

Causes of anorexia nervosa

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Abstract

This article gives an overview of the biological, psychological, and social components that may play a role in the pathogenesis of anorexia nervosa (AN). It examines aspects that contribute to a vulnerability for AN, such as genes, personality traits, cognitions; considers a range of factors that may trigger disease onset (stress, life events, media); and explores the biopsychosocial factors that maintain the illness (physical, psychological, social responses). The attempt to develop an understanding of predisposing, precipitating, and perpetuating factors is important in the development of effective strategies to prevent and treat AN, as well as in predicting those at greatest risk of a poor outcome.

Keywords aetiology; anorexia nervosa; causes; maintaining factors; risk factors

Introduction

Establishing causality for specific eating disorders has so far proved to be difficult. Prospective longitudinal studies are sparse; hence causality cannot be established readily. A number of putative risk factors with differing levels of empirical support and correlation to anorexia nervosa (AN) have been identified¹ (Table 1).

The onset of AN is commonly during puberty, which is characterized by significant biological and psychological changes and exposure to a wide range of social influences. The interaction between genetic and non-specific biological risk factors, psychological predisposition, and environmental stressors may trigger disease onset during this sensitive developmental period, causing an exponential pathogenic effect beyond the threshold for disease onset. Biological, psychological, and social reinforcements may

maintain the illness, and determine the severity and chronicity of the clinical course (Figure 1).

Predisposing factors

Genetic factors

It has been proposed that many of the psychological risk factors may be a reflection of genetic predisposition and gene-environment interactions² (Figure 2). Current research efforts focus on genome-wide screening in affected families in an attempt to locate susceptible genes. Molecular genetic studies, such as linkage analysis and association studies, have examined allele sharing among family members at several genetic markers across the genome (candidate genes) with the intention of identifying particular alleles as fixed markers in the future.

- Eating disorders cluster in families, with a 10-fold increased genetic risk.³ Twin studies suggest a heritability of between 58%⁴ and 74%.⁵
- Body mass index (BMI) is heritable.⁶
- Symptoms of eating disorder, including dietary restraint, self-induced vomiting, eating and weight concerns, body dissatisfaction, and weight preoccupation, have a heritability of 32–72%.⁷
- Linkage to chromosome 1 has been demonstrated for restrictive-type AN.⁸
- Genetic effects on overall eating pathology vary across pubertal timing, with no effects found in 11-year-old twins compared with 52–57% in an older cohort.⁹

Neurodevelopment

Critical periods during development are thought to play a key role in the pathogenesis of neurodevelopmental disorders and other conditions, including AN.

Both early and late complications during pregnancy have been observed to have a dose-response effect in increasing the risk and reducing the age of onset for AN.¹⁰ The subtle neurocognitive deficits observed in AN¹¹ may be related to a number of prenatal, perinatal, and postnatal complications. For example, inadequate nutrition before and after birth is thought to alter nutritional status and appetite programming throughout life.^{12,13} Prematurity, low birth weight,¹⁴ and cephalhaematoma are documented at higher rates in patients with AN compared with controls. Other factors are severe stress and increased parental anxiety, associated with insecure attachment¹⁵ and overprotective parenting. Being born in the spring increases the risk of AN in non-equatorial vs equatorial regions.^{16,17} The greater the number of siblings, the greater the risk of developing AN.¹⁸ It is also possible that intrauterine infection may play a role in increasing the risk of AN.¹⁹

The lasting and subtle effect of these heterogeneous events may be explained by an epigenetic effect, which refers to the process of modification and alteration of gene expression without changing the gene sequence.

Predisposing and maintaining factors

Personality traits

Obsessive-compulsive traits, including rigidity, need for order, and control, preoccupation with detail, and perfectionism are apparent in childhood, after recovery, and in relatives.^{20–22}

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Aetiology of anorexia nervosa

	Physical	Psychological	Social
Predisposing	Genes Epigenetic effects Obstetric complications Prematurity Feeding difficulty in infancy HPA axis deficits	OCD/OCPD Anxiety disorders Avoidant coping style Cognitive deficits Negative self-evaluation Low self-esteem	Isolation Occupation (e.g. athlete, ballet dancer) Abuse Overprotective parenting Attachment difficulties
Precipitating	Puberty	Stress Dieting	Life events Cultural values
Perpetuating	GI changes Low 5HT Low dopamine Low BDNF Altered HPA axis Low leptin, adiponectin	OCD/OCPD Cognitive changes (e.g. increased rigidity) Anxiety Depression	Family dynamics High expressed emotion/criticism Social isolation

BDNF, brain-derived neurotrophic factor; GI, gastrointestinal; HPA, hypothalamic–pituitary–adrenal; OCD, obsessive–compulsive disorder; OCPD, obsessive–compulsive personality disorder.

Table 1

Evidence suggests that these traits are heritable.²³ Low novelty seeking, harm avoidance, a lack of self-directedness, and low cooperativeness have also been reported in AN. These are features shared with anxious, avoidant, and dependent personality disorder, and obsessive–compulsive personality disorder.

Deficits in cognitive strategies, including weakness in set-shifting, central coherence, learning, and reward, are linked to these traits and may play a role in mediating and moderating disease.

Biological factors

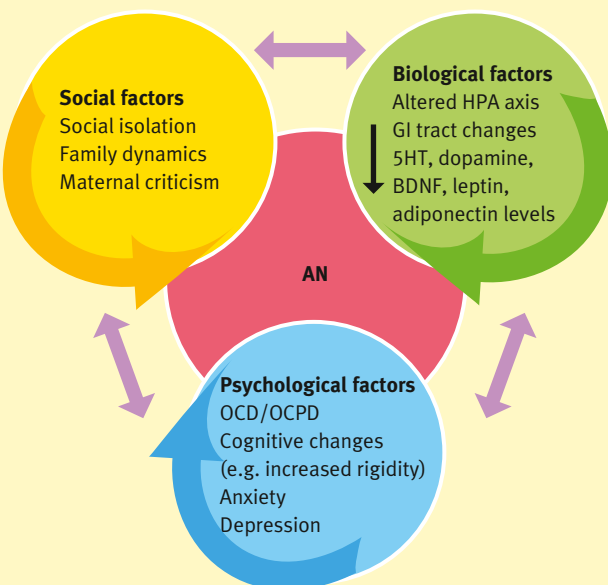
A range of biological factors and mechanisms, including metabolic and neural networks as well as candidate genes, participate in the pathological processes that initiate and maintain AN. It is unclear whether biological factors are trait or state related. These factors are altered during illness and remain changed in some recovered patients. Persistence after recovery may indicate a higher vulnerability for these changes, with perhaps less chance of a full recovery (e.g. amenorrhoea), or the underlying pathological mechanism maintaining AN may be different from that in patients who have an early and full remission.

Central neurotransmitters:

The serotonin system is downregulated in AN during the acute state and after recovery. Dieting reduces tryptophan intake and therefore serotonin production. This may result in reduced anxiety symptoms and a sense of well-being, which is reinforcing.²⁴

The serotonin system is part of the punishment system that counteracts the reward system, and is linked to harm avoidance and reward dependence. 5HT type 1A receptors are autoreceptors on the cell body of 5HT neurons that reduce synaptic 5HT release. Increased 5HT_{1A} activity is a vulnerability factor for developing AN.²⁵ 5HT_{1A} receptor activity in the supragenual cingulate, frontal, and parietal regions is increased during illness and after recovery, and is linked to harm avoidance.²⁶ Reduced 5HT_{2A} binding in the parietal lobe has been demonstrated during illness in the binge–purging subtype of AN; this correlates with the trait of reward dependence. Decreased 5HT_{2A} binding

Maintaining factors for anorexia nervosa



AN, anorexia nervosa; BDNF, brain-derived neurotrophic factor; GI, gastrointestinal; HPA, hypothalamic–pituitary–adrenal; OCD, obsessive–compulsive disorder; OCPD, obsessive–compulsive personality disorder

Figure 1

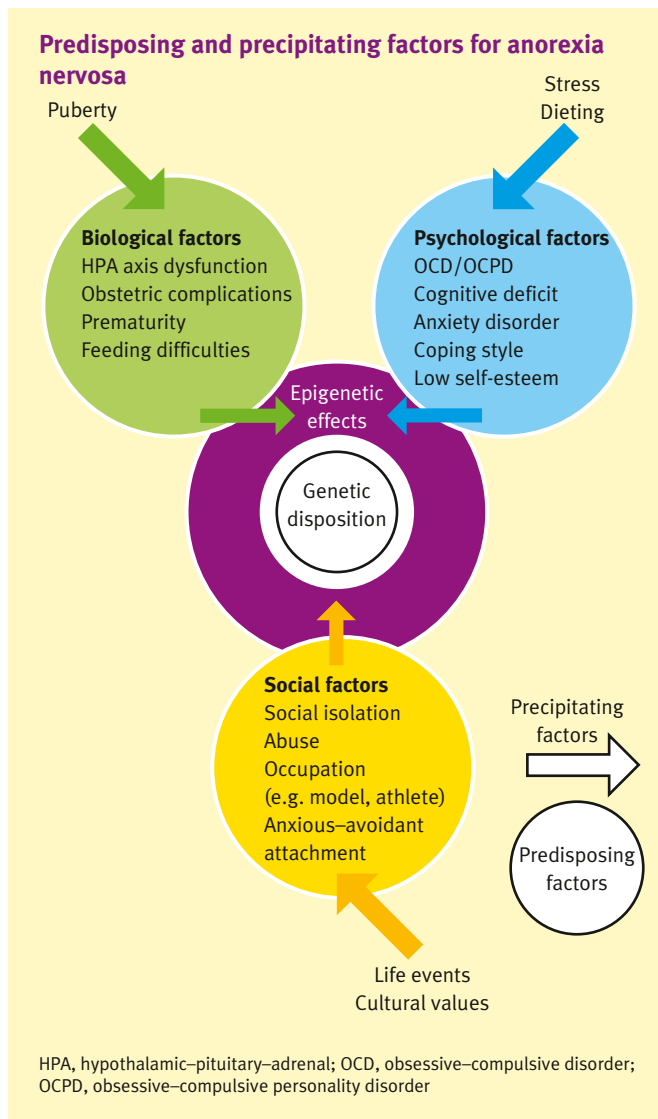


Figure 2

in the subgenual cingulate region has also been demonstrated in recovered patients with binge-purging AN.

The dopamine system— during and after recovery, decreased intrasynaptic dopamine levels with increased D2/3 density and plasma levels of homovanillic acid have been observed, and are associated with weight loss, excessive exercise, and insensitivity to normal reward.²⁷

Brain-derived neurotrophic factor (BDNF) and its tyrosine kinase receptor are expressed in various hypothalamic nuclei implicated in the *regulation of eating behaviour*. BDNF is anabolic and exerts a satiety effect. Low BDNF levels increase hunger and may be an adaptive physiological response to starvation. However, animal studies have demonstrated that reduced hypothalamic BDNF expression leads to *increased locomotor activity*.²⁸ It could be speculated that low BDNF levels contribute to sustained increased physical activity in AN.

BDNF levels are significantly reduced in underweight patients with AN²⁹ and are not restored after weight recovery.³⁰ Evidence suggests that BDNF function is heritable.

The dehydroepiandrosterone (DHEA)/DHEA sulphate ratio in AN resembles that found in the pre-pubertal stage and has a suppressive effect on appetite.³¹

Endocrinology

Hypothalamic-pituitary-adrenal (HPA) axis – during illness the HPA axis is hyperactive and cortisol levels are raised. This is in keeping with a *state of chronic stress*. Whether the HPA axis normalizes after recovery is controversial. A deficit in feedback mechanisms (e.g. insensitivity to arginine vasopressin) has been proposed as a perpetuating factor in the abnormal HPA axis response observed in patients with AN. This promotes a chronic increase in cortisol levels, with the *effect of reduced appetite and weight loss*.

Growth hormone (GH) levels are increased, and concentrations of insulin-like growth factor-1, GH and IGF-I binding proteins are decreased, during illness. This resembles a state of GH resistance and failure to thrive.

Peptides

- **Adiponectin** is a protein produced in adipocytes that modulates insulin sensitivity. Its concentration is high in AN, with an inverse correlation to BMI and body fat. Evidence from animal studies suggests that adiponectin *induces weight loss* and may therefore be a pathogenic factor in AN.

- **Leptin** is a key factor for many physiological processes including *signalling of body energy balance and puberty*. It also plays a role in regulating the level of physical activity, and its levels are low in AN. Leptin may play an important *role in various pathological mechanisms that maintain AN*.

Precipitating and maintaining factors

Sociocultural factors

Family factors:

- There is no evidence to suggest that family style and interaction are causative factors for AN.
- Insecure attachment³² may be a non-specific predisposing factor.
- Unresolved loss and trauma are reported to be high among mothers and their affected children, and may trigger disease onset.
- Family factors are viewed largely as *maintaining factors*.
- Family dynamics reorganize around chronic illness, although this is not specific to AN. No specific pattern of interaction or style of communication has been identified.³³ Existing communication styles within families may, however, become more pronounced when illness occurs. Although some studies have reported increased rates of family dysfunction in AN, these findings are not consistent. Many studies find no difference in family interaction in AN compared with controls. Some research evidence suggests there may be discrepancies in the accounts of interaction between family members,^{34–37} as well as various family members and clinicians.³⁸ Other studies highlight maladaptive parental behaviour impacting on the course of eating disorders. A recent 5-year follow-up study demonstrated that maternal criticism may be a moderator of treatment rather than a maintaining factor for illness.³⁹

Social factors:

- Risk factors⁴⁰ and expression of eating pathology^{41–43} differ between the sexes. Thinness for females and muscularity for

males are the internalized body image ideals in Western society, reinforced by media and advertisements.

- Peer influence predicts body dissatisfaction and dieting behaviour, and may influence disordered eating. Dieting may be a trigger for binge-purging AN.
- Although patients with AN strive for social acceptance, social isolation is extreme during illness and persists after recovery.⁴⁴ Social anxiety with fear of negative evaluation occurs in a significant number of patients, and predates onset of the illness.⁴⁵
- Athletes, models, and ballet dancers have an increased risk of developing AN.
- External precipitants, such as separation, loss, and adverse sexual experience in childhood, have been identified as risk factors for AN.

Ethnicity:

- Specificity between ethnicity and eating disorders is not established.
- Caucasian females are at highest risk⁴⁶ and Asian females appear to have the lowest rate of AN.⁴⁷ AN rates are lowest among African American adults and adolescents.⁴⁸
- Differences in genetic predisposition and gene-environment interactions may be at the core of these findings.

Summary

- Risk factors are non-specific and the threshold of disease varies for each patient.
- Formulations based on a biopsychosocial approach, determining antecedents, triggers, and maintaining factors, should be at the core of clinical practice.
- Effective treatment interventions need to take predisposing personality characteristics and perpetuating cognitive styles, as well as social maintenance factors, into account.
- Much is still unknown about causative pathological mechanisms and the interaction and significance of various risk factors leading to AN. ♦

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