From Department of Medical Epidemiology and Biostatistics
Karolinska Institutet, Stockholm, Sweden

GENETIC AND ENVIRONMENTAL INFLUENCES ON EATING DISORDERS AND ASSOCIATED ADVERSITIES AND COMORBIDITIES

Shuyang Yao

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Genetic and environmental influences on eating disorders and associated adversities and comorbidities

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Shuyang Yao

Principal Supervisor:
Professor Henrik Larsson
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics
Örebro University
School of Medical Sciences

Co-supervisor(s):
Professor Cynthia M. Bulik
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics
University of North Carolina at Chapel Hill
Department of Psychiatry
Department of Nutrition

Doctor Ralf Kuja-Halkola
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Opponent:
Professor Ilona Koupil
Stockholm University
Centre for Health Equity Studies

Examination Board:
Professor Eva Billstedt
University of Gothenburg
Gillberg Neuropsychiatry Centre

Professor Øyvind Rø
University of Oslo
Institute of Clinical Medicine

Professor Pär Sparén
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

ABSTRACT

Eating disorders (EDs), including anorexia nervosa (AN) and bulimia nervosa (BN), are severe psychiatric disorders. Adversities (including suicide) and comorbidities have been illustrated in clinical observations with varying sample sizes, but evidence from large epidemiological research is still lacking. Further, the mechanisms underlying the observed associations remain largely unclear. Taking advantage of the unique Swedish national registries, this thesis aims to examine the associations between EDs and between EDs and potential adversities and comorbidities at population level and deepen the understanding of the mechanisms underlying these associations using genetically informative study designs.

Study I applied quantitative genetic modeling to estimate genetic and environmental effects on AN and BN and their overlap. This study used registry data in siblings and half-siblings, which significantly increased the sample size and extended the literature from self-reported behavioral measures to clinical diagnosis. Consistent with twin studies, moderate heritability was found for both AN and BN. Furthermore, moderate genetic and environmental correlations were found between clinically diagnosed AN and BN, suggesting partially overlapped etiologies between the two EDs in the general population.

Study II focused on the associations between EDs and suicide attempts and death by suicide. At population level, significantly increased risks of both suicide attempts and death by suicide were found in individuals with EDs (over 5 times the risk) compared to in individuals without EDs. Individuals with full-sibling or cousins with EDs were also at increased risks of suicide attempts. The familial co-aggregation pattern suggested that EDs and suicide attempts might share familial liabilities, which could include genetic and/or environmental risk factors shared by family members.

Study III assessed the risks of committing theft and other crimes in EDs in a nationwide female cohort. Firstly, significantly higher risks of both theft and other crimes were found in exposed females (i.e., had been diagnosed with AN or BN) than in unexposed females; theft was more common than other crimes altogether in exposed groups; and both the absolute and relative risks were higher in BN than in AN. Next, sibling comparison design, where the risks were compared between differentially exposed full-sisters, was applied to account for potential confounding effects of familial factors shared between sisters. The relative risk of theft decreased but remained statistically significant in BN and did not decrease in AN. The finding suggests that familial confounders (e.g., genetic and/or familial environmental confounders) were likely to explain part of the association between BN and theft but not the association between AN and theft, potentially reflecting different etiologies of the two EDs.

Study IV examined the genetic associations between EDs and attention-deficit/hyperactivity disorder (ADHD) using multiple approaches, namely assessing familial co-aggregation, quantitative genetic modeling, and analysis of polygenic risk scores (PRS, a measure of genetic risk of a disorder). 1) Increased risks of being diagnosed with AN and non-AN EDs

(including BN) were found in individuals diagnosed with ADHD and their full- and maternal half-siblings and cousins, compared to individuals without ADHD and their relatives, suggesting familial liabilities shared between ADHD and the EDs. 2) Moderate genetic correlations were found between non-AN EDs and ADHD and between BN and ADHD, and mild genetic correlation was found between AN and ADHD. 3) ADHD PRS significantly predicted ED symptoms including drive for thinness and body dissatisfaction in a large genotyped population sample, indicating that the polygenic risk of ADHD influenced some ED symptoms. The findings of the three approaches converged and together illustrated significant genetic correlations between EDs, especially non-AN EDs, and ADHD at both diagnostic and symptomatic levels. Both ADHD and theft behaviors (in Study III) might reflect multi-impulsive forms of EDs which, as suggested by previous studies, may be associated with relatively poorer treatment response.

Taken together, this thesis highlighted the seriousness of EDs by revealing their associations with adversities (suicide and crime) and comorbidity (ADHD) at population level. Further, it revealed the genetic and/or environmental influences on these associations and the associations among EDs. The findings suggest that EDs are correlated yet different disorders and provide insights on the etiologies underlying these important associations, encouraging future research to identify specific risk factors that target the shared etiologies. Clinical implications include the identification of subgroups in individuals with EDs who display high impulsivity and high risk of suicide as well as vigilance of forensic issues that could complicate treatment and recovery. The findings also highlighted increased risks of EDs, adversities, and comorbidity in family members of individuals with EDs, calling for clinical attention to the psychological robustness of the relatives especially when they serve as the caregivers of ED patients and are expected to engage intensively in treatment.

LIST OF SCIENTIFIC PAPERS

I. Yao S, Larsson H, Norring C, Birgegård A, Thornton LM, Bulik CM, Kuja-Halkola R. Genetic and environmental contribution to diagnostic fluctuation in anorexia and bulimia nervosa. *Manuscript*.

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III. Yao S, Kuja‐Halkola R, Thornton LM, Norring C, Almqvist C, D'onofrio BM, Lichtenstein P, Långström N, Bulik CM, Larsson H. Risk of being convicted of theft and other crimes in anorexia nervosa and bulimia nervosa: A prospective cohort study in a Swedish female population. *International Journal of Eating Disorders*. 2017 Sep 1;50(9):1095-103.

IV. Yao S, Kuja-Halkola R, Martin J, Lu Y, Lichtenstein P, Norring C, Birgegård A, Yilmaz Z, Hübel C, Watson H, Backer J, Thornton LM, Magnusson P, Lundström S, Bulik CM, Larsson H. Genetic associations between ADHD and eating disorders: A Swedish nationwide population study using multiple genetically informative approaches. *Manuscript*.

RELATED PUBLICATIONS

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II. Javaras KN, Runfola CD, Thornton LM, Agerbo E, Birgegård A, Norring C, Yao S, Råstam M, Larsson H, Lichtenstein P, Bulik CM. Sex- and age-specific incidence of healthcare-register-recorded eating disorders in the complete Swedish 1979–2001 birth cohort. *International Journal of Eating Disorders*. 2015 Dec 1;48(8):1070-81.

III. Schaumberg K, Welch E, Breithaupt L, Hübel C, Baker JH, Munn-Chernoff MA, Yilmaz Z, Ehrlich S, Mustelin L, Ghaderi A, Hardaway AJ, Bulik-Sullivan EC, Hedman AM, Jangmo A, Nilsson IAK, Wiklund C, Yao S, Seidel M, Bulik CM. The science behind the Academy for Eating Disorders' Nine Truths About Eating Disorders. *European Eating Disorders Review*. 2017 Nov 1;25(6):432-50.

IV. Capusan AJ, Yao S, Kuja-Halkola R, Bulik CM, Thornton LM, Bendtsen P, Marteinsdottir I, Thorsell A, Larsson H. Genetic and environmental aspects in the association between attention-deficit hyperactivity disorder symptoms and binge-eating behavior in adults: a twin study. *Psychological Medicine*. 2017 Dec;47(16):2866-78.

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LIST OF ABBREVIATIONS

A-TAC	The Autism-Tics, ADHD, and Other Comorbidities inventory
ADHD	Attention-deficit/hyperactivity disorder
AIC	Akaike information criterion
AN	Anorexia nervosa
BN	Bulimia nervosa
CATSS	The Child and Adolescent Twin Study in Sweden
CCR	The Criminal Conviction Register
CDR	The Cause of Death Register
DSM	The diagnostic and statistical manual of mental disorders
EDI-2	The Eating Disorder Inventory-2
EDNOS	Eating disorder not otherwise specified
EDs	Eating Disorders
GWAS	Genome-wide association studies
HR	Hazard ratio
ICD	International Classification of Diseases
LD	Linkage disequilibrium
MAF	Minor allele frequency
MDD	Major depressive disorder
MGR	The Multi-Generation Register
NPR	The National Patient Register
OR	Odds ratio
OSFED	Other specified feeding and eating disorders
Pastill	The Clinical Database for Child and Adolescent Psychiatry in Stockholm
PC	Principal component
PDR	The Prescribed Drug Register
PRS	Polygenic risk scores
RCT	Randomized controlled trails
Riksät	The Swedish National Quality Register for Eating Disorder Treatment

SNP	Single-nucleotide polymorphism
Stepwise	The Quality Assurance System for Eating Disorders
STR	The Swedish Twin Register
SUD	Substance use disorder
TPR	The Total Population Register

1 INTRODUCTION

Eating disorders (EDs) are psychiatric conditions marked by dysfunctional eating and feeding behaviors that significantly impair physical health and psychosocial functioning[1]. Serious and potentially lethal medical complications across multiple organ systems arise in individuals with EDs, often related to extremely low energy intake and/or the effects of inappropriate behaviors to control weight gain, such as vomiting or laxative abuse[2,3]. Comorbid psychiatric conditions are also commonly observed in clinical settings[4-6]. Anorexia nervosa (AN) is an ED characterized by restricted energy intake, significantly low body weight, and intense fear of weight gain. It carries the highest premature mortality risk of all mental disorders[7], and one in five deaths in AN is death by suicide[8]. Bulimia nervosa (BN) is characterized by recurrent episodes of binge-eating and inappropriate compensatory behaviors to prevent weight gain (such as self-induced vomiting and laxative abuse); it is associated with adverse medical complications such as dangerous electrolyte abnormalities, erosion of dental enamel, and cathartic colon syndrome[2,9] and is also associated with elevated mortality[8]. Although the onset of EDs is typically during late adolescence and early adulthood, and the prevalences are higher in females than in males, EDs can affect all age groups and both sexes[10]. The severe impairments at individual level impact the families of afflicted individuals, too[11], and bring significant disease burden to society[12]. Despite the seriousness of EDs, our understanding of the etiology of these disorders remains restricted.

For instance, AN and BN share the core symptoms of dysfunctional eating and feeding behaviors and fear of weight gain; however, dysfunctional eating behaviors manifest differently in AN and BN. In addition, diagnostic crossover between EDs during the disease course has been commonly observed in clinical settings[13]. The evidence poses questions about etiology—how different are the EDs and how do they correlate with each other? Do they share genetic and environmental risk factors? Such questions can not only improve our understanding of the etiologies of EDs but also provide insight into the diagnostic schema. However, most studies lacked the measures of genetic and/or environmental effects; very few studies that had relevant information were statistically underpowered to quantify the effects[14].

Examining the associations between EDs and other traits, such as potential adverse outcomes and psychiatric comorbidities, is also essential. On one hand, clinically, it can provide information on potential adverse outcomes and comorbidities in individuals with EDs. On the other hand, the associations, on not only phenotypic level, but also etiological level, may suggest directions to identify (shared) etiological factors and inform treatment. Although many important associations between EDs and adversities (such as suicide[8]) and comorbidities[15] have been suggested by previous studies, the mechanism underlying the associations and/or the explanatory factors of the associations are less clear.

One obstacle in ED research lies in the relative lack of population-based data. Limited by the low prevalences of EDs[16], much of the current knowledge about EDs is based on small clinical samples. Many larger survey-based studies relied on self-reported data rather than

clinical diagnosis[14,17-19]. These studies have important contributions to the current body of knowledge about EDs and revealed important associations. Nevertheless, they often lacked necessary information on critical explanatory factors and the statistical power to adjust for them in order to further explore the mechanisms underpinning these associations.

Large population-based registry data provide an excellent opportunity to address the issues. Register-based studies contain measures of a variety of variables and are usually sufficiently large to retain adequate statistical power when adjusting for relevant variables. Of particular value, registry data that contain information on family pedigree make it possible to apply genetically informative study designs. Combined with traditional epidemiological study designs, they allow for better quantification of or adjustment for the genetic and environmental influences on traits (including disorders) and their associations, which can advance our understanding of the etiology of the target illnesses.

In this thesis, four studies were conducted to examine the associations between EDs (especially AN and BN) and between EDs and potential adverse outcomes (such as suicide and criminal behavior) and psychiatric comorbidity (such as ADHD) at population level. Moreover, this thesis took advantage of genetically informative study designs and explored the mechanisms underpinning these important associations. As a whole, this thesis provides novel insights into the severity and comorbid conditions of EDs and reflects on etiological correlations and variations between different EDs—adding a few pieces to the understanding of these puzzling disorders.

2 BACKGROUND

2.1 EATING DISORDERS

Eating disorders (EDs) are serious psychiatric disorders characterized by a persistent disturbance of eating or eating-related behaviors characterized by dysregulated consumption of food that significantly impairs physical health and psychosocial functioning[1]. EDs include distinct but correlated types. The current thesis focuses on typical and atypical anorexia nervosa (AN), typical and atypical bulimia nervosa (BN), and EDs in general.

2.1.1 Diagnostic criteria and prevalences of eating disorders

2.1.1.1 Anorexia nervosa

AN is characterized by significantly low body weight (emaciation), an intense fear of gaining weight even though at a dangerously low body weight, and disturbed perception of own body weight and shape[1]. AN includes two subtypes—the restrictive subtype, marked by restricted energy intake, and the binge-eating/purging subtype, marked by recurrent episodes of binge-eating and purging[1,8]. Patients who meet all diagnostic criteria for AN but who remain at a normal weight range fulfill the diagnosis of atypical AN[1,20]. AN was first formally described in modern medical literature in 1870s[21,22], with emphasis on social and psychological aspects of the role of starvation[23]. In the Swedish diagnostic system, AN is identifiable as an independent psychiatric disorder in the Swedish version of the International Classification of Disease, 9th version (ICD-9, since 1987)[24], ICD-10 (since 1997)[20], and the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, since 1999)[25].

AN typically begins around puberty but also affects young children and older adults[23]. More females than males are affected by AN, with a sex ratio around 10:1 based on clinical populations[1]. The lifetime prevalence of AN is estimated to be approximately 0.5%-0.9% in females and 0.1%-0.3% in males in the US and six European countries[16,26]. Atypical AN is slightly more prevalent than AN, with prevalence estimated to be approximately 1.3% in female and 0.4% in male adolescents and young adults[27]. In a Swedish adult twin sample with self-reported eating behavior data, the prevalence was 0.7% in females, and 0% in males for AN and 3.6% in females and 0.09% in males for broad-sense AN, i.e., AN and atypical AN combined[14]. The register-based prevalence of clinically diagnosed broad-sense AN was 0.7% in females and 0.04% in males in a Swedish cohort (aged 8-30)[28].

2.1.1.2 Bulimia nervosa

BN is characterized by recurrent episodes of binge-eating (i.e., consuming an unusually large amount of food accompanied by a feeling of loss of control) coupled with inappropriate compensatory behaviors to prevent weight gain, such as excessive exercise and purging (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or other medications)[23]. The diagnostic threshold for the frequency of binge-eating and compensatory behavior is at least once a week for 3 months in DSM-5 (since 2013)[1]. Patients who meet all diagnostic criteria

for BN but have lower frequency of binge-eating and purging behaviors fulfill the diagnosis of atypical BN[1,20]. The term "bulimia" was first listed in DSM-III with a main focus on binge-eating but not compensatory behaviors[29,30]; whereas BN was first recognized as an independent disorder in DSM-III-R[31,32]. In the Swedish diagnostic system, BN is identifiable as an independent psychiatric disorder in ICD-10[20] and DSM-IV[25].

BN typically begins in late adolescence and young adulthood[1]. The lifetime prevalence is estimated to be between 0.5% and 2.8% in females and between 0.1% and 0.5% in males for BN[16,26], and 1.5% in females and 0.6% in males for atypical BN in a sample of adolescents and young adults[27]. Data from a Swedish adult twin sample with self-reported eating behaviors revealed a prevalence approximately 1.1% in females and 0.07% in males for BN and 2.7% in females and 0.2% in males for broad-sense BN, i.e., BN and atypical BN combined[14]. The register-based prevalence of clinically diagnosed broad-sense BN was 0.3% in females and 0.01% in males in a Swedish cohort (aged 8-30)[28].

2.1.1.3 Other eating disorders

In ICD-10, AN (F50.0), atypical AN (F50.1), BN (F50.2), and atypical BN (F50.3) are coded separately and thus differentiable. EDs other than these types are categorized into "other EDs" or "EDs, unspecified"[20].

In DSM-IV, EDs that do not meet the criteria for AN and BN are classified as Eating Disorder Not Otherwise Specified (EDNOS). This category includes atypical AN and atypical BN, amongst others.

In DSM-5, binge-eating disorder, previously categorized within EDNOS (DSM-IV), became an independent category. It is characterized by recurrent episodes of binge-eating (at least once a week for 3 months) that is *not* accompanied by inappropriate compensatory behaviors[1]. Binge-eating disorder has a lifetime prevalence of 1.9%-3.5% in females and 0.3%-2.0% in males[16,26], and the twelve-month prevalence among adults in the US is approximately 1.6% in females and 0.8% in males[1]. EDs that meet some but not all of the criteria for AN, BN, or binge-eating disorder are categorized as other specified feeding and eating disorders (OSFED) in DSM-5.

2.1.1.4 Diagnostic crossover across eating disorders

Diagnostic crossover between EDs over time is not uncommon. Despite variable follow-up time and baseline characters, previous observations have reported considerable proportions of crossover between subtypes of AN (around 17%-64%)[13], from AN to BN (around 10%-54%), and from BN to AN (around 2%-27%) during the course of illness[13]. A recent study reported 7.5%, 0.5%, and 39.9% of 1,139 AN patients transferred to BN, binge-eating disorder, and other EDs, respectively, over a mean follow-up time of 9.8 years[33]. Large diagnostic flux between binge-eating disorder and other ED diagnoses, in both directions, has been observed in a Swedish sample of 850 treatment-seeking individuals[34].

On one hand, the diagnostic flux implies potentially shared etiology between different EDs. On the other hand, it raises concerns on the validity and utility of the current diagnostic schema (e.g., whether the distinction between two EDs is obvious enough to separate them as independent categories)[13,35]. Such concerns will be better addressed by not only focusing on the diagnostic flux, but also further elucidating the shared etiology between EDs based on the current schema. For instance, research on the genetic and environmental correlations between EDs can provide additional information on underlying etiological similarities and differences.

2.1.2 Genetics of eating disorders

That there is a genetic liability to EDs was first demonstrated in studies of familial aggregation. The risk of lifetime AN in the first-degree female relatives of individuals with AN is approximately 11 times the risk in the first-degree female relatives of individuals without AN; the same relative risk is approximately four for BN[36] and two for binge-eating disorder[37] in US samples. Numerous twin studies have quantified genetic effects on EDs in several populations. The heritability, i.e., proportion of variance of a trait in a population explained by genetic variance in the population[38], is estimated to be 27%-74% in AN, 28%-83% in BN[39], and 26%-77% in binge-eating disorder[40].

Genome-wide association studies (GWAS) provide a hypothesis-free approach to identify single nucleotide polymorphism loci (SNP, markers of genetic variants in the genome) that are associated with EDs on a genome-wide significant level[41]. Although limited by insufficient sample sizes, previous GWAS on AN have demonstrated the potential of finding SNPs that are significantly associated with AN[42,43]. By now the largest publicly available AN GWAS has identified the first genome-wide significant SNP locus associated with AN—rs4622308, which has also been related to type 1 diabetes and autoimmune-related phenotypes[44]. Linkage disequilibrium (LD) score regression[45] on the GWAS findings has revealed exciting new findings, such as positive genetic correlations between AN and some other psychiatric disorders (e.g. schizophrenia[44] and obsessive-compulsive disorder[45]) and, interestingly, negative genetic correlation between AN and obesity and other metabolic parameters (e.g., extreme body mass index [BMI])[44]. More downstream analyses on, e.g., gene-sets and pathways that are associated with AN are promising given statistically well-powered GWAS on AN, which is underway[46]. However, GWAS on EDs other than AN are still lacking. Given the success in elucidating the genetic etiology in AN, GWAS and downstream analyses on other EDs are highly encouraged to expand our knowledge.

2.1.2.1 Genetic overlap between anorexia and bulimia nervosa

Genetic methods can be used to determine the extent to which AN and BN share genetic risk. The co-aggregation of AN and BN in families may imply their genetic overlap. In a controlled family study, the risk of having lifetime AN in first-degree female relatives of individuals with BN was around 12 times the risk in the first-degree female relatives of individuals without BN; the same relative risk of having lifetime BN was around four in first-

degree female relatives of individuals with AN compared to the relatives of individuals without AN[36].

To our knowledge only one twin study based on self-reported eating behaviors has explored this question and reported a moderate-to-high genetic correlation (0.78, 95% confidence interval [95%CI]=[0.51, 1.00]) between broad-sense AN and BN[14]. Despite the relatively large sample size of this study (N=7,000), the small numbers of concordant pairs (pairs where both twins had the same ED or one had AN and the other had BN) limited the statistical power. Moreover, studies based on clinical diagnosis are needed to confirm this observation.

2.1.3 Adversities associated with eating disorders

Severe medical complications across multiple organ systems have been observed in individuals with EDs[2,9,18,47-50]. In addition, EDs have also been associated with significant problems in psychosocial functioning, such as suicide and criminal behaviors.

2.1.3.1 Eating disorders and suicide

EDs are associated with increased mortality risk[8], and approximately 20% of deaths associated with AN are attributable to suicide[8]. The suicide-specific standardized mortality ratio was estimated to be 18.1 in AN[51] and 7.5 in BN[8] based on meta-analyses. The interpretation of the estimates was limited by the variations in follow-up time, source of data, sample size, and representativeness of samples in the studies included in the meta-analyses. Large population-based studies are needed to provide more representative estimates.

Comorbid psychiatric disorders, such as major depressive disorder (MDD), anxiety disorder, and substance use disorder (SUD), have been associated with suicide and suicide attempts[52-54]. However, the extent to which these comorbidities contribute to the increased risk of suicide in EDs is less clear. Similar to EDs, suicide risk exhibits familial clustering[55], but little research has explored the co-aggregation pattern of EDs and suicide (and suicide attempts) within families.

Research that clarifies the factors that contribute to the strong association between EDs and suicide are essential and could inform efforts to reduce mortality associated with the illnesses. Such work has the potential to help identify high-risk groups within patients and/or identify risk factors or clinical characteristics for targeted interventions.

2.1.3.2 Eating disorders and theft and other crimes

Moderately high prevalence of theft behaviors (around 24%-55%) has been reported in clinical samples of individuals with EDs, especially BN and binge-eating/purging subtype AN[56], across different cultures[56-61]. Research on a population-based sample also reported increased risk of criminal behaviors other than theft in individuals with higher levels of ED symptoms[17]. However, the sample sizes of the clinical studies were relatively small, and observations in the population-based sample mainly relied on an informal measure of ED (e.g., self-reported “any binge disorder”[17]).

Both criminal behaviors and BN are associated with impulsivity and sensation seeking[62-64], which might give rise to their overlap[65]. Although individuals with AN, especially restrictive subtype AN, are usually constrained and display low levels of sensation-seeking behaviors[62], starvation may trigger adaptive neurobiological changes which may lead to impulsive and sensation-seeking behaviors in some cases[66].

Understanding this mechanism is of considerable clinical importance, as criminal behaviors and related legal proceedings could increase stress in individuals suffering from EDs and even interfere with treatment and recovery[67-69]. However, several knowledge gaps need to be addressed. Firstly, the associations observed in clinical settings need to be examined in larger samples with better population representativeness and with clinical and forensic records that are valid. Second, despite the plausible hypothesis on the role of impulsivity as mentioned above, the mechanism underlying increased risk of criminal behaviors and EDs remains obscure. Research on factors that contribute to the associations between EDs and criminal behaviors will improve our understanding of the association and potentially inform strategies in preventing the criminal behaviors and in addressing crime-related stress during treatment.

2.1.4 Psychiatric comorbidities in individuals with eating disorders

Psychiatric comorbidities are common in individuals with EDs[6,16,34,70], including, but not limited to, mood disorders, anxiety disorders, impulse-control disorders, and SUD[1,16,71,72] in both sexes[73]. The pattern of comorbidity differs across EDs. For example, SUD and attention-deficit hyper activity disorder (ADHD) are more prevalent in individuals with BN than in those with AN[16].

Shared familial liabilities have been established between EDs and some comorbidity. A recent study found AN and obsessive-compulsive disorder co-aggregate in families and revealed moderate genetic correlation (approximately 0.52) between them in twins[74]. Molecular genetic studies based on GWAS findings have found positive genetic correlations between AN and schizophrenia (approximately 0.19-0.29)[44,75]. However, the genetic mechanism underlying the associations between AN and other comorbid psychiatric disorders and between other EDs and comorbid disorders is less clear.

2.1.4.1 Eating disorders and attention-deficit/hyperactivity disorder (ADHD)

ADHD is characterized by inattentive and/or hyperactive/impulsive symptoms[1]. It affects around 3.4%-7.2% of children and adolescents worldwide[76,77] and around 2.5% of adults[78,79] and is associated with substantial disease burden[80,81]. It is one of the comorbidities of EDs but the mechanism underlying their comorbidity remains unclear.

Increased prevalence of any ED and concerns about weight and body shape have been observed in individuals with ADHD[82,83]. ADHD symptoms are also overrepresented in individuals with ED-related problems in the general population[84]. Longitudinal studies suggest that individuals with ADHD are at increased risk of subsequent EDs[85] and ED symptoms such as drive for thinness, bulimia, body dissatisfaction, and binge-eating[86,87].

Population-based studies reveal that self-reported ADHD symptoms are significantly associated with binge-eating behaviors, but not with restrictive behaviors[88,89]. Some studies were able to distinguish specific types of EDs and have reported higher prevalence of screened ADHD in patients with BN, binge-eating/purging subtype AN (35%-37%), and binge-eating disorder (26%-31%) than in those with restrictive subtype AN (18%)[90].

Mechanisms underlying the co-occurrence of ADHD and EDs are poorly understood, despite the familial and genetic liability established separately for the disorders by twin and family studies[14,36,91,92] and GWAS[93,94]. A twin study has explored the overlap between ADHD symptoms and binge-eating behaviors and reported a moderate genetic correlation (0.35, 95% confidence interval [95% CI]=[0.25, 0.46]) based on self-reported symptoms in a Swedish adult twin sample[95]. LD score regression reported a non-significant genetic correlation between ADHD and AN[96], based on summary statistics of GWAS that were potentially underpowered. Whether clinically diagnosed ADHD and EDs share genetic risk remains to be investigated.

2.2 EXPLORE GENETIC AND ENVIRONMENTAL EFFECTS IN EPIDEMIOLOGY

2.2.1 Causal inference and confounding effects in epidemiology

Epidemiology studies disease and health patterns in population and has as a primary goal to determine whether a factor causes a disorder/disease in order to develop targeted interventions/treatments, or whether an intervention/treatment is effective to prevent/cure the disorder/disease in population. (For the sake of convenience, in the following text a factor or an intervention/treatment under investigation is termed as an "*exposure*", and a disorder/disease or the outcome of an intervention/treatment is termed as an "*outcome*".) Ideally, in order to determine whether an exposure causes an outcome, we should compare the outcomes in exposed individuals to the outcomes in *the same individuals if they had not been exposed*. However, this comparison is counterfactual in our world, as we are unable to move back in the dimension of time (at least for now). Different study designs are therefore applied to infer causality in epidemiology.

Randomized controlled trails (RCT) are a type of experimental study design, where participants are randomized to exposed or unexposed groups before comparing their outcomes. As randomization balances all the other factors between the exposed and unexposed groups, the comparability between these groups more closely approximates the counterfactual ideal, and the result of well-conducted RCT provides an excellent approximation of causality, given large enough sample size. However, RCT are expensive and sometimes unethical to perform (e.g., when the exposure is hazardous). Additionally, RCT can suffer from threats to internal validity (e.g., threats to randomization) and limited generalizability.

A majority of causal inference in epidemiology results from observational studies, where researchers cannot perform randomization, but rely on careful assessment of the associations directly observed between exposure and outcome in population. A common challenge in causal inference in observed associations is to address confounding effect, where a factor (a *confounder*) causes both exposure and outcome and therefore creates an association between them that is independent of their causal relationship (illustrated in by a Directed Acyclic Graph[97] in Figure 2.2.1). An observed association between an exposure and an outcome can be entirely or partially explained by confounding effect.

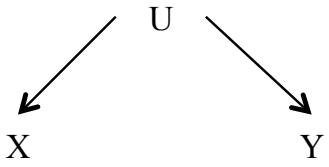

Figure 2.2.1 Confounder illustrated by a Directed Acyclic Graph. *A Directed Acyclic Graph (DAG) is a causal diagram adapted to epidemiological research[97]. It illustrates the underlying causal relationships between variables, offering a useful tool to critically evaluate confounding effects and provide insights on variables to measure and study designs to choose. This DAG illustrates that U is a confounder of X and Y. By causing both X and Y, U creates an association between X and Y, regardless whether there is a direct causal relationship between X and Y.*

2.2.2 The role of genetic and environmental factors

Genetic and environmental factors have been found to be associated with multiple human traits[98] and, when they are the causal factors of the traits, can confound the associations between these traits. For instance, genetic risk factors may cause impulsivity that gives rise to both binge-eating behavior in BN and theft behavior[99] and thus confound the association between BN and theft. Likewise, environmental factors may cause impulsivity[100] and also confound the association.

Traditional observational studies avoid confounding effect by adjusting for or stratifying by the confounders, which requires clear measurement. However, many genetic and environmental confounders are difficult to measure or unknown. Moreover, environmental factors often have genetic foundation as well (or passive genetic-environmental correlation)[101], making it more complicated to disentangle and measure each factor.

Genetically informative designs can assist with addressing unmeasured genetic and environmental confounders. However, before introducing the designs, it is necessary to clarify that avoiding the confounding effect is not the only way to address confounders in epidemiology. Depending on the research questions, some studies require avoiding the confounding effects of genetic and environmental factors, whereas some seek to test and quantify them.

2.2.3 Genetically informative designs in brief

2.2.3.1 To avoid genetic and environmental confounding

- *Sibling comparison*

Comparing between matched pairs is an option to account for confounders without having to measure them. *Sibling comparison* is a design that compares outcomes between differentially exposed siblings in a family and therefore controls for factors that are constantly shared by the siblings (termed as *familial factors*), regardless whether they are measured. These factors can include part of the genetic background and some familial environmental factors, i.e., non-genetic factors that make relatives similar to one another[38]. If familial factors (partially) confound the association under investigation, it would be highly likely that the estimated association in sibling comparison design is different from (and mostly weaker than) the estimated association in traditional designs.

Evidence from sibling comparisons has shown that familial factors can explain some associations completely[102] but only partially for some other associations[103,104]. In the current thesis, this design has been applied to explore the clinically observed association between EDs and theft and other criminal behaviors, which might be confounded by genetic and environmental factors that are hard to measure and had not been accounted for in previous research.

2.2.3.2 To test and quantify genetic and environmental confounding

Confounding effects are part of the mechanism underlying an association between two traits., It is interesting to test and quantify them in many scenarios to advance our understanding of the association.

- *Familial co-aggregation of traits*

Family members are generally more similar to each other in terms of genetic and familial environmental factors. If two traits (A and B) share genetic and/or familial environmental risk factors, they are likely to co-aggregate in families, meaning that the chance of possessing trait A should be higher in relatives of individuals with trait B than in the same type of relatives of individuals without trait B. Familial co-aggregation of AN and BN has been illustrated in a previously mentioned example, where the risk of lifetime BN is higher in the relatives of individuals with lifetime AN, in comparison to the risk of lifetime BN in the same type of relatives of individuals without lifetime AN[36]. This design has been used to examine common familial liability to multiple traits, and various models have been proposed to analyze the familial co-aggregation of traits[105,106]. Nevertheless, familial co-aggregation may also be explained by causal relationship between the traits, rather than familial liability shared by the traits (detailed explained in section 5.2).

In this thesis, familial co-aggregation of EDs and suicide has been examined to determine whether suicide risk shares genetic and/or familial environmental liabilities with different

types of EDs. Familial liability to different EDs and ADHD has also been examined by exploring their familial co-aggregation pattern.

- *Quantitative genetic modeling*

Quantitative genetic modeling also takes advantage of the genetic and environmental similarities between relatives and further quantifies the genetic and environmental effects on a trait or the association between traits[107]. For instance, *heritability*, a commonly used term to measure the relative importance of the genetic contribution to a trait, is defined as the proportion of variance of a trait explained by genetic variance in a population[38].

Twin studies are classic examples of quantitative genetic modeling. In the past decades, they have been employed to estimate heritability and have established the genetic foundation for numerous complex traits in human behaviors[98]. Apart from twins, data from other types of relatives can also inform the quantification of genetic and environmental effects on traits, under reasonable assumptions on genetic and familial environmental sharing[108].

In the current thesis, quantitative genetic modeling has been generalized to data in full-sisters and maternal half-sisters to quantify the relative importance of genetic and environmental effects on the association between AN and BN, to understand the etiological overlap between these two EDs. This design has also been applied to evaluate the relative importance of genetic and environmental effects on the comorbidity of ADHD in individuals with different EDs.

- *Polygenic risk score analysis*

Increasing numbers of GWAS of human traits have given rise to multiple methods to analyze genetic risks based on common genetic variants. Polygenic risk scores (PRS) are a measure of individual genetic predisposition to a disorder. They are derived based on individual genotype and results of GWAS[109,110]. PRS are useful in exploring the genetic liability underlying the association between two traits, too. For instance, the PRS of ADHD have been associated with neurodevelopmental symptoms in the general population[111], illustrating the genetic liability to the overlap between ADHD and neurodevelopmental disorders in general.

In this thesis, PRS analysis has been applied to examine how ADHD PRS (i.e., the common genetic risks of ADHD) predict ED-related symptoms in the general population and vice versa—how PRS of AN predict ADHD symptoms. If, for example, ADHD PRS predicts ED symptoms, it would suggest that the genetic risk of ADHD also affects ED-related behaviors, reflecting their genetic correlation.

3 AIM

The overarching aim of this thesis is two-fold: 1) to evaluate the associations among EDs and between EDs and the adverse outcomes and psychiatric comorbidity at population level, and 2) to estimate the genetic and environmental influences on these associations to advance the understanding of the etiology of EDs.

The specific aims of the four included studies are:

Study I: To quantify the relative importance of genetic and environmental influences on the overlap between clinically diagnosed AN and BN in a Swedish population

Study II: To evaluate the association between clinically diagnosed EDs and suicide at population level and to examine the familial liability to the association

Study III: To evaluate the association between clinically diagnosed AN and BN and the risk of being convicted for theft and other crimes at population level

Study IV: To assess the genetic association between ADHD and EDs at both diagnostic and symptomatic levels

4 DATA SOURCE AND MEASURES

4.1 DATA SOURCE

The Swedish registers contain demographic data, medical data, familial pedigree, and more. The registers can be linked through the unique individual identification number that has been assigned to each resident in Sweden since 1947[112].

4.1.1 Swedish national registers

Independent Swedish governmental agencies (Statistics Sweden and the Swedish National Board of Health and Welfare) merged the data from multiple Swedish national registers and de-identified and merged data for research purposes[113]. Registers below were included in this thesis.

The Total Population Register (TPR, since 1968) provides information on sex, birth year and month, place of birth, date of death, type (immigration or emigration) and date of migration, and other information[113]. It includes individuals who were born since 1932 and alive in 1968.

The Multi-Generation Register (MGR) provides information on biological parents of individuals who were born after 1932 and lived in Sweden any time after January 1st 1961[114], except those whose parents died or emigrated before 1947. The register was used in this thesis to identify relatives, including full-siblings (individuals born to the same parents), maternal half-siblings (individuals born to the same mother but different fathers), paternal half-siblings (individuals born to the same father but different mothers), cousins, and half-cousins (offspring of half-siblings).

The National Patient Register (NPR, since the 1960's) contains inpatient psychiatric diagnoses since 1973 and outpatient psychiatric diagnoses since 2001[115]. Diagnoses in the NPR are based on ICD-8 (Swedish version, 1973-1986), ICD-9 (Swedish version 1987-1996), and ICD-10 (international version, since 1997).

The Swedish National Quality Register for Eating Disorder Treatment (Riksät, since 1999) and **the Quality Assurance System for Eating Disorders (Stepwise**, since 2005) are two quality registers for EDs. They provide ED diagnoses from specialized treatment centers across Sweden[116,117], with increased coverage over time.[118] Diagnoses in the two quality registers are based on the DSM-IV-TR[25].

The Swedish Twin Register (STR, since the 1950's) contains over 194,000 pairs of twins, and over 75,000 of them had determined zygosity based on questionnaires (on within-pair similarity) or genotype data[119].

The Cause of Death Register (CDR) was established in 1952 and gained complete coverage since 1961. It contains information on principal and secondary causes of death, coded according to ICD-8, ICD-9, and ICD-10.

The Criminal Conviction Register (CCR, since 1973) contains criminal conviction records from Swedish lower courts, despite the medico-legal disposition of the convicted offender[120]. Law-breaking behaviors are not registered before age 15 years (the age for criminal responsibility in Sweden)[120].

The Clinical Database for Child and Adolescent Psychiatry in Stockholm (Pastill, since 2001) contains diagnoses of psychiatric disorders based on ICD-10 or DSM-IV from Child and Adolescent Mental Health Services in Stockholm County[121].

The Prescribed Drug Register (PDR, since July 2005) contains information on medication prescriptions. Active ingredients are coded according to the anatomical therapeutic chemical classification system[122].

4.1.2 The Child and Adolescent Twin Study in Sweden

The Child and Adolescent Twin Study in Sweden (CATSS) is an on-going population-based twin study since 2004[123]. CATSS identifies all 9-year-old twins from STR and systematically approaches their parents and conducts telephone interview about the somatic and mental health of the twins. Informed consents were provided by parents of the participants. During 2004-2006, CATSS also included 12-year-old twins[123]. Follow-up questionnaires are distributed when the twins reach ages 15 and 18 to collect more phenotypic information. Data on ADHD symptoms collected at 9 or 12 years old and on ED symptoms collected at 15 years old were used in Study IV in this thesis.

In 2008, saliva samples were collected for DNA extraction after the first telephone interview. Twins who were born earlier were re-contacted for saliva samples[119]. By 2017 a total of 11,551 individuals in CATSS were genotyped using the Illumina Infinium PsychArray-24 BeadChip[111].

4.2 MEASURES

4.2.1 In Swedish national registers

Data from multiple registers were retrieved to measure EDs, suicide attempts and death by suicide, criminal behavior, ADHD, and other psychiatric conditions. The definitions were described below, followed by a summary (Table 4.2.1).

4.2.1.1 Eating disorders

EDs were identified based on diagnosis from the NPR and the ED quality registers Riksät, and Stepwise. Different studies in this thesis focused on slightly varied categorizations of EDs, but the definition of each type was unified across the studies.

Any ED (Studies II and IV) was defined as having a diagnosis of any ED in the registers. It is identified with ICD-9 (Swedish version) codes 307B or 307F or ICD-10 codes F50.0-F50.3, or F50.9 from the NPR, or meeting DSM-IV criteria for EDs from the quality registers, i.e., 307.1, 305.51, and 307.50.

AN (all studies) included diagnoses of AN or atypical AN, identified with 307B (ICD-9) or F50.0 or F50.1 (ICD-10) from the NPR, or meeting DSM-IV criteria for AN (307.1) or atypical AN (307.50, criteria 1 and 2) from the quality registers. Restrictive and binge-eating/purging subtypes can be distinguished from DSM-IV codes in the quality registers but not from ICD codes in the NPR.

BN (all studies) included diagnosed BN or atypical BN, identified with F50.2 or F50.3 (ICD-10) from NPR, or meeting DSM-IV criteria for BN (307.51) or atypical BN (307.50, criterion 3) from the quality registers. BN was not identifiable in the Swedish version of ICD-9.

OED (Study IV) was defined as EDs other than AN, i.e., having a diagnosis of any ED that was not AN. In Study IV individuals could have both AN and OED, and BN was a subset of OED.

4.2.1.2 Suicide attempts and death by suicide (Study II)

Suicide attempts were defined as any suicide attempt reported in the NPR or death by suicide reported in the CDR, based on ICD-9 codes E950-E959, E980-E989 and ICD-10 codes X60-X84, or Y10-Y34[124]. Death by suicide was identified by the same code from the CDR only.

4.2.1.3 Criminal behavior (Study III)

Criminal behavior was identified by the conviction registered in the CCR, according to the Swedish Penal Code. Convictions of theft were identified based on Chapter 8 Sections 1-4, 7-11, and 13 (i.e., theft, petty theft, gross theft, vehicle theft, unlawful dispossession, self-repossession, unlawful diversion of energy, unlawful takes from a forest or field if not considered as trespassing, and theft committed against a person living with or closely related to the convicted person). Convictions of other crimes were defined as any non-theft conviction in the CCR. The study design required information on the date of the first criminal behavior. It was defined as the date of committing the crime, if registered; otherwise, the registered date of conviction was used.

4.2.1.4 Attention-deficit/hyperactivity disorder (Study IV)

ADHD was defined as having a diagnosis of ADHD or a prescription of ADHD medication. It was identified through diagnosis code 314 (ICD-9, Swedish version) or F90 (ICD-10) in the NPR or Pastill, or 314 (DSM-IV) in Pastill, or drug prescription of methylphenidate (N06BA04), amphetamine (N06BA01), dexamphetamine (N06BA02), or atomoxetine (N06BA09) in the PDR[92].

4.2.1.5 Potential confounders (Studies II and III)

Study II: Potential confounders for the association between EDs and suicide attempts were identified from the NPR and included MDD (ICD-9: 296.3, 300.4, or 311; ICD-10: F32-F39, except F34.0), anxiety disorder (ICD-9: 300, 300.09, or 300.29; ICD-10: F40-F41), and SUD (ICD-9: 303-304, 305.0, or 305.9; ICD-10: F10-F16, or F18-F19)[125]. These comorbidities

were included as potential confounders because they have been associated with both EDs and suicide[16,52,53,126].

Study III: Potential confounders for the association between AN and BN and criminal behaviors might include: personality disorders, ADHD, and non-exposure EDs, because they have been associated with both EDs and criminality in the literature[14,16,17,127]. Personality disorders were identified with ICD-9 code 301 or ICD-10 codes F60-F61. ADHD was defined as described before (in section *4.2.1.4*). Non-exposure EDs were defined as having any ED diagnosis other than the exposure, i.e., when the exposure was AN other EDs were any ED except AN; when the exposure was BN, other ED were any ED except BN (e.g., BN can be a confounder for the association between AN and criminal behaviors and AN can be a confounder for the association between BN and criminal behaviors).

Table 4.2.1 Summary of primary register-based measures in this thesis (registers, study, and criteria)

	Registers	**Study**	**ICD-9**	**ICD-10**	**DSM-IV**	**Drug**	**Swedish Penal Code**
Any ED	NPR, Riksät, Stepwise	II, IV	307B, 307F	F50.0-F50.3, F50.9	307.1, 307.51, 307.50	.	.
AN	NPR, Riksät, Stepwise	I-IV	307B	F50.0, F50.1	307.1, 307.50 (1-2)	.	.
BN	NPR, Riksät, Stepwise	I-IV	.	F50.2, F50.3	307.51, 307.50 (3)	.	.
OED	NPR, Riksät, Stepwise	IV	307F	F50.2, F50.3, F50.9	307.51, 307.50 except 370.50 (1-2)	.	.
Suicide attempts	NPR, CDR	II	E950-E959, E980-E989	X60-X84, or Y10-Y34	.	.	.
Death by suicide	CDR	II					
Conviction of theft	CCR	III	.	.	.	.	Chapter 8 Sections 1-4, 7-11, and 13
Conviction of other crimes	CCR	III	.	.	.	.	Any conviction except theft
ADHD	NPR, Pastill, PDR	III, IV	314	F90	314	N06BA01, N06BA02, N06BA04, N06BA09	.
MDD	NPR	II	296.3, 300.4, 311	F32-F39, except F34.0	.	.	.
Anxiety disorder	NPR	II	300, 300.09, 300.29	F40-F41	.	.	.
SUD	NPR	II	303-304, 305.0, 305.9	F10-F16, F18-F19	.	.	.
Personality disorder	NPR	III	301	F60-F61	.	.	.

4.2.2 In the Child and Adolescent Twin Study in Sweden (Study IV)

4.2.2.1 Symptom measures for EDs and ADHD

In CATSS, ED symptoms were measured by the Eating Disorder Inventory-2 (EDI-2)[128] at age 15. EDI-2 includes 11 subscales in total and this thesis focused on three of them, namely drive for thinness (7 items), bulimia (7 items), and body dissatisfaction (8 items). Questions were answered on a scale with 6 options ranging from "never"(1) to "always"(6). The EDI-2 has been validated in Nordic countries in females[129,130]. The mean scores of EDI-2 full scale (i.e., all questions in the three subscales of drive for thinness, bulimia, and body dissatisfaction) and subscales were calculated for PRS analysis in Study IV.

ADHD symptoms were measured with the Autism-Tics, ADHD, and Other Comorbidities inventory (A-TAC)[131], a validated instrument in CATSS, at age 9 or 12. The A-TAC contains 19 items on lifetime symptoms of ADHD, with 9 on inattention and 10 on hyperactivity/impulsivity. Questions were answered on a scale of "no" (coded 0), "yes, to some extent" (coded 0.5), and "yes" (coded 1)[123]. The sum scores of all A-TAC ADHD questions (19 items) and two subscales (inattention and hyperactivity/impulsivity) were calculated for analysis.

4.2.2.2 Genetic measure

After stringent quality control[111], 11,081 individuals remained with 561,187 SNPs. Genotypes of 2,495 monozygotic twins were imputed using their genotyped co-twins, resulting in 13,576 individuals with genotypes. Imputation on autosomes was performed in Minimac3[132] with 1000-Genomes data (Phase 3, Version.5)[133] as the reference panel. Next, LD-pruning was conducted and SNPs located in long-range LD regions were removed. Principal components (PCs) were then derived to account for population stratification using PC analysis in PLINK. In Study IV, genotype data was available for 13,472 individuals, after the aforementioned data processing and further exclusion of individuals with cerebral palsy, brain injury, Down syndrome, and chromosomal abnormalities.

5 METHODS

5.1 QUANTITATIVE GENETIC MODELING

5.1.1 Basic model

A basic model in quantitative genetic modeling assumes that a phenotype is influenced by genetic and environmental effects. Genetic effects are usually categorized into additive genetic effects (A) and dominance deviations (D), and environmental effects are usually categorized into effects shared within family (C, shared environmental effects) and effects that are not shared (E, unique environmental effects)[38]. The model can be written as:

$$P_i = \mu + A_i + D_i + C_i + E_i + \xi_i$$

where *P* stands for an observed trait; *i* indexes the i^{th} individual in the population; μ is the population mean; ξ is random error. Assuming that A, D, C, E, and ξ are independent (ξ is usually unmeasured and modeled into E), the variance in the trait is explained by the variance in A, D, C, and E:

$$Var(P) = Var(A) + Var(D) + Var(C) + Var(E)$$

The proportion of variance in the trait explained by the variance of each component reflects the relative importance of the component. For instance, narrow-sense heritability (h^2) is defined as the proportion of variance in the trait explained by the variance in A:

$$h^2 = \frac{Var(A)}{Var(P)}$$

A, D, C, and E are not measured directly, but their relative importance to the trait can be estimated through the variance and covariance of the trait observed in relatives with known genetic and environmental sharing (such as twins). The genetic and environmental effects on the association between two (or more) traits can be estimated in the same way.

5.1.2 Estimating the effects: Structural equation modeling

Structural equation modeling (SEM) is a framework to model covariance matrices and is used in quantitative genetic models to estimate unmeasured genetic and environmental effects based on observed variance and covariance of traits. In this thesis, it is employed to quantify the genetic and environmental effects on associations between AN and BN (Study I) and between EDs and ADHD (Study IV). Data in full-sisters and maternal half-sisters were used.

Each disorder was measured by a binary variable (i.e., clinical diagnosis: yes/no) and was treated under a liability-threshold model, where a normally distributed liability to the disorder is assumed, and the disorder only presents with the liability above a certain threshold[134]. A tetrachoric correlation is the inferred correlation between two binary traits under the liability-threshold model. In quantitative genetic models in this thesis, the following tetrachoric correlations were obtained: 1) pairwise correlation, correlation of a disorder between two

sisters in a pair, 2) phenotypic correlation, correlation of two disorders in an individual, and 3) cross-sister cross-trait correlation, correlation of one disorder in one sister and the other disorder in the other sister in a pair.

Next, bivariate models were fitted using the OpenMx package in R (version 3.2.2)[135]. At most three of the four free parameters (A, C, D, and E) might be estimated at a time given two types of relatives. Models with A, C, and E (ACE model), A, D, and E (ADE model), and A and E (AE model) were fitted to estimate the proportions of phenotypic variances and covariance of two traits explained by the corresponding components in each model.

Full-sisters share 50% of their segregating alleles on average and therefore 50% A and 25% D; whereas maternal half-sisters share 25% of A and no D (as they share only one parent); by definition, C is shared 100% within a pair regardless of the type of sisters, and E is not shared within a pair. A path diagram[38] (Figure 5.1) bellow illustrates the A component in the study of AN and BN (Study I). D, C, and E were not included for simplicity.

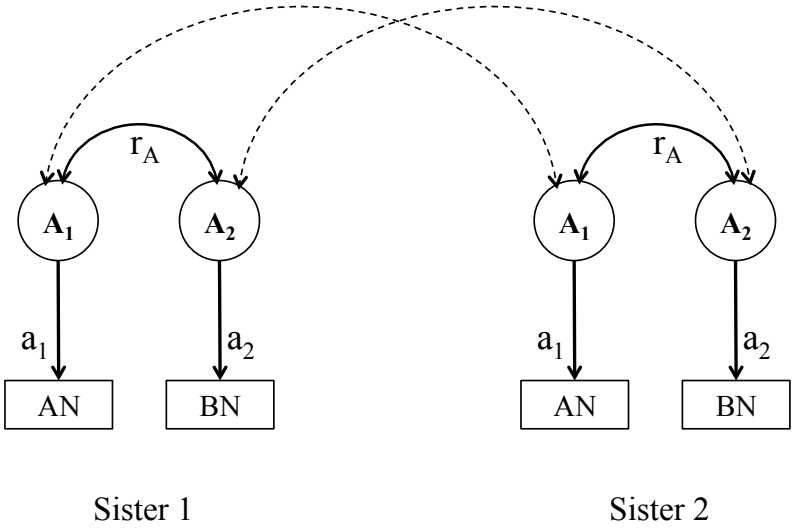

Figure 5.1 Path diagram of the additive genetic effects on AN and BN. *A_1 represents the latent additive genetic effects that contribute a_1 to AN; A_2 represents the latent additive effects that contribute a_2 to BN. The additive genetic correlation between AN and BN is represented by r_A. Parameters a_1, a_2, and r_A are the unknown parameters. The dashed double arrows indicate the additive genetic correlation between two sisters in a pair; they are 0.5 for full-sisters and 0.25 for maternal half-sisters.*

A_1 represents the latent additive genetic effect that contributes a_1 to AN; A_2 represents the latent additive effect that contributes a_2 to BN. The additive genetic correlation between AN and BN is represented by r_A. Parameters a_1, a_2, and r_A are the unknown parameters. The corresponding parameters for D, C, and E, are d_1, d_2, r_D, c_1, c_2, r_C, e_1, e_2, and r_E. Observed correlations can be expressed by these unknown parameters. For instance, in an ACE model, the variance and covariance for AN and BN are:

$$Var(AN) = Var_A(AN) + Var_C(AN) + Var_E(AN) = {a_1}^2 + {c_1}^2 + {e_1}^2$$

$$Var(BN) = Var_A(BN) + Var_C(BN) + Var_E(BN) = {a_2}^2 + {c_2}^2 + {e_2}^2$$

$$Cov(AN, BN) = Cov_A(AN, BN) + Cov_C(AN, BN) + Cov_E(AN, BN)$$
$$= a_1 \cdot a_2 \cdot r_A + c_1 \cdot c_2 \cdot r_C + e_1 \cdot e_2 \cdot r_E$$

And the phenotypic correlation is:

$$Corr(AN, BN) = \frac{Cov(AN, BN)}{\sqrt{Var(AN) \cdot Var(BN)}} = \frac{a_1 \cdot a_2 \cdot r_A + c_1 \cdot c_2 \cdot r_C + e_1 \cdot e_2 \cdot r_E}{\sqrt{({a_1}^2 + {c_1}^2 + {e_1}^2) \cdot ({a_2}^2 + {c_2}^2 + {e_2}^2)}}$$

Similarly, these unknown parameters can be used to express all the other observed correlations (pairwise correlations and cross-sister cross-trait correlations in each type of relative) and therefore be estimated and used to quantify other measures of interest, e.g., the "co-heritability" (the proportion of phenotypic covariance explained by their genetic covariance). It measures the relative importance of additive genetic effect on the overlap between AN and BN:

$$co - heritbaility = \frac{Cov_A(AN, BN)}{Cov(AN, BN)} = \frac{a_1 \cdot a_2 \cdot r_A}{a_1 \cdot a_2 \cdot r_A + c_1 \cdot c_2 \cdot r_C + e_1 \cdot e_2 \cdot r_E}$$

5.2 FAMILIAL CO-AGGREGATION

Familial co-aggregation design explores how two traits cluster together within families. The DAG[97] below (Figure 5.2.1) illustrates the causal relationships between two traits (X_j and Y_j; j=1, 2 stands for the two relatives in a pair), factors shared in families (C, confounder of X and Y, shared by the two relatives, such as genetic background; U_X, common causes of X_1 and X_2, independent of trait Y; U_Y, common causes of Y_1 and Y_2, independent of X), and confounders for X and Y that are not shared in families (U_1 and U_2). The association between X_1 and Y_2 (symmetric with the X_2 and Y_1) is often assessed, and a significant association suggests familial co-aggregation of X and Y.

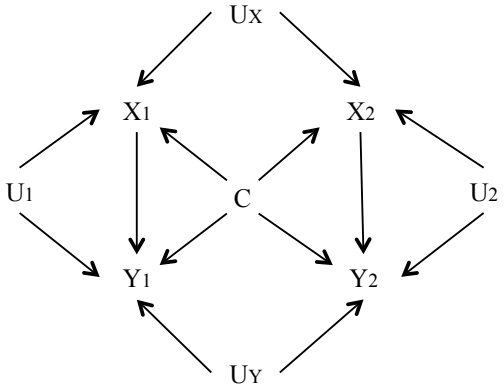

Figure 5.2 DAG to illustrate the familial co-aggregation of two traits. *X_j and Y_j represent the two traits in individual j in a given pair; j = 1, 2. U_X represents common causes for X_1 and X_2, and U_Y represents common causes for Y_1 and Y_2. U_j represents common causes for X_j and Y_j that are not shared within the pair, and C represents common causes for X_j and Y_j that are constantly shared within the pair.*

However, the familial co-aggregation of X and Y, i.e., a significant association between X_1 and Y_2, does not sufficiently demonstrate the existence of C. For instance, when there is a direct causal effect between X and Y, the observed association between X_1 and Y_2 is not only explained by path 1) $X_1 \leftarrow C \rightarrow Y_2$, but also by 2) $X_1 \leftarrow C \rightarrow X_2 \rightarrow Y_2$ and 3) $X_1 \leftarrow U_X \rightarrow X_2 \rightarrow Y_2$, which does not presume the existence of C.

To test whether C exist we can, in an analysis of the association between X_1 and Y_2, adjust for X_2. This accounts for the effects due to paths 2) and 3), but it introduces new effects between X_1 and Y_2 because of adjusting for a collider[136] in paths 4) $X_1 \leftarrow C \rightarrow X_2 \leftarrow U_2 \rightarrow Y_2$, 5) $X_1 \leftarrow U_X \rightarrow X_2 \leftarrow C \rightarrow Y_2$, and 6) $X_1 \leftarrow U_X \rightarrow X_2 \leftarrow U_2 \rightarrow Y_2$. Any adjusted (for X_2) association between X_1 and Y_2 can be explained by any or all of paths 1), 4), 5), and 6), among which path 6) does not presume the existence of C. However, the effects introduced by paths 4), 5), and 6) are most likely to be negative, when assuming that U_X affect X_1 and X_2 in the same direction and that U_2 affect X_2 and Y_2 in the same direction[136]. If C exists, then it is possible to observe a significant adjusted (for X_2) association between X_1 and Y_2 (to the same direction as the unadjusted association). Therefore, if a significant association between X_1 and Y_2 remains after adjusting for X_2, it will offer a sufficient (but not necessary) evidence for the existence of C—familial confounders for the two traits.

Logistic regression is commonly used in case-control studies to estimate odds ratios (OR) as the measure of familial co-aggregation[36,105]. Other methods such as quantitative methods based on SEM are also available[137]. In Studies II and IV, logistic regression was applied.

5.3 SIBLING COMPARISON

5.3.1 Rationale

Sibling comparison design is developed to account for unmeasured confounding effects that are shared by siblings, such as genetic background and *in utero* effects[138]. In contrast to familial co-aggregation design, sibling comparison design focuses on testing the causality between two traits (illustrated by the arrow $X_j \rightarrow Y_j$ in Figure 5.2.1) instead of testing the existence of C. By comparing between differentially exposed siblings, the design accounts for factors shared between siblings (e.g., C, U_X, and U_Y in Figure 5.2.1).

5.3.2 Analytical method in sibling comparison

Analytical methods that estimate within-cluster effect (i.e., the association between exposure and outcome within a pair of siblings) allow for implicit adjustment of unmeasured factors shared within the cluster. Such methods include conditional logistic regression and stratified Cox proportional hazards regression. For instance, stratified Cox proportional hazards regression was used in a longitudinal study on maternal pre-pregnancy BMI and to offspring ADHD[139], where the hazard ratios (HRs) were estimated to evaluate the effect of the exposure on the outcome, accounting for the unmeasured familial factors.

In Study III sibling comparison was nested in a cohort design where individuals were followed from age 15 years for up-to 20 years (detailed explained in section 5.5.3). Stratified Cox proportional hazards models were applied to estimate the HR of criminal convictions in AN and BN.

5.4 POLYGENIC RISK SCORE ANALYSIS

5.4.1 Derive polygenic risk scores

In Study IV, PRS of AN and ADHD were derived for 13,472 eligible individuals in CATSS. ***AN PRS*** were generated with the largest available AN GWAS (3,495 cases and 10,982 controls)[94]. Quality control was first performed to remove duplicated and ambiguous SNPs in the overlapping SNPs between the CATSS individual genotype data and the summary statistics of the AN GWAS. Next, LD-clumping was performed on the remaining SNPs in PLINK.v.1.9[140] using the 1000-Genomes data as reference population[133]. After LD-clumping, a total of 84,278 SNPs remained. AN PRS were derived by summarizing these SNPs weighted by their effect size[109]. ***ADHD PRS*** were generated with the same procedure based on the largest available ADHD GWAS (19,099 cases and 34,194 controls)[93]. ADHD PRS were derived from 84,969 SNPs after LD-clumping. The PRS were derived across seven p-value thresholds ($p<0.00001$, $p<0.001$, $p<0.01$, $p<0.05$, $p<0.1$, $p<0.5$, and $p<1$). All PRS were standardized for analysis.

5.4.2 Application of polygenic risk scores

PRS are a measure of the genetic risk of a trait on the level of common genetic variants (defined as minor allele frequency ≥ 5% in Study IV) and can be flexibly applied in analyses. An example of its application was to test if individuals with higher PRS of a disorder were at increased risk of being diagnosed with the disorder compared to individuals with lower PRS; significantly increased risk of being diagnosed with ADHD has been found in individuals with higher levels of ADHD PRS compared to individuals with lower levels of ADHD PRS[93], suggesting the importance of common genetic variants in explaining the risk of ADHD. In Study IV, PRS was used in linear regressions to examine 1) whether the genetic risk of ADHD (ADHD PRS) predicted ED symptoms and 2) whether the genetic risk of AN (AN PRS) predicted ADHD symptoms.

5.5 METHOD BY STUDY

Table 5.5 Method by study at a glance

Study	Theme	Participants	Study design	Analytical methods	Main output
I	**Genetic and environmental overlap between AN and BN**	Full-sister (334,433 pairs) and maternal half-sister (57,036 pairs) born 1970-2005, random sample	Quantitative genetic modeling	SEM	Co-heritability and phenotypic covariance explained by environmental covariance Genetic and environmental correlations
II	**Familial liability for EDs and Suicide attempts**	Nationwide population born 1979-2001 (N=2,268,786)	Familial co-aggregation	Logistic regression	OR of suicide attempts in EDs
III	**EDs (exposures: AN and BN) and criminal behavior (outcomes: theft and others)**	Nationwide female cohort born 1979-1994 (N=957,106)	- Cohort design (time-varying exposure) - Sibling comparison	- Cox proportional hazards regression - Stratified Cox proportional hazards regression	- HR of criminal outcomes in EDs in general population - HR (stratified) of criminal outcomes in EDs in sibling comparison
IV	**Genetic association between EDs and ADHD**	- Nationwide population born 1970-2005 (N=3,550,188) - Full-sister (334,433 pairs) and maternal half-sisters (57,036 pairs), random sample - CATSS (N=13,472)	- Familial co-aggregation - Quantitative genetic modeling - PRS analysis	- Logistic regression - SEM - Linear regression	- OR of EDs in ADHD - Co-heritability and genetic correlation - Variance explained and regression coefficients of phenotypes predicted by PRS (cross disorder)

5.5.1 Study I

5.5.1.1 Study population

Study I modeled clinical diagnosis of AN and BN in full-sisters and maternal half-sisters. The study base were all females born between 1970 and 2005, with data updated until December 31, 2013. Males were not included due to very low prevalences of both AN and BN. Individuals who died or emigrated before age 6, who were adoptees, and whose biological parents were unidentifiable from the MGR were excluded. A random selection of one pair of full-sisters or maternal half-sisters from each mother was performed, resulting in 334,433 pairs of full-sisters (excluding twin pairs) and 57,036 pairs of maternal half-sisters.

5.5.1.2 Design and statistical analysis

Within pair correlation, phenotypic correlation, and cross-sister cross-trait correlation were estimated, with adjustment of birth year. Bivariate ACE, ADE, and AE models were then fitted adjusting for birth year (OpenMx 2.8.3 in R 3.3.3). Weighted least squares method was used for model fitting and the delta method was used to estimate standard errors. The best model was then selected based on model fitting and Akaike information criterion (AIC)[141]; output from the model with the lowest AIC and fitted the data equally well as other models was interpreted. The principal output included heritability and proportion of phenotypic variance explained by environmental variance in AN and BN, respectively, co-heritability and proportion of phenotypic covariance explained by environmental covariance of AN and BN, and the genetic and environmental correlations of AN and BN.

5.5.2 Study II

5.5.2.1 Study population

Study II was based on individuals born in Sweden during1979-2001. Exclusion criteria were the same as described in Study I, resulting in 2,268,786 eligible individuals. Each individual was linked to his/her biological full-siblings, maternal half-siblings, paternal half-siblings, cousins, and half-cousins through the MGR. Data were updated until December 31, 2009.

5.5.2.2 Design and statistical analysis

First, the association between EDs and suicide attempts was examined at population level; logistic regressions were applied to estimate crude ORs. Next, the models were adjusted for comorbid psychiatric disorders (MDD, anxiety disorder, and SUD) to test how they explained the observed association. Familial co-aggregation was then assessed by fitting a logistic regression model in each of the five types of relatives. ORs of suicide attempts in individuals (index individuals) who had any relative (of one type) with an ED compared to individuals whose relatives (of the same type) did not have an ED were estimated.

To test the existence of familial liability, the analyses for familial co-aggregation were repeated and adjusted for EDs in the index individual. If significant association remained after adjustment, it would provide a sufficient evidence for familial liability to EDs and

suicide attempts. All models were adjusted for birth year, sex, and number of relatives (except the first model), and non-independence of data due to familial clustering was addressed with a robust (sandwich) estimator of standard errors[142].

5.5.3 Study III

5.5.3.1 Study population

Study III explored the association between AN and BN (the two exposures) and the risk of subsequent committing criminal behavior (measured by convictions of theft and others, the two outcomes) using a cohort design with time-varying exposure. A sibling comparison nested in the design was applied to account for some unmeasured familial confounders.

5.5.3.2 Cohort design with time varying exposure

The study population consisted of 957,106 females who were born in Sweden between 1979 and 1994 and living in Sweden at least until age 15 years; adoptees and those whose biological parents were not identifiable from the MGR were excluded. Sibling comparisons were conducted on data from 410,026 full-sisters from 189,458 families; data were updated until December 31, 2013. Individuals in the study population were followed from their 15th birthday to the earliest of the following occasions: 1) experiencing the outcome, 2) censored (death or emigration), and 3) December 31, 2013.

The time-varying feature of the exposures was defined as: a) if the individual was not exposed at the start of follow-up, the exposed period would start when she received the first diagnosis of the exposure, and the time between age 15 years and the time of diagnosis was defined as unexposed period; b) if the individual had been exposed by the start of follow-up (i.e., 15 years old), she was defined as exposed since the follow-up started. Figure 5.5.3 provides an illustration of the design.

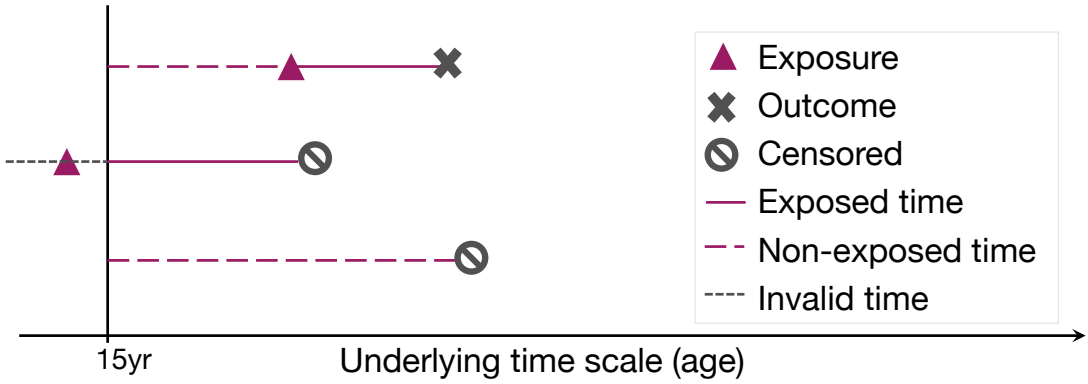

Figure 5.5.3 Cohort design with time-varying exposure in Study III. *A line represents an individual in the study; each individual in the study population was followed from their 15th birthday; age was used as the underlying time scale. Individuals were treated as exposed since the time of exposure if the exposure happened after the start of follow-up (1st line in the figure) or since the start of follow-up if the exposure had happened by then (2nd line). In the former (1st line), time between the start of follow-up and the exposure was treated as unexposed.*

5.5.3.3 Statistical analysis

Cox proportional hazards regressions were first applied to estimate HRs of criminal behaviors in EDs at population level (Model 1). Personality disorders, ADHD, non-exposure EDs were adjusted for to examine their effects on the associations (Model 2). Next, sibling comparison was performed to account for familial confounders. Stratified Cox proportional hazards models were applied to estimate HRs of criminal behaviors in exposed individuals compared to their unexposed full-sisters in the study population (Model 3).

All models had attained age as the underlying time scale and were adjusted for birth year. A cluster-robust estimator of standard error was used to address non-independence of data in Cox proportional hazards regressions. Visual examination of the Schoenfeld residuals verified the validity of the proportional hazards assumption.

5.5.4 Study IV

5.5.4.1 Study populations

Study IV assessed the genetic association between EDs and ADHD using three approaches: 1) familial co-aggregation, 2) quantitative genetic modeling, and 3) PRS analysis. The study base was the nationwide population born in Sweden between 1970 and 2005 including 3,550,188 individuals (same as the study base in Study I). Data were updated until December 31, 2013. Clinical diagnoses of EDs (including any ED, AN, OED, and BN) and ADHD were analyzed. Familial co-aggregation was assessed in the following types of relatives were identified in the MGR including full-siblings (4,191,852 pairs), maternal half-siblings (697,763 pairs), paternal half-siblings (829,126 pairs), and cousins (16,347,002 pairs). The study population in quantitative genetic modeling was full- and maternal half-sisters randomly selected from the entire study population (also the same as that in Study I). A total of 13,472 participants in CATSS born between 1992 and 2005 were eligible for PRS analysis.

5.5.4.2 Design and statistical analysis

Logistic regressions were applied to estimate 1) crude OR of EDs in ADHD to assess their association at population level and 2) ORs of EDs in relatives of individuals with ADHD to assess familial co-aggregation. Sensitivity tests were performed to further test shared familial liabilities, where the models on familial co-aggregation were additionally adjusted for ADHD in the relatives. All models were adjusted for birth year, sex, and non-independence of data.

Bivariate ACE, ADE, and AE models were performed for each comparison of clinically diagnosed ADHD and EDs (namely AN, OED, and BN). Models were fitted using full information maximum likelihood (OpenMx 2.7.9 in R 3.3.2). The co-heritability and genetic correlation from the best model (selected by the lowest AIC) were interpreted.

ED symptom measures were regressed on ADHD PRS, and ADHD symptom measures were regressed on AN PRS using linear regressions, adjusting for birth year, sex, and the first five PCs (shown below).

$$\textit{ED symptom measures} \sim \textit{ADHD PRS} + \textit{birth year} + \textit{sex} + \textit{PCs}$$

$$\textit{ADHD symptom measures} \sim \textit{AN PRS} + \textit{birth year} + \textit{sex} + \textit{PCs}$$

Differences of variance explained (R^2) between these models and the corresponding models without the PRS variable were calculated to evaluate the variance in outcomes explained by PRS. Regression coefficients (beta) of the PRS were also used to estimate the effects of PRS on the outcomes. Generalized estimating equation (GEE) was used to estimate beta, yielding standard errors accounting for the non-independence of data due to twin pairs. PRS at p-value threshold $p<1$, i.e., with all eligible SNPs, were used as the primary PRS[143].

6 RESULTS

6.1 ANOREXIA AND BULIMIA NERVOSA SHARE GENETIC AND ENVIRONMENTAL ETIOLOGY

For both AN and BN, the prevalences were comparable between full-sisters and maternal half-sisters (0.8%-0.9% for AN and 0.5% for BN); phenotypic correlation was also comparable between the two types of sisters. Full-sisters had higher pairwise correlation for AN and BN and higher cross-sister cross-trait correlation than maternal half-sister (Table 6.1.1), suggesting genetic influence on AN and BN respectively and on their overlap.

Table 6.1.1 Observed correlations of AN and BN in full- and maternal half-sisters

Type of correlation	Full-sister	Maternal half-sister
Pairwise correlation for AN	0.22 (0.02)	0.03 (0.06)
Pairwise correlation for BN	0.20 (0.03)	0.13 (0.07)
Phenotypic correlation	0.59 (0.01)	0.60 (0.02)
Cross-sister cross-trait	0.14 (0.02)	0.03 (0.06)

***Note**: All correlations were tetrachoric correlations (with standard error) and adjusted for birth year.*

Bivariate ACE, ADE, and AE models were fitted to the data. Likelihood ratio test suggested that the goodness-of-fit did not differ significantly between the models and the saturated model. AE model had the lowest AIC, suggesting it was more parsimonious than ACE and ADE models (Table 6.1.2). Output from AE model was therefore selected for interpretation.

Table 6.1.2 Model fitting of the bivariate models

	Estimated parameters	AIC	p-value
Saturated model	29	303.13	.
ACE model	20	295.02	0.31
ADE model	20	295.02	0.24
AE model	**17**	**291.61**	**0.41**

***Note**: Likelihood ratio test was performed to compare the ACE, ADE and AE models to the saturated model; p-value >0.05 indicates that the model fit the data similarly well as the saturated model.*

As shown in Table 6.1.3, the heritability was around 40% for both AN and BN; similar proportions of their overlap (i.e., phenotypic covariance) were explained by genetic (46%) and environmental (54%) influences. AN and BN were found to have moderate genetic correlation (0.66) and environmental correlation (0.55).

Table 6.1.3 Genetic and environmental influence on AN and BN and their overlap

	A	E
AN	0.43 (0.36, 0.50)	0.54 (0.50, 0.64)
BN	0.41 (0.31, 0.52)	0.60 (0.48, 0.70)
Overlap	0.46 (0.35, 0.58)	0.54 (0.42, 0.65)
Correlation	0.66 (0.49, 0.82)	0.55 (0.43, 0.66)

***Note**: A represents additive genetic effect; E represents unique environmental effect. Estimates in the first three lines are proportions of phenotypic variance in AN and BN and phenotypic covariance*

between AN and BN explained by A and E. Estimates in the last line were the genetic and environmental correlations between AN and BN. Estimates are presented with 95% CI in prentices.

6.2 EATING DISORDERS AND SUICIDE ATTEMPTS CO-AGGREGATE IN FAMILIES

6.2.1 Increased suicide risk in eating disorders in the population

In the study population, the prevalence of any ED was 1.4% in females and 0.09% in males; the corresponding prevalence was 0.7% and 0.04% for AN, and 0.3% and 0.01% for BN. Individuals with any ED had significantly increased risks of suicide attempts and death by suicide, which were partially explained by comorbid MDD, anxiety disorder, and SUD. Similar results were found for AN and BN (Table 6.2.1).

Table 6.2.1 Increased risk of suicide attempts and death by suicide in EDs

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Suicide attempts				
Any ED	5.28 (5.04, 5.54)	<.001	1.82 (1.71, 1.93)	<.001
AN	4.42 (4.12, 4.74)	<.001	1.70 (1.56, 1.85)	<.001
BN	6.26 (5.73, 6.85)	<.001	1.88 (1.68, 2.10)	<.001
Death by suicide				
Any ED	5.39 (4.00, 7.25)	<.001	2.04 (1.49, 2.80)	<.001
AN	6.46 (4.38, 9.54)	<.001	2.67 (1.78, 4.01)	<.001
BN	4.52 (2.44, 8.11)	<.001	1.48 (0.81, 2.72)	0.20

***Note**: ORs (95% CI) of suicide attempts and death by suicide in EDs are presented. Crude ORs were adjusted for sex, birth year, and non-independence of data. Adjusted ORs were adjusted for comorbid psychiatric disorders including MDD, anxiety disorder, and SUD.*

6.2.2 Co-aggregation of eating disorders and suicide attempts in families

Females and males were combined for assessing familial co-aggregation as no sex difference was detected. Increased risk of suicide attempts was found in individuals (index) who had a full-sibling with any ED, AN, or BN compared to individuals whose full-siblings did not have the EDs (Figure 6.2.2). The risk was attenuated in more-distant relatives. This familial co-aggregation pattern remained stable after adjusting for the index individuals' EDs, further supporting the

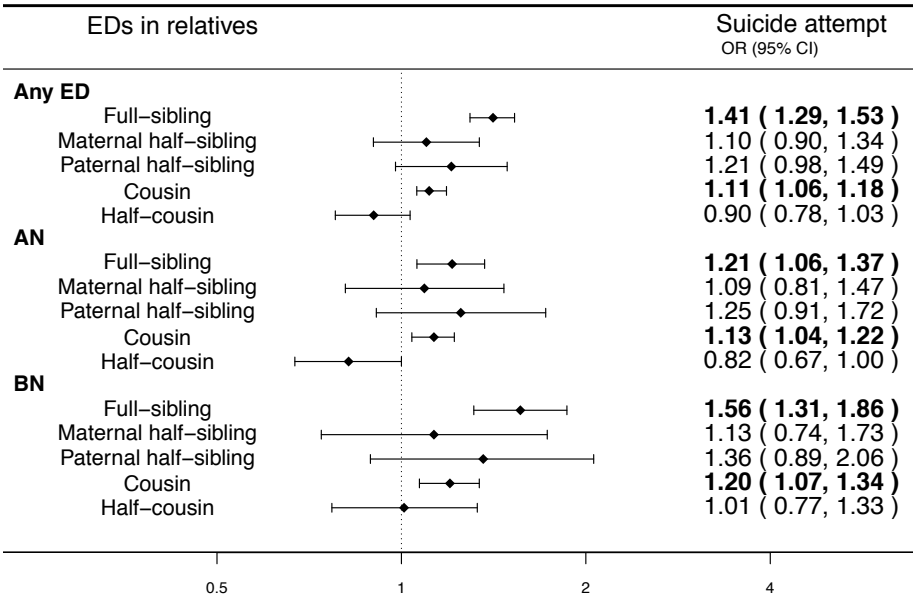

Figure 6.2.2 ORs of suicide attempts in individuals with relatives with EDs

existence of familial factors influencing both EDs and suicide attempts. A slightly higher OR was found in full-siblings than in maternal half-siblings for any ED (p=0.024).

6.3 ASSOCIAITON BETWEEN EATING DISORDERS AND COMMITING CRIMES

6.3.1 Increased risk of committing theft and other crimes in eating disorders

In the study cohort, around 1.2% individuals had been exposed to AN during follow-up and around 0.5% to BN. Increased overall incidence rate of theft conviction was found in those exposed to AN (overall incidence rate ratio [95% CI]=1.59 [1.46, 1.74]) and BN (1.40 [1.20, 1.64]); the overall incidence rate of other convictions was increased in BN (1.33 [1.14, 1.55]) but not in AN (0.95 [0.85, 1.06]). The estimated cumulative incidence rates of theft and other crimes (Figure 6.3.1) were higher in exposed individuals compared to unexposed individuals for both AN and BN. By the age of 35 years, the estimated cumulative incidence rate of theft was 11.6% (95% CI [10.5%, 12.8%]) in individuals exposed AN and 18.0% [14.2%, 22.6%] in individuals exposed BN, versus around 5% in unexposed individuals; the numbers for other crimes were 7.4% [6.5%, 8.4%] in individuals exposed to AN and 13.2% [10.8%, 16.0%] in those exposed to BN, versus around 6% in unexposed individuals.

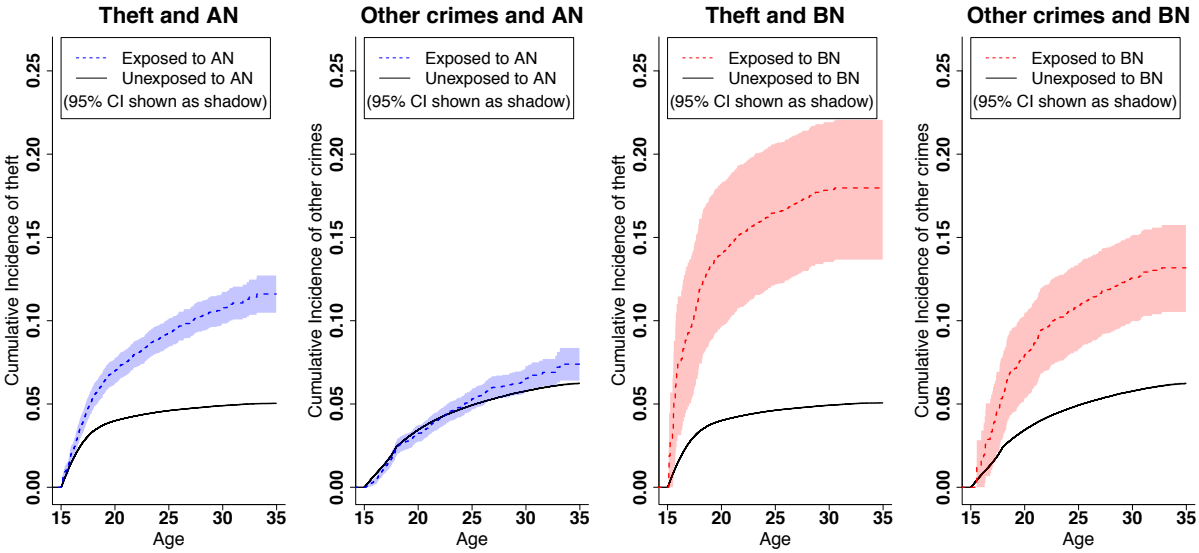

Figure 6.3.1 *Cumulative incidence of being convicted of theft and other crimes in females exposed and unexposed to anorexia nervosa (AN) and bulimia nervosa (BN)*[144]

6.3.2 Associations remained in sibling comparison

Both AN and BN showed significant associations with convictions of theft at population level (Model 1) which were partially explained by personality disorders, ADHD, and non-exposure EDs, (Model 2). The association with theft was strong in BN than in AN. In sibling comparison, the association attenuated in BN but not in AN (Model 3). This suggests that the increased risk of committing theft in BN might be partially explained by familial confounders, but AN might have a more direct association with increased risk of committing theft. BN was also associated with increased risk of receiving other criminal convictions,

which was partially explained by the adjusted psychiatric comorbidities and familial confounders (Table 6.3.2).

Table 6.3.2 HRs of receiving convictions of theft and other crimes in AN and BN

	AN		BN	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Theft				
Model 1	**2.51 (2.29, 2.74)**	<.001	**4.31 (3.68, 5.05)**	<.001
Model 2	**1.84 (1.67, 2.02)**	<.001	**2.62 (2.23, 3.09)**	<.001
Model 3	**3.31 (2.57, 4.28)**	<.001	**2.78 (1.69, 4.60)**	<.001
Other crimes				
Model 1	**1.16 (1.04, 1.29)**	0.01	**2.15 (1.85, 2.51)**	<.001
Model 2	0.93 (0.83, 1.04)	0.2	**1.47 (1.26, 1.73)**	<.001
Model 3	1.14 (0.86, 1.52)	0.36	**1.91 (1.23, 2.95)**	0.004

6.4 EATING DISORDERS AND ADHD SHARE GENETIC ETIOLOGY

The prevalence of ADHD was 3.1% in the study population during the observation period (2.2% in females and 3.8% in males). Compared to individuals without ADHD, individuals with ADHD had significantly higher prevalence of any ED (2.7% vs 0.9%), AN (0.9% vs 0.4%), OED (2.4% vs 0.7%), and BN (0.7% vs 0.2%). Similar prevalence of each ED was observed across different types of relatives.

6.4.1 Clinically diagnosed eating disorders and ADHD co-aggregate in family

Individuals with ADHD had increased risk of any ED (OR [95% CI]=3.97 [3.81, 4.14]), AN (2.68 [2.51, 2.86]), OED (4.66 [4.47, 4.87]), and BN (5.01 [4.63, 5.41]). The risk of EDs in the relatives of individuals with ADHD was also elevated (Figure 6.4.1), and the magnitude of association was stronger in relatives with greater relatedness.

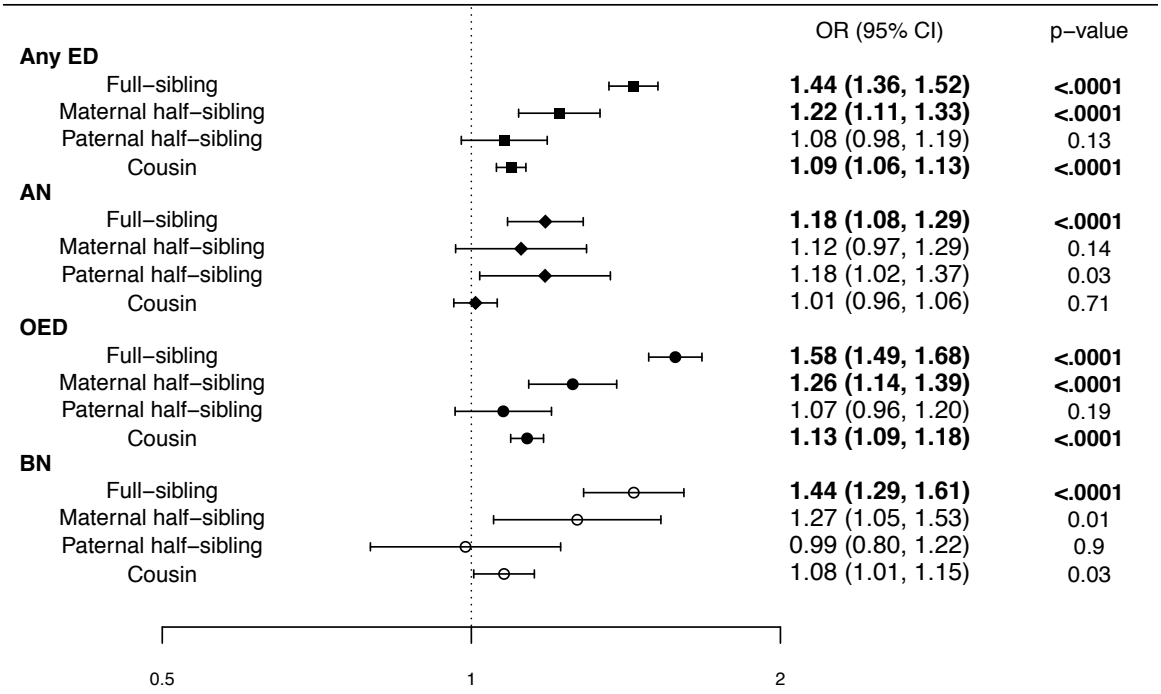

Figure 6.4.1 ORs of EDs in relatives of individuals with ADHD *All models were adjusted for birth year, sex, and non-independence of data.*

6.4.2 Genetic correlation between clinically diagnosed eating disorders and ADHD

Pairwise correlations for all EDs and ADHD were greater in the full-sisters (334,433 pairs) and maternal half-sisters (57,036 pairs), suggesting genetic influence on these disorders. Greater cross-sister cross-trait correlations between EDs and ADHD were observed in full-sisters compared to that in maternal half-sisters, suggesting genetic influence on the overlap between EDs and ADHD. The phenotypic correlation between each ED and ADHD was comparable between full-sisters and maternal half-sisters, and the phenotypic correlation with ADHD appeared stronger in OED and BN compared to AN.

Table 6.4.2.1 Observed correlations for EDs and ADHD in full- and maternal half-sister pairs

Type of correlation		Full-sister	Maternal half-sister
Pairwise correlation	AN	0.21 (0.18, 0.25)	0.03 (-0.10, 0.15)
	OED	0.23 (0.20, 0.25)	0.02 (-0.05, 0.10)
	BN	0.20 (0.16, 0.24)	0.13 (-0.02, 0.27)
	ADHD	0.41 (0.39, 0.42)	0.22 (0.19, 0.25)
Phenotypic correlation	AN-ADHD	0.19 (0.17, 0.21)	0.17 (0.13, 0.21)
	OED-ADHD	0.31 (0.30, 0.33)	0.28 (0.25, 0.31)
	BN-ADHD	0.28 (0.26, 0.30)	0.23 (0.19, 0.28)
Cross-sister cross-trait	AN-ADHD	0.04 (0.04, 0.04)	0.004 (-0.05, 0.06)
	OED-ADHD	0.11 (0.09, 0.13)	0.04 (0.01, 0.08)
	BN-ADHD	0.07 (0.07, 0.07)	0.07 (0.01, 0.13)

***Note**: All correlations (presented with 95% CI) were tetrachoric correlations and were adjusted for birth year.*

Bivariate ACE, ADE, and AE models were fitted to quantify the genetic influence on the associations between EDs and ADHD. For each association, the three models had comparable goodness-of-fit, and AE model had the lowest AIC compared to ACE and ADE model. Results from the bivariate AE models were selected for interpretation (Table 6.4.2.2).

Table 6.4.2.2 Genetic and environmental effects on EDs, ADHD, and their overlaps

	A	E
Variance explained		
AN	0.42 (0.35, 0.49)	0.58 (0.52, 0.65)
OED	0.45 (0.39, 0.49)	0.56 (0.51, 0.61)
BN	0.40 (0.35, 0.51)	0.60 (0.50, 0.70)
ADHD	0.82 (0.78, 0.85)	0.18 (0.15, 0.22)
Overlap		
AN-ADHD	0.42 (0.16, 0.69)	0.58 (0.31, 0.84)
OED-ADHD	0.73 (0.60, 0.85)	0.27 (0.15, 0.40)
BN-ADHD	0.58 (0.35, 0.81)	0.42 (0.19, 0.65)
Correlation		
AN-ADHD	0.14 (0.05, 0.22)	0.33 (0.18, 0.48)
OED-ADHD	0.37 (0.31, 0.42)	0.26 (0.14, 0.38)
BN-ADHD	0.28 (0.20, 0.39)	0.33 (0.15, 0.53)

***Note**: A stands for additive genetic effects, E stands for unique environmental effects. The results were based on AE models for AN-ADHD, OED-ADHD, and BN-ADHD as they had comparable goodness-of-fit as the corresponding ACE and ADE models but the lowest AIC.*

Moderate heritability was found for each ED and high heritability was found for ADHD. Approximately 42% of the overlap (covariance) between AN and ADHD was explained by genetic covariance, in contrast to over 70% between OED and ADHD and approximately 58% between BN and ADHD. Genetic correlation with ADHD was greatest for OED, followed by BN and AN; environmental correlations with ADHD were similar in magnitude across the EDs (Table 6.4.2.2).

6.4.3 Polygenic risk scores for ADHD predicted eating disorder symptoms

ADHD PRS (at p<1 threshold) was significantly associated with the EDI-2 full scale (R^2=0.0012, beta [95%CI]=0.027 [0.005, 0.049], p=0.015), drive for thinness (R^2=0.0010, 0.032 [0.005, 0.059], p=0.022), and body dissatisfaction (R^2=0.0013, 0.042 [0.011, 0.072], p=0.007), but not with bulimia (0.004 [-0.013, 0.021], p=0.654). AN PRS were not significantly associated with ADHD full-scale measure or subscales inattention or hyperactivity/impulsivity (Table 6.4.3).

Table 6.4.3.1 ADHD PRS and ED symptoms and AN PRS and ADHD symptoms

	Individual with outcome measures No. (%)	**Mean of outcome measures (SD)**	**R^2**	**Beta (95% CI)**	**p-value**
ADHD PRS and ED symptom measures					
EDI-2 full scale*	5680 (42.2)	2.1 (0.77)	0.0012	0.027 (0.005, 0.049)	**0.015**
Drive for thinness	5674 (42.1)	2.1 (0.98)	0.0010	0.032 (0.005, 0.059)	**0.022**
Bulimia	5668 (42.1)	1.5 (0.57)	0.0000	0.004 (-0.013, 0.021)	0.654
Body dissatisfaction	5679 (42.2)	2.6 (1.13)	0.0013	0.042 (0.011, 0.072)	**0.007**
AN PRS and ADHD symptom measures					
ADHD full scale	13451 (99.8)	1.8 (2.89)	0.0003	-0.049 (-0.101, 0.002)	0.062
Inattention	13454 (99.9)	1.0 (1.65)	0.0003	-0.029 (-0.058, 0.000)	0.053
Hyperactivity/impulsivity	13455 (99.9)	0.9 (1.57)	0.0002	-0.021 (-0.049, 0.007)	0.145

***Note**: ADHD PRS and AN PRS were at the p<1 threshold. R^2 was the difference of variance explained in the models with the PRS variables and the models without the PRS variables. The regression coefficients, beta, were estimated using GEE. * EDI-2 full scale means the sum score of the three subscales drive for thinness, bulimia, and body dissatisfaction.*

The ADHD PRS at different p-value thresholds showed similar R^2 (Figure 6.4.3.2 a) and beta (Figure 6.4.3.2 b) as the primary ADHD PRS (at p<1) for EDI-2 full-scale measure and subscales drive for thinness and body dissatisfaction. The effects of AN PRS at different p-value thresholds on ADHD symptoms were less consistent; AN PRS at some thresholds (p<0.00001, p<0.01, and p<0.05) showed weak associations with inattention, and they pointed towards the negative direction (Figure 3.1 c and d).

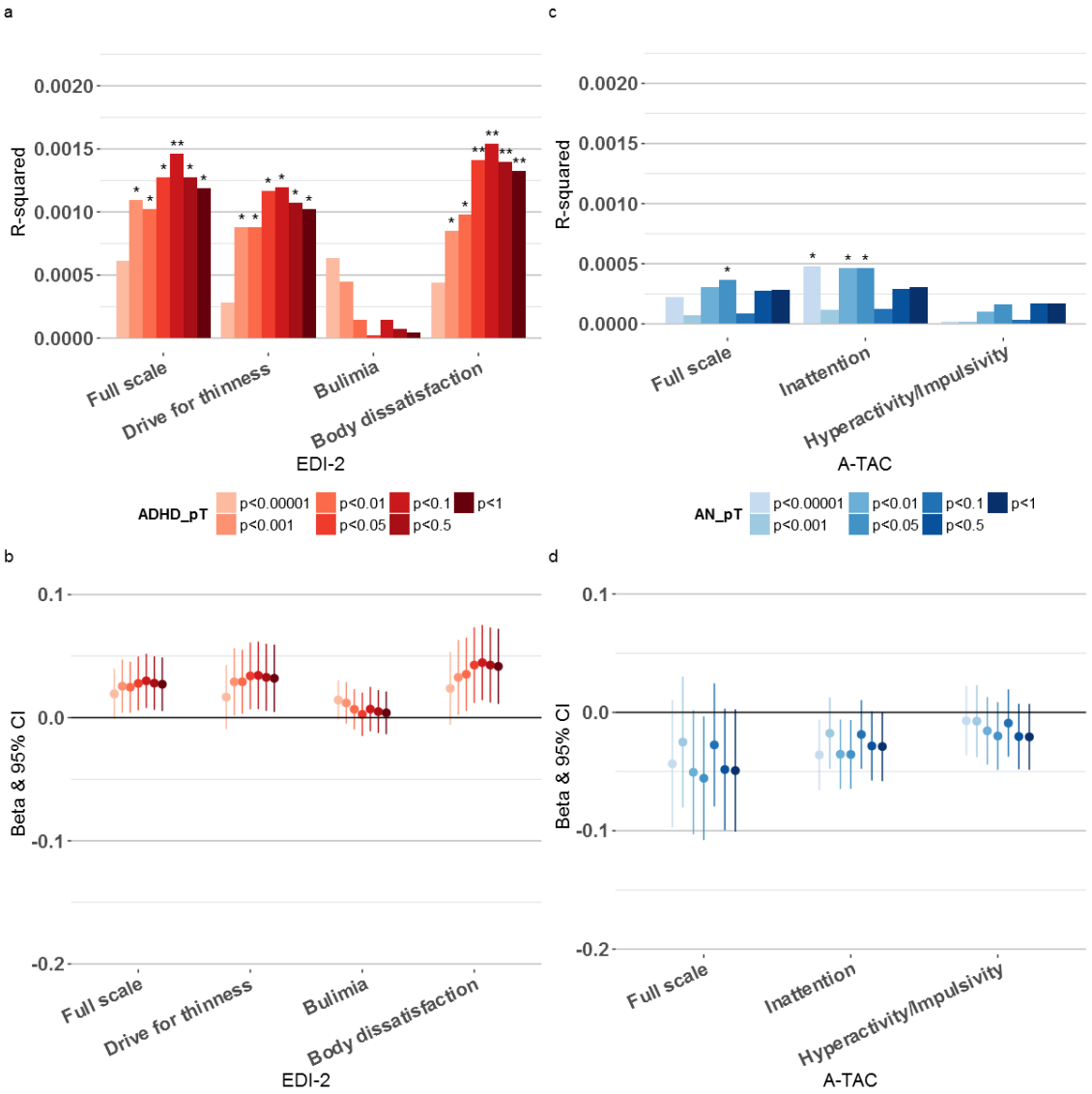

Figure 6.4.3.2 R^2 and beta of ADHD PRS at different p-value thresholds predicting ED symptoms (red, left half of the figure) and of AN PRS at different p-value thresholds predicting ADHD symptoms (blue, right half of the figure) *Stars represent significant levels at which PRS explained the corresponding symptoms of * $p \leq 0.05$; ** $p \leq 0.01$. EDI-2: The Eating Disorder Inventory-2; A-TAC: The Autism-Tics, ADHD, and Other Comorbidities inventory. Panels a and b are R^2 and beta showing how ADHD PRS predict ED symptoms. Panels c and d are R^2 and beta showing how AN PRS predict ADHD symptoms. "ADHD_pT" and "AN_pT" stand for p-value thresholds for ADHD PRS and AN PRS, respectively. EDI-2 full scale means the sum score of the three subscales drive for thinness, bulimia, and body dissatisfaction.*

7 DISCUSSION

7.1 MAIN FINDINGS AND IMPLICATIONS

7.1.1 Main findings and discussion

Study I: AN and BN share genetic and environmental etiology. In Study I, moderate diagnostic overlap (phenotypic covariance around 0.6) was found for clinically diagnosed AN and BN in the study population, which was explained by genetic and environmental effects to similar extents. Moderate genetic correlation (0.66, 95%CI=[0.49, 0.82]) and unique environmental correlation (0.55 [0.43, 0.66]) were found between AN and BN. The results are consistent with the previous twin study based on self-reported eating behaviors in a Swedish twin sample, where a high genetic correlation (0.78, with wide CI that might suggest insufficient statistical power) and moderate unique environmental correlation (0.44) were observed[14]. The findings in Study I expanded our understanding of the genetic and environmental overlap between AN and BN to clinically diagnosed cases detected by the healthcare system. Using non-twin siblings randomly sampled from the population significantly increased sample size and improved precision in the estimates.

Considerable clinical crossover between EDs raised considerations on the validity and utility of the diagnostic schema, primarily for AN subtypes (restrictive and binge-eating/purging AN) but also concerning AN and BN[13,35,145]. Although results in Study I demonstrated the etiological overlap between AN and BN, their distinction has also been reflected. The genetic and environmental correlations were moderate, and none of the confidence intervals included one, suggesting that the two disorders are not completely dependent. As the subtypes of AN were not distinguishable based on ICD code in the register, the study was unable to test the genetic and environmental overlap between AN subtypes. Studies that could identify the two AN subtypes and have sufficient statistical power should be performed to examine the etiological overlap between AN subtypes (and their etiological overlap with BN if available). Evidence from such studies could further inform the diagnostic schema of EDs.

Study II: EDs and suicide are correlated and co-aggregated in families. Consistent with previous findings[8], Study II showed significantly elevated risks of suicide attempts and death by suicide in individuals diagnosed with any ED, AN, and BN. It further illustrated that comorbid psychiatric disorders partially explained the observed associations. Moreover, the risk of suicide attempts was also significantly elevated in individuals with full-siblings or cousins with EDs, illustrating familial liability shared by the EDs and suicide attempts. Contrasting the results at population level with in familial co-aggregations can further inform the genetic and/or environmental origin of the familial risk factors. Particularly, a higher OR was found in full-siblings than in maternal half-siblings for any ED (p=0.024), which potentially suggests genetic influence on the association between any ED and suicidal behavior, as full-siblings have greater genetic sharing than maternal half-siblings in general, while the two types of siblings are assumed to share familial environment to a similar extent.

A previous study showed genetic liabilities shared between AN and MDD, AN and suicide attempts, and MDD and suicide attempts respectively[146]. Another twin study showed that the genetic correlation between MDD and suicidality remained after accounting for the genetic effects of lifetime ED[147], but less is known about the genetic (and environmental) association between EDs and suicidal behaviors after accounting for the genetic (and environmental) effects of MDD and other psychiatric comorbidities. Applying quantitative genetic methods to registry data may offer a solution to answer such questions.

Study III: AN and BN are associated with increased risk of being convicted of theft, and BN is also associated with increased risk of other crimes. Results from Study III meaningfully expand the observed association between EDs and criminal behavior in previous studies[17,56-61] to population level with valid clinical and forensic measures. Study III also showed that lifetime comorbidities (including personality disorder, ADHD, and the non-exposure EDs) partially explained the associations between AN and BN and theft and between BN and other crimes. Further, the associations between BN and theft and other crimes attenuated in sibling comparisons compared to the association observed at population level, suggesting potential familial confounding effects on the increased risks of theft and other crimes in individuals with BN. However, the magnitude of the association between AN and theft remained in sibling comparison as compared to association at population level, suggesting that the association between AN and theft might be more direct or confounded by other factors than familial factors. Previous research suggested that theft behavior might stem from the impact of starvation behavior and other psychopathological factors of AN[148]. If AN has a direct effect on theft behavior, it is important to address what the underlying mechanism could be.

Recent research suggested that the severity of EDs and socioeconomic status might influence the risk of theft behavior in ED patients[149]. With the available registry data, future studies could test the effect of socioeconomic status on the association between EDs and criminal behaviors. The observed effect of the impulsive-related comorbidities (e.g., ADHD and personality disorder) on the associations might imply a role of impulsivity in explaining the observed associations. However, detailed factors such as the severity of the EDs and measures of impulsivity may not be available from registers. Studies with different designs and measurements may be able to measure and assess more detailed etiological factors such as the motivations to better address the mechanism underlying EDs and criminal behaviors.

Study IV: EDs share genetic liabilities with ADHD, as illustrated by converging evidence from multiple genetically informative approaches in Study IV. The study first showed that individuals with an ADHD diagnosis had an increased risk of also having an ED diagnosis (any ED, AN, and OED including BN) in a nationwide population, which is consistent with previous literature[84,86-88,90]. Further, the risks of EDs were significantly elevated in the relatives of individuals with ADHD compared to the relatives of individuals without ADHD, implying shared familial liability for ADHD and EDs. Quantitative genetic modeling revealed mild-to-moderate genetic correlations between EDs and ADHD. Greater genetic

correlations were found between ADHD and OED and between ADHD and BN than that found between ADHD and AN, suggesting that non-AN EDs may be more etiological related with ADHD compared to AN. In CATSS, ADHD PRS predicted increased level of EDI-2 overall measure and measures of drive for thinness and body dissatisfaction. This finding extended the genetic overlap with ADHD from clinically diagnosed EDs to dimensional measures of ED traits in the general population, reflecting the connection between the categorical and dimensional conceptualizations of mental disorders[150] and the value of both in genomic research.

7.1.2 Clinical implications

Findings of this thesis highlight the seriousness of EDs. Population-level observations confirmed the association between EDs with lethal and stressful adverse events and comorbidities. Increased risks of criminal behaviors and comorbid ADHD observed in BN might reflect a multi-impulsive form of BN, which is associated with other impulsive behaviors and poorer prognosis of treatment[151]. The following efforts could be considered clinically to tailor treatment: 1) to monitor suicidal ideation and identify high-risk groups, 2) to identify comorbidity with impulsivity (e.g., by evaluating the patient's own impulsive behaviors and inquiring about personal and family history of ADHD), and 3) to inquiry about forensic history and estimate and address its psychological influence on patients during treatment.

The familial co-aggregations found in Studies II and IV suggested increased risk of suicide attempts and ADHD in family members of the index patients with EDs, and the genetic overlap found between AN and BN in Study I also suggested potentially increased risk of EDs in the relatives of individuals with EDs. In many cases family members are the primary caregivers for patients and can offer considerable support during the patient's recovery[10]. Especially in the treatment of younger individuals with EDs, family-based therapy[152] shows superior efficacy in medically stable patients with relatively short ED duration[153,154] but also places considerable responsibility and stress on family members[152]. As suggested by this thesis, relatives themselves are at increased risks of EDs and other potential adverse conditions; care should be taken to ensure that parents and other relatives who are caregivers for ED patients are sufficiently robust psychologically to engage in such intensive interventions.

Shared etiologies between traits suggested by the findings of thesis might imply common treatment strategies. Study III suggested that BN and theft behavior may share some genetic and/or familial environmental liabilities. A previous study reported that pharmacological treatment reduced symptoms of both BN and kleptomania that were comorbid within individuals[155]. Whether and how the biological pathways targeted by the medication is related with BN and theft behavior could be a future direction for research. Likewise, as demonstrated in Study IV, significant genetic correlation between ADHD and EDs, especially non-AN EDs, may also suggest common treatments for the two disorders. Lisdexamfetamine is an ADHD medication and has been approved for treating binge-eating

disorder by the US Food and Drug Administration in 2015, and recent research has supported its effectiveness in treating binge-eating disorder[156-158]. How the pharmacological treatment is related to the shared etiology between ADHD and (non-AN) EDs requires more research, and the shared etiology revealed by Study IV may inform other types of treatment that target the common etiological factors for both illnesses.

7.2 METHODOLOGICAL CONSIDERATIONS

7.2.1 Measurement errors and misclassifications

A source of measurement error is the potential misclassification of disorders or traits. Other survey-based[159] or self-reports-based studies[160] have found higher prevalences of AN and BN than those reported in this thesis, which may suggest under-diagnosis of EDs in registry data. This might be attributed to several reasons. First, registry data captured only treatment-seeking cases; individuals who had the disorders but did not seek medical help would not be identified as having the disorders from the registers. Second, the coverage of the ED quality registers has increased over time[118], suggesting potential under-diagnosis of cases in the earlier years. Third, BN was not recognized as an independent disorder before ICD-10 (1997) in the Swedish diagnostic system. This could lead to greater levels of under-diagnosis in BN compared to AN. However, under-diagnosis was most likely to misclassify individuals with the disorders as disorder-free; the likelihood of false-positive conditions was relatively low.

The misclassification of other traits in this thesis also needs to be acknowledged. Suicide attempts identified from the NPR and CDR might suffer from the same kind of misclassifications, but the identification of death by suicide has been validated by previous studies in Sweden[161]. Regarding criminal convictions, many law-breaking behaviors in Sweden were not reported and therefore did not result in convictions[162]. ADHD was identified by diagnoses in NPR and Pastill and by medication prescriptions from the PDR. In Sweden, ADHD medications were prescribed exclusively for ADHD[163], which diminished bias due to false-positives. Additionally, ADHD medications have been recommended only when patients do not respond to non-pharmacological treatments[164] and therefore mainly reflected the more severe ADHD cases.

Misclassifications may bias the results in certain conditions. If the misclassifications were non-differential between the comparison groups, they were more likely to bias the results towards the null. Specifically, if the misclassifications of suicide attempts, criminal behaviors, and ADHD were independent of the individuals' ED status, the associations were more likely to be underestimated/diluted. However, if the misclassifications were differential between comparison groups, they might bias the results towards either direction. If, for instance, the diagnosis of EDs contributed to the discovery of ADHD in the individual, the association between EDs and ADHD in Study IV would be overestimated. Nevertheless, this might be less likely to happen across individuals, i.e., the diagnosis of EDs in an individual might not significantly influence the chance of discovering ADHD in the relatives. Therefore, the estimates for familial co-aggregations might be less biased.

7.2.2 Considerations in genetically informative study designs

That "all models are wrong but some are useful", wisely said by George E.P. Box[165], provides an excellent guide to consider methodological limitations. In this thesis, models were wrong in the sense that they could not perfectly reflect the etiological factors and their complex relationships underlying the traits and their associations. Nevertheless, based on assumptions, they can provide useful approximations of the concepts.

7.2.2.1 Quantitative genetic modeling

Quantitative genetic modeling in this thesis rests on multiple assumptions, including, but not limited to, the following ones. **1) The correlation of additive genetic effects (A) is 0.5 between full-sisters and 0.25 between maternal half-sisters**[38]. This might be violated by assortative mating. Assortative mating means that the two parents of a child are more similar to each other (in terms of traits and the underlying genetic and/or environmental liabilities) than two random individuals in the population. Assortative mating has been observed in several psychiatric traits[120,166] and could lead to underestimated heritability in twin studies, as it makes dizygotic twins more genetically similar but does not influence the genetic similarity between monozygotic twins[38]. However, its influence on heritability estimated from studies based on full- and half-sibling data is less predictable. The correlation of A between two full-sisters might be higher than 0.5 due to assorative mating. However, whether the correlation of A between two maternal half-sisters in a pair is higher or lower than 0.25 depends on how similar their fathers are in terms of the A. The deviation of the genetic correlation between half-sisters from 0.25 in relation to the deviation of the genetic correlation between full-sisters from 0.5 could influence the direction and magnitude of bias in the estimates. The current thesis did not examine the effect of assortative mating on the results, but previous research has suggested that its impact on heritability estimation was mostly mild in twin and sibling studies[120,167].

2) Equal environment assumption assumes that the shared environmental effects, i.e., C, affect full- and half-sisters to the same extent. Violation of this assumption might inflate the estimation of heritability[38]. This assumption was not tested in this thesis. However, it has been reported that most children lived with their mother after parental separation, suggesting that the maternal half-sisters were likely to live in the same household as full-sisters and therefore have similar familial environmental share, lending support to the assumption[168]. Additionally, the estimates of C were trivial for both EDs and ADHD as estimated in previous research[14,91,160,169], as well as in this thesis, which may suggest that violation of this assumption is unlikely to influence the results to a significant extent.

3) The lack of interaction between A, D, C, and E. This assumption can be tested by, e.g., separately estimating the genetic effects (A and D) on different strata of a specific environmental factor. This thesis did not quantify the interaction between the A, D, C, and E components. Nevertheless, gene-gene interaction and gene-environment interaction are

interesting directions for research. Future studies may combine quantitative genetic models and molecular genetic methods to test these interaction effects.

7.2.2.2 Sibling comparison

A potential issue of sibling comparison is that only data of **differentially exposed siblings** primarily contribute to the estimation of relative risk. One might consider the following questions: What led the siblings to be differentially exposed? Could these factors also lead to different outcomes? If this is the case, selection of differentially exposed siblings for analysis could lead to biased estimation of the association. A previous study on this study design showed that 1) the association would be less biased if the siblings share confounders to a greater extent than they share the exposure; however, 2) when the siblings are more similar in terms of the exposure than the confounders, the estimated association will suffer greater bias[170]. Additionally, relying on data of differentially exposed sibling decrease the sample size used for analysis.

Furthermore, sibling comparison design also **controls for mediators shared by siblings**[171]. Therefore, when a reduced association is observed in sibling comparison compared to the association observed at population level, careful consideration is needed to determine whether the reduction is due to controlling for familial confounding effects or mediating effects or due to reduced statistical power.

The design assumes the **lack of sibling contagion effect and carry-over effect**[172,173]. Sibling contagion effect means that the outcome in one sibling directly causes the outcome in the other sibling; carry-over effect means that the exposure in one sibling directly causes the outcome in the other sibling[173,174]. Carry-over effect was unlikely in Study III, i.e., it is unlikely that one's EDs directly cause criminal behavior in one's sister. However, sibling contagion effect might be possible, i.e., one's criminal behavior might directly cause the criminal behavior in the sister. If this were the case, the association would be underestimated in a sibling comparison, which was unlikely to change the conclusion in Study III.

7.2.2.3 Polygenic approaches and quantitative genetic models

In Study IV, most results converged across the polygenic and quantitative genetic approaches. However, although positive genetic correlation was found for ADHD and AN in the quantitative genetic models, AN PRS did not significantly predict ADHD symptoms. One explanation could be that the AN PRS was insufficiently powered due to relatively small sample size of the AN GWAS. Another explanation could be that quantitative genetic modeling and PRS capture different genetic effects. The genetic effect estimated by quantitative genetic modeling is a mixture of common genetic variants, rare variants, gene-gene interaction, and more[175], whereas the genetic effect captured by PRS is mainly the common genetic variants (defined as SNPs with minor allele frequency above 5% in Study IV). The discrepancy reflects the complexity of genetic effects. Given the increasing amount of findings in molecular genetic studies, downstream analyses on functions of genes are

highly encouraged to identify genetic effects beyond the additive effect of common genetic variants.

7.2.3 Generalizability

Cautions are needed when generalizing the conclusions in the thesis to other settings. Heritability and the relative to the importance of environmental effect on a trait are sensitive to study population. For instance, in a population with little variance in the environmental effects, the phenotypic variance would be mostly due to genetic variance; genetic effects would therefore be more important than environmental effects relatively, i.e., a high heritability would be observed. The relative importance of genetic and environmental effects can also change over time in the same population[176]. Therefore, the conclusions of the quantitative genetic models might only be generalized to populations with similar genetic background and environment background (e.g., cultural factors and age structure).

7.3 ETHICAL CONSIDERATIONS

The studies in this thesis are register-based observational studies. Although no intervention has been performed on the participants, sensitive data, i.e., personal medical information, has been used for analysis, which raises concerns on invasion of privacy. Great caution has been paid when handling the registry data in all the studies. All data from national registers used in this thesis had been de-identified by independent governmental agencies (Statistics Sweden and the Swedish National Board of Health and Welfare) before delivered for research. The data were entirely anonymous during the research procedures. The application of the genotype and phenotype data from CATSS in Study IV had been approved by the ethics committee at Karolinska Institutet, with informed consent collected from the custodians of the participating children. The data had also been de-identified before being delivered for research. For all studies, data were not allowed to be taken outside the institute and were handled under strict regulations.

Communication of the study findings is another major ethical consideration. Stigmatizing is the foremost issue I as a researcher want to avoid. Adversities observed to be associated with EDs in this thesis, especially criminal behaviors, carry the risk of misinterpretation and stigmatization of patients. In Study III, we stressed that forensic issues can bring extra psychosocial burden to patients and negatively affect recovery. An important point we want to convey is to call for attention in inquiring and addressing these issues during clinical practice. Additionally, the etiological associations suggested by the findings imply that treatments for EDs can be effective in reducing the criminal behavior, as has been observed in clinical settings[155]. Stigmatization is in general more severe in mental disorders than in other medical conditions, which has obstructed research and hampered affected individuals from seeking medical help. Destigmatizing mental disorders is crucial, and researchers can have considerable influence when communicating our findings with the general public.

Likewise, stigmatization of families is a critical issue to avoid. Familial co-aggregation should not lead to blame on genetic heredity or parenting style. In contrast, family members

are usually the primary caregivers and can contribute to the recovery of the patients[10]. Moreover, family members themselves are at increased risk of adversities (Study II) and psychiatric disorders (Studies I and IV). This thesis work underscores the importance of considering the psychological burden in family members of individuals with EDs, especially when they are expected to be intensively involved in the treatment.

Genetic liabilities to EDs and their associations with other traits have been one of the main findings. It is not uncommon among the public to misinterpret the genetic effects as something deterministic. This is incorrect, especially for complex traits such as mental illness and behaviors—genetic risk is far from a sufficient cause for the disorders and the effects can be modified by many other factors in the environment (e.g., healthy lifestyle) and other genetic factors.

8 CONCLUSIONS

Taken together, this thesis highlights the seriousness of EDs by revealing the associations among EDs and between EDs and adverse events (suicide and crime) and comorbidity (ADHD). Moreover, it underscores the etiologies underlying these associations from the perspective of genetic and environmental influences. Findings from the thesis provides several important and novel clinical implications in 1) identifying high-impulsivity group and group with high suicidal ideation in ED patients and tailoring treatment strategies when needed to, 2) attending to the psychological condition of relatives who are caregivers of ED patients and are expected to be intensively engaged into treatment, and 3) exploring common treatment for EDs and other conditions based on their shared etiologies. In terms of methodology, the studies in this thesis have demonstrated the advantages of combining population-based registry data and genetically informative epidemiological designs in exploring the mechanism for observed associations.

9 FUTURE PERSPECTIVES

The rapid development of the field of molecular genetics offers diverse and novel approaches to study mental disorders and behaviors. For instance, the genetic overlap between AN and BN illustrated by quantitative genetic modeling in Study I can be revisited using different methods with molecular genetic data, such as LD score regression and GCTA[177], once BN GWAS data is available. Nevertheless, it is important to acknowledge the limitations of each method and the differences between methods; e.g., as discussed above, heritability captured by traditional quantitative genetic studies could be different from heritability captured by methods based on GWAS results such as PRS and LD score regression that focus on common genetic variants (it is important to revisit the definitions of heritability and other genetic measures in different scenarios, too). Genetic overlap between *other* EDs can also be tested using these methods. To date, GWAS data have only been available for AN. Sample collections for the GWAS for BN and BED are underway but lag far behind the AN research.

This thesis has illustrated genetic and environmental influences on EDs and their associations with other traits and encourages future research to further identify specific genetic and environmental risk factors and understand how they correlate and interact with each other. With sufficiently powered GWAS, secondary analyses can be conducted to further interrogate findings from the GWAS. At the DNA level, SNPs can be mapped to genes. When combined with GWAS results (e.g., for a disorder), the mapping can help identify genes that are related to the disorder. This can be further combined with prior knowledge on the functions of genes to identify gene-sets associated with the disorder and to annotate biological functions[178] to GWAS findings; multiple tools have been developed to achieve such enrichment analysis and annotations[179-181]. A recent study integrated the GWAS results of schizophrenia with gene expression data by examining the heritability enrichment in genetic expression patterns specific to different cell types; by doing so, it identified specific brain cell types that underlie schizophrenia[182]. These are examples of how downstream analyses can take the GWAS findings further towards the understanding of the biological etiology. Such analyses require sufficiently powered GWAS. Larger GWAS for AN is underway, providing the potential to support secondary analyses[46] and calling for sufficiently powered GWAS for other EDs.

Quantitative genetic modeling has contributed significantly to the field of behavioral genetics since last century. Its value continues, albeit in modified forms, in the "omics" era[183]. Quantitative genetic modeling is highly flexible; it does not only handle overall genetic and environmental effects, but can also incorporate omics findings, such as GWAS results. For instance, a recent study incorporated ADHD PRS in SEM and revealed that ADHD PRS is associated with a general factor of childhood psychopathology[111]. Such designs could be applied to explore the genetic risk of EDs in relation to other conditions. Combining ED omics study results with quantitative genetic modeling may also enable explorations of other

meaningful topics, such as assessing specific gene-environment interactions to identify environmental risk factors that can be targeted for prevention or treatment.

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素心凭风起，
始得探云间。
空高不足惧，
缘有一线牵。

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