A Systematic Review: Genetic and Environmental Risk Factors of Human Eating Disorders under Adoption and Twin Study Designs

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Abstract: Behavioral genetic methods have been largely used in research to study the genetic and environmental risk factors of human mental disorders, including the eating disorders (EDs). Among these quantitative methods, twin and adoption study designs are powerful tools in identifying the nature and nurture components leading to EDs. Molecular genetic methods are introduced in studying EDs recently to study specific candidate genes on human genome. The present work is to (a) review twin and adaption studies of the eating disorders; (b) summarize the major findings in the context of heritability, environmentality, and their interplay under the ACE model; (c) explore the candidate genes for understanding the fundamental cause of EDs on a molecular base. On the basis of this review, the contribution of heritability lies in the range of 0.41 to 0.65. Shared environmental influences are considered neglectable and non-shared environmental influences occupy 0.35 to 0.64. Anorexia Nervosa (AN) and Bulimia Nervosa (BN) vary in these categories but only to a limited extent. Different sexualities and specific experiences of individuals might interact with the genetic risk of EDs. Several candidate genes are identified at the molecular level, but more are yet to be discovered in future studies. Based on the reviewed twin studies and adoption studies, we conclude that heritability contributes to a large extent to general EDs while the rest is accounted by non-shared environmentality. Other specific factors, including subcategories AN and BN, sexualities, specific symptoms, exhibit different variabilities on the heritable and environmental risks of EDs.

1. Introduction

According to Diagnostic and statistical manual of mental disorders: DSM-5 [1], eating disorders (EDs) includes two major types, Anorexia Nervosa (AN) and Bulimia Nervosa (BN). The patients of AN always adopt restrictive energy intake relative to their body's metabolic requirements because of their intense fear of gaining weight. The persistent behaviors to interfere with weight gain always led the anorexics to significantly low body weights. BN is much more common than AN. The diagnosed individuals will have recurrent episodes of binge eating, which occur at least once a week for 3 months on average. During binge eating, the bulimics suffer from three or more of the following: (1) eating much more rapidly than normal; (2) eating until feeling uncomfortably full; (3) eating large amounts of food when not hungry; (4) eating alone because of embarrassment; (5) feeling disgusted, depressed, or very guilty afterward. Moreover, binge eating is usually accompanied by inappropriate compensatory behaviors to prevent weight gain, including but not limited to self-induced vomiting, misuse of laxatives or other medications, fasting, and excessive exercise. Notably, the diagnosed individuals of EDs, either AN or BN, always have disturbance in self-evaluation in body weight or shape as well as lack of recognition of the seriousness of their current low body weight.

Since the late 1980s, EDs have become more and more popular in society. Starting then, many scientists have conducted works to investigate the contributions of the genetic and environmental risks of EDs. To detect the genetic influences of medical disorders and behavioral traits in humans, such as the eating disorder, quantitative genetic methods, including adoption design and twin design, are largely used. These designs could quantify eating disorders into heritability (additive & non-additive genetic influences) and environmentality (shared & non-shared environmental influences) [2]. This research helps with the understanding of the genetic and environmental influences of the eating disorder. Diagnosed patients are more likely to recover from these mental illnesses, whereas the potential candidates are more protected from developing eating disorders.

In the present work, the genetic and environmental influences for EDs are revealed. The percentages of additive genetic (A), shared environment (C) and non-shared environment (E) influences are identified under the full ACE model for quantitative methods, and the percentage of non-additive influence (D) is identified under the ACDE model. Variances on these factors are observed in sex-specific and symptoms-specific models. Additionally, several candidate genes for EDs are located genome-wide to account for the abnormal neurotransmission in ED individuals.

2. Additive Genetic Influences (A)

Twin design utilizes data on monozygotic and dizygotic twins to show the effect of heritability and environmental influences of many medical disorders and behavioral traits [2]. The ACE model has been popular to access the liability of the EDs, including additive genetic factors (A), shared environment (C), and non-shared environment (E). As shown in Table 1, results from many previous studies are presented using the ACE model under different specificity of EDs as well as different sexualities.

Table 1. Model-fitting result in ACE model.

Author(s), Year	Source	Sample Size	Specificity	Sexuality	A	C	E
Kendler et al., 1991	Virginia Twin Registry	2163	Broad BN	Females	0.38	0.13	0.50
			Narrow BN	Females	0.55	0	0.45
Bulik et al., 1998	Virginia Twin Registry	1897	BE	Females	0.50	0	0.50
			BN	Females	0.60	0	0.40
Wade et al., 1999	Telephone interview	325	BN	Females	0.62	0	0.38
Reichborn-Kjennerud et al., 2004	Norwegian Twin Panel	8045	BE	Both	0.41	0	0.59
			BE	Males	0.26	0.11	0.64
			BE	Females	0.46	0	0.54
Culbert et al., 2015	Primary literatures	-	Narrow ED	-	0.50	0	0.50
			Broad ED	-	0.49	0	0.51
Klump et al., 2009	Minnesota Center for Twin and Family Research	358	ED	Females	0.85	0	0.15
Dinkler et al., 2019	Child and Adolescent Twin Study in Sweden	1481	ED	Females	0.65	0	0.35
Javaras et al., 2008	Norwegian Twin Panel	7831	Broad ED	Both	0.57	0	0.43
Beaver et al., 2012	National Longitudinal Study of Adolescent Health	> 3000	Unhealthy habits	Both	0.42	0	0.58
			Healthy habits	Both	0.51	0	0.49
			Fast-food meals	Both	0.33	0.09	0.58
			Number of meals	Both	0.26	0.15	0.59

A = additive genetic; C = shared environment; E = non-shared environment;
BE = binge eating; BN = bulimia nervosa.

Data from 2163 female twins showed that BN aggregates in families solely due to genetic factors [3]. Broadly defined BN has a heritability (0.38) smaller than narrowly defined BN (0.55). This genetic factor both increases the risk of full syndrome BN and the risk for less severe bulimia-like syndromes.

Members of 854 female twin pairs were interviewed about their lifetime history of binge-eating and of broadly defined BN [4]. Data from two interviews (approximately 5 years apart) suggested the high level of additive genetic to latent binge-eating (0.50) and BN (0.60). Based on previous research, a review of twin studies before 2000 further confirmed a reasonable proportion (and perhaps most) of the observed familial aggregation of bulimia nervosa due to additive genetic effects [5].

To explore the relationship between heritability and prevalence of eating disorder, 45 pairs of female twins selected on the basis of at least one individual having a lifetime incidence of BN and 106 pairs of unselected female twins were taken as the sample [6]. The best-fitting model showed that individual variation was best explained by additive genetic influences (0.62) and non-shared environmental influences (0.38).

A population-based twin study involving data from 8,045 twins from a Norwegian twin registry indicated that BE's heritability was 0.41 [7]. Evidence also indicated that binge-eating disorder is in part caused by familial factors distinct from other factors for obesity [8]. These BED-specific familial factors then, in turn, account for the increased risk of obesity, especially severe obesity.

According to Klump et al., differences between adoptive and biological sibling correlations were statistically significant or approached significance, suggesting the presence of significant genetic, but little shared environmental, influences on disordered eating [9]. Notably, the pattern of sibling correlations in the two subsamples was highly similar to that of the full sample, suggesting that genetic influences were prominent in these samples as well.

As more measurements were collected, Culbert et al. compared the data from different populations, especially the recent adoption studies, and integrated them into a more throughout system [10, 11]. Data have shown moderate-to-high heritability of general EDs (0.50), including AN, BN, and BED, and specific disordered eating symptoms (0.49) in females and males during adolescence adulthood. The expression of genetic risk to cause eating pathology interacted with and was influenced by psychological and environmental factors [10].

Eating disorders (EDs), as one of many mental disorders, might represent either extreme end of dimensionally distributed features or distinct entities of the disorders. The self-reported by 1481 female twin pairs at age 18 years were examined and showed the heritability of 0.65 in DeFries–Fulker extremes analyses and liability threshold models [12]. In joint categorical-continuous models, AN and other EDs showed different twin-based genetic correlations with the severity of ED (0.26 for AN and 0.52 for other EDs). Therefore, while some EDs can partly be conceptualized as the extreme manifestation of continuously distributed ED features, AN might be more distinctly genetically demarcated from ED features in the general population than other EDs [12].

3. Additive Genetic Under Different Specificity of Eating Disorder

On the foundation of the previous works, the prevalence of eating disorders differs by sex and by age was noticed. Works conducting a family study and a twin study have been done in an attempt to find different heritability among the varying sex and age group [13]. Their results estimated the heritability of eating disorders at 0.57 with the fact that allowing sex- and age-specific heritability did not improve the model’s fit. This consistency among different sexualities contradicted with the prevalence of eating disorders among females in the society. A possible explanation was that the genetic influence stays unchanged among the diagnosed individuals in sexes or age groups and is independent of the proportion or percentage of the diagnosed individuals of eating disorders across sexes and ages [13].

The heritability for eating disorders also varies with other aspects of eating behaviors [14]. In adolescents, the heritability shows the variance of eating habits in an unhealthy eating habits scale (0.42) and a healthy eating habits scale (0.51). Moreover, the numbers of eating behaviors also show

different genetic influences between the number of meals eaten at a fast-food restaurant (0.33) and the total number of meals eaten per week (0.26). Their tendency for eating different kinds of food contains significant genetic influences, with a heritability of 0.20 for eating dessert foods, 0.37 for eating vegetables, 0.71 for eating fruits, and 0.78 for eating protein foods. Other variances are defined by the environment. Notably, their additional analyses conducted separately for males and females revealed a similar pattern of findings.

Genetic influences on food use patterns are analyzed on about 2000 pairs of young adult twin pairs [15]. The researchers found out that in the measurement of healthy food, high-fat food, sweets, and meat, genetic factors account for about 0.40 to 0.45 of the differences. The heritability of the healthy eating habits scale was 0.51 for the full sample, 0.63 for the all-female sample, and 0.38 for the all-male sample. This indicates that heritability varies for males and females, and females are more likely to inherit healthy eating habits than males.

4. Shared Environmental Influences (C)

A shared environment or common environment creates behavioral similarities between siblings. It has been determined to have none or little contribution to liability to binge-eating than additive genetic factors in general. In female twins, the magnitude of the contribution of the shared environment was determined to be less prominent than heritability [4]; 0.09 on average in reviewing the research before 2000 [5]; negligible as it did not substantially improve the model's fit [10, 13]. On the other hand, in males, shared environmental influences on the liability to BE could not be ruled out [7].

However, because of the lack of ability of classical twin studies in distinguishing the shared environmental effects from additive genetic influences, the first adoption study to examine genetic/environmental effects for disordered eating [11]. The study didn't suggest any presence of shared environmental influences (0), while significant genetic influences (0.85) and moderate non-shared environmental influences (0.15) appeared. Therefore, the adoption study also supported the results of twin studies by confirming the lack of shared environmental influences on eating disorders.

5. Non-Shared (Unique) Environmental Influences (E)

Since shared environment did not contribute to much of the liability of eating disorder, the remaining variance was accounted for by a unique (individual-specific) environment, which leads to the behavioral differences between siblings. In twin studies, significant contributions of nonshared environmental factors were found (0.40 – 0.50 [4]; 0.38 [6]; 0.43 on average [5]; 0.59 [7]; 0.5 on average and ranging from 0.50 for narrow ED and 0.51 for broad ED [10]; 0.60 for AN and 0.52 for other EDs [12]). The results of adoption showed 0.15 non-shared environmental influences [9], which was moderately less than the conclusion of twin studies.

A number of significant life events were assessed as correlates of ED epidemiology. Having experienced significant stress in general (reporting major stressors, higher pressure, or provoking agents) was associated with greater ED prevalence. Other events were less often studied; however, preliminary evidence may suggest an effect of disruptive events such as moving to a new house address and change in the family structure.

While the heritability of eating disorder was well-investigated as an intact mental disorder, the heritability of specific eating disorder symptoms can also vary on the local level. In a twin study, the item-level analyses showed that not all symptoms of EDs are equally heritable [16]. Results displayed a strong non-shared environment influence on the self-evaluation of weight or body shape (0.63), while other symptom levels lie within 0.33 to 0.57. For this single trait of the eating disorder, important interventions usually occur outside of the family, such as competing in dance, modeling, gymnastics, teasing by peers, or being abused by others, which are only experienced by one member twin pair. The influence of these experience at the window stage of children and adolescents are still yet to be investigated.

Evidence has shown that people have different eating disorders due to dissatisfaction with their bodies and high or low racial identity in different cultures [17]. In African American culture, the frequency of eating disorders in women is significantly lower than that in white people, and they are less likely to diet or vomit to control weight. Reasons include the higher social status brought by body size in some societies. However, in fact, African American women may face a greater risk of obesity and overeating. Individuals with a high level of ethnic identities may eat excessively to achieve their ideal shape. On the contrary, white women may go on a diet because of the social definition of beauty, leading to some eating disorders, such as anorexia.

Genotype and environment also interact with each other and act as a combined effect on the individuals with eating disorder, mostly as an enhancement. A number of other factors influence ED epidemiology, most notably genetics, female sex, younger age, participation in esthetic or leanness sports, and has been a victim of sexual or physical abuse [18]. Importantly, they also found a number of factors unlikely to influence variability in ED epidemiology, for instance, ethnicity, educational attainment, socioeconomic status, urbanicity, and participating in general sports.

6. Non-additive / Dominance Genetic Influences (D)

While the classical ACE model only accounts for the additive genetic influences (A), the ACDE includes non-additive genetic influences (D) as the extended ACE model in some research. In twin studies, non-additive genetic influences change with, and it is not possible to identify exactly in addition to additive genetic influences. However, as additive genetic influences account for 100% heritability in MZ twins and 50% in DZ twins, the genetic correlation of MZ twins, which is more than twice as large as DZ twins, suggests the possible presence of non-additive genetic influence.

Joint categorical-continuous models showed that correlation between ED severity scale and AN symptom were 0.26 between MZ twins and 0.01 between DZ twins and correlation between ED severity score and other eating disorder symptom were 0.34 between MZ twins and 0.13 between DZ twins [12]. Non-additive genetic influence might exist on the association between ED severity scale score and AN/OEDs after adjusting for genetic influence.

7. Molecular Genetic Methods

Recently, more advanced laboratory instruments allow the identity of specific candidate genes of EDs by molecular genetic methods. These genes are usually involved in abnormal neurotransmission in human physiology, mostly by providing an elevated level of positive feedback for uncontrollable eating behaviors. Targeting the candidate genes gives space for better medical treatment for EDs.

Agrawal & Lynskey focused on the classical twin design and discussed the heritable influences on alcohol, nicotine, cannabis, and other illicit drug addictions [19]. They found moderate to high genetic influences on addiction with estimates ranging from 0.30 to 0.70. Moreover, these heritable factors change as a function of gender, age, and cultural characteristics and interplay with the environment to change the risk of addiction to psychoactive substances. This provides evidence for the high genetic factor on eating disorders as it also involves psychoactive substances in the signaling pathway of eating like dopamine. On the genomic basis, while no single is deterministic about either the genetic or the environmental basis to addiction, multiple genes of modest, cumulative, and interactive effect cause the addictive behaviors.

On the genomic basis, the serotonin transporter gene (SLC6A4, 5-HTT) mediates sodium-dependent presynaptic reuptake of serotonin, thus terminating serotonergic neurotransmission [20]. The short or s-allele in the 5-HTT gene-linked polymorphic region (5-HTTLPR) is associated with lower transcriptional activity of the promoter as compared to the long or l-allele and has been suggested to lead to lower expression of 5-HTT mRNA, less serotonin (5-HT) binding, and less 5-HT reuptake [20]. The association between the s-allele and anxiety, affective instability, and alcohol dependence has been revealed.

However, when investigating the association between the 5-HTTLPR and binge eating behaviors in a population-representative sample of women, no 5-HTTLPR genotype effect on binge eating is found even after the covarying effect of impulsivity and anxiety was controlled for [20]. Even though this rules out the possibility that the 5-HTTLPR genotype influences the severity of binge eating, the s-allele, and especially the s/s genotype among women with binge eating increases the risk for affective instability and symptom severity [21]. This suggests the possible role of the s-allele in connecting eating disorders and other mental disorders such as anxiety and higher impulsivity. Evidence to support the association between the 5-HTT gene and compulsive eating has been found in the absence of such gene in AN individual [22]. Possible candidate genes for future research have already been identified (5-HT2A receptor gene, UCP-2/UCP-3 gene, estrogen receptor ß gene).

Dopamine, as one specific psychoactive molecule, involves in the signaling pathway of eating. Its composite genetic index influences food addiction by certain aspects of reward-responsive overeating [23,24]. However, no evidence of a higher possibility of any subset of the population developing food addiction was found, even among those who excessively overeat and are obese. Most individuals who frequently have highly palatable food do not develop a dependence on the addictive substances caused by foods. This conclusion was consistent with the fact that the unselected sample did not provide a significant change in the liability of low-prevalence psychiatric disorders, such as eating disorders on the basis of the ascertained sample [6]. The genetic effect was shown to be the deterministic factor in additive substances. Other psychoactive substances that might serve as a high genetic factor in eating disorders suggested by Agrawal & Lynskey [19] are yet to be explored.

8. Conclusion

In conclusion, this review identified the eating disorders (EDs) as a great proportion of genetic contribution, the modest influence of the non-shared environment, and none or very little shared environment. The previous works hold different experimental results toward the relatedness between EDs and sexualities. While some works show data for similar genetic and environmental risk factors for EDs, other works present the opposite perspectives. Moreover, the present work shows that the hereditability of EDs varies among its specific symptoms, including self-evaluation, vomiting, food choice, eating habits, and culture.

The present works have shown the overall power of quantitative genetic methods, twin and adoption study designs, for testing heritable mental diseases like eating disorders. Future studies should continue on such large-scale quantitative genetic methods for the heritability and environmentality in sub-areas, such as specific ED symptoms and particular experiences from surroundings during the window stage in childhood. If the substantial influence of unique unshared experiences on the development of eating disorder symptoms is found, individuals with known genetic risk for ED could be specially protected from developing eating disorders.

Furthermore, the present work only depicts the genetic and environmental risk factors for eating disorders on a large-scale quantitative level. Regarding the genetical component of EDs, the important value lies in the molecular genetic studies for identifying and treating genes that potentially lead the EDs. Molecular genetic methods have the potential in finding particular heritable transcriptional factors in DNA or protein and neurotransmitter intrigued by environments that mislead the individuals' signaling pathway for uncontrollable and unhealthy eating behaviors.

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