Anorexia nervosa

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Abstract | Anorexia nervosa (AN) is a psychiatric condition characterized by severe weight loss and secondary problems associated with malnutrition. AN predominantly develops in adolescence in the peripubertal period. Without early effective treatment, the course is protracted with physical, psychological and social morbidity and high mortality. Despite these effects, patients are noted to value the beliefs and behaviours that contribute to their illness rather than regarding them as problematic, which interferes with screening, prevention and early intervention. Involving the family to support interventions early in the course of the illness can produce sustained changes; however, those with a severe and/or protracted illness might require inpatient nursing support and/or outpatient psychotherapy. Prevention programmes aim to moderate the overvaluation of 'thinness' and body dissatisfaction as one of the proximal risk factors. The low prevalence of AN limits the ability to identify risk factors and to study the timing and sex distribution of the condition. However, genetic profiles, premorbid features, and brain structures and functions of patients with AN show similarities with other psychiatric disorders and contrast with obesity and metabolic disorders. Such studies are informing approaches to address the neuroadaptation to starvation and the other various physical and psychosocial deficits associated with AN. This Primer describes the epidemiology, diagnosis, screening and prevention, aetiology, treatment and quality of life of patients with AN.

Anorexia nervosa (AN) is a disorder that predominantly affects women in early adolescence[1]. The characteristic features of AN include severe weight loss and secondary problems associated with malnutrition. Weight loss is caused primarily by a reduction in food intake, but other behaviours that increase energy expenditure — such as exercise, taking metabolic stimulants and cold exposure — or that reduce energy intake — such as chewing, spitting and purging — can also contribute to the disease. Although the most common current explanation for this behaviour is a fear of becoming overweight, other reasons include a drive for perfection and low self-worth (that is, not deserving to eat)[2]. In some patients, no reason for the disinclination to eat can be ascertained, but patients typically resist attempts to help restore nutrition and weight[3]. A notable feature of AN is that the individual does not experience herself or himself as 'sick', which contrasts with the overt features of malnutrition perceived by others.

AN follows a persistent course with a median duration of >6 years[4]. A proportion of patients experience anxiety, obsessive–compulsive features and social difficulties in childhood, and these often remain as persistent lifetime traits[5–7]. Loss of control of eating can occur transiently or evolve into bulimia nervosa or binge-eating disorder[8–10]. During the ill state of AN, patients are underweight because of food restriction, which is in some cases interspersed with binge eating, excessive exercise or purging behaviours.

One theory that explains the tendency of AN to follow a protracted time course and why the duration of illness is such a key prognostic feature[11] is that, over time, the behaviours that accompany the disease become habitual rather than goal directed[12]. In addition, the problems associated with persistent poor nutrition accumulate, and a form of adaptation occurs[13] in which many of the consequences of starvation on the brain and body serve to maintain the illness[14] (FIG. 1). For example, problems in social cognition serve to isolate and alienate the individual, cognitive inflexibility prevents change and low oestrogen levels and other secondary hormonal and metabolic consequences of malnutrition reduce energy levels and affect well-being. In addition to these biological consequences, genetic findings and the characterization of possible neuropsychological endophenotypes have also led to a shift away from a simple sociocultural explanatory model of eating disorders, such as AN, towards one based on the integration of environmental and biological factors.

For over a century, the treatment for AN developed by Sir William Gull, recommending separation of the patient from his or her family and inpatient care, was a mainstay of clinical practice[15]. By contrast, contemporary treatment programmes that actively involve the family

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early in the treatment course are regarded as best practice[16]. Indeed, collaboration with families involves training caregivers with skills to aid recovery, and evidence suggests that this approach is helpful both in the early[17] and in the later[18] phases of the illness. Nevertheless, there remains much room for improvement in the treatment of patients with AN. Furthermore, many uncertainties remain about screening, detection, classification, causes, neurobiology and prevention. In this Primer, we give an update on these areas and look to future understanding about this enigmatic disorder.

Epidemiology

Research into the epidemiology of AN has been steadily growing; however, a series of methodological challenges need to be taken into account when designing epidemiological studies and interpreting available literature[19,20]. For example, the ego-syntonic nature of AN — that is, the fact that individuals who have AN perceive the illness as congruent with their values and needs — requires a multi-informant-type approach to studying epidemiology; parents and caregivers of patients must be involved in the data-gathering exercise. In addition, the low prevalence and incidence of AN necessitate sampling strategies that can capture all relevant cases. Finally, cultural or sex-specific presentations require reliable and valid screening and interview measures that enable consistent identification of cases. Difficulties in implementing these strategies in previous studies might have led to the variations in estimates that are evident across the studies described below.

Incidence

Both community-based and register-based sampling strategies have been used to measure the incidence of AN. Given that the diagnostic criteria for AN have recently changed (specifically, amenorrhoea has been removed as a criterion)[3], most studies have focused on the previous iteration of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) rather than the current DSM-5 (REF. 21).

As might be expected, incidence rates from community studies are higher than from treatment-seeking samples (that is, data from primary and secondary care registers) owing to the fact that the majority of individuals do not access treatment[22]. Overall incidence rates from register studies are fairly comparable[1,23–25] (TABLE 1). A recent meta-analysis suggested that the incidence of AN in treatment-seeking samples increased up to the 1990s, when a plateau was reached, which is probably attributable to improved diagnosis and identification of patients[26]. All studies consistently highlight a higher incidence in women and girls than in men and boys, with sex ratios of approximately 10/1 to 15/1. Good evidence supports the conclusion that the rate of first diagnosis of AN is highest among individuals 15–20 years of age[3,22,24] in both males and females. Very few studies have investigated the incidence of AN in non-western populations; a study in the Caribbean island Curaçao showed lower incidence of AN than European estimates[27] (TABLE 1).

Three studies (from the United Kingdom[28], Australia[29] and Canada[30]) on the incidence of AN in children <13 years of age presenting to paediatricians (and child psychiatrists in the United Kingdom) using comparable methodology (surveillance methods) showed similar incidence rates; for example, incidence in the United Kingdom was shown to be 1.1 per 100,000 person-years[28].

Prevalence

Epidemiological studies have explored varying definitions of AN — that is, relaxing thresholds for criteria, such as body mass index (BMI), weight and shape concerns, and amenorrhoea, to produce 'broad' and 'narrow' definitions of illness. Estimates of the lifetime prevalence of AN in community settings have been in the range of 0.3–0.6% for strictly defined AN[31–33] and 0.64% for broadly defined AN[31] (TABLE 2). Among females (both adults and adolescents), estimates vary between 0.6% and 2.2% for strictly defined AN[22,34–37]; the range for broadly defined AN is 1.7–4.3%[11,19,22]. The lifetime prevalence of AN in males has been estimated to be 0.2–0.3% in the few studies that have included males[33,35,38] (TABLE 2).

In relation to adolescents, a large study in a representative sample from the United States showed a 12-month prevalence of 0.2% in girls and boys (13–18 years of age)[35]. Higher estimates for AN were determined among Dutch adolescents using the DSM-5 diagnostic criteria (point prevalence: 1.2% of females and 0.1% of males)[39]. Comparability of these two studies is limited by differences in diagnostic measures used and changes in diagnostic criteria.

Non-western samples have been less studied. A study on female students in Ghana found that 1.5% (95% CI: 0.6–2.4) of girls had self-imposed starvation resembling AN (although no weight and shape concern was reported)[40]. Similarly, a study of female adolescents sampled through schools in Iran showed a comparable lifetime prevalence to other studies[37].

Mechanisms/pathophysiology

Genetics

The risk for AN is strongly familial. The most comprehensive population register-based study to date was conducted in Denmark and revealed that the proportion of

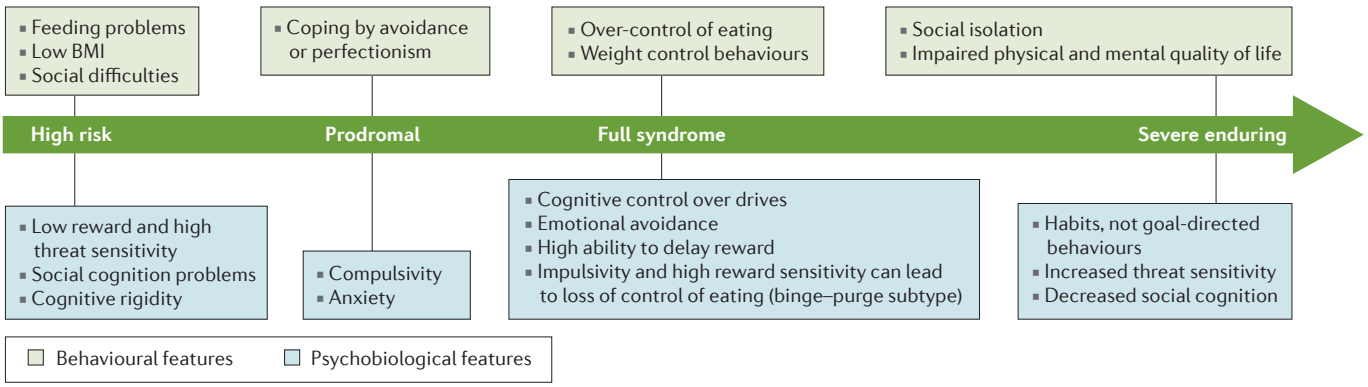

Figure 1 | **The behaviours and possible underpinning psychobiological features of anorexia nervosa across the various stages of the disorder.** Several risk factors, including a high sensitivity to threat (anxiety), ability to delay reward, problems in social areas and a tendency to cognitive rigidity might increase the vulnerability of an individual developing anorexia nervosa (AN). Coping strategies to manage these vulnerabilities, such as avoidance and perfectionism, further increase the risk (prodromal). The full eating disorder (full syndrome) emerges when control over eating is used as a coping strategy. Over time, these behaviours are thought to become embedded as habits linked to food and are no longer goal directed (severe-enduring AN). Furthermore, secondary adaptations to starvation, such as problems in social cognition, increased anxiety and/or changes in reward sensitivity, add to the burden of disease. Those who develop the binge–purge subtype of AN might differ in terms of reward sensitivity and/or impulsivity. BMI, body mass index.

case proband relatives with the condition was fourfold greater than control relatives of those without AN[41]. Specifically, mothers of individuals with AN were shown to be six-times more likely to have the condition than mothers of healthy controls; siblings of affected individuals were four-times more likely to have AN than controls, and offspring of affected women were five-times more likely to develop the condition than controls — all significant increases[41]. Widely replicated twin studies in European ancestry populations have reported AN heritability estimates ranging from 0.28 to 0.74. The interpretation of these statistics is that up to 74% of the phenotypic variation in AN is attributable to additive genetic factors[42]. The narrower the definition of AN, the higher the heritability estimates — suggesting that subthreshold conditions (with higher BMI, fewer body image concerns and the absence of amenorrhoea) might be less influenced by genetic factors[43,44].

Although AN is clearly heritable, candidate gene and linkage studies conducted over the past decade are being de-emphasized because they did not identify reliably replicable genetic variants that were uniquely associated with AN. By contrast, modern genome-wide approaches represent discovery science in which the entire genome can be scanned, generating hypotheses instead of requiring them[45]. Standards for statistical significance are rigorous to account for multiple testing[46].

Two genome-wide association studies (GWAS) have been published on AN, although both are considered to be underpowered by contemporary standards. The first included 1,033 individuals with AN and 3,733 controls and yielded no genome-wide significant loci in the analysis[47]. The second — conducted by the Wellcome Trust Case–Control Consortium 3 — included 2,907 cases with European ancestry in the discovery meta-analysis and 14,860 ancestry-matched female controls[48]. No genome-wide significant findings were obtained in the discovery data set; however, when comparing discovery with replication results, 76% of the effects were aligned. This finding strongly suggests that the sample was underpowered to detect candidate genes[48] and encouraged initiatives to increase sample sizes worldwide, which are currently underway (see http://www.med.unc.edu/psych/eatingdisorders/our-research/angi and http://www.charlotteshelix.net). At the current collection rate, ≥20,000 samples will have been collected by 2016.

GWAS cannot only identify genetic variants that contribute to a single disorder such as AN but might also explain patterns of co-morbidity by revealing genetic variants that influence several phenotypes. An extension of the Wellcome Trust study explored shared genetic determinants of AN and co-morbid psychiatric disorders by testing how well polygenic risk scores derived from genome-wide data of other psychiatric disorders can predict AN status. A polygenic risk score is a single measure that quantifies the number of risk alleles an individual has for a particular disorder[49]. The study revealed nominally significant evidence for overlap of polygenic risk between AN and autism spectrum disorder, major depressive disorder, schizophrenia and bipolar disorder (E. Zeggini, personal communication).

Intriguingly, a new method — linkage disequilibrium score regression[50] — has been developed that enables the calculation of genetic correlations across GWAS using only summary statistics. A birds-eye analysis of >20 metabolic, somatic and psychiatric phenotypes showed that valuable information on co-morbidity emerged from GWAS in AN even in the absence of disease-specific significant loci. Specifically, AN was negatively correlated with obesity and positively correlated with schizophrenia[51]. Additional suggestive negative correlations were observed between AN and other metabolic traits, such as triglyceride levels, fasting insulin levels,

fasting glucose levels and type 2 diabetes[51]. These results encourage deeper exploration of the metabolic aspects of AN and suggest that the same genetic factors that influence normal variation in body mass might also be operative in psychiatric disorders associated with extreme dysregulation of body mass.

The positive correlation of AN with schizophrenia also suggests further areas of inquiry. Schizophrenia is not among the most commonly reported co-morbid conditions observed in individuals with AN; however, the positive genetic correlation suggests that we should consider whether the grossly distorted thinking and perception and profound lack of insight associated with AN might be manifestations of similar processes that underlie psychosis. Linkage disequilibrium score regression has also been applied to the association between AN and obsessive–compulsive disorder, revealing a strong positive genetic correlation between the two conditions ($r_g = 0.55$)[52], which, intriguingly, mirrors both reported twin-based genetic correlations ($r_g = 0.52$)[53] as well as frequently observed co-occurrences of these disorders in the clinic. The next steps in the approaches that could be used to reveal the neurobiology underpinning AN are shown in FIG. 2.

Rapidly advancing technology is facilitating the detection of rare variants (minor allele frequencies of <1%) and making sequencing more affordable. One study sequenced 152 candidate genes in a sample of 261 patients with AN and 73 healthy controls and did not yield any genome-wide significant findings, although epoxide hydrolase 2 (*EPHX2*) — one of the top 'hits' in the sequence analysis — was associated with depression and anxiety scores in a small independent replication sample, and to BMI and increased levels of cholesterol in controls from a larger population study[54]. These results reinforce the association of AN with other psychiatric disorders and with metabolic parameters. A preliminary study combined linkage analysis, exome sequencing and whole-genome sequencing and examined two families who had multiple members with eating disorders (that is, dense pedigrees). A missense mutation in oestrogen-related receptor-α (*ESRRA*) was reported in the first family, and a potentially deleterious mutation in histone deacetylase 4 (*HDAC4*) in the second[55]. Although intriguing, owing to the role of these genes in the oestrogen system and the fact that AN onset tends to be around puberty, this study has not yet been replicated.

Neuroimaging

Alongside genetic research, brain imaging might help to elucidate mechanisms related to brain pathophysiology that drive eating disorder behaviours. Indeed, we are only beginning to distinguish secondary full syndrome effects (which might result from neuroadaptive processes to starvation) from mechanisms that drive the disorder[56]. Overall, brain alterations found in AN could drive abnormal food intake and high anxiety, in which detrimental interactions of traits and environmental factors lead to AN illness (FIG. 3). There are also various endocrine alterations in AN, especially when patients are underweight, including low gonadal hormone levels, altered thyroid function and low levels of appetite-regulating hormones, such as leptin[57]. However, such endocrine alterations frequently normalize with weight restoration, and whether they specifically affect the brains and behaviours of patients with AN is uncertain.

A range of techniques are available to study the brain, including MRI (for brain structure), diffusion tensor imaging (DTI; for water diffusion in white matter tracts[58]), functional MRI (fMRI; for blood flow[59]) and PET (for the distribution of neurotransmitter receptors). Several brain regions have been found to be of importance in food reward processing and are, therefore, regions of interest in terms of functional and structural change in individuals with AN (FIG. 4). A key issue in AN research is that extremes of eating or food restriction behaviour can alter brain structure and function during the ill state[56]. To avoid these potential confounders, some studies have focused on imaging in patients who have recovered from AN. However, how to define the recovered state is under debate; a commonly used approach is to consider individuals as recovered when they have had normal weight and eating patterns for ≥1 year, have regular menstrual cycles (in women) and do not exercise excessively (FIG. 1).

Table 1 | **The incidence of anorexia nervosa**

Study (year)	Timeframe	Sample	Location	Estimates (95% CI)	Refs
van Son *et al.* (2006)	1995–1999	Primary care register*	Netherlands	7.7 (5.9–10) per 100,000 person-years‡	23
Keski-Rahkonen *et al.* (2007)	N/A	Female twins; 15–19 years of age	Finland	270 (180–360) per 100,000 person-years§ 490 (370–610) per 100,000 person-years‖	22
Micali *et al.* (2013)	2000–2010	Primary care register; 10–49 years of age	United Kingdom	7.9 (6.8–9) per 100,000 per year‡	1
Zerwas *et al.* (2015)	1989–2006	National patient register; 6–24 years of age	Denmark	18.1 (17.2–19) per 100,000 person-years‡,§ 26.3 (25.3–27.4) per 100,000 person-years‡,‖	24
Hoek *et al.* (2005)	1995–1998	Health care records and providers*	Curaçao	1.82 (0.74–2.89) per 100,000 person-years	27

N/A, not applicable. *Age range not reported. ‡Age-adjusted and sex-adjusted. §Strictly defined anorexia nervosa (with amenorrhoea). ‖Broadly defined anorexia nervosa (without amenorrhoea).

Table 2 | **Lifetime prevalence of anorexia nervosa**

Study (year)	Sample	Location	Estimates (%; 95% CI)	Refs
Keski-Rahkonen *et al.* (2007)	Female twins; 15–19 years of age (*n* = 2,881)	Finland	2.2 (1.6–2.7)* 4.2 (3.4–5)‡	22
Wade *et al.* (2006)	Female twins; 28–39 years of age (*n* = 1,002)	Australia	1.9 (1.1–2.7)* 4.3 (3–5.6)‡	34
Bulik *et al.* (2006)	Adult twins (*n* = 31,406)§	Sweden	0.36 (0.29–1.43)* 0.64 (0.55–0.735)‡	31
Preti *et al.* (2009)	Community-dwelling adults; >18 years of age (*n* = 4,139)	Europe	0.48 (0.3–0.8)	32
Hudson *et al.* (2007)	Community-dwelling adults; >18 years of age (*n* = 2,980)	United States	Total: 0.6 (SE: 0.2) Females: 0.9 Males: 0.3	33
Swanson *et al.* (2011)	Community-dwelling adolescents; 13–18 years of age (*n* = 10,123)	United States	Total: 0.3 (SE: 0.06) Females: 0.3 Males: 0.3	35
Stice *et al.* (2009)	School-based sample of females; 20 years of age (*n* = 496)	United States	0.6 (0–1.2)	36
Smink *et al.* (2014)	Community-dwelling adolescents; 19 years of age (*n* = 1,584)	Netherlands	Females: 1.7 (1–2.9) Males: 0.1 (0–0.8)	39
Kjelsas *et al.* (2004)	School-based sample of adolescents; 14–15 years of age (*n* = 1,960)	Norway	Females: 0.7‖ Males: 0.2‖	38
Nobakht and Dezhkam (2000)	School-based sample of adolescent females; 15–18 years of age (*n* = 3,100)	Iran	0.9‖	37

SE, standard error. *Strictly defined anorexia nervosa (with amenorrhoea). ‡Broadly defined anorexia nervosa (without amenorrhoea). §Age range not reported. ‖95% CI not reported.

Altered brain structure. Research on brain structure in AN has been inconsistent[60]. Some hypotheses have been proposed based on recent brain research, but require specific testing. For example, given that the orbitofrontal cortex controls when to stop eating, regulating the so-called sensory-specific satiety[61], a larger orbitofrontal gyrus rectus in individuals with eating disorders could 'enable' a person to stop eating before his or her physiological needs are met. Another hypothesis states that body image distortion in patients with AN could derive from abnormal functioning of the insula, the area of the brain that integrates interoceptive awareness[62].

Early studies reported reduced grey matter and white matter volumes in patients with AN, which tended to normalize with recovery[60]. Similarly, cortical thinning in ill patients with AN remitted with long-term recovery[63]. However, these results were not adjusted for age, overall brain volumes, AN type (restricting-type versus binge–purge AN), co-morbid diagnoses, medication use, hydration status, severity of starvation state or excessive exercise[56]. A recent study in a nutritionally highly controlled environment, which took these factors into account, demonstrated larger left medial orbitofrontal cortex grey matter volumes in those with AN who were in the ill state and after recovery in adult and adolescent patients[64,65]. In addition, people who were ill with or had recovered from AN had increased right insula grey matter volumes compared with healthy controls[64,65]. These findings across disease states and age groups suggest that alterations in brain development might be traits of AN.

White matter integrity (the so-called fractional anisotropy) has been studied in patients with AN using DTI (TABLE 3). Specifically looking at the fornix, which is part of the limbic system involved in reward processing, emotion and feeding regulation as well as behaviour extinction, three studies (reviewed in REF. 66) in patients with acute full syndrome AN showed reduced fornix white matter integrity. However, the clinical significance of these findings is, as yet, uncertain.

Altered brain function. Neurotransmitter receptor imaging studies using PET have assessed the 'functional availability' of neurotransmitter receptors in the brain — specifically, the serotoninergic (involved in inhibition, anxiety and eating regulation) and dopaminergic (involved in reward, motivation and learning) systems. These studies have found increased serotonin 1A (also known as 5-hydroxytryptamine 1A (5-HT_{1A})) receptor binding in ill and recovered patients; recovered patients also showed reduced 5-HT_{2A} receptor binding, but normal 5-HT transporter binding across widespread cortical areas (TABLE 3). These results might indicate that 5-HT_{1A} and 5-HT_{2A} receptor expression are altered before illness is apparent (that is, premorbid) or as a result of the illness, but that the 5-HT_{2A} receptor is affected by food restriction. One study in individuals with AN found increased dopamine D2 receptor binding after recovery[67]. Importantly, most of those studies found a positive correlation between both serotonin and dopamine receptor binding and harm avoidance, suggesting that these receptors could be mechanistically involved in driving increased anxiety in individuals with AN. Furthermore, animal studies have shown that malnutrition can decrease or increase serotonin and dopamine receptor expression[68], and it remains to be determined whether altered neurotransmitter receptor expression is a premorbid vulnerability for developing AN. An alternative hypothesis is that individuals who develop AN are particularly sensitive to neurotransmitter expression or sensitivity in the context of food restriction.

fMRI studies using exposure to high-calorie versus low-calorie visual food cues have also revealed different patterns of limbic and paralimbic activation, which are associated with salience and reward processing, between people with AN and healthy controls[69]. One study in restricting-type AN used chocolate milk as a taste stimulus, and produced greater activation in the amygdala and medial temporal gyrus than in controls; this was associated with heightened vigilance and anxiety[70] (TABLE 3). Individuals who had recovered from AN showed a reduced functional brain response to repeatedly given — but increased response to randomly given — sugar solutions[71–73]. Furthermore, some studies investigated

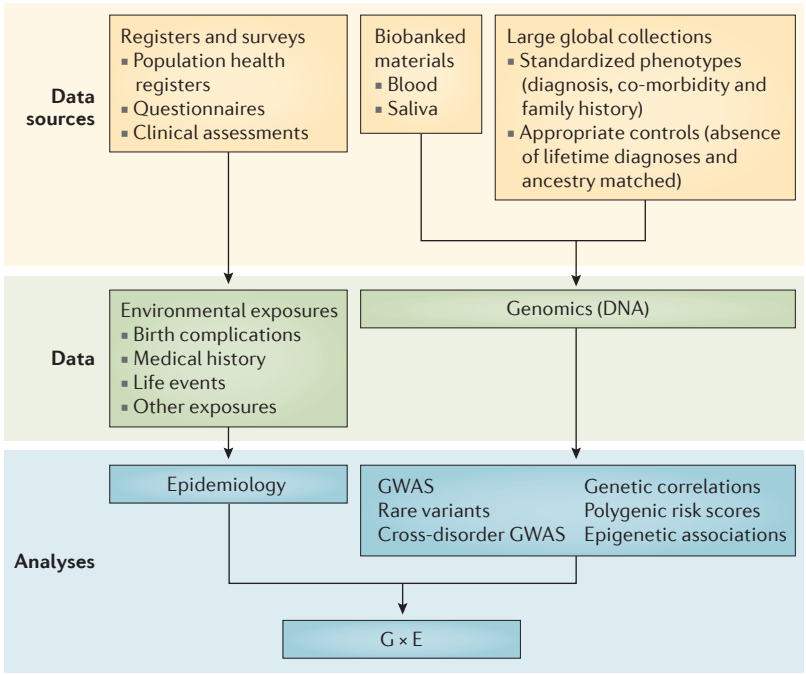

Figure 2 | **Discovery science in anorexia nervosa.** Genomic discovery science is designed to identify genes that influence the risk for particular disorders. To identify common genetic variants of small effect involved in anorexia nervosa, large samples of cases and ancestrally matched controls are required. The inclusion of genomic and environmental data enables the elucidation of genetic and environmental (G × E) mechanisms of risk. GWAS, genome-wide association studies.

whether alterations in the brain's reward system are limited to taste or food reward, or whether these are pervasive and apply to monetary reward stimuli. Those studies tended to show increased brain response in the ventral and dorsal striatum to win or loss, which, in part, tests 'unexpectancy' response; one study showed reduced response in the dorsolateral prefrontal cortex to delaying a monetary reward[74–77]. Overall, it seems that heightened reward system responsiveness to unexpected stimuli is associated with AN, whereas the opposite might be the case for salient stimuli when they are expected. The interaction between higher-order cognitive–emotional limbic and basal ganglia reward circuit function is not yet well understood. However, it is possible that when stimuli are expected but feared, top-down control could modulate reward response to maintain a sense of control. By contrast, when stimuli are unexpected, they might lead to a strong, subjectively uncontrolled, reward system response that might reinforce anxiety.

Studies testing a dopamine-related conditioning task (unexpected receipt or omission of sweet taste) revealed greater activation in the ventral striatum, insula and frontal cortex in ill patients with AN than demonstrated in individuals with bulimia and obesity compared with controls[78,79]. This finding suggests heightened dopamine-related reward system sensitivity in individuals with AN, but reduced responsiveness in bulimia and obesity, which is consistent with basic research findings that show restrictive food intake increases and excessive eating increases dopamine reward circuit function[80,81].

Functional networks and brain–body integration. Various functionally connected brain networks have been identified that drive behaviour, including the default mode network (DMN), which includes the prefrontal, posterior cingulate and parietal cortices; the salience network, which includes the insula and the anterior cingulate cortex; the executive network (including the dorsolateral prefrontal and parietal regions); and the sensorimotor network (SMN; including the sensorimotor association and the motor and middle-frontal cortices). Anomalies in the salience network have been found in patients with AN. For instance, during a task that presented visual food cues, patients with AN demonstrated significant interactions between the left anterior insula and the right insula and the right inferior frontal gyrus compared with controls[82], indicating heightened excitability that is potentially related to expectation and fear. In another study, patients with full syndrome AN and those who had recovered from AN showed reduced salience network activity compared with controls during a taste conditioning task, which could be a trait-related biomarker altering the basic orientation to salient stimuli — including the drive to approach food[83]. Individuals with acute full syndrome AN, but not those recovered from AN, also had reduced DMN and SMN activity, suggesting state-dependent abnormalities[83]. However, reduced DMN and SMN activity might be related to altered interoception and body image in individuals with AN in the underweight state.

fMRI studies examining brain responses to paradigms that include body perception or cognitive and emotional components of body image have found altered activation across the prefrontal and parietal cortices, insula, amygdala, ventral striatum, extrastriate body area, precuneus and fusiform gyrus[84]. However, the research hitherto is fragmented; how these areas map onto the functional networks described above needs further study. Importantly, the mechanism by which the extremes of body distortion are driven, and by which circuitry, is not known yet. Whether these regions of the brain could be targets for novel treatment is also unclear.

Diagnosis, screening and prevention

Diagnostic criteria

Although the core features of AN (BOX 1) have not changed much over the different iterations of diagnostic criteria, there have been some recent changes to specific criteria in DSM-5 (REF. 3). In seeking to ascertain whether the current criteria for the condition are met, it is important to understand the rationale for these changes. First, the criterion relating to low weight status has been reworded such that low weight is not defined by one particular number[85]. In the past, the use of specific cut-off values resulted in some diagnostic decisions that were not clinically useful or meaningful. DSM-5 now defines low weight as less than minimally normal in adults, or that minimally expected in children and adolescents. For adults, low weight would typically mean a BMI of <18.5; for children and adolescents, a BMI-for-age of <5th percentile denotes low weight.

Second, individuals are no longer required to articulate a fear of weight gain because of the challenges in eliciting this information. In particular, children and younger adolescents often experience difficulty verbalizing the motivation for their eating restriction[85]. Instead, the DSM-5 suggests using evidence of weight-gain-interfering behaviour to make a diagnosis.

Last, the requirement for amenorrhoea has been eliminated, enabling diagnosis of AN in males, in adolescents who have not yet reached menarche, in individuals who continue to menstruate despite severe emaciation and in women who use exogenous reproductive hormones[85]. This change is also based on a large body of accumulated evidence showing no meaningful clinical differences between women with AN who menstruate and those who do not[86,87].

Co-occurring characteristics. Several laboratory abnormalities can be observed in the presence of AN[3,88] (BOX 1), and biomarkers for nutritional and cardiovascular decompensation (poor functioning) can also be assessed[89]. BMI is generally not considered a useful index of nutritional compromise[6] given the influence of many other co-occurring events, such as purging, binge eating, water retention and co-morbidities associated with other medical disorders. Although many of the physiological abnormalities that accompany AN are reversible with nutritional rehabilitation, AN that occurs during childhood and adolescence can permanently disrupt optimum growth and development, resulting in dental problems, growth retardation, osteoporosis and fertility problems[88,89].

Psychiatric co-morbidity with AN has been described as the rule rather than the exception[89], and clinicians can commonly observe co-occurring depressive symptoms, personality disorders, anxiety disorders, suicidality (suicidal ideation and attempted or completed suicide), self-harm, obsessive–compulsive disorder, social phobia and autistic traits of clinical significance in terms of repetitive and stereotyped behaviour[90–94]. Successful nutritional rehabilitation can resolve some of this co-morbidity, but premorbid vulnerabilities might also be present and persist until after recovery. For example, an investigation of weight-restored adolescent-onset patients with AN at 10-year follow-up showed an over-representation of Cluster C personality disorders (displaying patterns of anxious and fearful behaviour) and autism spectrum disorders compared with healthy controls[94], with 16% of the AN group experiencing persistent problems with social interaction and obsessive–compulsive behaviours from childhood into early adulthood.

Endophenotypes or intermediate phenotypes, some of which can present before the onset of AN, might also be viewed in unaffected family members and remain after recovery[95]. Increased perfectionism (including striving for high standards and a need for order)[67,96], weak set shifting (reduced mental flexibility as indicated by the ability to move back and forth between tasks)[95,97], weak central coherence (a bias towards focusing on detail at the expense of seeing the general picture)[97], a sensitivity to praise and reward[96] and anxiety sensitivity or harm avoidance have all been suggested to be endophenotypes of AN.

Factors that can hinder diagnosis. AN has often been described as ego-syntonic because patients experience their symptoms as congruent with their own values, for example, self-control, mastery and perfection[98]. Accordingly, most patients respond negatively to suggestions that they are ill and express ambivalence about their symptoms — hence the early description of a patient by Lasègue in 1873 (REF. 99) that "not only does she not sigh for recovery, but she is not ill-pleased with her condition". This impaired insight (also known as a lack of recognition of the illness and denial) is more marked in patients with restricting-type AN, with 44% having impaired recognition of the illness compared with 25% of patients with the binge–purge type[100]. This impaired recognition influences the diagnosis of AN and has three implications for the assessment process.

First, general psychiatric assessment tools that have skip rules (that is, once a negative answer is obtained for a probe question, the remaining questions related to the diagnosis are not asked), such as the Composite International Diagnostic Interview[101], should not be used as they have been shown to underdiagnose eating disorders[20,102]. More than one-third of people with an eating disorder demonstrate symptoms that would have been missed if skip rules had been used and this uncaptured symptom pattern is associated with increased psychosocial impairment[20]. Instead, the use of eating-disorder-specific assessment tools is recommended, such as the Eating Disorder Examination[103] (BOXES 1,2).

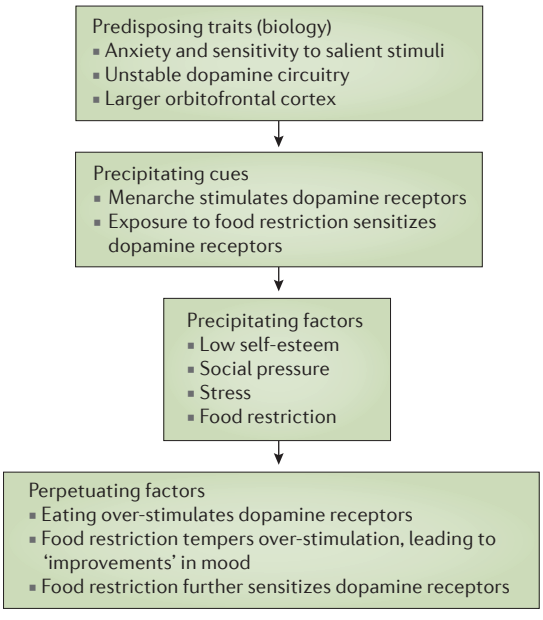

Figure 3 | **A neurobiological model for the development of anorexia nervosa.** Interplay between predisposing, precipitating and perpetuating neurobiological factors account for the onset and maintenance of anorexia nervosa.

Second, particularly with children and adolescents, it is helpful to have multiple informants. Parents and adolescents have been found to be largely discordant on symptom reports (variability, $\kappa < 0.3$), with parents generally less likely to report bulimic symptoms than the adolescent but more likely to report behaviours related to thinness[19].

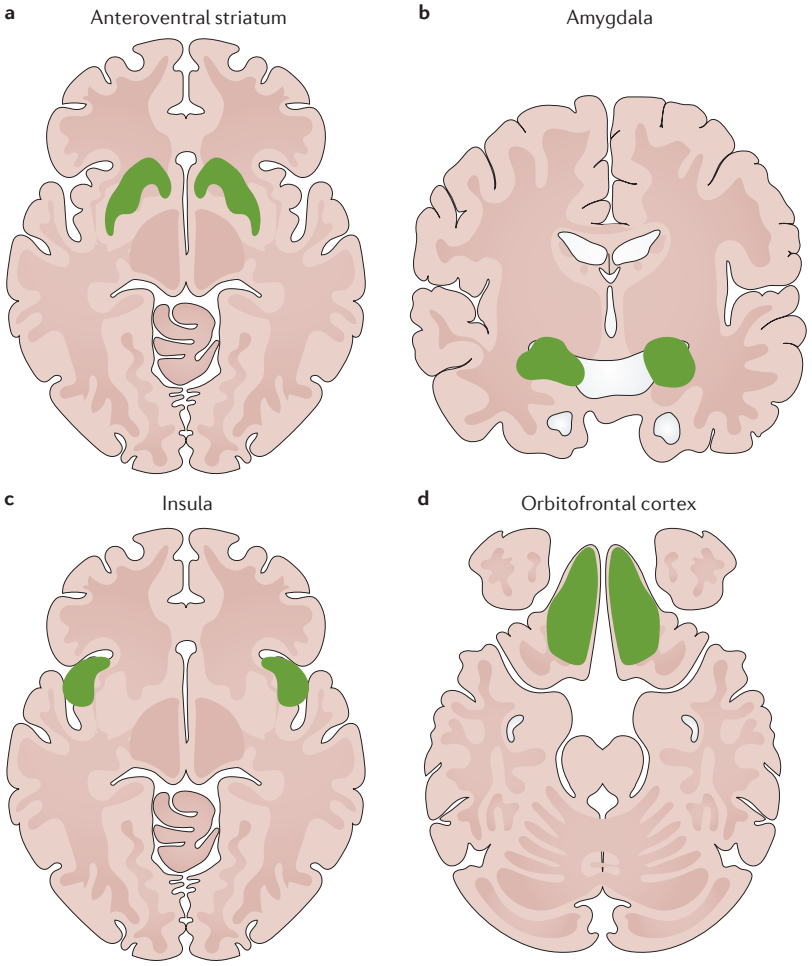

Figure 4 | **The neural circuits associated with reward.** **a** | The striatum contains both dopamine and opioid receptors and is involved in reward approach and motivation (wanting), as well as hedonic experience (liking). The ventral striatum has shown increased response during dopamine-related reward tasks (prediction error), suggesting a hyper-responsive dopamine system[78], as well as increased or decreased response in monetary reward paradigms[74,75,77]. **b** | The amygdala is associated with fear and anxiety; it is here that the association between stimulus and emotion is processed. The amygdala is also thought to activate midbrain dopaminergic cells. One study showed that amygdala activation was higher in those with anorexia nervosa (AN) than in control individuals during hunger when receiving chocolate milk (taste stimulus)[70]. **c** | The insula is the primary taste cortex and the gateway to higher-order cognitive and emotional taste processing. In ill and recovered patients with AN, insula response has been shown to be increased to unexpected taste stimuli receipt[71,78] but reduced to repeated application of sweet stimuli[72]. Both adult and adolescent individuals with AN have increased right-sided insula volume, indicating structural alterations that could interfere with normal taste processing and interoception. **d** | The orbitofrontal cortex is important for reward value computation and when to stop eating a certain food (sensory-specific satiety). In addition, the orbitofrontal cortex fine tunes ventral striatal dopamine activation. Left-sided orbitofrontal cortex volume has been shown to be enlarged in adult and adolescent patients with AN, which could indicate altered satiety regulation in AN[64,65].

Third, the use of motivational interviewing techniques can elicit more information than a series of closed questions[104]. Motivational interviewing was developed for use in addictions that are also characterized by ambivalence but, instead of acceptance of the patient's autonomy over a decision to change, motivational interviewing with AN recognizes that many patients lack the capacity to make autonomous decisions because of their age or their debilitation caused by starvation[104].

Prevention

Only three prevention programmes have been shown to significantly reduce the symptoms of AN (according to DSM-IV)[105–107], and only three have significantly reduced future eating disorder onset in randomized trials[106–108]. A group-based prevention programme that used mindfulness (that is, increased awareness and acceptance of experience in the present moment) techniques to promote body acceptance delivered during weekly 1-hour meetings for 3 weeks produced reductions in eating disorder symptoms compared with those who underwent assessment only, but the effects were no longer significant after 1 month and 6 months of follow-up[105].

Another multifaceted intervention involved lectures, e-mail messages and social media campaigns that focused primarily on enhancing self-esteem and self-efficacy. The programme was delivered over a 1-year period to female and male athletes 13–15 years of age, producing a reduction in eating disorder symptoms relative to assessment-only controls for the female athletes, although effects did not persist over a 9-month follow-up, and reduced future onset of eating disorders over a 9-month follow-up for female atheles[108].

A group-based prevention programme — the Body Project (BOX 3) — in which adolescent girls and young women discuss through Socratic questioning the costs of pursuing the thin ideal espoused for women in the media was designed to produce cognitive dissonance about pursuing this ideal. The results included greater reductions in eating disorder symptoms and future eating disorder onset relative to assessment-only controls and alternative interventions in efficacy and effectiveness trials, with several effects persisting through 3 years of follow-up assessment in three trials[106,109–111]. Furthermore, completion of high-dissonance versions of this programme resulted in greater symptom reductions than completion of low-dissonance versions[112,113].

Another group-based prevention programme is the Healthy Weight intervention, in which adolescent girls and young women make participant-driven gradual reductions in dietary intake and increases in physical activity in an effort to balance energy intake with expenditure. The programme is delivered in three or four 1-hour meetings and has been shown to produce significant reductions in eating disorder symptoms and future eating disorder onset relative to assessment-only controls and alternative interventions, with several effects persisting through a 3-year follow-up[106,107,114]. FIGURE 5 shows the hazard curves that illustrate the reduction in eating disorder onset over follow-up for the Body Project and the Healthy Weight programmes. Notably,

Table 3 | **Summary of key findings from neuroimaging studies in anorexia nervosa**

Target or test	Anorexia nervosa population (*n*)*	Healthy controls (*n*)	Findings	Refs
PET				
Cannabinoid 1 receptor	Ill patients (14)	19	Increased receptor availability in the insula, and frontal and temporal cortices	220
Dopamine D2 receptor	Ill patients (21)	25	No difference	221
Dopamine D2 receptor	Recovered patients (10)	12	Increased receptor availability in the anteroventral striatum	222
Histamine H1 receptor	Ill patients (12)	12	Increased receptor availability in the amygdala and basal ganglia	223
5-HT_{1A} receptor	Ill patients (8) Recovered patients (9)	7	Increased receptor availability in the temporal, frontal and parietal cortices	224
5-HT_{1A} receptor	Ill patients (15)	29	Increased receptor availability in the temporal, frontal and parietal cortices and in the midbrain raphe	225
5-HT_{1A} receptor	Recovered patients (13)	12	Increased receptor availability in the temporal, frontal and parietal cortices and in the midbrain raphe	226
5-HT_{2A} receptor	Ill patients (15)	29	No difference	225
5-HT_{2A} receptor	Recovered patients (10)	16	Decreased receptor availability in the cingulate, parietal and occipital cortices	227
5-HT_{2A} receptor	Recovered patients (16)	23	Decreased receptor availability in the cingulate cortex, amygdala and hippocampus	228
5-HT transporter	Recovered patients (18)	10	No group difference compared with controls	229
Functional MRI				
Taste reward	Recovered patients (14)	14	Decreased blood flow in the insula during repeated sucrose intake	72
Taste reward	Recovered patients (15)	16	Increased blood flow in the ventral striatum in response to unexpected pleasant taste, and increased blood flow in the insula and putamen in response to unexpected aversive taste	71
Taste reward	Ill patients (21)	23	Increased blood flow in the ventral striatum and insula in response to unexpected conditioned sucrose (prediction error signal)	78
Taste reward	Ill patients (12)	12	Increased blood flow in the amygdala and temporal cortex in response to chocolate milk when hungry, and increased blood flow in the temporal cortex in response to chocolate milk when sated	70
Monetary reward	Recovered patients (30)	30	Increased blood flow in the dorsolateral prefrontal cortex during reward anticipation and feedback	76
Monetary discounting	Ill patients (30)	22	Decreased blood flow in the striatum and anterior cingulate cortex that normalizes with treatment	75
Monetary reward	Ill patients (10)	12	Increased blood flow in the striatum during monetary loss	74
Monetary reward	Recovered patients (13)	13	Increased blood flow in the caudate nucleus during win and loss feedback	77
Diffusion imaging				
DTI and DWI	Recovered patients (24)	24	Increased structural connectivity between the insula and the striatum and orbitofrontal cortex, and decreased fractional anisotropy in the anterior corona radiata, exterior capsule and cerebellum	230
DTI	Ill patients (19)	19	Decreased fractional anisotropy in the fornix and superior longitudinal fasciculus	231
DTI	Ill patients (17)	18	Decreased fractional anisotropy in the cerebellum, and decreased mean diffusivity in the fornix	232
DTI	Ill patients (19)	22	Decreased fractional anisotropy in the fornix, and the posterior frontal and parietal lobes	64
DTI	Recovered patients (12)	10	No difference	233
DTI	Ill patients (12) Recovered patients (9)	20	Decreased fractional anisotropy in the thalamic radiation	234
DTI	Ill patients (16)	17	Decreased fractional anisotropy in the fornix, fronto-occipital fasciculus and cingulum	235

5-HT, 5-hydroxytryptamine (also known as serotonin); DTI, diffusion tensor imaging; DWI, diffusion-weighed imaging. *Recovered is typically defined as normal weight and eating patterns for ≥1 year, regular menstrual cycles (in women) and no excessive exercising.

participants who completed the Body Project and the Healthy Weight intervention showed lower rates of onset of threshold and subthreshold AN than assessment-only controls, paralleling the reductions observed in threshold and subthreshold bulimia nervosa (E.S., unpublished observations). Furthermore, onset of threshold or subthreshold binge-eating disorder was lower for participants who completed the Healthy Weight intervention relative to assessment-only controls, but participants in the Body Project programme did not show reductions in onset of binge-eating disorder relative to controls.

Adapted versions of the Body Project programme are currently being implemented in more than 150 high schools and universities in the United States and in 112 other countries through the Girl Guides and Girl Scouts organizations. The Body Project programme has also been implemented successfully in primary care settings[115]. Most often, the Body Project programme has been implemented in a selective manner to young women with or without body image concerns. However, a version of the Body Project programme that was adapted for homosexual males, who are at increased risk for eating disorders, has also produced significant reductions in eating disorder symptoms[116].

Box 1 | **Description and diagnosis of anorexia nervosa**

Core features

- Behavioural disturbance related to eating or weight control practices that leads to a significantly low body weight
- Disturbance in the experience of body shape and/or weight
- Disturbance results in substantial impairment in physical, social and/or mental functioning
- Disturbance is not secondary to any other medical or psychiatric disorder

Possible laboratory abnormalities

- Endocrine: low serum oestrogen (female) or testosterone (male) levels; and low-to-normal thyroid hormones levels (T3 and/or T4)
- Haematological: mild leukocytopenia with apparent lymphocytosis; anaemia; and thrombocytopenia
- Cardiovascular: abnormalities on echocardiogram; sinus bradycardia; and significant prolongation of the QTc interval
- Gastrointestinal: delayed gastric emptying; and decreased colonic motility (with laxative use)
- Other abnormalities: electrolyte disturbance; significantly increased osteopenia, osteoporosis and risk of fracture; pseudoatrophy (enlarged cerebral ventricles and external cerebrospinal fluid spaces); reduction in resting energy expenditure; dehydration; and hypercholesterolaemia

Selected open resources for assessment

- Eating Disorder Examination (EDE) 17.0D: a semi-structured interview for *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) eating disorder diagnoses and a self-report version (EDE-Q) (http://www.credo-oxford.com/7.2.html)
- The Structured Inventory for Anorexic and Bulimic Eating Disorders: available as a structured clinical interview for experts (SIAB-EX) and as a self-rating questionnaire (SIAB-S) (http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/en/forschung/epidemiologie/AssessmentInstrumentsOfEatingDisorders/Inventory.html)
- Munich Eating Disorder Questionnaire and the Anorexia Nervosa Inventory for self-rating (Munich ED-Quest): http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/en/forschung/epidemiologie/AssessmentInstrumentsOfEatingDisorders/Questionaire.html
- The Eating Disorder Assessment for DSM-5 (EDA-5): for feeding or eating disorders or related conditions according to the DSM-5 criteria (https://modeleda5.wordpress.com/?ref=spelling)
- Anorexia Nervosa Inventory for Self-rating (ANIS): http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/en/forschung/epidemiologie/AssessmentInstrumentsOfEatingDisorders/Anorexia.html

Screening

Early identification and intervention for AN is important because treatment is often more effective in individuals who have had the disorder for a shorter period of time than for those who have had the disorder for longer. Of the several self-report eating disorder symptom screening questionnaires, only the Eating Disorder Diagnostic Screen provides provisional eating disorder diagnoses; this self-report measure has shown good agreement with the Eating Disorder Examination diagnostic interview (BOX 2). The fact that this questionnaire is short (1 page) should facilitate broad screening at schools during adolescence and young adulthood, which are the periods during which AN most typically emerges.

Recent findings also suggest that it might be fruitful to target youth who are at risk for future AN with eating disorder prevention programmes that are specifically tailored for AN. Two prospective studies have shown that preadolescent and adolescent females with a low BMI show increased future onset of diagnostic interview-confirmed AN[117,118], opening up the possibility of targeting youth who are at increased risk for AN with a selective prevention programme. No other risk factors have been shown to robustly predict future-onset AN. The only risk factors that have been found to predict the future onset of bulimia nervosa, binge-eating disorder and purging disorder — which include perceived pressure to be thin, thin-ideal internalization, body dissatisfaction, negative affect and social support deficits[117,119–124] — imply that it might be necessary to develop qualitatively different selective eating disorder prevention programmes for AN compared with binge-eating and purging disorders.

Management

Evidence-based medicine is built from three perspectives: scientific data from high-quality trials, clinical expertise and patient preference[125]. Clinical expertise plays an important part in the management of patients with AN because several dimensions need to be considered to build a management plan. Physical health, medical risk, the stage (duration) of illness, age, co-morbidity and psychosocial context are of key importance[13]. Interventions need to be mapped onto the needs of the individual and their family with these facets in mind. Both the proposed WHO *International Classification of Diseases*, 11th Revision (ICD-11) and the DSM-5 criteria for AN recommend severity qualifiers to decide the type of intervention to use based on weight status because very low weight is a prognostic factor associated with increased mortality (a BMI of <17.5 kg per m^2 increases risk, but a BMI of <11.5 kg per m^2 sharply increases the mortality risk). However, weight-based markers alone do not suffice, and a multisystem assessment to measure mortality risk and resilience is required. Factors that

Box 2 | **Eating Disorder Examination diagnostic interview probes***

- 1. Over the past 4 weeks, have you felt fat? If yes, how many days out of each week over the past 4 weeks have you felt fat?
- 2. Over the past 4 weeks, have you been afraid that you might gain weight (or become fat)?
- 3. Over the past 4 weeks, has your weight and/or shape been important in influencing how you feel about yourself as a person (how you judge, think of and evaluate yourself)?
- 4. Over the past 4 weeks, have you done any specific behaviours to avoid gaining weight (such as only eating fruits and vegetables)?

*In addition to these questions, the body mass index at the time of the interview must also be confirmed as <85% of that expected for age and sex.

can be incorporated into such assessments include, but are not limited to, rapid weight loss (especially in children), orthostatic hypotension, bradycardia or postural tachycardia, hypothermia, cardiac dysrhythmia and biochemical disturbance.

Nutritional restoration (re-feeding) is the cornerstone of treatment, which can be reliably attained by admission to a unit with skilled nursing staff to manage meal support. However, for some patients, improved nutrition is often not sustained after discharge, particularly in adults with an enduring form of the illness[18]. Thus, an interest in outpatient psychotherapy has gained favour (see below) for those with a moderate degree of AN severity (for example, a BMI of >15). For adolescent patients, this therapy usually involves the family. For adults, various models of outpatient care are available (often 'borrowed' from those devised to treat other forms of disorder), but no front-runner has yet emerged and the longer-term results have rarely been studied (for more see section below). Those who have failed to respond to outpatient therapy are often offered inpatient care.

There are many unresolved questions about the use of inpatient care that stem from the lack of reliable evidence around the use of the varying available techniques. For example, very little attention has been given to the process of re-feeding. Nutritional and behavioural strategies have often been used in an ad hoc way; therapeutic interventions (nutritional, psychotherapeutic and medical) that are used in inpatient care have been shown in one systematic review not to provide benefit, although most of the included studies were of limited quality[126]. Accordingly, which patients should be admitted for inpatient care and at what illness stage and level of severity this should occur remain unclear. The 'correct' length of stay and target weight for patients are also uncertain. Two recent studies in young adolescents with a short duration of illness indicated that admission with the goal of harm reduction rather than full-weight restoration is probably more cost effective than treatments as usual with longer inpatient stays for weight restoration if there is continued high-quality aftercare (in these studies, day care or family-based therapy (FBT) was used)[127,128]. Results from a multicentre study in the United Kingdom suggest that most treatment units for adults currently practice a harm reduction approach[129], which led to an overall gradual reduction in eating disorder symptoms[130].

Some of the physical consequences of AN also require specific management. For example, patients with multi-organ failure are usually admitted to general hospital care. In the United Kingdom, the Management of Really Sick Patients with AN (MARSIPAN) protocol for adult and adolescent patients describes a management strategy for such patients[131]. Drug or hormone treatments have been used to remediate some of the secondary consequences of starvation, such as osteoporosis (TABLE 4). Three randomized controlled trials (RCTs) have indicated improvement in bone mass density with physiological oestrogen replacement in girls (12–18 years of age)[132] and with recombinant human insulin-like growth factor 1 or risedronate in adults compared with placebo treatment[133]. The use of bisphosphonates in adolescents raises concerns owing to their long half-life and risk of teratogenicity[134]. In addition, one meta-analysis concluded that hormone therapy (such as with growth hormone or oestrogen), which is primarily used to treat low bone density, had a small effect on weight gain. However, this conclusion is uncertain as the risk of bias and heterogeneity within the studies was high[135].

Furthermore, patients and/or caregivers have strong views about what form of treatment is acceptable. For example, in a study comparing inpatient treatment with two forms of outpatient service, a large number of patients (~50%) did not accept inpatient care[136]. In addition, problems with recruitment and retention in studies involving pharmacological interventions led to them being disbanded or restructured[137,138]. Accordingly, the low acceptability of pharmacological treatment translates to the trial results not being representative of the population as a whole.

Psychotherapy

According to international treatment guidelines[139–142], systematic reviews[16] and recent reports[143,144], psychotherapy represents the treatment of choice for individuals with AN. Unlike in adolescents (for whom FBT produces superior results), no specific form of psychotherapy has yet been shown to be superior in adult patients. Accordingly, an approach that combines weight rehabilitation and a specific psychotherapeutic treatment is recommended for adults; for adolescent patients, FBT should be prioritized[140].

Family-based treatment. FBT was designed as a three-phase treatment. 24 1-hour sessions are provided over a 1-year period. Phase I typically includes 8–10, usually weekly, sessions. Here, therapy is characterized by attempts to absolve the parents from the responsibility of causing the disorder and by complimenting them on the positive aspects of their parenting. Families are encouraged to work out for themselves how best to help restore the weight of their child with AN. Phase II (11–16 sessions) involves parents helping to transition eating and weight control back to their child in an age-appropriate manner. Phase III (17–20 sessions) focuses on establishing a healthy relationship between the patient and their parents[145].

Focal psychodynamic psychotherapy. The initial manual version of focal psychodynamic psychotherapy[146] was designed as a 40-hour outpatient programme for moderately ill patients with AN (a BMI of >15 kg per m^2). Given that patients with AN struggle with questions of identity and boundaries, at the beginning of the programme, psychodynamically relevant foci are identified using a standardized diagnostic interview (operationalized, psychodynamic diagnostic interview; OPD-II). The first phase of treatment focuses mainly on therapeutic alliance, pro-anorexic behaviour, ego-syntonic beliefs and self-esteem. In the second phase of treatment, the main focus is placed on relevant relationships and the association between interpersonal relationships and eating (anorexic) behaviour. The pertinent aspects of the third and final phase of focal psychodynamic psychotherapy are the transfer of the interactions between the patient and the therapist to situations of everyday life, anticipation of treatment termination and parting. Before every treatment session, the patient's weight is assessed and documented.

Enhanced cognitive–behavioural therapy. According to Fairburn[147], enhanced cognitive–behavioural therapy (CBT-E) refers to a 'transdiagnostic' personalized psychological treatment for eating disorders. It was developed as an outpatient treatment for adults, but there is a version for day patient and inpatient settings, and a version for younger people. A detailed treatment guide is available[147]. Although CBT-E is a highly individualized treatment, it can be divided into four stages. In stage one, the focus is on gaining a mutual understanding of the person's eating problem and helping him or her to modify and stabilize their pattern of eating. In the brief, second stage, progress is systematically reviewed and plans are made for the main body of treatment. Stage three focuses on the processes that are maintaining the person's eating problem (such as addressing concerns about shape and eating). In stage four, the emphasis shifts to the future, in which there is an emphasis on dealing with setbacks and maintaining the changes that have been achieved.

Specialist supportive clinical management. Specialist supportive clinical management (SSCM) was designed as an active comparison treatment in a clinical trial to be delivered by therapists with expertise in the treatment of eating disorders and to provide a standardized form of usual outpatient treatment[148]. SSCM combines clinical management — that is, the giving of information, advice and encouragement — with a supportive therapeutic style, and is designed to build a positive therapeutic relationship and to foster change. Therapy content includes the assessment, identification and regular review of target symptoms, psychoeducation, monitoring of physical status, establishing a goal weight range and nutritional education and advice. The aim is to help patients make a link between their clinical symptoms and their abnormal eating behaviour and weight, and to support patients in a gradual return to normal eating and weight. Additional therapy content is determined by the patient.

Maudsley Model of Anorexia Treatment for Adults. The Maudsley Model of Anorexia Treatment for Adults (MANTRA) is an empirically based cognitive–interpersonal treatment, which proposes that four broad factors linked to underlying obsessional and anxious–avoidant personality traits are central to the maintenance of AN[143]. These factors are: a thinking style characterized by inflexibility, excessive attention to detail and fear of making mistakes; impairments in the socio-emotional domain (for example, avoidance of emotional experience, regulation and expression); positive beliefs about how AN helps the person in their life; and unhelpful responses of close friends and family (for example, over-involvement, criticism and accommodation to symptoms). These factors are targeted in treatment with the aim of improving weight, eating disorder and other symptoms and psychosocial adjustment. The treatment style is motivational and centred around a patient manual. MANTRA has core (formulation) and optional modules, such as one on building a 'non-anorexic' identity, but individual tailoring of treatment arises from flexibility on how modules are combined and how much emphasis they are given. Nutrition and other symptom management, information on behavioural changes and advice are given if the patient is motivationally ready for this. Differences from other treatments include that this model was developed specifically for AN, is based on biological and psychological research and is tailored to characteristic temperamental traits that are evident in those with AN. It is unique in its use of a patient work-book, developed by patients and therapists. MANTRA is also unique in its involvement of carers in both the formulation of the strategy and the treatment delivery. Separate carer materials (based on the model) are available[143].

Box 3 | **The Body Project group-based prevention programme**

- Session 1: participants collectively define the thin appearance ideal promoted for women in western cultures, discuss costs of pursuing this ideal and are assigned home exercises. Exercises include writing an essay about the costs associated with pursuing the thin ideal and standing in front of a mirror with minimal clothing and recording positive attributes about their bodies
- Session 2: participants discuss the costs of pursing the thin-ideal essay and the body acceptance mirror home exercise, dissuade facilitators from pursuing the thin ideal in role-plays and are assigned additional exercises. These exercises include writing a letter describing the adverse effects to someone who pressured the participant to be thin and generating a 'top 10' list of things young women can do to challenge the thin ideal
- Session 3: participants discuss letter writing and the top 10 home exercises, conduct role-plays that challenge the thin-ideal statements, discuss personal body image concerns and are assigned home exercises. The exercises include engaging in a behaviour that challenges their body image concerns, engaging in two activities that challenge the thin ideal and writing a letter to a younger self about how to avoid body image concerns
- Session 4: participants discuss behavioural challenge, body activism and the letter to their younger self home exercises, discuss how to respond to future pressures to be thin, discuss perceived benefits of the group and are assigned exit home exercises. Exit home exercises include committing to doing a self-affirmation activity that will promote body acceptance, encouraging other women to complete the Body Project intervention and participating in some type of body activism activity as a group

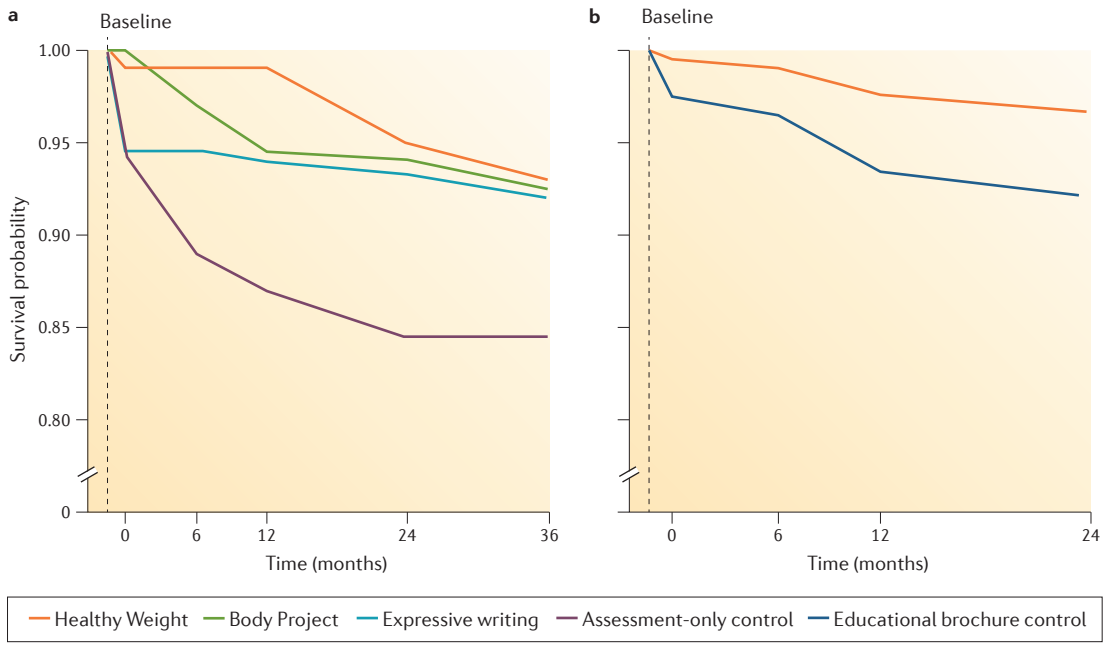

Figure 5 | **The effect of prevention programmes in individuals with anorexia nervosa. a** | A significant reduction in eating disorder onset for participants in the Body Project and Healthy Weight eating disorder prevention programmes is evident relative to participants in the assessment-only control group[106]. However, participants who took part in an expressive writing intervention did not differ significantly from the experimental interventions, and this approach was also more effective than assessment only. **b** | A significant reduction in eating disorder onset is evident for participants in the Healthy Weight eating disorder prevention programme over a 2-year follow-up relative to the educational brochure control condition from REF. 107.

Evidence base in adolescents. In total, 12 RCTs have compared different psychological treatments, summarizing information from 1,060 adolescent patients ≤18 years of age. A 2015 systematic review concluded that there is clear and growing evidence supporting the efficacy of FBTs in adolescents with AN[16].

Adults and late-stage illness. Overall, 12 RCTs ($n = 1,157$) have compared different psychological treatments in adult patients with AN (>18 years of age) in outpatient settings. The AN Treatment Outpatient (ANTOP) study, the largest outpatient multicentre study to date, demonstrated some evidence for the effectiveness of FPT and CBT-E[144,149]. One trial demonstrated that by the end of treatment, SSCM was superior to cognitive–behavioural therapy and interpersonal psychotherapy[150]. However, a long-term follow-up study did not support the superiority of any treatment[151].

MANTRA has been compared to SSCM in two trials[143,152]. Although overall no significant differences in outcome between groups was evident, patients preferred MANTRA to SSCM, and in those with a more-severe illness, there was greater weight gain in the MANTRA group[143]. A recent RCT of outpatient psychotherapy for the subgroup of patients with SEED-AN[152] supported the efficacy of modifying psychological approaches in long-standing illness such that the focus shifts from weight regain and recovery to improved quality of life.

Families and carers. Given the burden of AN on families and partners, and evidence suggesting that carers' distress and behaviours can (inadvertently) maintain the illness[153], several studies have trialled interventions that target carers of adults with AN. These data show that carer outcomes (distress and unhelpful behaviours) can be improved and that this in turn might positively affect relationships with the patient and patients' clinical outcomes[130,154–156]. Carers are given information about the risk and maintaining factors, particularly those that relate to social functioning. They are taught how to 'step back' from emotionally driven behaviours that maintain the illness (such as criticism, overprotection, accommodating and enabling behaviours). Finally, they are taught skills of positive communication and behaviour change strategies.

Pharmacotherapy

Pharmacotherapy has a secondary role in the treatment of AN and should not be considered as a sole or primary intervention[139–141]. Since the publication of the UK National Institute for Health and Care Excellence (NICE)[141] and American Psychiatric Association (APA)[139] guidelines, extensive reviews covering evidence-based treatments for AN[89,157,158] — including meta-analytic studies on the effects of pharmacotherapy[135] and antipsychotics[159–161] — have been conducted. Updates of the World Federation of Societies of Biological Psychiatry[162]

and the Royal Australian and New Zealand College of Psychiatrists guidelines[140] for eating disorders have also been published.

Drug treatments have been mainly aimed at facilitating weight gain and reducing the core preoccupations and behaviours, or some of the mood or compulsive co-morbidity, in those with AN — either in the acute phase or as a form of relapse prevention after weight restoration[163,164]. The rationale for using psychotropic agents to treat patients with AN is based on the hypothesis that the underlying traits (that is, compulsivity, anxiety and depression) and co-morbidity with mood or obsessive–compulsive disorders might be caused by shared neurobiological and/or genetic risk factors that respond in a similar way to treatment[165–167].

Negative findings have been reported for most agents or classes of drugs (TABLE 4). The available evidence is limited by small, underpowered and time-limited trials. The samples tend to not be stratified by subtypes or co-morbidity, drug compliance is not reported systematically and the attrition rate is high. The initial interest in antidepressant treatment declined after the disappointing findings from studies in acute[168] and maintenance[163,164] phases of the illness. The emergence of second-generation antipsychotics with their potential to modulate serotonergic and dopaminergic imbalance[165] renewed interest in the use of this type of drug. In the past decade, eight RCTs (six of which were placebo-controlled) have tested olanzapine (five RCTs)[169–173], quetiapine (two RCTs)[174,175] and risperidone (one RCT)[176]. However, three meta-analyses have shown that there is insufficient evidence that antipsychotics improve weight gain or reduce core eating disorder symptoms[159–161]. Interestingly, the conclusion from one meta-analysis was that depressive symptoms improved but at the cost of more anxiety[160]. Thus, currently, there is no evidence-based pharmacological treatment that shows long-term benefits for treating AN[140,157,158], although it is possible that a subgroup of patients could benefit in the form of some symptom reduction[161,171].

Clinically, the use of antipsychotic or antidepressant drugs should be balanced for potentially helpful versus harmful effects[177], and patients should be informed and closely monitored. Indeed, their poor nutritional state already renders patients with AN at increased medical risk and more susceptible to the adverse effects of these drugs, such as cardiac risk (prolonged QTc interval), sedation, fatigue, drowsiness, increases in the levels of prolactin, fasting insulin and glucose, or triggered binge eating[140,159,169,173,175,176].

Table 4 | **Evidence base for pharmacological and nutritional treatments in anorexia nervosa**

Treatment*	Weight	Eating disorder psychopathology	Psychological co-morbidity‡	Physical co-morbidity§
Antidepressants (acute phase)				
SSRIs: fluoxetine and citalopram	Negative	Negative	Negative	Lack of evidence
TCAs: clomipramine and amitriptyline‖	Weak	Negative	Negative	Lack of evidence
Antidepressants (relapse prevention)				
SSRI: fluoxetine	Negative	Negative	Weak	Lack of evidence
Antipsychotics (acute phase)				
Olanzapine‖	Weak	Negative	Weak	Lack of evidence
Quetiapine	Negative	Negative	Negative	Lack of evidence
Risperidone‖	Negative	Negative	Negative	Lack of evidence
Nutritional supplements				
Zinc‖	Weak	Lack of evidence	Weak	Lack of evidence
Hormones or drugs to treat osteoporosis¶				
Gonadal steroid replacement‖	Negative	Negative	Weak	Weak
Recombinant human growth hormone‖	Negative	Lack of evidence	Lack of evidence	Negative
Insulin-like growth factor 1‖	Negative	Lack of evidence	Lack of evidence	Weak
Biphosphonates: alendronate‖, risedronate and etidronate	Negative	Lack of evidence	Lack of evidence	Weak

Evidence is based on systematic reviews and meta-analyses of randomized controlled trials (RCTs) or RCTs testing drugs and hormones against placebo or treatment as usual[89,132,134,135,140,157–161,236–240]. The levels are defined according to the Australian National Health and Medical Research Council[241]. Lack of evidence is defined as no RCT reported on the measure; negative is defined as existing RCTs or meta-analyses that do not show improvement; weak is defined as at least one RCT showing some improvement or inconsistent findings among existing RCTs or meta-analyses. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. *Acute phase treatments include trials that enrolled patients who were underweight and presenting the diagnostic features of AN; relapse prevention treatments include trials that enrolled patients who had restored weight to normal standards and improved symptoms of anorexia nervosa and would not, therefore, fulfil the diagnosis any longer, but could relapse within the first years after treatment. ‡Anxiety, compulsivity or depression. §Bone measures used; interventions that improve factors that affect bone turnover and improve bone mineral density or reduce fracture risk were examined. ‖At least one trial included had a mean age of participants of <19 years (mainly adolescents), but most trials have mixed samples of adolescents and adults. ¶Except for REFS 135,236, weight-related variables are not commonly measured in trials as a main outcome but as a measure used to control the potential effects of hormones or drugs in bones that are secondary to nutritional status.

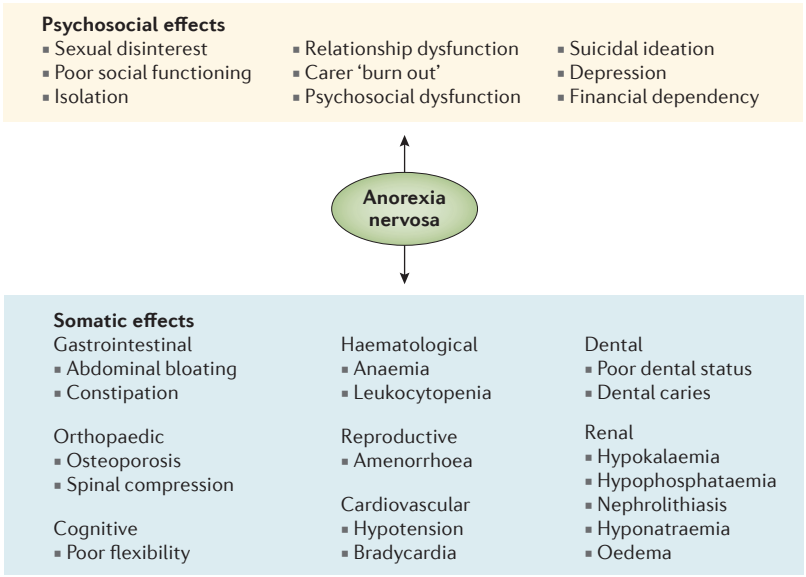

Figure 6 | **Somatic and psychosocial effects of anorexia nervosa affecting quality of life.** Most somatic effects can be observed in the acute phase of anorexia nervosa (AN), and these effects are related to malnutrition and underweight. Spinal compression, an orthopaedic complication secondary to osteoporosis, occurs predominantly among those with a severe and enduring form of AN (SEED-AN). Poor dental status, including enamel lesions and caries, is usually caused by self-induced vomiting and occurs primarily in those with SEED-AN. Psychosocial effects — including psychiatric morbidity, financial dependency and poor social functioning pertaining to nuclear family, potential partner and friends — have greater influence on quality of life in individuals with SEED-AN as opposed to those with acute AN.

There are various possible drug targets within the neural circuits linked to AN that have not been explored. For example, recent research[178] — which revives previous investigation[179] and interest on appetitive effects of stimulation of cannabinoid receptor 1 — examined dronabinol in a small placebo-controlled RCT for patients with enduring-type AN. This study showed a greater increase in weight gain for dronabinol over placebo without an effect on psychological measures of eating disorders or on the development of severe adverse events. It is possible that findings from brain-focused research in AN will identify new targets for drug interventions (for example, glutamate, which could also affect dopaminergic reward systems)[180]. It is also expected that a more-personalized approach can be formulated in the future — guided by potential biomarkers of illness and genetics[157].

Quality of life

Quality of life is a subjective measurement first acknowledged in AN in the mid-1990s[181]; researchers stressed the need for comparable data across different patient groups to evaluate treatments and prioritize health care. Although in the early stage of AN no subjective impairment in quality of life has been documented, in the long term, somatic and psychosocial effects become a more of a handicap (FIG. 6) and this, therefore, becomes a salient treatment goal[182].

The most commonly used generic instrument to measure quality of life is the Short Form-36 Health Survey (SF-36)[183], which has a physical and a mental dimension. The SF-36 profiles of patients with AN are lower — particularly on the mental domain — than the general population[184], and is similar to that measured in clinically depressed patients[185]. Indeed, quality of life in patients with AN corresponds to patients with other forms of eating disorders[184,185]. Severity, chronicity and willingness to change have been found to be reliable prognostic factors that can influence quality of life in AN[186].

The wider psychosocial implications of AN in the long term can be estimated using instruments such as the Morgan–Russell Outcome Assessment Schedule[187] and case registers. Discouraging long-term follow-up data on psychosocial outcome were reported in the 1990s; only half of the individuals had married and a smaller proportion had children than those without AN[188], which are both rough indicators of well-being. Lower birth weight has been observed in the children of recovered patients than in children born to unaffected parents[189]. By contrast, recent reports on reproduction show normal fertility and birth rates in recovered patients[190].

In addition, employment has been demonstrated to be an informative psychosocial outcome measure; register studies have reported that >20% of women and 10% of men with a history of inpatient treatment had financial dependency on society (welfare) at long-term follow-up evaluation[191]. A community-based study found that 25% of female patients had no paid employment owing to psychiatric disability at 18-year follow-up assessment[192]. Furthermore, psychiatric morbidity continued to be prevalent, even if most individuals had recovered from the eating disorder per se. Over the 18-year period, these individuals continued to demonstrate poor results in the psychosexual, social functioning and employment domains. Individuals with the poorest psychosocial outcome also exhibited persistent autism spectrum features[193].

Outcome pertaining to somatic morbidity is important for quality of life. Osteoporosis is a well-known sequelae of AN and can cause painful and aesthetic complications due to vertebral compression[194]. Poor dental status and gastrointestinal morbidity can also influence quality of life[195,196].

The standardized mortality ratio (SMR), which is the ratio of observed to expected deaths, in older reports was >9 in the AN patient population[197], but recent studies report a SMR of ~5 (REF. 198). The mortality rates for AN are much higher than other psychiatric disorders, including schizophrenia and unipolar depression[198]. Older age and low BMI at presentation, alcohol abuse, history of hospitalization and suicidal behaviour are strong predictors of mortality. Indeed, suicide accounts for 20–30% of deaths in those with AN, with the remaining mortality being caused by somatic complications related to (or probably independent of) AN[198].

Outlook

In contemporary western societies, highly palatable food is abundant, obesity is commonplace and to conform to a thin (women) or muscular (men) body ideal suggests

perfection and admirable self-control. Thus, body dissatisfaction in men and women is ubiquitous and starts early in life. Despite these pressures, AN remains relatively rare (compared with other eating disorders), and its incidence and prevalence have not risen as much as those of other eating disorders. This reality suggests the need to look beyond societal or environmental pressures to the underlying biology in order to understand, prevent and treat AN.

Despite recent advances in the classification of AN, we still have a long way to go in terms of achieving the aspiration of the Research Domain Criteria initiative of the US National Institute of Mental Health — to move from a categorical system, based on clinical symptom constellations and descriptions of behaviour, towards a neurobiologically grounded and dimensional classification of eating disorders. With this in mind, several remaining research questions must be addressed in the field that concern all aspects of the illness.

Key questions include whether AN is essentially one condition or whether there are multiple 'anorexias' with different aetiologies, co-morbidities and illness trajectories. For example, differences between binge–purging and restricting-type AN in terms of clinical presentation and outcome have long been recognized, but how and why people switch between these is not well understood. In addition, although different psychological co-morbidities are the norm in patients with AN, we do not know which of these and how strongly these are causally related to the disorder. Despite the typical peripubertal onset of AN, and strong female preponderance, we do not fully understand the role of puberty and sex in the onset. We have a rudimentary understanding of what predicts outcome, in terms of severity of weight loss and illness duration, but we do not know what predicts outcome at an individual level. Finally, and above all, our knowledge in relation to the prevention and treatment of AN remains limited and we do not know what works best and for whom.

At present, psychological therapies are the treatment of choice for people with AN. FBTs for children and adolescents are effective and underscore the importance of intervening at an early stage of the illness. By contrast, interventions for adults with an established illness are much less successful. Encouragingly, the evidence base on treatments for adults is growing, and well-designed large-scale trials of established and novel psychotherapies are emerging[130,143,144]. However, across the age range, little is known about how to sequence and/or combine treatments if initial interventions do not lead to sustained improvement or recovery.

Furthermore, the evidence base on treatments for those with a severe acute form of the illness, who are medically unstable and who require hospitalization

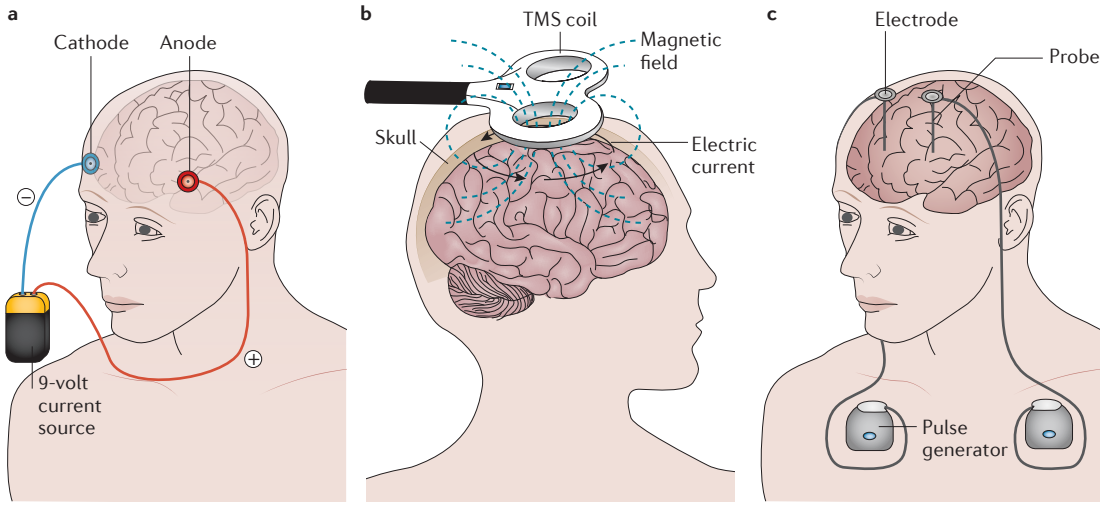

Figure 7 | **Neuromodulation for anorexia nervosa treatment.** **a** | Transcranial direct current stimulation is a non-invasive form of brain stimulation. It involves the application of a low-intensity constant current (1–2 mA) applied directly to the brain through electrodes on the scalp, which is thought to alter the electrical potential of nerve cell membranes. Anodal (+ terminal) stimulation generally has cortical excitatory effects, whereas cathodal (– terminal) stimulation inhibits neural activity. Effects on cortical excitability can last beyond the stimulation period — for up to 90 minutes. Long-term effects seem to operate through modifications of postsynaptic nerve connections, similar to long-term potentiation and long-term depression. **b** | Transcranial magnetic stimulation (TMS) uses an electrical current run through a TMS coil, which emits a magnetic field. When the TMS coil is held up against the head, the magnetic field induces a secondary electrical current (that is, activation of nervous cells) in the targeted brain region. Although TMS refers to the delivery of single electromagnetic pulses with short-lived effects (5–10 ms), repetitive TMS (rTMS) involves the delivery of multiple pulses over a short period of time with effects that outlast the stimulation period (30–60 minutes). Low-frequency rTMS (<5 Hz) is thought to suppress neural activity, but high-frequency rTMS (>5 Hz) is thought to enhance neural activity. **c** | Deep brain stimulation (DBS) is a reversible neurosurgical intervention, in which electrodes are implanted into a defined brain region and a battery-operated pulse generator (usually implanted in the chest) sends electrical pulses to the defined brain region to alter neural activity. Once implanted, the DBS device can be activated and programmed wirelessly, permitting real-time titration of stimulation parameters.

remains extremely limited. How should we optimally treat these high-risk patients? Studies of acutely ill adolescents suggest that 'less may be more', in that alternatives to prolonged inpatient treatment such as brief inpatient stabilization followed by day care treatment[127] or brief inpatient nasogastric re-feeding followed by FBT[128] produced equivalent or better outcomes and at lower cost.

And what about those with SEED-AN who survive in the community and often lead impoverished and lonely lives? Recently, the first ever trial to be conducted in patients with SEED-AN has shown that psychological treatments can significantly improve the quality of life of patients, together with moderate improvements in weight and eating disorder symptoms[152]. More studies that focus on this hard-to-treat population are needed.

Beyond these incremental advances, further progress in prevention and treatment crucially depends on improved understanding of disease mechanisms. The aetiology of the disorder is complex, with evidence for multiple overlapping and distinct environmental and biological risk and maintaining factors for AN and other eating disorders[199]. The past 15 years have witnessed an unprecedented rise of interest in and improved understanding of the neurobiology involved in AN, including for the use of prospective cohort designs to characterize — for the first time — neurocognitive and neural risk factors[200,201] and related behaviours, such as compulsivity[202]. A prominent model, based on neuroimaging and other evidence, suggests that childhood temperament and personality traits, including anxiety, cognitive inflexibility, obsessionality and perfectionism, might reflect neurobiological risk factors for the development of AN and that motivated eating restriction might be a means of lowering negative effects caused by an imbalance between serotoninergic and dopaminergic systems[67,203].

Other neurobiologically informed models of AN have highlighted alterations in stress, anxiety and fear-related processes[204], the rewarding nature of AN symptoms[205] and the shift over time to compulsivity or habitual behaviours[12,206] as key factors in the persistence of the illness. In line with these models, we are seeing changes in treatment away from traditional 'talking' therapies to much more targeted psychobiological and neurobiological interventions that are tailored to the psychobiology and neurobiology of the disorder[207]. For example, cognitive remediation therapy for AN attempts to ameliorate neurocognitive inefficiencies, such as poor cognitive flexibility. Available evidence from small-scale and medium-scale trials suggests that cognitive remediation therapy has promise[208,209], although rigorous large-scale evaluations against credible comparison treatments are still lacking.

Altered fear learning, both in terms of conditioning and extinction processes, has also been thought to be causally implicated in AN development[210,211]. On the basis of this idea, treatments using systematic exposure to food stimuli or one's own body (that is, mirror exposure) might be another promising treatment for individuals with AN[211], although this work is very much at the proof-of-concept stage. It remains to be seen whether this translates into effective standalone or adjunct treatment.

Other promising psychobiological treatments include cognitive bias modification interventions[212], based on converging evidence that suggests a range of cognitive biases (attention, interpretation and memory) in relation to illness-relevant and socio-emotional stimuli in AN. An interesting proof-of-concept study demonstrated that intranasal oxytocin reduced attentional biases towards eating-related and negative shape stimuli compared with placebo in patients with AN[213]. These authors and others[214] suggest that oxytocin administration might be a useful adjunct to treatment of the condition.

Further advances in genetics will facilitate the development of new diagnostic tools and new treatments by improving understanding of the pathophysiology and genetic aetiology of eating disorders. Genetic risk scores will enable the evaluation of the extent to which individuals harbour risk loci for AN, and will enable us to understand — on a biological level — why some individuals are more vulnerable to the effect of high-risk behaviours such as extreme dieting and excessive exercising than others. Further work might enable us to identify actionable drug targets leading to medications that act directly on pathways that underlie the core biology of the illness.

Finally, improved understanding of the neurocircuitry involved in AN[215] has given rise to the use of neuromodulation techniques (FIG. 7), both as a probe of disease mechanisms and as treatment. These techniques include deep brain stimulation, repetitive transcranial magnetic stimulation and transcranial direct current stimulation[216]. As yet, no RCTs of therapeutic use of neuromodulation treatments have been published. Case studies have targeted different brain regions, and findings suggest that deep brain stimulation might have promise in ameliorating eating disorder symptoms and improving mood in highly selected patients with SEED-AN[217].

Taken together, emerging evidence from these experimental treatments suggests that we are in the middle of a paradigm shift. We now have conceptual frameworks for understanding the aetiology and potential tools for probing and targeting disease mechanisms, which should facilitate us moving from 'one-size-fits-all' imprecise treatments[218] to diagnostic precision and targeted treatments[219] to achieve substantial advances in treatment.

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Author contributions

Introduction (J.T.); Epidemiology (N.M.); Mechanisms/pathophysiology (C.M.B. and G.K.F.); Diagnosis, screening and prevention (T.W. and E.S.); Management (J.T., S.Z. and A.C.); Quality of Life (E.W.); Outlook (U.S.); Overview of the Primer (J.T.).

Competing interests

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