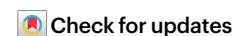# Editorial

Breaking down the microbiota–nutrition connection

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Microbiota-targeted interventions for malnutrition are under investigation, but complex illnesses associated with malnutrition, such as eating disorders, may not be straightforward to treat.

Anorexia nervosa (AN) is an eating disorder characterized by distorted body image, restrictive eating and psychological changes, which can culminate in severe malnutrition and hospitalization. It is more common in women, and diagnosis typically occurs in adolescents (10–19 years old) when individuals are developing patterns of behaviour related to diet and nutrition, as well as social and emotional habits. A combination of genetic and environmental factors likely contributes to AN, but its aetiology is still unclear. Standard of care is usually a combination of talking therapies and supervised weight gain, but effective, evidence-based treatments are lacking. Given that AN has a higher mortality rate than any other mental health disorder, with 5% of patients dying within four years of initial diagnosis, and that it can cause serious long-term morbidity, new interventions are urgently needed.

A growing number of studies have characterized the gut microbiota associated with this eating disorder. Individuals with AN have a compositionally and functionally altered gut microbiota compared with control individuals deemed to be a healthy weight. Alterations in the gut microbiota are typified by a decrease in beneficial microorganisms, such as short-chain fatty acid producers, an increase in potentially problematic microorganisms, for example, Enterobacteriaceae, and an altered capacity for nutrient metabolism[1,2]. However, it is unclear whether the gut microbiota is associated with the range of behaviours and symptoms seen in AN. In this issue of *Nature Microbiology*, Oluf Pedersen and colleagues studied a cohort of women with AN using shotgun metagenomics and metabolomics, together with a mouse model and faecal microbiota transplant experiments, to determine links between the gut microbiota and AN-associated metabolic and psychological symptoms. Interestingly, the authors found that microbial taxa and functions were correlated with measures of eating behaviour and mental health in AN. Notably, shifts in gut metabolites were associated with appetite regulation and mood indicating a potential gut–brain connection. Faecal microbiota transplant experiments using samples from women with AN in a mouse model of restricted feeding resulted in reduced weight gain and altered expression of genes related to eating behaviour and energy metabolism. This provides stronger support for the suggestion that gut microorganisms can contribute to the pathogenesis of AN.

In a linked News and views, Tom Hildebrandt and Deena Peyser propose that AN could now be recognized as a psycho-metabolic disorder, rather than solely psychological, in which the gut microbiota contributes to symptoms and responses to refeeding treatments. Another recent study observed that in-patient refeeding treatment involving high calorie consumption improved weight gain, but the gut microbiota remained distinct from healthy weight controls across two eating disorder units[2]. Current interventions usually have high fat and protein content, but are low in fibre; a component essential for a healthy gut microbiota. Whether microbiota-directed foods could be used to improve weight gain, or to improve the metabolic and psychological symptoms observed with eating disorders, is unclear. We do not know whether the observed microbiota shifts are a result of restricted food intake caused by AN, whether the microbiota shifts cause the altered feeding behaviour and other symptoms of AN, or whether the changes in the microbiota exacerbate existing symptoms. Hildebrandt and Peyser conclude that we must understand the direction of causation in AN before the microbiota is targeted for interventions. Owing to the complex nature of eating disorders, and substantial associated morbidity and mortality, caution must be taken before attempting to apply these findings to devise potential treatments.

The unresponsiveness of the gut microbiota to refeeding that is observed in AN is not dissimilar to that observed in childhood malnutrition. Research carried out in the past two decades has highlighted the importance of the gut microbiota in breaking down dietary components, and extracting nutrients and energy. How we nourish ourselves has knock-on effects for our microbial residents, which in turn impact our risk of developing various diet-related diseases. Given the tight links between diet and the gut microbiota, several research groups have been targeting the microbiota to treat malnutrition. Childhood malnutrition is typically treated with fortified foods, but unfortunately this approach does not mitigate longer-term complications of starvation. This is in part due to a lack of consideration for the gut microbiota, which does not recover to resemble a healthy child microbiota, even after fortified foods have been consumed. Jeffrey Gordon and colleagues tackled this issue by designing microbiota-directed complementary foods (MDCFs), based on the gut microbiota and serum metabolome and proteome profiles of malnourished Bangladeshi children[3]. MDCFs were tested in mice and piglets colonized with defined microbiotas to identify foods that promoted strains associated with weaning at specific developmental ages in healthy children. The most promising MDCF was tested in a randomized, double-blind controlled study. This confirmed its ability to shift the gut microbiota and physiological markers towards that of healthy children, providing a promising path forward for treating malnutrition.

Starvation and eating disorders are forms of malnutrition, which itself comprises a large set of nutrition-associated diseases. The coexistence of undernutrition (stunting, wasting and micronutrient deficiencies) and overnutrition (overweight and obesity) is rising across populations, with a growing burden of all forms of malnutrition in low- and middle-income countries. Malnutrition (the over or under provision of energy and nutrients in the diet) affects all age groups and is particularly acute in childhood and

older age. This can be caused by inadequate dietary intake, infectious and non-infectious disease, as well as other socioeconomic factors. In 2020, 149 million children (less than 5 years old) were stunted (too short for age), 45 million children were too thin for their height, and 38.9 million children were overweight or obese, according to the World Health Organization. These nutritional imbalances have implications for short- and long-term health, that range from impaired cognitive function, bone development and immune function, to the development of chronic non-communicable diseases and death. It is not surprising that nutrition is being prioritized by the United Nations Decade of Action on Nutrition, due to end in 2025, and is an important component of multiple Sustainable Development Goals.

Malnutrition causes substantial morbidity and mortality worldwide, and it is clear that the gut microbiota can have a role in diseases associated with nutrition. By highlighting the role of the gut microbiota in human nutrition in our journal, we hope to contribute to efforts to further understand nutritional disease pathogenesis in the context of the microbiota, which in turn will inform the development of effective interventions.

References

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