Reconceptualizing anorexia nervosa

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Anorexia nervosa (AN) has one of the highest mortality rates of any psychiatric disorder. Treatments are often ineffective and relapse is common. Most research attempting to understand the underlying causes and maintenance factors of AN has focused on environmental contributions, yet there is much to be explored in terms of biological risk and maintenance factors. In this paper, we focus primarily on AN research related to genetics and the complex microbial community in the gut (intestinal microbiota), and how these impact our conceptualization of this disorder. Emerging research identifying significant negative genetic correlations between AN and obesity suggests that the conditions may represent ‘metabolic bookends’. The identification of underlying biological mechanisms may provide both insight into extreme weight dysregulation on both ends of the spectrum and new possible points of entry for AN treatment.

Anorexia nervosa (AN) is perplexing and widely misunderstood. Decades of focus on sociocultural and familial factors have hindered our ability to truly understand the causes and maintaining factors of this devastating illness. In 2015, the Academy for Eating Disorders released the ‘Nine Truths About Eating Disorders’ (Fig. 1). The ‘Nine Truths’ is an aspirational document designed to widely disseminate additional information to establish their veracity. For example, Truth #5 states: ‘Eating disorders affect people of all genders, ages, races, ethnicities, body shapes and weights, sexual orientations, and socioeconomic statuses.’ Although we know this to be true clinically, much of the science that has been conducted on AN has been conducted on females of European ancestry between adolescence and young adulthood. Indeed, much of the work that we review here reflects what is known about that population. Concerted efforts are required to ensure that our understanding about the causes of AN and its treatment, as well as science about the other eating disorders (e.g., bulimia nervosa, binge-eating disorder [BED], avoidant and restrictive food intake disorder), accurately captures the diversity of individuals who suffer from these illnesses.

In this review, we summarize a plenary address delivered at the World Congress of Psychiatric Genetics in Glasgow, Scotland in 2018. Our focus is on recent advances in science that address Truths #7 (‘Genes and environment play important roles in the development of eating disorders’) and #8 (‘Genes alone do not predict who will develop eating disorders’). We report primarily on AN as most of the research has been done on that illness, but highlight work on the other eating disorders that is currently underway.

What is anorexia nervosa?

AN is characterized by dangerously low bodyweight, indifference to the seriousness of the illness, and female preponderance.1–5 The prevalence of AN in Japan has increased significantly over recent decades and has been reported as 0.11% (0.03–0.28%; 1982); 0.13% (0.04–0.31%; 1992); and 0.43% (0.20–0.67%; 2002) in women.6 Reasons put forward to account for this increase have focused on sociocultural phenomena, including Westernization7 as well as non-Western ideals, such as modesty and collectivism (harmony with the values of society).6

AN is associated with high psychiatric comorbidity,9 high suicide risk,10,11 and has the highest mortality rate of any psychiatric disorder.11–14 With the advent of DSM-5,2 a presentation of ‘atypical AN’ has also been recognized in which an individual meets all of the diagnostic criteria for AN, except that despite significant weight loss, the individual’s weight is within or above the normal range. It is unknown whether the underlying biology of AN and atypical AN are the same.

Phenomenology of anorexia nervosa

AN is intriguing as many of its behaviors are counterintuitive and diverge from typical human experience. For example, for most of us, starvation and even hunger are deeply unpleasant and to be avoided at all costs. Humans strive to achieve energy balance (equal energy intake as output) and, as evidenced by the global obesity epidemic,15 an ever-increasing portion of the world finds itself in prolonged...
NINE TRUTHS ABOUT EATING DISORDERS

Truth #1: Many people with eating disorders look healthy, yet may be extremely ill.

Truth #2: Families are not to blame, and can be the patients’ and providers’ best allies in treatment.

Truth #3: An eating disorder diagnosis is a health crisis that disrupts personal and family functioning.

Truth #4: Eating disorders are not choices, but serious biologically influenced illnesses.

Truth #5: Eating disorders affect people of all genders, ages, races, ethnicities, body shapes and weights, sexual orientations, and socioeconomic statuses.

Truth #6: Eating disorders carry an increased risk for both suicide and medical complications.

Truth #7: Genes and environment play important roles in the development of eating disorders.

Truth #8: Genes alone do not predict who will develop eating disorders.

Truth #9: Full recovery from an eating disorder is possible. Early detection and intervention are important.

Produced in collaboration with Dr. Cynthia Bulik, PhD, FAED, who serves as distinguished Professor of Eating Disorders in the School of Medicine at the University of North Carolina at Chapel Hill, "Nine Truths" is based on Dr. Bulik’s 2014 "8 Eating Disorders Myths Busted” talk at the National Institute of Mental Health. Leading associations in the field of eating disorders also contributed their valuable input.


Fig.1 Academy for Eating Disorders’ nine truths about eating disorders.

positive energy balance (i.e., caloric intake greater than expenditure). In stark contrast, individuals with AN report starvation to be reinforcing, anxiolytic, and occasionally euphorogenic and deny the presence of typical hunger signals, potentially in part due to reduced perception of body signals. 17–19 Individuals predisposed to AN tend to be anxious at baseline and report that food restriction has a calming effect. Second, fats, favored by most humans especially when combined with sugar,20,21 are aversive to individuals with AN.22,23 Third, for many people with AN, activity is more reinforcing than food.24,25 Pathologically elevated activity is observed in between 37% and 80% of individuals with AN,26–28 and is associated with poor treatment outcome.27 Recent evidence from a genome-wide association study (GWAS) revealed a positive genetic correlation between measured physical activity and AN, suggesting that the mechanism underlying this association may be in part under genetic control.29 Fourth, individuals with AN often experience an unexplained hypermetabolic period during renourishment, which can last for variable durations and complicate recovery.30–32 Fifth, despite prolonged under- or malnutrition and frank cachexia, individuals with acute AN typically do not exhibit sickness behaviors commonly associated with inflammatory processes seen in other somatic and psychiatric illnesses,33,34 and only report feeling poorly once renourishment has begun. Finally, weight loss after therapeutic weight restoration (weight relapse) is common35 as the bodies of individuals with AN appear to be pulled to revert to a low set or settling point36 even after weight restoration.

To partially address some of these intriguing characteristics, we are engaging in a programmatic line of research that explores actions and interactions of genetics, the environment, and the intestinal microbiota on AN risk and maintenance (Fig. 2). Herein, we discuss progress in all three domains.

Genetics
The past decade has witnessed remarkable advances in identifying the genetic basis of many psychiatric disorders.37 With the advent of GWAS and large consortia and collaborations (representing over 40 countries across Europe, North America, Asia, South America, Africa, and Australasia) that make collection of large samples feasible, AN has been included in these efforts via the actions of the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED). It is uncontested that AN is familial, with female relatives of individuals with AN being 11 times more likely to develop the illness than relatives of individuals without anorexia.38 Consistent with the diagnostic fluctuation seen across eating disorder presentations,39 eating disorders do not breed true in families (i.e., they co-aggregate). For example, the relative risks of full and partial anorexia syndromes as well as DSM-IV eating disorder not otherwise specified are elevated in first-degree relatives of individuals with AN and bulimia nervosa.38,40

Replicated twin studies have confirmed heritability, with estimates ranging from 0.28 to 0.7441 and narrower diagnostic criteria being associated with higher heritability estimates.45 The consistency of this work encouraged us to undertake a GWAS of AN and, in 2017, we reported the first adequately powered study representing a collaborative effort including 3495 individuals with AN and nearly 11,000 controls without eating disorder histories from 12 case-control cohorts.46 We estimated the single-nucleotide polymorphism-based heritability H2SNP to be 0.20, which is consistent with estimates for other psychiatric disorders. We also identified the first genome-wide significant locus on chromosome 12 – a locus previously implicated in type 1 diabetes47 and rheumatoid arthritis.48 Although revealing the first significant association was a milestone, even more intriguing results emerged from the pattern of observed genetic correlations. Using linkage disequilibrium score regression, a technique that allows you to calculate genetic correlations between phenotypes using summary statistics, we calculated genetic

Fig.2 Model for actions and interactions of genetics, the environment, and the intestinal microbiota in risk for and maintenance of anorexia nervosa.
correlations between AN and 159 psychiatric, medical, educational, and personality phenotypes. These phenotypes included summary statistics from GWAS studies from global collaborative investigations of body mass index (BMI), obesity, anthropometric, and metabolic traits. After correcting for multiple comparisons, 29 correlations emerged as significant, including schizophrenia; personality traits, such as neuroticism; and educational attainment. Less expected, we observed significant genetic correlations between AN and an array of metabolic and anthropometric traits, including waist circumference with high-density lipoprotein cholesterol and negative genetic correlations with BMI, obesity, fasting insulin, and fasting glucose. These findings led to our initial statement on the importance of considering both psychiatric and metabolic factors in understanding the etiology of AN. We took this as preliminary evidence of shared genetics underlying extremes of weight dysregulation (i.e., obesity vs AN). These shared genetic factors may speak directly to the perplexing feature of how individuals with AN reach, sustain, and relapse to dangerously low BMI despite clinical renourishment. We hypothesized that this ‘weight relapse’ may represent the biological inverse of the reversion to high set points commonly seen in the unsuccessful treatment of obesity.51,52 Our findings supported the proposition that some of the same genetic factors that influence normal variation in BMI, body shape, and body composition may also influence dysregulation in the opposite direction of these features in AN.

The second wave of investigations of the PGC-ED group yielded a GWAS of 16 992 AN cases and 55 525 controls and identified eight independent genome-wide significant loci.53 Results of this larger study were more robust and revealed an even clearer pattern of genetic correlations. Importantly, with increased statistical power, we were able to show that the genetic correlations with metabolic traits remained significant even when correcting for the effects of common variants associated with BMI, raising the question of whether a fundamental metabolic dysregulation may explain the challenges faced with treating the illness and helping sufferers gain and retain healthy bodyweights. We encourage new lines of collaboration to further elucidate what these metabolic parameters might be and to broaden our conceptualization of the illness to include both psychiatric and metabolic factors.

Results from this work raise the question of whether AN and obesity may be metabolic mirror images on some dimensions. Clinically, it is fairly easy for individuals with obesity to lose weight in the short-term if they adhere to a ‘diet’, but weight regain is common, and interindividual variability in response to weight loss interventions is considerable.53–55 Explanations for weight regain are many and are controversial, but it may reflect a biologically driven process to settle at a previously attained high weight or fat mass.56 The field has not uniformly conceptualized AN as the opposite of obesity, with constitutional thinness (i.e., underweight, normal eating behavior, desire to maintain their renourished weight vs those who experience weight relapse) will be an important source of this information.

Our observations suggest that harbingers of BMI dysregulation may emerge very early in life. A recent study with participants of the Avon Longitudinal Study of Parents and their Children (ALSPAC) suggests that deviations from healthy BMI trajectories can be observed very early in life in youth who go on to develop eating disorders. Significant divergence below expected BMI trajectories begins in boys by age 2 and in girls by age 4 who later go on to develop AN.62 The opposite pattern, namely significant divergence above the expected BMI trajectory, emerged for those who later developed bulimia nervosa, binge-eating disorder, or purging disorder. Although a strength of the ALSPAC study is the premorbid and longitudinal measurements, other studies in the field report conflicting findings, including higher childhood BMI being associated with later AN.63 Notably, several studies similarly report higher pre-morbid BMI or obesity in the binge-type eating disorders.64,65 Although additional work is required to reconcile some of the observed differences, premorbid metabolic factors and weight may be relevant to the etiology of eating disorders. In AN, premorbid low weight may represent a key biological risk factor or early manifestation of an emerging disease process.

Genetic studies of AN have limitations that can be overcome. As alluded to earlier, the samples included in the current GWAS are primarily from European ancestry female populations. Although we have some Asian and male samples, the sample sizes are inadequate to determine the extent to which the same genetic factors are operative in the illness across populations, and we have very few samples from individuals of other ancestral backgrounds. Concerted efforts are required to diversify our samples to address this critical research question.

Epigenetics

The study of epigenetics in eating disorders is nascent. ‘Epigenetics’ refers to biochemical mechanisms that lead to changes in gene regulation. These changes are either heritable or stable over the long term.66 We conducted a systematic review of epigenetics in eating disorders and identified a small number of discoverable investigations: AN (n = 13), bulimia nervosa (n = 6), and BED (n = 1; January 2003 to October 2017).67 Although epigenetic processes fall into three categories – DNA modifications, histone modifications, and non-coding RNA – most eating disorder studies explored methylation at candidate genes (n = 13). Samples were small, and replication was non-existent. As such, results were inconclusive and should be considered to be exploratory. We encourage the scientific community to adopt sound methodological approaches, to coordinate protocols across centers to increase sample size, and to apply genome-wide designs, including epigenome-wide association studies.

The external environment

Returning to the Academy for Eating Disorders’ Nine Truths, Truth #7 underscores the role of the environment in eating disorder risk and Truth #8 cautions that genes alone do not determine who develops eating disorders. The majority of research on eating disorder risk factors has focused on the external environment, with an emphasis on sociocultural risk factors contributing to thin ideal internalization and body dissatisfaction. Perceived pressure to be thin, social pressure,68,69 and peer context70 are associated with increases in differences in the underlying biology of weight dysregulation in the presence versus absence of the cognitive factors associated with AN. If we can identify the biological mechanisms that influence the return to low weight and distinguish them from those seen in assisting individuals with constitutional thinness with weight gain, we may be able to isolate the processes underlying extreme weight dysregulation in AN that extends beyond our current understanding from psychological, environmental, and behavioral perspectives. Genetic and biological studies of treatment outcome (i.e., comparing those who maintain their renourished weight vs those who experience weight relapse) will be an important source of this information.
eating pathology and onset of disordered eating behaviors. Along similar lines, studies have demonstrated associations among social pressures, social comparison, and body dissatisfaction (e.g., van den Berg et al.); additionally, eating-disorder-related social comparison may mediate the relationship between thin ideal internalization and body dissatisfaction.22 Looking beyond an individual’s immediate social circle and the associated social pressures and comparisons, those who experience greater exposure to media and thin ideal images are more likely to diet, feel dissatisfied with their body, and exhibit negative affect, potentially putting them at greater risk for engaging in behaviors that increase risk for developing an eating disorder.28

Finally, there is mixed research on the impact of socioeconomic status as well as race and ethnicity,73 yet experiencing adverse life events, a common risk factor associated with many psychiatric disorders, remains a significant, but non-specific, risk factor for eating disorders.

Research on environmental risk factors for AN has been unable to definitively determine why some individuals are more prone to environmental pressures toward thinness than others. While exposure to societal thin ideals is nearly ubiquitous (especially with the globalization of media and social media), why some individuals are more vulnerable to the messages and more likely to engage in behaviors that are entrees into frank eating disorders remains unknown and could be answered by ongoing biological research.

The gut environment

Although much has been written about environmental risk factors in eating disorders, the focus has primarily been on external environmental influences.73 Indeed, the Academy for Eating Disorders’ Nine Truths generally refer to the role of the external environment in influencing AN risk and maintenance. Our work has focused on another, internal, environment, namely that of the complex microbial community residing in the gut: the intestinal microbiota. We address the research question of the gut environment in individuals with AN in fimo (samples derived from human excrement and examined scientifically)75 and consider the biological setting created by an illness characterized by severe and prolonged food and nutrient restriction.

As background, just like many organisms, enteric microbes also have preferences for their environments. For example, altering the dietary composition of fats, carbohydrates, and protein leads to observable changes in the ratios of human intestinal microbes.76,77 We also know that food preferences (for sweet, bitter, sour, and umami) can be influenced by host genotype.78

What are the characteristics of the gut environment of individuals with AN? In the broadest terms, the gut environment is marked by chronic caloric restriction, macronutrient imbalance (food groups are often summarily avoided), micronutrient deficiencies, fluctuating food availability (associated with binge–fast cycles in some), osmotic perturbation (caused by laxative abuse in a subtype of patients as a compensatory behavior), and high fiber content.79-84 Our programmatic line of work rests on the fact that the human intestine is a competitive environment and we hypothesize that the environment created by AN may select for microbes that can subsist on low energy and imbalanced nutrients. Compelling evidence suggests that the intestinal microbiota not only influences host metabolism,85 but also affects brain function and behavior.86 Accordingly, we hypothesize that the microbial community selected by the AN-associated gut environment might in turn affect host behavior and metabolic profile, further contributing to the maintenance of the illness. We do not disregard the possibility that a gut microbial imbalance, or dysbiosis of the gut microbiota, might precede the onset of AN, although this is much more difficult to study.

The relevance of the gut microbiota for the key features of AN, including weight regulation, energy metabolism, anxiety, and depression, has been discussed in detail elsewhere.87,88 To expand on the rationale for exploring the role of intestinal microbiota in AN and other eating disorders, here we discuss the effect of gut microbes on regulation of satiety – another important aspect of AN (and other eating disorders). Research in laboratory animals suggests that bacterial metabolites can influence brain mechanisms that control appetite and energy homeostasis through the gut–brain axis.89 In an elegant study conducted in mice, gut commensal Escherichia coli in its stationary phase was found to produce a peptide mimetic of α-melanocyte stimulating hormone, an anorexigenic and anxiogenic neuropeptide. This bacterial peptide is called ‘caseinolytic proteinase B’ and was shown to activate hypothalamic proopiomelanocortin-expressing neurons directly or through stimulation of gut hormones, and thus regulate feeding behavior.90 In patients with eating disorders (AN, bulimia nervosa, and BED), plasma levels of caseinolytic proteinase B were reported to be elevated compared to healthy controls.90 However, results must be interpreted cautiously as sample sizes were small and significance was marginal as results were not corrected for multiple comparisons.

Another bacterial metabolite that was shown to influence energy homeostasis through direct gut–brain neural communication is propionate.91 Propionate, acetate, and butyrate are the most abundant short-chain fatty acids (SCFA) in the colon and feces.83 SCFA are the end products of fermentation of dietary fibers by anaerobic bacteria in the colon, and have been extensively investigated in gut microbiome research. SCFA have been linked to multiple beneficial effects on host energy metabolism.92 One of the identified SCFA mechanisms of action, which connects cellular metabolism to gene expression, is inhibition of histone deacetylases.93 Post-translational histone modifications are known to be important regulators of gene expression. Interestingly, in a study conducted on a small group of participants in Japan, Morita et al.94 showed that the concentrations of acetic and propionic acid were significantly lower in AN patients compared to healthy controls. In a European study with a relatively larger number of samples, the total SCFA levels were shown to be comparable between AN patients and participants with normal weight.95 However, AN patients had lower concentrations of butyrate correlated with decreased levels of butyrate-producing Roseburia spp. compared with controls. A possible explanation for the discrepancies between these two findings could be differences in the lifestyle and diet in Japanese versus European participants. In two more recent publications, AN patients were reported to have reduced excretion of fecal butyrate and propionate compared to healthy individuals.96,97 In addition, the concentrations of butyrate were inversely correlated with levels of anxiety in patients with AN.96

Future studies investigating alterations in microbial metabolites and their mechanisms of action in larger well-characterized samples of individuals with AN – both during the acute phase of the illness and after recovery – will lead to a more comprehensive understanding of the role of gut microbiota in eating disorders and potentially delineate between the effects of starvation versus the effects of illness. In summary, the results of these studies, although intriguing, are limited by the small samples sizes and the employed targeted approaches for sequencing and measuring specific microbial metabolites. We do not yet have a complete picture of the functional capacity of the microbiota in AN.

Formative work

Our early work in the area, conducted by Kleiman et al.98 on small samples, characterized the taxonomy and diversity of the intestinal microbiota in individuals with AN at low weight (acute illness at hospital admission < 75% ideal body weight [IBW]) and after inpatient therapeutic renourishment (>85% IBW) in comparison to healthy controls. Bearing in mind that a diverse microbiota is a healthy microbiota, our work revealed lower microbial diversity between patients with AN at both intake and discharge compared with controls, with some normalization across treatment, but not matching the diversity in healthy controls. The observed lower microbial diversity even after renourishment could be a potential contributing factor to the high relapse rate reported in AN patients. Further research aimed at
investigating the role of microbiota in treatment outcomes in terms of retaining therapeutically restored weight is warranted.

In this sample, we also observed a significant correlation between mood and microbial diversity such that lower diversity was associated with higher self-report depression scores. Of note, this was not observed in an independent sample of healthy controls who had a much more restricted range of responses on the mood measures. Together, these observations raised the question of whether this aspect of the microbe–gut–brain axis is only detectable at more extreme levels of psychopathology. A recent large population investigation provided intriguing and replicated evidence for an association between the gut microbiome and quality of life and depression. In addition, over the past decade, the number of clinical trials investigating the effect of probiotics on mood and anxiety disorders has increased. Although there is still a need for more extensive mechanistic studies and trials in both healthy and clinical populations, the promising results point to the therapeutic potential of targeting gut microbiota in the treatment of mood and anxiety symptoms. Herpertz-Dahlmann and coworkers have reviewed the therapeutic implications of gut microbiota specifically in relation to AN. In brief, the authors discuss the benefits of targeting the microbiota with approaches including nutritional interventions, pre- and probiotics, and drugs to improve energy retrieval, anxiety, and depressive symptoms in individuals with AN.

Other studies have confirmed differences in the diversity and composition of the intestinal microbiota in individuals with AN compared to healthy controls and across the course of therapeutic renourishment. Whether the microbial profile is distinct in each of the two types of AN (restrictive and binge-purging), has only occasionally been explored, and another reporting distinct perturbations in microbial composition in each AN type and decreased microbial diversity in those who had history of laxative use. Previous research in mice and humans suggests that acute use of laxatives can cause long-term alterations in the gut microbiome. However, the long-term impact of regular use of laxatives on microbiota in AN individuals is still unknown. In general, the shifts in the intestinal microbial community can potentially affect the production and release of various metabolites and signaling molecules by gut microbial communities. When integrated with the sequencing data, studying microbial metabolites will potentially yield a more in-depth understanding of the biological role of the gut microbiota and its interactions with the host.

**Ongoing work**

Our current work funded by the National Institute of Mental Health, called ‘Anorexia Nervosa: Investigation of the Gut Microbiome and Anxiety (ANIGMA)’, is building on our formative work to explore the key scientific questions in greater depth. We are testing 100 female patients with AN at admission (<75% IBW) and discharge (>85% IBW) compared to healthy controls to characterize and correlate the composition and diversity of the intestinal microbiota with adiposity, anxiety, and stress. In addition, we will be performing fecal microbiota transplants from AN patients into germ-free (GF) mice (mice grown in the absence of microbes). The use of GF mice has proven to be a valuable approach for functional and mechanistic investigation of illness-associated microbiota. We are exploring whether the presence and abundance of certain taxa within the microbiota of AN patients will be associated with adiposity and BMI in formerly GF mice. We are testing this hypothesis by performing dual-energy X-ray absorptiometry (DEXA) on the mice after colonization and adaptation to the human transplanted microbiota. In the second aim of ANIGMA, we are exploring whether behavioral traits are transmitted into GF mice via fecal slurries from AN patients at admission. Here we hypothesize that formerly GF mice that are colonized by AN patient feces will display greater anxiety-like behaviors in open field and other behavioral tests. If observed, this will provide evidence for the gut–brain–behavior axis and show that one of the core features of AN, namely anxiety, can be transmitted microbially.

**Future directions**

Ultimately, our goal and that of others is to probe in greater depth the ways in which the intestinal microbiota and host genetics act and interact to influence disease risk, trajectory, and recovery from AN. Evidence from twin studies suggests that the gut microbiota can be affected by host genetic variation, and that the interaction between the microbiome and host genome can influence the phenotype in the host. Of relevance, the concordance rate of carriage of the archaeon *Methanobrevibacter smithii* was found to be significantly higher in monozygotic compared to dizygotic twin pairs. The levels of *M. smithii* were reported to be elevated in AN patients and associated with efficiency of fermentation of dietary components.

To advance this science, we are currently recruiting large samples of individuals with eating disorders from whom we obtain saliva for genotyping, stool samples for sequencing, and extensive phenotypic information. Our goal is to explore how host genomics and the intestinal microbiota act and co-act in AN, bulimia nervosa, and BED. This is an evolving field with vastly different perspectives and opinions. Some teams posit that exploring the ways in which host genomics and the microbiome interact to influence disease phenotypes is an open frontier whereas others claim that environment dominates over host genetics in shaping the human gut microbiota. Fortunately, we will have the samples and data to address this question directly relative to eating disorders.

In addition, we have received approval from the Food and Drug Administration to test fecal microbiota transplantation (FMT) in the treatment of severe AN. Our field has struggled to find interventions for chronic AN and recent publications have begun to move toward quality of life, palliative care, and even euthanasia for those with severe and enduring forms of the illness. As such, we believe it is important to test interventions that have been shown to give hope to others with chronic and debilitating illnesses, for which we have some evidence of involvement of the intestinal microbiota in the disorder. FMT is a safe and effective therapy for *Clostridium difficile* infection, which can cause life-threatening disease of the colon. Studies involving transplantation of intact, uncultured microbiota from healthy humans to individuals with *C. difficile*-induced colitis or patients with metabolic syndrome have yielded proof-of-principle that the intestinal microbiota represents a valid therapeutic target for treating or preventing disease. These findings provide a basis for the use of FMT beyond the treatment of *C. difficile*. Careful monitoring of outcomes will inform as to whether FMT is worthy of additional study in controlled randomized placebo-controlled investigations.

Ultimately, we hope that this line of work will lead to novel interventions for AN, and potentially bulimia nervosa and BED as well. We know, for example, that renourishment can be uncomfortable and even painful for individuals with AN and that delayed gastric transit time can complicate efforts at renourishment. We look toward prebiotic supplementation during refeeding to reduce discomfort, and potentially targeted probiotics to assist with reducing anxiety, depression, and eating disordered cognitions. Results of our FMT pilot will inform as to whether this approach may be of value in the treatment of severe AN.

**Conclusion**

Our understanding of the etiology of AN is evolving and empirical support is expanding for the Academy for Eating Disorders’ Truths #7 (‘Genes and environment play important roles in the development of eating disorders’) and #8 (‘Genes alone do not predict who will develop eating disorders’). As GWAS sample sizes increase and results become more robust, the importance of considering both psychiatric and metabolic factors in understanding AN is becoming
increasingly clear. By paying closer attention to metabolic factors, we may improve the interventions we deliver and outcomes we achieve for AN. That said, the current work sheds light on the direction we should follow. Scientific study should be directed toward uncovering the mechanisms that underlie the metabolic dysregulation in AN, with an eye toward developing targeted interventions. Moreover, the accumulating evidence forwarding the intestinal microbiota as an integrated facet of metabolism and a critical player affecting the host behavior has inspired a holobiont approach toward human health and illness, and AN is no exception. Even though gut microbiome research in AN is in its infancy and needs to be expanded beyond associations, the findings from obesity at the other end of the spectrum provide a blueprint for future research directions. Finally, we propose that concomitant attention to genetics, external, and internal (gut microbiome) environment and their interactions has the potential to improve our understanding of the etiology and inform the development of novel empirically informed therapeutic approaches for AN.

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Author contributions
C.M.B. takes responsibility for all content of the paper. I.C. takes responsibility for all content of the paper. A.A. contributed primarily to the section on the gut microbiota. R.F. contributed primarily to background research and the sections on the environment and sample and participant diversity.

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