies suggest both genetic and shared environmental factors to be important for males while others indicate only environmental factors are of importance. In sum however, results from the studies reviewed suggest that environmental factors are more important for aspects of body dissatisfaction and drive for thinness in males. Studies also suggest similar heritability estimates in males and females for binge eating.
<table>
<thead>
<tr>
<th>Author</th>
<th>Sample Size</th>
<th>Age</th>
<th>Disordered Eating Examined</th>
<th>Sex-effects</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eiben et al., unpublished*</td>
<td>864 MZ; 723 DZ twins</td>
<td>16-17-years-old</td>
<td>Body dissatisfaction, drive for thinness, bulimia from Eating Disorder Inventory</td>
<td>Comparison of male/female parameter estimates</td>
<td>Lower heritabilities and higher shared environmental estimates for males compared to females on all measures</td>
</tr>
<tr>
<td>Keski-Rahkonen, Bulik et al., 2005€</td>
<td>1,408 MZ; 1,470; DZ twins</td>
<td>22-27-years-old</td>
<td>Body dissatisfaction and drive for thinness from Eating Disorder Inventory</td>
<td>Comparison of male/female parameter estimates</td>
<td>Only environmental factors indicated for males on all measures</td>
</tr>
<tr>
<td>Keski-Rahkonen, Neale et al., 2005€</td>
<td>1,408 MZ; 1,470; DZ twins</td>
<td>22-27-years-old</td>
<td>Intentional weight loss</td>
<td>Comparison of male/female parameter estimates</td>
<td>Lower heritability for males compared to females on all measures. No shared environment indicated for males</td>
</tr>
<tr>
<td>Reichborn-Kjennerud, Bulik, Kendler et al., 2004¥</td>
<td>8,045 same and opposite-sex twins</td>
<td>18-31-years-old</td>
<td>Influence of weight on self-evaluation</td>
<td>Qualitative/quantitative sex-limitation twin modeling</td>
<td>No sex-differences</td>
</tr>
<tr>
<td>Reichborn-Kjennerud, Bulik, Tambs et al., 2004¥</td>
<td>8,045 same and opposite-sex twins</td>
<td>18-31-years-old</td>
<td>Binge eating absent of compensatory behaviors</td>
<td>Qualitative/quantitative sex-limitation twin modeling</td>
<td>No sex-differences</td>
</tr>
</tbody>
</table>
Reichborn-Kjennerud et al., 2003
8,045 same and opposite-sex twins
18-31-years-old
Binge eating
Qualitative/quantitative sex-limitation twin modeling
Qualitative effects

Slane et al., 2007
168 male; 292 female twins
Mean age of 20
Binge eating, body dissatisfaction, weight preoccupation from MEBS
Quantitative sex-limitation twin modeling
Quantitative effects for body dissatisfaction

Tholin et al., 2005
456 MZ; 326 DZ male pairs
23-29-years-old
Cognitive restraint, emotional eating, uncontrolled eating
None; only a male sample utilized
Heritabilities ranging from 45-60%

Note. MZ = monozygotic. DZ = dizygotic. MEBS = Minnesota Eating Behaviors Survey. * = Results obtained from the same twin sample used in the current study. € = Both studies utilized the same twin sample. ¥ = These three studies utilized the same twin sample.
Structure of Disordered Eating

To our knowledge, only two previous studies have examined the factor structure of the genetic and environmental influences on disordered eating (Neale et al., 2003; Wade et al., 1999). No study as examined for sex-differences in this factor structure. Results indicate a common latent factor is largely responsible for the genetic influences on disinhibition (i.e. disinhibition of control of eating in response to a variety of cues) and hunger in females, while restraint is largely distinct (Neale, Mazzeo, & Bulik, 2003). Examining the covariation between three assessments of disordered eating (i.e. self-report, semi-structured psychiatric interview, semi-structured ED interview); a single underlying latent factor was also found to explain covariance (Wade et al., 1999).

Taken together, results indicate genetic factors likely play a role in the etiology of disordered eating in males and females. However, it is still unclear whether the same genetic factors are at play. The structure of the genetic and environmental influences on disordered eating is also unclear. Specifically, it is not well known whether there is a common underlying liability to the symptoms of disordered eating or whether distinct genetic factors influence symptoms. It is also unknown whether this possible underlying liability differs between males and females.

Study One: Purpose Statement

The purpose of this investigation is to answer the following questions: (a) are there quantitative and qualitative sex-differences in the genetic risk factors for aspects of body dissatisfaction, drive for thinness and bulimia, (b) is there a single latent factor
responsible for the development of these three facets of disordered eating and, (c) are there sex-differences in the genetic and environmental risk factors on this latent factor?

From previous research three hypotheses can be made. First, quantitative and qualitative sex-differences will be exhibited for body dissatisfaction and drive for thinness. Second, a single latent factor will be responsible for the development of these facets of disorders eating. Finally, quantitative and qualitative sex-differences in genetic and environmental risk will be exhibited on this single latent factor.
Chapter 2 Method

Participants

Participants for the current study have been drawn from The Swedish Twin study of CHild and Adolescent Development (TCHAD). TCHAD includes 1,480 twin pairs followed since 1994 (Lichtenstein, Tuvblad, Larsson, & Carlstrom, 2007). The current sample includes 246 and 238 monozygotic (MZ), 181 and 169 dizygotic (DZ) female-female and male-male twin pairs respectively, and 366 opposite-sex twin pairs. So far twins have gone through four waves of data collection. The last data collection, wave 4, was in 2005 and at this time the twins were 19-20 years old.

Twins were aged 13-14 at wave 2 while at wave 3 twins were 15-17 years old. Disordered eating was examined at wave 3. Response rates were examined at waves 3 and 4 and there was an 82% and 59% response rate, respectively (Lichtenstein et al., 2007). Analyses have been conducted to investigate the effect attrition has on the data. Results showed non-significant results for sex (Lichtenstein et al., 2007). TCHAD does have very good response rates. However, as the twins aged to 19-20 years old when they would be likely to move from their parent’s homes cooperation rates decreased. In this twin sample, there is also an under-reporting of individuals from lower socioeconomic (SES; Lichtenstein et al., 2007) classes, so the generalizability of these findings may not apply to those of lower SES.

Participants in TCHAD include same sex male and female pairs as well as opposite sex twin pairs. Zygosity of twin pairs is determined based on computer
algorithms of questionnaire responses created from analyses of twin pairs participating in
the clinical study with known zygosity (Lichtenstein et al., 2007).

Measures

_Eating Disorder Inventory-II (EDI; Appendix B)._ The EDI was given to
participants at wave 3 interviews. The EDI was designed to measure the construct of
eating attitudes and behaviors that are relevant to eating disorders. This Swedish version
of the EDI has been translated and validated on a female population (Nevonen, Clinton,
& Norring, 2006; Norring & Sohlberg, 1988). The EDI is composed of eight subscales
and these scales can be separated into two factors. The first factor assesses attitudes and
behaviors associated with eating and weight and is comprised of the subscales Drive for
Thinness (DT), Bulimia (B) and Body Dissatisfaction (BD). BD reflects the belief that
specific parts of the body are too large, DT indicates excessive concern with dieting,
preoccupation with weight and entrenchment in an extreme pursuit of thinness, and B
indicates the tendency toward episodes of binge eating that may be followed with the
impulse to induce vomiting (Garner, Olmsted, & Polivy, 1983).

The EDI was normed and created for use with female populations. However, it
has been shown to function similarly in males. The EDI is able to differentiate between
males with eating disorders and controls (Olivardia et al., 1995) and produces the same
factor structure, and similar factor loadings, invariances and intercorrelations in college
males and females (Spillane, Boerner, Anderson, & Smith, 2004). Reliability of the EDI
in males has also been shown to be acceptable (Eiben, Lissner, & Lichtenstein,
unpublished; Keel, Baxter, Heaterton, & Joiner, 2007; Keski-Rahkonen, Bulik et al.,
Cronbach’s alpha coefficients’ were previously reported for the identical sample used in the present study and were estimated at 0.88 / 0.81 for DT, 0.75 / 0.70 for B, and 0.91 / 0.88 for BD, in females and males respectively (Eiben et al., unpublished).

The EDI was scored as indicated by the EDI manual (Garner, 1991). Missing data was handled as follows: if subjects responded with more than 75% valid items but less than 100%, the missing values were imputed with the mean for that specific question. If there were less than 75% valid items available the score for the scale was considered missing. Thus, sample sizes may vary across subscale analyses. Scores will be normalized using SAS “Rank” (due to a likely positive skew), which assumes an underlying normal distribution of the observed scores. Items will be normalized in this manner in order to remain consistent with previous research from TCHAD utilizing the EDI (Eiben et al., unpublished).

**Statistical Analyses**

*Twin Methodology*

“The goal of the classical twin study is to use the similarities and differences between MZ, or identical, and DZ, or fraternal, twin pairs to identify and delineate genetic and environmental causes for a particular trait” (Bulik et al., 2000). MZ twins are created when a single zygote separates in to two separate embryos, so they are genetically identical, while DZ twinning occurs from the fertilization of two ova so they are as genetically similar as nontwin siblings sharing only about half their genes identical by descent. This means that differences found between MZ twins provides strong evidence
for environmental influences (or possible errors of measurement) on a trait while differences between DZ twins can be due to genetic or environmental influences.

Univariate analyses. The sources of variation in a trait that are revealed in the classical twin design include additive genetic effects (A), shared environmental effects (C), and unique environmental effects (E). Additive genetic effects result from the combined impact of many genes, each of which only has a small effect. MZ twins have a perfect correlation (1.0) on this parameter because they have identical genes, while DZ twins are correlated 0.5 because they only share on average half of their genes.

Shared environment refers to environments that both members of a twin pair are exposed to. Both MZ and DZ twins are correlated 1.0 on this parameter because they are reared together in the same environment. This can include family, community, school, or neighborhood effects. Finally, unique environment refers to environments that only one member of the twin pair is exposed to. Because this is an individual-specific environment, MZ and DZ twins are not by definition correlated at all on this parameter. As well as assessing unique environment, the E factor also includes any measurement error that may be occurring in assessments because this measurement error can also make twins differ. This creates the possibility of the unique environmental parameter being inflated because it includes both measurement error and unique environment. By squaring the standardized parameter estimates for A, C, and E we are able to determine the proportion of variance in the trait being investigated that can be attributed to that specific parameter.
Sex-Differences. By including opposite-sex twins in the classical twin study we are able to examine for sex-differences in the genetic and environmental influences on a particular trait. A twin model examining for sex-differences includes all of the basic information obtained in the classical twin study (i.e. ACE parameters). However, some special information in regard to sex-differences is also given. From these models we can obtain statistics such as the genetic ($r_g$) correlation across sexes. This correlation gives the degree of resemblance between the genetic risk factors for males and females (Kendler & Prescott, 2006).

There are two types of sex-differences that can be examined, quantitative and qualitative sex-effects. Having quantitative sex-effects indicates that the magnitude of the genetic factors on a particular trait are different between the sexes. In other words, quantitative effects answers the question as to whether genetic factors are more important for the etiology of disordered eating in males or females (Kendler & Prescott, 2006). While it is possible to fit quantitative models with only same-sex twin pairs, opposite-sex twin pairs are needed to examine for more interesting qualitative effects. If qualitative sex-effects are present this indicates that at least a proportion of the genetic risk factors for the trait are different in males and females. In other words, qualitative effects ask whether the same genes are involved in the etiology of disordered eating in the two sexes (Kendler & Prescott, 2006).

Quantitative effects can be examined using MZ and DZ same-sex twin pairs and are indicated if the correlations are different for female and male same-sex twins. Qualitative effects are indicated if the correlation between the twins is lower than that
seen in same-sex DZ pairs. If the opposite-sex correlation equals the geometric mean of the same-sex correlations we would expect $r_g$ to approximate unity, meaning the genetic risk factors completely overlap (Turner, Cardon, & Hewitt, 1995). If the opposite-sex correlation were zero we would expect $r_g$ to equal zero indicating completely different genetic risk factors in males and females for a trait (Kendler & Prescott, 2006).

Assumptions. The twin method has three central assumptions that must be met. Violations of these assumptions could lead to bias. First, accurate determination of zygosity is critical. Misdiagnosing zygosities could potentially cause a downward bias in heritability estimates. However, self-report questionnaires used to diagnose zygosity, including those used in the current study, have been shown to have an accuracy rate of >95% when compared to diagnoses made through DNA testing (Lichenstein et al., 2007).

The second assumption of twin studies is that the findings can be generalized to nontwins. For twin study results to extrapolate to the general population it must be shown that twin and nontwin populations are not significantly different from one another. Fortunately, empirical studies have found twins and nontwins have similar risks for psychiatric disorders (Kendler, Pedersen, Farahmand, & Persson, 1996).

The third assumption of the twin model is referred to as the equal environments assumption (EEA). The EEA states that MZ and DZ twins are equally correlated for their exposure to environmental influences that are relevant to the trait under investigation. If this assumption is violated the greater resemblance of MZ twins compared to DZ twins could be attributed to environmental factors producing an upward bias in heritability estimates. However, violating this assumption does not necessarily invalidate results but
it could influence the magnitude of the genetic and environmental estimates (Bulik et al., 2000). One such study examining the EEA in twins did raise concerns, suggesting that physical similarity may significantly influence twin resemblance for BN (Hettema, Neale, & Kendler, 1995). However, several more recent empirical studies have been conducted testing the EEA and in regards to psychiatric disorders in general, little evidence has been found for violations of the EEA (Kendler & Gardner, 1998), while testing the validity of the EEA in eating disorders has generally supported its validity (Bulik et al., 2000; Klump, Holly, Iacono, McGue, & Willson, 2000).

Power. The statistical power of twin studies has currently received a considerable amount of attention (Neale, Eaves, & Kendler, 1994). The power of the twin study depends on the effect that is attempting to be detected. Power is greatest for unique environmental effects, lowest for additive genetic effects, and intermediate for shared environmental effects (Bulik et al., 2000).

Power is also substantially greater when continuous rather than dichotomous variables are used in analyses (Neale et al., 1994). The use of continuous measures of disordered eating in this study will allow for better detection of sex-differences. However, the lower prevalence of disordered eating in males still could make it difficult to obtain statistical evidence of sex-differences.

The power of the twin study also is influenced by the MZ to DZ ratio. In order to increase power it is important to have a similar number of MZ and DZ twins, otherwise the power to estimate genetic effects will be quite low. With this knowledge it can be determined that previous twin studies have had the power to detect familial aggregation
of eating disorders ($a^2$ and $c^2$), however the power of these studies to disentangle A and C from one another has been low (Bulik et al., 2000).

Issues of power are particularly relevant for twin studies examining for sex-differences. While twin studies are a useful technique for exploring sex-differences in the liability to a specific phenotype, the statistical power of these analyses is quite modest in the absence of very large samples (Neale et al., 1994). For phenotypes that are relatively rare in the population exceptionally large samples are necessary to reliably detect sex-differences in genetic risk factors (Prescott & Gottesman, 1993). Previous research has indicated that with modest sized samples with low power, more valid parameter estimates are obtained using the full model rather than obtaining parameter estimates from the best-fit model by constraining certain parameters to zero (Sullivan & Eaves, 2002). This will be the approach used in the current study. As such, our full model includes both quantitative and qualitative sex-effects. This full model allows for the estimation of sex-dependent genetic and environmental parameters and also estimates the correlation between the genetic factors influencing disordered eating in males and females.

Twin Analyses. Structural equation modeling (SEM) is a popular statistical technique used to tease apart genetic and environmental effects of a particular trait. SEM allows parameter estimates ($a^2$, $c^2$, & $e^2$) and confidence intervals to be estimated for A, C, and E. This is crucial because it allows for an effect size to be estimated and informs of the precision of the estimate (Bulik et al., 2000).
The Bayesian information criterion (BIC) will be used to determine best-fitting models (i.e. comparison of common and independent pathways). The BIC is a function of a model’s df and $\chi^2$ (Raftery, 1995). Models that provide the best fit while retaining the fewest parameters yield lower BIC values.

All twin analyses in the current study will be conducted using a raw data approach in the statistical package Mx (Neale, 1997). This approach allows data from both incomplete and complete twin pairs to be utilized. Mx is a program used for SEM and is popular in the use of twin analyses. It is similar to commercial software used for SEM. Mx allows for maximum-likelihood model fitting analyses.

*Univariate Model-Fitting Analyses Examining Sex-Differences*

Our univariate twin model for study one utilizes data from the five twin-zygosity groups: female-female MZ, female-female DZ, male-male MZ, male-male DZ, and male-female DZ. We will fit the full sex-limitation twin model allowing for qualitative and quantitative sex-effects. These models will be fit to normalized EDI scores.

*Multivariate Twin Model-Fitting Analyses*

Multivariate model-fitting analyses will initially be conducted in males and females separately. First, an independent and common pathway model will be fit to normalized EDI data (Figures 1a and 1b). Both models assume a common factor influences the observed variables. The models differ in the way the common factors are hypothesized to influence variables. In the independent pathway model, the common genetic and environmental factors influence the measured variables directly as do residual ACE components. The common pathway model would assume there is a single
latent factor underlying the facets of disordered eating. The variance in this factor can be partitioned into higher order factors, in this case A, C, and E and also residual ACE components for each variable being measured that are not accounted for by common factor. The common pathway model uses fewer parameters and is therefore, more parsimonious than the independent pathway model. Because of this, if the common pathway model fits as well as the independent pathway model it is preferred.

Next we will fit a multivariate model utilizing data from the five twin-zygosity groups to examine for quantitative and qualitative sex-differences in this structure of disordered eating. This will be done utilizing the full sex-limitation model described previously. We will use either the independent or common pathway model, depending on which model fits the male and female data best in the separate analyses.
Figure 1a. Independent pathway model.

A = additive genetic effects. C = shared environmental effects. E = unique environmental effects. PH1 = first phenotype. PH2 = second phenotype. PH3 = third phenotype. a = phenotype specific genetic effects. c = phenotype specific shared environmental effects. e = phenotype specific unique environmental effects.
Figure 1b. Common pathway model.

A = additive genetic effects. C = shared environmental effects. E = unique environmental effects. PH1 = first phenotype. PH2 = second phenotype. PH3 = third phenotype. as = residual genetic effects not accounted for by common factor. cs =
residual shared environmental effects not accounted for by common factor. es = residual unique environmental effects not accounted for by common factor.
Chapter 3 Results

Descriptive Statistics

Table 2 presents the means, standard deviations, and intraclass correlations for the raw EDI scales. Overall, the pattern of correlations suggests genetic influences on all three scales as all the observed correlations in MZ twins are higher than those observed in DZ twins. The correlations between opposite-sex twin pairs suggest that the familial factors influencing disordered eating are not entirely the same in the sexes because the observed correlations are lower than those observed in same-sex DZ pairs. However, these correlations are greater than zero suggesting that some familial factors influence both male and female liability to disordered eating. Finally, with the exception of B in MZ pairs, the observed correlations were larger in female twin pairs. This would be expected if the specific traits were more heritable in females.
<table>
<thead>
<tr>
<th>Scale</th>
<th>Females</th>
<th></th>
<th></th>
<th>Males</th>
<th></th>
<th></th>
<th>Opposite-Sex Twins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>MZ</td>
<td>DZ</td>
<td>All</td>
<td>MZ</td>
<td>DZ</td>
<td>OSF</td>
</tr>
<tr>
<td><strong>Drive for Thinness</strong>†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M (SD)</td>
<td>r</td>
<td>M (SD)</td>
<td>r</td>
<td>M (SD)</td>
<td>r</td>
<td>M (SD)</td>
</tr>
<tr>
<td></td>
<td>2.13</td>
<td>0.61**</td>
<td>2.00</td>
<td>0.32**</td>
<td>2.36</td>
<td>0.30**</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>(3.90)</td>
<td>(4.00)</td>
<td>(4.01)</td>
<td>(4.00)</td>
<td>(1.40)</td>
<td>(1.43)</td>
<td>(4.00)</td>
</tr>
<tr>
<td><strong>Bulimia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M (SD)</td>
<td>r</td>
<td>M (SD)</td>
<td>r</td>
<td>M (SD)</td>
<td>r</td>
<td>M (SD)</td>
</tr>
<tr>
<td></td>
<td>0.54</td>
<td>0.30**</td>
<td>0.50</td>
<td>0.23**</td>
<td>0.51</td>
<td>0.33**</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>(1.51)</td>
<td>(1.40)</td>
<td>(1.12)</td>
<td>(1.27)</td>
<td>(1.2)</td>
<td>(1.15)</td>
<td>(1.15)</td>
</tr>
<tr>
<td><strong>Body Dissatisfaction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M (SD)</td>
<td>r</td>
<td>M (SD)</td>
<td>r</td>
<td>M (SD)</td>
<td>r</td>
<td>M (SD)</td>
</tr>
<tr>
<td></td>
<td>5.74</td>
<td>0.64**</td>
<td>5.04̍</td>
<td>0.35**</td>
<td>6.24</td>
<td>0.45**</td>
<td>1.93</td>
</tr>
<tr>
<td></td>
<td>(6.20)</td>
<td>(5.90)</td>
<td>(6.21)</td>
<td>(3.60)</td>
<td>(3.30)</td>
<td>(3.60)</td>
<td>(4.00)</td>
</tr>
</tbody>
</table>

Note. Means and standard deviations for unstandardized scores. Drive for thinness includes question dropped from twin analyses due to low loading on factor. M = mean. SD = standard deviation. MZ = monozygotic; r = intraclass correlation. DZ = dizygotic; ¥ = intraclass correlation between male and female of opposite-sex twin pair. OSF = opposite-
sex twin female. OSM = opposite-sex twin male. T = significant mean difference between males and females on subscale. €
= Significant mean difference between MZ and DZ twins. ** Observed correlation significant at p < 0.01. * Observed
correlation significant at p < 0.05.
Univariate Twin Analyses

As seen in Table 4, results indicate genetic factors influence disordered eating in both sexes. Heritabilities were estimated at 61% and 20% for DT, 16% and 33% for B, and 57% and 40% for BD for females and males, respectively. However, it is important to note the 95% confidence intervals for genetic effects in males for DT and B include zero. The full model provided genetic correlations between the sexes of +0.49, +1.00, and +0.66 for DT, B, and BD respectively (see Table 3), suggesting that the genetic risk factors for DT and BD are not entirely the same in the sexes.

Unique environmental influences are also important for all three scales in both sexes. These estimates were fairly large for DT and BD in males as well as for B in both sexes which could suggest a large amount of error in estimates. However, large estimates can also come from true E effects and we are unable to differentiate these two possibilities.
Table 3

*Model-fitting Results From Univariate and Multivariate Twin Models*

<table>
<thead>
<tr>
<th>Model</th>
<th>( r_g )</th>
<th>df</th>
<th>-2LL</th>
<th>( \Delta \chi^2, p^* )</th>
<th>BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drive for Thinness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated</td>
<td>--</td>
<td>2171</td>
<td>4600.20</td>
<td>--</td>
<td>-5358.77</td>
</tr>
<tr>
<td>Sex-effects</td>
<td>0.49</td>
<td>2185</td>
<td>4613.92</td>
<td>13.70, 0.48</td>
<td>-5380.03</td>
</tr>
<tr>
<td><strong>Bulimia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated</td>
<td>--</td>
<td>2169</td>
<td>4895.50</td>
<td>--</td>
<td>-5182.95</td>
</tr>
<tr>
<td>Sex-effects</td>
<td>1.00</td>
<td>2177</td>
<td>4910.54</td>
<td>15.04, 0.06</td>
<td>-5203.50</td>
</tr>
<tr>
<td><strong>Body Dissatisfaction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated</td>
<td>--</td>
<td>2181</td>
<td>5429.00</td>
<td>--</td>
<td>-4958.43</td>
</tr>
<tr>
<td>Sex-effects</td>
<td>0.66</td>
<td>2189</td>
<td>5435.00</td>
<td>6.00, 0.65</td>
<td>-4983.58</td>
</tr>
<tr>
<td><strong>Multivariate Common</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex-effects</td>
<td>0.71</td>
<td>6570</td>
<td>14445.04</td>
<td>--</td>
<td>-15891.23</td>
</tr>
</tbody>
</table>

Note. Sex-effects model compared to saturated model. Saturated model = in model fitting, the saturated model, which estimates all parameters, is used as a starting point for the comparison of different, nested models. Sex-effects model = model
estimating sex-dependent parameters and genetic correlation. \( r_\text{g} = \) genetic correlation. \( \text{df} = \) degrees of freedom. \( \text{BIC} = \) Bayesian information criterion.

* p-value associated with chi-square change in model.
Table 4

Parameter Estimates for Univariate Models of EDI Subscales

<table>
<thead>
<tr>
<th>Scale</th>
<th>$a^2$</th>
<th>95% CI</th>
<th>$c^2$</th>
<th>95% CI</th>
<th>$e^2$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drive for Thinness</td>
<td>0.61</td>
<td>(0.20)</td>
<td>0.01</td>
<td>(0-0.25)</td>
<td>0.38</td>
<td>(0.31-0.46)</td>
</tr>
<tr>
<td></td>
<td>(0-0.43)</td>
<td>(0.11)</td>
<td>(0-0.35)</td>
<td>(0.69)</td>
<td>(0.57-0.82)</td>
<td></td>
</tr>
<tr>
<td>Bulimia</td>
<td>0.16</td>
<td>(0.33)</td>
<td>0.16</td>
<td>(0-0.36)</td>
<td>0.69</td>
<td>0.57-0.81</td>
</tr>
<tr>
<td></td>
<td>(0-0.44)</td>
<td>(0)</td>
<td>(0.0.30)</td>
<td>(0.67)</td>
<td>(0.56-0.80)</td>
<td></td>
</tr>
<tr>
<td>Body Dissatisfaction</td>
<td>0.57</td>
<td>(0.40)</td>
<td>0.07</td>
<td>(0-0.31)</td>
<td>0.36</td>
<td>0.30-0.44</td>
</tr>
<tr>
<td></td>
<td>(0.06-0.57)</td>
<td>(0.07)</td>
<td>(0-0.35)</td>
<td>(0.53)</td>
<td>(0.44-0.64)</td>
<td></td>
</tr>
</tbody>
</table>

Note. Male estimates shown in parentheses. Total parameter estimates may be slightly above or below 1.00 due to rounding error. EDI = Eating Disorder Inventory. CI = Confidence interval. $a^2$ = additive genetic variance. $c^2$ = shared environmental variance. $e^2$ = unique environmental variance.
Multivariate Twin Analyses

In females, the common pathway model (BIC = -4313.00) fit better than the independent pathway model (BIC = -4304.74). Results were similar for males: the common pathway model (BIC = -4267.33) fit better than the independent pathway model (BIC = -4259.36).

Sex-differences in Genetic and Environmental Influences. The full common pathway model estimated a genetic correlation of +0.71 between the latent liability for disordered eating in males and females (see Table 3 and Figure 2). By squaring the higher order path estimates from Figure 2 (Af and Am), the heritability on this latent liability is estimated at 45% for females and 66% for males. However, when the proportion of genetic variance for each subscale is calculated, common genetic factors account for more of the variance in females for all subscales (see Table 5). Specifically, common genetic factors account for 36% (calculated by \([0.67\times0.89]^2\), in Figure 2) of the variance in DT for females and 32% in males, 7% of the variance in B for females and 1% in males, and 27% of the variance in females for BD and 21% in males.

While the higher heritability for the latent factor in males compared to females may seem contradictory, the total heritability for each of the subscales (including the proportion of genetic variance from the common factor, as well as the proportion specific to the subscale) is higher in females for all three subscales. The fact that the heritability for the latent factor is higher in males versus females reflects the fact that the genetic factors that are in common between the three scales explain more of the variance of the
latent factor in males but are partly different from those in females ($r_g = +0.71$).

However, a smaller proportion of the variance of each of the subscales is accounted for by the common factor in males than females (lower factor loadings).

As can be seen in Table 5, common shared and unique environmental factors also account for more of the variance in females for all subscales. Common shared and unique environmental variance was greatest for DT at 29% ($[0.60*0.89]^2$, Figure 1) and 15% ($[0.44*0.89]^2$, Figure 2), respectively. Males have substantially more variable specific unique environmental influences for all subscales. The greatest amount of specific unique environmental influence was estimated at 67% for B. This statistic can be calculated by squaring the subscale, sex-specific residual path estimate (see Figure 2). For B this is calculated by squaring 0.81.

Several results from these analyses are noteworthy. First, the genetic risk factors for the disordered eating common factor are not entirely the same in both sexes. Second, common genetic factors account for more of the variance in this factor for females. Third, the loadings for all three subscales on the common factor were larger for females. Fourth, B is the least discriminating subscale and DT the most salient indicator of the factor in both sexes.
Figure 2. Genetic and environmental path estimates from multivariate common pathway model including all five zygosity groups.

Rg = genetic correlation. Af = female common factor additive genetic path estimate. Cf = female common factor shared environmental path estimate. Ef = female common factor unique environment path estimate. Am = male common factor additive genetic path estimate. Cm = male common factor shared environmental path estimate. Em = male common factor unique environment path estimate. % = Squared parameter estimates indicating percentage of variance accounted for by factor. DT = drive for thinness subscale. B = bulimia subscale. BD = body dissatisfaction subscale. a = residual additive genetic path estimate. c = residual shared environmental path estimate. e = residual

39
unique environment path estimate. Male path/parameter estimates for factor loadings and residual genetic and environmental factors indicated in parentheses.
Table 5  
*Proportion of Variance Accounted for by Common and Specific Genetic and Environmental Factors in Females and Males from Multivariate Common Pathway Model (Figure 2)*

<table>
<thead>
<tr>
<th>Scale</th>
<th>Genetic</th>
<th></th>
<th>Shared Environment</th>
<th></th>
<th>Individual-specific (unique) Environment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%Common</td>
<td>%Specific</td>
<td>Total</td>
<td>%Common</td>
<td>%Specific</td>
<td>Total</td>
</tr>
<tr>
<td>Drive for Thinness</td>
<td>36 (32)</td>
<td>4 (0)</td>
<td>39 (32)</td>
<td>29 (7)</td>
<td>0 (0)</td>
<td>29 (7)</td>
</tr>
<tr>
<td>Bulimia</td>
<td>7 (1)</td>
<td>11 (27)</td>
<td>18 (28)</td>
<td>5 (0)</td>
<td>10 (4)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Body Dissatisfaction</td>
<td>27 (21)</td>
<td>16 (4)</td>
<td>43 (25)</td>
<td>22 (4)</td>
<td>4 (20)</td>
<td>26 (24)</td>
</tr>
<tr>
<td></td>
<td>15 (10)</td>
<td>17 (50)</td>
<td>32 (60)</td>
<td>3 (0)</td>
<td>64 (67)</td>
<td>67 (67)</td>
</tr>
</tbody>
</table>

Note. Male proportion of variance accounted for by common and specific genetic and environmental factors indicated in parentheses. Total common and specific genetic and environmental proportions may be slightly above or below 100% due to rounding error.
Chapter 4 Discussion

Summary of Findings

This investigation had three aims. First was to examine the structure of disordered eating (i.e. whether a single common factor accounts for the association among the three disordered eating facets). As hypothesized, findings show that a single underlying factor accounts for the association among our three facets of disordered eating (DT, B, BD) in both males and females. Second, was to examine for quantitative and qualitative differences in the revealed structure of disordered eating. As hypothesized, both quantitative and qualitative effects were exhibited for the latent liability to disordered eating. Approximately 50% of the genetic factors responsible for this liability are shared. Results also suggest genetic factors are more important in males and shared environment for females for this liability. Third, was to examine for quantitative and qualitative sex-differences in the three specific facets of disordered eating. As hypothesized, quantitative and qualitative differences were shown for DT and BD. Genetic effects were more important for DT and BD in females while environment was more important for males. Results of this report suggest that distinct genetic and environmental factors are in part responsible for the development of disordered eating in males and females.

Discussion of Findings

Structure of Disordered Eating
To our knowledge, only two previous studies have examined the factor structure of the genetic and environmental influences on disordered eating and both indicate a single underlying factor is responsible (Neale et al., 2003; Wade et al., 1999). Results of the current study corroborate and extend these findings by indicating this structure is quite similar in males and females. However, our three subscales tend to discriminate individual differences more sharply on the factor for females than they do in males. This is not surprising given that the EDI was developed for use with a female population (Garner, 1991).

Of note, the B subscale was a poor indicator of this latent liability. The common factor only accounted for 15% (0.39²) and 2% (0.15²) of the variance in B for females and males, respectively (see Figure 3). Similarly however, the two previously discussed studies also had a variable, specifically a measure of restraint (Neale et al., 2003) and a semi-structured eating disorder interview (Wade et al., 1999), for which the latent factor did not account for a large proportion of variance.

Sex-differences in Disordered Eating

Quantitative Sex-effects. Our modeling produced evidence for quantitative sex-effects. Genetic factors showed a stronger contribution in males whereas shared environment contributed more in females when accounting for variability in latent liability to disordered eating. Unique environmental factors appear to be contributing at an equal magnitude in the sexes. Quantitative effects were also revealed at the univariate level for DT and BD. Heritability estimates were greater for females and 95% confidence intervals also indicate lower genetic variability. These results are similar to previous
research by Slane and colleagues (2007), whose population age and sample size were similar to the present study.

**Qualitative Sex-effects.** Only two previous reports, both examining binge eating, have examined qualitative sex-differences in disordered eating. Our results suggest the genetic risk factors for disordered eating in general, and particularly for DT and BD, are not entirely the same in males and females. Only approximately 50% of the genetic risk factors are shared between the sexes.

In contrast, our univariate results indicate all of the genetic risk factors for B are shared. This is also in discrepant to previous reports examining binge eating (Reichborn-Kjennerud et al., 2003; Reichborn-Kjennerud, Bulik, Tambs et al., 2004). Although binge eating alone was not assessed in the current study, the B subscale would be the most comparable. Reichborn-Kjennerud and colleagues (2003) showed a very slight improvement in model fit when the genetic correlation was allowed to be estimated, revealing a genetic correlation of +0.57. However, the results of our multivariate model do provide evidence of qualitative differences on B, as the genetic risk for the disordered eating factor does not completely overlap between the sexes.

This discrepant result might arise from several methodological differences between the studies. First, our study had a considerably smaller sample size so with more power, we might have detected these qualitative sex-effects at the univariate level. Second, the age range for the current study (16-17) is younger than in the study of Reichborn-Kjennerud et al. (19-31; 2004a, 2004b). Differences in assessment could also have impacted results. For example, our measures examine aspects of disordered eating
that relate to eating disorders, while the previous study utilized questions designed to capture DSM-IV criteria for binge eating. We also utilized a Swedish population while the former was a Norwegian population. However, these two populations are culturally similar.

**Candidates for sex-differences in disordered eating**

Our study provided evidence for qualitative sex-differences in disordered eating but no direct information about the nature of these differences. Several plausible hypotheses are worth considering. First, results are consistent with the hypothesis that gonadal hormone exposure creates a differential eating disorder risk in males and females (Klump et al., 2005; Reichborn-Kjennerud et al., 2003). For example, research indicates estrogen may play an important role in disordered eating (Klump, Burt, Sisk et al., 2007; Klump et al., 2005). Disordered eating in females is also related to effects of cyclic hormonal changes (Edler et al., 2006; Lester, Keel, & Lipson, 2003; Price, Torem, & DiMarzio, 1987), which would not be expressed in males.

Age could also explain the differential genetic risk for BD and DT. A recent study showed that at a 20-year follow-up, males DT scores increased more from baseline compared to females and males were also more dissatisfied and females more satisfied with their bodies as they aged (Keel, Baxter, Heatherton, & Joiner, 2007). This indicates that as males aged their disordered eating attitudes increased which is suggestive that something is occurring as male age that increases these attitudes. One hypothesis could be that genetic factors influencing disordered eating are more salient in older males and this could be influenced by testosterone levels. Levels of testosterone typically decline in
males as they age (e.g. Feldman et al., 2002; Mitchell et al., 2001; Morley et al., 1997; Zmuda et al., 1997) and this hormone has been previously shown to be a protective factor against disordered eating (Culbert, Breedlove, Rosenberg, & Klump, 2006). Because testosterone levels decline in males as they age, one can hypothesize that as testosterone levels decrease males become more susceptible to disordered eating. Decreased levels of testosterone have previously been linked to AN in males (APA, 2000). However, testosterone levels in males with AN improve with weight gain (Scott, 1986) and studies have been unable to replicate results suggesting testosterone to impact risk for disordered eating (Baker, Lichtenstein, & Kendler, in press; Raevuori et al., 2008).

This would indicate that the genetic risk factors for disordered eating in males are different across development. A developmental trajectory has previously been shown for females that is related to estrogen. It has been reported that disordered eating symptoms begin at puberty (Hayward et al., 1997), tend to remit by the menopausal years (Strober, Freeman, & Morrell, 1997; Keel et al., 1999), and that genetic influences on disordered eating substantially increase once females enter puberty (Klump, McGue, & Iacono, 2003). Taken together, results indicate a developmental trajectory to disordered eating may be occurring in both sexes and that in males this trajectory occurs through middle-age.

Finally, several social and psychological factors relevant to eating disorders could be the basis for this sex-difference in genetic risk. For example, cultural pressure to be thin is much greater for females than for males. Additional psychological factors such as childhood sexual abuse, personality characteristics, and symptoms of depression or
anxiety may also play a role. These differing social and psychological factors could produce separate pathways to eating disorder development in males and females, whereby creating a distinct genetic variation in risk. For example, given the different cultural influences on body shape in males and females, the kinds of temperamental effects that impact on body shape could differ across sexes. This in turn would drive different genetic effects, driving males to be more muscular and females to be thin and have small waists.

Study Limitations and Strengths

Several limitations warrant discussion. One possible limitation is our sample size and the associated modest statistical power, especially for the detection of sex-effects. Our sample also comes from a single birth cohort in Sweden so there may be possible cohort effects. This may be especially true for examining disordered eating in our male twins. Additionally, the prevalence of eating disorders may differ between the United States and Sweden which would impact the generalizability of results. However, studies suggest that the prevalence of eating disorders in Sweden and other Scandinavian countries are similar to slightly less prevalent compared to the United States (Ghaderi & Scott, 2001; Rastam, Gillberg, & Garton, 1989). For example, in one of the largest twin studies of females within Sweden examining the 1935-1958 birth cohorts, the lifetime prevalence of AN was estimated at 1.2% (Bulik et al., 2006). Additionally, the lifetime prevalence of BN within a Finnish sample of twins was estimated at 2.3% for females (Keski-Rahkonen et al., 2008). Similarly, in the United States it is estimated that 0.5-
3.7% females will suffer from AN in their lifetime and 1.1-4.4% will suffer from BN (National Institute of Mental Health, 2008).

There are also limitations to our use of the EDI. First, because of our low mean scores, especially within the B subscale, there may not have been adequate variability to detect sex-differences at the univariate level. Second, males and females likely have differential thresholds for expressing disordered eating, which would impact results. For example, the B subscale may represent more normative aspects of behaviors in males (Eiben, 2007). Many of the subscale items deal with binge eating behaviors, and 16-17 year old boys may commonly consume large amounts of food (Eiben, 2007; Katzman et al., 1984). Males are also less likely to label the consumption of large quantities of food a “binge” or to report feeling out of control during consumption (Carlat & Camargo, 1991; Franco et al., 1988; Lewinsohn et al., 2002). Finally, as previously noted, males typically desire to be more muscular while females desire to be smaller, and the BD scale of the EDI focuses on the latter. BD also focuses on core areas of the body which females are more likely to express dissatisfaction (i.e. stomach and thighs).

Despite its’ weaknesses, the current study has several strengths. The most critical strength of the current study is its representativeness. The sample was taken from the general population of a birth cohort in Sweden which eliminates the possibility of biases, specifically Berkson’s bias which we would see if the sample were clinically based. The use of disordered eating data rather than eating disorder diagnosis also reduces the potential of Berkson’s bias and affords the opportunity to examine how these domains act at a more generalizable level.
A second strength of the current study is that the creators of TCHAD were able to keep the attrition rate for each wave rather low which can be an issue with both twin registries and longitudinal data collection in general. They also made an attempt to contact those twins who did not return questionnaires by telephone and were able to interview 156 twins by telephone who did not responded to wave 3 questionnaire packets.

Study Implications and Future Directions

This study represents one of the first to compare the genetic and environmental risk factors for multiple measures of disordered eating in males and females. We found more similarities than differences in the genetic and environmental risk factors for disordered eating. However, we did find some differences between adolescent males and females that indicate the symptom structure of disordered eating may be different between males and females at this age. Our results suggest that disordered eating patterns related to B may be more similar between males and females compared to patterns more related to DT and BD. This is in line with previous research suggesting a different etiology for eating disorders and disordered eating in adolescent males, with males seeking to increase weight and pursue muscularity (e.g. Ricciardelli & McCabe, 2004). This difference in symptom structure and etiology has possible clinical implications as well. It suggests to clinicians that different treatment approaches may be necessary to treat males and females with an eating disorder. Treatments found to be beneficial for females with an eating disorder may not be as effective for males because of this difference in symptom structure and because the ultimate goal of the disordered eating patterns are different.
Replicating this study with a larger sample size and at different ages is needed to make definitive conclusions about etiologic differences in disordered eating, as our results are limited to adolescence. Future research should also examine genetic and shared environmental similarities and differences in AN and BN diagnoses and focus on examining developmental trajectories of disordered eating in males as it is possible genetic and environmental influences change across development.
Chapter 5 Genetic Risk Factors for Substance Use in Males and Females

Introduction

While eating disorders are relatively rare in the general population, substance use/misuse is much more common. Studies indicate that approximately 50% of the population has used an illegal or nonmedical drug (Warner, Kessler, Hughes, Anthony, & Nelson, 1995). Substance use is also relatively common during adolescence. The National Institute on Drug Abuse (National Institute of Drug Abuse [NIDA], 2007) reports lifetime prevalence rates of alcohol, illicit drug, and cigarette use by 8th graders at 38.9%, 19.0%, and 22.1%, respectively.

Similar to eating disorders, there is also a sex-difference in the use/misuse of substances. This difference is exhibited in adolescence and adulthood. It has been well established that males are significantly more likely to use substances and to have an abuse/dependence diagnosis, especially in regard to illicit substances and alcohol, compared to females (Grant, 1996; Haas, 2004; Hasin, Stinson, Ogburn, & Grant, 2007; Kessler et al., 2005; Miller & Plant, 1996; Opland, Winters, & Stinchfield, 1995; Robbins, 1989; Warner et al., 1995). Warner and colleagues (1995) reported that approximately 46.4% of females have used illicit drugs in their lifetime compared to 55.8% of males, while 5.9% of females have a dependence diagnosis compared to 9.2% of males. In regard to alcohol, a recent survey showed a lifetime prevalence of any alcohol use disorder of 19.5% in females and 42% in males (Hasin et al., 2007).
However, it appears females tend to exhibit similar to increased rates of cigarette smoking compared to males (Miller & Plant, 1996; NIDA, 2000; Wallace et al., 2003).

Research has also established a genetic influence on substance use/misuse in both males and females. In fact, it has been suggested that these influences are not substance specific, but general across substances (Kendler, Jacobson, Prescott, & Neale, 2003; Tsuang et al., 1998; Young, Rhee, Stallings, Corley, & Hewitt, 2006). The magnitude of genetic and environmental influences also appears to vary across development (Hicks et al., 2007; Kendler, Schmitt, Aggen, & Prescott, 2008; Koopmans, Doornen, & Boomsma, 1997; Malone, Taylor, Marmorstein, McGue, & Iacono, 2004; Pagan et al., 2006; Viken, Kaprio, Koskenvuo, & Rose, 1999; White, Hopper, Wearing, & Hill, 2003). However, it is still unknown whether a developmental trajectory is seen across this general substance use factor and if this varies between sexes. The current study examines whether there is a developmental change in the genetic and environmental risk factors on substance use/misuse and if this differs between the sexes.

Review of the Literature

Substance Use and Disorders

Definition of Substance Use Disorders

In order to obtain a diagnosis of substance dependence three or more of the following symptoms must be occurring in a 12-month period and be causing impairment or distress: tolerance, withdrawal, substance is taken in larger amounts over longer periods of time, persistent desire or unsuccessful efforts to control substance use, a great deal of time is spent in activities necessary to obtain the substance, other activities are
reduced because of substance use, and substance use is continued despite knowledge of having a physical or psychological problem caused by the substance (APA, 2000). The criteria for substance abuse is less stringent, requiring only one of the following symptoms, which must be causing distress or impairment in a 12-month period: substance use resulting in failure to fulfill major role obligations, use in situations that are hazardous, substance related legal problems, and continued use despite having social or interpersonal problems because of substance use (APA, 2000).

**Sex-differences in Substance Use/Misuse**

Historically, the use and misuse of substances was perceived as a “male problem”. Similar to eating disorder research however, examining sex-differences in substance use disorders has often revealed more similarities than differences (Agrawal, Neale, Jacobson, Prescott, & Kendler, 2005; NIDA, 2000; Opland et al., 1995). However, some general differences have been found (for review see (Brady & Randall, 1999).

First, sex-differences are exhibited in the health consequences of substance use and in vulnerability to substance initiation, dependence, and relapse (Brady & Randall, 1999; Nelson-Zlupko, Kauffman, & Dore, 1995; NIDA, 2000; Society for Women's Health Research, 2004; Virginia Department of Mental Health, Mental Retardation, and Substance Abuse Services, 2004). Second, females are also more likely to attribute their substance abuse to a biological predisposition, family history, or environmental stressors (Brady & Randall, 1999; Kauffman, Silver, & Poulin, 1997; Nelson-Zlupko et al., 1995). Third, females also tend to report using substances in order to escape emotionality (Opland et al., 1995). Finally, females are significantly more likely to have comorbid
depression or anxiety disorders and males are more likely to have comorbid antisocial personality disorder (Brady & Randall, 1999; Kessler et al., 1997; Nelson-Zlupko et al., 1995; Robbins, 1989).

Hypotheses have been developed as to why males tend to use substances more frequently than females. Analogous to eating disorder research, many of these hypotheses have focused on social reasons. For instance, one hypothesis states males are more likely to use substances because of the effect of gender role socialization (Huselid & Cooper, 1992; Robbins, 1989). Risk taking behaviors in males are often encouraged and rewarded (i.e. “boys will be boys” mentality) while these types of behaviors in females are often punished. Therefore, when males reach adolescence this risk-taking tendency may influence more experimentation with substances (Haas, 2004).

Additionally, certain personality characteristics, such as sensation-seeking or impulsivity, are more common in males possibly increasing their likelihood to use substances (Haas, 2004). A third hypothesis is that females are exposed to higher levels of parental control and supervision while males exhibit a higher level of exposure to peer deviances, creating more of an opportunity for males to engage in substance use (Haas, 2004).

Biological/genetic hypotheses have also been proposed to explain the sex-difference in substance use and misuse. They often propose males and females have a different biological response to substances whereby creating a differing susceptibility to becoming dependent (Brady & Randall, 1999; NIDA, 2000; Society, 2004). However, research has not been able to definitively confirm nor deny this hypothesis. Similar to
eating disorders, it is still quite unclear why there is a sex-difference in the prevalence of substance use/misuse. As stated, most research indicates the patterns and risk for substance use/misuse are similar in males and females. However, some identified differences in regard to nicotine, alcohol, and illicit drug use will be discussed below.

**Nicotine.** As previously stated, males and females tend to have similar rates of nicotine use. However, physiological differences in the effects of nicotine have been exhibited. Females metabolize nicotine slower and are also less sensitive to the discriminative effects of nicotine (Benowitz, 1997 as cited by Brady & Randall, 1999) (Brady & Randall, 1999; Perkins, 1996; Zeman, Hiraki, & Sellers, 2002). Moreover, there is a stronger association between depression and nicotine dependence in females (Brady & Randall, 1999; Perkins, 1996). Finally, sex-differences in reasons for use are also exhibited. Females often report using nicotine in order to reduce stress and lose weight while males report starting to smoke to be more alert and energetic (Pogun, 2001; Society, 2004).

**Alcohol.** Males are five times as likely to have an alcohol use disorder compared to females (Reiger et al., as cited by (Brady & Randall, 1999). Several differences have been cited between males and females. Moreover, important sex-differences exist in the physiological effects of alcohol. Specifically, females become intoxicated faster than males and also have a lower concentration of the enzyme responsible for metabolizing alcohol (Brady & Randall, 1999; Frezza et al., 1990; Marshall, Kingstone, Boss, & Morgan, 1983; Witt, 2007).
Research has also shown differences in drinking motivations between the sexes. Females have lower scores on measures examining drinking motivations related to relieving social anxiety and increasing mental clarity. However, drinking to relieve social anxiety is more predictive of an alcohol use disorder in females compared to males (Prescott, Cross, Kuhn, Horn, & Kendler, 2004). Compared to males with an alcohol use disorder, females with an alcohol use disorder also report higher scores on a measure of drinking to increase gregariousness (Prescott et al., 2004).

*Illicit Drugs.* Males are 2-3 times more likely to have an illicit drug use disorder compared to females (Reiger et al., as cited by (Brady & Randall, 1999). However, drug use disorders are strikingly analogous in males and females. One of the largest differences noted in research is that females with an illicit drug disorder tend to report differing comorbid conditions. For example, illicit drug use in females is associated with an increased history of physical and sexual abuse (Brady & Randall, 1999; K. S. Kendler, Bulik, Silberg, & Hettema, 2000; Nelson-Zlupko et al., 1995; Society, 2004; Virginia Department of Mental Health, 2004).

*Familial Risk Factors for Substance Use/Misuse*

A multitude of twin studies have examined the genetic epidemiology of substance use/misuse in both males and females. Results suggest genetic factors play a substantial role in both substance use and disorders (Agrawal & Lynskey, 2008). These results remain similar in both adolescent and adult samples. However, shared environmental influences are often implicated during adolescence (Hopfer, Crowley, & Hewkitt, 2003;
McGue, Elkins, & Iacono, 2000; Rhee et al., 2003). Specific results in regard to nicotine, alcohol, and illicit drug use/misuse will be discussed in detail.

Nicotine. There is substantial evidence that nicotine dependence is heritable (Li, Cheng, Ma, & Swan, 2003; Sullivan & Kendler, 1999). Depending on the assessment method used, heritability estimates often range from 30-75% (Agrawal & Lynskey, 2008; Kendler, Neale et al., 1999; True et al., 1997; Vink, Willemsen, & Boomsma, 2005). Familial factors also play an important role in smoking initiation (Kendler, Neale et al., 1999; True et al., 1997). For example, one study estimates heritability to be between 78% and 85% for females (Kendler, Neale et al., 1999). Shared environmental factors also appear to play a role in smoking initiation assessed within adult samples (True et al., 1997). However, there is little evidence for shared environmental influences on nicotine dependence or persistent smoking during adulthood. Shared environment does contribute to nicotine dependence during adolescence (Agrawal & Lynskey, 2008; McGue et al., 2000; True et al., 1997).

Genetic factors have also been implicated for nicotine use and initiation in adolescence. Heritabilities typically range from 11-60% (Boomsma, Koopmans, Doornen, & Orlebeke, 1994; Han, McGue, & Iacono, 1999; Hopfer et al., 2003; Koopmans, Slutske, Heath, Neale, & Boomsma, 1999; Maes et al., 1999; McGue et al., 2000; Rhee et al., 2003). Similar to nicotine dependence, shared environment is also important for nicotine use and smoking initiation during adolescence (Boomsma et al., 1994; Han et al., 1999; Koopmans et al., 1997; Koopmans et al., 1999; Maes et al., 1999; Rhee et al., 2003).
It also appears there may be a sex-difference in these shared environmental influences, with one study indicating significantly higher shared environmental effects in males (Rhee et al., 2003). In contrast however, substantially higher shared environmental estimates were obtained for females on a measure of ever used tobacco in a study by Han (1999) and colleagues. Additionally, one study revealed that genetic factors did not account for any of the variance in smoking involvement for males (White et al., 2003).

Alcohol. Numerous studies have investigated the heritability of alcohol abuse and dependence in males and females. It is well accepted genetic factors play an important role for both sexes (Agrawal & Lynskey, 2008; Heath, 1995; Kendler et al., 2008; McGue, 1999; Prescott, Aggen, & Kendler, 1999; Prescott & Kendler, 1999; Svikis, Velez, & Pickens, 1994). Heritabilities range from 0% (McGue, Pickens, & Svikis, 1992) to 56% (Kendler, Heath, Neale, Kessler, & Eaves, 1992) in females and studies have consistently found heritabilities ranging from 50-60% in males (Prescott & Kendler, 1999). Analogous heritability estimates have been shown for heavy consumption of alcohol (Agrawal & Lynskey, 2008; Heath & Martin, 1994).

During adolescence, alcohol use has a relatively small heritability however, frequency of use appears to have a stronger genetic component (Han et al., 1999; Hopfer et al., 2003; Koopmans et al., 1997; Koopmans et al., 1999; Rhee et al., 2003; Viken et al., 1999). Also similar to nicotine use, shared environmental factors have been implicated in alcohol use during adolescence (Han et al., 1999; Hopfer et al., 2003; Koopmans & Boomsma, 1996; Koopmans et al., 1997; Maes et al., 1999; Pagan et al., 2006; Rhee et al., 2003; Viken et al., 1999). For example, in one study 88% of the
variance in drinking could be attributed to shared environmental effects (Koopmans & Boomsma, 1996). Similarly, individual variance in drinking to intoxication during adolescence is also impacted by both genetic and shared environmental factors (Viken et al., 1999).

**Illicit Drugs.** The familial resemblance of illicit drug abuse/dependence in both males and females is in large part due to genetic factors (Agrawal et al., 2005; Jang et al., 1997; Karkowski, Prescott, & Kendler, 2000; K. S. Kendler, & Prescott, 1998; Kendler, Karkowski, & Prescott, 1999; K. S. Kendler & Prescott, 1998; Tsuang, Lyons, & Eisen, 1996; Tsuang et al., 1998; van den Bree, Johnson, Neale, & Pickens, 1998). For example, one study indicates that the variance in any drug abuse or dependence could be attributed to 47% and 79% genetic and 4% and 9% shared environmental factors in females and males, respectively (van den Bree et al., 1998).

Studies investigating illicit drug use have found similar results (Agrawal et al., 2005; Karkowski et al., 2000; K. S. Kendler, Karkowski et al., 1999; van den Bree et al., 1998). For example, one study attributed the individual variance for drug use to 23% and 16% genetic influences and 69% and 23% shared environmental influences in females and males respectively (van den Bree et al., 1998). Jang and colleagues (1997) also report additive genetic and shared environmental influences of similar magnitude for females on the question “I have used a number of illicit drugs”.

Genetic factors have also been implicated for illicit substance use/misuse in adolescence but, heritability estimates are generally smaller than those reported in adult samples (Han et al., 1999; Hopfer et al., 2003; Koopmans et al., 1997; Maes et al., 1999;
Genetic factors have, however, been shown to have a modest to moderate impact on problem use compared to measures of any use or initiation (Rhee et al., 2003). Analogous to nicotine and alcohol, shared environment is also important for the use and misuse of illicit drugs in adolescence, often much more so than genetic factors (Han et al., 1999; Maes et al., 1999; Rhee et al., 2003).

Taken together, the aforementioned results suggest that genetic factors are more important for the development of a substance use disorder while shared environment is more important for use. In fact, this is what previous research shows. Shared environmental factors have been shown to be more important for the use of illicit substances than for the progression to an illicit substance use disorder in females (Karkowski et al., 2000; Kendler, & Prescott, 1998; Kendler et al., 2008).

**Specificity and Developmental Trajectory of Familial Factors**

Twin studies have examined the specificity of the genetic and environmental influences on substance use as well as for a developmental trajectory on these influences. These studies are investigating (a) whether the genetic and environmental risk factors on substance use are substance specific or indicate a “general vulnerability” and (b) whether the genetic and environmental influences on substance use change across development, typically from early childhood through adulthood.

Results of these studies indicate that the genetic risk for substance use/misuse is not substance specific. This genetic risk predisposes individuals to a general vulnerability to use or misuse a wide range of substances (Kendler et al., 2003; Tsuang et al., 1998; Young et al., 2006). For example, examining illicit substance use and
dependence in adult male twins, results indicated that both the genetic and shared
environmental effects on the risk for use and misuse were largely or entirely nonspecific,
while unique environmental experiences determined which substance predisposed
individuals would use (Kendler et al., 2003).

This general vulnerability also occurs across substance classes and in adolescence
(Han et al., 1999; Young et al., 2006). For example, Han and McGue (1999) report that a
common underlying factor accounts for the covariation among tobacco, alcohol, and
other substance use in adolescence. Familial factors accounted for a majority of the
variance on this common factor, with genetic factors accounting for 23% and shared
environment 63%. However, one study revealed that the genetic risk factors for
substance dependence could not be explained by a single factor. Rather, two factors were
needed, one predisposing largely to illicit drug dependence and the other primarily to licit
drug dependence (Kendler, Myers, & Prescott, 2007).

Examining whether the genetic and environmental influences on substance
use/misuse change over development exhibits interesting results. In general, it’s
suggested that genetic influences are relatively small during childhood and increase
through adolescence and adulthood, while shared environmental factors are more
important during childhood and decrease across development (B. M. Hicks et al., 2007;
Kendler et al., 2008; Koopmans et al., 1997; Malone et al., 2004; Pagan et al., 2006;
Viken et al., 1999; White et al., 2003). For example, examining alcohol use from
adolescence into early adulthood Pagan and colleagues (2006) report that shared
environmental factors play a large role in initiation however, no shared environmental factors were implicated on alcohol problems in early adulthood.

Taken together, there is substantial evidence for genetic influences on nicotine, alcohol, and illicit drug use and misuse. These genetic factors appear to be nonspecific; simply predisposing individuals to use or misuse substances in general. Genetic factors also change throughout development, with increasing influences through adolescence and young adulthood.

*Sex-Differences in the Genetic Risk for Substance Use/Misuse*

In contrast to eating disorder research, much more research has examined the genetic epidemiology of substance use/misuse in both sexes. Similar to eating disorder research however, fewer studies have examined sex-differences in genetic risk by implementing sex-limitation twin models. Most twin studies examining differing genetic risks in males and females have simply compared heritability estimates by inspection. As previously described, most studies find similar heritability estimates in males and females. However, there is a general trend for heritability estimates to be greater in males compared to females. Specific results in regard to nicotine, alcohol, and illicit drugs will be discussed.

*Nicotine.* Studies examining sex-differences in the genetic risk for nicotine use/misuse are limited. Much of this research has focused on alcohol and illicit drugs. However, in a meta-analysis examining genetic and environmental effects on smoking behavior in males and females, results indicate that genetic factors play a greater role for smoking initiation in females, while genetic factors were more important for males for
smoking persistence (Li et al., 2003). Li and colleagues also report that shared environmental influences are significantly greater in females for smoking persistence and significantly greater in males for smoking initiation. However, within adolescent samples genetic factors appear consistent in males and females. Implementing sex-limitation models, no quantitative differences were found for initiation, use, problem use and dependence of tobacco (Boomsma et al., 1994; Han et al., 1999; Koopmans et al., 1999; McGue et al., 2000; Rhee et al., 2003).

Alcohol. Studies examining sex-differences in the genetic risk for alcohol use/misuse have revealed somewhat inconsistent results. Typically heritability estimates are greater for alcohol use/misuse in males (Han et al., 1999; Hicks et al., 2007; Poelen et al., 2008; Svikis et al., 1994) however, the reverse has also been shown (Hicks et al., 2007; Prescott et al., 1999). For example, one study found a significant sex-difference in the heritability estimates for alcohol dependence, with females having a higher estimate compared to males at age 17 (Hicks et al., 2007). This indicates a quantitative sex-difference in risk. Authors did however, report the reverse effect at age 24 with males having a significantly higher heritability (Hicks et al., 2007). Quantitative and qualitative sex-differences have also been revealed in the genetic and nonshared environmental influences on alcohol abuse and dependence (Prescott et al., 1999). In contrast, additional reports examining adolescent samples provide no evidence for quantitative sex-differences in the genetic and environmental risk factors for drinking initiation, frequency of drinking, drinking to intoxication, problem use, and frequency of intoxication (Han et al., 1999; Poelen et al., 2008; Rhee et al., 2003; Viken et al., 1999).
Illicit Drugs. Research examining sex-differences in the genetic risk for illicit drug abuse/dependence have generally found stronger heritabilities for males than for females (van den Bree et al., 1998). In one such study, males were shown to have a significantly higher heritability for drug dependence at age 17 compared to females (Hicks et al., 2007). However, some studies indicate similar genetic and environmental risk factors. For example, examining quantitative sex-differences in illicit and licit drug dependence no differences have been found between males and females (Agrawal et al., 2005; Kendler et al., 2007). In regard to illicit drug use, results consistently find similar heritability estimates for males and females (van den Bree et al., 1998). Similarly, no sex-differences were found for illicit drug use or abuse in an adolescent sample (Han et al., 1999; McGue et al., 2000).

Taken together, results suggest that the genetic risk factors for substance use/misuse are the same in adolescence however, often differ significantly in magnitude during adulthood. It is still unclear however, whether a sex-difference exists in the specificity and developmental trajectory of substance use/misuse.

Study Two: Purpose Statement

The purpose of this investigation is to answer the following questions: (a) is there a general vulnerability to substance use/misuse occurring throughout adolescence to young adulthood, (b) if so, do the genetic and environmental influences on this general vulnerability change across development, and (c) do these influences differ between males and females? From previous research hypotheses can be made. A general vulnerability will be exhibited for substance use/misuse across development with genetic
factors increasing in importance and shared environmental factors decreasing in importan
tance from adolescence to young adulthood. We will also find no evidence for sex-
differences in the genetic and environmental influences on substance use/misuse.
Chapter 6 Method

Participants

The same participants from TCHAD that were discussed in study one will be utilized for the current study. However, all three assessment waves will be utilized. This includes 1,480 twin pairs assessed at ages 13-14, 16-17, and 19-20.

Measures

Substance Use (Appendix A). All information for the current study was drawn from self-report questionnaires. Substance use information was asked at waves 2, 3, and 4. Waves 3 and 4 have relatively similar questions while wave 2 questions were slightly different including more frequency options. The exact differences between questions can be viewed in the Appendix. Because of these differences in questions asked, questions regarding nicotine, alcohol, and illicit drug use were broken down into categorical variables in order to make the questions comparable across waves. Categories were created based on wave 2 questions. Wave 2 questions regard specific frequency options as “never”, “sometimes”, and “often”. These frequencies were used to establish never, sometimes, and often within waves 3 and 4.

A category was created for “regular” smoking which includes the following categories: not a smoker, smoke sometimes/once in a while, and smoke often. The “not a smoker” category includes those individuals who responded stating they’ve never smoked and also those individuals who indicated they have only “tried it” or “quit” and don’t consider themselves smokers. This was done because of the phrasing of the
question. Participants were asked: “are you a smoker?” and two responses state: “No, I’ve only tried it” or “No, I quit”. The three alcohol use categories indicate whether or not the twin has ever been intoxicated (never), if they get intoxicated sometimes, or intoxicated often. The “never” intoxicated category includes those individuals who responded stating they don’t use alcohol as well as those participants who stated they’ve used but never been intoxicated. Categories were reflected to indicate intoxication because the wave 2 alcohol use question simply asks the twin about their intoxication frequency while waves 3 and 4 ask the twin whether they have drank alcohol followed-up with intoxication frequency questions.

A binary category was created for illicit drug use indicating whether or not the twin has used any type of illicit drug. This was done because at waves 3 and 4 the questionnaire simply asks participants whether or not they have ever used illicit drugs. If the participants answer yes, they are then asked to identify which illicit drugs they have ever used from a list. At wave 2 participants were only asked if they have ever tried illicit (identified as narcotic) drugs and not asked to identify which drugs were used. This made making multiple categories across waves difficult.

Unfortunately, this questionnaire is not standardized so there is no information about psychometric properties. In the future, it would be important to assess the reliability of these measures obtained across waves since the information is available.

**Statistical Analyses**

*Univariate Twin Model-Fitting Analyses*
Univariate analyses will be conducted on all substance use/misuse variables as described within the twin methodology section of study one. Again, these analyses were conducted in males and females separately. However, sex-differences were not examined at the individual substance level as was done for the disordered eating data. This was decided *a priori* because the author had a greater interest in examining sex-differences at the multivariate level rather than at the univariate level and also to limit the number of analyses conducted as a multitude of possible models could be used to examine this data.

*Multivariate Twin Model-Fitting Analyses*

Multivariate analyses will be conducted with the substance use/misuse data similar to that described in study one. However, because the substance use data is available across multiple assessment waves additional analyses will be conducted. First, a common pathway model, as previously described, will be fit to the three substance use variables (nicotine, alcohol, and illicit drug) within the three assessment waves, in males and females separately and compared to the fit of the independent pathway model. This will be done in order to assess whether a common, underlying latent factor is responsible for substance use at each wave, regardless of the specific substance being used. The best-fitting model (common vs. independent) will then be used in follow-up analyses examining for developmental change and sex-differences.

*Longitudinal, Multivariate Twin Model-Fitting.* Finally, a multivariate model examining all three waves simultaneously will be examined. This model will be identical to that described for study one, with the addition of longitudinal analyses. Because we have multiple substance use measures, as well as information from multiple waves, we
are able to conduct a multivariate longitudinal model with the substance use data. This model will be conducted with all five zygosity groups allowing for the examination of quantitative and qualitative sex-differences. A discussion of these sex-differences is provided in study one. This model will provide sex-dependent genetic and environmental parameter estimates as well as the correlation between the genetic factors responsible for substance use in males and females. This model is shown in Figure 3 and has three main features. First, it contains a common substance use factor for each assessment wave (i.e. common factor for wave 2, 3, and 4). These common factors encompass those influences that impact the three specific substances: nicotine, alcohol, and illicit drug use. These common factors are then themselves influenced by genetic and environmental parameters which are parameterized as a trivariate Cholesky decomposition (Kendler, Gardner, Annas, & Lichenstein, in press).

Within this multivariate, longitudinal Cholesky decomposition, the first additive genetic factor influences the common substance use factor at all three time waves. The second genetic factor influences the common substance use factor at wave 2 and wave 3 while the third genetic factor only influences the common factor at wave 3. If the additive genetic risk factors for the common substance use factor were highly stable over time we would expect the paths from the first genetic factor to be large across all three waves while the paths from the second and third genetic factors would approach zero (Kendler, et al., in press). In contrast, if the genetic risk factors for the common substance use factors change across development there would be large estimates arising from the second and third common substance factor paths indicating innovation, or new
genetic influences (Kendler). The structure of shared and unique environmental influences on the substance use common factor is similarly indicated.

Secondly, this model contains paths from each of the common substance use factors to the specific substances at each time wave. These paths indicate the degree to which the liability to the use of the individual substances is reflected by the common factor. Finally, this model also includes residual genetic and environmental influences that are specific to each substance. Similar to the three common factors, these factors are also modeled as a trivariate Cholesky decomposition. This includes additive genetic and environmental influences that are time and substance specific as well as cross paths within-substance cross-time. For example, regular smoking at wave 4 includes additive genetic factors from waves 2 and 3 as well as any residual genetic factors accounted for regular smoking at wave 4 that are not accounted for by the residual effects of the previous two waves. The magnitude of these paths is interpreted in the same way as described above for the common factors.

The Bayesian information criterion (BIC) will be used to determine best-fitting models (i.e. comparison of common and independent pathways). The BIC is a function of a model’s df and χ² (Raftery, 1995). Models that provide the best fit while retaining the fewest parameters yield lower BIC values.

All twin analyses in the current study will be conducted using a raw data approach in the statistical package Mx (M. C. Neale, 1997). This approach allows data from both incomplete and complete twin pairs to be utilized. Mx is a program used for SEM and is
popular in the use of twin analyses. It is similar to commercial software used for SEM.

Mx allows for maximum-likelihood model fitting analyses.

Figure 3. Genetic components of the full model fitted to self-report measures of nicotine (SM), alcohol intoxication (ETOH), and illicit drug use (DU) at ages 13-14 (SU 13-14), 16-17 (SU 16-17), and 19-20 (SU 19-20). This model includes both a common substance use factor and specific effects on each specific substance at each assessment wave. Genetic and environments effects on the common and specific substances are modeled as a trivariate Cholesky decomposition with the first factor accounting for effects over the three waves, the second factor accounting for effects at waves 2 and 3 and the third factor impacts only wave 3. Common and unique environmental components broken down similarly.

SU = substance use; SM1 = nicotine use wave 2; ETOH1 = alcohol intoxication wave 2; DU1 = illicit drugs wave 2; SM2 = nicotine use wave 3; ETOH2 = alcohol intoxication wave 3; DU2 = illicit drugs wave 3; SM3 = nicotine use wave 4; ETOH3 = alcohol intoxication wave 4; DU2 = illicit drugs wave 4.
Chapter 7 Results

Descriptive Statistics

Table 6 presents the frequency of substance use within the sample across all three waves. In general, the rates of substance use increase across waves. With the exception of smoking at wave two, alcohol intoxication was the most prevalent substance use in all waves.
Table 6

Frequency of Substance Use

<table>
<thead>
<tr>
<th>Substance</th>
<th>Wave 2</th>
<th>Wave 3</th>
<th>Wave 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>75 (n = 1683)</td>
<td>78.4 (n = 1850)</td>
<td>73.4 (n = 1241)</td>
</tr>
<tr>
<td>1</td>
<td>23.4 (n = 526)</td>
<td>13.7 (n = 324)</td>
<td>14.8 (n = 250)</td>
</tr>
<tr>
<td>2</td>
<td>2.0 (n = 41)</td>
<td>8.0 (n = 187)</td>
<td>11.8 (n = 199)</td>
</tr>
<tr>
<td>Alcohol Intoxication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>82.5 (n = 1857)</td>
<td>38.3 (n = 876)</td>
<td>12.5 (n = 210)</td>
</tr>
<tr>
<td>1</td>
<td>16.4 (n = 365)</td>
<td>36.2 (n = 827)</td>
<td>46.6 (n = 784)</td>
</tr>
<tr>
<td>2</td>
<td>1.1 (n = 25)</td>
<td>25.6 (n = 585)</td>
<td>41.0 (n = 690)</td>
</tr>
<tr>
<td>Illicit Drug Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>98.5 (n = 2225)</td>
<td>95.4 (n = 2247)</td>
<td>86.7 (n = 1451)</td>
</tr>
<tr>
<td>1</td>
<td>1.4 (n = 32)</td>
<td>4.6 (n = 108)</td>
<td>13.3 (n = 222)</td>
</tr>
</tbody>
</table>

Note. % = percentage of sample. N = number of individuals in sample. Percentages may not equal 100% due to rounding error.
**Twin Correlations**

Within wave twin correlations by sex are presented in Table 7. Overall, the pattern of correlations suggests genetic influences on all substances as most observed correlations in MZ twins are higher than those observed in DZ twins. The only exception to this pattern is illicit drug use at Wave 2 for females where correlations suggest strong shared environmental effects are of importance since the DZ correlation is higher than the MZ correlation. Importantly, there was a low frequency of individuals who endorsed using illicit drugs at Wave 2 which makes these results very statistically unstable.

Shared environmental effects are also indicated for several of the substances as the DZ correlation exceeds half that of the MZ correlation. The correlations between opposite-sex twin pairs suggest that the familial factors influencing substance use are not entirely the same in the sexes because, in general, the observed correlations are lower than those observed in same-sex DZ pairs. However, these correlations are greater than zero suggesting that some familial factors influence both male and female liability to substance use. Finally, comparing the MZ correlations between male and female pairs suggests two interesting findings. First, smoking appears to be more heritable in females than males at younger ages but this difference becomes almost non-existent in late adolescence. Second, alcohol intoxication is similarly heritable at younger ages in males and females but increases in females in adolescence and decreases in males.
Table 7

*Twin Correlations for Substance Use/Misuse Across Waves*

<table>
<thead>
<tr>
<th>Substance</th>
<th>Females MZ(DZ)</th>
<th>Males MZ(DZ)</th>
<th>Opposite-Sex Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wave 2</td>
<td>Wave 3</td>
<td>Wave 4</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.96</td>
<td>0.85</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>(0.58)</td>
<td>(0.58)</td>
<td>(0.66)</td>
</tr>
<tr>
<td>Alcohol Intoxication</td>
<td>0.84</td>
<td>0.82</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>(0.59)</td>
<td>(0.69)</td>
<td>(0.33)</td>
</tr>
<tr>
<td>Illicit Drug Use</td>
<td>[-0.81*]</td>
<td>0.92</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>(0.99)</td>
<td>(0.52)</td>
<td>(0.60)</td>
</tr>
</tbody>
</table>

Note. MZ = Monozygotic twin pairs. DZ = Dizygotic twin pairs. DZ twin pair correlations shown in parentheses.

Opposite-sex twin pair correlation between male and female of pair.

* [not] a meaningful correlation. Results from the lack of any concordant twin pairs.
**Univariate Twin Analyses**

As seen in Table 8, model-fitting results indicate both genetic and shared environmental influences are important for a majority of the substance use/misuse variables examined. Differences were however, revealed between males and females and across waves. First, in regard to smoking, results suggest that genetic factors are slightly more important for females across the waves and shared environment more important for males at waves two and three. However, across the waves genetic factors decrease and shared environmental effects increase for both sexes. Second, for alcohol intoxication, genetic factors appear more important for males and shared environment for females at Wave 2. However, estimates become similar at Wave 4 with only genetic and unique environment factors remaining important. Lastly for illicit drug use, genetic factors increase in importance for females at Wave 3 and remained similar in Wave 4. For males, shared environment increased in importance for illicit drug use across waves.
Table 8

*Results from Univariate Analyses of Substance Use Variables*

<table>
<thead>
<tr>
<th>Substance</th>
<th>Wave 2</th>
<th>Wave 3</th>
<th>Wave 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>a²</td>
<td>c²</td>
<td>e²</td>
</tr>
<tr>
<td></td>
<td>72 (56)</td>
<td>24 (26)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Alcohol Intoxication</td>
<td>a²</td>
<td>c²</td>
<td>e²</td>
</tr>
<tr>
<td></td>
<td>43 (54)</td>
<td>42 (24)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Illicit Drug Use</td>
<td>a²</td>
<td>c²</td>
<td>e²</td>
</tr>
<tr>
<td></td>
<td>0 (27)</td>
<td>90 (29)</td>
<td>10 (45)</td>
</tr>
</tbody>
</table>

Note. Male parameter estimates shown in parentheses. Percentages may not equal 100% due to rounding error.

Table 9

*Model-fitting results for Within Wave Common and Independent Pathway Models*

<table>
<thead>
<tr>
<th>Model BIC</th>
<th>Wave 2</th>
<th>Wave 3</th>
<th>Wave 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Pathway Model</td>
<td>-5859.36</td>
<td>-5699.18</td>
<td>-4438.00</td>
</tr>
<tr>
<td></td>
<td>(-5525.62)</td>
<td>(-5224.65)</td>
<td>(-2700.25)</td>
</tr>
<tr>
<td>Independent Pathway Model</td>
<td>-5849.13</td>
<td>-5690.91</td>
<td>-4429.00</td>
</tr>
<tr>
<td></td>
<td>(-5514.30)</td>
<td>(-5208.13)</td>
<td>(-2691.13)</td>
</tr>
</tbody>
</table>

Note. BIC = Bayesian Information Criterion. Male model-fits shown in parentheses.
Multivariate Twin Analyses

For all waves in both males and females the common pathway model fit better than the independent pathway model. The exact model fits are shown in Table 9. This suggests a general vulnerability to substance use/misuse is occurring throughout adolescence to young adulthood. Because of this, the common pathway model will be used in the follow-up longitudinal analyses.

Longitudinal Model. Path estimates from the longitudinal, multivariate substance use/misuse model are shown in Figure 4. Unfortunately, we were unable to estimate quantitative and qualitative sex-differences within this model so we could not obtain sex-dependent parameters. As discussed in study one, the power is low to detect quantitative and qualitative sex-differences without large sample sizes and our sample size likely did not provide us with enough power to complete this analysis. Technical problems were insurmountable with this model and we were unable to obtain reasonable and accurate results within the model estimating sex-dependent parameters. The model in Figure 4 therefore, includes no quantitative or qualitative sex-effects and contained A,C and E impacting the general substance use/misuse factors and A,C and E influences that are substance specific.

Several results are noteworthy. Examining the factor loadings of the substances across time reveals that illicit drug use becomes a better representative of the latent factor with increasing age while smoking and alcohol intoxication become less representative as the twins age. Focusing on the general substance use factors, total heritabilities remain
relatively stable across development. Heritabilities were estimated at 44% for age 13-14 and 16-17 and at 45% for age 19-20. Genetic effects on the common factors also demonstrated evidence for stable and developmentally dynamic risk. While genetic factors at age 13-14 did account for a moderate amount of the genetic effects at age 16-17 (68%) and 19-20 (82%), some innovation was exhibited. Of the total genetic influences at Wave 3, 32% (14% out of a total of 44%) are new genetic factors specific to age 16-17, and at Wave 4, 18% (8% out of a total of 45%) of the genetic influences are new.

In regard to environmental effects, shared environmental influences on the common factor declined across the three ages and new effects virtually disappeared in young adulthood. These effects also demonstrated evidence of stable and developmentally dynamic risk. Shared environmental factors at age 13-14 accounted for 83% (38% out of a total of 46%) of the variance at age 16-17 and 56% (20% out of a total of 36%) at age 19-20. A small amount (8%) of new shared environmental effects was introduced at age 16-17. Common unique environmental effects increased slightly in importance across waves and showed almost no continuity.
Figure 4. Path estimates for multivariate, longitudinal common pathway model.

SU = substance use; SM2=smoking wave 2; ETOH2=alcohol intoxication wave 2;
DU2=illicit drugs wave 2; SM3=smoking wave 3; ETOH3= alcohol intoxication wave 3;
DU3=illicit drugs wave 3; SM4=smoking wave 4; ETOH4= alcohol intoxication wave 4;
DU4=illicit drugs wave 4.
Examining the substance specific estimates also provides interesting results. Total heritability estimates for each of the substances as well as the sources of those genetic effects are shown in Table 10. For example, for illicit drug use, the total heritability at age 13-14 was 18%. This came from two sources: 8% from the common factor and 10% from genetic effects specific to illicit drug use. At age 16-17 the total heritability was 56%. The common and specific effects now come from two sources. For the common effects, 14% come from genetic factors that began at age 13-14 and 6% are new genetic factors at age 16-17. For specific effects, 36% are from genetic factors that began at age 13-14 and have a continued effect up to age 16-17, and 0% are from new genetic factors at age 16-17. At age 19-20, the heritability for illicit drug use increased further to 63%, of which 31% comes from specific genetic effects and 32% from the common genetic substance use factor. The common and illicit drug use specific effects at age 19-20 now have three sources. For specific effects, 11% are genetic factors that began at age 13-14 and have continued effect at age 19-20, 7% are genetic factors that began at ages 16-17 and are also impacting at age 19-20 and 13% are genetic effects specific to illicit drug use at age 19-20. Total common genetic effects include 6% new genetic factors at age 19-20, 2% that are carried over from age 16-17 and 25% that began at age 13-14 and have continued in effect.
Table 10

*Estimates of and Sources for Additive Genetic Effects on Smoking, Alcohol Intoxication, and Illicit Substance Use*

<table>
<thead>
<tr>
<th>Factor/Sources</th>
<th>Age 13-14</th>
<th>Age 16-17</th>
<th>Age 19-20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time1</td>
<td>Total</td>
<td>Time1</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td>38</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>46</td>
<td>46</td>
<td>33</td>
</tr>
<tr>
<td><strong>Alcohol Intoxication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td>34</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>36</td>
<td>39</td>
<td>44</td>
</tr>
<tr>
<td><strong>Illicit Drug Use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific</td>
<td>10</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>General</td>
<td>8</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>18</td>
<td>56</td>
<td>63</td>
</tr>
</tbody>
</table>

Note. T1 = contribution from time1 or ages 13-14. T2 = contribution from time2 or ages 16-17. T3 = contribution from time3 or ages 19-20.
Several patterns shown in the Table 10 are worth noting. First, with the exception of smoking, total heritabilities increase across the three waves. Illicit drug use has the highest heritability at age 19-20, estimated at 63% and smoking the least estimated at 33%. For alcohol intoxication a smooth trend of genetic effects becoming more specific across the waves was revealed. However, this trend was not as clear for smoking and illicit drug use. For illicit drug use, specific genetic effects increased at age 16-17 and remained fairly stable to age 19-20. In contrast, specific genetic effects for smoking remained somewhat stable across ages. The cross-time continuity in the specific genetic effects also differed widely across the substances being highest for illicit drug use and lowest for smoking.

The picture for environmental effects was somewhat different. For smoking a clear trend of the specific shared environmental factors increasing across development was revealed, which was somewhat unexpected (Table 11). However, for alcohol intoxication these specific effects increased slightly at age 16-17 and remained consistent at age 19-20. Illicit drug use shared environmental specifics decreased substantially across development. Specific unique environmental effects are less clear (Table 12). For smoking, specific unique effects increased across the three ages while for alcohol intoxication specific effects at 13-14 and 16-17 remained similar and almost doubled at age 19-20. For illicit drug use almost no specific environmental influences were estimated at any age.

The cross-time continuity in the specific environmental effects also differed widely across the substances. For shared environment, a greater continuity across waves
was seen for illicit drug use at age 16-17 and for smoking at age 19-20. Very little shared environmental continuity was revealed for alcohol intoxication at any wave. Similarly, specific unique environmental effects did not show a substantial amount of continuity across waves. However, a small amount of the shared environmental variance from age 13-14 and 16-17 continued at age 19-20 for smoking.
Table 11

*Estimates of and Sources for Shared Environmental Effects on Smoking, Alcohol Intoxication, and Illicit Substance Use*

<table>
<thead>
<tr>
<th>Factor/Sources</th>
<th>Age 13-14</th>
<th>Age 16-17</th>
<th>Age 19-20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time1</td>
<td>Total</td>
<td>Time1</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td>43</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Alcohol Intoxication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific</td>
<td>10</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>General</td>
<td>38</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Illicit Substance Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific</td>
<td>71</td>
<td>71</td>
<td>20</td>
</tr>
<tr>
<td>General</td>
<td>10</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>81</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

Note. T1 = contribution from time1 or ages 13-14. T2 = contribution from time2 or ages 16-17. T3 = contribution from time3 or ages 19-20.
Table 12

Estimates of and Sources for Unique Environmental Effects on Smoking, Alcohol Intoxication, and Illicit Substance Use

<table>
<thead>
<tr>
<th>Factor/Sources</th>
<th>Age 13-14</th>
<th>Age 16-17</th>
<th>Age 19-20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time1</td>
<td>Total</td>
<td>Time1</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td>6</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol Intoxication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific</td>
<td>11</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>General</td>
<td>5</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td><strong>Illicit Substance Use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Note. T1 = contribution from time1 or ages 13-14. T2 = contribution from time2 or ages 16-17. T3 = contribution from time3 or ages 19-20.
**Sex-Differences.** Because we were unable to examine quantitative or qualitative sex-differences on the common factors within the longitudinal model because of technical constraints likely due to inadequate sample size in certain sex-zygosity groups, we decided to examine the parameter estimates revealed in the within wave within sex common pathway models for indications of possible sex-differences. The estimates from these models are shown in Tables 13. As can be seen, the results obtained in the longitudinal model are, in general, an average of the results obtained in our males and females separately.

Table 13

**Genetic and Environmental Effects on Common Factors in the Within Wave Common Pathway Models By Sex**

<table>
<thead>
<tr>
<th></th>
<th>Wave 2</th>
<th>Wave 3</th>
<th>Wave 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a^2</td>
<td>c^2</td>
<td>e^2</td>
</tr>
<tr>
<td>Females</td>
<td>69</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Males</td>
<td>50</td>
<td>31</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>86</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>42</td>
<td>6</td>
</tr>
<tr>
<td>Estimates from longitudinal model</td>
<td>44</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>46</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>36</td>
<td>14</td>
</tr>
</tbody>
</table>

Note. Percentages may not equal 100% due to rounding error.
As can be seen in Table 13, estimates for the longitudinal model, in general, fall in between the separate male and female estimates. The only exceptions to this are the genetic and shared environmental estimates at Wave 2 for the longitudinal model. Genetic effects were estimated slightly higher and shared environmental slightly lower within the longitudinal model compared to the separate male and female estimates. Four patterns are noteworthy within the Table. First, for both males and females, shared environmental factors increased in importance at Wave 3 while genetic factors decreased. In fact, for males, genetic effects approached zero. However, at Wave 4 shared environment declined while heritabilities increased to rates similar to those of Wave 2. This pattern could account for the new genetic effects that “come on line” at Wave 3 within the longitudinal model. Second, genetic factors appear to be more important for females for the common factor at all three age periods compared to males. Third, shared environment appears to be similarly important at Wave 2 for the sexes but is 2-3 times more important in males for Waves 3 and 4. Fourth, unique environmental effects decrease in importance for males across the waves and for females increase from Wave 2 to 3 and remain stable at Wave 4.

These results suggest there may be quantitative differences in the genetic and environmental influences on our substance use common factors, most strikingly at age 16-17. Similarly, as previously noted, opposite-sex correlations are suggestive of qualitative differences because, in general, the observed correlations were lower than those observed in same-sex DZ pairs.
Chapter 8 Discussion

Summary of Findings

The purpose of study two was to address three questions. First we were interested in whether there is a general vulnerability to substance use/misuse occurring throughout childhood to young adulthood. As we hypothesized, results show there is, in fact, a general vulnerability to substance use that predisposes individuals to use a wide range of substances, specifically nicotine, alcohol, and illicit drugs. This pattern was shown at all three ages of assessment. Second, we addressed whether the genetic and environmental influences on this general vulnerability change across development. The longitudinal analysis showed that the genetic and environmental factors impacting this general vulnerability to substance use have both stable and dynamic elements. In general, genetic effects became more substance specific and shared environmental effects decreased across development which provides some support for our hypothesis that genetic effects would increase and shared environmental effects would decrease in importance across development. Finally, we wanted to examine if the genetic and environmental influences within this longitudinal model differ between males and females. Unfortunately, we were not able to address this question directly due to technical issues with the data. However, the results from the within wave within sex analyses reveal possible quantitative sex-differences.

Discussion of Findings

Specificity of Substance Use/Misuse
A limited number of studies have examined the structure of substance use/misuse as examined within the current study especially within younger populations. However, the results of the current study do corroborate previous research. Our results suggest there is a general vulnerability to substance use. That is, the genetic and environmental factors influencing substance use are not entirely substance specific, but place individuals at risk to use or misuse a wide range of substances. This was revealed in the within wave data because the common pathway models fit better than the independent pathway models. This suggests a similar pattern of general vulnerability is occurring within all three age periods assessed. However, it appears the representativeness of our common factor for the three substances changed across development. Factor loadings for smoking and alcohol intoxication decreased from childhood to young adulthood while loadings for illicit substance use increased.

These results are in line with a previous report that suggests a common underlying factor is responsible for the covariation among tobacco, alcohol, and other substance use during adolescence (Han et al., 1999). The heritability estimate for this substance use common factor was reported at 23% while shared environment contributed 62% and unique environment contributed 14% to the variance. Authors also reported that during adolescence smoking had the highest factor loadings on the common factor while illicit substance use had the lowest, which corroborates our results. Two additional studies examining the sources of covariance between tobacco and alcohol use provide similar results (Koopmans et al., 1997; Young et al., 2006). Young and colleagues (2006) reported that tobacco use, problem tobacco use, and alcohol use in adolescence have
significant genetic and shared environmental covariance. Koopmans and colleagues (1997) found that relationships between alcohol use and tobacco use were largely mediated by shared environmental factors from age 12-16 but by genetic factors from age 17-25. While these authors did not utilize a common pathway model approach, the genetic and environmental overlap found between the substances is suggestive of an underlying vulnerability.

Similar results are exhibited for adult samples examining substance use and dependence (Kendler et al., 2003; Swan, Carmelli, & Cardon, 1996; Tsuang et al., 1998). For example, Swan and colleagues (1996) posited that a single underlying factor was responsible for tobacco, alcohol, and coffee use in adult male twins. A substantial amount of the genetic variance for the substances was accounted for by this factor. A similar study examining the covariance of alcohol, tobacco, and caffeine use in adults also showed a common pathway model to fit better than an independent pathway model in males and females (Hettema, Corey, & Kendler, 1999). However, one study examining substance dependence in an adult male population, utilizing a wide range of substances, showed that two underlying, but highly correlated, factors were needed: one for illicit drug dependences and the other representing licit drug dependence (Kendler et al., 2007) This difference may explain why the factor loadings for our licit substances decreased.

*Developmental Trajectory*

Possibly some of the most interesting results of the current study come from aim two. Multivariate, longitudinal twin designs provide means to address more complex
questions about the genetic and environmental effects on behavior. Few studies have examined the developmental trajectory of the general vulnerability to substance use so the current results are somewhat novel.

The longitudinal modeling conducted in this study suggests that as our participants transitioned from childhood to young adulthood shared environmental factors became less important, both on the common factor and substance specific residuals. There was however, a small peak of new shared environmental effects during adolescence. The within wave within sex results also showed a dramatic increase in shared environmental effects at this time. It appears that within adolescence, not only is the same shared environmental factors (and amount of their impact) at play, but new factors also “come on line”. This slight increase in shared environmental factors is in contrast to some previous studies which have shown a smooth decline (Koopmans & Boomsma, 1996; Koopmans et al., 1997; Viken et al., 1999). These new effects may be due to a life transition in the lives of the participants during this age. For example, at the age of 16 Sweden adolescents’ transition to “upper secondary school”. This would be the equivalent of high school in the United States. During this time the students choose the type of studies they will pursue (e.g. vocational vs. university preparation). This could be impacting the results obtained at Wave 3 since the twins were assessed during this time period and may therefore account for the new shared environmental factors that appear. This impact would likely appear as shared environmental effects because both members of the twin pair (and all of the sample) would “share” this transition at the same time. However, similar to the current study, one study examining externalizing disorders
(which included alcohol, nicotine, and drug dependence) showed increasing environmental effects for females from age 17 to age 24 (Hicks et al., 2007)

In contrast to studies examining substance specific development trajectories, the current report also did not find a steady increase of genetic effects within the common factors (Hicks et al., 2007; Koopmans & Boomsma, 1996; Koopmans et al., 1997; Viken et al., 1999). The reasons for this discrepancy are difficult to determine, but it may be due to sample characteristics, length of assessment period, our use of a common factor, or the way our use variables were defined.

Results show common genetic influences slightly decrease in adolescence and then increase in young adulthood to a similar magnitude of those effects in childhood. However, substance specific genetic factors showed a steady increase from childhood to young adulthood. That is, our modeling suggests that, with increasing age, genetic influences on substance use tended to become more specific in their effect. This increase in effect is similar to previous studies examining specific substances. For example, examining several different aspects of adolescent alcohol drinking behaviors Viken and colleagues (1999) report that for all variables shared environmental effects declined from age 16 to age 17, while genetic effects increased. Interestingly, at age 16, shared environment had the greatest impact on most of the alcohol variables included within this study. This was most strikingly seen for alcohol initiation for which shared environment accounted for 79% of the variance (Viken et al., 1999). Similarly, 67% of drinking to intoxication at age 16 and 52% at age 17 was accounted for by the shared environment corroborating the current results. An additional study examining externalizing disorders
from late adolescence to early adulthood showed that genetic factors increased for males from age 17 to 24 (Hicks et al., 2007).

Compared to genetic and shared environmental influences, we found almost no continuity in unique environmental effects across development. This is not surprising given the fact unique environmental effects are also confounded with measurement error which would have a time specific impact. However, there was a very small amount of enduring effects for smoking from adolescence to young adulthood. One might also expect the impact of unique environmental effects to increase with increasing age as twins spend more time outside of the family home yet this pattern was not found. This may be reflected in the increase of substance specific genetic effects as one’s choice of nonfamilial environments might be genetically influenced (Viken et al., 1999). For example, in their examination of smoking behaviors from adolescence to young adulthood White and colleagues (2003) report that, after controlling for the smoking behaviors of peers and parents, the role of genetic effects was reduced by 100% at age 13-18 and by 30% at age 16-21.

Our small amount of unique environmental influences (both common and specific) was also a somewhat surprising result. This is especially true because unique environment includes measurement error. This lack of unique environmental influences estimated is most striking within illicit drug use as almost all of these environmental effects estimated were common in nature and in these types of models measurement error would arise within the specific estimates. However, examining the twin correlations in Table 7 corroborates this finding of lower unique environment. Several of the male and
female correlations reach 0.80 and 0.90 and a majority of the correlations exceed 0.50. This suggests that within our sample, there was a large amount of concordance between the individual twins (both MZ and DZ) for substance using behaviors. Similarly, Han and colleagues (1999) report a minimal amount of unique environmental variance (14%) on their substance use factor.

Examining the genetic and environmental influences of the specific substances also corroborates previous studies (Koopmans & Boomsma, 1996; Koopmans et al., 1997; Pagan et al., 2006; Viken et al., 1999). Total genetic effects for illicit drug use and alcohol intoxication increased across development. A similar pattern was revealed within our univariate results. However, for males, shared environment increased across development and became substantially important at age 19-20 within the univariate models. This discrepancy in results from our longitudinal and univariate modeling are likely due to the fact estimates were not allowed to vary by sex. In contrast, genetic influences slightly decreased for smoking from childhood to young adulthood. This pattern is corroborated by our univariate results in both males and females and by previous studies. For example, examining smoking during adolescence and young adulthood, White and colleagues (2003) reported that environmental factors played the greatest role in tobacco smoking among both adolescents and young adults.

Consistent with previous research, shared environmental effects for all three substances decreased across development (Koopmans & Boomsma, 1996; Koopmans et al., 1997; Viken et al., 1999). Within the longitudinal model for smoking, total shared environmental effects decreased from 46% to 38%, for alcohol intoxication from 48% to
25%, and for illicit drug use from 81% to 25%. In general, this pattern was again confirmed by our univariate results with the exception of smoking and illicit drug use in males where shared environmental effects increased. Again, this discrepancy in results is likely due to equating males and females in the longitudinal model. Interestingly, previous research also suggests that, for males, only environmental factors and no genetic effects, account for the variance of smoking behaviors at three assessment age (13-12; 16-21; 20-25; White et al., 2003). Additional research also suggests that shared environment continues to have an impact, albeit decreasing, on substance use until approximately 35-40 years of age (Kendler et al., 2008).

This finding that shared environment has more than a minimal or almost non-existent impact on our substance use variables adds to the increasing amount of literature showing the importance of shared (or family) environmental influences on psychological and behavioral outcomes. Until recently, research often argued that these influences on outcomes were minimal at best (McGue & Bouchard, 1998; Plomin, Asbury, Dip, & Dunn, 2001; Plomin & Daniels, 1987). However, similar to the current study, recent research examining genetically informative samples of adolescents tells a different story. Results show that in adolescence, shared environmental factors contribute substantially to individual differences in substance use (Agrawal & Lynskey, 2006; Hopfer, Crowley, & Hewkitt, 2003; Rende & Slomkowski, 2008; Rhee et al., 2003).

While twin studies examining for the specific shared environmental factors at play for substance use are in their infancy, a relative dearth of studies has examined specific environmental risks for substance initiation at the phenotypic level, especially in
childhood and adolescence. One of the most consistent findings is the importance of the peer group to initiation (Bauman & Ennett, 1996; Hawkins, Catalano, & Miller, 1992; Hops, Andrews, Duncan, Duncan, & Tildesley, 2000). However, recent research shows the causal influence of peers may be overestimated and due to a substantial degree to assortative friendship (Bauman & Ennett, 1996; Heath & Martin, 1988; Hill, Emery, Harden, Mendle, & Turkheimer, 2008; Kandel, 1996). Certain family environments also appear to play a role. For example, low levels of parental attachment and low parental monitoring predict initiation while proactive parents and clear parental communications discouraging use decrease the likelihood of initiation (Chilcoat & Anthony, 1996; Kosterman, Hawkins, Guo, Catalano, & Abbott, 2000; Sargent & Dalton, 2001; Stice & Barrera, 1995).

To date, two behavior genetic studies have sought to identify the sources of shared environmental variance on externalizing behaviors. One such study showed that 77% of the shared environmental variance in early substance initiation could be accounted for by peer deviance and parent-child relationship problems (Walden, McGue, Iacono, Burt, & Elkins, 2004). Examining additional externalizing phenotypes provides similar results. For example, approximately 15% of the shared environmental variance in adolescent delinquency can be accounted for by the parent-child relationship (Burt, McGue, Krueger, & Iacono, 2007).

Sex-Differences

Unfortunately we were unable to incorporate specific sex-differences in the genetic and environmental risk factors on the general vulnerability to substance use
within our longitudinal model. To the author’s knowledge only two previous studies have examined this. Han and colleagues (1999) examined for sex-differences in the underlying liability to tobacco, alcohol, and other substance use in adolescents. The authors report greater heritability estimates in males and greater shared environmental estimates in females. However, these differences were not significant. Hicks and colleagues (2007) examined for sex-differences and developmental change in the underlying liability to externalizing disorders (including nicotine, alcohol, and illicit drug dependence). They report increasing heritability estimates for males from age 17 to 24 on their “externalizing factor”. However, authors showed decreasing genetic variation and increasing environmental effects for females on this factor from age 17 to 24.

While we were not able to directly address these differences in our sample, we can make comparisons to these previous studies from our within sex within wave common pathway models. In contrast to both studies, our results show greater genetic variance in females and greater shared environmental variance in males across the three time waves. However, similar to our results, an additional cross-sectional study reported shared environment to be more important for males (Pagan et al., 2006; White et al., 2003). Pagan and colleagues (2006) reported 61% and 47% shared environmental variance in males and females for alcohol initiation, respectively, at age 25. Our results appear suggestive of quantitative differences but we were unable to assess whether the differences in estimates found were significant.

Currently, there is not enough information in the literature to draw definitive conclusions about sex-differences in the developmental trajectory of the underlying
liability to substance use. The information we have to date is limited and inconsistent. While it appears there may be sex-differences in the impact of genes and environment on these common factors across development, the differences obtained may not be significant.

Study Limitations and Strengths

In addition to the limitations discussed in study one with regard to the sample, there are limitations to the current study that warrant discussion. The most important limitation was our inability to differentiate between males and females within the longitudinal model. As previously noted, the statistical power to detect sex-differences is quite modest in the absence of very large samples (Prescott & Gottesman, 1993). While it is not quite clear why our models were unable to properly estimate male and female results in the combined longitudinal model, the most likely reason is low power. Therefore, it still is not known whether the same developmental trajectory would be exhibited in males and females.

Five important additional limitations warrant discussion. First, the substance use questionnaire is not standardized, so nothing is known about its’ psychometric properties. However, using self-report questionnaires does have strengths. Participants’ may be more likely to reveal private information in a self-report format compared to an interview correct. Second, the substance use data was categorized. Using the variables in the continuous format would have been ideal. However, in order to have comparable questions across waves the creation of categories was necessary. Third, our measures of substance use are over a relatively limited age period (13-20). This age range is likely
insufficient to detect all the important developmental processes in substance use. Fourth, the questions in regard to substance use were phrased differently across the waves. Finally, similar to study one, the rates of substance use may differ between the United States and Sweden which would impact the generalizability of results. However, the rates of substance use reported within our sample are similar to those reported in the United States. For example, the 2008 Monitoring the Future study reported annual prevalence of substance use in children in the United States. It was reported that 13% of 8th graders had been intoxicated and 14% had used any illicit drug within the past year. A lifetime prevalence of 20% for cigarette use was reported within this same sample (Monitoring the Future, 2008). These are similar to our 13-14-year-old 12-month-rates of cigarette use (25%) and alcohol intoxication (17.5%). However, our Swedish sample had a dramatically different prevalence for illicit drug use (1.4%) at this age. Therefore, there are likely differences between our sample and the United States in regard to aspects related to illicit drug use.

Despite its’ weaknesses, the current study has strengths. In addition to the general strengths in regard to the sample discussed in study one there are strengths specific to the current study. First, our analytic methods permitted us to examine both the continuity and discontinuity of the genetic and environmental effects unique to the individual substances as well as common to the substances. Second, we utilized substance use data rather than substance abuse or dependence. This again, decreases the possibility of bias and affords the opportunity to examine how these domains act at a more generalizable level.
Study Implications and Future Directions

The most important implication of the current study is in regard to the developmentally dynamic results obtained. Psychiatric genetics and gene identifying efforts in general, assume a static genome. That is, that the genetic effects on psychological traits are temporally stable. Findings of the current study, suggest that this assumption is, in fact, an incorrect one. This is especially true during adolescence where 14% of the genetic effects are new. Therefore, gene identification studies need to take into consideration the age of the sample being utilized and that genes found to be important for substance use within one age group may not be as important within another age group.

Another important implication is in regard to the increasing specificity of the genetic effects for the substances across development. While the common factor is a relatively good representative of our three substances, it is unclear what neurobiological or psychological processes are responsible for the increasing specialization of genetic effects. This would be an important area for future research to examine.

Lastly, our results have possible implications for the prevention of substance initiation. Significant evidence is provided for the importance of environmental-level influences on substance initiation, especially those environments shared between the twins. This could include the home environment or even the peer group environment. Our results suggest that, similar to genetic effects, shared environmental effects are also developmentally dynamic. Therefore, it may be especially important for parents to exert clear communications about their attitudes toward substance use and “practice what they
preach” by modeling substance abstinent behavior in the home throughout the course of the child’s development – even throughout adulthood. This is an important consideration for prevention efforts given the role of early initiation in later substance use and other externalizing behavior problems.

It will be important for future studies to examine this developmental trajectory across a wider range of age groups allowing for differences for males and females. Future research should also examine this trajectory and for differences between substance use and substance disorders. Additionally, it would be interesting to incorporate in specific illicit drugs rather than using a broad “any illicit drug use” category.
Chapter 9 Examination of the Genetic Covariation between Disordered Eating and Substance Use

Introduction

Comorbidity between psychiatric disorders is common place, especially within clinical settings. This phenomenon is described by Berkson, and within comorbidity research literature referred to as Berkson’s bias (Berkson, 1946). Berkson’s bias results because individuals with more than one disorder, whether psychological or physical, are more likely to seek treatment. Therefore, individuals with comorbid disorders are more likely to be found in clinical settings. Despite this bias, comorbibidity is often examined in clinical settings. We can also investigate comorbidity in community samples, which eliminates Berkson’s bias.

Review of the Literature

Eating Disorders and Substance Use/Misuse in Females

Within the comorbidity literature, research has shown there is a significant association between eating disorders and substance use/misuse. This association is strongest with Bulimia Nevosa (BN; Grilo, Sinha, & O'Malley, 2002; Holderness, Brooks-Gunn, & Warren, 1994). Despite the fact a clear association has been found, research is still sparse on why individuals with eating disorders are more likely to use substances and develop substance use disorders compared to the general population. Because of this, it is important to get a clearer understanding as to why these two disorders are commonly associated. The objective of the current project is to examine for common genetic and environmental influences on disordered eating and substance
use/misuse in males and females. We will be utilizing a community sample so eliminate the possibility of Berkson’s bias. The relation between disordered eating and nicotine, alcohol, and illicit drug use will be discussed in further detail.

**Nicotine.** Regular nicotine use is frequently exhibited in females with eating disorders; however, this association has not been given as much attention in the literature as associations with alcohol and illicit substance use. Despite this, previous research shows a higher proportion of females with BN are regular smokers when compared to controls or females with Anorexia Nervosa (AN; Bulik et al., 1992; Corte & Stein, 2000; Haug, 2001; Killen et al., 1987; Luce, Engler, & Crowther, 2007; Welch & Fairburn, 1996b; Wiederman & Pryor, 1996a, , 1996b). Females with BN also report more difficulty maintaining abstinence from smoking in part, because of concerns of gaining weight (Welch & Fairburn, 1996b). Compared to non-smokers, females who smoke are also more likely to meet at least one criterion for an eating disorder (John, Meyer, Rumpf, & Hapke, 2006).

Similar results have been found in adolescent samples. For example, a higher proportion of adolescents with BN are smokers compared to adolescents with AN (Killen et al., 1987; Wiederman & Pryor, 1996b; Wiseman, Turco, Sunday, & Halmi, 1998). The association between nicotine use and disordered eating may occur because of the belief that nicotine helps control appetite. This would be especially true for females with an eating disorder (French, Perry, Leon, & Fulkerson, 1994; McKee, Nhean, Hinson, & Mase, 2006; Welch & Fairburn, 1996b).
Alcohol. A myriad of studies report a significant association between eating disorders and alcohol abuse/dependence, especially BN. Rates of alcohol abuse/dependence in females with BN often range from 11-47% (Bulik, Sullivan, Carter, & Joyce, 1997; Corte & Stein, 2000; Dansky, Brewerton, & Kilpatrick, 2000; Franko et al., 2005; Grilo et al., 2002; Holderness et al., 1994). These rates are much higher than the 12-month prevalence of any alcohol use disorder recently estimated at 5% in a general population of females (Hasin et al., 2007). Females with comorbid BN and an alcohol use disorder also often report primary onset of the eating disorder (Bulik et al., 2004). Risk for developing an eating disorder is also strongly associated with alcohol misuse. It was shown that females with an increased risk for an eating disorder (as measured by the Eating Attitudes Test) are 3 to 4 times more likely to also be misusing alcohol (Gadalla & Piran, 2007).

Illicit Drugs. Females with eating disorders have significantly higher rates of illicit substance use and disorders than those without. Intriguing also, is the substantially higher rates of eating disorders among females with illicit substance abuse/dependence than those without (Brewerton et al., 1995; Bulik et al., 1992; Courbasson, Smith, & Cleland, 2005; Herzog, Keller, Sacks, Yeh, & Lavori, 1992; Holderness et al., 1994; Jackson & Grilo, 2002; Kassett et al., 1989; D. Krahn, 1991; Selby & Morenho, 1995; Welch & Fairburn, 1996a; Wiederman & Pryor, 1996a). This association is greatest with BN and AN binge purge type (Bulik et al., 1992; Holderness et al., 1994; Wiederman & Pryor, 1996a). Substance use disorders have also been shown to increase risk of eating disorder symptoms in adolescents (Shrier, Harris, Kurland, & Knight, 2003).
In a review of this literature, Holderness and colleagues (1994) report approximately 20% of females with drug abuse/dependence have a current or past history of BN or bulimic behaviors, 21.4% of females with BN have a current or past history of drug use, and 17% of BN females report a current or past history of substance abuse or dependence. For instance, Bushnell and colleagues (1994) reported that 32% of a clinical sample with BN and 24% of the general population with BN had a lifetime diagnosis of drug abuse/dependence. For comparison, the National Comorbidity Study (NCS) reports the lifetime prevalence of drug abuse in females in the general population is 4% which is substantially lower than the rates reported in females with BN.

Similarly, rates of eating disorder symptomatology reported in females with a history of drug abuse are much higher than the population base rate of BN. For example, in one study examining psychiatric disorders among drug dependent individuals, eating disorders were seen in 5% of the sample, a rate that is higher than the rate of eating disorders found in the general population (Compton, Cottler, Phelps, Abdallah, & Spitznagel, 2000).

In regards to specific drug use, studies have generally found marijuana, cocaine, and amphetamines to be the most frequently used illicit drugs among clinical samples of females with BN (Bulik et al., 1992; Walfish, Stenmark, Sarco, Shealy, & Krone, 1992). Epidemiological studies have found similar results (Duhm et al., 2002; Gadalla & Piran, 2007; von Ranson, McGue, & acono, 2002; Welch & Fairburn, 1996a). For instance, one study reports that 59% of a community sample of Caucasian females with BN had ever used marijuana and 21% qualified for an abuse diagnosis, 26% had used cocaine and 7%
qualified for a cocaine abuse diagnosis, and 26% had used a stimulant and 9% qualified for stimulant abuse (Duhm et al., 2002). For comparison, the National Household Survey on Drug Abuse reports 36.2% of females in the general population have used marijuana, 11.6% have used cocaine, and 7.6% have used stimulants in their lifetime; rates that are much lower than those seen in females with BN (National Survey of Drug Use and Health, 2007).

Eating Disorders and Substance Use/Misuse in Males

Very few reports have examined the comorbidity of eating disorders and substance use/misuse in males. However, studies investigating this association have found results similar to those utilizing female samples. For example, examining disordered eating attitudes and behaviors in a clinical sample of substance abusers, no significant differences were found between males and females on binge eating, inappropriate compensatory behaviors, dietary restraint, and body dissatisfaction (Jackson & Grilo, 2002). Within this same report, females did however, have higher scores on measures of eating concerns and weight and shape concerns. Alcohol and amphetamine use are also associated with increased risk for an eating disorder in males (Gadalla & Piran, 2007). Finally, examining general disordered eating attitudes and behaviors in an adolescent sample, cigarette use, binge drinking, and illicit drug use were significantly associated with disordered eating in males (Pisetsky, Chao, Dierker, May, & Striegel-Moore, 2008).

Disordered Eating and Substance Use/Misuse
Previous research on the comorbidity between eating disorders and substance use/misuse has not been definitive (Wiederman & Pryor, 1996a). It remains unclear whether the specific diagnostic category (AN vs. BN) increases risk of comorbid substance use/misuse or whether it is specific symptomatology that increases risk. Few studies have examined the relation between eating disorder symptomatology and substance use/misuse. However, there have been some intriguing results.

In general, research reveals the more severe the eating disorder symptoms the greater the number of substances classes used (Piran, 2006; Wiederman & Pryor, 1996a, , 1996b). In regard to specific substances, independent of diagnosis, caloric restriction is related to amphetamine use while binge eating is predictive of tranquilizer use (Wiederman & Pryor, 1996a). Severe bingeing is also consistently associated with alcohol use (Krahn, Kurth, Gomberg, E., & Drewnowski, A., 2005; Piran, 2005, , 2006)). Frequency of dieting in sixth grade was also reported to predict frequency of alcohol intake in ninth grade (Krahn et al., 1996). Purging behaviors have also been shown to be predictive of drugs typically used in social settings (i.e. alcohol, cocaine, and cigarettes) as well as the use of stimulants and amphetamines (Franko et al., 2005; Piran, 2005, , 2006; Ross, 1999; Wiederman & Pryor, 1996a). Finally, body image concerns and drive for thinness tend to be more prevalent in smokers compared to nonsmokers (Penas-Lledo, 2002; Wiseman et al., 1998).

Similar results are exhibited in adolescent samples. Disordered eating attitudes and behaviors are strongly associated with cigarette use, binge drinking, and illicit drug use in females (French et al., 1994; Killen et al., 1987; Pisetsky et al., 2008). Symptoms
of BN and AN in early adolescence also predict increases in substance abuse problems in late adolescence (Measelle, Stice, & Hogansen, 2006). Finally, weight concerns were shown to predict smoking initiation and drinking to intoxication one year later (Field et al., 2002).

**Comorbidity Hypotheses**

Even though the association between eating disorders and substance use disorders has been consistently demonstrated, the reasons for this association are poorly understood. Several hypotheses have been developed to explain this association. In a recent discussion of these hypotheses, Wolfe and Maisto (2000) partitioned them into two categories: shared etiology and causal etiology. Shared etiology hypotheses suggest both disorders have a common predisposition. Causal etiology hypothesis suggest having one disorder increases risk for developing the other disorder.

*Shared Etiology Hypotheses*

**Personality.** Wolfe and Maisto (2000) discuss four shared etiology hypotheses. An additive personality style is thought to predispose individuals to becoming addicted to both food and substance. Inherent to this hypothesis is that eating disorders, specifically BN, can be classified as an addictive disorder and that personality characteristics can be identified in both populations that make individuals vulnerable to these disorders (Yeary & Heck, 1989).

Classifying BN as an addiction is based on various arguments including: BN patients show an addiction like behavior, relatives of BN patients have high rates of substance abuse, and treatment for BN inspired by current treatments for addictions have
been beneficial (Vandereycken, 1990). Whether BN can be conceptualized as an addictive disorder is still debated (Krahn, 1991; Vandereycken, 1990; Wilson, 1991, 2000) and investigations comparing personality characteristics in females with eating disorders to females with substance use disorders have found both similarities and differences (Wolfe & Maisto, 2000). However, some researchers believe that the presence of a personality disorder, affective instability, and impulsivity place females with BN at an increased risk for developing a substance use disorder (Wolfe & Maisto, 2000).

**Family history.** The family history hypothesis states there is a shared etiology between substance use/misuse and BN because these two disorders have shared familial risk factors, whether they be environmental or genetic. Family studies have been conducted to assess whether these two disorders aggregate together within families. Studies show increased rates of substance abuse/dependence in relatives of bulimic females (Holderness et al., 1994; Kassett et al., 1989). However, studies investigating whether substance use disorder rates are increased in relatives of probands with BN, controlling for proband substance use disorder, have indicated BN and substance use disorders show independent familial transmission and do not show characteristics of cross-transmission (Kaye et al., 1996; Kendler et al., 1995; Schukit et al., 1996; von Ranson, McGue, & Iacono, 2002).

Because a familial predisposition for both disorders does not appear to adequately explain the relationship between the two, it has been thought that, if in fact these disorders do share familial risk factors, these risk factors must be mediated through some
other mechanism. This brings up the concept of the endophenotype. In psychiatry, the endophenotype is defined as “an internal phenotype(s) discoverable by a biochemical test or microscopic examination” (Gottesman & Gould, 2003) p.637 An endophenotype must be associated with the illness in the population, be heritable, primarily state-independent, and the endophenotype found in affected family members must be seen in nonaffected family members at a higher rate than in the general population (Gottesman & Gould, 2003). Therefore, a possible mediator, or endophenotype, between the familial risk factors for BN and substance use/misuse is impulsivity. Lilenfeld and colleagues (1997) hypothesized that a familial vulnerability for “multi-impulsivity” (Wiseman et al., 1999) and affective instability may contribute to the development of BN and substance dependence.

The authors developed this hypothesis based on their study examining the effects comorbid substance abuse has on psychiatric disorders in first degree relatives of females with BN. Authors report relatives of probands with comorbid substance use and BN had significantly higher lifetime rates of alcohol dependence, drug abuse, and drug dependence. Finally, results also show social phobia, panic disorder, and Cluster B personality disorders occurred at a higher rate in relatives of females with BN and substance abuse then with BN alone, and major depression occurred at higher rates in females with BN and substance use compared to controls. These results support a familial vulnerability for impulsivity because females with both BN and substance use come from families where there are problems with substance use disorders, anxiety, impulsivity, and affective instability. It is essential to note that most of the
aforementioned family studies look at substance abuse as a combination of alcohol and drug use or only investigate alcohol use.

In contrast to the aforementioned studies, one study did show evidence of shared familial factors on BN and illicit drug dependence. Utilizing a twin design, it was revealed that BN and illicit drug dependence share genetic risk factors. A genetic correlation of +0.39 was estimated between the genetic influences on BN and illicit drug dependence (Baker, Mazzeo, & Kendler, 2007). Therefore, it is still unclear whether eating disorders and substance use/misuse share a familial predisposition.

**Developmental perspective.** The last shared etiology hypothesis suggests that some females may be more susceptible to social and culture pressures for the thin ideal and for experimenting with drugs that are common in adolescence (Krahn, Kurth, Demitrack, & Drewnowski, 1992). This results in an increased risk for both eating disorders and substance abuse. Some support has been found for this hypothesis (Fisher, Schneider, Pegler, & Politano, 1991), however it “falls short in explaining why most female adolescences can engage in dieting behavior and recreational drug use without encountering serious problems or developing a disorder” (Wolfe and Maisto, 2000, p. 622).

**Brain Biology Hypotheses**

**Endogenous opioids.** Another hypothesis developed following the addiction model of both BN and substance abuse calls into play the role of endogenous opioids. This hypothesis does imply there is a shared etiology between the two disorders however, because these theories are at very different levels, this hypothesis is placed into its own
category. It is thought that the frequent co-existence of BN and substance use/misuse may be explained by a shared vulnerability “for addiction to exogenous substances and the endogenous opioids implicated in binge eating” (Wolfe and Maisto, 2000, p.621). As of yet, this hypothesis has not been tested empirically but work in this area is promising.

Causal Etiology Hypotheses

Self-medication. The self-medication hypothesis states individuals use substances to relieve painful affective symptoms. This has been applied to the BN-substance use/misuse relationship because of the high occurrence of depression among individuals with eating disorders (Bulik, 1987). This hypothesis proposes that females with eating disorders use substances in order to alleviate their depressive symptoms. There is insufficient support for this hypothesis at this time, so it is still unknown whether females with BN use drugs to alleviate their depression. It is possible females with BN use substances in order to dampen bulimic urges or as a way to deal with the self-disgust that often follows binge eating.

Another aspect of the self-medication hypothesis is that females with BN abuse substances in order to alleviate symptoms of anxiety. Again, this hypothesis arises from the fact that females with eating disorders have disproportionately high rates of anxiety disorders (Fornari et al., 1992). Most females with eating disorders and a comorbid anxiety disorder report their anxiety disorder preceded the eating disorder (Bulik et al., 1997). Therefore, proponents of this hypothesis believe that anxiety is the antecedent for substance abuse. However, it is unclear whether substances actually serve the function of
improving the mood of females with BN, so this hypothesis is purely speculative (Wolfe & Maisto, 2000).

*Food deprivation.* This hypothesis arises from animal study findings. Studies using rats have found that food deprivation results in increased rates of the self-administration of ethanol, cocaine, nicotine, amphetamine, phencyclidine, and etonitazene (Carroll, France, & Meisch, 1979). From this it has been hypothesized that with the removal of food, alcohol and drugs increase in reinforcement value, because food is no longer an available reinforcer. Carroll and colleagues also suggest that the reinforcing properties of substances are increased when food is deprived as a result of the pairings of internal hunger stimulation and substance reinforcement. However, food deprivation research using human subjects is sparse so it is unclear how this hypothesis will pan out in humans.

Taken together, research examining the etiology of the comorbidity of substance use/misuse and eating disorders has not been definitive. Despite the multitude of studies conducted examining this comorbidity, it is still unknown why these two disorders frequency co-occur and if the comorbidity is similar in males and females. It is also unclear whether it is specific symptoms of an eating disorder that may predispose individuals to use and abuse symptoms.

**Study Three: Purpose Statement**

The purpose of this investigation is to answer the following questions: (a) are there common genetic and environmental influences on symptoms of disordered eating and substance use/misuse and (b) is there a sex-difference exhibited in the action of these
common influences? From previous research one hypothesis can be made. Results will show shared genetic and environmental factors between symptoms of disordered eating and substance use.
Chapter 10 Method

Participants

Participants for the current study were obtained from the third wave of TCHAD. A detailed description of this sample can be found in study one methods.

Measures

The Eating Disorder Inventory-II (EDI) which includes the Drive for Thinness (DT), Bulimia (B), and Body Dissatisfaction (BD) subscales and the substance use questionnaires previously described will be utilized.

Statistical Analyses

Results obtained from studies one and two were used to determine the exact type of comorbidity analyses conducted. Because the common pathway model fit better than the independent pathway model for the EDI subscales in study one and for Wave 3 substance use/misuse data in study two for both males and females, a multivariate common pathway model will be used. An in depth description of the common pathway model was provided in study one.

Twin Analyses

A multivariate, common pathway model was used to decompose the genetic and environmental covariance between the underlying latent factors responsible for disordered eating and substance use in adolescent males and females. This model is similar to the longitudinal model described in study two, replacing the longitudinal aspect with the disordered eating variables (Figure 5). There are several important aspects of
this model. First, the current model includes two latent factors: one representing the
disordered eating variables and one representing the substance use variables. Second, the
model includes cross-path estimates that examine the amount of genetic and
environmental covariance between the latent disordered eating factor and the latent
substance use factor. Third, this covariance is decomposed through a Cholesky
decomposition within the higher order path estimates. An in depth description of the
Cholesky decomposition can be found in study two. Fourth, the correlation between the
genetic factors responsible for disordered eating in males and females and the correlation
between the genetic factors responsible for substance use is provided. Finally, the
proportion of the covariance between disordered eating and substance use in males and
females that results from genetic and environmental factors can be calculated.

All twin analyses in the current study will be conducted using a raw data approach
in the statistical package Mx (M. C. Neale, 1997). This approach allows data from both
incomplete and complete twin pairs to be utilized. Mx is a program used for SEM and is
popular in the use of twin analyses. It is similar to commercial software used for SEM.
Mx allows for maximum-likelihood model fitting analyses.
Figure 5. Path diagram of the decomposition of genetic and environmental covariance between disordered eating and substance use.

A = additive genetic effects for common factors. C = shared environmental effects for common factors. E = unique environmental effects for common factors. DE = disordered eating. SU = substance use. DT = drive for thinness. B = bulimia. BD = body dissatisfaction. SM = smoking. ETOH = alcohol intoxication. DU = illicit drug use. a = residual additive genetic effects. c = residual shared environmental effects. e = residual unique environmental effects.
Sex-Differences. Quantitative and qualitative sex-differences were also examined. Within this model, quantitative effects examine whether the magnitude of the genetic or environmental effects on the latent liability to disordered eating and substance use are the same in males and females. Qualitative effects examines whether the genetic risk factors for either disordered eating or substance use are the same. For qualitative effects, our model provides an estimate of the genetic correlation \( r_g \), which estimates the correlation between the genetic effects on the liability to disordered eating or substance use in males and females. If this genetic correlation is estimated at unity it means the genetic factors that influence risk in males and females are identical. A thorough description of the genetic correlation is provided in study one.

Additionally, from this model, we are also able to calculate relevant statistics from the obtained path estimates. The estimated phenotypic correlation between latent disordered eating and latent substance use separately in males \( r_m \) and females \( r_f \) can be calculated. The correlation between the genetic \( r_a \), shared environmental \( r_c \), and unique environmental \( r_e \) risk factors responsible for disordered eating and substance use in males and females can also be calculated from the model. For example, if \( r_a \) is estimated at unity here it means that the same genetic risk factors contribute to risk for both phenotypes.

Two models will be tested to determine the best-fitting model. First, a full sex-limitation model will be examined which estimates all parameters, as previously discussed, for males and females. Second, a similar model will be tested which constrains all of the higher order genetic and environmental paths to be equal in males
and females. Both models allow for $r_g$ to be estimated freely and all relevant statistics are able to be calculated within all models. The Bayesian information criterion (BIC) will be used to determine best-fitting models. The BIC is a function of a model’s df and $\chi^2$ (Raftery, 1995). Models that provide the best fit while retaining the fewest parameters yield lower BIC values.

There is an important consideration that must be discussed when examining for quantitative sex-differences at the multivariate, or bivariate level, as we are doing within the current study. The basic principle behind quantitative differences is that the same factors are responsible for the risk of a specific phenotype between the sexes, but the magnitude of the effect of these factors is different in males and females. Since these factors are the same between the sexes, they must covary with one another to the same extent (M. C. Neale, Roysamb, & Jacobson, 2006). That is, the model requires that there is only one correlation structure for males and females, but allows for different loadings on the factors (M. C. Neale et al., 2006). However, the Cholesky decomposition allows for different correlation structures to be estimated for males and females. Thus a constraint was added to the model in order to meet the basic principle of quantitative differences.
Chapter 11 Results

Descriptive Statistics

EDI subscales were trichotomized in order to conduct multivariate twin analyses with Wave 3 substance use data. Categories were created as follows: (1) those individuals scoring a total score of zero for the subscale; (2) those individuals scoring one standard deviation of the mean and above; (3) and individuals scoring above zero and below one standard deviation above the mean. Means were calculated separately for males and females for each subscale and shown in Table 14. Categories were created in this manner in an effort to retain as much information as possible. We did not want to lose those individuals who did score at the higher end of possible scores. The frequency of individuals found within each of these groups is shown in Table 15. The distribution of raw EDI subscale scores is also shown in Figure 6a-c for comparison. As can be seen from the figures, a significant proportion of the sample obtained a score of 0 on the three subscales. However, a wider range of scores was obtained for the BD subscale compared to B and DT.
Table 14

Mean Scores for EDI Subscales

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>DT</td>
<td>2.1 (3.9)</td>
<td>0.34 (1.4)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0-18</td>
</tr>
<tr>
<td>B</td>
<td>0.54 (1.5)</td>
<td>0.49 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0-21</td>
</tr>
<tr>
<td>BD</td>
<td>5.7 (6.2)</td>
<td>2.2 (3.6)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0-24</td>
</tr>
</tbody>
</table>

Note. EDI = Eating Disorder Inventory. SD = standard deviation. DT = drive for thinness subscale. B = bulimia subscale. BD = body dissatisfaction subscale. Range = subscale score range.

Table 15

Frequency of Subjects within Trichotomized EDI Subscales

<table>
<thead>
<tr>
<th>Category</th>
<th>DT</th>
<th>B</th>
<th>BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>70% ($n = 1646$)</td>
<td>76% ($n = 1789$)</td>
<td>38% ($n = 889$)</td>
</tr>
<tr>
<td>1</td>
<td>20% ($n = 453$)</td>
<td>11% ($n = 266$)</td>
<td>46% ($n = 1085$)</td>
</tr>
<tr>
<td>2</td>
<td>11% ($n = 258$)</td>
<td>12% ($n = 291$)</td>
<td>16% ($n = 387$)</td>
</tr>
</tbody>
</table>

Note. EDI = Eating Disorder Inventory-II. DT = drive for thinness. B = bulimia. BD = body dissatisfaction. % = percentage of sample. $n$ = number of individuals in sample. Percentages may not equal 100% due to rounding error.
Figure 6a. Bar Graph of Raw Drive for Thinness Scores.

dtscore = drive for thinness subscale scores. Percent = percentage of sample obtaining score.
Figure 6b. Bar Graph of Raw Bulimia Scores.

bscore = bulimia subscale scores. Percent = percentage of sample obtaining score.
Figure 6c. Bar Graph of Raw Body Dissatisfaction Scores.

bdcore = body dissatisfaction subscale scores. Percent = percentage of sample obtaining score.
Twin Correlations

The correlations between the EDI subscales and substance use/misuse variables by sex and zygosity are shown in Table 16. In general, the correlations between the EDI subscales and substance use/misuse variables are greater in females. Interestingly, results suggest a minimal association between DT and smoking and between DT, BD and illicit drug use in males. Comparing MZ and DZ correlations suggests that shared environment effects are important for the overlap between several of the EDI subscales and the substances examined in both males and females. This is indicated by the fact several of the DZ correlations are greater than or equal to the MZ correlations. However, for illicit drug use, alcohol intoxication, and B and BD in females the association appears to be due mostly to genetic effects as the MZ correlations are greater than the DZ correlations.

Table 16

Correlations Between EDI Subscales and Substance Use/Misuse by Sex and Zygosity

<table>
<thead>
<tr>
<th>Substance</th>
<th>Females MZ (DZ)</th>
<th>Males MZ (DZ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DT</td>
<td>B</td>
</tr>
<tr>
<td>Smoke</td>
<td>0.30</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>(0.36)</td>
<td>(0.21)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.23</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>(0.26)</td>
<td>(0.14)</td>
</tr>
<tr>
<td>Intoxication</td>
<td>0.34</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>(0.26)</td>
<td>(0.03)</td>
</tr>
</tbody>
</table>

Note. EDI = Eating Disorder Inventory-II. MZ = monozygotic. DZ = dizygotic.

DT = drive for thinness. B = bulimia. BD = body dissatisfaction.
Twin Analyses

Comparing model fits of the free sex-limitation model (BIC = -37806.36) and the model constraining the genetic and environmental path estimates to equality (BIC = -37834.79) revealed that the model equating the sexes was better fitting by a reasonable margin. This suggests that the genetic and environmental influences on the latent liability to disordered eating, substance use and their covariance are impacting males and females to a similar degree.

As can be seen in Figures 7, the underlying common factor accounted for a moderate amount of the variance in the EDI subscales and a majority of the variance for substance use. Similar to studies one and two, DT and smoking had the highest factor loadings while B and illicit drug use had the lowest factor loadings. A few differences were noted however, between the current study and the two previous studies. First, constraining the male and female parameters to equality proved to be a better fitting model. Although, we did not directly examine whether these estimates could be constrained to equality in studies one and two, results did show differences in the parameters estimates between the sexes. However, these results suggest these differences in estimates are not beyond chance expectation and then are in fact acting similarly in the two sexes. Second, while factor loadings were relatively similar for smoking, alcohol intoxication, and illicit drug use on the common factor, subtle differences were found. The loadings estimated for alcohol intoxication and smoking in the current study were
slightly lower, while the loading estimated for illicit drug use was slightly higher than the estimates in study two from Wave 3.
Figure 7. Path diagram of the best-fitting model of the decomposition of genetic and environmental covariance between disordered eating and substance use.

Male factor loadings and residuals shown in parentheses. A = additive genetic effects for common factors. C = shared environmental effects for common factors. E = unique environmental effects for common factors. DE = disordered eating. SU = substance use. DT = drive for thinness. B = bulimia. BD = body dissatisfaction. SM = smoking. ETOH = alcohol intoxication. DU = illicit drug use. a = residual additive genetic effects. c = residual shared environmental effects. e = residual unique environmental effects.
Covariance Between Disordered Eating and Substance Use

The genetic and shared environmental risk factors for latent disordered eating and latent substance use were moderately correlated. The correlation between the genetic risk factors responsible for disordered eating and the genetic risk factors responsible for substance use were estimated at $r_g = +0.20$. The correlation between the shared environmental influences on disordered eating and shared environmental influences on substance use were estimated at $r_c = +0.48$. Unique environmental correlations were estimated at $r_e = -0.02$. These results suggest that the shared environmental factors that influence disordered eating and substance use are more closely related than are the genetic factors which impact on the two traits. However, it appears the genetic and shared environmental risk factors for disordered eating and substance use are not entirely the same as these estimates are far short of unity.

The phenotypic correlation between the disordered eating and substance use latent factor can be calculated as, from Figure 7, $0.76 \times 0.16 + 0.40 \times 0.36 + 0.51 \times -0.01 = 0.25$. Because the model constraining males and females to equality was the better fitting model, only one phenotypic correlation is calculated from the model. Genetic factors accounted for 48% $[(0.76 \times 0.16)/0.25]$ of this correlation and shared environment 57% $[(0.40 \times 0.36)/0.25]$. These exceed unity due to the negative covariance that results from the unique environmental factors (-4%). This suggests the unique environmental factors responsible for disordered eating decrease the risk for substance use slightly.

Qualitative sex-differences. Examining for qualitative sex-differences between the genetic risk for disordered eating and the genetic risk for substance use in males and
females corroborates previous results. Similar to study one, results suggest that the genetic risk factors for our disordered eating common factor are not entirely the same in males and females. Within the best-fitting model the genetic correlation for disordered eating was estimated at $r_g = +0.24$. This suggests that only approximately 25% of the genetic factors responsible for latent disordered eating are shared between the sexes. Results for the substance use common factor tell a different story. The genetic correlation between males and females was estimated at $r_g = +1.00$. This suggests that 100% of the genetic factors responsible for our substance use common factor are shared between the sexes.
Chapter 12 Discussion

Summary of Findings

The purpose of study three was to bring together study one and study two in a meaningful way in order to address two questions. First, we asked whether there are common genetic and environmental influences on symptoms of disordered eating and substance use. Our results suggest there is a moderate amount of familial covariance between the underlying latent liability to disordered eating and substance use. This finding supports our hypothesis that shared genetic factors would be found. However, shared environmental effects were also shown to be of importance for covariance.

Second, we questioned whether there was a sex-difference exhibited in the action of these common influences. Results suggest the action of these influences is similar in males and females as we were able to constrain the parameters to equality without worsening the fit of the model. Within the best-fitting model, genetic and shared environmental effects each accounted for approximately 50% of the covariance between disordered eating and substance use.

Discussion of Findings

Covariance Between Disordered Eating and Substance Use

No study to date has examined the genetic covariance between the latent liability to disordered eating and substance use in adolescent males and females. These results are best compared to two recent studies which examined the genetic and environmental covariance between aspects of eating disorders and substance use. First, examining the
association between bulimia nervosa (BN) and illicit drug use disorders in an adult female population Baker and colleagues (2007) reported that genetic and unique environmental influences accounted for a majority of the overlap between these two disorders. The correlation between the genetic factors responsible for BN and illicit drug use disorders was estimated at +0.39 which is slightly higher than the genetic correlation estimated between our latent disordered eating and substance use factors (+0.20). It was also reported that 83% of the phenotypic association between BN and illicit drug use disorders could be accounted for by genetic factors and 17% by unique environment (Baker et al., 2007). Second, examining the genetic and environmental covariance between weight preoccupation and binge eating and alcohol use in males and females, genetic and unique environmental factors were again shown to account for the covariance for all associations in both sexes (Slane, Burt, & Klump, 2008). Our results corroborate these results by also showing genetic covariance. However, our results suggest that shared environment rather than unique environment may be more important during adolescence.

This difference is likely because of two factors. First, the current study utilized an adolescent sample while the two previous studies used adult samples. Previous research has suggested a developmental trajectory for the genetic and environmental risk factors for disordered eating. For example, Klump and colleagues (2007) examined the genetic and environmental risk for disordered eating in 10-13, 13-16, and 17-20-year-old twins. They found that across development, genetic factors increased while shared environmental influences decreased. Within this report, shared environment accounted
for 10% of the variance in disordered eating (Klump, Burt, McGue, & Iacono, 2007). A similar amount of shared environmental variance was obtained in our female sample (16%). As discussed in study two, a similar developmental trajectory is often found for substance use. In fact, this trend of increasing genetic and decreasing shared environmental effects is exhibited for many phenotypes with aging (Bergen, Gardner, & Kendler, 2007). Therefore, it is not surprising that we might find shared environmental effects to be important for covariance during adolescence. Second, results may have differed because the current report examined disordered eating attitudes and behaviors and substance use from a common factor design rather than examining diagnoses or specific aspects of disordered eating.

A plausible hypothesis can be made from the differences noted between the current study and previous studies. A developmental trajectory is exhibited for covariance between disordered eating and substance use across development in that shared environmental factors decrease in importance while genetic and unique environmental effects increase. This hypothesis is supported by the fact an increase in the genetic and unique environmental factors responsible for covariance is seen between the adolescent and adult populations while no shared environmental covariance is exhibited in adulthood. Our shared environmental factors may be shifting to genetic and unique environmental effects in older populations.

Finding common genetic and shared environmental influences between disordered eating and substance use provides some evidence for the family history hypothesis previously discussed. This hypothesis suggests there are shared familial (genetic or
shared environmental) risk factors between eating disorders and substance disorders. Previous family studies have generally found evidence against this hypothesis as BN and substance disorders are shown to have independent familial transmission and do not show characteristics of cross-transmission (Kaye et al., 1996; Kendler et al., 1995; Schukit et al., 1996; von Ranson, McGue, & Iacono, 2002). However, the current results and the results by Baker (2007) and Slane (2008) are consistent with this hypothesis.

As stated, little research has examined the association between disordered eating (and eating disorders) and substance use (and disorders) from a behavior genetics perspective so it is not clear exactly what familial factors, specifically those of the shared environmental variety, may account for covariance. However, previous studies examining risk factors and correlates of eating disorders and substance disorders may provide some interesting insights. These studies in fact, suggest that several familial factors may be important to consider. For example, family history of alcoholism and depression are both significant correlates of the development of both an eating disorder and substance use disorder (Baker et al., 2007; Fairburn et al., 1998; Holderness et al., 1994; Jacobi et al., 2004)

Many family studies have documented elevated rates of depression and substance disorders in first-degree relatives of probands with an eating disorder (Lilenfeld et al., 1998; Mangweth et al., 2003; Strober, Freeman, Lampert, Diamond, & Kaye, 2001). Results have generally found having a family member with BN is associated with increased likelihood of an affective disorder, especially major depression, and alcoholism (as well as posttraumatic stress disorder and cluster B personality disorders) compared to
controls (Bulik et al., 1987; Kassett et al., 1989; Lilenfeld et al., 1998). However, the results of these studies are inconsistent about the reasons for this familial transmission. Some studies document patterns of independent familial transmission while others show patterns of common transmission.

Studies specifically examining the association between family history of alcoholism and disordered eating also show interesting results. Children who report parental misuse of substances have higher rates of weight dissatisfaction and higher frequencies of dieting, binge eating, and use of compensatory behaviors and demonstrate increased rates of eating pathology (Chandy, Harris, Blum, & Resnick, 1994; Redgrave, Coughlin, Heinberg, & Guarda, 2007). Examining the impact of a family history of alcoholism on the association between disordered eating and alcohol problems in a sample of college females revealed a significant interaction between disordered eating and a family history of alcoholism (Harrell, Slane, & Klump, 2009). Harrell and colleagues (2009) reported that higher levels of disordered eating were associated with more alcohol problems for females with a family history of alcoholism. Similarly, Fairburn and colleagues (1998) also report parental depression as a risk factor for binge eating disorder, and maternal depression has been shown to be associated with selflessness within anorexic daughters (Bachar et al., 2008).

Similarly, a family history of substance misuse is also a well-documented and well accepted risk factor for substance use/misuse while elevated rates of affective disorders are often found in relatives of individuals who misuse substances. One study, examining the prevalence rates of several diagnoses in male and female relatives of
individuals seeking treatment for substance abuse, indicated the most prevalent diagnosis in female relatives was an affective disorder, with 14% of female relatives qualifying for a diagnosis (Mirin, Weiss, Griffin, & Michael, 1991). In a study investigating psychiatric disorders in relatives of opiate addicts, it was found that, compared to controls; family members had substantially higher rates of alcoholism and depression (Rounsaville et al., 1991). Parental depression has also been shown to increase the risk for a substance use disorder in adolescents (Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002; Tully, Iacono, & McGue, 2008). Tully and colleagues (2008) reported that adolescents with a depressed parent are approximately 2 times more likely to develop a substance use disorder. However, this result was not significant.

It is important to note that since results are inconsistent as to whether eating, substance, and depressive disorders show independent or cross transmission with one another, these familial factors may not directly cause one to develop disordered eating behaviors or use substances. For example, having a parent who is alcohol dependent (or depressed) may not directly cause the child to become eating disordered (or use substances), but create additional behavior and psychological problems within the home that may lead to an eating disorder (or substance use). Therefore, these family history variables may be more accurately construed as non-specific risks. Certainly having a parent who misuses substances or is experiencing major depression places the child at risk for a variety of problems, including psychological conditions. This can be most clearly seen for substance use. Parents who are problem drinkers may provide less
support to children or may be unable to monitor their behaviors which may then lead to substance use by the offspring (Chassin, Pillow, Curran, Molina, & Barrera, 1993).

Additionally, certain family dysfunctions also appear to play a role in both disordered eating and substance use. For example, low levels of parental attachment and parental monitoring predict substance initiation while proactive parents and clear parental communications discouraging use decrease the likelihood of initiation (Chilcoat & Anthony, 1996; Kosterman et al., 2000; Sargent & Dalton, 2001; Stice & Barrera, 1995). Family discord and conflict has also been shown to be a risk factor for substance use disorders in offspring (Pilowsky, Wickramaratne, Nomura, & Weissman, 2006). Parent-child relationship problems has also been shown to account for a significant amount of the shared environmental variance in adolescent delinquency (including substance use) and substance initiation (Burt et al., 2007; Walden et al., 2004).

Dysfunctional family systems and family conflict also play a role in the development of eating disorders (Haslam, Mountford, Meyer, & Waller, 2008; Kluck, 2008; Lundholm & Waters, 1991; Wade, Gillespie, & Martin, 2007). For example, dysfunctions in parental bonding and attachment are associated with eating disorders and disordered eating (Canetti, Kanyas, Lerer, Latzer, & Bachar, 2008; Meesters, Muris, Hoefnagels, & van Gemert, 2007; Sharpe et al., 1998). Comparing females with anorexia nervosa (AN) to controls, females with AN report their mothers’ as less caring (i.e. less warm, affectionate, and empathetic) and fathers’ as more controlling (Parker, 1983; Sharpe et al., 1998). Individuals with an eating disorder are also more likely to be insecurely attached than individuals without an eating disorder (Armstrong & Roth, 1989;
Meesters et al., 2007). For example, Armstrong and Roth found that 96% of an adult population with an eating disorder showed insecure attachment. Examining parental rearing styles and attachment in a sample of male and female adolescents Meesters and colleagues (2007) reported that social and familial factors were more predictive of eating problems and muscle preoccupation in males. However, it is important to note that a previous examination of shared genetic and environmental risk factors between disordered eating and parenting variables (perceptions of parental protection and care) showed no common environmental risk factors (Wade et al., 2000).

It is also important to consider plausible explanations for genetic covariance between disordered eating and substance use. The genetic effects on these two syndromes or their covariance may be partly mediated through a third variable. This suggests a possible third variable may account for comorbidity. Baker and colleagues (2007), in their examination of BN and illicit drug use, hypothesized that the genetic effects shared between the two disorders could also be related to the genetic influences on depression and neuroticism (both of which are also moderately heritable). This was hypothesized based on mediation regression analyses that showed that a history of major depression and neuroticism scores mediated the association between BN and illicit drug use disorders regardless of which disorder was used as the dependent variable.

Research examining the personality profiles of individuals with an eating disorder and individuals with a substance use disorder reveal several similarities between these profiles, especially with regard to neuroticism or tendencies towards negative emotionality. Higher scores on measures of neuroticism are positively associated with
substance use/misuse (Kilbey, Breslau, & Andrewski, 1992; Terracciano, Lockenhoff, Crum, Bienvenu, & Costa, 2008; Trull & Sher, 1994). For example, comparing 13-18-year-olds to their adolescent siblings it was reported that youth with a substance use disorder had higher neuroticism scores than siblings of similar age (Anderson, Tapert, Moadab, Crowley, & Brown, 2007). Comparing personality profiles between psychoactive drug users, Terracciano (2008) reported that similarly elevated neuroticism scores were obtained in cigarette smokers and cocaine/heroin users. However, the elevated neuroticism scores in heroin/cocaine users were more extreme. A genetic overlap has also been revealed between neuroticism and substance use (Agrawal, Jacobson, Prescott, & Kendler, 2004).

In regard to eating disorders and disordered eating, aspects of negative emotionality and neuroticism have also been identified as a nonspecific risk factor for eating disorders (Jacobi et al., 2004). For example, Leon and colleagues (1999) found negative affectivity to be a significant predictor of eating disorder risk in a population of adolescents. Individuals with eating disorders also score higher on measures of neuroticism than controls. A similar association was shown with bulimic symptomatology in a small university sample of males (Cassin & von Ranson, 2005). Neuroticism also appears to share genetic risk factors with aspects of disordered eating. Klump and colleagues (2002) report that approximately 60% of the phenotypic association between negative emotionality and disordered eating can be attributed to genetic factors. However, examining for genetic covariance between neuroticism and
disordered eating revealed only shared unique environmental risk factors and no genetic covariance (Wade et al., 2000).

No study has established a causal link between personality, disordered eating, and substance use so it is also possible that having both an eating disorder and a substance use disorder increases neurotic tendencies. Yet, this conclusion seems unlikely. High neurotic traits would appear early in an individual’s life, most likely before the development of an eating disorder. Personality scores also tend to be consistent throughout an individual’s life and previous studies (although not looking at neuroticism) have shown personality characteristics to remain similar before and after recovery from an eating disorder (Klump et al., 2004).

A similar argument can be made for major depression as a possible genetic mediator. Depression is a common comorbid condition seen in individuals with eating disorders and substance use disorders and often seen in family members of probands with these disorders as discussed earlier (Bulik, 1987). Shared genetic risk factors have also been revealed between depression and eating disorders and substance use (Kendler, Heath, Neale, Kessler, & Eaves, 1993; Prescott, Aggen, & Kendler, 2000; Wade et al., 2000; Walters et al., 1992). It is then possible that the genetic effects on disordered eating and substance use are themselves partly mediated by the genetic effects on depression. The genetic influences on depression could also account for covariance as individuals with disordered eating attitudes and behaviors or who use substances who are also depressed may turn to the other (disordered eating/substance use) to alleviate the depressive symptoms. However, it is equally plausible that individuals who experience
symptoms of disordered eating may use substances to dampen bulimic urges or that symptoms of disordered eating and substance use are causing one to be depressed.

**Sex-differences**

Results showed no significant sex-differences in the magnitude of the genetic and environmental factors impacting covariance between disordered eating and substance use. Approximately 50% of the covariance between the common factors was due to shared environment and 50% due to genetic effects. This result corroborates previous research which shows males and females with an eating disorder show more similarities than differences. For example, a previous comparison of disordered eating attitudes and behaviors in substance abusing males and females showed no significant differences between males and females on binge eating, inappropriate compensatory behaviors, dietary restraint, and body dissatisfaction (Jackson & Grilo, 2002).

Examining for qualitative effects within our disordered eating and substance use common factors also corroborates previous results. For the latent liability to disordered eating only approximately 25% of the genetic risk factors are shared between the sexes. This percentage is lower than what was obtained in study one. In study one $r_g = +0.71$ while in the current study $r_g = 0.24$. This discrepancy is likely due to the loss of information due to the categorization of the EDI data. Possible reasons for this qualitative sex-difference are provided in study one.

In contrast, it appears 100% of the genetic risk factors for the latent liability to substance use are shared between the sexes. This result may be somewhat surprising given the fact the within wave within sex estimates in study two showed striking
differences in the heritability estimates for the Wave 3 common factor in males and females. However, this result suggests that while the impact these genetic factors have on substance use may be different in males and females, it is the same genetic effects influencing this impact.

This result is in line with previous research examining for sex-differences in substance use during adolescence. Several reports suggest no evidence for quantitative differences for tobacco initiation, use, problem use and dependence, illicit drug use or abuse, and alcohol initiation, frequency of use, intoxication, problem use, and frequency of intoxication (Boomsma et al., 1994; Han et al., 1999; Koopmans et al., 1999; McGue et al., 2000; Poelen et al., 2008; Rhee et al., 2003; Viken et al., 1999).

Study Limitations and Strengths

In addition to the limitations discussed in studies one and two in regard to the participants, our use of the EDI, and the substance use variables there are additional limitations to the current study. First is the categorization of the EDI. The use of continuous measures is always best when possible, especially within twin models. Categorization is especially problematic for phenotypes which are rare in the population which would be the case here, specifically within the male participants. However, because our substance use data was categorical we were forced to categorize the EDI subscales. Secondly, we did not examine for possible differential relationships between the specific EDI subscales and substances. It is possible there may be differences which we were unable to detect with our use of a common factor model. For example, this could explain our finding of shared environmental importance while previous studies
showed unique environment important for covariance (Baker et al., 2007; Slane et al., 2008). Third, we only examined a single snapshot of development. Because a developmental trajectory has been previously shown for both disordered eating and substance use, it is possible the genetic and environmental risk factors responsible for covariance may change across development. Finally, we also did not directly model causal effects of disordered eating on substance use or vice versa.

Despite its weaknesses, the current study has strengths. The most critical strength of the current study is its representativeness. The sample was taken from the general population of a birth cohort in Sweden which eliminates the possibility of biases, specifically Berkson’s bias which we would see if the sample were clinically based. Because our sample is a community based sample followed through young adulthood, we have eliminated this common problem with researching comorbidity with clinical samples. The use of substance use data as well as disordered eating data rather than eating disorder and substance disorder diagnoses also reduces the potential of Berkson’s bias and affords the opportunity to examine how these two domains are related at a more generalizable level.

Study Implications and Future Directions

The results within the current study have important implications for future research on the comorbidity between eating disorders and substance disorders, specifically in regard to how this comorbidity should be examined. In an effort to clarify comorbidity research, Neale and Kendler (1995) devised six possible models to explain comorbidity between disorders and to guide researchers in their studies. These models
include: (1) alternate forms, in which two disorders have the same underlying liability; (2) random multiformity, in which having one disorder increases risk for a second disorder; (3) extreme multiformity where only extreme cases of the first disorder increase risk for the second; (4) three independent disorders, in which the comorbid cases constitute a third independent disorder; (5) correlated liabilities, where risk factors for the disorders correlate and (6) direct causal models, where the liability for one disorder is the direct cause of the second disorder (Neale & Kendler, 1995). Results provide support for a correlated liabilities model between disordered eating and substance use. Future research on this association should focus on this model and examine for possible developmental differences in the covariance of these two psychological constructs.

These results also have clinical implications. Results inform clinicians there is a significant familial overlap between disordered eating and substance use, so when an individual presents for treatment for one of these disorders it is pertinent to be aware of the high possibility of the other disorder being seen comorbidly. Taken together, the results of the current study add to the growing body of literature that shows more similarities than differences in aspects related to eating disorders in males and females.
List of References
List of References


illicit drug use among American 8th, 10th and 12th grade students. *Addiction*, 98(2), 225-234.


172


### APPENDIX A

### Substance Use Questions

#### Wave 2 Questions

How many times have you done the following in the past 12 months?

<table>
<thead>
<tr>
<th>Substance</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoked cigarettes or other tobacco?</td>
<td>1 no, never  2 1-2 times (occasionally)  3 I smoke once in a while  4 I often smoke</td>
</tr>
<tr>
<td>Used snuff?</td>
<td>1 no, never  2 1-2 times (occasionally)  3 I use snuff once in a while  4 I often use snuff</td>
</tr>
<tr>
<td>Drunk beer, wine, liquor or other alcohol so that you felt intoxicated?</td>
<td>1 never  2 1-2 times (occasionally)  3-5 times (a few times)  6-10 times (quite a few times)  11-50 times (often)  11-50 times (very often, once a week or more)</td>
</tr>
<tr>
<td>Smoked pot or marijuana?</td>
<td>1 never  2 1-2 times  3-5 times  6-10 times  11-50 times  11-50 times</td>
</tr>
<tr>
<td>Tried other narcotic drugs? (e.g. amphetamine, heroine, ecstasy or similar)</td>
<td>1 never  2 1-2 times  3-5 times  6-10 times  11-50 times  11-50 times</td>
</tr>
<tr>
<td>Sniffed? (e.g. thinner, lighter gas, petrol)</td>
<td>1 never  2 1-2 times  3-5 times  6-10 times  11-50 times  11-50 times</td>
</tr>
<tr>
<td>Used anabolic steroids?</td>
<td>1 never  2 1-2 times  3-5 times  6-10 times  11-50 times  11-50 times</td>
</tr>
<tr>
<td>Sold pot or marijuana?</td>
<td>1 never  2 1-2 times  3-5 times  6-10 times  11-50 times  11-50 times</td>
</tr>
<tr>
<td>Sold other narcotic drugs?</td>
<td>1 never  2 1-2 times  3-5 times  6-10 times  11-50 times  11-50 times</td>
</tr>
</tbody>
</table>

174
Wave 3 Questions

Sometimes people do things that are not really allowed. Here are quite a few questions about if you have done something like that any time during the past 12 months. Remember that we in the research group are bound by professional secrecy and that no one outside the group will be able to read what you've written.

How many times have you done the following in the past 12 months?

<table>
<thead>
<tr>
<th>Never</th>
<th>1-2 times</th>
<th>3-5 times</th>
<th>6-10 times</th>
<th>11-50 times</th>
<th>More than 50 times</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

29. [c3crim29] Been selling hashish or marihuana?

30. [c3crim30] Been selling other drugs?

The next section is about tobacco, alcohol and drugs

1. [c3smk] Do you smoke?
   1  No, I have never smoked.
   2  No, I've only tried it.
   3  No, I quit.
   4  Yes, but only sometimes.
   5  Yes, but only at parties.
   6  Yes, but only on weekends.
   7  Yes, almost every day -> How much? .....[c3smka].....cigarettes per day
   8  Yes, every day -> How much? .......... [c3smkb].............cigarettes per day

2. [c3snus] Do you use snuff?
   1  No, I have never used snuff.
   2  No, I have only tried it.
   3  No, I quit.
   4  Yes, but only sometimes.
3. [c3alc] In the last month have you been drinking beer, wine or liquor?
   1 ☐ No.
   2 ☐ Yes once
   3 ☐ Yes, several times

4. [c3drunk] Have you ever drunk so much that you got drunk?
   1 ☐ No
   2 ☐ Yes
   4 a. On a scale from 1 to 10, how drunk were you the last time it happened?
       Not much.       Very drunk so I couldn't stand up.
       [c3drunka] ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
       1 2 3 4 5 6 7 8 9 10

   [c3drunkb] 4 b. How often do you get drunk when you drink alcohol?
       1 ☐ Don’t drink
       2 ☐ Never/seldom
       3 ☐ Sometimes
       4 ☐ Nearly every time
       5 ☐ Always

5. [c3sniff] Have you ever been sniffing
   1 ☐ No
   2 ☐ Yes once
   3 ☐ Yes, several times

6. [c3stills] Are you still sniffing
   1 ☐ No
   2 ☐ Yes, a couple of times per year
   3 ☐ Yes, a couple of times per month
   4 ☐ Yes, a couple of times per week
   5 ☐ Yes, every day
7. [c3drug]
Have you ever used drugs? By narcotics we mean for example haschish, marihuana, amphetamine, ecstasy, LSD, cocaine, heroin and GHB.

1  No
2  Yes

7 a. What kind of drugs
[c3type]  □ Haschish
1
□ Marihuana.
2
□ Amphetamine
3
□ Heroin (smoking).
4
□ Heroin (injected).
5
□ Morphine.
6
□ Cocaine
7
□ LSD
8
□ Ecstas.
9
□ GHB
10
□ Other type of drug. What? ..........................................................
11
□ Don’t know
12

[c3stildd]  7 b. Do you use drugs now?
1  □ No
2  □ Yes, nearly every day
3  □ Yes, a couple of times per week
4  □ Yes, a couple of times per month
5  □ Yes, a couple of times per year.
Wave 4 Questions

Sometimes people do things that are not really allowed. Here are quite a few questions about if you have done something like that any time during the past 12 months. Remember that we in the research group are bound by professional secrecy and that no one outside the group will be able to read what you’ve written.

<table>
<thead>
<tr>
<th>In the past 12 months...</th>
<th>Never</th>
<th>1-2 times</th>
<th>3-5 times</th>
<th>6-10 times</th>
<th>11-50 times</th>
<th>More than 50</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

29. [c4crim29] Been selling hashish or marihuana?

30. [c4crim30] Been selling other drugs?

The following section is about tobacco, alcohol and drugs.

1. [c4smk] Do you smoke?

   1. No, I have never smoked.
   2. No, I’ve only tried it.
   3. No, I quit.
   4. Yes, but only sometimes.
   5. Yes, -> How much? ....... [c4smka]........ cigarettes per day

2. [c4snus] Do you use snuff?

   1. No, I have never used snuff.
   2. No, I have only tried it.
   3. No, I quit.
   4. Yes, but only sometimes.
   5. Yes, -> How much? ........ [c4snusa].... boxes per week.

3. [c4alk1] How often do you drink alcohol? Include also small amounts of alcohol, for example half a glass of wine

   1. Daily.
   2. A couple of times per week.
   3. Once a week
   4. A couple of times per month
   5. Once a month
   6. Once every second month
Here are some questions about drugs

9. [c4drug1]  
Have you ever sniffed or used drugs? Drugs are for example cannabis, amphetamine, ecstasy, LSD, cocaine, heroin, GHB, rohypnol, gas, or glue.

1. No
2. Yes?
   a. Which?
      1=mention .=not mention
      [c4drug2] □ Cannabis (e.g. hashish, marihuana, cannabis extracts).
      [c4drug3] □ Opium (e.g. heroin, codeine, methadone, morphine, fentanyl).
      [c4drug4] □ Hallucinogenic drugs (e.g. LSD, PCP "Angel Dust", peyote, mescaline, ecstasy).
      [c4drug5] □ GHB
      [c4drug7] □ Tranquilizers (e.g. xanax, valium, librium, quaalude, rohypnol).
      [c4drug8] □ Sniffed glue, gas, petrol
      [c4drug9] □ Other type of drugs. What? ..........................................
      [c4drug10] □ Don’t know.

[c4stilld]  
b. Do you use drugs now?
1. No
2. Yes, nearly every day
3. Yes, a couple of times per week
4. Yes, a couple of times per month
5. Yes, a couple of times per year.

[c4anab]  
10. Have you ever used anabolic steroids?

1. No
2. Yes
### APPENDIX B

#### Eating Disorder Inventory-II Questions

<table>
<thead>
<tr>
<th></th>
<th>Always (1)</th>
<th>Very Often (2)</th>
<th>Often (3)</th>
<th>Sometimes (4)</th>
<th>Rarely (5)</th>
<th>Never (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>[c3eat1]</td>
<td>I eat candy and carbohydrates without worrying.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.B</td>
<td>I think my belly is too big</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.C</td>
<td>I eat when I feel sad or worried</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>I binge eat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.E</td>
<td>I’m thinking of dieting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.F</td>
<td>I think my thighs are too fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>I get an awfully bad conscience when</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>I think I’ve eaten too much</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.H</td>
<td>I think my stomach has the right size.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.I</td>
<td>I’m terrified of gaining weight.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>I’m happy with my body.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>I exaggerate or deprecate the importance of weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Sometimes I can’t stop eating.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>I’m fixated on wishing to get slimmer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>I think my thighs are too wide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>With others I eat moderately, when alone I eat a lot.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>If I gain 1 kilo I get scared that the weight gain will continue.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>It gets in my head that I should try and vomit to lose weight.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>I think my thighs look good enough</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>I think my bottom is too big</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

180
21. I eat or drink in secret
   U

22. I think my hips look good enough.
   V

23. I’m happy with my height

24. [c3eat24]
   I’d like to be more muscular.